Estimating Psychosis Risk in Individuals at Clinical High Risk using Event–Related Brain Potential Indices of Cognitive Processing

by

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Abstract

Background: The N400 event-related brain potential waveform occurs in response to potentially meaningful stimuli and this effect is thought to reflect greater activation of related versus unrelated concepts in long-term semantic memory. In normal participants, related targets elicit smaller (less negative) N400 amplitudes than do unrelated items. These N400 semantic priming effects are found to be attenuated in schizophrenia patients, suggesting impaired activation of related concepts. Individuals at clinical high risk (CHR) for schizophrenia experience subthreshold symptoms of the disorder, including decreased functioning. The event-related potential Mismatch Negativity (MMN), P3a and gamma ASSR measures have been found to be abnormal in CHR patients compared to controls.

Aim: We aimed to examine whether N400 semantic priming deficits are a biomarker of the CHR state, whether decreased N400 semantic priming predicts conversion to psychosis in this population over two years, and whether N400 effects predict high-risk symptomatology and impaired functioning over time.

Methods: We examined the N400 ERP semantic priming effect, the MMN, P3a and gamma ASSR in a sample of CHR participants and healthy controls. We then re-assessed the CHR group

at one and two years to measure global functioning, positive psychotic symptoms, and conversion status.

Results: We found a deficient N400 effect in the CHR group compared to controls. In this group, the N400 was related to role functioning and cognitive defects at baseline, social functioning at one-year follow-up, and improvement of positive symptoms and functioning over two years' follow-up.

Conclusion: This study indicates that the N400 priming effect is deficient at the CHR state and may contribute to the worsening of positive symptoms and functioning over time. Given that only a minority of CHR individuals will go on to develop schizophrenia, efforts to refine our ability to identify those at highest risk are critical. These findings may help to target limited resources to those individuals at risk who need it the most and minimize unnecessary treatment and side effects.

To My Dad

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Statement of Contributions

Jennifer Lepock (author) - recruited and assessed participants, executed study visits, contacted for follow ups, executed follow up visits, conducted EEG data processing, data analysis and results interpretation, and dissertation write up.

Dr. Michael Kiang (supervisor) - study conception and design, guidance in study execution, data processing, data analysis, results interpretation and dissertation write-up, constant mentorship, and instruction throughout study duration.

Dr. Romina Mizrahi (co-supervisor) - provided mentorship throughout and expertise with the CHR population and participant recruitment, supplied guidance and feedback throughout the study, assisted with dissertation write up.

Dr. Michael Bagby (Program Advisory Committee member) - provided expertise and feedback on the study, published works and the dissertation write up.

Dr. Elizabeth Pang (Program Advisory Committee member) - provided expertise and feedback on the study, published works and the dissertation write up.

Dr. Cory Gerritsen - assisted with participant recruitment, administration of assessments and study visits, as well as provided expertise and mentorship throughout the study duration.

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List of Abbreviations

APS - Attenuated Psychotic Symptoms

AR-C - At Risk Converted

AR-NC - At Risk Not Converted

ASSR – Auditory Steady State Response

BIPS – Brief Intermediate Psychotic Symptoms

BLIPS - Brief Limited Intermediate Psychotic Symptoms

BSABS - Bonn Scale of the Assessment of Basic Symptoms

CAARMS - Comprehensive Assessment of the At-Risk Mental Status

CHR - Clinically High Risk

CHR-NR – Clinically High-Risk Non Remitters

CHR-R – Clinically High-Risk Remitters

COGDIS – Cognitive Deficits

COPS - Criteria of Prodromal States

CRN – Correct Response Negativity

CSZ - Chronic Schizophrenia

DIPD - Diagnostic Interview of Personality Disorders

E-BARS - Early/Broad At Risk Mental State

EIPS - Early Initial Prodromal State

ERI (retrospective)- Early Recognition Inventory based on the retrospective assessment of the onset of schizophrenia

ERN - Error-Related Negativity

ESZ – Early Schizophrenia

ERP – Event-Related Potential

FEP - First Episode Psychosis

FESZ - First Episode Schizophrenia

GF – Global Functioning

GHR - Genetically High Risk

GRD - Genetic Risk and Deterioration

HC - Healthy Control

K-SADS-PL - Schedule for Affective Disorders and Schizophrenia for School Aged Children-

Present and Lifetime Version.

LDAEP - Loudness Dependence of Auditory Evoked Potentials

LIPS - Late Initial Prodromal State

MMN – Mismatch Negativity

PANSS - Positive and Negative Syndrome Scale

PS - Psychosis

PRS – Psychosis Risk Syndrome

PP - Prodrome Patients

SANS - Scale for the Assessment of Negative Symptoms

SAPS - Scale for the Assessment of Positive Symptoms

SCID - Structured Clinical Interview for the DSM-IV

SIPS - Structured Interview for Prodromal Symptoms

SM – Semantic Memory

SOA – Stimulus Onset Asynchrony

SOPS - Scale of Prodromal Symptoms

SPI-A - Schizophrenia Proneness Instrument, Adult version

SZ - Schizophrenia

TP-DIS - Thought/Perception Diagnostic Interview Schedule

Chapter One

General Introduction

This chapter contains sections that have been published in modified form: Lepock JR, Mizrahi R, Korostil M, Bagby RM, Pang, EW, Kiang M. Event-related potentials in the clinical high risk (CHR) state for psychosis: a systematic review. Clinical EEG and neuroscience, 49 (4), 215-25, ©2018. DOI: https://doi.org/10.1177/1550059418755212

Schizophrenia is a chronic psychiatric disorder characterized by psychotic symptoms (delusions and hallucinations), disorganized speech and behaviour, deficits in motivation (i.e., "negative symptoms") and cognition. It affects approximately 1% of the population and is the seventh leading cause of years lived with disability worldwide, according to the World Health Organization's Global Burden of Disease Study (Mathers, Fat, & Boerma, 2008). Patients with schizophrenia struggle considerably with functional impairment that affects their independent living skills, social relationships, and occupational and educational performance. 80-90% of schizophrenia patients describe having experienced a period of less intense symptoms in the time preceding psychosis with changes in thought content, interests, mood, and behavior (Addington & Heissen, 2012). In relation to schizophrenia, this period is variously referred to as the prodrome, at-risk mental state, clinical high risk (CHR) state, ultra high risk (UHR) state, or psychosis-risk syndrome. Paralleling the symptoms of schizophrenia, those of the psychosis prodrome may be classified into four categories: positive, disorganized, negative, and general (e.g., sleep disturbances, depressed or anxious mood) (McGlashan et al., 2001). By definition, positive symptoms are less severe in intensity or duration than psychotic symptoms meeting criteria for schizophrenia or another psychotic disorder. Thus, these symptoms may include anomalous self-experiences or ideas of reference that are not of delusional intensity, perceptual illusions or pseudohallucinations; or full-blown delusions or hallucinations that are brief and intermittent. For example, a commonly-used set of criteria used to define the CHR state, based on the Scale of Prodromal Symptoms (SOPS) (Table 2) (McGlashan et al., 2001), include the presence of either: "attenuated positive symptoms," with one or more of the 5 SOPS Positive items scoring in the prodromal range (rating of 3-5) and symptoms beginning or increasing within the past year and occurring at least weekly for one month; "brief intermittent psychotic symptoms," with one or more of the Positive items scoring in the psychotic range, symptoms beginning in the past three months and occurring at least several minutes per day at least once per month; and "genetic risk and deterioration," where a person with schizotypal personality

disorder or a first-degree relative with a psychotic disorder has a substantial deterioration in functioning over the past year. CHR individuals also demonstrate significant cognitive impairment in comparison to normal controls, with deficits in processing speed, attention, memory, language and executive function (Carrión et al., 2015).

A number of longitudinal studies have examined the risk of progression to schizophrenia or another psychotic disorder in individuals meeting criteria for a psychosis-risk syndrome. Most studies have found rates of conversion to a psychotic disorder of 16-40% over two-three years (Atkinson, Michie, & Schall, 2012; Bodatsch et al., 2011; Cannon et al., 2016; Frommann et al., 2008; Gee & Cannon, 2011; Hsieh et al., 2012; Van Der Stelt, Lieberman, & Belger, 2005). There is emerging evidence that identification and treatment of CHR individuals can reduce the probability of conversion to psychosis, and assessing the efficacy of such interventions is an ongoing focus of research. Randomized controlled trials have shown moderate effects of cognitive-behavioral therapy (CBT) on preventing transition to psychosis, (Fusar-Poli et al., 2015; Hutton & Taylor, 2014) and antidepressant medications have also shown promise in this regard (Cornblatt et al., 2007; Fusar-Poli et al., 2015). Converters are defined as those CHR patients who develop a psychotic disorder as determined by their score on a standardized diagnostic interview, e.g., the Structured Interview of Psychosis-Risk Syndromes (SIPS) (McGlashan et al., 2001). Given that only a minority of CHR individuals will go on to develop psychosis, efforts to refine our ability to identify those at highest risk are critical. This would enable health-care providers to allocate limited resources to those who need it the most and minimize unnecessary treatment and side effects. Thus, it is crucial to seek additional predictors of psychosis risk within the CHR group. Across studies, factors that have been found to predict conversion to a psychotic disorder include: severity of unusual thought content and suspiciousness/paranoia, low social functioning, substance abuse, and history of psychosis in a first-degree relative (Addington & Heinssen, 2012; Cannon et al., 2008a; Fusar-Poli et al., 2013). A risk calculation algorithm combining unusual thought content, suspiciousness, decline in social functioning, lower verbal learning and memory performance, slower speed of processing, and younger age was found to have positive predictive value for conversion to psychosis over two years' follow-up of 28%, compared to the sample base rate of 16%, with sensitivity of 67% (Cannon et al., 2016).

Event-related brain potentials (ERPs) are a non-invasive neurophysiological technique that holds promise for improving our understanding of neurocognitive processes underlying the

CHR state, and their relation to symptoms. ERPs are obtained from the scalp-recorded electroencephalogram (EEG) and represent the averaged voltage changes associated with classes of cognitive events (e.g. particular types of stimuli or responses). This electrical activity is thought to reflect the synchronous postsynaptic activity of groups of cortical pyramidal neurons (Luck, 2014). A number of ERP waveforms, or components, have been found to be reliably abnormal in schizophrenia, contributing to our knowledge about its underlying neurocognitive pathophysiology. ERPs have the advantage of millisecond-level temporal resolution and are thus helpful in determining the precise stage of information processing in the brain affected by disease states, potentially helping to identify targets for novel treatments (Javitt, Spencer, Thaker, Winterer, & Hajós, 2008). Characterizing whether or not ERP abnormalities associated with schizophrenia are shared by the CHR population, and by unaffected relatives of schizophrenia patients, can help distinguish whether these abnormalities reflect early disease processes associated with psychosis, or underlying familial risk factors, respectively; as opposed to more chronic disease processes or medication effects of schizophrenia. Identification of ERP biomarkers specifically linked to development of the CHR state could inform efforts to design novel, stage-specific interventions to prevent or reverse disease progression. Moreover, the degree to which individual CHR patients express such biomarkers could help in more precisely predicting their risk for developing psychosis, in order to target more intensive interventions to those individuals most at risk.

1.1. Clinical High Risk and Predictive Measures

A major goal of recent research on those at high risk for psychosis is to identify neurocognitive dysfunctions and features that are associated with transition to psychosis. The NAPLS-1 study found a 16% conversion rate over 2 years and this grew to 35% at 2.5 years in 596 CHR patients (Cannon et al., 2008a). Features that significantly predicted conversion were higher levels of unusual thought content and suspiciousness, decline in social functioning, lower verbal learning and memory, slower processing speed and younger age. Hua and Blau (2017) found that the longer the duration of untreated psychosis from initial symptoms to the time of treatment, the poorer the outcomes and increase risk of conversion. Thus, increased efforts to identify patients with symptoms early on are important for CHR individuals, in order to engage them in early intervention programs to modify risk and prevent transition.

One of the defining characteristics of those at clinical high risk for psychosis is that of a significant cognitive decline. Recent literature has shown that those at high risk who convert to schizophrenia show greater cognitive deficits at baseline compared to those who do not convert and healthy controls (Lam et al., 2020; Seidman et al., 2010; Shakeel et al., 2019a). Lam (2020) found that at baseline, the CHR remitters' cognitive performance was similar to those of non-remitters, but at follow-up their performance was more similar to controls, and the cognitive deficits in non-remitters tended to be more constant and in all areas. Shakeel (2019) looked at social cognition using awareness, emotion recognition and differentiation, and relationships at CHR baseline. They showed that those who transitioned did not show improvement in their social cognition scores over 24 months, whereas there was an effect of time on the improvement of social cognition for those who did not transition. Contrarily, Shakeel, Lu, Woods, Perkins, and Addington (2019b) found that when controlling for IQ and education, social cognition was found not to be a significant predictor of transition.

Youn et al. (2019) examined cognitive disturbances in CHRs and found that while the severity of these disturbances did not predict transition to psychosis, those who met criteria for impaired cognition at baseline were nearly twice as likely to meet for attenuated psychotic symptoms (APS) 12 months later than those who did not. Cognitive deficits may be more useful for predicting transitions over a longer period (such as 24 months), or for more severe clinical cases where patients are less likely to show remission of APS. In isolation, these deficits are unlikely to be significant predictors of transition; however, together they have more predictive power. The most common cognitive deficits in those who transition are verbal memory, processing speed, verbal learning, verbal fluency, working memory and attention (Addington & Barbato, 2012)

In schizophrenia, Prominent Negative Symptoms (PNS) are characterized as primary negative symptoms that persist for at least twelve months, are not responsive to treatment and cause functional impairment. These PNS were evident in CHR patients before the onset of psychosis with a prevalence of 6.1% (Yung, Nelson, McGorry, Wood, & Lin, 2019). Those individuals had poor premorbid social functioning from an early age, deficient verbal fluency at baseline and premorbid adjustment. In addition, they found higher rates of childhood maltreatment in the PNS group compared to the no-PNS group, suggesting childhood trauma, along with PNS, may increases a proneness to psychosis and its features. A previous meta-

analysis (Fusar-poli et al., 2017) found the mean prevalence of childhood trauma in CHR to be 86.8%, supporting the notion that exposure to traumatic events resulting in mood dysregulation could be a connective component to an affective pathway to psychosis onset. A review by Shakeel et al. (2019b) found that the most consistent factors of prediction in psychosis were history of childhood trauma and cannabis use. CHR patients are five times more likely to have a cannabis disorder (abuse or dependence) than controls, and users experience more severe unusual thought content and suspiciousness compared to non-cannabis users (Addington et al., 2019). Social and role difficulties have been observed in CHRs who transition, and recent studies show functioning at baseline, follow up and over time is poorer for those who transition to psychosis, with social functioning at early and late adolescence as a predictor. Fusar-poli et al. (2017) looked at 44 studies with 170 datasets and found that CHR individuals are more likely than controls to experience obstetric complications, tobacco use, physical inactivity, childhood trauma/emotional abuse, physical neglect, high perceived stress, low functioning, comorbidities, be male, be single, be unemployed and have a low education level. Other model predictors include unusual thought content, disorganized communication, visual perceptual abnormalities plus violent behavior and ideation, poor social cognition and functioning, and impaired cognitive domains. Genetic risk for schizophrenia with functional decline is also predictive of conversion to psychosis. Cannon et al. (2008b) and Fusar-poli et al. (2017) showed a genetic risk factor power of 5% among their reviewed studies.

Neuroimaging findings cannot identify who will transition; however, MRI images of increased rate of gray matter loss in frontal lobes and abnormalities in gyrification can be an added risk factor to conversion. Koutsouleris et al. (2015) looked at 73 CHR multisite individuals for over 4 years and aimed to identify neuroanatomical surrogates of the psychosis prodrome across independent high-risk cohorts. The neuroanatomical signature of prodrome may serve as accurate biomarker to predict outcome. Visual analysis revealed gray matter volume reductions in transitioned vs. non-transitioned CHRs in the prefrontal, cingulate, striatal and cerebellar brain structures, which are thought to be involved in higher-order cognitive processes. Observed gray matter volume increments in transitioned vs non-transitioned showed left temporal and inferior parietal distribution. Borgwardt et al. (2007) used a voxel-based morphometric (VBM) to examine regional gray matter volume in CHR patients. The CHR group had smaller gray matter volumes in the superior temporal gyrus, posterior cingulate gyrus and precuneus, and similar to reductions found in schizophrenia patients, in the left superior temporal

gyrus and insular volume. Consistent with the notion that transition to psychosis is associated with changes in regional gray matter volumes particularly in the inferior frontal, cingulate and medial temporal cortex, there were volumetric differences in gray matter between those who transitioned and those who did not. Hypoconnectivity in the cerebello-thalamo-cortical network at baseline in CHR patients has also been linked to transition (Addington et al., 2019), as are elevated baseline plasma levels of inflammation markers and oxidative stress and dysregulation of hypothalamic-pituitary-adrenal axis (Riecher-Rössler & Studerus, 2017).

Using neurophysiology techniques as a predictor variable, Duffy, D'Angelo, Rotenberg, and Gonzalez-Heydrich (2015) sought to find scalp EEG differences between CHR individuals and controls using quantitative spectral and spectral coherence analyses. They found that, compared to controls, the coherence patterns in the CHR individuals did not manifest in a typical pattern, mostly located over temporal lobes, predominantly the posterior temporal regions, then the occipital and frontal index. Waking-state EEG provided reliable group separation, and these variables could contribute to a composite multivariate discriminant function to serve as a potential biomarker for CHRs.

Several interventions have been tested as a means to delay or halt the transition to psychosis. Devoe, Farris, Townes, and Addington (2019) examined 41 intervention studies with APS in CHR youth. It was found that cognitive behavioural therapy (CBT) was the only intervention that trended towards an APS reduction at 12 months follow up, and interventions of CBT and family therapies combined significantly reduced symptoms after twelve months. In terms of pharmaceutical intervention, antipsychotic medication combined with CBT may help delay the onset of psychosis but not prevent it (Addington & Barbato, 2012). Omega-3 Polyunsaturated Fatty Acids (PUFA) could be another possible intervention for those at risk. After taking the supplement for a twelve-week period, CHR individuals with more severe negative symptoms and higher levels of alpha-linolenic acid had a lower rate of conversion and predicted more functional improvement than in the placebo group (4.9% converted vs 27.5% in placebo group). These findings could indicate that PUFA metabolism is relevant to negative symptoms in schizophrenia and that an omega-3 supplement may be beneficial for those at risk (Amminger et al., 2015).

Schmidt et al. (2017) ran a systematic review of models used to improve prediction of psychosis onset in those at clinical high risk, using an investigation of three-stage testing

following the initial CHR assessment. When focusing on positive predictive values delivered by models with biological, neurocognitive or environmental data, they found that the best model showed a probability of transitioning of 98%. This consisted of three positive tests of one combined (EEG and clinical) and two biological predictive models (MRI and blood markers). Finding the best models could improve benefits associated with early detection and intervention and reduce the cost of unnecessary pharmacological treatment. Recent research of CHR patients explored cognition, symptoms, trauma and MRI imaging as possible predictors to the transition to a psychotic illness. A measure which could be useful in this regard is that of electroencephalographic event-related potentials, which has successfully been shown to elicit similar deficiencies in schizophrenia and CHR, thus proving to be one of the leading tools of exploration into the mind of the CHR.

1.2. Event-Related Potentials in Schizophrenia and CHR

In order to fully appreciate the impact of event-related potentials in those at risk for psychosis, we must understand the importance of the recent literature of these measures on schizophrenia and CHR patients. Event-related brain potential (ERP) waveforms, or components, have been found to be reliably abnormal in schizophrenia, contributing to our knowledge about its underlying neurocognitive pathophysiology.

1.2.1. P300 (P3b) and P3a

The P300 (also referred to as P3b or P3) is an ERP positivity peaking around 300 ms after the onset of task-relevant rare ("target") stimuli embedded among frequent ("standard") stimuli. It is largest medially and typically increases in amplitude from frontal to parietal sites (Knight, 1997; Polich & Kok, 1995). The P300 is most frequently elicited using the "oddball paradigm." For example, when participants hear a random sequence consisting of frequent lower-pitched tones and rare higher-pitched tones, and are instructed to press a button in response to the latter, the rare target tones elicit a P3b (Duncan-Johnson & Donchin, 1977). Although auditory stimuli are most commonly used to elicit the P300, it has also been observed with visual, tactile, and olfactory stimuli (Soltani & Knight, 2000). P300 amplitude is thought to reflect processes occurring when the eliciting stimulus is compared with a pre-existing

contextual representation in working memory and a difference is detected, resulting in updating of this representation (Polich & Kok, 1995). Consistent with this view, P300 amplitude is larger when the probability of the oddball stimulus is lower (Duncan-Johnson & Donchin, 1977) or it is quantitatively more different from the standards (Goldstein, Spencer, & Donchin, 2002).
In addition, when the subject is not required to attend to the stimuli such as watching a silent film, and infrequent stimuli are presented among frequent stimuli, they elicit a positivity P3a instead of a P3b. The P3ais larger over frontal/central areas and has a shorter peak latency (around 250 ms) compared to the canonical P300 or P3b (Polich, 2007). Thus, this P3a component is observed in response to distractor (task-irrelevant and infrequent) stimuli embedded in a classical oddball paradigm (Katayama & Polich, 1998) or to infrequent stimuli embedded among frequent ones when the subject is instructed not to attend to the stimuli (Squires, Squires, & Hillyard, 1975). The P3a is considered to be related to the P3b because of similarities and overlap in the conditions that elicit them; however, whereas the P3b is thought to result from activity in temporoparietal areas reflecting working memory updating, the P3a is thought to have frontal generators reflecting orienting of attention to novel stimuli (Polich, 2007). In accordance with conventional nomenclature in the CHR literature, in this article we use "P300" to refer specifically to the P3b and use the term "P3a" to indicate that component.

1.2.1.1. Schizophrenia

P300 amplitude reduction in an auditory oddball paradigm is one of the most reliable biological markers of schizophrenia (Ford, 1999). Such P300 amplitude deficits have been identified in both chronic (Ford, 1999) and antipsychotic-naive first-episode schizophrenia patients (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; Wang et al., 2005) and have also been found in first-degree biological relatives of schizophrenia patients (Winterer et al., 2003). A multi-site study (Turetsky et al., 2015) found that there was an overall deficit in P300 amplitudes across 587 schizophrenia patients (d=0.62) with site differences in symptomatology. Both dopaminergic agents and anti-psychotic administration have effects on the P300 (Mondragón-Maya et al., 2013). Consistent with dopaminergic hypotheses of schizophrenia, dopaminergic agents have been found to decrease P3b in normal individuals (Albrecht, Martin-Iverson, Price, Lee, & Iyyalol, 2011), whereas a meta-analysis found that antipsychotic treatment with dopamine D2 antagonists is associated with less abnormal P300 amplitudes in schizophrenia patients (Bramon et al., 2004). Auditory P300 reduction has also been found in

unaffected biological relatives of individuals with schizophrenia, suggesting that it may reflect earlier stages of pathophysiology or an underlying risk for schizophrenia (Ford, 1999). Visual P300 reductions are found less consistently in patients with schizophrenia (Javitt et al., 2008). This finding may be because auditory stimuli are more obligatory than visual stimuli, and may be related to the same mechanisms that cause more frequent auditory than visual hallucinations in schizophrenia patients (Ford, 1999). P300 have been linked with functioning in schizophrenia patients (Jahshan et al., 2012; Light et al., 2015; Perlman et al., 2015; Rissling et al., 2014; Tricht et al., 2010); however, a recent study found both P3a and P3b amplitudes were reduced in schizophrenia regardless of functioning, compared to healthy control (Hamilton et al., 2018a).

1.2.1.2. CHR

Studies of P300 amplitude in CHR individuals in the literature used auditory (del Re et al., 2015; Frommann et al., 2008; Fusar-Poli et al., 2011; Kim, Lee, Lee, Kim, & Kwon, 2015; Özgürdal et al., 2008; Van Der Stelt et al., 2005; van Tricht et al., 2010) or visual stimuli (Lee, Namkoong, Cho, Song, & An, 2010; Oribe et al., 2013). They varied in the percentage of oddball stimuli, and in whether these differed from standard stimuli in frequency or duration. All of these studies found that CHR individuals' P300 amplitudes were reduced compared to those of healthy individuals, but not by as much as those of schizophrenia patients (in the cases where these were also examined) (Mondragón-Maya et al., 2013; Özgürdal et al., 2008; Van Der Stelt et al., 2005). Overall, the data suggested that P3 amplitude deficits are proportional to CHR symptom severity. For example, studies show that participants with brief intermittent psychotic symptoms had larger reductions in P300 amplitude than other prodromal individuals (Frommann et al., 2008; Fusar-Poli et al., 2011). Since the neural processes generating the P300 depend on the amount of attention to a task, this makes the P300 more variable in children than adults. Graber et al. (2019) examined the P300 in young participants (before age 13) at very early onset psychosis (VEOP), and clinically high risk. VEOP is associated with more severe neurodevelopmental abnormalities, greater frequency of comorbid development, speech, language and educational disabilities and poorer treatment outcomes. Using an oddball paradigm with auditory tones, they found that the P300 amplitudes differed between VEOP group and healthy controls, between VEOP and CHR, but not between the CHR group and HC. This could reflect a clinical heterogeneity in the CHR group. As the P300 matures, younger participants seem more susceptible to more variable amplitudes, and neurological changes underlying VEOP may differ

even from adolescent psychosis (Graber et al., 2019).

Kim et al. (2018a) aimed to identify which aspect of the P300 is associated with genetic risk (GHR) compared to symptoms using an inter-trial variability analysis. Those at CHR and with schizophrenia showed reduced P300 amplitudes when compared to healthy controls and had larger inter-trial variability. They found a significant association between the P300 inter-trial variability and PANSS negative symptom score and neurocognitive performance. There was a significant reduction in P300 amplitude in GHR and CHR groups compared to healthy controls, reflecting a genetic predisposition for schizophrenia.

The severity of P300 abnormalities could help further identify subgroups of CHR patients who are most at risk and thus would benefit most from early interventions. Hamilton et al. (2019b) used a visual oddball paradigm to evaluate whether the P300 would predict clinical outcomes in those at clinical high risk. They found that although there was no difference in P300 between the CHR group and the HC group at baseline, baseline target P3b and novelty P3a amplitudes were significantly reduced in CHRs who later converted to psychosis compared to those who did not convert. P300 amplitudes predicted the time to psychosis onset in CHR participants, such that more deficient P300 amplitudes were associated with shorter time to conversion (Hamilton et al., 2019b). In other recent research, Tang et al. (2019) looked at a P300 auditory novel and oddball paradigm in those at high risk who converted and those who remitted. Those at high risk who converted over one year had lower frontocentral P300 novel amplitudes and marginally lower oddball amplitudes, and those who did not convert and remitted had P300 novel amplitudes significantly larger than those who did not remit and those who converted (Tang et al., 2019).

Moreover, P300 amplitude deficits in CHR patients have been found to correlate with neuroanatomical and neuropsychological abnormalities. These abnormalities include reduced parietal gray matter volume, which is associated with greater risk of transition to psychosis (Fusar-Poli et al., 2011). CHR individuals' impaired performance on tasks requiring attention and executive processes are also correlated with P300 reductions (Fusar-Poli et al., 2011). Together, these results suggest that P300 amplitude deficits in the CHR state are a reliable biomarker of severity of pathophysiological processes underlying progression to psychosis, and thus may be useful in predicting which CHR individuals are at highest risk of transition to first-episode psychosis. In line with this hypothesis, Nieman et al. (2014) found that in CHR

individuals a 1μV reduction in P300 amplitude was associated with a 27% increase in the risk of conversion to psychosis over 3 years (Nieman et al., 2013; Nieman et al., 2014; van Tricht et al., 2010).

Fewer studies have examined the P3a in the CHR population. These studies measured auditory P3a in response to distractor stimuli in a classic oddball paradigm (del Re et al., 2015), or to infrequent stimuli embedded among frequent ones when the stimuli were unattended (Atkinson et al., 2012; Jahshan et al., 2012; Mondragón-Maya et al., 2013). All of these studies found a significantly reduced P3a amplitude compared to healthy control participants, except for Atkinson et al. (2012), who found no difference in amplitude or latency at baseline, but did find that the P3a correlated with positive symptoms, including hallucinations. Thus, this limited evidence suggests that P3a amplitude reductions may also be an early biomarker of the psychotic process.

1.2.2. Mismatch Negativity

Like the P300, the mismatch negativity (MMN), a negative-going ERP component, also occurs in response to infrequent, deviant stimuli embedded among frequent, standard stimuli. However, in contrast to the P300, it does not require the subject's conscious attention to these stimuli. For example, MMN has often been studied in response to auditory stimuli which the subject is instructed to ignore while watching a silent video or reading a book. The auditory MMN is elicited by various types of deviance in comparison to standard stimuli, including stimulus intensity, location, frequency or duration. Moreover, the MMN is observed not only in response to individual stimuli, but also to a sequence of stimuli that is infrequent within the overall stimulus sequence (Brattico, Winkler, Näätänen, Paavilainen, & Tervaniemi, 2002). The MMN peaks around 150-250 ms after the onset of deviant stimuli. The MMN is thought to be generated in the auditory and frontal cortices by a process in which the central auditory system uses the neuronal memory trace of preceding stimuli as a template for change detection (Näätänen, Astikainen, Ruusuvirta, & Huotilainen, 2010).

1.2.2.1. Schizophrenia

Auditory MMN amplitudes have consistently been shown to be reduced in patients with schizophrenia (Erickson, Ruffle, & Gold, 2016; Haigh, Coffman, & Salisbury, 2017; Umbricht &

Krljes, 2005). These deficits are thought to reflect glutamate N-methyl-D-aspartate (NMDA) receptor dysfunction, given that NMDA receptor antagonists reduce MMN and cause schizophrenia-like symptoms in healthy individuals (Michie, Malmierca, Harms, & Todd, 2016). In schizophrenia, it is thought that the MMN impairment progresses over the first 18 months of the illness but then stabilizes. The glutamatergic imbalances thought to underlie the MMN deficiency in schizophrenia may also be underlying the MMN deficiency seen in other pathologies such as bipolar disorder, indicating a failure of auditory expectations rather than stimulus detection (Erickson et al., 2017).

A recent study looked at the effects of ketamine NMDAR antagonist and nicotine, a nAChR agonist, on MMN in healthy controls (Hamilton et al., 2019a). Ketamine produced a reduction in MMN for all deviant types used in the auditory paradigm, but nicotinic agonists (shown to increase the MMN amplitude) were not able to overcome the impairments produced in the acute NMDA receptor blockage. Similarly, Koshiyama et al. (2018a) found that MMN amplitude was reduced in first-episode schizophrenia, correlated with intertrial phase coherence (ITC) gamma band ASSR. This reduced MMN in first-episode psychosis may represent a dysfunction of NMDAR and gamma ASSR indices, suggesting that there is a GABAergic interneuron dysfunction in early psychosis. The correlation between MMN and gamma may reflect an abnormal excitatory/inhibitory balance, as the dysfunction of the NMDAR causes dysfunction of GABAergic interneurons which cause disinhibition of pyramidal neurons. Tada et al. (2019) found that the NMDAR antagonist PCP reduced the amplitude of duration MMN (dMMN), and one meta-analysis, Rosburg and Kreitschmann-andermahr (2016), shows NMDA antagonist ketamine attenuated the MMN, although there was no difference between duration and frequency.

The degree of MMN reduction in schizophrenia patients has been found to correlate with impaired verbal memory and comprehension, and psychosocial functional impairment (Carrión et al., 2015; Kiang et al., 2007b). Thus, researchers have proposed that reduced MMN reflects auditory processing deficits that contribute to difficulty in responding appropriately to the real-world environment, with consequent disruption in higher cognitive domains and psychosocial functioning (Jahshan et al., 2012). Using a duration deviant auditory oddball experiment, Light et al. (2015) found a P3a and MMN deficits in a sample of 966 schizophrenia patients compared to controls from multi-site studies. Predictor values included an older age, male, African American, and first-generation antipsychotics. Anticholinergic medication predicted smaller MMN

amplitudes, as did smoking. There were significant correlations between MMN and age of onset, positive and negative symptoms, global functioning, independent functioning, role functioning and psychosocial functional status. Hamilton et al. (2018a) sought to determine the functional significance of MMN and P300 in patients with low and high functioning. They found that patients with poorer functioning showed greater MMN deficits when compared to high functioning patients and healthy controls, whereas both P3a and P3b amplitudes were reduced regardless of functioning compared to healthy controls. Therefore, the MMN may be associated with work and independent living domains of functioning; for example, in a long-term inpatient care unit (the lowest functioning level), patients were found to have impaired basic tone discrimination, indicative of a deficient MMN. MMN reflects an automatic response to an auditory deviance that requires little cognitive effort to generate (Hamilton et al., 2018a).

MMN has been shown to correlate with schizophrenia symptoms. Symptom severity in those who have remitted have been found to associate with baseline MMN amplitude (Kim et al., 2020). Schizophrenia patients who had remitted showed larger MMN at follow up and at baseline than the non-remission group. Age and symptom severity at baseline predicted later remission, and baseline MMN amplitude predicted symptom improvement in patients with schizophrenia. At follow up, MMN correlated with the PANSS total and negative symptoms, and a regression analysis showed that initially, age and MMN amplitude at FZ predicted schizophrenia remission. MMN amplitude also predicted improvement of psychotic symptoms in those who remitted. A meta-analysis (Erickson et al., 2017), used predictive coding to examine MMN impairment and positive and negative symptoms across 68 studies. Results showed no significant association with MMN amplitude and positive and negative symptoms in schizophrenia; however, first-episode patients had more severe symptoms and a significantly smaller MMN than chronic schizophrenia patients.

MMN has been examined in schizophrenia patients in response to more complex deviants. Since complex deviants are harder to detect, sensory impairments would generate a larger deficit. These deviants are thought to involve subcortical as well as cortical mechanisms and indicate a higher-order processing dysfunction (Salisbury, McCathern, Coffman, Murphy, & Haigh, 2018). A meta-analysis examined MMN in schizophrenia using simple and complex deviants (double-deviants, omissions and conceptual); Avissar et al. (2018) found that MMN to complex deviants was as significantly reduced in schizophrenia patients as it was with simple deviants. Salisbury et al. (2018) looked at complex MMNs and found that chronic schizophrenia

patients showed a large MMN deficit using the complex deviants, whereas the first-episode patients were not as impaired. This suggest that these complex MMN deficits may develop with disease progression. Also, poor working memory was found to be associated with a smaller complex MMN in first-episode patients, suggesting an automatic cognitive deficit early in the disease progression.

The effect of treatment on MMN amplitudes in schizophrenia individuals has been reviewed in recent literature. Biagianti et al. (2017) administered 6 computerized exercises of auditory training (AT) to improve speed and accuracy of speech to participants at 3 years of illness. At baseline, the schizophrenia group had a smaller MMN amplitude compared to controls, and these MMN deficits correlated with worse cognitive performance. After training, there was only a small effect of treatment on cognition, and there was no significant increase in MMN amplitude. This study indicates that MMN cannot be regarded as a representative for neurophysiological changes in auditory processing or in the central auditory system. A more recent study showed that the P300, MMN and N400 amplitudes increased to normal levels after 25 treatments of rTMS were administered to schizophrenia patients, indicating that these markers could reflect cognitive function in the patients (Lin et al., 2018).

1.2.2.2. CHR

There is substantial evidence that the MMN is compromised before the onset of psychosis. Most of the studies of MMN in CHR individuals that we examined showed a reduction in auditory MMN amplitude in this group compared to healthy controls (Atkinson et al., 2012; Bodatsch et al., 2011; Brockhaus-Dumke et al., 2005; Carrión et al., 2015; Fisher, Labelle, & Knott, 2012; Hsieh et al., 2019; Kim, Lee, Yoon, Lee, & Kwon, 2018b; Koshiyama et al., 2017) although a smaller number did not find any significant MMN amplitude abnormalities (Brockhaus-Dumke et al., 2005; Mondragón-Maya et al., 2013). MMN amplitudes in CHR patients have been found to be of intermediate amplitudes between those of healthy control individuals and schizophrenia patients (Brockhaus-Dumke et al., 2005; Hsieh et al., 2012; Jahshan et al., 2012),' suggesting that conversion to psychosis is associated with progressive amplitude reduction (Jahshan et al., 2012). Like in schizophrenia, in CHR patients greater MMN deficits have been found to be associated with greater impairment in memory, language, and level of psychosocial function (Carrión et al., 2015; Higuchi et al., 2013; Koshiyama et al.,

2018b; Lavoie et al., 2018). Reduced dMMN might reflect altered expectations of auditory stimuli in an environment that might result in low functioning. Overall, results of these studies also suggest that the MMN response to certain types of stimulus deviance may be more sensitive to pre-psychotic processes.

Similar to findings in first-episode psychosis (Haigh et al., 2017), differences in duration MMN have been found to be greater than differences in frequency MMN in the CHR stage (Bodatsch et al., 2011; Higuchi et al., 2013). In contrast, however, two studies (Carrión et al., 2015; Perez et al., 2014) found that CHR patients showed similarly reduced MMN amplitudes to *both* duration and frequency, relative to healthy controls. Several studies have reported that reductions in MMN predict conversion to psychosis among CHR individuals. Shaikh (2012) found that CHR patients who subsequently converted to psychosis had smaller duration MMNs than did non-converters (Shaikh et al., 2012). In another study, the degree of reduction in duration but not frequency MMN, predicted CHR patients' transition to schizophrenia within 24 months (Atkinson et al., 2012). Lavoie et al. (2018) found that those at risk had smaller MMN amplitudes at baseline and that there was a significant decline in MMN amplitude for those that transitioned to psychosis from baseline to follow up, whereas those that did not transition had a non-significant increase in amplitude. Also, there was a significant decline in fMMN amplitude immediately after those at risk began to exhibit psychotic symptoms, meaning that MMN could be reflected in the progression of the disease. Kim et al. (2018b) aimed to determine whether the MMN baseline would later predict remission and symptomatic or functional improvement during a six year follow up. MMN baseline amplitudes at frontal sites were reduced in non-remitters compared to remitters and healthy controls, and a larger MMN amplitude at the frontocentral site Fz was the only significant predictor of remission. They reported a relationship between the MMN and positive symptom severity and functioning in patients with schizophrenia and at risk for psychosis, and the baseline MMN amplitude later predicted remission by both the positive subscale score and the GAF score (Kim et al., 2018b).

Perez et al. (2014) found that decrements in MMN responses to duration/frequency double-deviants, but not duration or frequency single-deviants, predicted risk of psychosis onset in CHR patients. Specifically, individuals with MMN amplitude at the 25th percentile for the group had three to four times the risk of developing psychosis compared to those whose MMN amplitudes were at the 75^{th} percentile (Perez et al., 2014). In a systematic review on the predictive power of ERPs for forecasting conversion to psychosis, Bodatsch (2015) concluded

that, at present, MMN is the ERP component which is the most promising in this regard, although this is partly because research of this type on other ERP components has been relatively limited (Bodatsch, Brockhaus-Dumke, Klosterkötter, & Ruhrmann, 2015).

A meta-analysis by Erickson et al. (2017) showed an effect size of 0.4 for MMN amplitude reduction in CHR in 16 studies, and the effect of dMMN reduction was significantly larger than the fMMN reduction. A review by Tada et al. (2019) looked at MMNs relationship with early psychosis including CHRs and their relationship with functional abilities, and reports MMN's ability to predict remission in CHR, as baseline MMN amplitudes are reduced in non-remitters compared to remitters.

1.2.3. Early Auditory ERPs

Although most ERP studies in the CHR population have examined the auditory P300 and MMN, a smaller number have focused on ERP components representing earlier, sensory perceptual stages of auditory processing. The N1 (or N100) is an ERP negativity occurring approximately 100 ms after onset of auditory stimuli. Like the P50, a positivity which immediately precedes it, it is thought to have generators in the primary auditory cortex and to index early, perceptual stages of auditory processing (Näätänen & Picton, 1987).

1.2.3.1. Schizophrenia

Numerous studies have found N1 amplitude deficits in schizophrenia (Brockhaus-Dumke et al., 2008; Foxe et al., 2011; Salisbury, Collins, & McCarley, 2009), which are thought to reflect impairment in auditory perceptual and attentional processing (Gonzalez-Heydrich et al., 2015; Hsieh et al., 2019; Rosburg, Boutros, & Ford, 2008). Hsieh et al. (2019) found a smaller N100 amplitude difference in its patient group (FEP and CHR), but no significant differences were found with just the CHR group compared to healthy controls. Whitford et al. (2018) found that schizophrenia patients had significant lower levels of N1 suppression in response to self-generated speech relative to healthy controls, and had significant lower levels of fractional anisotropy (FA) and high levels of radial diffusivity (RD) in the arcuate fasciculus. RD, a measure of myelin integrity, in the arcuate fasciculus was found to account for a significant amount of variance in the N1 suppression across groups, suggesting that these abnormalities may be causally related. Rosburg et al. (2008) found N100 suppression in schizophrenia was

dependent on experimental factors including attention, arousal, motivation, fatigue, hearing, drugs, medication and smoking.

P50 inhibitory processing deficits may be a core feature of schizophrenia. Although P50 gating is consistently reduced in schizophrenia (Bramon et al., 2004; De Wilde, Bour, Dingemans, Koelman, & Linszen, 2007; Javitt et al., 2008; Patterson et al., 2008), some (Brockhaus-Dumke et al., 2008; Chang et al., 2019; Myles-Worsley, Ord, Blailes, Ngiralmau, & Freedman, 2004) but not other (Hsieh et al., 2019; Hsieh et al., 2012; Van Tricht et al., 2015; Ziermans et al., 2012) studies have reported that it is attenuated in CHR patients. Schizophrenia patients have poorer P50 suppression compared to controls (Bramon et al., 2004; Salisbury, Kohler, Shenton, & McCarley, 2019), and this suppression is associated with impaired performances in verbal, visual and working memory tasks (Hamilton et al., 2018b), and hallucinations and significant impairment (Salisbury et al., 2009).

1.2.3.2.CHR

Two studies reported decreased N1 amplitudes in CHR patients compared to controls (del Re et al., 2015; Gonzalez-Heydrich et al., 2015). Moreover, van Tricht et al. (2011) found that N1 amplitude decreased after 18 months compared to baseline in CHR patients who converted to psychosis, but not in those who did not convert, suggesting that it is a marker of disease progression. Other studies have examined CHR patients on characteristics of early auditory ERP components that are thought to reflect neural responsiveness to different conditions. Thus, the N1 and P50 are normally reduced in response to the second of two closely spaced stimuli, with these N1 and P50 “gating” effects thought to reflect inhibition of processing of redundant sensory information (Yadon, Bugg, Kisley, & Davalos, 2009). The degree of N1 gating has been found to be attenuated in CHR patients, and the degree of attenuation differentiated subsequent converters to psychosis from nonconverters (Brockhaus-Dumke et al., 2008; Van Tricht et al., 2015). Chang et al. (2019) investigated auditory sensory gating performance by evaluating the differences in brain function networks among first-episode psychosis patients, clinical high risk and healthy controls. They found at the gating response stage significant differences in connectivities between those at high risk and controls. These findings suggest that these network connectivities could provide insight into mechanisms of P50 suppression. Different impaired brain regions were located in FEP and CHR patients - the superior frontal gyrus and insula in

FEP, and the paracentral lobule and middle temporal gyrus in CHR. Both these patient groups showed enhanced connections between these brain regions compared to controls, supporting the hypotheses that impairment in P50 sensory gating in CHR occurs mostly in the gating period. Brain function network based on the P50 paradigm may be helpful for identification of different stages of schizophrenia and assist in early diagnosis (Chang et al., 2019).

The N1 loudness dependence of the auditory evoked potential (LDAEP), or the degree to which its amplitude increases with stimulus volume, has likewise been found to be reduced in CHR patients (Gudlowski et al., 2009). N1 amplitude is normally reduced in response to a self-generated sound (e.g., speech) compared to an external one (Timm, SanMiguel, Saupe, & Schröger, 2013). This "N1 suppression" is not as reduced in schizophrenia (Ford, Gray, Faustman, Roach, & Mathalon, 2007; Ford et al., 2001). Antipsychotic-free CHR patients have been found to exhibit suppression levels intermediate to schizophrenia patients and controls, not differing significantly from those of either group (Perez et al., 2012a). Mathalon et al. (2018), found a significant main effect of group due to healthy controls having a greater N1 suppression than CHR or FEP. CHR and FEP groups showed equivalent levels of suppression; however, those who converted over twelve months did not have significantly less N1 suppression compared to those who did not convert, demonstrating this suppression was not progressive with the illness. Corollary discharge dysfunction during speech occurs in CHR before the onset of the illness and remains reduced in patients consistent to what has been shown in chronic schizophrenia. In addition, there was an association where increased unusual thought content in the patients showed less N1 suppression (Mathalon et al., 2018).

In summary, several studies have found CHR patients to exhibit reductions in the amplitude of early auditory ERPs, or in other characteristics of these responses that are thought to reflect normal adaptation to external or internal states. It is important to note, however, that the paradigms used in these studies varied – for example the studies in which N1 was elicited variously used oddball, click-pair and LDAEP paradigms. Further research is needed to directly compare these measures on their sensitivity to the CHR state, and their utility for predicting future disease progression within this group.

1.2.4. Visual ERPs

We identified one study that examined early visual ERPs in the CHR population. The P1

component primarily indexes perceptual stages of cortical visual processing. It peaks between 80 and 120 ms after stimulus onset, and its amplitude is influenced by stimulus intensity and selective attention (Rosburg et al., 2008). Deficits in P1 amplitudes have been established in chronic schizophrenia (Foxe, Doniger, & Javitt, 2001; Friedman, Sehatpour, Dias, Perrin, & Javitt, 2012; Yeap et al., 2008). Oribe et al. (2013) examined visual P1 in a visual oddball paradigm in CHR, first-episode psychosis (FEP) patients and controls, and did not find any P1 amplitude differences between the groups.

1.2.5. Error-related Negativity

Error monitoring in the brain is reflected by the error-related negativity (ERN) and error positivity (Pe) ERP components. The ERN is a negative ERP component that begins around the time of incorrect responses and peaks roughly 100 ms thereafter (Yeung, Botvinick, & Cohen, 2004). It is followed by the Pe, a positive-going component occurring 200-500 ms following the erroneous response.

1.2.5.1.Schizophrenia

Numerous studies of error monitoring in schizophrenia demonstrate ERN amplitude reduction; while some but not all studies show schizophrenia patients to have reduced Pe amplitudes (Alain, McNeely, He, Christensen, & West, 2002; Bates, Kiehl, Laurens, & Liddle, 2002; Perez et al., 2012b).

1.2.5.2.CHR

We identified a single ERP study of error monitoring in CHR patients, which found them to have significantly reduced ERNs but normal Pe's compared to controls (Perez et al., 2012b). Thus, further study is warranted to corroborate these ERN reductions in the CHR state and to examine whether they can contribute to predicting conversion to psychosis.

1.2.6. Auditory Steady-State Gamma

Unlike conventional ERPs, such as the P300, N400 and MMN, which are measured in amplitude, gamma band oscillations are measured in evoked power and phase coherence.

Gamma oscillations are synchronous neural oscillations in the 30-80 Hz range that are fundamental to cortico-cortical communication and integration of information across neural networks (Buzsáki & Wang, 2012; Light et al., 2006). Changes in gamma power and phase coherence are event-related and seen in response to higher-order cognitive tasks including sensory processing, attention, working memory and executive functioning, which are all impaired in schizophrenia (Sun et al., 2011). Reduced gamma power and phase coherence have been found in schizophrenia patients (Light et al., 2006). Gamma oscillations can be examined in terms of amplitude, power and phase (Sun et al., 2011); power characterizes a signal over time and is often used in conjunction with time-frequency analysis to produce spectral information at set points. Gamma band phase locking has been observed in EEG to occur with a wide range of perceptual and cognitive operations, including sensory gating, visual masking, attention, language processing, memory and working memory (Sun et al., 2011). Fast Fourier Transform (FFT) quantifies event-related gamma responses by measuring a power spectrum of the averaged EEG signal.

EEG recordings are separated into frequency bands using a Fourier or wavelet analyses. Oscillatory responses can be defined as entrained, evoked, induced and spontaneous. Entrained oscillations are elicited by repetitive, steady-state stimuli presented at a set frequency. Evoked gamma are transient time locked responses to a stimulus and are examined by time averaging single trial responses, and induced gamma are responses that are not phase locked to a stimulus (Schroeder & Lakatos, 2009). Spontaneous gamma results from the internal processes of the brain that are present in the resting state (Sun et al., 2011). Behavioural paradigms that are used to study gamma include steady-state auditory stimulation, sensory gating, corollary discharge, oddball recognition and cortical inhibition. The most widely studied is the auditory steady-state stimulation which comprises of auditory click trains at different stimulus frequencies (20 Hz, 30 Hz, 40 Hz) to determine the brain's ability to generate and maintain steady-state oscillations at the same frequency (Sun et al., 2011).

1.2.6.1. Schizophrenia

Researchers have tested whether schizophrenia patients can support and maintain the gamma range synchronization that is necessary for neural network communications. It is suggested that gamma deficits may reflect a genetically mediated trait to schizophrenia, as seen in recent findings of reduced gamma in patients and their first-degree relatives (Light et al.,

2006). This suggests that schizophrenia patients may have abnormalities in their capacity to support coherent oscillations within the gamma frequency band, and that gamma oscillations that are abnormal in schizophrenia may lead to cognitive impairment and may account for some symptoms of the disorder (Sun et al., 2011).

Frequencies in the brain represent different oscillating networks and rely on the combinations of different types of neurons, such as GABAergic neurons (Davis & Kahn, 1991; Sun et al., 2011). Through animal studies, activating GABAergic interneurons has been shown to produce gamma oscillations in hippocampal and neocortical networks (Traub, Whittington, Colling, Buzsaki, & Jefferys, 1996), and by decreasing activity of GABAergic interneurons, gamma oscillations are suppressed. The synthesis and reuptake of GABA neurotransmitters in dorsolateral prefrontal cortex is also reduced in schizophrenia (Volk, Austin, Pierri, Sampson, & Lewis, 2000, 2001). NMDA receptors have been shown to affect gamma network oscillations in the hippocampus (Faulkner, Traub, & Whittington, 1999). In animal studies, administration of NMDA antagonist in vivo led to dose dependent increase in gamma oscillations in rat neocortices. Deficits in GABAergic neurotransmission are central to irregular gamma oscillations and may contribute to cognitive deficits in schizophrenia (Sun et al., 2011).

The EEG power abnormalities in auditory steady-state gamma entrainment found in schizophrenia is likely caused by the interaction of several mechanisms. In schizophrenia patients, there is markedly less gamma power over the frontal region than controls, particularly with 30 and 40 Hz stimulation (Sun et al., 2011). Gamma found in the auditory system has been linked with auditory hallucinations, and deficits in maintaining gamma rhythms have been found in the auditory system of schizophrenia patients (Metzner, Schweikard, & Zurowski, 2016). Light et al. (2006) found that schizophrenia patients demonstrate reduced levels of 40 Hz average evoked power, deficits in the phase synchronization of gamma band oscillations, and correlations between gamma range oscillatory deficits and associated neurocognitive impairments. The study demonstrated that schizophrenia patients have specific deficits in the ability to generate gamma frequency oscillations in response to steady-state auditory stimulation. They found reductions in both evoked gamma band power and intertrial coherence under 40-Hz stimulation (Jahshan et al., 2012). This gamma phase synchronization has been hypothesized to be critical for supporting important domains of normal cognition and may contribute to organizational and cognitive deficits of schizophrenia patients.

1.2.6.2. CHR

Few studies have examined gamma ASSR and the CHR state. These found gamma evoked power to be significantly reduced in CHR patients (Perez et al., 2013; Tada et al., 2016). Perez (2013) found a trend toward reduction of phase locking factor in CHR patients; however, total power was not reduced in CHR patients as it was in schizophrenia patients. This suggests the magnitude of gamma may be more intact in the early course of psychosis while phase locking is deficient. Gamma deficiency may represent a neurobiological abnormality apparent in those at risk regardless of whether they transition or not. Gamma has been found to be significantly correlated with clinical symptoms such as attentional functioning in CHR patients (Tada et al., 2016) and these difficulties may underlie attentional deficits that lead to poor functioning in patients with schizophrenia.

Most recently, Oribe et al. (2019) examined early auditory evoked gamma band response (EAGBR) in CHR, first-episode psychosis (FEP) and healthy controls at baseline and one year follow up. EAGBR PLF and evoked power did not differ between CHR and FEP groups, or CHR patients and controls. At follow up, PLF and evoked power did not change in the CHR or control group, and there was only a significant reduction in PLF at follow up for the FEP. Late adolescence is a vulnerable period of neurodevelopment where connectivity and receptors, including NMDA and GABA, mature to adult stages. Progressive reduction of gray volume of the primary auditory cortex may be present and these patterns could reflect abnormal gamma generating circuits of frontal and temporal areas in those at risk to those in first-episode psychosis.

1.2.7. ERP Abnormalities in the CHR Population: Summary

ERP components each reflect distinct sensory and cognitive processes, and thus can help identify areas of brain function that are specifically affected by the CHR state and could thus be a target for novel treatments. In the studies reviewed, ERP components were reduced in amplitude, or (in the case of N100 and P50 gating) less responsive to normally modulating factors. Together, these findings can be viewed as reflecting a general reduction in the ability to respond appropriately to the environment, beginning at the most basic levels of sensory processing, and extending downstream to higher levels of cognitive function. These processing deficits, in turn, could underlie symptoms such as perceptual abnormalities, communication

difficulties, and unusual ideas in this at-risk population, just as they are thought to contribute to qualitatively similar but more severe symptoms in psychosis (Javitt & Freedman, 2014).

Among ERP abnormalities that have been consistently found in schizophrenia, some (e.g., auditory P300 and duration MMN) appear to be more reliably present than others (P50 gating, frequency MMN) in CHR patients, suggesting that these measures may differ in the stages of the disease process which they reflect. This information could be helpful in identifying early pathophysiological mechanisms of the psychotic process as targets for stage-specific novel interventions.

1.2.8. Utility of ERP Measures for Predicting Development of Psychosis

In addition, ERPs in at-risk individuals can potentially help improve our ability to distinguish which individuals are most at risk for developing psychosis. In this regard, P300 and MMN reductions appear promising, although further study of other ERP components (e.g., auditory N1, ERN) is warranted. Moreover, further research could help ascertain which combination of ERP components is most useful in this regard. For instance, although both P300 and MMN show amplitude reductions in CHR populations and predict transition to psychosis (Atkinson et al., 2012; Bodatsch et al., 2011), these reductions are minimally correlated in schizophrenia and at-risk groups (Price et al., 2006), suggesting that an algorithm combining measures could improve our ability to predict psychosis compared to using each alone. ERP algorithms could potentially be introduced in clinical settings as objective, reliable, relatively economical, and easily administered tools for improving prediction of psychosis in CHR individuals. This could aid efforts to target resources toward those most in need of early intervention to prevent psychosis.

1.3. The N400 Event-Related Potential

One ERP component that has previously been found to be abnormal in schizophrenia, but has not been studied in the CHR population, is the N400 ERP response to semantic (meaningful) stimuli. The N400 is a negative-going ERP waveform occurring around 400 ms (between 200 and 600 ms), largest over centro-parietal sites, with a slight right hemisphere bias. It begins 200-300 after a word has been presented auditorily, visually or physically and peaks after 400 ms

(Lau, Phillips, & Poeppel, 2008). The N400 is used to study how meaning-related information is stored in the brain in semantic memory. In semantic memory, individual concepts can be viewed as nodes in a neural network, and meaningful relationships between these concepts as connections between nodes (Figure 4). The N400 effect indicates how stored conceptual knowledge associated with words and retrieval cues is retrieved in semantic contexts. These effects are generally observed in paradigms when a target word is related or unrelated to an immediately preceding prime word, or with an anomalous ending of a sentence that shares semantic features with its predictive ending, compared to one that is not semantically related (Figure 3). The N400 is reflective of this context – the amplitude is greater in semantically anomalous sentences because more work is required to process a sentence that does not integrate into a person's current world knowledge. This word priming effect for congruent sentence endings has been reported in both monolinguals and bilinguals; with bilinguals showing N400 effects in both languages, with the effects being later and smaller for less well-learned languages (Kutas & Federmeier, 2011a).

The N400 may reflect processing prior to word recognition and understanding and can be characterized as the integration of lexical retrieval and semantic extraction from nonlinguistic modalities (Baggio & Hagoort, 2011). All types of potentially meaningful stimuli are thought to elicit some amount of N400 activity depending on the perceptual state of the individual when semantic processing is initiated. The N400 measures activity that is flexible, context-dependent and emerges through time.

As for experimental paradigms, auditory N400 tends to begin earlier, last longer and have slightly more frontal and less right-biased topography than visual N400 (Kutas & Federmeier, 2011b). In visual paradigms, pictures elicit a more frontally distributed N400 similar to that for concrete words. Brain regions associated with the production of the N400 include the anterior medial temporal lobe, middle and superior temporal areas, inferior temporal areas, and prefrontal areas. These areas are also associated with networks involved with semantic memory processing and storage (Kutas & Federmeier, 2011b). The test-retest reliability suggest that N400 semantic priming effects have high reliability over a one week interval, but may decrease in magnitude with repeat testing, possibly because of changes in participant motivation (Kiang, Patriciu, Roy, Christensen, & Zipursky, 2013).

N400 responses are directly involved in an individuals' semantic and working memory. Yang, Zhang, Zhang, Zhang, and Li (2020) used reading tasks with high and low working memory span and semantic anomalies, to elicit an N400. They found that only the high-span working memory groups exhibited a N400 regardless of whether anomalies were manipulated at the sentence or discourse level. This result suggests that high span readers could integrate upcoming words with prior sentential context, therefore exhibiting an N400 response, whereas the absence of an N400 in the low-span group possibly represents a failure of temporal semantic integration.

Recent findings on the N400 across ages are mixed. When exposed to expected words compared to unexpected words in different visual fields, the literature states that young adults show an asymmetric pattern with a left hemisphere bias related to the N400 amplitudes (Federmeier & Kutas, 2019). Federmeier and Kutas (2019) found that older adults (mean age = 67) show no asymmetries and no evidence for prediction with left hemisphere, suggesting that this left hemisphere mechanism involved in prediction during language processing is less involved in later adulthood. Schneider and Maguire (2019) investigated changes in the neural indices underlying semantic and syntactic processing of auditory sentences in childhood and adolescence and found that the N400 was not sensitive to processing differences in the 8 to 9 years old group compared to older participants. These findings suggest underlying semantic processing may occur somewhat in childhood and continue to develop more strongly through adolescence.

The N400 is representative of knowledge and beliefs specific to the individual. Troyer and Kutas (2018) used a single domain of Harry Potter (HP) knowledge to manipulate context on a subject by subject basis. They found that participants had higher accuracy for HP sentences than control sentences, and that N400 amplitudes were reflected in the participants individual HP knowledge. Specific context affects semantic processing, and the N400 is a function of each individuals' knowledge in such context. Also, Bradford, Brunsdon, and Ferguson (2020) looked at how belief-state processing changes over the lifetime using a false-belief auditory ERP task to illicit an N400 as a maker of belief integration. They found that in true-belief contexts, the N400 was more negative-going for belief-inconsistent than for belief-consistent outcomes, and in false-belief contexts, belief-consistent outcomes led to more negative-going N400 effects than belief-inconsistent outcomes. This suggests that participants use their own understanding of world knowledge to process the stories. Age influenced the magnitude of false-belief N400 amplitude,

in that older adults continued to maintain an egocentric stance and reflect the stories according to their own knowledge of reality, compared to younger participants.

1.4. N400 and Schizophrenia

Researchers have used the N400 to probe for abnormalities in the functional organization of semantic memory in schizophrenia. The majority of studies have reported larger than normal N400s to target stimuli related to preceding prime stimuli – and/or smaller than normal N400 semantic priming effects – in schizophrenia, when prime-target stimulus-onset asynchronies (SOA) are longer than 400 ms (Bobes, Lei, Ibanez, Yi, & Valdes-Sosa, 1996; Condray, Siegle, Keshavan, & Steinhauer, 2010b; Ditman & Kuperberg, 2007; Iakimova, Passerieux, Laurent, & Hardy-Bayle, 2005; Kiang, Christensen, Kutas, & Zipursky, 2012; Kiang, Christensen, & Zipursky, 2011; Kiang, Kutas, Light, & Braff, 2008;Kostova, Passerieux, Laurent, & Hardy-Bayle, 2005; Kostova, Passerieux, Laurent, Saint-Georges, & Hardy-Bayle, 2003; Ohta, Uchiyama, Matsushima, & Toru, 1999; Salisbury, 2008; Strandburg et al., 1997). Moreover, several of these studies found that schizophrenia patients' larger than normal N400s to related targets, and smaller than normal N400 semantic priming effects, correlated with ratings of positive psychotic symptoms (delusions and hallucinations) (Kiang, Kutas, Light, & Braff, 2007a; Kiang et al., 2008; Salisbury, O'Donnell, McCarley, Nestor, & Shenton, 2000). Furthermore, some studies have reported that these N400 abnormalities improved together with psychotic symptoms after patients were treated with antipsychotics (Besche-Richard, Iakimova, Hardy-Bayle, & Passerieux, 2014; Condray, Siegle, Cohen, van Kammen, & Steinhauer, 2003). These results are consistent with the hypothesis that an abnormally rapid decay of activation of contextually related concepts (at least over intervals of $\geq$ 400 ms) may underlie development and maintenance of delusions. In contrast, although some N400 studies in schizophrenia employing shorter SOAs of <400 ms also found decreased semantic priming, (Condray et al., 2003; Kiang et al., 2008; Mathalon, Roach, & Ford, 2010; Niznikiewicz, Mittal, Nestor, & McCarley, 2010) others found increased semantic priming (Kreher, Holcomb, Goff, & Kuperberg, 2008; Mathalon, Faustman, & Ford, 2002; Salisbury, 2008) – but the latter may be specific to patients with disorganized speech, and conditions sensitive to detecting more automatic spread of activation (Kreher, Goff, & Kuperberg, 2009; Kreher et al., 2008; Salisbury, 2008). Thus, disorganized schizophrenia patients, in particular, may experience an abnormally increased spread of activation for short periods of time after meaningful stimuli, and this may contribute to production of weakly related sequences of concepts in speech (Kreher

et al., 2008; Spitzer, 1997).

Nestor et al. (1997) found enhanced N400 negativity for sensible as well as for nonsensical sentences, and increased N400 latency in schizophrenia patients, suggesting failure of using semantic context to activate related concepts. Niznikiewicz et al. (1997) found a more negative amplitude to both the unrelated and related stimuli in the schizophrenia group in both the visual and auditory modalities. This suggests that language dysfunction in schizophrenia may stem from a semantic system abnormality that is not affected by type of a sensory input (Niznikiewicz et al., 1997).

Kuperberg, Delaney-Busch, Fanucci, and Blackford (2018) used the N400 to probe semantic activity prior to language production in schizophrenia patients. They found that when exposed to prime and target words that overlapped in semantic features, ie. word forms, the schizophrenia group had a larger N400 (more negative) when naming targets that had the same semantic properties and word form as the prime word, as compared to the unrelated targets. This effect is the opposite of what one would expect in normal individuals and may reflect a disruption at the level of making connections between semantic features and the lexical form in schizophrenia patients. In contrast, a smaller number of studies have found larger than normal N400 semantic priming effects due to hyperpriming of related stimuli, specifically at SOA's of < 300ms (short), in schizophrenia patients scoring relatively high in severity of disorganized speech (Kreher, Holcomb, Goff, & Kuperberg, 2007). This suggests that there is a further spread of activation of node associates within a shorter period of time in schizophrenia.

The activation-maintenance model of schizophrenia thought disorder proposes that schizophrenia patients have a semantic bias towards the dominant meanings of ambiguous words despite their context. This bias can initiate overactivation in semantic memory, where semantic biases become random and weak words and associations are lost. At long time intervals patients cannot maintain information in verbal working memory (Salisbury, 2010). Salisbury (2010) examined different hemispheric patterns of N400 at long SOA in schizophrenia and controls to determine if there were any hemispheric differences, and the degree which patients showed such effects. Schizophrenia patients showed a reduced N400 effect for unambiguous unrelated target words compared to controls and were more likely to say unrelated words were related. Both groups showed a greater right hemisphere N400 effect to unrelated and dominant targets, and a

greater left hemisphere N400 effect to subordinate targets. The left and right hemispheres react to ambiguity differently, and this seems to be the case for schizophrenia patients. Kiang, Christensen, and Zipursky (2011) compared N400 priming effects in patients with schizophrenia and controls using a semantic processing task and a non-semantic orthographic task to detect a processing level of effect on patients. Similar to controls, in the patient group, the N400 priming effect was larger in the semantic task then in the orthographic task; however, schizophrenia patients exhibited attenuated effects in both tasks. Patients were able to use meaningful stimulus to activate related concepts and process them semantically at a below normal level.

The semantic memory dysfunction reflected in these N400 abnormalities could underlie some of the symptoms in schizophrenia. A common symptom in schizophrenia is disorganized speech, which is classified as loose associations, tangentiality and loss of global focus and deficits in verbal production, sentence complexity, comprehension and semantic processing. The severity of disorganized speech has been found to be inversely correlated with larger (more negative) N400 amplitudes to related target words, for example smaller N400 semantic priming effects (Ditman & Kuperberg, 2007; Kostova, Passerieux, Laurent, & Hardy-Baylé, 2005; Kreher et al., 2007; Laurent, Kostova, & Passerieux, 2010). Thus, one hypothesis for how disorganized speech in schizophrenia may result from abnormal activation in semantic memory is that patients are impaired in using contextual information to activate related items (Barch et al., 1996). Within the schizophrenia patient group, higher clinical disorganization scores correlated with a greater N400 priming deficit, suggesting an increased activity within semantic memory networks that is related to clinically observed disorganized speech (reviewed in Mohammad & DeLisi, 2013).

In disorganized speech there is a semantic bias towards dominant meaning words over more ambiguous words. Abnormalities of network pathways may lead to formal thought disorder symptoms, as well as delusions and hallucinations (Mohammad & De Lisi, 2013). Patients with schizophrenia have difficulty using context in sentence processing, and studies often show abnormal N400 priming effects when compared with healthy controls. Olichney, Iragui, Kutas, Nowacki, and Jeste (1997) found a larger reduction in N400 effect in early onset compared to late onset psychosis, and higher clinical disorganization was associated with a smaller N400 amplitude, suggesting abnormal semantic network organization may be related to a formal thought disorder. Mild to moderate thought disorder may relate to slight deficits in memory

maintenance, whereas more severe thought disorder may lead to failure of verbal working memory (Salisbury, 2010).

Another common symptom of schizophrenia is that of delusions, which are false beliefs or misinterpretations of events and their significance. Several studies have found N400 semantic priming deficits to correlate with delusions and delusion-like ideation (Mohammad & DeLisi, 2013). These results provide further evidence for less activation in response to related items in schizophrenia, suggesting that these patients might construct subjective or unusual experiences from unrelated stimuli to have some meaningful connection to their context, promoting delusions (Kiang, Kutas, Light, & Braff, 2008). Similarly, abnormal processing of stimuli both strongly and weakly meaningfully related to their context may play a role in pathogenesis of schizophrenic delusions. This fits with the finding that psychosis correlates with smaller in N400 amplitudes.

Certain medications have been found to affect the N400 effect in schizophrenia patients. In haloperidol and haloperidol-free groups, Condray, Siegle, Keshavan, and Steinhauer (2010a) found the N400 priming effect to be significantly reduced in both groups when compared with controls at the short SOA. However, patients medicated with high affinity muscarinic receptor binding drugs, such as clozapine, showed significant N400 priming, suggesting that neuromodulators can facilitate access to semantic representations (Condray et al., 2010). Wu et al. (2018) compared the effects of risperidone and paliperidone on the brain-derived neurotropic factor (BDNF) and the N400 in first-episode schizophrenia. After twelve weeks treatment with risperidone and paliperidone under congruent conditions, they found improvements in the N400 amplitude and latency for both medications.

Recently, studies have been conducted to determine if N400 is a reflection of psychosis, pathological genetics or both. Wang et al. (2019) compared electrophysiological semantic processing features in patients with bipolar disorder (BPD) and schizophrenia using a semantic priming task to elicit the N400. The patients with BPD and schizophrenia showed longer response time and N400 latency compared to healthy controls, with the BPD patients showing an enhanced N400 effect over the left frontal region and frontal pole compared to the healthy controls. Patients with schizophrenia exhibited a similar effect over the left frontal region with a decreased N400 over the two posterior regions. The N400 effect correlated with both positive

and manic symptoms in schizophrenia and BPD patients. Both schizophrenia and BPD patients demonstrate disorganized speech, and the abnormal semantic processing shown in this study may be an underlying mechanism. Schizophrenia showed a more negative N400 amplitude and a more reduced semantic priming effect than the BPD, which could indicate a more severe placing on the psychosis spectrum.

Sharma et al. (2017) looked at twins to see whether the N400 abnormalities reflected a genetic liability or was related to the process of schizophrenia. They examined the N400 in twin pairs concordant for schizophrenia, twin pairs discordant for schizophrenia, and healthy control twin pairs. Using a lexical-decision task with prime and target letter strings, the concordant twins for schizophrenia had a significantly smaller N400 priming effect compared to the healthy controls, and the discordant twins showed a trend towards a smaller N400 priming effect compared to controls. These results indicate that the N400 priming effect reflects a disturbance in the spread of activation in semantic networks in schizophrenia, and that the N400 reduction reflects the disease process in schizophrenia and not a genetic trait. These results are consistent with first-degree relative studies, that showed the N400 priming effect to be significantly smaller in those with schizophrenia and but not their relatives (Kiang, Christensen, & Zipursky, 2014). This study provides evidence for disrupted connectivity of frontotemporal networks in schizophrenia and demonstrates the utility of a direct N400 priming effect as a marker for related processes.

Similar to schizophrenia, delusional ideas and disorganized speech are also symptoms for CHR. It is unknown whether the N400 abnormality is apparent in people at risk for development of schizophrenia or psychosis, or whether its severity predicts their level of risk for the illness. As the N400 has not yet been tested in the CHR population, further studies are needed to focus on the N400 response as a possible biomarker for psychosis risk.

1.5. Overall Aims and Hypotheses

ERP measures that are found to be abnormal in prodromal individuals may be able to help us predict more accurately which individuals within this group will develop psychosis. Although algorithms comprising clinical symptoms and signs can help predict conversion to

psychosis (Cannon et al., 2016), many standardized clinical measures are time-consuming and require extensive training to administer. ERP indices of N400, gamma, P3a and MMN thus could serve as objective, easily obtainable measures that, on their own or in combination with clinical variables, refine our ability to predict the degree of risk for developing psychosis within the CHR group. A novel feature of this project is that it obtains these measures in the same sample. In the proposed study our primary aim is to examine for the first time whether the N400 semantic priming deficits are a biomarker of the CHR state, and whether decreased N400 semantic priming predicts conversion to psychosis in this population.

In Experiment 1, we sought to examine for the first time the N400 semantic priming effect in an antipsychotic, drug naïve population of CHR and healthy controls. We hypothesized that, similar to schizophrenia patients, CHR patients would exhibit smaller than normal N400 semantic priming effects, due to larger than normal N400 amplitudes to related targets at least at relatively long SOA. This would provide evidence for semantic priming deficits' contribution to the pathogenesis of psychosis.

In Experiment 2, our goal was to examine the magnitude of correlations between neurophysiological indices that may be useful for predicting development of psychosis in CHR patients. Some different neurophysiological biomarkers of psychosis show low cross-correlation, presumably representing distinct processes towards the development of schizophrenia. We sought to examine the association of gamma ASSR evoked power and PLF, MMN and P3a amplitudes, and N400 semantic priming effects in a population of antipsychotic-naïve CHR patients. For Experiment 2, we hypothesized that ASSR evoked power and PLF would correlate with MMN amplitude across patients. This is based on the view that ASSR gamma synchrony indexes parvalbumin-expressing GABAergic interneuron dysfunction, which is related to NMDA receptor hyperfunction in a feedback loop, which is thought to cause deficits in MMN (Hirano et al., 2015; Koshiyama et al., 2018a). Schizophrenia patients' neurophysiological abnormalities in attention-dependent processing have been found to be independent of abnormalities in pre-attentive processing, Therefore, we hypothesized that the N400 priming effects at the long and short time intervals would not be correlated with MMN amplitude or gamma ASSR measures in the CHR sample. We would then be able to combine the highly correlated neurophysiological indices of cognitive deficits to improve their predictive power as biomarkers of clinical outcome.

For Experiment 3, we aimed to examine whether ERP biomarkers were related to social, role and cognitive functioning in CHRs. We investigated the N400 at short and long SOAs in CHR individuals and its association with real-world functional impairment and overall neurocognitive dysfunction. Because deficits in activating contextually related concepts may interfere with the ability to comprehend or navigate real-world situations, we hypothesized that in the CHR patients severity of N400 priming deficits would be correlated with social and role functional impairment, and with deficits in global cognitive function, measured across a broad range of domains. Thus, these results could reinforce the N400 as a reliable neurophysiological biomarker for dysfunction in this population.

In Experiment 4, we followed our CHR sample over two years post baseline to examine the N400 relationships to clinical outcomes. We hypothesized that in CHR patients, decreased N400 semantic priming (i.e., smaller N400 amplitude differences between related and unrelated targets) would predict conversion to a psychotic disorder over two years of follow-up. We also hypothesized that N400 for related items would positively correlate with positive and disorganized symptoms (a smaller priming effect), and negatively correlated with role and social functioning at both baseline and at one and two years follow up.

In Experiment 5, we investigated the MMN, P3a and gamma ASSR in our CHR sample longitudinally. We hypothesized that CHR patients would have deficits in auditory steady-state gamma phase coherence and evoked power compared to healthy controls, and that decreased auditory steady-state gamma phase coherence and evoked power would predict conversion to a psychotic disorder or an increase in positive symptoms over two years' of follow-up. We also theorized that, consistent with previous results, MMN and P3a amplitude would be smaller in CHR patients than in controls, and that MMN and P3a amplitude would predict conversion to a psychotic disorder or an increase in positive symptoms over two years' of follow-up. Next, we hypothesized that, in CHR patients, a combination of MMN, N400, P3a and gamma would have greater power for predicting conversion to psychosis, compared to any of these measures alone. Based on previous findings in schizophrenia and MMN (Fisher et al., 2012), we expected to see a relationship between deficient MMN amplitude and increased auditory hallucinations as part of positive symptoms, at baseline and over two years' follow-up.

In sum, this research aimed to use neurophysiological indices as potential biomarkers to

distinguish those at risk for schizophrenia with worsening symptomatology, deficient cognition and global functioning, and eventual conversion to a psychotic disorder. These studies aimed to utilize event-related potentials already established as abnormal in CHR and combine them into an algorithm with the N400 as a predictive measure. The results of these studies could potentially establish the N400 as a predictive biomarker in those at risk for psychosis, therefore contributing to more targeted intervention and treatment.

Table 1.1. Event-Related Potential Studies with Clinical High-Risk Samples.

Study	Measure	N	CHR Diagnostic Criteria	CHR Diagnostic Instrument	Test	Effect Size d(where able to calculate)	Outcome
Auditory MMN							
Brockhaus-Dumke et al. (2005)	MMN	31 SZ 43 CHR 33 HC	BSABS	BSABS "Cognitive Disturbances"	Auditory oddball paradigm. 80% standard, 10% frequency deviant, 10% duration deviant	Recording site: 0.21 CHR<HC: 0.30	Duration MMN amplitudes: SZ<CHR<HC
Bodatsch et al. (2011)	MMN	33 FESZ 62 CHR (25 AR-C, 37 AR-NC) 67 HC	APS/BLIPS	ERI (retrospective)	Auditory oddball paradigm. 80% standard, 10% frequency deviant, 10% duration deviant	Duration FZ site AR-NC<HC : 0.11 AR-C<HC: 0.21	Duration MMN amplitudes: AR-C<AR-NC, AR-C<HC, AR-NC=HC
Shaikh et al. (2012)	MMN	41 CHR 50 HC	CAARMS	SCID	Auditory oddball paradigm. 85% standard, 15% duration deviant	FZ site CHR <HC: 0.38	MMN amplitude: CHR<HC. CHR converters

							<CHR non-converters
Hsieh et al. (2012)	MMN	37 E-BARS (at risk) 32 FEP 30 CHR 56 HC	APS/BLIPS	TP-DIS	Auditory oddball paradigm. 90% standard, 10% duration deviant	CHR<HC: 0.54	MMN amplitude: CHR<HC, FEP, E-BARS
Atkinson et al. (2012)	MMN P3a	30 CHR 10 FEP 20 HC	CAARMS	SCID	Auditory oddball paradigm. 92.5% standard, 7.5% duration deviants (either short or long)	MMN: duration deviant CHR<HC: -0.76 P3a: duration deviant CHR<HC:-0.29	MMN amplitude: CHR<HC P3a amplitude: CHR<HC
Jahshan et al (2012)	MMN P3a	33 SZ 31 FEP 26 CHR 28 HC	APS/GRD	SIPS	Auditory oddball paradigm. 90% standard, 10% duration deviant	MMN: CHR<HC: -0.49 P3a: CHR<HC: 0.56	MMN amplitude: CHR<HC P3a: CHR<FEP<HC
Higuchi et al. (2013)	MMN	31 SZ 17 CHR	CAARMS	SAPS SANS	Auditory oddball paradigm. 90% standard, 10%	FZ site CHR=HC: 0	MMN amplitude:

		20 HC			duration deviant		ARMS=HC; ARMS converters < ARMS nonconverters
Mondragon-Maya et al. (2013)	MMN P3a	20 FEP 23 CHR 24 HC	COPS	SIPS	Auditory oddball paradigm. 90% standard, 10% frequency deviant	FZ site MMN CHR<HC: 0.21 FZ site P3a CHR<HC: 2.5	MMN amplitude: FEP = CHR, HC P3a : FEP=CHR<HC
Perez et al. (2014)	MMN	19 SZ 38 CHR (15 NonConverters, 16 Converters, 7 drop out) 44 HC	COPS	SIPS	Auditory oddball paradigm. 90% standard, 10% deviant (either duration, frequency, or both duration and frequency)	NA	MMN amplitude (each deviant type): CHR<HC, SZ <HC, C<NC
Carrion et al. (2015)	MMN	34 CHR 33 HC	APS	SIPS	Auditory oddball paradigm. 67% standard, 11% duration deviant, 11% frequency deviant, 11% intensity deviant	duration deviation for CHR<HC: -0.79	MMN amplitude (across all deviant types): CHR < HC

Koshiyama et al. (2017)	MMN	14 FEP 16 CHR 16 HC	APS	SIPS	Auditory oddball paradigm. 90% standard, 10% deviant (duration and frequency)	NA	Duration MMN amplitudes: FEP = UHR<HC Frequency MMN amplitudes : FEP=UHR=HC
Lavoie (2018)	MMN	56 UHR 29 HC	APS BLIPS	SIPS	Auditory oddball paradigm. 90% standard, 10% frequency deviant	fMMN difference score: d=0.57	Frequency MMN: UHR<HC
Koshiyama (2018)	MMN	26 FEP 30 UHR 20 HC	APS	SIPS	Auditory oddball paradigm. 90% standard, 10% deviant (duration and frequency)	dMMN ROSZ<HC: 0.92	Duration MMN amplitudes: FEP=UHR UHR=HC FEP>HC Frequency MMN amplitudes : FEP=UHR=HC
Kim (2018)	MMN	17 CHR-R 31 CHR-NR	APS BLIPS	SIPS	Auditory oddball paradigm. 81.8% standard, 18.2%	FZ site CHR-NR<CHR-R: 0.72	CHR-NR< CHR-R=

		47 HC			duration deviant		HR
Hsieh (2019)	MMN P50 N100	19 FEP 23 UHR 120 HC	APS BLIPS	PANSS	Auditory oddball paradigm. 90% standard, 10% duration deviant	FZ site CHR<HC: 0.39	FEP=UHR<HC
Auditory P300							
van der Stelt et al. (2005)	P300	14 SZ 10 FEP 10 CHR 14 HC	COPS	SIPS	Auditory oddball paradigm. standard 91.5% and deviant frequency 8.5%	FZ site CHR<HC: 1.0	P300: SZ<CHR<HC
Ozgurdal et al. (2008)	P300	27 SZ 31 FEP 54 CHR 54 HC	APS BLIPS	SOPS PANSS	Auditory oddball paradigm. 76% standard 24% ifrequency deviant	NA	P300: SZ<CHR<HC
Frommann et al. (2008)	P300	50 EIPS (early initial prodromal state) CHR 50 LIPS (late intitial prodromal	APS BLIPS	BSABS	Auditory oddball paradigm stimuli. 90% standard, 10% frequency deviant.	FZ site LIPS<HC: 0.43	P300: EIPS left temporal<HC P300: LIPS midline<HC

		state) CHR 50 HC					
van Tricht et al. (2010)	P300	18 CHR conv 43 CHR non conv 28 HC	APS BLIPS GRD	SCID	Auditory oddball paradigm. standard 80% frequency deviant 20%	PZ site CHR-T<HC: 2.21 CHR-NT<HC: 0.93	P300: CHR converters <CHR non-converters<HC
Fusar-Poli et al. (2011)	P300	39 CHR 41 HC	APS BLIPS GRD	CAARMS	Auditory oddball paradigm. 80% standard and 20% frequency deviant.	NA	P300: ARMS<HC
Del Re et al. (2015)	P3a, P3b	20 FESZ 21 CHR 25 HC	COPS	SIPS/DIPD	Auditory oddball task. 80% standard 20% deviant frequency. Novelty oddball task. 60% standard 20% target, 20% novel	P3b group: 0.36	P3a: CHR=FESZ<HC P3b: CHR=FESZ<HC
Kim et al. (2015)	P300	45 CHR (divided into	SIPS	SCID	Auditory oddball paradigm. 82%	CZ site CHR R<HC:	P300: CHR non-remitters=CHR

		remitters and prodromal)			standard 18% frequency deviants	0.02 CHR NR<HC:0.01	remitters
Kim et al (2018)	P300	45 SZ 32 CHR 32 GHR 52 HC	SOPS	SIPS PANSS	Auditory oddball paradigm. 82.3% standard 17.6% frequency deviants	CZ site CHR<HC: -0.64	SZ=CHR=GHR<HC
Graber et al. (2019)	P300	43 CHR 28 PS 24 HC	APS BIPS GRDS	SOPS	Auditory oddball paradigm. 85% standard, 15% frequency deviants	NA	PS<CHR=HC
Hamilton et al. (2019)	P300	19 SZ 43 PRS 43 HC	APS BIPS GRDS	SIPS	Auditory oddball paradigm. 80% standard, 10% infrequent, 10% novel targets	CZ site PRS<HC:0.71	SZ=PRS<HC
Tang et al. (2019)	P300	104 CHR 69 HC	APS	SOPS POPS PQ-B	Auditory oddball paradigm: 144 standard, 36 target tones Auditory novel paradign:108 standard, 36	NA	Oddball: CHR=HC Novel: CHR-

					target, 6 environmental tones		C<HC=CHR-NC
ERN and other error-related							
Perez et al. (2012)	ERN, CRN, Pe	88 SZ 50 CHR 135 HC	APS BIPS GRD	SIPS	picture-word verification tasks	NA	ERN: CHR<HC CRN and Pe: CHR=HC
Auditory N1							
Perez et al. (2012)	N1	81 SZ 40 CHR 89 HC	COPS	SIPS	Talk/Listen paradigm	NA	No significant group difference
Brockhaus-Dumke et al. (2008)	N1	20 CSZ 46 FESZ 21 CHR-T 18 CHR-NT 46 HC	APS BLIPS	BSABS	Auditory paradigm. 96 click pairs with S1 and S2 with 500 msec interval	N100 SI CHR<HC: 0.71	N1: CSZ< FESZ=CHR-NT=CHR-T< HC

Gudlowski et al. (2009)	N1/P2 (LDAEP)	60 CHR 34 FESZ 28 CSZ 57 HC	APS BLIPS	SOPS BSABS PANSS SCID	Auditory paradigm. 1000 Hz tones presented binaurally on randomly determined interstimulus interval.	NA	N1/P2: CHR, FESZ, CSZ< HC
van Tricht et al. (2011)	N1	38 CHR: 15 CHR-T (transition) 23 CHR-NT (non-transition) 17 HC	GRD APS BLIPS	SCID	Auditory oddball paradigm. 80% standard targets and 20% non targets.	N1 baseline CZ CHR NT<HC: 0.2 CHR T<HC: 0.39	N1: CHR-T < HC CHR-NT
Gonzalez-Heydrich et al. (2015)	N1	22 PS 29 CHR 17 HC	K-SADS-PL	SIPS SOPS	Auditory paradigm. 1000 Hz tones presented binaurally on randomly determined interstimulus interval.	CHR<HC: 0.49	N1: CHR, PS < HC

Hseih et al. (2019)	N100 P50 MMN	19 FESZ 23 UHR 120 HC	APS BLIPS	PANSS	Auditory paradigm: click pairs 1ms, 85 db with 500 msec interstimulus	N100 difference FESZ=UHR<HC: 0.46	N100 difference: FSZ<HC FSZ=CHR CHR=HC
Mathalon et al. (2018)	N100	84 ESZ 71 CHR 103 HC	COPS	SIPS	Talk listen paradigm	NA	N1 peak suppression: ESZ=CHR<HC
Visual P300							
Lee et al. (2010)	P300	22 FESZ 25 CHR 17 HC	BIPS APPS GRDS	SIPS	Visuospatial recognition task using the oddball paradigm. 28% target stimuli and 72% non-targets	FZ CHR<HC: -0.68	P300: FESZ=CHR<HC
Visual N1 and P1							
Oribe et al. (2013)	N1, P1, P300	17 FESZ 23 CHR 31 HC	COPS	SIPS BSABS DIPD	Visual oddball paradigm. 80% standard 20% infrequent target stimuli	FZ site CHR<HC: 0.53	P300: CHR, FESZ < HC N1: FESZ < HC

							P1: FESZ = CHR = HC
P50							
Brockhaus-Dumke et al. (2008)	P50	20 CSZ 46 FESZ 21 CHR-T 18 CHR-NT 46 HC	APS BLIPS	BSABS	Auditory paradigm. 96 click pairs with S1 and S2 with 500 msec interval	P50 S1 CHR<HC: 0.078	P50 gating: CSZ< FESZ, CHR-NT, CHR-T, HC
Myles-Worsley et al. (2004)	P50	44 GHR 43 CHR 39 HC	APS BLIPS	CAARMS	Auditory paradigm. Click pairs with S1 and S2 with 500 msec interval	CHR<HC: 0.18	P50 ratio: HC<GHR=CHR
Van Tricht et al. (2015)	P50, N100, P200	61 UHR 28 HC	GRD APS BLIPS	SIPS PANSS	Auditory paradigm. 72 click pairs with S1 and S2 with 500 msec interval	P50 S1 UHR T<HC: 0.17 UHR NT<HC: 0.25	P50 ratio: HC=UHR
Hsieh et al.	P50	37 E-BARS	APS	TP-DIS	Auditory oddball	P50 S1	P50 gating:

(2012)		(at risk) 32 FEP 30 CHR 56 HC	BLIPS		paradigm. 90% standard, 10% duration deviant	CHR<HC: 0.069	CHR=HC=FEP =E-BARS
Ziermans et al.(2012)	P50	63 CHR 68 HC	GRD APS BLIPS COGDIS	SIPS BSABS	Auditory paradigm. 36 click pairs with S1 and S2 with 500 msec interval	CHR<HC: 0.25	P50 ratio: HC=CHR
Chang et al. (2019)	P50	35 FESZ 30 UHR 40 HC	COPS	SIPS	Auditory paradigm: SI(S2) 1 ms, 75 db with 500 msec interstimulus	S2 CHR<HC: -0.14	S2 amplitude: FESZ<CHR=H C
Hseih et al. (2019)	P50 N100 MMN	19 FESZ 23 UHR 120 HC	APS BLIPS	PANSS	Auditory paradigm: click pairs 1ms, 85 db with 500 msec interstimulus	P50 S2 FESZ=UHR<H C: 0.48	P50 ratio: FSZ=UHR=HC

Figure 1.1. 32-site electrode scalp topography

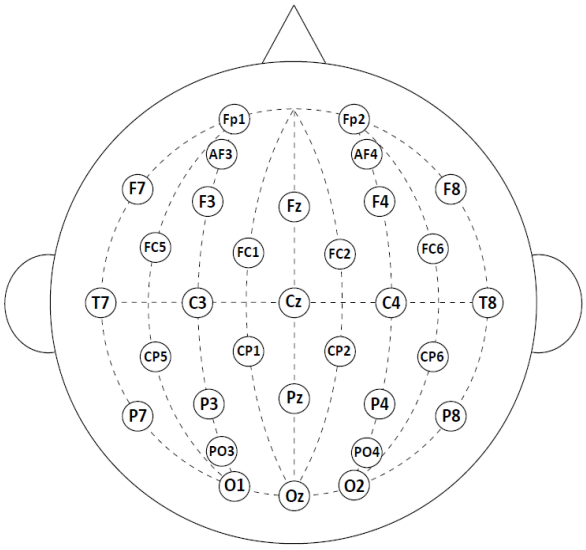


Table 1.2. Organization of the SIPS and SOPS including Symptoms (Miller et al. 2003)

Structured Interview for Prodromal Symptoms (SIPS)	**Scale of Prodromal Symptoms (SOPS)**
Measures	**Positive Symptoms**
Scale of Prodromal Symptoms (SOPS)	Unusual Thought Content/Delusional Ideas
Schizotypal Personality Disorder Checklist (DSM-IV)	Suspiciousness/Persecutory Ideas
Family History Questionnaire	Grandiosity
Global Assessment of Functioning scale (GAF)	Perceptual Abnormalities/Hallucinations
Criteria	Disorganized Communications
Presence of Psychotic Syndrome (POPS)	**Negative Symptoms**
Criteria of Prodromal Syndrome (COPS)	Social Anhedonia
Brief Intermittent Psychotic Symptom syndrome (BIPS)	Avolition
Attenuated Positive Symptom syndrome (APS)	Expression of Emotion
	Experience of Emotions and Self
	Ideational Richness
	Occupational Functioning

Genetic Risk and Deterioration syndrome (GRD)	**Disorganization Symptoms** Odd Behaviour and Appearance Bizarre Thinking Trouble with Focus and Attention Personal Hygiene **General Symptoms** Sleep Disturbance Dysphoric mood Motor Disturbances Impaired Tolerance to Normal Stress

Figure 1.2. Example of MMN and P3a amplitude

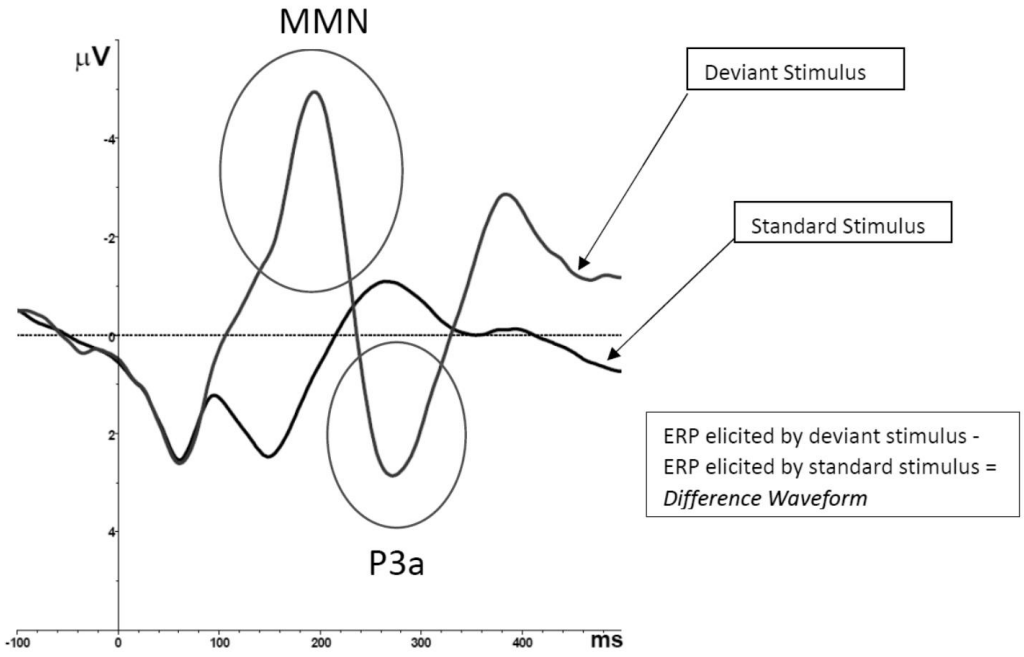


Figure 1.3. The N400 and the semantic priming effect

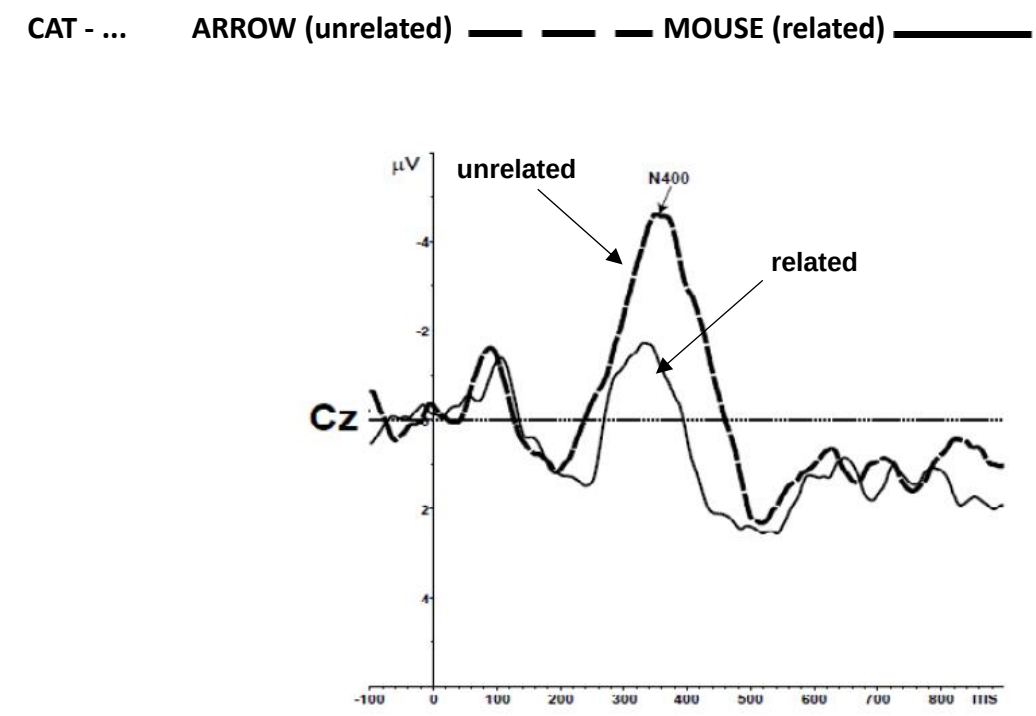
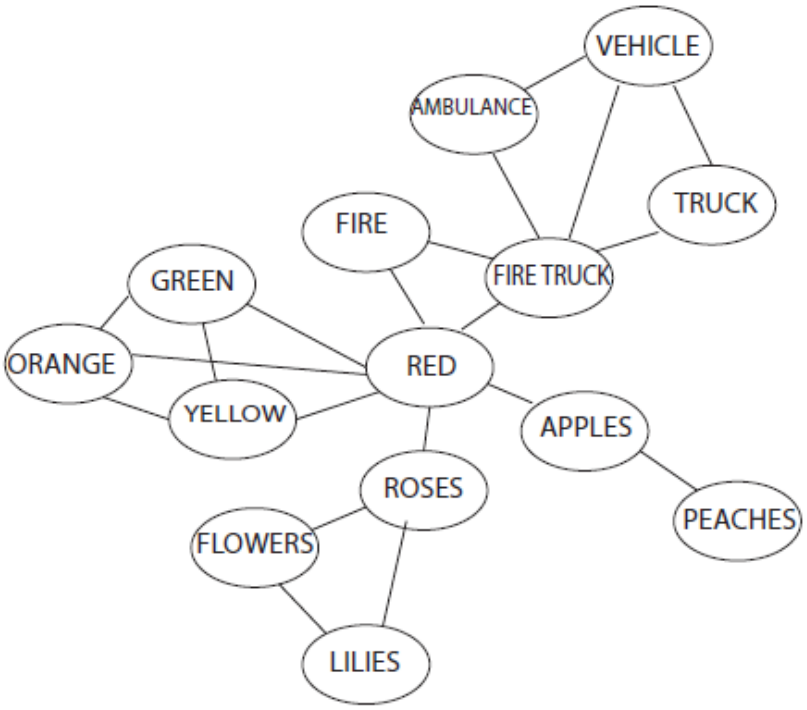


Figure 1.4. Node network as a concept of relatedness established by Collins and Loftus (1975)



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Chapter 2

Experiment 1 - Event-Related Brain Potential Evidence for Semantic Priming Deficits in the Clinical High Risk State for Psychosis

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2.1. Abstract

Background: In healthy individuals, the N400 event-related brain potential (ERP) waveform occurs in response to any potentially meaningful stimulus. Its amplitude is smaller (less negative) for stimuli that are related versus unrelated to a preceding stimulus. This N400 semantic priming effect is thought to reflect greater activation of related versus unrelated concepts in long-term semantic memory. N400 semantic priming effects have been found to be attenuated in schizophrenia patients, suggesting impaired activation of related concepts. We tested the hypothesis that patients at clinical high risk (CHR) for developing schizophrenia or a related psychotic disorder would exhibit similar abnormalities, consistent with a role for semantic priming deficits in the development of psychosis.

Methods: We recorded ERPs in 20 CHR patients and 20 healthy control participants who viewed prime words each followed by a target which was either a related or unrelated word, or a nonword, in a lexical-decision task. Equal numbers of each word target type were presented at prime-target stimulus-onset asynchronies (SOAs) of 300 and 750 ms.

Results: In controls, across SOAs, as expected, N400 amplitude was larger (more negative) to unrelated compared to related targets. In contrast, in CHR patients, N400 amplitudes did not differ between these target types at the longer SOA.

Conclusions: The results indicate a reduction in the relative activation of related versus unrelated concepts at longer intervals following a meaningful stimulus in CHR patients, pointing to a possible role for this neurocognitive abnormality in the pathogenesis of psychotic symptoms.

2.2. Introduction

Abnormalities in how meaningful stimuli facilitate processing of related concepts are a proposed neurocognitive mechanism of psychotic symptoms in schizophrenia, such as disorganized speech and delusions. Normally, after people encounter a meaningful stimulus such as a word or an object, it is easier for them to process related information – for example, after seeing the word *cat*, they are quicker to recognize the related word *mouse* than the unrelated word *arrow* (Neely, 1977). This "semantic priming effect" is thought to occur because the priming stimulus activates the neural representation of its concept in long-term semantic memory, our store of knowledge about the world (Collins & Loftus, 1975). According to this view, this activation then in turn spreads to related concepts, making corresponding stimuli easier to process. Deficient or aberrant semantic priming in schizophrenia could plausibly underlie disorganized speech, in which patients produce sequences of apparently unrelated or loosely related ideas (Kuperberg, Deckersbach, Holt, Goff, & West, 2007); or delusions, which frequently involve false beliefs that unrelated stimuli are connected or, conversely, that stimuli congruent with their context are unexpected or unusual (Kiang, Kutas, Light, & Braff, 2008).

One neurophysiological technique that has been useful for studying semantic priming at the neural level is that of event-related brain potentials (ERPs). ERPs measure voltage changes at the scalp associated with cognitive events such as stimuli or responses, and reflect synchronous postsynaptic activity of groups of cortical pyramidal neurons (Luck, 2005). Thus, ERPs offer a window on cognitive brain activity that is non-invasive and has millisecond-level resolution. The N400 is a negative-going ERP waveform peaking around 400 ms after any potentially meaningful stimulus such as a word (Kutas & Hillyard, 1989) or a picture (Barrett & Rugg, 1990); it is broadly distributed over the scalp, although largest over centroparietal sites (Kutas & Federmeier, 2011), and has generators in the anterior medial temporal lobe (Nobre & McCarthy, 1995). In normal individuals, following meaningful stimuli, related items elicit smaller (less negative) N400 amplitudes than do unrelated items, reflecting greater activation of the related concepts in semantic memory (Kutas & Federmeier, 2011). This N400 semantic priming effect can thus be used to study how information is organized in semantic memory in healthy and clinical populations.

Researchers have used the N400 to probe for abnormalities in the functional organization

of semantic memory in schizophrenia. The preponderance of studies have reported larger than normal N400s to target stimuli related to preceding prime stimuli – and/or smaller than normal N400 semantic priming effects – in schizophrenia, when prime-target stimulus-onset asynchronies (SOA) are longer than 400 ms (Bobes, Lei, Ibanez, Yi, & Valdes-Sosa, 1996; Condray, Siegle, Keshavan, & Steinhauer, 2010; Ditman & Kuperberg, 2007; Iakimova, Passerieux, Laurent, & Hardy-Bayle, 2005; Kiang, Christensen, Kutas, & Zipursky, 2012; Kiang, Christensen, & Zipursky, 2011; Kiang et al., 2008; Kostova, Passerieux, Laurent, & Hardy-Bayle, 2005; Kostova, Passerieux, Laurent, Saint-Georges, & Hardy-Bayle, 2003; Ohta, Uchiyama, Matsushima, & Toru, 1999; Salisbury, 2008; Strandburg et al., 1997). Moreover, several of these studies found that schizophrenia patients' larger than normal N400s to related targets, and smaller than normal N400 semantic priming effects, correlated with ratings of positive psychotic symptoms (delusions and hallucinations) (Kiang, Kutas, Light, & Braff, 2007; Kiang et al., 2008; Salisbury, O'Donnell, McCarley, Nestor, & Shenton, 2000). Furthermore, some studies have reported that these N400 abnormalities improved together with psychotic symptoms after patients were treated with antipsychotics (Besche-Richard, Iakimova, Hardy-Bayle, & Passerieux, 2014; Condray, Siegle, Cohen, van Kammen, & Steinhauer, 2003). These results are consistent with the hypothesis that an abnormally rapid decay of activation of contextually related concepts (at least over intervals of $\geq$ 400 ms) may underlie development and maintenance of delusions. In contrast, although some N400 studies in schizophrenia employing shorter SOAs of <400 ms also found decreased semantic priming (Condray et al., 2003; Kiang et al., 2008; Mathalon, Roach, & Ford, 2010; Niznikiewicz, Mittal, Nestor, & McCarley, 2010), others found increased semantic priming (Kreher, Holcomb, Goff, & Kuperberg, 2008; Mathalon, Faustman, & Ford, 2002; Salisbury, 2008) – but the latter may be specific to patients with disorganized speech, and conditions sensitive to detecting more automatic spread of activation (Kreher, Goff, & Kuperberg, 2009; Kreher et al., 2008; Salisbury, 2008). Thus, disorganized schizophrenia patients, in particular, may experience an abnormally increased spread of activation for short periods of time after meaningful stimuli, and this may contribute to production of weakly related sequences of concepts in speech (Kreher et al., 2008; Spitzer, 1997).

It is yet unknown whether N400 semantic priming abnormalities precede the onset of frank psychosis. If so, this would further support the view that these abnormalities represent an

underlying neurocognitive mechanism of psychotic symptoms, and are not a manifestation only of chronic psychosis, or an effect of antipsychotic treatment. To address this question, the present study aimed to test for the first time whether N400 abnormalities similar to those seen in schizophrenia are also present in individuals at clinical high risk (CHR) for developing a psychotic disorder. Most schizophrenia patients describe having experienced a period of less intense symptoms preceding psychosis with changes in thought content, perception, concentration, mood, and behavior (Addington & Heinssen, 2012). These CHR symptoms may include anomalous self-experiences or ideas of reference that are not of delusional intensity, perceptual illusions or pseudohallucinations; or full-blown delusions or hallucinations that are brief and intermittent.

Help-seeking individuals presenting with such symptoms who meet research diagnostic criteria for a CHR state have a much higher than normal incidence of developing a psychotic disorder. A recent meta-analysis estimated this incidence to be 22% within one year and 32% within 3 years (Nieman et al., 2013) – representing a relative risk of approximately 400 compared to the incidence of all forms of psychosis in the general population (Cannon et al., 2008). Moreover, approximately 90% of CHR patients who convert to a psychotic disorder will develop schizophrenia or another primary psychotic disorder, rather than a psychotic mood disorder (Fusar-Poli et al., 2013).

In the present study, we recorded ERPs in CHR patients and healthy control participants (HCPs) while they viewed prime-target pairs in which the targets were words related or unrelated to the prime word, or pronounceable nonwords. Participants' task was to indicate by pressing a button whether or not the target was a real word. This response was delayed to minimize motor effects on ERPs. Equal numbers of related and unrelated word pairs were presented at a short and a long SOA (300 and 750 msec) for each participant. Previously, using similar stimuli, we found across studies that schizophrenia patients had smaller than normal N400 semantic priming effects, due to larger than normal N400 amplitudes to related targets, across both SOAs (Boyd, Patriciu, McKinnon, & Kiang, 2014; Kiang, Christensen, & Zipursky, 2014; Kiang et al., 2008). Moreover, most other N400 studies of schizophrenia patients employing relatively long SOAs (≥400 ms) found similar results; however, studies employing shorter SOAs were mixed in this regard, raising the possibility that CHR patients might exhibit more reliable N400 semantic

priming deficits at a longer compared to a shorter SOA. Therefore, we hypothesized that, similar to schizophrenia patients, CHR patients would exhibit smaller than normal N400 semantic priming effects, due to larger than normal N400 amplitudes to related targets, at least at the longer SOA. This result would provide evidence that these abnormalities are associated with prodromal stages of the psychotic disease process, consistent with a role for semantic priming deficits in the pathogenesis of delusions. Furthermore, in accordance with this neurocognitive model, we hypothesized that across CHR patients, who vary in severity of delusion-like ideation, this severity would correlate with smaller N400 semantic priming effects.

2.3. Methods and Materials

2.3.1. Participants

Participants included 20 CHR individuals and 20 healthy control participants (HCPs). CHR patients were help-seeking patients referred to the Focus on Youth Psychosis Prevention outpatient clinic at the Centre for Addiction and Mental Health (CAMH) in Toronto. HCPs were recruited from the community by advertising online, in newspapers, and on bulletin boards. The protocol was approved by the CAMH Research Ethics Board. All participants gave written informed consent. Participants received cash compensation.

CHR individuals met diagnostic criteria for a psychosis-risk syndrome, namely the Criteria of Psychosis-Risk States based on the Structured Interview for Psychosis-Risk Syndromes (SIPS) (McGlashan, Walsh, & Woods, 2014), where criteria was met with a score of 3 or more on at least one out of 5 Positive scale items. Patients had no history of current or lifetime Diagnostic Statistical Manual-IV-TR (American Psychiatric Association, 2000) Axis I psychotic disorder, or mood disorder with psychotic features, as determined via the Structured Clinical Interview for DSM-IV-TR (SCID) (First, Spitzer, Gibbon, & Williams, 2002); had no history of DSM-IV substance abuse or dependence in the last 6 months (except nicotine); and were antipsychotic-naive. HCPs did not have any current or past DSM-IV psychiatric diagnoses as determined via the SCID, or any first-degree relatives with a history of psychotic disorder, and were not currently taking psychotropic medication. Other exclusion criteria for all participants included: visual or hearing impairment; having learned English after age 5; reading disability;

and lifetime self-reported neurological disorder. Table 2.1. shows group demographic, neuropsychological and clinical characteristics. Patients and controls did not differ significantly on demographic variables or on National Adult Reading Test (Nelson & Willison, 1991) scores, an estimate of patients' premorbid verbal IQ.

2.3.1.1. Sample Size

In a previous study (Kiang et al., 2014), N400 amplitudes for related, but not unrelated, targets in a prime-target word-pair paradigm with SOA of 750 ms were significantly larger in patients with schizophrenia compared to HCPs, with an interaction effect size (Cohen's f) of 0.66. Conservatively assuming a smaller effect size of 0.25; 2 groups of equal size (CHR vs. HCP); and power $\beta=0.80$ to detect a Group x Target Type effect in an ANOVA, at a two-tailed significance of $\alpha=0.05$; we anticipate that testing this hypothesis will require n=17 in each group (17 CHR and 17 HCP).

2.3.2. Stimuli and task

Stimuli included 80 related (e.g., *METAL-STEEL*) and 80 unrelated (*DONKEY-PURSE*) prime-target word pairs. For each related pair, the target was among the words most commonly given as associates to the prime by participants in the University of South Florida word-association norms (Nelson, McEvoy, & Schreiber, 1999); mean response probability of related targets (i.e., proportion of individuals producing that word in response to the prime) was 0.61 (SD=0.12). For each unrelated pair, prime and target were not associates in the norms. Across these conditions, targets were matched for mean length and log-transformed frequency (Francis & Kucera, 1982), and primes were also matched on these parameters. Stimuli also included 160 word-nonword prime-target pairs (*DRESS-ZORES*), whose targets were pronounceable nonwords. No word occurred more than once among the stimuli.

The 320-trial stimulus list included all prime-target pairs in a fixed randomized order, in four blocks of 80 trials each. The list had two versions, each one administered to half the participants, in which the order of prime-target SOAs across blocks was counterbalanced. In version A, SOA was 300 ms in blocks 1 and 2, and 750 ms in blocks 3 and 4; in version B, order of SOAs was reversed.

Participants were seated 100 cm from a video monitor on which stimuli were centrally presented, in yellow letters on a black background, with each letter subtending on average 0.36° of visual angle horizontally, and up to 0.55° vertically. Each participant was presented with the stimulus list, with short rest breaks between blocks. Each trial consisted of: (a) row of preparatory fixation crosses for 500 msec; (b) blank screen for 250 msec; (c) prime word for 175 msec; (d) blank screen for 125 msec (in 300-msec SOA trials) or 575 msec (in 750-msec SOA trials); (e) target for 250 msec; (f) blank screen for 1250 msec; (g) prompt *Yes or No?* until participants responded via button-press; and (h) blank screen for 3000 msec until onset of the next trial (see Figure 1).

At the prompt, participants were required to press one of two buttons, positioned under their right and left thumbs. One button (labeled "Yes") signaled that prime and target were related; the other button ("No") signaled that they were not. Assignment of buttons was divided equally among participants, counterbalanced across the two stimulus list versions.

2.3.3. Electroencephalographic data collection and analysis

During the task, the electroencephalogram (EEG) was recorded using an actiCHamp amplifier (Brain Products, Gilching, Germany), from 32 active Ag/AgCl electrodes embedded in a cap (actiCAP system, Brain Products) at sites approximately equally spaced across the scalp, positioned according to a modified International 10-20 System (Fp1-Fp2-F7-F3-Fz-F4-F8-FC5-FC1-FC2-FC6-T7-C3-Cz-C4-T8-TP9-CP5-CP1-CP2-CP6-TP10-P7-P3-Pz-P4-P8-PO9-O1-Oz-O2-PO10). Electrode impedances were kept below 25 kΩ. The EEG was referenced online to FCz, and continuously digitized at 500 Hz. Blinks and eye movements were monitored via electrodes on the supraorbital and infraorbital ridges and on the outer canthi of both eyes. Offline, the EEG was re-referenced to the algebraic mean of the mastoids, and bandpassed at 0.25-60 Hz. Continuous data were algorithmically corrected for eyeblink artifact (Makeig, Jung, Bell, Ghahremani, & Sejnowski, 1997). ERPs were computed for epochs from 100 msec pre-stimulus to 900 msec post-stimulus. Individual trials containing artifacts due to eye movement, excessive muscle activity or amplifier blocking were rejected off-line by visual inspection before

time-domain averaging; mean percentage of trials lost to such artifacts was 18% for patients and 9% for controls.

For each participant, separate ERP averages were obtained for trials with related and unrelated targets at each SOA. N400 amplitude was defined as mean voltage from 300-500 msec post-stimulus, consistent with previous methods (Federmeier, Wlotko, De Ochoa-Dewald, & Kutas, 2007; Kiang et al., 2008; McLaughlin, Osterhout, & Kim, 2004).

2.3.4. Statistical analysis

P-values in analyses of variance (ANOVAs) with within-subject factors are reported after Greenhouse-Geisser Epsilon correction. For significant effects, comparisons of all pairs of factor-level means were made with the Tukey HSD test, with family confidence coefficient of 0.95. All *p*-values are two-tailed. Percentage of correct responses was analyzed by repeated-measures ANOVA, with Group (CHR vs. HCP) as between-subject variable; and SOA (300-msec vs. 750-msec) and Target (related vs. unrelated vs. nonword) as within-subject variables.

N400 amplitude was analyzed by repeated-measures ANOVA with Group (CHR vs. HCP) as between-subject variable; and SOA (300- vs. 750-msec), Target (related vs. unrelated) and Electrode (12 levels: T7/Cz/T8/CP5/CP1/CP2/CP6/P7/P3/Pz/P4/P8, corresponding to a contiguous array of centroparietal sites where N400 effects were most prominent) as within-subject variables.

To examine the relationship between delusion-like ideation and N400 semantic priming effects in CHR patients, Spearman correlation coefficients ρ were calculated across patients between N400 priming effects (difference in N400 amplitude for unrelated minus related targets) at each SOA at Pz (midline parietal); and scores on each of the Scale of Psychosis-Risk Symptoms (SOPS) (McGlashan et al., 2014) Positive Symptom scale items (P1: unusual thought content, P2: suspiciousness/persecutory ideas, P3: grandiose ideas, P4: perceptual abnormalities/hallucinations, P5: disorganized communication).

2.4. Results

2.4.1. Behavioral data

The correct-response rates for schizophrenia patients and HCPs in the lexical-decision task (Table 2.2.) indicate that, overall, participants were attending to the stimuli. Across groups, there was no effect of Target ($F_{2,76}$=2.48, η^2_P=0.06, p=0.11) or SOA ($F_{1,38}$=0.19, η^2_P=0.01, p=0.67). There was no effect of Group ($F_{1,38}$=2.32, η^2_P=0.06, p=0.14); and no Group x Target ($F_{2,76}$=0.93, η^2_P=0.02, p=0.38), Group x SOA ($F_{1,38}$=1.68, η^2_P=0.04, p=0.20), or Group x Target x SOA interaction ($F_{2,76}$=1.09, η^2_P=0.03, p=0.33), suggesting that patients and controls did not differ significantly in their attention to the stimuli.

2.4.2. Grand average ERPs

Grand average ERPs are shown for representative midline electrodes Cz (central) and Pz (parietal), for CHR and HCP groups, for the 300-msec prime-target SOA in Figure 2.2. and the 750-msec SOA in Figure 2.3.

2.4.3. N400 amplitude

N400 amplitudes for CHR patients and HCPs, averaged across the 12 centroparietal electrodes used for analysis, are shown in Table 2.3. The repeated-measures ANOVA showed that across groups, N400 amplitude was larger (more negative) for unrelated than related targets (Target effect: $F_{1,38}$=31.75, η^2_P=0.46, p<0.0001). N400 effects were broadly distributed although largest medially (Target x Electrode interaction: $F_{11,418}$=13.51, η^2_P=0.26, p<0.0001). There was no Group effect ($F_{1,38}$=0.38, η^2_P=0.01, p=0.54); and no Group x Target ($F_{1,38}$=2.67, η^2_P=0.07, p=0.11), Group x SOA ($F_{1,38}$=0.89, η^2_P=0.02, p=0.35), or SOA x Target ($F_{1,38}$=0.31, η^2_P=0.01, p=0.58) interactions. In the control group, there was a Group x Target x SOA interaction ($F_{1,38}$=4.14, η^2_P=0.10, p=0.049). The Tukey HSD test indicated that at the long SOA, the N400 amplitude was larger for unrelated than for related targets. In the patient group there was no significant difference in N400 amplitude between these conditions.

2.4.4. Correlations of N400 semantic priming effects with symptom ratings

Within the CHR group, N400 semantic priming effects at each SOA were not significantly correlated with any of the SOPS Positive items (all $p>0.22$).

2.5. Discussion

In this study, we examined for the first time whether patients at CHR for psychosis exhibit abnormalities in the degree to which meaningful stimuli activate related concepts in long-term semantic memory, as measured by the N400 ERP waveform. We hypothesized that, like schizophrenia patients, CHR patients would exhibit deficits in the normal reduction of N400 amplitudes in response to related versus unrelated stimuli (N400 semantic priming effects), due to larger than normal N400 amplitudes to related items, at least when the interval between the prime and target stimulus was relatively long (750 msec). Consistent with this hypothesis, we found that CHR patients' N400 semantic priming effects were smaller than normal when the prime-target SOA was 750 msec, although not when it was 300 msec. In other words, whereas control participants, as expected, had smaller N400s to related than to unrelated items, CHR patients exhibited no difference in N400 amplitude between related and unrelated items at the longer SOA. However, we were unable to ascertain whether this was because patients' N400 amplitudes were larger than normal for related targets, smaller than normal for unrelated targets, or both, because N400 amplitudes for both related and unrelated targets did not differ significantly between patients and controls. Larger studies with greater statistical power would be required to distinguish between these possibilities.

Our results suggest that, after encountering meaningful stimuli, CHR patients have abnormalities in selectively activating related concepts in long-term semantic memory. In particular, CHR patients appeared to activate related concepts normally at a shorter interval (i.e., 300 msec) after a prime stimulus, but to be deficient in maintaining this activation normally over a longer time interval (750 msec) after the prime. On balance, N400 studies of schizophrenia patients have indicated that they have similar deficits in activating related concepts over longer prime-target SOAs of approximately 400 msec or more. Results at shorter SOAs are mixed, with

studies variously showing either larger or smaller than normal N400 semantic priming effects (reviewed in Mohammad & DeLisi, 2013). Researchers have proposed that hyperpriming of related concepts at short SOAs in schizophrenia may be specific to conditions promoting more automatic processing and to patients with higher levels of disorganization, with hypopriming occurring more generally (Kreher et al., 2008; Mohammad & DeLisi, 2013; Salisbury, 2010). Our findings in CHR patients suggest that, at this early stage of the psychotic disease process, initial activation of related concepts is normal, whereas maintenance of this activation over longer intervals is deficient like in schizophrenia. Thus, N400 semantic priming deficits at longer SOAs, in particular, may be a reliable neurophysiological biomarker of psychosis risk.

In line with connectionist computational modeling suggesting that N400 amplitude reflects prediction error in semantic memory (Rabovsky & McRae, 2014), our present findings in unmedicated CHR patients provide further neurophysiological evidence for the hypothesis that an impairment in predicting contextually related concepts in semantic memory (as reflected in a lack of N400 priming effects for contextually related versus unrelated stimuli) may cause patients to perceive contextually related stimuli in the real world as unexpected or aberrantly salient, in turn predisposing to development of delusions in an attempt to explain these experiences (Hemsley, 2005; Kiang et al., 2008). Apparently inconsistent with this hypothesis, however, was the absence of a significant correlation between CHR patients' N400 semantic priming deficits and severity of delusion-like ideation. Further studies using larger sample sizes would help to ascertain whether this negative finding was due to a lack of statistical power. Alternatively, N400 deficits may reflect an underlying neurocognitive factor in the development of psychosis, but be uncorrelated with ratings of psychosis-like symptoms due to phenotypic variation in the manifestation of this neurocognitive abnormality, or a lack of sensitivity of clinical rating scales to aberrant subjective experiences (Ford, 2018).

A strength of our study was that patients were antipsychotic-naive, hence their ERPs were not subject to possible confounding effects of these medications. A limitation of the study was its relatively small sample size. Thus, although our results suggest that N400 semantic priming deficits, at least at the 750-msec SOA, are an early neurophysiological biomarker of psychotic illness, replication studies are necessary to further validate this finding. Another limitation of our study was its cross-sectional nature. Longitudinal studies could help ascertain

whether the severity of N400 semantic priming deficits further predicts risk of developing psychosis within the CHR population. If so, like other ERP biomarkers of the CHR state (Lepock et al., 2018; Nieman et al., 2014; Perez et al., 2014), this N400 abnormality could be a useful tool in efforts to develop algorithms that refine our ability to predict outcome in this population (Cannon et al., 2016; Nieman et al., 2014; Schmidt et al., 2017), in order to provide patients with more personalized prognostic information, and target interventions to those most at risk.

Figure 2.1. Stimulus presentation sequence for experimental trail

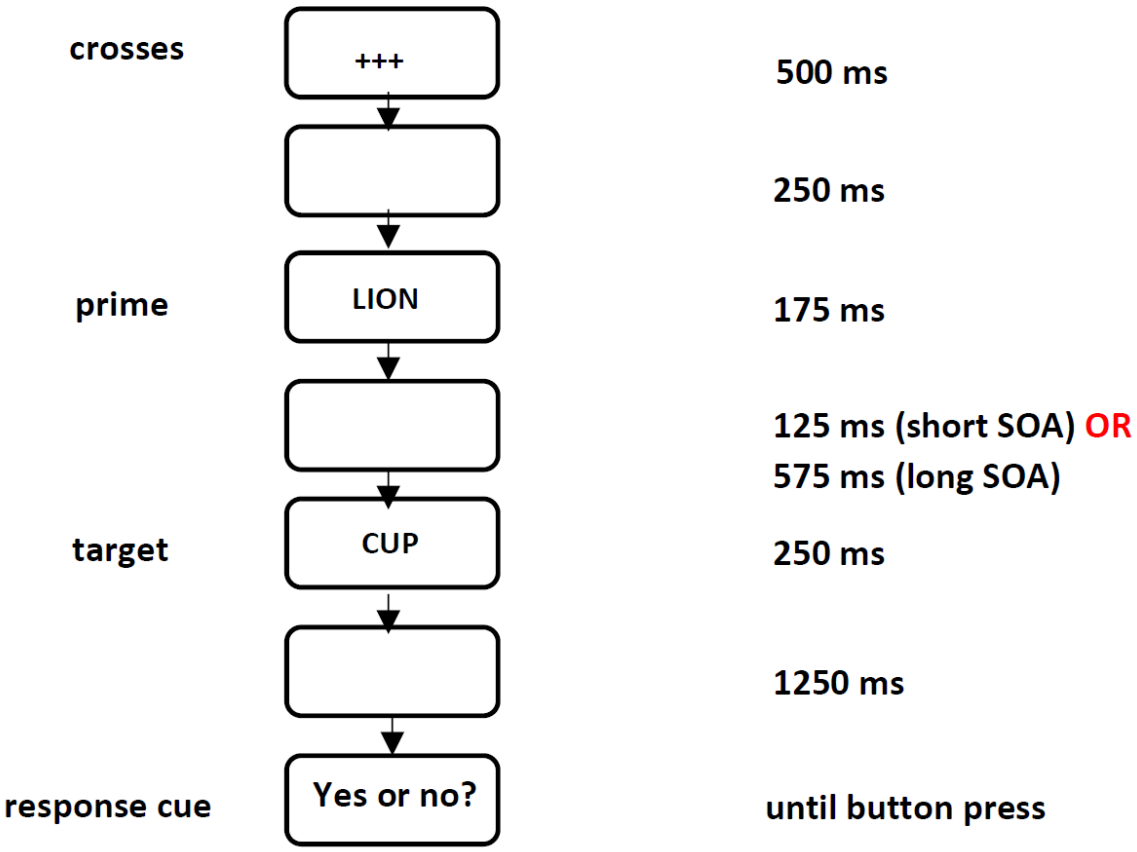


Table 2.1. Demographic and clinical characteristics of the study sample (means ± SD given for continuous variables)

	Healthy Controls (*n*=20)	**Clinical High-Risk Patients (*n*=20)**
Age, years	21.8±3.1	20.7±1.8
Sex	13 female, 7 male	7 female, 13 male
Handedness	18 right, 2 left	18 right, 2 left
Parental socioeconomic status	50.5±13.0	50.1±16.2
Years of education[a]	15.2±1.6	14.2±1.5
National Adult Reading Test estimated verbal IQ	110.1±5.7	109.4±6.4
Scale of Psychosis-Risk Symptoms		
Positive Scale Total	-	11.2±4.1
Negative Scale Total	-	13.4±5.1
Disorganized Scale Total	-	5.8±3.6
General Scale Total	-	10.7±2.9

Table 2.2. Percentage of correct lexical-decision responses, by participant group and target condition

	Healthy Control Participants (*n*=20)		**Clinical High-Risk Patients (*n*=20)**	
	Mean	**SD**	**Mean**	**SD**
Short SOA				
Related	99.0	3.0	97.3	4.3
Unrelated	97.5	4.7	96.1	4.8
Nonwords	99.0	1.3	95.1	8.5
Long SOA				
Related	98.5	3.5	98.2	2.7
Unrelated	97.6	4.2	96.5	5.6
Nonwords	97.9	4.2	96.6	5.3

Table 2.3. Mean N400 amplitude (μV), averaged across 12 centroparietal electrodes (T7/Cz/T8/CP5/CP1/CP2/CP6/P7/P3/Pz/P4/P8), by participant group and target condition

	Healthy Control Participants (*n*=20)		**Clinical High-Risk Patients (*n*=20)**	
	Mean	**SD**	**Mean**	**SD**
Short SOA				
Related	0.57	2.24	-0.07	3.38
Unrelated	-0.64	2.35	-1.37	3.07
Long SOA				
Related	1.32	3.31	0.71	2.54
Unrelated	-0.44	2.65	0.37	2.80

SOA, stimulus-onset asynchrony

Figure 2.2. Grand average event-related potentials to related (solid line) and unrelated (dashed line) word targets, at the 300-msec prime-target stimulus-onset asynchrony, at the electrode sites Cz (midline central) and Pz (midline parietal), for healthy control participants and clinical high-risk patients.

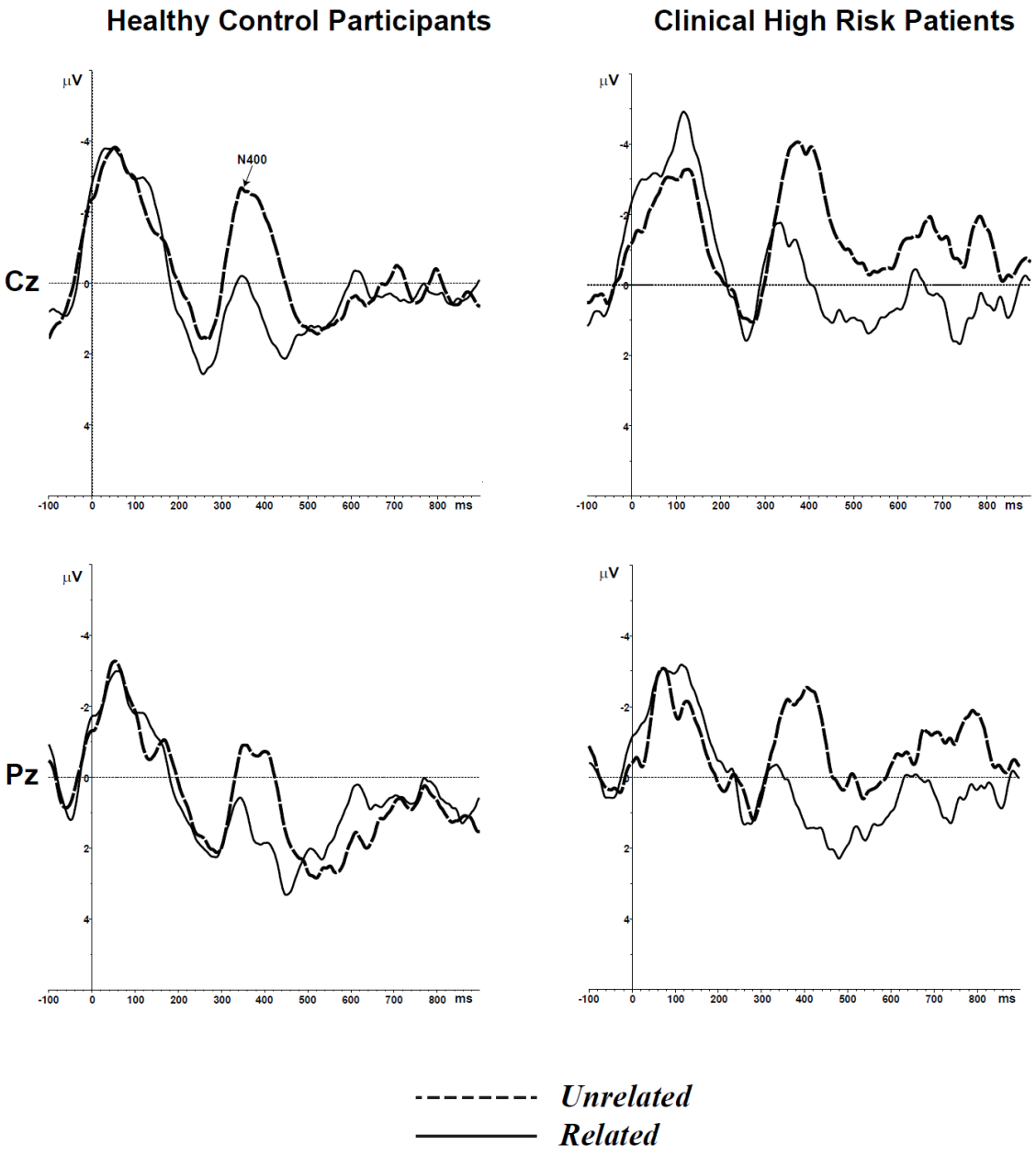
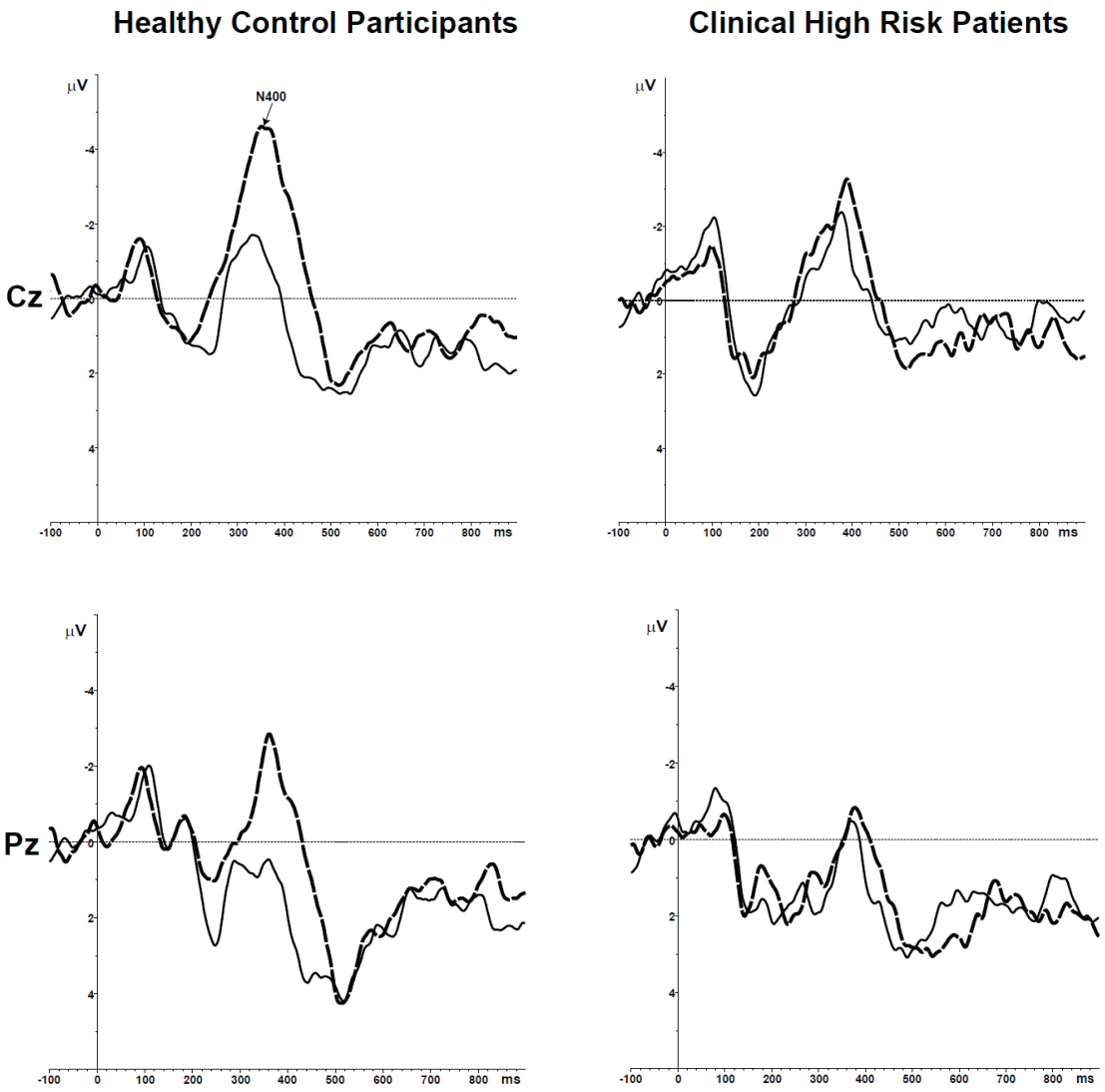


Figure 2.3. Grand average event-related potentials to related (solid line) and unrelated (dashed line) word targets, at the 750-msec prime-target stimulus-onset asynchrony, at the electrode sites Cz (midline central) and Pz (midline parietal), for healthy control participants and clinical high-risk patients.



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Chapter 3

Experiment 2 - Relationships between cognitive event-related brain potential measures in patients at clinical high risk for psychosis

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3.1. Abstract

Background: Neurophysiological measures of cognitive functioning that are abnormal in patients with schizophrenia are promising candidate biomarkers for predicting development of psychosis in individuals at clinical high risk (CHR).

Methods: We examined the relationships among event-related brain potential (ERP) measures of early sensory, pre-attentional, and attention-dependent cognition, in antipsychotic-naïve help-seeking CHR patients (n=36) and healthy control participants (n=22). These measures included the gamma auditory steady-state response (ASSR; early sensory); mismatch negativity (MMN) and P3a (pre-attentional); and N400 semantic priming effects – a measure of using meaningful context to predict related items – over a shorter and a longer time interval (attention-dependent).

Results: Compared to controls, CHR patients had significantly smaller P3a amplitudes (d=0.62, p=0.03) and N400 priming effects over the long interval (d=0.64, p=0.02). In CHR patients, gamma ASSR evoked power and phase-locking factor were correlated (r=0.41, p=0.03). Reductions in mismatch negativity (MMN) and P3a amplitudes were also correlated (r=-0.36, p=0.04). Moreover, lower gamma ASSR evoked power correlated with smaller MMN amplitudes (r=-0.45, p=0.02). MMN amplitude reduction was also associated with reduced N400 semantic priming over the shorter but not the longer interval (r=0.52, p<0.002).

Conclusions: This pattern of results suggests that, in a subset of CHR patients, impairment in pre-attentional measures of early information processing may contribute to deficits in attention-dependent cognition involving rapid, more automatic processing, but may be independent from pathological processes affecting more controlled or strategic processing. Thus, combining neurophysiological indices of cognitive deficits in different domains offers promise for improving their predictive power as prognostic biomarkers of clinical outcome.

3.2. Introduction

Efforts to prevent schizophrenia have targeted persons at "clinical high risk" (CHR), who are characterized by attenuated psychotic symptoms but do not meet the diagnostic threshold for schizophrenia or another psychotic disorder (Addington and Heinssen, 2012). Approximately 3% of young adults seeking mental health care meet CHR criteria (Loewy et al., 2012). These individuals have a much higher than normal incidence of developing a psychotic disorder, estimated at 32% within three years (Nieman et al., 2014), a relative risk of approximately 400 compared to non-CHR populations (Cannon et al., 2008). Identifying CHR patients and providing them with psychiatric care can improve outcomes and decrease health care costs (Valmaggia et al., 2009) by reducing conversion to psychosis via pharmacological (Fusar-Poli et al., 2014) or psychological treatment (Hutton and Taylor, 2014; van der Gaag et al., 2012). According to a recent meta-analysis, treatment of CHR patients reduces rates of conversion to psychosis by 56% over one year (Schmidt et al., 2015). There is also evidence that such treatment shortens duration of untreated psychosis (Valmaggia et al., 2009) and improves outcomes in those who do develop psychosis (Fusar-Poli et al., 2016).

The ability to predict conversion to psychosis based solely on symptoms, however, is still limited. The majority of CHR patients will not go on to develop psychosis, but their psychiatric follow-up requires substantial time and cost to the person and the mental health-care system, and carries the risk of treatment side effects and stigmatization (Yang et al., 2010). Therefore, in order to target interventions toward individuals at highest imminent risk, and to provide patients with better prognostic information, it is crucial to seek additional predictors for conversion to psychosis in CHR patients (Schmidt et al., 2017). In this context, Cannon et al. (2016) found that an algorithm combining five demographic, clinical, and neuropsychological variables – younger age, higher levels of unusual thought content and suspiciousness, verbal learning and memory deficits, slower processing speed, and social functional decline – had 48% positive predictive value for conversion to psychosis over two years' follow-up.

Neurophysiological indices have also shown potential for predicting development of psychosis in CHR patients. These indices are objective and rater-independent, and could be useful either alternatively or adjunctively to clinical or neuropsychological measures (Javitt et

al., 2008). One neurophysiological technique that has been used to index cognition in CHR patients is that of electroencephalographic event-related potentials or ERPs (reviewed in Lepock et al., 2018), which non-invasively measure voltage changes at the scalp associated with cognitive events such as stimuli or responses, reflecting synchronous postsynaptic activity of groups of cortical pyramidal neurons (Luck, 2005).

In this context, the auditory mismatch negativity (MMN) ERP waveform has been shown to reliably predict CHR individuals' risk of developing a psychotic disorder (Bodatsch et al., 2015; Bodatsch et al., 2011; Perez et al., 2014). The MMN is a negative-going voltage deflection occurring approximately 150 ms after rare (deviant) auditory stimuli interspersed among frequent (standard) ones – e.g., rare long-duration tones among frequent short tones. Importantly, the MMN is elicited even in the absence of directed attention, e.g., when tones are played in the background while the subject is watching a silent movie (Naatanen et al., 1989). Thus, the MMN is regarded as a robust probe of pre-attentional information processing (Naatanen et al., 1989). In unattended stimulus paradigms, the MMN is typically followed by a positive waveform, the P3a, which is thought to reflect automatic re-orienting of attention (Light et al., 2007; Squires et al., 1975). MMN amplitude reductions are a robust finding in schizophrenia patients (Javitt et al., 2008; Light et al., 2015), in whom they have been found to correlate with impairment in multiple clinical, cognitive and psychosocial domains (Fisher et al., 2014; Hamilton et al., 2018; Kawakubo and Kasai, 2006; Kawakubo et al., 2006; Kiang et al., 2007b; Light and Braff, 2005b; Rissling et al., 2014; Rowland et al., 2016; Wynn et al., 2010). In this context, Thomas et al. (2017) demonstrated evidence that impairments in the MMN-P3a response complex "cascade" forward to produce cognitive deficits, which in turn impact clinical symptoms and real-world function in a large cohort of schizophrenia patients. Along these lines, in the CHR state, a reduced ability at the neural level to distinguish novel features of the environment from their background at early stages of cognitive processing, as indexed by MMN-P3a, could predispose to psychotic symptoms such as misinterpretations of one's surroundings; or to milder prodromal symptoms such as perceptual illusions or the experience of ordinary stimuli as unusually intense, distracting or salient (Jahshan et al., 2012; Javitt and Freedman, 2015; Javitt and Sweet, 2015). Consistent with this view, MMN amplitude has been found across most studies to be smaller than normal in CHR patients (reviewed in Lepock et al., 2018); although one recent, relatively large study did not find such a difference (Atkinson et al., 2017). MMN amplitude deficits may

reflect a neurochemical risk factor for psychosis, such as NMDA receptor dysfunction, which has been linked to both MMN reductions (Umbricht et al., 2000) and psychotic symptoms (Krystal et al., 1994). A recent meta-analytic review concluded that, of ERP measures studied to date as potential predictors of conversion to psychosis in CHR patients (including also P50/N100 sensory gating and P300 amplitude), evidence is strongest for the MMN in this regard (Bodatsch et al., 2015). Conversely, less abnormal MMN amplitudes appear to predict symptomatic improvement, recovery and remission in CHR patients (Kim et al., 2018).

There are other ERP measures that have been found to be abnormal in CHR individuals but whose predictive value for forecasting psychosis in this population is unknown. One example is the gamma band auditory steady-state response (ASSR). The ASSR is elicited by rhythmic auditory stimulation – e.g., a series of clicks at a given frequency – and manifests as an increase in electroencephalogram (EEG) power at that frequency, reflecting entrainment of oscillatory neural activity to the stimuli (O'Donnell et al., 2013; Picton et al., 2003). The ASSR does not require attention to the stimuli although it is larger when they are attended (Griskova-Bulanova et al., 2011). The component of this power increase that is phase-locked to the stimuli can be measured by "evoked power" (power of the average EEG response over multiple stimulus trials, which cancels out non phase-locked activity), and by intertrial phase coherence (ITC) or "phase-locking factor" (PLF) of the EEG response (Kirihara et al., 2012; Light et al., 2006). Gamma (40-Hz) ASSR evoked power and PLF have been found across studies to be less than normal in schizophrenia (Kwon et al., 1999; Light et al., 2006; O'Donnell et al., 2013; Spencer et al., 2008) and these deficits have been reported to correlate with symptom severity (Tada et al., 2016). Convergent evidence from animal models and neurochemical and behavioral studies, suggest that these abnormalities of gamma synchrony result from dysfunction of parvalbumin-expressing GABAergic inhibitory interneurons and contribute to cognitive impairment (Gonzalez-Burgos et al., 2016). A few studies have also reported gamma ASSR deficits in CHR patients (Koshiyama et al., 2018; Tada et al., 2016). Thus, further study is warranted to test whether these deficits predict risk of conversion to psychosis in CHR individuals.

In contrast to measures that reflect largely pre-attentive functions in response to simple sensory stimuli, the N400 is a negative-going waveform occurring around 400 ms after any semantic (meaningful) stimulus such as a word or a picture that is also abnormal in

schizophrenia and CHR patients. Normally, N400 amplitude is smaller (less negative) when the eliciting stimulus is more related to preceding ones (Holcomb and McPherson, 1994; Holcomb and Neville, 1990; Kutas and Hillyard, 1980). Thus, after seeing the prime word *CAT*, individuals exhibit a smaller N400 to the related target word *MOUSE* than the unrelated word *ARROW*. These "N400 semantic priming effects" are thought to reflect use of context to predict upcoming items by pre-activating neural representations of related concepts in long-term semantic memory, our store of knowledge about the world (DeLong et al., 2005; Kutas and Federmeier, 2000). On this view, greater activation of a concept results in facilitated processing of corresponding stimuli, as indexed by smaller N400 amplitudes (Kutas and Federmeier, 2011). The N400 has thus been used as a neurophysiological probe of abnormal semantic processing in schizophrenia. Numerous studies have found larger (more negative) than normal N400s to targets that are related to preceding primes, and/or smaller than normal N400 semantic priming effects, in schizophrenia, at least when the time between the occurrence of the prime and target (i.e., stimulus-onset asynchrony; SOA) is approximately 400 ms or more (reviewed in Mohammad and DeLisi, 2013; Salisbury, 2008). These results suggest that schizophrenia patients are unable to use meaningful context to activate or maintain related concepts in semantic memory normally. In contrast, results from studies using shorter prime-target SOAs have been more mixed, with some finding reduced N400 semantic priming, and others reporting increased priming. The latter subset of studies predominantly examined patients with disorganized speech, and employed implicit tasks; along with short prime-target SOAs, these characteristics are thought to engage more automatic rather than controlled or strategic processing. Taken together, these results point to a generalized deficit of semantic priming in patients with schizophrenia, that exists alongside automatic hyperpriming in disorganized patients specifically (Kuperberg et al., 2010; Mohammad and DeLisi, 2013).

Some studies have found that smaller than normal N400 semantic priming effects in schizophrenia are associated with delusions (Besche-Richard et al., 2014; Kiang et al., 2007a, 2008; Salisbury et al., 2000), and improved by antipsychotic treatment (Besche-Richard et al., 2014; Condray et al., 1999; Debruille et al., 2013), indicating that they may be a biomarker of delusional ideation. Recently we have also found N400 semantic priming deficits in CHR patients at a longer (750 ms) but not a shorter (300 ms) SOA (Lepock et al., 2019). It is not yet known, however, whether N400 priming deficits predict conversion to psychosis in the CHR

state. This is plausible given that they are associated with schizophrenia, and that neuropsychological and fMRI measures of semantic processing have been found to be predictive in this regard (Bearden et al., 2011; Sabb et al., 2010).

Because different neurophysiological biomarkers of schizophrenia generally show low cross-correlation (Hall et al., 2006; Hamilton et al., 2018; Price et al., 2006), likely reflecting distinct pathological processes that can separately contribute to psychosis, these biomarkers may be most sensitive for diagnostic or prognostic purposes when used in combination (Javitt et al., 2008; Price et al., 2006). Therefore, additional research is warranted to examine putative ERP biomarkers of psychosis in the same at-risk cohort to elucidate their interrelationships and relative effect sizes, which could help inform efforts to develop multivariate phenotypes that improve psychosis prediction (Bodatsch et al., 2015). Thus, ERP measures that are highly correlated may be unlikely to individually add independent predictive value to a prognostic model. Moreover, measures that are more reliably abnormal in both the schizophrenia and CHR populations may be the most promising candidates for predicting progression to psychosis within CHR samples.

In the present study, we examined gamma ASSR evoked power and PLF, MMN and P3a amplitudes, and N400 semantic priming effects, in antipsychotic-naïve CHR patients. We selected this combination of ERP measures because they have been previously found to be abnormal in both schizophrenia and the CHR state, and represent a range of cognitive functions in the form of early sensory, pre-attentive, and higher-order attention-dependent cognitive processing, respectively. Because deficits in ASSR gamma synchrony are proposed to index parvalbumin-expressing GABAergic interneuron dysfunction which is related to NMDA-receptor hypofunction in a feedback loop (Hirano et al., 2015; Jadi et al., 2016; Koshiyama et al., 2018; O'Donnell et al., 2013), and the latter abnormality is also thought to cause MMN deficits, we hypothesized that ASSR evoked power and PLF would correlate with MMN amplitude across patients. Further support for this hypothesis comes from recent findings that MMN amplitude was correlated with PLF in recent-onset schizophrenia patients (although not in CHR patients) (Koshiyama et al., 2018); and that memantine, an NMDA receptor antagonist, improved deficits in MMN as well as gamma ASSR evoked power and PLF in schizophrenia patients, and these improvements were correlated (Light et al., 2017).

In contrast, we did not expect that N400 semantic priming effects would be associated with MMN or P3a amplitude, or gamma ASSR evoked power or PLF. To examine more automatic versus more controlled semantic priming, N400 effects were assessed over both a shorter and a longer interval following the prime stimulus, i.e., at a 300-ms and a 750-ms prime-target SOA, respectively. The correlation between N400 effects and the other ERP measures have not, to our knowledge, been previously examined in schizophrenia or CHR patients. However, a recent study found that schizophrenia patients' MMN amplitude deficits in an unattended paradigm were not correlated with their deficits in P3b amplitude in an oddball task (Hamilton et al., 2018), which, like N400 semantic priming effects, (Bentin et al., 1995; Brown and Hagoort, 1993) are a measure of attention-dependent, higher-order cognition. This result provided evidence that schizophrenia patients' neurophysiological abnormalities in attention-dependent processing may be independent of abnormalities in pre-attentive processing. Thus, we did not expect that N400 priming effects would be correlated with MMN amplitude or gamma ASSR measures in our CHR sample.

3.3. Materials and Methods

3.3.1. Participants

Participants included 36 CHR patients and 22 healthy control participants (HCPs). Twenty of the CHR participants were included in a previous report on N400 effects in this population (Lepock et al., 2019). CHR participants were help-seeking patients referred to the Focus on Youth Psychosis Prevention outpatient clinic at the Centre for Addiction and Mental Health (CAMH) in Toronto. HCPs were recruited from the community by advertising online, in newspapers, and on bulletin boards. The study was approved by the CAMH Research Ethics Board and all participants gave written informed consent. Participants received cash compensation.

CHR individuals met diagnostic criteria for a psychosis-risk syndrome, namely the Criteria of Psychosis-Risk States based on the Structured Interview for Psychosis-Risk Syndromes (SIPS) (McGlashan et al., 2014); had no history of current or lifetime DSM-IV-TR

Axis I psychotic disorder, or mood disorder with psychotic features (American Psychiatric Association, 2000), as determined via the Structured Clinical Interview for DSM-IV-TR (SCID) (First et al., 2015); had no history of DSM-IV substance abuse or dependence in the last 6 months (except nicotine); and were antipsychotic-naive. HCPs did not have any current or past DSM-IV psychiatric diagnoses as determined via the SCID, or any first-degree relatives with a history of psychotic disorder, and were not currently taking psychotropic medication. Other exclusion criteria for all participants included: visual or hearing impairment; having learned English after age 5 (for the N400 procedure only); reading disability; and lifetime self-reported neurological disorder. Table 1 shows group demographic, neuropsychological and clinical characteristics.

3.3.2. Stimuli and tasks

3.3.2.1. Gamma ASSR stimuli and task

Following established methods (Kirihara et al., 2012; Light et al., 2006), participants passively heard 1-ms, 93-dB clicks presented at 40 Hz in 500-ms trains. The stimulus block consisted of 200 trains of clicks with 500-ms intertrain intervals.

3.3.2.2. MMN/P3a stimuli and task

Similar to established methods (Kiang et al., 2009; Light and Braff, 2005a; Light et al., 2015; Takahashi et al., 2013; Thomas et al., 2017), participants were presented with 1800 binaural tones (1-kHz 85-dB, with 1-ms increase/decrease) with SOA of 500 ms. Standard (P = .90, 50-ms duration) and deviant (P = .10, 100-ms duration) tones were presented in pseudorandom order through foam insert earphones (Model ER-3C, Etymotic Research, Elk Grove Village, IL). During the session, participants watched a silent, benign cartoon video to divert attention from the tones.

3.3.2.3. N400 stimuli and task

These were the same as those used by Kiang et al. (2014), and included 80 related (e.g., *METAL-STEEL*) and 80 unrelated (*DONKEY-PURSE*) prime-target word pairs. For each related pair, the target was among the words most commonly given as associates to the prime by

participants in the University of South Florida word-association norms (Nelson et al., 1998); mean response probability of related targets (i.e., proportion of individuals producing that word in response to the prime) was 0.61 (SD=0.12). For each unrelated pair, prime and target were not associates in the norms. Across these conditions, targets were matched for mean length and log-transformed frequency (Francis and Kucera, 1982), and primes were also matched on these parameters. Stimuli also included 160 pairs with word primes and pronounceable nonword targets (*DRESS-ZORES*). No word occurred more than once among the stimuli.

The stimulus list included all prime-target pairs in fixed randomized order, in four blocks of 80 trials each. The list had two versions, each one administered to half the participants, in which the order of prime-target SOAs across blocks was counterbalanced. In version A, SOA was 300 ms in blocks 1 and 2, and 750 ms in blocks 3 and 4; in version B, order of SOAs was reversed. Each participant was presented with stimuli on a video monitor. Each trial consisted of: (a) row of preparatory fixation crosses for 500 msec; (b) blank screen for 250 msec; (c) prime word for 175 msec; (d) blank screen for 125 msec (in 300-msec SOA trials) or 575 msec (in 750-msec SOA trials); (e) target for 250 msec; (f) blank screen for 1250 msec; (g) prompt Yes or No? until participants responded via button-press; and (h) blank screen for 3000 msec until onset of the next trial. At the prompt, participants were required to press one of two buttons, positioned under their right and left thumbs. One button (labeled "Yes") signaled that prime and target were related; the other button ("No") signaled that they were not. Assignment of buttons was divided equally among participants, counterbalanced across the two stimulus list versions.

3.3.3. EEG collection and analysis

3.3.3.1. General procedures

Each participant completed the above tasks during the same test session, in the following order: N400, MMN, ASSR. During these tasks, continuous EEG was recorded using an actiCHamp amplifier (Brain Products, Gilching, Germany), from 32 active Ag/AgCl electrodes embedded in a cap (actiCAP system, Brain Products) at sites approximately equally spaced across the scalp, positioned according to a modified International 10-20 System (Fp1-Fp2-F7-F3-Fz-F4-F8-FC5-FC1-FC2-FC6-T7-C3-Cz- C4-T8-TP9-CP5-CP1-CP2-CP6-TP10-P7-P3-Pz-P4-P8-PO9-O1-Oz-O2-PO10). Electrode impedances were kept below 25 kΩ. The EEG was

referenced online to FCz, and continuously digitized at 500 Hz. Blinks and eye movements were monitored via electrodes on the supraorbital and infraorbital ridges and on the outer canthi of both eyes. Offline, the EEG was re-referenced to the algebraic mean of the mastoids, and bandpassed at 0.5-100 Hz for gamma ASSR analyses, and 0.25-60 Hz for N400 and MMN/P3a analyses. Continuous data were algorithmically corrected for eyeblink artifact (Makeig et al., 1997). Individual trials containing artifacts due to eye movement, excessive muscle activity or amplifier blocking were rejected offline by visual inspection before time-domain averaging. Gamma ASSR data from three patients and two controls, and MMN/P3a data from two patients were excluded due to excessive artifact.

3.3.3.2. Gamma ASSR analysis

Similar to established methods (Light et al., 2006; Spencer et al., 2008), to obtain ASSR gamma evoked power, the Morlet wavelet transform was applied to single-trial epochs in 1 Hz steps from 1-100 Hz at each time point from -200 to 800 ms. Evoked power was measured as mean power at 40 Hz (wavelet frequency 33-47 Hz) of the average evoked potential from 0 to 500 ms, after subtracting prestimulus baseline values (-100 to 0 ms). Gamma PLF was measured as (1 – the circular variance of phases) at 40 Hz, and ranges from 0 (random distribution of phases) to 1 (perfect phase locking). For gamma ASSR evoked power, five patient and three control participants had values that were outliers (1.5 × the interquartile range above the third quartile or below the first quartile) and these were excluded from further analyses. For gamma ASSR PLF, one patient and one control participant were outliers and were excluded.

3.3.3.3. MMN/P3a analysis

ERPs were computed for epochs from 100 msec pre-stimulus to 500 msec post-stimulus. ERP waveforms were generated by averaging responses to standard and deviant tones, respectively. MMN/P3a waveforms were generated by subtracting the average for standard tones from the average for deviant tones. Following established methods (Kiang et al., 2009; Light and Braff, 2005a; Light et al., 2015; Takahashi et al., 2013), MMN and P3a amplitudes were measured as mean voltage from 135 to 205 ms, and 250 to 300 ms, respectively.

3.3.3.4. N400 analysis

ERPs were computed for epochs from 100 msec pre-stimulus to 900 msec post-stimulus. For each participant, separate ERP averages were obtained for trials with related and unrelated targets at each SOA. The N400 semantic priming effect was defined as mean voltage of the difference wave obtained by subtracting the average for related trials from the average of unrelated trials, from 300-500 msec post stimulus-onset, consistent with previous methods (Federmeier and Kutas, 2005; Kiang et al., 2010; McLaughlin et al., 2004).

3.3.3.5 Statistical analysis

N400 effects at the 300-ms and 750-ms SOAs at Cz (where these effects were maximal); MMN and P3a amplitudes at Fz (where these were maximal); and gamma ASSR evoked power and PLF at Fz (consistent with previous analyses (Light et al., 2006)) were compared between CHR patients and HCPs using independent-samples *t*-tests. To examine relationships between the above variables in the CHR group, pairwise Pearson correlation coefficients *r* among these variables. A significance level of α=0.05 (two-tailed) was used for all tests.

3.4. Results

3.4.1. ERP grand averages

Grand averages for CHR and HCP groups are shown for ASSR evoked power in Fig. 1, gamma ASSR PLF in Fig. 2, MMN and P3a ERPs in Fig. 3, and N400 ERPs in Fig. 4. Mean values and between group effect sizes for these measures for the two groups are shown in Table 2.

In contrast to our expectations, gamma ASSR evoked power ($t(42)=0.86$, $p=0.39$) and PLF ($t(48)=0.27$, $p=0.79$) did not differ between groups. Although MMN amplitudes also did not differ between the groups ($t(53)=1.13$, $p=0.26$), P3a amplitudes were significantly smaller in patients than controls ($t(53)=2.24$, $p=0.029$). N400 effects were smaller (less negative) for patients than controls at the 750-ms SOA ($t(55)=2.41$, $p=0.020$), but did not differ between the groups at the 300-ms SOA ($t(55)=0.83$, $p=0.41$). The between group differences in P3a amplitudes and N400 effects at the 750-ms SOA remained significant after controlling for

multiple comparisons using the Benjamini-Hochberg procedure with false discovery rate of 0.15 (Benjamini and Hochberg, 1995).

3.4.2. Correlations between ERP measures

Pairwise Pearson correlation coefficients *r* among the above ERP measures for the CHR patient group are shown in Table 3. As hypothesized, lower gamma (40-Hz) ASSR evoked power was correlated with smaller (less negative) MMN amplitudes. Contrary to our hypothesis, 40-Hz ASSR PLF was not correlated with MMN amplitude. In addition, 40-Hz evoked power and PLF were significantly correlated with one another, and smaller (less negative) MMN amplitudes correlated with smaller (less positive) P3a amplitudes. We did not expect that N400 semantic priming effects would correlate with pre-attentive ERP measures, and consistent with this, N400 semantic priming effects were not significantly correlated with other pre-attentive ERP measures, including P3a amplitudes and 40-Hz ASSR evoked power and PLF.

In contrast and unexpectedly, smaller N400 semantic priming effects (i.e., smaller differences between related and unrelated targets) at the short SOA (but not the long SOA) were significantly correlated with smaller MMN amplitudes. The correlations reported as significant above remained so after controlling for multiple comparisons using the Benjamini-Hochberg procedure with false discovery rate of 0.15 (Benjamini and Hochberg, 1995).

Pairwise Pearson correlation coefficients *r* among the above ERP measures for the healthy control group are shown in Table 4. The pairs of ERP measures which were correlated in the CHR group were not significantly correlated in the control group, with the exception of 40-Hz evoked power and PLF, which were also significantly correlated in the control group.

3.5. Discussion

This study investigated the relationships among leading candidate neurophysiological biomarkers of early sensory, pre-attentive, and higher-order attention-dependent cognitive processing in a sample of antipsychotic-naïve, help-seeking CHR patients. These measures included auditory gamma ASSR evoked power and PLF (early sensory), MMN and P3a

amplitudes (pre-attentive), and N400 semantic priming effects (attention-dependent). N400 effects were assessed at both a 300-ms and a 750-ms prime-target SOA to probe semantic priming over a shorter and a longer time interval after a prime stimulus, respectively. We found that, compared to HCPs, CHR patients had smaller P3a amplitudes, and smaller N400 semantic priming effects (smaller N400 amplitude differences between related and unrelated targets) at the long SOA. Within the CHR group, smaller MMN amplitudes were significantly correlated with lower gamma (40-Hz) ASSR evoked power, smaller P3a amplitudes, and smaller N400 semantic priming effects at the short SOA.

All of the above ERP measures have previously been reported to be reduced in schizophrenia and CHR patients. Not all the measures, however, were reduced in our sample. P3a amplitude and N400 priming effects at the long SOA were smaller in CHR patients than HCPs; while gamma ASSR evoked power and PLF, MMN amplitude, and N400 priming effects at the short SOA did not differ between groups. This reflected larger effect sizes of the between group differences in P3a amplitude (d=0.62) and N400 semantic priming at the long SOA (d=0.64) compared to the other measures. Of these measures, MMN has been studied most extensively in CHR individuals. Studies comparing CHR individuals with controls have obtained a wide range of between group effect sizes, from 0 to 0.96 (Atkinson et al., 2017; Lepock et al., 2018; Nagai et al., 2013); the effect size detected in the present cohort (d=0.32) was within this range. Variation in effect sizes across studies could be due to differences in duration or severity of illness, recruitment methods, or medication status. Importantly, the present study included only antipsychotic-naïve patients whereas some studies included patients on antipsychotics. Future studies are needed to determine the impact of antipsychotic medications on neurophysiological biomarkers and conversion to psychosis in CHR patients. Likewise, other studies that have reported on both auditory MMN and P3a amplitude elicited in a duration deviant paradigm have variously found that effect sizes for patients' deficits were larger (Jahshan et al., 2012), similar (Atkinson et al., 2017; Atkinson et al., 2012) or smaller (Nagai et al., 2013) for P3a compared to MMN. Taken together, these results suggest that there is wide variability between CHR samples in the degree of abnormality of both MMN and P3a amplitude, and further study is needed to ascertain whether P3a is a more sensitive biomarker for psychosis risk than MMN.

We found that CHR patients had smaller N400 semantic priming effects than controls at the 750-ms SOA, with a moderate to large effect size of d=0.64 (Cohen, 1988). Although this result requires further replication, it suggests that this measure of attention-dependent cognitive processing may be a relatively sensitive biomarker for the CHR state. The effect size we found for this N400 semantic priming at the long SOA is comparable to effect sizes that a recent large study found for CHR patients' deficits in neuropsychological measures involving verbal tasks, including verbal working memory (Letter Number Sequencing, d=0.40); verbal short-term memory (Digit Span, d=0.48; California Verbal Learning Test – Immediate Recall, d=0.44); and semantic set-shifting (Verbal Fluency Test – Category Switching Accuracy, d=0.56) (Atkinson et al., 2017). Semantic priming at this relatively long SOA is thought to predominantly reflect relatively controlled or strategic use of context to activate related items in semantic memory, in contrast to priming at a shorter SOA, which reflects more rapid and automatic spread of activation to related items (Kuperberg et al., 2010; Mohammad and DeLisi, 2013), and which did not differ between CHR patients and controls in our study. Thus, at this early stage of the psychotic illness trajectory, CHR patients may be relatively intact in more automatic semantic priming but present with impairment in more controlled processing of semantic relationships.

In the CHR group, smaller MMN amplitudes were associated with reductions in several other ERP measures – namely, gamma ASSR evoked power, P3a amplitude, and N400 semantic priming effects at the short SOA. Although none of these measures were significantly smaller in CHR patients than controls, their correlations with MMN suggest that the latter may index a core neurophysiological deficit present in those at highest risk of progressing to schizophrenia. These correlations were specific to CHR patients and not present in controls, further supporting a link to a pathophysiological process. A link between MMN and gamma ASSR evoked power is in line with the findings of Light et al. (2017) that the NMDA receptor antagonist memantine improved deficits in MMN as well as gamma ASSR evoked power and PLF in schizophrenia patients, and these improvements were correlated. This result also accords with the view that deficits in ASSR gamma synchrony index parvalbumin-expressing GABAergic interneuron dysfunction which is related to NMDA-receptor hypofunction in a feedback loop (Hirano et al., 2015; Jadi et al., 2016; Koshiyama et al., 2018; O'Donnell et al., 2013).

The correlation we found between MMN and P3a amplitude reductions in the CHR group is consistent with some but not all previous reports. Earlier studies have found divergent results that these variables were correlated in controls but not in CHR patients (Atkinson et al., 2012), or were not correlated in either group (Nagai et al., 2013). However, a recent study with a much larger sample found a correlation between MMN and P3a amplitudes in CHR patients but not controls (Atkinson et al., 2017), consistent with our results. Moreover, a large study of schizophrenia patients found that their MMN and P3a deficits were correlated (Light et al., 2015). These findings suggest that common factors may underlie deficits in both of these indices of pre-attentive sensory discrimination in the schizophrenia spectrum, including in a subset of CHR patients who are most at risk.

We found an unexpected correlation in the CHR group between smaller MMN amplitudes and smaller N400 semantic priming effects at the short (but not the long) prime-target SOA. Although there is convergent evidence that glutamatergic dysfunction causes MMN deficits (Javitt et al., 2008; Light and Naatanen, 2013), there have been few studies of the effect of glutamatergic modulation on the N400. Ketamine was found to reduce N400 priming for repeated stimuli (Grunwald et al., 1999), and the NMDA receptor antagonist memantine was found to improve this priming in patients with fragile X-associated tremor/ataxia syndrome, which is associated with overactivity of this receptor (Yang et al., 2014). Thus, a common glutamatergic dysfunction may underlie reductions in both MMN amplitude and N400 semantic priming over shorter intervals. Although our results require replication, they indicate that this common dysfunction may underlie deficits in earlier, more automatic semantic priming, but be unrelated to deficits in later, more strategic priming processes.

A limitation of the present study was its moderate sample size. This may have been insufficient to detect differences in ERP measures between CHR patients and controls with small to medium effect sizes. Another limitation was the cross-sectional nature of the study. Although we found correlations between ERP measures, the cross-sectional design did not allow examination of the relative developmental trajectories of reductions in these measures over the course of the pre-psychotic disease process. Longitudinal studies are needed to clarify these relative trajectories, which could provide further evidence to support causal relationships between the cognitive deficits indexed by these measures.

In summary, we found that in CHR patients, reductions in MMN amplitude were associated with reductions in two other measures of pre-attentive early auditory processing, gamma ASSR evoked power and P3a amplitude; and with reductions in N400 semantic priming effects, an index of attention-dependent higher-order cognition, over a shorter but not a longer time interval. Overall, these results suggest that MMN may index a core neurophysiological abnormality present in CHR individuals at highest risk of progressing to schizophrenia, which in turn contributes to deficits in attention-dependent cognitive processes that are relatively rapid and automatic. We did not find evidence that MMN reductions were associated with CHR patients' N400 semantic priming deficits over a longer time interval, which are thought to index dysfunction in more controlled or strategic processing. This finding suggests that further, longitudinal study is warranted to examine whether N400 semantic priming at a long SOA may add predictive power to CHR prognostic algorithms that include the MMN.

Table 3.1. Demographic, neuropsychological, and clinical characteristics of the study sample (means ± SD given for continuous variables).

	Healthy Controls (*n*=21)	**Clinical High-Risk Patients (*n*=36)**
Age (years)	21.7±3.0	21.3±3.4
Sex	13 female, 8 male	12 female, 24 male
Handedness	18 right, 2 left	18 right, 2 left
Parental socioeconomic status (Blishen et al., 1987)	53.8 ± 13.0	49.3 ± 15.2
Years of education[a]	15.6 ± 2.5	14.2 ± 2.3
National Adult Reading Test (Nelson and Willison, 1991) estimated premorbid verbal IQ	109.9 ± 6.3	110.2 ± 7.1
Scale of Psychosis-Risk Symptoms, based on the Structured Interview for Psychosis-Risk Syndromes (McGlashan et al., 2014)		
Positive Scale Total	-	10.3 ± 3.6
Negative Scale Total	-	13.1 ± 4.9
Disorganized Scale Total	-	5.5 ± 3.6
General Scale Total	-	9.0 ± 4.4

[a]Patients differed significantly from controls, p=0

Table 3.2. Event-related potential measures for the healthy control and clinical high-risk groups (means ± SD), at the indicated electrode sites, and Cohen's effect sizes (d) for the differences between groups.

	Healthy Controls	**Clinical High-Risk Patients**	**Cohen's effect size *d***
Gamma (40-Hz) auditory steady-state response, Fz			
Evoked power, (μV^2)	0.65 ± 0.41 (n=16)	0.85 ± 0.88 (n=28)	0.29
Phase-locking factor	0.28 ± 0.15 (n=18)	0.29 ± 0.15 (n=32)	0.07
MMN amplitude, Fz (μV)	-5.43 ± 2.20 (n=21)	-4.64 ± 2.68 (n=34)	0.32
P3a amplitude, Fz (μV)[a]	4.24 ± 2.81 (n=21)	2.55 ± 2.66 (n=34)	0.62
N400 semantic priming effect, Cz (μV)			
300-ms stimulus-onset asynchrony (SOA)	-2.19 ± 2.73 (n=21)	-1.43 ± 3.63 (n=36)	0.24
750-ms SOA[b]	-2.90 ± 3.63 (n=21)	-0.81 ± 2.86 (n=36)	0.64

[a]Patients differed significantly from controls, p=0.03.

[b]Patients differed significantly from controls, p=0.02.

Table 3.3. Pearson correlation coefficients r between ERP variables, for the clinical high-risk patient group.

Variables	1	2	3	4	5	6
1. Gamma (40-Hz) auditory steady-state response evoked power	-					
2. Gamma (40-Hz) auditory steady-state response phase-locking factor	0.41[a] (n=28)	-				
3. MMN amplitude	-0.45[b] (n=27)	-0.31 (n=31)	-			
4. P3a amplitude	-0.20 (n=27)	0.06 (n=31)	-0.36[c] (n=34)	-		
5. N400 semantic priming effect, 300-ms stimulus-onset asynchrony (SOA)	-0.18 (n=28)	0.15 (n=32)	0.52[d] (n=34)	-0.19 (n=34)	-	
6. N400 semantic priming effect, 750-ms SOA	0.19 (n=28)	0.08 (n=32)	-0.07 (n=34)	0.01 (n=34)	0.14 (n=36)	-

[a] p=0.03

[b] p=0.02

[c] p=0.04

[d] p=0.002

Table 3.4. Pearson correlation coefficients r between ERP variables, for the healthy control group.

Variables	1	2	3	4	5	6
1. Gamma (40-Hz) auditory steady-state response evoked power	-					
2. Gamma (40-Hz) auditory steady-state response phase-locking factor	0.75[a] (n=19)	-				
3. MMN amplitude	0.08 (n=19)	0.06 (n=19)	-			
4. P3a amplitude	-0.02 (n=19)	-0.07 (n=19)	-0.33 (n=21)	-		
5. N400 semantic priming effect, 300-ms stimulus-onset asynchrony (SOA)	0.53[b] (n=19)	0.34 (n=19)	0.15 (n=21)	0.06 (n=21)	-	
6. N400 semantic priming effect, 750-ms SOA	-0.12 (n=19)	-0.40 (n=19)	0.10 (n=21)	0.12 (n=21)	0.30 (n=21)	-

[a] p=0.0002

[b] p=0.02

Figure 3.1. Time-frequency maps of auditory steady-state electroencephalogram response evoked power at electrode site Fz (midline frontal), for the clinical high-risk patient and healthy control participant groups, in response to 40-Hz stimulation.

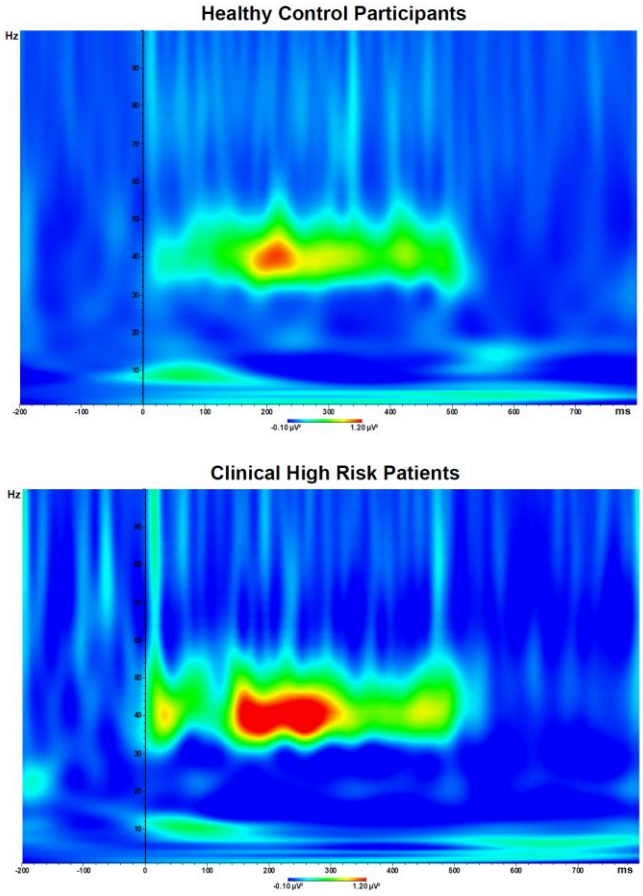


Figure 3.2. Phase locking factor (PLF) time series from the auditory steady-state electroencephalogram response at electrode site Fz (midline frontal), for the 40-Hz frequency, for the clinical high-risk patient and healthy control participant groups.

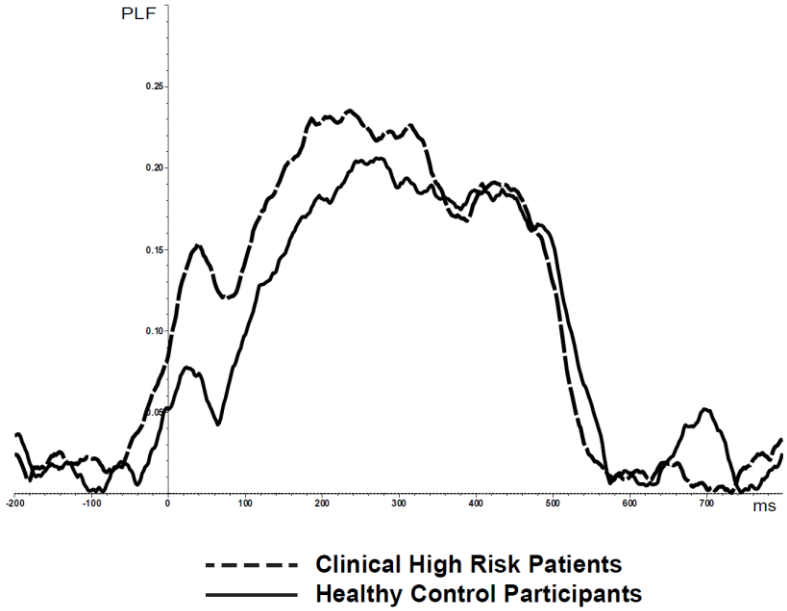


Figure 3.3. Grand average event-related potential (ERP) difference waves, formed by subtracting the average ERP elicited by standard (50-ms duration) tones from the average ERP elicited by deviant (100-ms duration) tones, for the clinical high-risk patient and healthy control participant groups, at electrode site Fz (midline frontal).

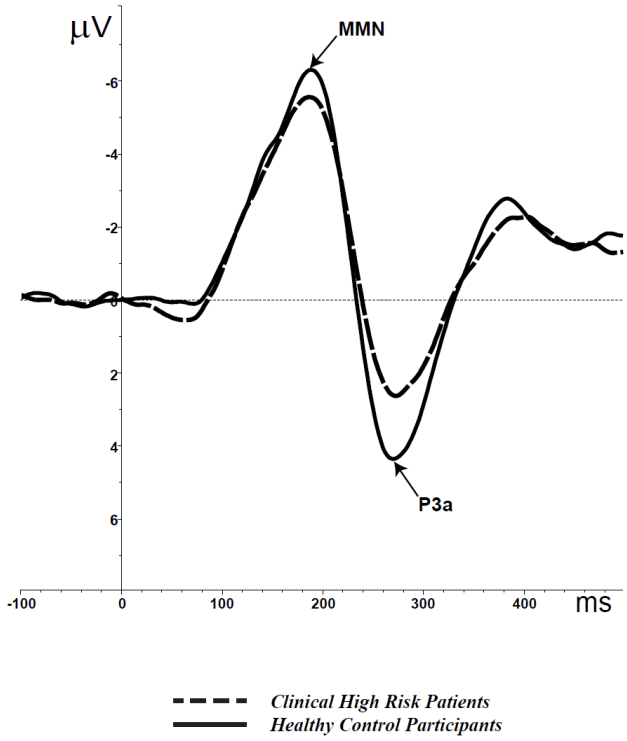
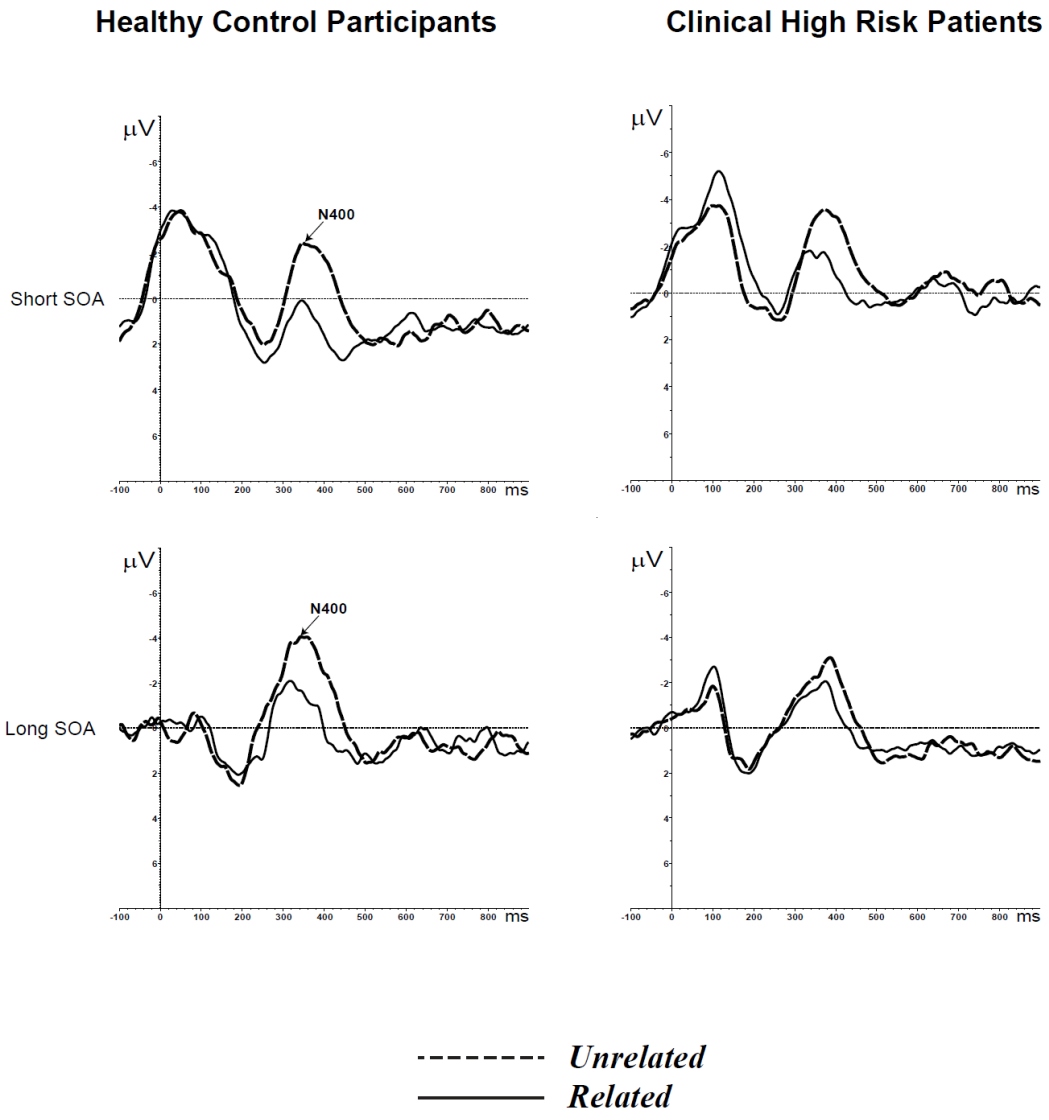


Figure 3.4. Grand average event-related potentials elicited by target words related and unrelated to a preceding prime word, shown for the clinical high-risk patient and healthy control participant groups, in the 300-ms and 750-ms prime-target stimulus-onset asynchrony (SOA) conditions, at electrode site Cz (midline central).



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Chapter 4

Experiment 3 - The N400 event-related brain potential as an index of real-world and neurocognitive function in patients at clinical high risk for schizophrenia

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4.1. Abstract

Background: The N400 event-related potential is a neurophysiological index of cognitive processing of real-world knowledge. In healthy populations, N400 amplitude is smaller in response to stimuli that are more related to preceding context. This "N400 semantic priming effect" is thought to reflect use of context to activate related information in semantic memory (SM), facilitating processing of such information. N400 semantic priming deficits have been found in schizophrenia, and in patients at clinical high risk (CHR) for this disorder, suggesting impairment in activating related concepts in SM. Because this abnormality in processing relationships between meaningful stimuli could affect ability to navigate everyday situations, we hypothesized it would be associated with real-world functional impairment in CHR patients. Secondarily, we hypothesized it would be associated with global neurocognitive impairment in this group.

Method: We measured N400 semantic priming in 35 CHR patients who viewed prime words each followed by a related or unrelated target word, at stimulus-onset asynchrony (SOA) of 300 or 750 ms. We measured academic/occupational and social function with the Global Function (GF): Role and Social scales, and cognitive function with the MATRICS Consensus Cognitive Battery (MCCB).

Results: Decreased N400 semantic priming at the 300-ms SOA correlated with lower GF:Role scores. Decreased N400 semantic priming at the 750-ms SOA correlated with lower MCCB composite scores.

Conclusions: Deficits in activating contextually related concepts in SM over short time intervals may contribute to functional impairment in CHR patients. Furthermore, N400 priming deficits over longer intervals may be a biomarker of global cognitive dysfunction in this population.

4.2. Introduction

Schizophrenia is a chronic mental disorder which usually first manifests in early adulthood. Its core features include psychotic symptoms (delusions, hallucinations, and disorganized speech and behavior); "negative" symptoms such as amotivation and lack of social interest; and deficits in fundamental cognitive functions such as attention and memory. Schizophrenia has a devastating impact on patients' social and occupational function. For example, the World Health Organization's Global Burden of Disease study found that, worldwide, schizophrenia is the seventh leading cause of years of life lived with disability, and the third leading cause among individuals aged 15 to 44 (Murray and Lopez, 1996). Although antipsychotic medications are the mainstay of treating schizophrenia, they are of only limited effectiveness in countering its associated functional impairment (Harvey et al., 2012). Thus, even with specialized treatment, at 7 years' follow-up after a first-episode of schizophrenia, only 27% of patients were in full-time employment, and only 22% had achieved both vocational and social recovery (Henry et al., 2010). Moreover, antipsychotics have only a modest effect on cognitive deficits in schizophrenia (Keefe et al., 2007a; Keefe et al., 2007b), which are a strong predictor of 'real-world' functional impairment (Shamsi et al., 2011; Torgalsboen et al., 2014). Thus, research that deepens our understanding of the neurophysiological substrates of cognitive and functional impairment in schizophrenia is needed to help identify novel targets for the development of more effective and safer therapies that treat or prevent such impairment.

One neurophysiological index of cognitive processing of 'real-world' knowledge is the N400 event-related brain potential (ERP) waveform. The ERP technique measures voltage changes at the surface of the scalp during cognitive processing, reflecting synchronous activity of cortical pyramidal neurons (Luck, 2005). This direct brain-based measure of cognitive processing is non-invasive, and does not rely on overt behavioral responses, which can be confounded by motor abnormalities in clinical populations. The N400 is an ERP negativity occurring around 400 ms after any potentially meaningful stimulus, and thus can be elicited by written and spoken words, pictures, gestures, videos of everyday events, or environmental sounds (Kutas and Federmeier, 2011). The N400 is broadly distributed across the scalp, and maximal centroparietally (Kutas and Federmeier, 2011). Typically, in healthy populations its amplitude is made smaller (less negative) by factors that activate or prime the corresponding concept, including relatedness to preceding context (Kutas and Federmeier, 2011; Kutas and

Hillyard, 1980). Hence, following the prime word *CAT,* the related target word *MOUSE* elicits a smaller N400 than the unrelated word *ARROW.* These *N400 semantic priming effects* (differences in N400 amplitude between contextually related and unrelated targets) are thought to reflect use of context to predict related items by pre-activating their representations in semantic memory (DeLong et al., 2005; Kutas and Federmeier, 2000). Thus, the N400 is an index of brain processes that make sense of environmental input by using world knowledge to predictively activate related information, which makes such information easier to process if it occurs subsequently (Kutas and Federmeier, 2000).

Researchers have found evidence for attenuated N400 semantic priming effects in patients with schizophrenia (Bobes et al., 1996; Condray et al., 2003; Condray et al., 2010; Ditman and Kuperberg, 2007; Iakimova et al., 2005; Kiang et al., 2012; Kiang et al., 2011; Kiang et al., 2008; Kostova et al., 2005; Kostova et al., 2003; Mathalon et al., 2010; Ohta et al., 1999; Salisbury, 2008; Strandburg et al., 1997), indicating that they have deficits in using meaningful stimuli to selectively pre-activate related concepts in semantic memory (Kiang and Gerritsen, in press). In contrast, a few other N400 studies in schizophrenia found increased semantic priming (Kreher et al., 2008; Mathalon et al., 2002; Salisbury, 2008) – but this appears specific to the combination of weakly related targets, short prime-target time intervals (i.e., *stimulus-onset asynchronies* or SOAs) of <300 ms, and patients with disorganized speech, suggesting that this subset of patients experiences hyperactivation of weakly related concepts over a short period after a meaningful stimulus, when processing is thought to be relatively automatic (Ditman and Kuperberg, 2007; Salisbury, 2008). On balance, however, N400 studies of schizophrenia patients provide evidence of a general reduction in semantic priming at longer time intervals of ≥ 300 ms (see Mohammad and DeLisi, 2013; Wang et al., 2011 for reviews), which could plausibly lead to deficits in linking related concepts, not only in language but also in navigating real-life situations more generally.

Additional evidence suggests that these N400 semantic priming deficits are a specific biomarker of psychosis. Double-blind placebo-controlled crossover studies (Condray et al., 2003; Condray et al., 1999; Goldberg et al., 2000) and a one-year longitudinal treatment study (Besche-Richard et al., 2014) have found that antipsychotic treatment is associated with normalization of N400 semantic priming deficits in patients with schizophrenia. Moreover, N400 semantic priming effects have been found to be normal in first-degree relatives of these patients,

including monozygotic twins (Kiang et al., 2014; Sharma et al., 2017), providing convergent evidence that N400 semantic priming deficits are a biomarker of the psychotic state itself rather than of genetic risk for developing such a disorder.

Recently we have found that the N400 semantic priming deficits are present at the earliest stages of the psychotic process, further suggesting that these deficits reflect neurocognitive mechanisms linked to this process, rather than effects of antipsychotic treatment or environmental deprivation caused by chronic mental illness. “Clinical high risk” (CHR) individuals, also referred to as “prodromal” or “ultra high risk,” are characterized by attenuated psychotic symptoms that do not meet severity or duration thresholds for a psychotic disorder (Addington and Heinssen, 2012). Populations selected using these criteria have a much higher than normal incidence of developing a psychotic disorder, estimated by a recent meta-analysis at 32% within 3 years (Nieman et al., 2014). Moreover, among persons seeking help for mental health problems, those who meet CHR criteria, compared to those who do not, have been found to be more likely to develop a psychotic disorder, but not more likely to develop or have persistence of other disorders, suggesting prognostic specificity of CHR criteria (Woods et al., 2018). We found help-seeking, antipsychotic-naïve CHR patients to exhibit significantly reduced N400 semantic priming compared to healthy control individuals, further supporting the view that these deficits directly reflect the psychotic disease process (Lepock et al., 2019).

In the hypothesized schizophrenic disease process, deficits in selectively activating contextually related concepts in semantic memory, as indexed by N400 semantic priming deficits, could in turn contribute to real-world functional disability. In healthy individuals, those with lower reading comprehension have been found to have smaller N400 semantic priming effects in a prime-target word pair paradigm, possibly reflecting reduced access to word meaning, which could in turn interfere with comprehension (Landi and Perfetti, 2007). Along these lines, schizophrenia patients’ deficits in this ability to access related semantic information could affect their capacity to appropriately navigate real-world social interactions by interfering with comprehension or integration of a range of semantic information in the world including written and spoken language, pictures and objects, and gestures and actions (Kuperberg et al., 2010). This cascade could emerge early in the disease trajectory, before the manifestation of frank psychosis. Indeed, CHR patients exhibit similar functional deficits to patients with

psychosis, with lower than average levels of employment (Addington et al., 2008; Fusar-Poli et al., 2010; Madsen et al., 2018), and impairments in real-world social and academic/occupational role function (Addington and Heinssen, 2012; Addington et al., 2008; Cornblatt et al., 2007; Fusar-Poli et al., 2010). Thus, we hypothesized that within the CHR population, severity of N400 priming deficits would be correlated with functional impairment. Secondarily, we hypothesized that CHR patients' N400 priming deficits would be correlated with overall neurocognitive dysfunction, which is present in CHR patients across a broad range of domains (Carrion et al., 2011; Fusar-Poli et al., 2012; Mourik et al., 2017; Seidman et al., 2010; Zheng et al., 2018) and predicts future social and role impairment and conversion to psychosis (Lam et al., 2018; Seidman et al., 2010; Velthorst et al., 2018). If this hypothesis were confirmed, it would indicate possible utility of the N400 as a reliable marker of global cognitive dysfunction in this population.

4.3. Methods

4.3.1. Participants

Participants included 35 CHR patients. We have previously reported N400 and other ERP data from a subset of this sample and healthy control participants (Lepock et al., 2019). CHR participants were help-seeking patients referred to the Focus on Youth Psychosis Prevention outpatient clinic at the Centre for Addiction and Mental Health (CAMH) in Toronto. The CAMH Research Ethics Board approved the study; all participants gave written informed consent and received cash compensation. CHR individuals met diagnostic criteria for a psychosis-risk syndrome, namely the Criteria of Psychosis-Risk States based on the Structured Interview for Psychosis-Risk Syndromes (SIPS) (McGlashan et al., 2014); had no history of current or lifetime DSM-IV-TR Axis I psychotic disorder, or mood disorder with psychotic features (American Psychiatric Association, 2000), as determined via the Structured Clinical Interview for DSM-IV-TR (SCID) (First et al., 2015); had no history of DSM-IV substance abuse or dependence in the last 6 months (except nicotine); and were antipsychotic-naive. Other exclusion criteria included: visual or hearing impairment; having learned English after age 5; reading disability; and lifetime self-reported neurological disorder. Table 1 shows group demographic, neuropsychological and clinical characteristics.

4.3.2. N400 stimuli and task

These were the same as those used by Kiang et al. (2014), and included 80 related (e.g., *METAL-STEEL*) and 80 unrelated (*DONKEY-PURSE*) prime-target word pairs. For each related pair, the target was among the words most commonly given as associates to the prime by participants in the University of South Florida word-association norms (Nelson et al., 1998); mean response probability of related targets (i.e., proportion of individuals producing that word in response to the prime) was 0.61 (SD=0.12). For each unrelated pair, prime and target were not associates in the norms. Across these conditions, targets were matched for mean length and log-transformed frequency (Francis and Kucera, 1982), and primes were also matched on these parameters. Stimuli also included 160 pairs with word primes and pronounceable nonword targets (*DRESS-ZORES*). No word occurred more than once among the stimuli.

The stimulus list included all prime-target pairs in fixed randomized order, in four blocks of 80 trials each. To examine more automatic versus more controlled semantic priming, N400 effects were assessed over both a shorter and a longer interval following the prime stimulus, i.e., at a 300-ms and a 750-ms prime-target SOA, respectively. The list had two versions, each one administered to half the participants, in which the order of prime-target SOAs across blocks was counterbalanced. In version A, SOA was 300 ms in blocks 1 and 2, and 750 ms in blocks 3 and 4; in version B, order of SOAs was reversed.

Each participant was presented with stimuli on a video monitor. Each trial consisted of: (a) row of preparatory fixation crosses for 500 msec; (b) blank screen for 250 msec; (c) prime word for 175 msec; (d) blank screen for 125 msec (in 300-msec SOA trials) or 575 msec (in 750-msec SOA trials); (e) target for 250 msec; (f) blank screen for 1250 msec; (g) prompt Yes or No? until participants responded via button-press; and (h) blank screen for 3000 msec until onset of the next trial.

At the prompt, participants were required to press one of two buttons, positioned under their right and left thumbs. One button (labeled “Yes”) signaled that prime and target were related; the other button (“No”) signaled that they were not. Assignment of buttons was divided equally among participants, counterbalanced across the two stimulus list versions.

4.3.3. EEG collection and analysis

During the task, continuous EEG was recorded using an actiCHamp amplifier (Brain Products, Gilching, Germany), from 32 active Ag/AgCl electrodes embedded in a cap (actiCAP system, Brain Products) at sites approximately equally spaced across the scalp, positioned according to a modified International 10-20 System (Fp1-Fp2-F7-F3-Fz-F4-F8-FC5-FC1-FC2-FC6-T7-C3-Cz- C4-T8-TP9-CP5-CP1-CP2-CP6-TP10-P7-P3-Pz-P4-P8-PO9-O1-Oz-O2-PO10). Electrode impedances were kept below 25 kΩ. The EEG was referenced online to FCz, and continuously digitized at 500 Hz. Blinks and eye movements were monitored via electrodes on the supraorbital and infraorbital ridges and on the outer canthi of both eyes. Offline, the EEG was re-referenced to the algebraic mean of the mastoids, and bandpassed at 0.25-60 Hz for N400. Continuous data were algorithmically corrected for eyeblink artifact (Makeig et al., 1997). Individual trials containing artifacts due to eye movement, excessive muscle activity or amplifier blocking were rejected offline by visual inspection before time-domain averaging.

4.3.4. N400 analysis

ERPs were computed for epochs from 100 msec pre-stimulus to 900 msec post-stimulus. For each participant, separate ERP averages were obtained for trials with related and unrelated targets at each SOA. The N400 semantic priming effect was defined as mean voltage of the difference wave obtained by subtracting the average for related trials from the average of unrelated trials, from 300-500 msec post stimulus-onset, consistent with previous methods (Federmeier and Kutas, 2005; Kiang et al., 2010; McLaughlin et al., 2004).

4.3.5. Functional and cognitive measures

We used the Global Functioning: Role (GF:Role) and Global Functioning: Social (GF:Social) Scales (Cornblatt et al., 2007) to rate severity of real-world functional impairment. These interviewer-rated scales were developed specifically to measure real-world function in CHR individuals, based on the need to capture subtle prodromal difficulties, apply to the typical young-adult age range of these individuals, differentiate role (academic/work) and social

functioning, and avoid confounding functioning with psychiatric symptoms; and have been validated in this population (Carrion et al., 2018; Cornblatt et al., 2007). Individuals receive a score of 1 to 10 on each of these scales, with anchors ranging from extreme impairment (1) to superior functioning (10).

As a measure of global cognitive function, we used participants' composite *T* scores on the MATRICS Consensus Cognitive Battery (MCCB; Kern et al., 2011), which was designed and validated for measuring cognitive function in schizophrenia (Nuechterlein et al., 2008). The MCCB assesses cognition over seven domains (processing speed, attention/vigilance, verbal learning, working memory, visual learning, reasoning and problem solving, and social cognition). The composite score sums and standardizes data from all seven domain scores, with the *T* score having a mean of 50 and standard deviation of 10 (Kern et al., 2008).

4.3.6. Statistical analysis

To examine the relationships between N400 effects and functional/cognitive measures, we calculated pairwise Spearman correlation coefficients ρ between (a) N400 effects at the 300-ms and 750-ms SOAs, averaged across five centroparietal electrodes (Cz, FC1, FC2, CP1, CP2) where these effects were maximal), and (b) functional and cognitive measures. This nonparametric correlation coefficient was used because the functional and cognitive measures were non-normally distributed.

A significance level of α=0.05 (two-tailed) was used for all tests.

4.4. Results

Means and standard deviations of N400 effects at the 300-ms and 750-ms SOAs, and functional and cognitive measures, are shown in Table 2. Correlations between (a) N400 effects and (b) functional and cognitive measures are displayed in Table 3. Negative-signed correlations indicate that larger N400 effects (i.e., more negative value for voltage difference of unrelated targets minus related targets) are correlated with higher functional or cognitive scores. Neither GF:Role nor GF: Social scores were significantly correlated with MCCB composite scores.

To illustrate the relation between N400 effects at the 300-ms SOA and GF:Role scores, we have plotted N400 ERPs for high (GF:Role scores of 6 or higher) and low role function (GF:Role scores of 5 or lower) groups in Figure 1. Mean N400 effects were significantly larger for the High GF:Role group (-1.83 mV; SD=2.52) than for the Low GF:Role group (-0.22 mV; SD=1.19), $F_{1,34}$=4.94, p=0.03.

4.5. Discussion

In this investigation we examined the association between N400 semantic priming effects and real-world function in help-seeking, antipsychotic-naïve CHR patients. We previously reported that this group exhibited smaller than normal N400 semantic priming effects, when the time interval or SOA between semantic stimuli was relatively long (750 ms), but not at a shorter SOA (300 ms) (Lepock et al., 2019). In the present study, as hypothesized, reduced N400 semantic priming in this group was correlated with poorer academic/occupational function, as measured by the GF:Role scale, but these results only held for N400 semantic priming at the short SOA. Thus, for the short SOA, smaller differences in N400 amplitude in response to target stimuli that were related versus unrelated to a preceding prime stimulus were associated with greater impairment in role function. N400 semantic priming effects at either SOA were not correlated with social function, as measured by the GF:Social scale. Secondarily, as hypothesized, N400 semantic priming deficits at the longer SOA were correlated with lower overall cognitive function, as indexed by the MCCB overall composite score.

CHR individuals exhibit significant impairments in managing academic and work tasks. For example, compared to control individuals, they have lower employment rates (Fusar-Poli et al., 2010), and more frequent difficulties with meeting standards for school performance (Ballon et al., 2007). These impairments, along with deficits in social function (Addington et al., 2017; Carrion et al., 2018), have been found to predict later psychosis (Fusar-Poli et al., 2010; Valmaggia et al., 2013). Our results suggest that deficits in selectively activating contextually related concepts in semantic memory, as indexed by N400 semantic priming deficits, could contribute to difficulties in functioning in academic or occupational settings. This fits with the view that N400 semantic priming deficits in schizophrenia patients affect their capacity to appropriately navigate real-world social interactions by interfering with comprehension or

integration of semantic information in the world (Kuperberg et al., 2010), which includes written and spoken language, pictures and objects, and gestures and actions (Kutas and Federmeier, 2011). Our results indicate that these deficits may already be present early in the schizophrenic disease process, before the emergence of frank psychosis.

We observed a correlation between N400 semantic priming deficits and impairment in role function only for the short prime-target SOA of the N400 stimulus paradigm. Conversely, as we previously reported (Lepock et al., 2019), CHR patients overall exhibited N400 semantic priming deficits compared to healthy controls only for the long and not the short SOA. Semantic priming at this relatively long SOA is thought to predominantly reflect relatively controlled or strategic use of context to activate and maintain related items in semantic memory, in contrast to priming at a shorter SOA, which reflects more rapid and automatic spread of activation to related items (Kuperberg et al., 2010; Mohammad and DeLisi, 2013). Thus, CHR patients as a whole may be relatively intact in automatic activation of related items while, like schizophrenia patients, exhibiting impairment in more controlled processing of semantic relationships – e.g., maintaining activation of related items in working memory (Salisbury, 2008); whereas a subset of CHR patients who also have deficits in automatic activation may be those most compromised in real-world function.

CHR patients exhibit cognitive impairment across a wide range of domains (Carrion et al., 2011; Fusar-Poli et al., 2012; Mourik et al., 2017; Seidman et al., 2010; Zheng et al., 2018), and our finding that N400 semantic priming deficits at the long SOA correlated with an overall measure of this impairment, the MCCB composite score, suggests that these deficits may be a reliable biomarker of global cognitive impairment in this population. Thus, this N400 biomarker could be useful as an early marker of target engagement in trials of candidate novel pharmacological agents for treating cognitive dysfunction in CHR patients.

In summary, we found that in help-seeking antipsychotic-naïve CHR patients, decreased N400 semantic priming over a short time interval was associated with lower academic and occupational function. In addition, CHR patients' N400 semantic priming deficits over a longer time interval were associated with decreased global neurocognitive function. We believe that one strength of our study was the patients' antipsychotic-naïve status; hence, their ERPs were not subject to the confounding effects of these medications. One limitation of the study was its

relatively small sample size; although our results suggest that N400 semantic priming deficits are an early neurophysiological biomarker of psychotic illness, more studies are necessary to replicated and further validate this finding. Another limitation of our study was its cross-sectional nature. Longitudinal studies could help ascertain whether the severity of N400 semantic priming deficits predict future functional and symptomatic outcome within the CHR population. If so, like other ERP biomarkers of the CHR state such as the auditory mismatch negativity and P300 (see Lepock et al. (2018) for review), the N400 could be a useful component of algorithms that refine our ability to predict outcome in this population (Bodatsch et al., 2015; Nieman et al., 2014; Perez et al., 2014; Schmidt et al., 2017), in order to provide patients with more personalized prognostic information, and target interventions to those most at risk

Table 4.1. Demographic, neuropsychological, and clinical characteristics of the study sample (means with SDs in parentheses given for continuous variables).

Age (years)	20.6 (3.3)
Sex	13 female, 22 male
Handedness	31 right, 4 left
Parental socioeconomic status (Blishen et al., 1987)	50.3 (15.7)
Years of education	13.8 (2.2)
National Adult Reading Test (Nelson and Willison, 1991) estimated premorbid verbal IQ	109.7 (5.6)
Scale of Psychosis-Risk Symptoms	
Positive Scale Total	10.5 (3.5)
Negative Scale Total	12.47 (4.8)
Disorganized Scale Total	5.44 (3.4)
General Scale Total	9.33 (3.8)

Table 4.2. N400 event-related potential, functional, and cognitive measures for the study sample (means with SDs in parentheses).

N400 semantic priming effect (mean over electrode sites Cz, FC1, FC2, CP1, CP2), in μV	
300-ms stimulus-onset asynchrony (SOA)	-1.19 (2.22)
750-ms SOA	-0.81 (1.86)
Global Function: Role (Cornblatt et al., 2007) score	5.8 (1.7)
Global Function: Social (Cornblatt et al., 2007) score	6.4 (1.2)
MATRICS Consensus Cognitive Battery (Kern et al., 2011) composite *T* score	48.8 (14.5)

Table 4.3. Spearman correlation coefficients ρ between N400 priming effects and functional/cognitive variables.

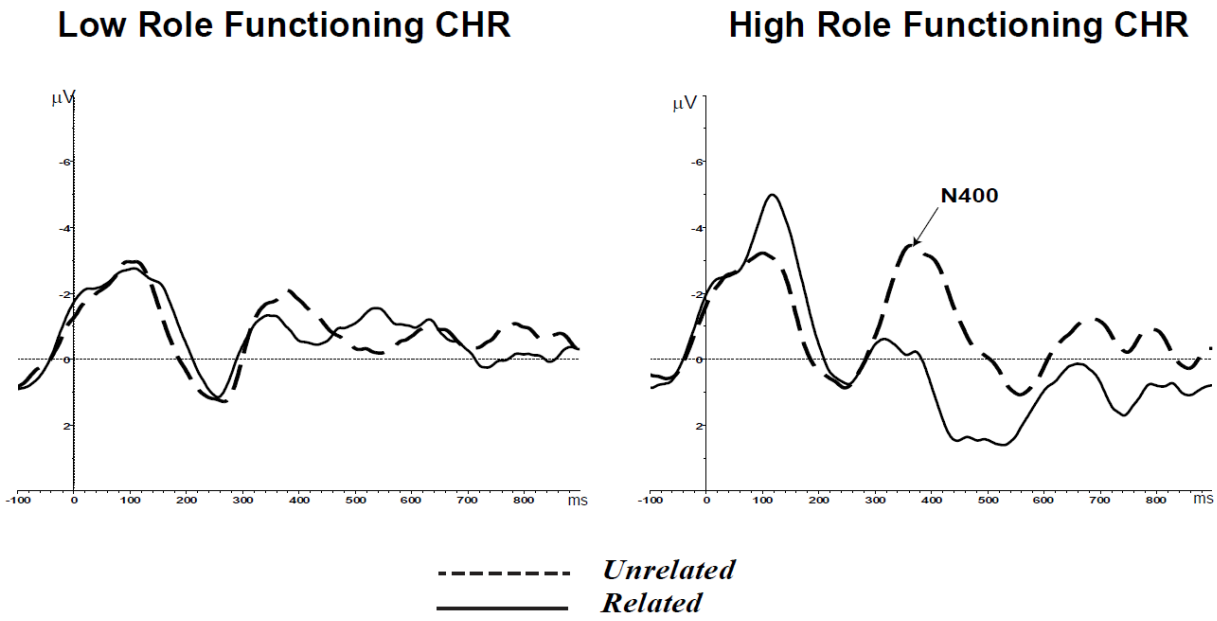
	Global Functioning: Role score	**Global Functioning: Social score**	**MCCB composite T score**
N400 semantic priming effect, 300-ms SOA	-0.39[a]	-0.09	-0.01
N400 semantic priming effect, 750-ms SOA	-0.02	-0.17	-0.435[b]

MCCB: MATRICS Consensus Cognitive Battery; SOA: stimulus-onset asynchrony.

[a] p=0.02

[b] p=0.009

Figure 4.1. Grand average event-related potentials elicited by target words related and unrelated to a preceding prime word, shown for clinical high-risk patients with high (≥6; *n*=21) and low (≤5; *n*=14) Global Function: Role scale scores, for the 300-ms prime-target stimulus-onset asynchrony condition, shown for the representative electrode site Cz (midline central).



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Chapter 5

Experiment 4 - Predicting Outcome Variables using the N400 in CHR Individuals

5.1. Abstract

Background: The N400 semantic priming effect is thought to reflect greater activation of related versus unrelated concepts in long-term semantic memory and has been found to be associated with global functioning and certain symptoms in schizophrenia patients. We tested the hypothesis that CHR patients would exhibit similar relationships with functioning, positive and disorganized symptoms over a follow up time of one and two years.

Methods: We measured N400 semantic priming in 47 CHR patients at stimulus-onset asynchrony (SOA) of 300 or 750 ms. We measured prodromal syndromes using the Structured Interview for Prodromal Symptoms (SIPS) and academic/occupational and social function with the Global Function (GF): Role and Social scales, at baseline, one year and two year follow up.

Results Decreased N400 semantic priming at the 750 ms SOA correlated with lower GF:Social functioning scores at one year, change in score from baseline to one year. There was a significant interaction between the N400 at the long SOA effect and time with Ptotal scores, paranoia scores and perceptual abnormalities scores, indicating that the change over time in these scores is moderated by the long SOA N400. A significant interaction between N400 at the short SOA and time was also found for GF:Role functioning.

Conclusions: The CHR patients with more deficient N400 effects had less improvement in positive attenuated psychotic symptoms and role and social functioning over two years post baseline. These findings contribute to the notion that ERPs may have a role in the prognosis of CHR syndromes.

5.2. Introduction

Longitudinal studies of psychotic disorders can provide details on the progression of symptoms, their impact on functioning and the manner in which neurophysiological, biological, and environmental factors influence the evolution of the disease. Only a portion of those at high risk for schizophrenia will go on to develop the illness, and this research is imperative for understanding predictors and rates of conversion, remission and symptom persistence, and the comorbidity of other disorders in this population. By longitudinally examining these factors and their impact on the high-risk population, it may be possible to develop an algorithm incorporating relevant risk factors to determine which patients at high risk will develop schizophrenia, which will remain stable and which will remit.

The positive symptoms of schizophrenia – unusual thoughts, delusions, paranoia, hallucinations, and disorganization – have devastating effects on patients' real-world social and occupational function, especially during and after the first-episode of psychosis. These symptoms, along with cognitive deficits, have been shown to have an impact on functional outcome and the likelihood of remission (Green, 1996; Green, Olivier, Crawley, Penn, & Silverstein, 2005). Schizophrenia patients whose symptoms remit have significant improvement in their overall cognitive functioning, and social functioning at remission is predicted by their social and role functioning scores at baseline and 6 months later (Torgalsbøen, Mohn, & Rund, 2014). The impact of cognition on individual functioning depends on what phase of schizophrenia they are in (Rajji, Miranda, & Mulsant, 2014), thus measuring these outcomes in the prodromal population may help to uncover predictors of developing psychosis.

Like schizophrenia patients, those at CHR who convert to psychosis tend to show an overall decrease in cognitive performance over time (Lam et al., 2018). There is also evidence of declining cognition in non-remitters compared to remitters, as CHR patients who do not remit have worse cognitive performance at baseline compared to controls and CHR patients who do remit (Lam et al., 2018), suggesting that cognition may be a prime risk factor for psychosis. Studies have found that a combination of scores on different cognitive tasks (verbal IQ, verbal memory, working memory, declarative memory, verbal fluency and speed of processing) predict conversion to psychosis in CHR, even when none of the scores on the individual task are a significant predictor (Addington & Heinssen, 2012; Shakeel, Lu, Woods, Perkins, & Addington,

2019). Those who transitioned to psychosis and had greater symptom severity and deficiency in social cognition at baseline, did not show improvement in social cognition over the following 24 months, whereas the non-transitioned CHRs did show improvement (Shakeel et al., 2019).

Whereas cognition is clearly an important baseline predictor of worsening symptomatology and conversion to psychosis in CHR patients, other variables have been established to increase risk to a similar degree. A review from Fusar-Poli et al. (2012) looked at 2502 patients (27 studies) and found that the risk of converting varied with age, treatment, and the manner in which the prodrome and psychosis transition were defined (ie. conditions of unusual thought content, low functioning, and genetic risk with functional decline). Older patients tended to have higher transition rates. The cumulative risk of psychosis in CHR individuals increased over time within the first 3 years and plateaued from 3 to 5 years (Fusar-Poli et al., 2012). Social and occupational impairment are seen before the onset of schizophrenia (Iyer et al., 2018; Velthorst et al., 2017), as CHR individuals have significant impairment in social and occupational/educational role functioning (Addington, Penn, Woods, Addington, & Perkins, 2008). Moreover, several studies have reported that at baseline, poor social (Addington et al., 2017; Cannon et al., 2008; Cannon et al., 2016b; Cornblatt et al., 2012; Fusar-Poli et al., 2010; Healey et al., 2018; Jang et al., 2011) and role functioning (Healey et al., 2018; Valmaggia et al., 2013) predict conversion to psychosis among CHR individuals. Certain neurophysiological indicators of cognition, such as event-related potentials, have demonstrated promising predictive results in CHR patients. The P300 and MMN have both been shown to predict psychosis across studies (Nieman et al., 2014; Shaikh et al., 2012; van Tricht et al., 2010). Nieman et al. (2014) found that combined with the lowest premorbid adjustment, a deficient P300 had a 74% conversion rate, 17 months earlier than those at lower risk.

The N400 ERP is used as a predictive marker in longitudinal studies looking at first-episode psychosis and patients with chronic schizophrenia. A key feature of schizophrenia thought to contribute to deficient functioning is disorganized speech. With disorganized speech (sometimes referred to as thought disorder), it is suggested that individuals with schizophrenia fail to make use of environmental context to respond appropriately (Mohammad & DeLisi, 2013). Symptoms, including delusions and hallucinations, may arise because of misperceived verbal communication, abnormalities in comprehension, and semantic processing defects.

Multiple studies have found that the severity of thought disorder is inversely correlated with the size of the N400 amplitude of unrelated compared to related words (Kostova, Passerieux, Laurent, & Hardy-Baylé, 2005; Kumar & Debruille, 2004; Salisbury, 2008). This suggests an increase in activity within semantic memory deficits before being initiated as clinically observed behaviour (Mohammad & DeLisi, 2013). Through these findings, it is apparent that the N400 abnormality may help to bridge the gap between symptomatology and pathophysiology of schizophrenia. Wang et al. (2020), using an N400 semantic priming task in both schizophrenia and bipolar groups, demonstrated deficient N400 amplitudes compared to controls, with individuals withschizophrenia group having the most reduced effect. The N400 effects correlated with positive symptoms in schizophrenic and manic symptoms in bipolar, with disorganized speech observed to be a biomarker for semantic abnormalities and symptoms detected in both disorders.

N400 latency and amplitudes have been observed to be reduced more in early onset rather than late onset psychosis (Olichney, Iragui, Kutas, Nowacki, & Jeste, 1997), and have been found to be associated with higher levels of psychotic (Kiang, Kutas, Light, & Braff, 2008; Kiang et al., 2007) and negative symptoms (Olichney et al., 1997). Also, smaller N400 priming effects have been found to correlate with delusions and delusion-like ideation in schizophrenia. These symptoms, which can also precede a psychotic episode, may be associated with deficits in processing how strongly a meaningful concept is related to its context, leading to an impairment of prediction. Correlations of N400 amplitudes for related targets with high levels of disorganized speech are also thought to reflect an impairment in using meaningful context to initiate and sustain a pre-activation of related concepts in semantic memory, and this is also associated with functional ability (Kiang & Gerritsen, 2019).

Longitudinal N400 studies have examined effects of antipsychotics on schizophrenia. Antipsychotic treatment attenuates schizophrenia N400 priming deficits (Debruille, Rodier, Prévost, Lionnet, & Molavi, 2013). Risperidone was found to alleviate psychotic symptoms and improve N400 amplitude and latency after 15 months, but not after 6 months (Du et al., 2015). In this sample, decrease of the N400 amplitudes (congruent and incongruent) were both negatively correlated with the symptoms of thought and attention disorder, demonstrating that the impairment of the N400 might be an important pathogenetic factor in these symptoms. Also,

patients medicated with clozapine have been shown to have significant N400 priming effects, suggesting that neuromodulators can influence access to semantic memory by the activation of connections among semantic representations (Condray, Siegle, Keshavan, & Steinhauer, 2010).

Studies of outcome measures in schizophrenia have demonstrated relationships between the N400 and symptoms specific to the illness. Thus, in order to understand the underlying mechanism of the N400 as a possible marker for impending illness, longitudinal studies are necessary in the prodromal phase of psychosis. As most CHR patients do not go on to develop a psychotic disorder, and many remit entirely, it is vital to evaluate the change in their psychotic symptoms and functioning over time. According to the NAPLS risk calculator, a validated tool with a 48% positive predictive value to conversion of CHR patients over 2 years (Cannon et al., 2016a), higher levels of unusual thought content and suspiciousness, greater decline in social functioning, lower verbal learning and memory performance, slower speed of processing, and younger age at baseline, each contribute to an individual risk for psychosis. Our goal is to contribute to this tool by determining which neurophysiological indices, when combined with these other factors would improve prediction of conversion to psychosis in CHR individuals.

In the present study, we aimed to test in our sample of CHR patients the hypothesis that the N400 at the short and long SOA would predict conversion to a psychotic disorder over 2 years. We also hypothesized that reduced N400 priming effects, and a larger N400 amplitude to related targets, would be associated with a change in positive symptoms: P1 – Unusual Thought Content/Delusional Ideas, P2 – Persecutory/Suspicious Ideas, P3 - Grandiosity, P4 – Perceptual Abnormalities, P5 – Disorganized Communication, role and social functioning from baseline. To our knowledge, this is the first longitudinal study using the N400 as a predictor of outcome variables in CHR patients.

5.3. Materials and Methods

5.3.1. Participants

Participants included 47 CHR individuals who were help-seeking patients referred to the Focus on Youth Psychosis Prevention (FYPP) program at the Centre for Addiction and Mental Health (CAMH) in Toronto. 30 CHRs completed the follow up at first year, and 18 completed

the two year follow up. The protocol was approved by the CAMH Research Ethics Board. All participants gave written informed consent. Participants received cash compensation.

CHR individuals met diagnostic criteria for a psychosis-risk syndrome, namely the Criteria of Psychosis-Risk States based on the Structured Interview for Psychosis-Risk Syndromes (SIPS) (McGlashan, Walsh, & Woods, 2014); had no history of current or lifetime Diagnostic Statistical Manual-IV-TR Axis I psychotic disorder, or mood disorder with psychotic features, as determined via the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 2002); and were antipsychotic-naive. Other exclusion criteria for all participants included: visual or hearing impairment; having learned English after age 5; reading disability; and lifetime self-reported neurological disorder.

5.3.1.1. Sample Size

N400 semantic priming effects will be used in a Cox model that has time to development of a psychotic disorder as dependent variable. Based on previous work (Kiang et al., 2011), we assume that N400 semantic priming effects will have a standard deviation of 2. Following Perez et al. (2014), we estimate that the proportion of CHR participants developing a psychotic disorder over 2 years is 1⁄3. We assume that $\alpha = 0.05$ and two-tailed testing is performed. Power calculation for Cox regression was conducted using PASS 2005 software. We base the simulation on effect sizes found in a study of the power of the MMN ERP amplitude to predict psychosis risk in CHR patients (Perez, Woods et al.,2014), i.e., hazard ratio (HR) = 2.2; and consider a range of effect sizes, from HR = 1.5 to 3.2. For the smallest effect size, HR = 1.5, the required sample size is 42 CHR patients to obtain 80% power. We note that a HR of 1.5 corresponds to a 50% increase in the hazard of developing a psychotic disorder associated with a unit (1 μ V) decrement in the N400 priming effect, where we assume that the N400 priming effect has standard deviation 2. Conservatively assuming a lower effect size 1.5, a sample of around n=42 CHR patients is required. Based on the totality of the above calculations, we estimate that the proposed sample size of n=50 CHR participants and n=25 HCPs will be sufficient.

5.3.2. Functional and Symptom Measures

5.3.2.1. SIPS P values

The Structured Inventory Psychotic Symptoms (SIPS) evaluates three prodromal syndromes that identifies individuals at clinical high risk for schizophrenia: brief intermittent psychotic symptoms (BIPS), attenuated psychotic symptoms (APS) and genetic risk with functional decline (GRD). The scale of prodromal symptoms (SOPS) is part of the SIPS and measures the severity of and changes to Positive, Negative, Disorganization and General symptoms. CHR participants were administered all areas of the SOPS with particular interest to the positive symptoms, as this subscale is used to make a prodromal diagnosis. This scale consists of 5 items: P1 – Unusual Thought Content/Delusional Ideas, P2 – Persecutory/Suspicious Ideas, P3 - Grandiosity, P4 – Perceptual Abnormalities, P5 – Disorganized Communication (McGlashan et al., 2001).

5.3.2.2. GF: Role and Social Scales

We administered the GF:Role and GF:Social Scales (Cornblatt et al., 2007) to rate real-world functional impairment. Individuals are scored from 1 to 10 on each scale, with anchors ranging from extreme impairment (1) to superior functioning (10). These scales are age appropriate ratings based on the quantity and quality of peer and family relationships, level of peer conflict, demands of work/school role, level of independence, and support needed. Examples of questions asked for role functioning: what are your job responsibilities? How many hours do you work? What are your grades in school? And for social functioning: do you have any friends? How many are close and how many are casual? Do you spend time with family members?

5.3.2.3. Structured Clinical Interview for DSM-IV (SCID-IV)

We administered the SCID at baseline and follow up to determine any comorbid DSM-IV Axis I Disorders and to determine no other disorders as a primary diagnosis. The SCID-IV is a

diagnostic exam used to determine DSM-IV Axis I Disorders (First et al., 2002).

5.3.3. Stimuli and Task

Stimuli included 80 related (e.g., *METAL-STEEL*) and 80 unrelated (*DONKEY-PURSE*) prime-target word pairs. For each related pair, the target was among the words most commonly given as associates to the prime by participants in the University of South Florida word-association norms (Nelson, McEvoy, & Schreiber, 1999); mean response probability of related targets (i.e., proportion of individuals producing that word in response to the prime) was 0.61 (SD=0.12). For each unrelated pair, prime and target were not associates in the norms. Across these conditions, targets were matched for mean length and log-transformed frequency (Francis & Kucera, 1982), and primes were also matched on these parameters. Stimuli also included 160 word-nonword prime-target pairs (*DRESS-ZORES*), whose targets were pronounceable nonwords. No word occurred more than once among the stimuli.

The 320-trial stimulus list included all prime-target pairs in a fixed randomized order, in four blocks of 80 trials each. The list had two versions, each one administered to half the participants, in which the order of prime-target SOAs across blocks was counterbalanced. In version A, SOA was 300 ms in blocks 1 and 2, and 750 ms in blocks 3 and 4; in version B, order of SOAs was reversed.

Participants were seated 100 cm from a video monitor on which stimuli were centrally presented, in yellow letters on a black background, with each letter subtending on average 0.36° of visual angle horizontally, and up to 0.55° vertically.

Each participant was presented with the stimulus list, with short rest breaks between blocks. Each trial consisted of: (a) row of preparatory fixation crosses for 500 msec; (b) blank screen for 250 msec; (c) prime word for 175 msec; (d) blank screen for 125 msec (in 300-msec SOA trials) or 575 msec (in 750-msec SOA trials); (e) target for 250 msec; (f) blank screen for 1250 msec; (g) prompt *Yes or No?* until participants responded via button-press; and (h) blank screen for 3000 msec until onset of the next trial.

At the prompt, participants were required to press one of two buttons, positioned under their right and left thumbs. One button (labeled “Yes”) signaled that prime and target were related; the other button (“No”) signaled that they were not. Assignment of buttons was divided equally among participants, counterbalanced across the two stimulus list versions.

5.3.4. Electroencephalographic Data Collection and Analysis

During the task, the electroencephalogram (EEG) was recorded using an actiCHamp amplifier (Brain Products, Gilching, Germany), from 32 active Ag/AgCl electrodes embedded in a cap (actiCAP system, Brain Products) at sites approximately equally spaced across the scalp, positioned according to a modified International 10-20 System (Fp1-Fp2-F7-F3-Fz-F4-F8-FC5-FC1-FC2-FC6-T7-C3-Cz-C4-T8-TP9-CP5-CP1-CP2-CP6-TP10-P7-P3-Pz-P4-P8-PO9-O1-Oz-O2-PO10). Electrode impedances were kept below 25 kΩ. The EEG was referenced online to FCz, and continuously digitized at 500 Hz. Blinks and eye movements were monitored via electrodes on the supraorbital and infraorbital ridges and on the outer canthi of both eyes. Offline, the EEG was re-referenced to the algebraic mean of the mastoids, and bandpassed at 0.25-60 Hz. Continuous data were algorithmically corrected for eyeblink artifact (Makeig, Jung, Bell, Ghahremani, & Sejnowski, 1997). ERPs were computed for epochs from 100 msec pre-stimulus to 900 msec post-stimulus. Individual trials containing artifacts due to eye movement, excessive muscle activity or amplifier blocking were rejected off-line by visual inspection before time-domain averaging; mean percentage of trials lost to such artifacts was 18% for patients and 9% for controls.

For each participant, separate ERP averages were obtained for trials with related and unrelated targets at each SOA from nine centro-parietal electrodes thought to be most prominent for N400 Fz/FC1/FC2/Cz/C3/C4/CP1/CP2/Pz. N400 amplitude was defined as mean voltage from 300-500 msec post-stimulus, consistent with previous methods (Federmeier, Wlotko, De Ochoa-Dewald, & Kutas, 2007; Kiang et al., 2008; McLaughlin, Osterhout, & Kim, 2004).

At approximately 1 year and 2 years post baseline, the CHR participants were contacted to return for the follow-up portion of the study. They completed the SIPS and SCID interview,

and the GF:Role and Social scales. Based on the results of the SIPS and any previous hospitalizations to CAMH because of a psychotic disorder, it was determined whether the CHR participants had converted to schizophrenia. CHR participants were compensated separately for the follow up visits.

5.3.5. Statistical Analysis

5.3.5.1. Conversion analysis

In our sample of 47 baseline CHRs, 43 reached the one year follow up time point during the study duration. Of these 43, 30 returned and were assessed on the SIPS, SCID and GF:Role and Social scales. 2 had converted to a psychotic disorder. 33 CHRs reached the two year follow up time point, 18 were assessed and 1 had converted (see Figure 1). A hazard ratio was to be calculated to test whether the N400 priming effects were significantly associated with risk of conversion to a psychotic disorder over the 2 year follow up. However, because of the low number of converters in our sample this prediction analyses was not possible. A Cox regression was also to be performed using the MMN, P3a and gamma ASSR as possible predictors to conversion; however, this was also unfeasible due to the low number of follow up assessments.

5.3.5.2. Correlations

To examine the relationship and the change over time between positive symptoms including delusion-like ideation, functioning and N400 semantic priming effects in CHR patients, Pearson correlation coefficients r were calculated across patients between N400 priming effects (difference in N400 amplitude for unrelated minus related targets) and N400 amplitudes for unrelated and related targets at each SOA at Cz (midline parietal); and scores on each of the Scale of Psychosis-Risk Symptoms (SOPS) (McGlashan et al., 2014) Positive Symptom scale items (P1: unusual thought content, P2: suspiciousness/persecutory ideas, P3: grandiose ideas, P4: perceptual abnormalities/hallucinations, P5: disorganized communication),and GF: Role and Social scales. Change in SIPS symptoms and GF: Role and Social were defined as the score at year one or year two minus the baseline score, meaning a negative score was a decrease and a positive score is an increase in functioning.

5.3.5.3. Mixed Effect Measures

Linear Mixed Effect models for repeated-measures were used to evaluate the non-linear N400 relationships at the short and long SOA with symptom and social and role functioning over time GF: Role and Social, and SIPS positive symptom values were used as dependent variables, fixed effects were N400 semantic priming effects values, taken as the 25th, median and 75th percentile and entered as smaller, intermediate, and larger values (the larger the effect the more negative and therefore more standard) and time (three points at baseline, year one and year two). Subjects were entered as a random effect.

5.4. Results

5.4.1. Demographics

Demographic characteristics of the study sample are summarized in Table 1.

5.4.2. Correlations of N400 semantic priming effects with symptom ratings

N400 event-related potential means at the short and long SOA are presented in Table 2, and clinical scales at year one and year two are presented in Table 3. Correlations within the CHR group between N400 variables at each SOA and SOPS positive items, and GF scores are displayed in Table 4. No significant correlations were found between N400 amplitudes for related and unrelated target stimuli, positive scores, and functioning. Negative-signed correlations indicate that larger N400 semantic priming effects (i.e., larger differences in N400 amplitude in response to unrelated versus related targets, resulting in more negative values obtained by subtracting N400 amplitude for related targets from N400 amplitude for unrelated targets) are correlated with higher GF scores.

The N400 effect at the long SOA was negatively correlated with GF:Social at one year follow up ($r = -0.392$, $p=0.039$) (Figure 1) and change in GF:Social from baseline to one year ($r= -0.392$, $p=0.037$) (Figure 2), meaning that as the N400 effect decreased (became less negative)

the GF:Social scores were smaller.

In our analysis, we examined eight correlations: N400 at the long and short SOA vs. two functional measures (GF:Role and GF:Social score) and six positive items (P1, P2, P3, P4, P5 and Ptotal). These variables are highly correlated with each other and do not act as independent outcome measures (Table 5), therefore a Bonferroni correction for multiple tests would not be warranted.

5.4.3. Mixed Effect Modeling

The long and short N400 priming effects at small, intermediate and large values were found to have a significant time interaction at baseline, year one and year two with total positive symptoms, delusions, hallucinations and functioning. The more negative the N400 priming effect value, the more normal the priming effect, which was comparable to the mean amplitude of the N400 at the long SOA in the healthy controls (-1.76) observed in Lepock (2019) There was no significant time interaction found between the long and short N400 effect at P1, P3 and P5 items.

5.4.3.1. P Total

For the total of the positive symptoms (Ptotal), a significant interaction between N400 SOA long effect and time was found ($F(2,41)=4.27$, $p = 0.02$), indicating some evidence that the change over time in Ptotal is moderated by the N400 at the long SOA. We explored this moderation effect by looking at the time effect at different values of N400 at the long SOA and found that as it becomes more negative (therefore larger), the Ptotal decreases over time. As N400 increased, the improvement over time of Ptotal increases, particularly the change from the second to the third time point (year one and two post baseline). This effect can be seen in Figure 4. This reflects an improvement in P total over the 2 years, with a greater improvement at the larger N400 effect.

5.4.3.2. P2 and P4

For P2, (suspiciousness/paranoia) a significant interaction of N400 effect at the long SOA

at baseline and time was found (F(2, 43) =4.29, p=0.02). A pairwise comparison was run at each time effect for each value of the N400 at the long SOA, and found that as the priming effect changes, so does the change in P2, especially for the low and medium N400 value from timepoint 2 to 3. A similar interaction of N400 at the long SOA and time was found for P4 (perceptual abnormalities) (F(2, 43)= 3.39, p=0.04). As the time effect at different N400 values increases, so does the change in P4 again especially from year one to year two (see Figure 4 and 5). For the larger N400 effect, there was a larger improvement in P2 and P4 from year one to year two specifically.

5.4.3.3. Functioning

For GF:Role, a significant interaction between N400 at the short SOA and time was found (F(2, 44) = 3.54, p=0.038). A pairwise comparison at each time point indicated that as the value for the N400 at the short SOA priming effect increased, so did the change in GF:Role especially from timepoint 1 to 2. This is demonstrated in Figure 6. For the small N400 effect group, there was no significant increase in role functioning from baseline throughout year two, whereas there was significant increase for the intermediate and large N400 effect groups. There was a trend toward an interaction of the N400 at the long SOA and time of GF:Social (F(2, 40) = 3.17, p= 0.053). Specifically, as the N400 effect at the long SOA increased, there was a significant increase in social functioning between the three time points, especially time 1 to time 3 (see Figure 7). From time 2 to 3, the large N400 effect group had the greatest increase in social functioning.

5.5. Discussion

In this study we sought to evaluate how the N400 at the long and short SOA predicted certain outcomes in a group at clinical high risk for schizophrenia. To our knowledge this is the first longitudinal study looking at the N400 event-related potential as a predictor variable in the CHR population. We were unable to confirm our initial hypothesis of the N400 as a predictor of conversion to schizophrenia, as only three individuals of our sample converted on follow-up. Nevertheless, we were able to use a linear mixed effect model to determine the relationship

between the N400 and certain outcome measures, such as positive symptoms from the SOPS measurement, role and social functioning.

5.5.1. Positive Symptoms

The N400 at the long SOA predicted P2 suspiciousness and P4 perceptual abnormalities and total positive symptoms over time points 1, 2 and 3, representing baseline, year one follow up and year two follow up. The larger (more negative) N400 priming represented a more standard N400, while the smaller N400 priming effect (less negative) represented a more abnormal N400. Over two years, larger N400 effects predicted a lower score of the positive scale, representing less severity of positive symptoms. Moreover, the larger N400 effect group showed significantly larger improvements in Ptotal from year one to year two.

From larger to smaller N400 effects there was a greater decrease in P2 from year one to year two. At the small, intermediate and large N400 effect groups there was a non-significant change in P2 from baseline to year one. However, the larger N400 effect group demonstrated a significant decrease in P2 from year one to year two. There was also a significant decrease of P4 in the larger N400 effect group from year one and year two, and an overall significant decrease from baseline to year two.

Suspiciousness/paranoia and perceptual abnormalities in those at CHR may be represented by the N400 effect as an abnormal organization of concepts within the semantic network, thereby leading to a deficiency in their ability to use meaningful context to determine the activation of related items in memory (Kiang et al., 2008). Delusional thinking underlies paranoia and hallucinations, and our results are supported by previous findings that an abnormal N400 may also reflect an underlying deficit in recognizing these beliefs as incongruent from reality (Jackson et al., 2014).

In summary, the group with the smaller N400 priming effect (more abnormal) had a reduced improvement in SIPS scores from baseline to two years, with a significant effect on the SIPS positive scores of suspiciousness, perceptual abnormalities and total scores. From one year after baseline to two years after baseline, the smaller N400 effect group improved the least

compared to the more typical N400 group. These findings suggest that those CHRs with larger N400 priming effects at the long SOA have a better recovery in their attenuated psychotic symptoms over two years' time. This decrease in paranoia, hallucinations, and total positive symptoms in the more standard N400 at the long SOA could be partially explained by follow up therapeutic mediations. Medications including antipsychotics and antidepressant, along with individual psychiatric intervention, could be an important mediator of the effect on N400 in CHRs (Fusar-Poli et al., 2015; Hutton & Taylor, 2014), as antipsychotics have been found to alleviate both psychotic symptoms and N400 semantic priming deficits (Debruille et al., 2013). Although this particular study started out with antipsychotic-naïve patients at baseline, we were unable to control for medication or interventions between baseline and follow ups. We did not find any correlations between the N400 and any of the SIPS positive symptoms, suggesting that the relationship may be limited to change over time.

5.5.2. Functioning

There was a trend towards a time interaction at N400 at the long SOA and social functioning over years one and two. From baseline to year two, there was an overall significant increase in social functioning in all the N400 priming effect groups, with the large N400 effect group having the greatest improvement from year one to year two. We also found a negative correlation between N400 at the long SOA and social function at year one and change in social functioning from baseline to year one. The less negative the N400 effect the lower the social functioning score with the least improvement.

Social functioning is a risk factor for psychosis and given our original postulate that the N400 is a biomarker for psychosis risk, our findings are consistent with this. As the NAPLS calculator found social functioning in CHR patients to be one of the contributing risk factors in conversion to psychosis (Cannon et al., 2016b), we would expect to see this relationship with the N400 priming effect and social functioning in this population.

Finally, the N400 priming effect at the short SOA had a significant time interaction with GF:Role. Specifically, the intermediate N400 effect group exhibited a significant increase in

GF:Role from baseline to year two. For the larger N400 effect group there was a greater increase in role functioning from year one to year two than the smaller N400 effect group. This could be due to CHR symptoms subsiding in the group with the larger N400 effect over time. Thus, these individuals are able to return to school or work, whereas those with abnormal N400s do not improve in their symptoms or functioning. These time interaction results are consistent with our findings in Lepock et al. (2019), where the N400 at the short SOA correlated with role functioning at baseline in CHRs. As was stated in that study, perhaps the CHRs who have deficiencies of the N400 at the short SOA (and are not able to activate the contextual semantic effect immediately), are the ones who would have the most difficulty when it comes to improving their functioning over time.

While this study did not reveal the N400 as a predictor of conversion as initially hypothesized, overall we were able to demonstrate an influence of the N400 effect, at the long SOA especially, on the symptomatology and functioning of CHR individuals over the two years after baseline. The more abnormal the N400, the less improvement observed in paranoia/suspiciousness, perceptual abnormalities, general positive symptoms, and functioning. The mechanism underlying an abnormal N400, a deficient semantic memory network and its relationship to thought disorder and positive symptoms (Borgwardt et al., 2007**)**, may be the connection between the early stages of psychosis and the development of schizophrenia.

This study suffered from two main limitations, follow up attrition resulting in a small sample size and low conversion rate. Attrition rate was 38% for year one and 49% over two years follow-up. Although measures were taken to contact the participants at the follow-up points, as well as to access CAMH health records for those who were lost to follow-up, we were only able to properly assess 30 participants at year one and 18 participants at year two. Of these follow ups, two had converted by year one and one had converted by year two. This is much lower than the previously reported rate of 25-35% conversion of CHRs over three years (Cannon et al., 2008). Moreover, we were only able to follow our sample for two years post baseline. Several CHR prediction studies follow their participants for more than two years and see a higher conversion rate (Fusar-Poli et al., 2012; Fusar-Poli et al., 2015; van Tricht et al., 2010), although many of the conversions took place within the first two years. With higher conversion

rates within our sample, we would be able to test a model to predict conversion in CHR individuals using the N400 at long and short SOA. Also, while our initial sample was antipsychotic naïve, our participants at follow up may have been exposed to medications and therapies which may have altered their functional outcome. A strength of this study was CHR patients' antipsychotic-naïve status at baseline (keeping the N400 unaltered), and its longitudinal nature. Replication studies with larger samples and longer follow ups are needed to validate the association between N400 priming effects and outcome variables such as functioning and positive symptoms.

Figure 5.1. Flow chart of participants baseline and follow up assessment rate and conversion status throughout the study.

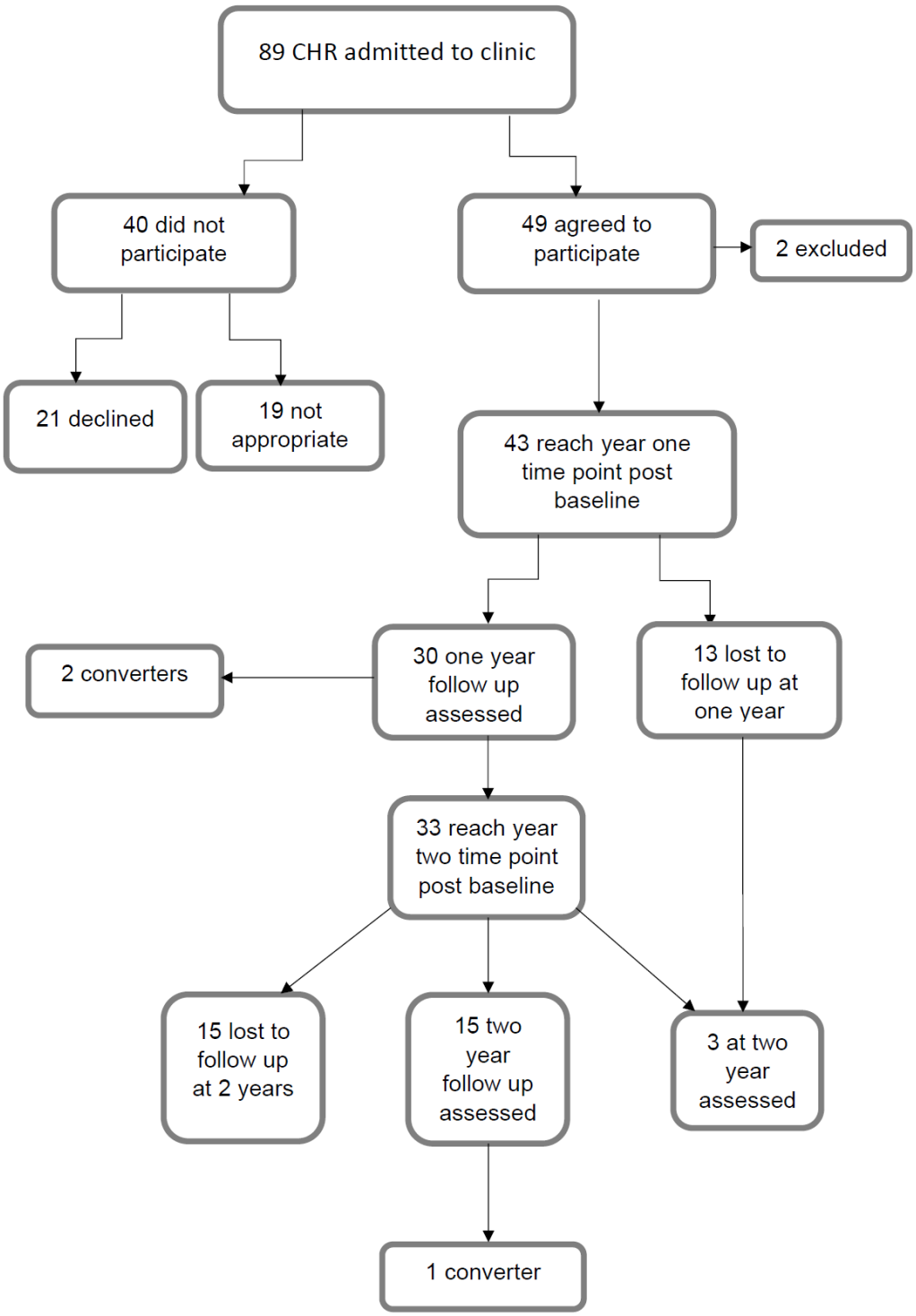


Table 5.1. Demographic, neuropsychological, and clinical characteristics of the study sample (means with SDs in parentheses given for continuous variables).

Age (years)	20.6 (3.1)
Sex	18 female, 29 male
Handedness	43 right, 4 left
Parental socioeconomic status (Blishen, Carroll, & Moore, 1987)	50.94 (14.35)
Years of education	13.64 (2.2)
National Adult Reading Test (Nelson & Willison, 1991) estimated premorbid verbal IQ	109.32 (8.58)
Baseline Scale of Psychosis-Risk Symptoms	
Positive Scale Total	10.96 (3.6)
Negative Scale Total	13.15 (4.96)
Disorganized Scale Total	5.74 (3.4)
General Scale Total	9.87 (3.9)
Baseline Functioning Scores **Global Assessment of Functioning (GAF) – Current**	47.32 (10.5)
Global Function: Role (Cornblatt et al., 2007) score	5.8 (1.7)
Global Function: Social (Cornblatt et al., 2007) score	6.4 (1.2)
Structured Clinical Interview for DSM-IV Disorders (SCID) Comorbidity	Number of pts with criteria met (%)
Depression	27 (57)
Anxiety	6 (13)

Table 5.2. N400 event-related potential (means with SDs in parentheses).

N400 semantic priming effect **(mean over electrode sites Fz/FC1/FC2/Cz/C3/C4/CP1/CP2/Pz), in μV**	
300-ms stimulus-onset asynchrony (SOA)	-0.95 (2.6)
750-ms SOA	-0.99 (2.2)

Table 5.3. Clinical scores over year 1 and year 2 follow up.

	Year 1 (*n*=30)	**Year 2 (*n*=18)**
Positive Scale Total	9.76 (4.9)	7.44 (5.6)
GF:Social	6.83 (1.6)	7.71 (0.9)
GF:Role	6.43 (2.0)	7.29 (0.9)

Table 5.4. Pearson correlation coefficients *r* between N400 priming effects at CZ and SOPS positive symptoms/functional variables at baseline.

	Ptotal	GFRole	GFSocial
N400 short	0.104	-0.239	-0.239
N400 long	-0.09	0.058	0.071

Table 5.5. Correlation matrix for outcome measures

	P1	P2	P3	P4	P5	Ptotal	GF role	GF social
P1		0.609**	0.606**	0.459*	0.650**	0.866**	0.135	0.166
P2			0.561**	0.428*	0.457*	0.805**	0.145	0.223
P3				0.396	0.385*	0.753**	0.343	0.155
P4					0.180	0.674**	-0.48	0.296
P5						0.668**	0.04	-0.075
Ptotal							0.158	0.221
GF role								0.233
GF social								

*p<0.05

**p<0.001

Table 5.6. Pearson correlation coefficients *r* between N400 priming effects at CZ and SOPS positive symptoms/functional variables at year 1

	Ptotal	GFRole	GFSocial
N400 short	-0.102	0.318	-0.082
N400 long	-0.241	-0.304	*-0.392**

Table 5.7. Pearson correlation coefficients *r* between N400 priming effects at CZ and SOPS positive symptoms/functional variables at year 2

	Ptotal	GFRole	GFSocial
N400 short	-0.168	0.567	-0.423
N400 long	-0.353	-0.285	0.089

Table 5.8. Pearson correlation coefficients r between N400 priming effects at CZ and change in SOPS positive symptoms/functional variables from baseline to year 1 and year 2

	PtotalΔyr1	PtotalΔyr2	GFRoleΔyr1	GFRoleΔyr2	GFSocialΔyr1	GFSocialΔyr2
N400 short	-0.120	-0.283	0.318	0.253	-0.039	-0.274
N400 long	-0.120	0.484	-0.247	0.309	*-0.397**	0.521

Figure 5.2. Scatterplots of the association of N400 long priming effect and social functioning at year 1

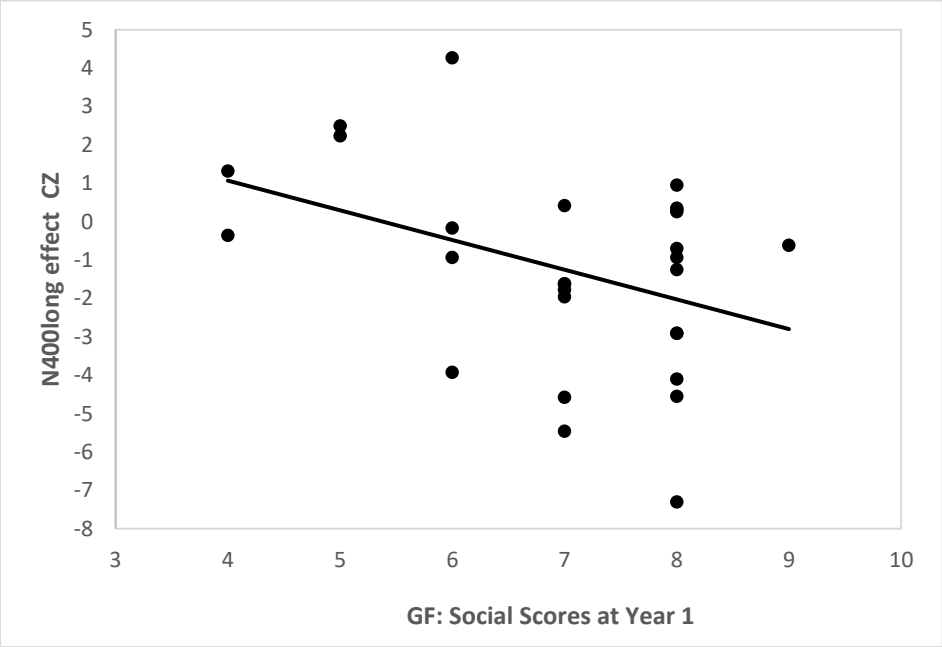


Figure 5.3. Scatterplots of the association of N400 long priming effect and change in social functioning at baseline to year 1

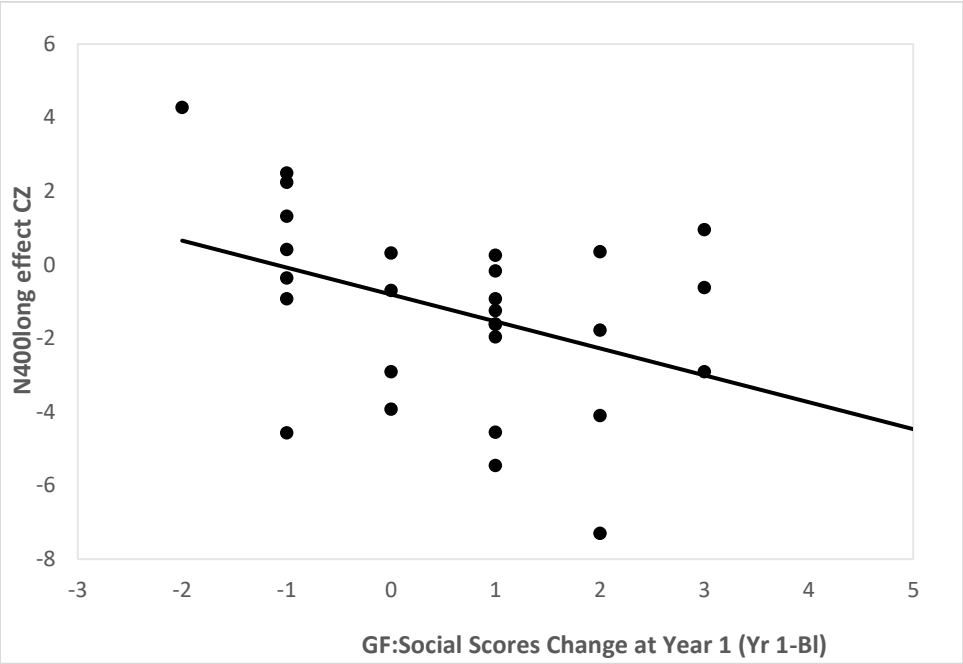


Figure 5.4. N400 long SOA x Time Interaction with Total Positive Symptoms

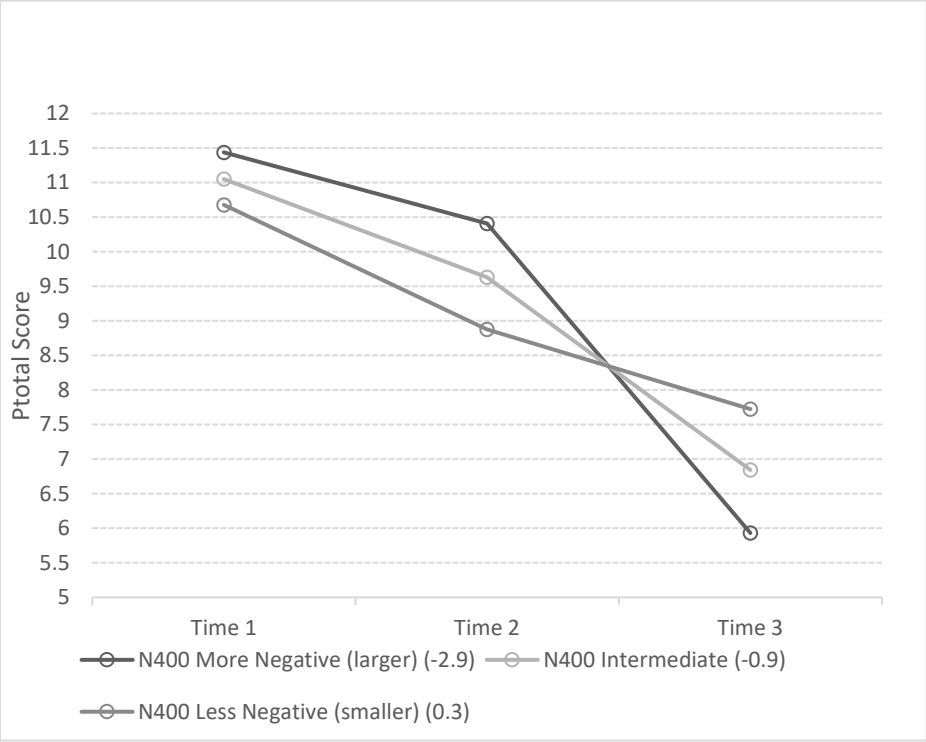


Figure 5.5. N400 long SOA x Time Interaction with Paranoia Scores (P2)

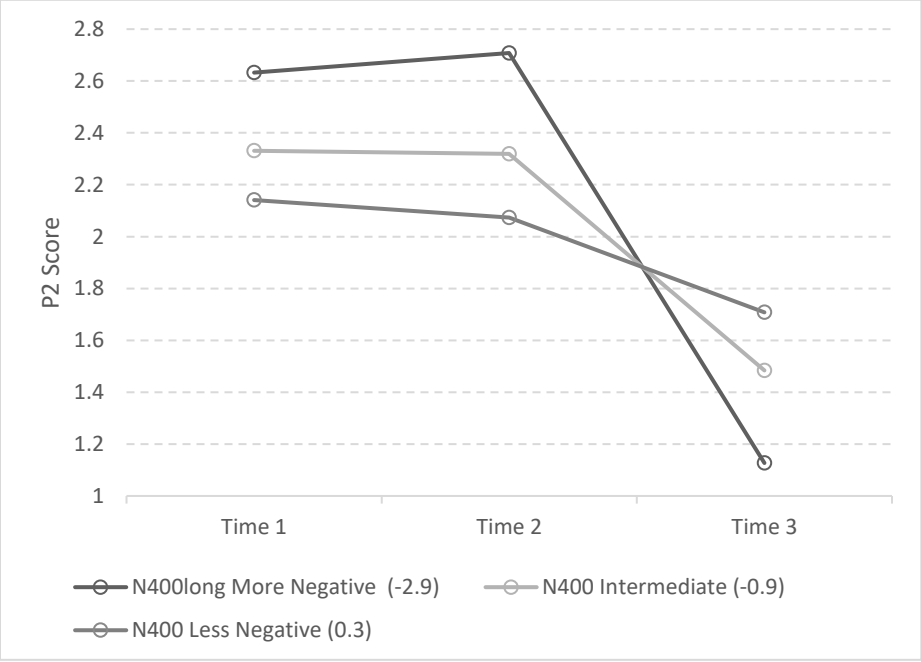


Figure 5.6. N400 long SOA x Time Interaction with Perceptual Abnormalities (P4)

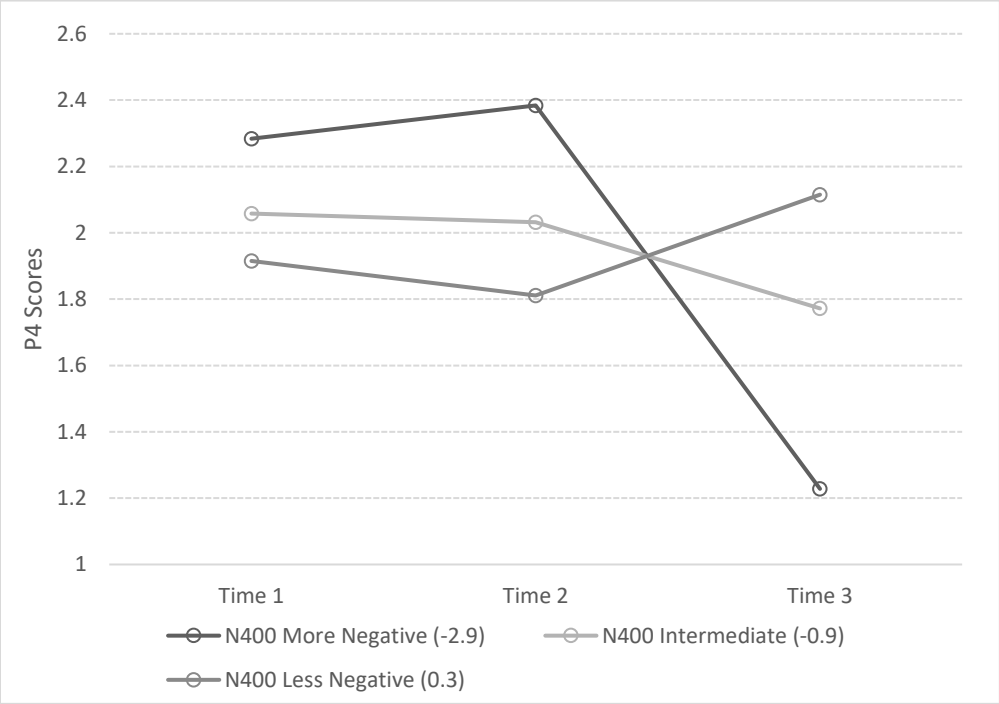


Figure 5.7. N400 short SOA x Time Interaction with GF:Role

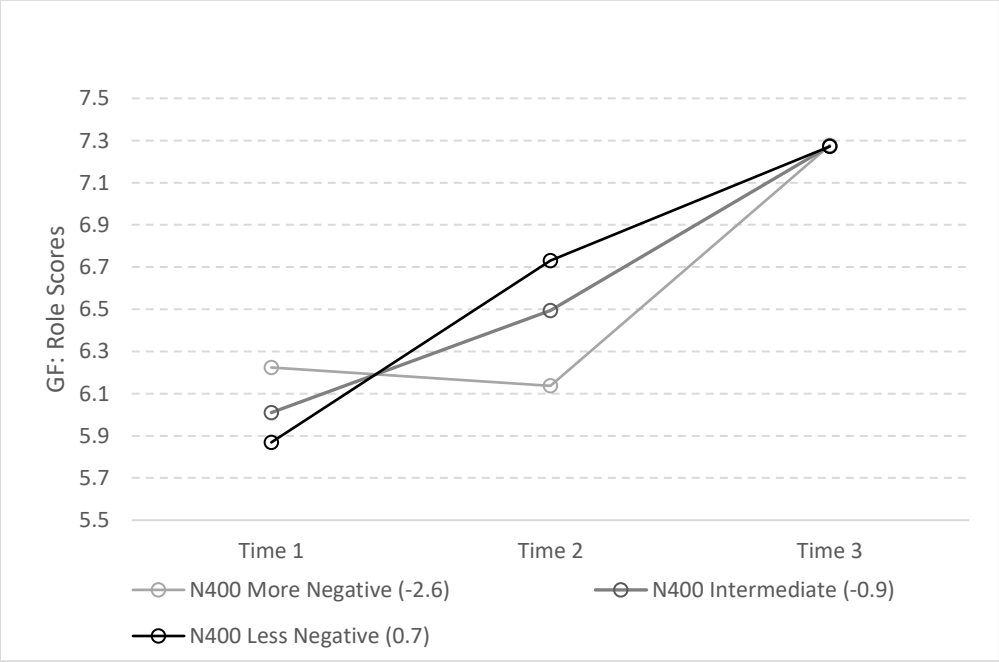
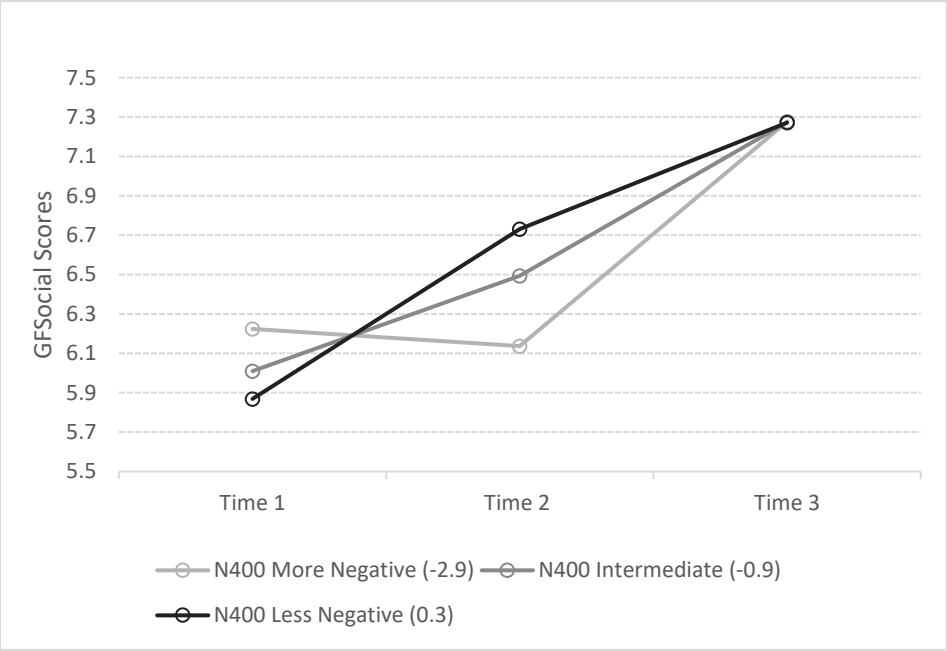


Figure 5.8. N400 long SOA x Time Interaction with GF:Social



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Chapter 6

Experiment 5: Relationships of real-world functioning with MMN, P3a and gamma ASSR event related potentials at baseline and follow up in clinically high-risk individuals

This chapter was submitted for publication in modified form: Lepock JR, Ahmed S, Mizrahi R, Bagby M, Korostil M, Gerritsen, Light G, Kiang M. Decreased gamma auditory steady-state response is associated with impaired real-world functioning in unmedicated patients at clinical high risk for schizophrenia, Clinical EEG & Neuroscience, 2020, submitted.

6.1. Abstract

Background: Schizophrenia is associated with persistent real-world functional impairment. A fundamental brain abnormality proposed to contribute to this impairment is that of deficits in synchronous, gamma band (30-100 Hz) neural oscillations thought to be crucial for information processing across cortical networks. This synchrony can be measured electroencephalographically using the gamma auditory steady-state response (ASSR). Along with Gamma ASSR, deficits in Mismatched Negativity (MMN) and P3a ERPs have been reported in schizophrenia patients, and in individuals at clinical high risk (CHR) for developing this disorder. We hypothesized that, in CHR patients, MMN, P3a and gamma ASSR measures would have greater deficiencies in CHR patients then healthy controls and would be associated with social and academic/occupational functioning.

Methods: Participants were 45 unmedicated, help-seeking CHR patients rated on social and academic/occupational role functioning using the Global Functioning: Social and Role scales, respectively; and 30 healthy control participants. We recorded participants' EEG while they were presented with a duration deviant auditory paradigm to elicit the MMN and P3a, and then listened to 1-ms, 93-dB clicks presented at 40 Hz in 500-ms trains. 40-Hz EEG evoked power (EP) and intertrial phase-locking factor (PLF) in response to these stimuli were obtained.

Results: No group differences between CHR patients and controls were detected in MMN, P3a, 40-Hz EP or PLF. In the patient group, lower 40-Hz ASSR EP correlated with lower social functioning.

Conclusion: This result suggests that gamma synchrony deficits may contribute to real-world impairment at the earliest stages of the schizophrenic disease trajectory.

6.2. Introduction

Multiple studies have shown deficiencies in first-episode psychosis (FEP) and chronic schizophrenia patients of the mismatch negativity and P300 ERP (Erickson, Ruffle, & Gold, 2016; Ford, 1999; Haigh, Coffman, & Salisbury, 2017; Kaur et al., 2011; Michie, Malmierca, Harms, & Todd, 2016; Xiong et al., 2019), where it has become a prevalent neurophysiological biomarker in the psychotic population. CHR populations, especially those who transition to a psychotic disorder, have also consistently demonstrated a deficiency in these ERPs. MMN and P3a have both been associated with functioning at baseline and over time (Hermens et al., 2010; Koshiyama et al., 2017; Lho, Kim, Lee, Kwak, & Kwon, 2019), as well as a predictor for conversion (Bodatsch et al., 2011; Kim, Lee, Lee, Kim, & Kwon, 2015; van Tricht et al., 2010), confirming its place as a significant indicator for CHRs who convert to schizophrenia. As a secondary analysis, we attempted to replicate these findings in our sample of CHRs, both as an abnormal event-related potential at baseline compared to HC and as a predictor of conversion and outcomes after 2 years follow up. We aimed to add to the existing literature and to strengthen the effect as these ERPs as significant biomarkers in the CHR state.

A few studies have reported gamma ASSR deficits in CHR patients (Koshiyama et al., 2018a, 2018b; Tada et al., 2016), suggesting that gamma synchrony abnormalities precede frank psychosis. Gamma band (30-100 Hz) oscillations reflect neural synchrony thought to be crucial for communication and integration of information across cortical networks (O'Donnell et al., 2013; Uhlhaas & Singer, 2015). This synchrony can be probed using the gamma auditory steady-state electroencephalographic (EEG) event-related potential response, in which a series of auditory stimuli presented at gamma (e.g., 40-Hz) frequency elicits entrainment of neural activity at that frequency (Picton, John, Dimitrijevic, & Purcell, 2003). This gamma auditory steady-state response (ASSR) is typically measured as a power increase in the average EEG response phase-locked to stimuli over multiple trials, known as “evoked power” (EP; which cancels out non-phase-locked activity); and by intertrial phase coherence (ITC) or “phase-locking factor” (PLF) which estimates phase consistency of EEG signals across trials independent of signal amplitude. Gamma ASSR EP and PLF are reliably reduced in schizophrenia (Kirihara, Rissling, Swerdlow, Braff, & Light, 2012; Kwon et al., 1999; Light et al., 2006; Thune, Recasens, & Uhlhaas, 2016;

Zhou et al., 2018), including during the first illness episode (Koshiyama et al., 2018b; Spencer, Salisbury, Shenton, & McCarley, 2008; Tada et al., 2016; Wang et al., 2018). Pre-clinical and post-mortem studies suggest these gamma ASSR deficits may result from dysfunction of both inhibitory parvalbumin-positive GABAergic interneurons and excitatory glutamate NMDA receptors (O'Donnell et al., 2013; Sun et al., 2011). Given the presumed importance of gamma synchrony for communication across neural networks, deficits in this synchrony may interfere with a wide range of cognitive function, in turn contributing to real-world functional impairment. Consistent with this view, gamma ASSR deficits correlate with lower function in independent living and meaningful activity in patients with psychotic disorders (Zhou et al., 2018).

In this study, as a secondary analysis, we aimed to investigate the relationship between the MMN, P3a and Gamma ASSR with positive symptoms, role and social functioning at baseline and one and two years follow up. Based on previous findings (Carrión et al., 2011; Hamilton et al., 2018), we hypothesized that MMN, P3a and gamma ASSR reductions are associated with decreased social and role functioning. This result would support the view that these ERP dysfunctions are a fundamental pathophysiological mechanism underlying functional impairment at the earliest stages of the schizophrenic disease trajectory. Although a previous study of CHR patients found no correlation between gamma ASSR and a single global rating of functioning (Koshiyama et al., 2018b), we aimed to separately measure social and role functioning, using scales specifically designed and validated to assess these in CHR patients, the Global Functioning: Role (GF:Role) and Global Functioning: Social (GF:Social) Scales (Cornblatt et al., 2007).

6.3. Materials and Methods

6.3.1. Participants

Participants included 45 CHR patients who were help-seeking outpatients recruited from the Focus on Youth Psychosis Prevention clinic at the Centre for Addiction and Mental Health (CAMH) in Toronto, and 30 healthy control (HC) participants recruited from the community by advertising online and on bulletin boards.

6.3.2. Measures of functioning

We used the SIPS as a measure of Positive Symptoms from P1 - P5 (McGlashan et al., 2001). We used GF: Social and GF: Role Scales (Cornblatt et al., 2007), to assess severity of real-world social and role functional impairment, respectively, in CHR participants. Individuals receive a score ranging from 1 (extreme impairment) to 10 (superior functioning) on each scale.

6.3.3. MMN and P3a stimuli and task

A continuous EEG was recorded from 32 electrodes in an electrode cap while participants were presented with a total of 1750 auditory tones. 90% of the tones were non-targets of a duration of 50 ms and a frequency of 633 Hz, and 10% of the targets were a duration of 100 ms and a frequency of 633 Hz. They were presented in a randomized sequence with a stimulus-onset asynchrony of 510 ms, and the participants were instructed to ignore the tones and to watch a silent cartoon video during their presentation (Perez et al., 2014).

6.3.4. Gamma ASSR stimuli and task

Following established methods (Kirihara et al., 2012; Lepock et al., 2019; Light et al., 2006), participants passively heard 1-ms, 93-dB clicks presented at 40 Hz in 500-ms trains. The stimulus block consisted of 200 trains of clicks with 500-ms intertrain intervals.

6.4 Data Analysis

6.4.1. EEG collection and analysis

During stimulus presentation, continuous EEG was recorded using an actiCHamp amplifier (Brain Products, Gilching, Germany), from 32 active Ag/AgCl electrodes embedded in a cap (actiCAP system, Brain Products) at sites approximately equally spaced across the scalp, positioned according to a modified International 10-20 System (Fp1-Fp2-F7-F3-Fz-F4-F8-FC5-FC1-FC2-FC6-T7-C3-Cz- C4-T8-TP9-CP5-CP1-CP2-CP6-TP10-P7-P3-Pz-P4-P8-PO9-O1-Oz-O2-PO10). Electrode impedances were kept below 25 kΩ. The EEG was referenced online to

FCz, and continuously digitized at 500 Hz. Blinks and eye movements were monitored via electrodes on the supraorbital and infraorbital ridges and on the outer canthi of both eyes. Offline, the EEG was re-referenced to the algebraic mean of the mastoids, and bandpassed at 0.5-100 Hz. Continuous data were algorithmically corrected for eyeblink artifact (Makeig, Jung, Bell, Ghahremani, & Sejnowski, 1997). Individual trials containing artifacts due to eye movement, excessive muscle activity or amplifier blocking were rejected offline by visual inspection before time-domain averaging.

6.4.2. MMN and P3a analysis

MMN amplitude was measured as a mean voltage of the averaged ERP for target stimuli from 135-205 ms post stimulus-onset and the P3a amplitude was measured as a mean voltage of the averaged ERP for target stimuli from 250-300 ms post stimulus-onset. Amplitude for CHR patients vs. HCP will be compared using a repeated-measures ANOVA.

6.4.3. Gamma ASSR analysis

Similar to established methods (Light et al., 2006; Spencer et al., 2008), to obtain ASSR gamma EP, the Morlet wavelet transform was applied to single-trial epochs in 1 Hz steps from 1-100 Hz at each time point from -200 to 800 ms. EP was measured as mean power at 40 Hz (wavelet frequency 33-47 Hz) of the average evoked potential from 0 to 500 ms, after subtracting pre-stimulus baseline values (-100 to 0 ms). Gamma PLF was measured as (1 – the circular variance of phases) at 40 Hz, and ranges from 0 (random distribution of phases) to 1 (perfect phase locking). For gamma ASSR EP, five patients were outliers (1.5 x the interquartile range above the third quartile or below the first quartile) and therefore excluded from further analyses. For gamma ASSR PLF, one patient was an outlier and was excluded.

6.4.4. Statistical analysis

We compared gamma MMN, P3a and ASSR EP and PLF at electrode site Fz (midline frontal), where effects are maximal, between CHR and healthy control participants using independent sample *t*-tests. To examine relationships in patients between non-normally

distributed (a) MMN and P3a and gamma EP and PLF, and (b) SIPS positive measures, and GF: Social and GF: Role measures, pairwise Spearman correlations were computed. Significance level of α=0.05 (two-tailed) was used for all tests.

6.5. Results

6.5.1. Demographics

Demographics characteristics of the study sample are summarized in Table 1. CHR and HC did not differ significantly on age, sex, parental social economic status, handedness, and IQ, but did differ years of education completed. HC had more years of education.

6.5.2. MMN and P3a

MMN and P3a mean amplitude at FZ are shown in Table 2. There was no significant difference in amplitudes found between the CHR and HC groups for either ERP. Correlation coefficients between MMN and P3a and Positive scores and functioning measures were not significant.

6.5.3. Gamma ASSR

Mean gamma (40-Hz) ASSR EP and PLF values at electrode site Fz for all participants, and GF: Social and GF: Role scores are shown in Table 2. EP (t(58)= -0.943, p = 0.349) and PLF (t(67)= -1.44, p = 1.53) did not differ significantly between groups. Correlation coefficients between (a) gamma ASSR and (b) functioning measures in CHR patients are shown in Table 3. Gamma PLF and EP were correlated (r = 0.526, p = 0.0004). Gamma PLF correlated with GF: Social scores (r=0.309, p=0.044), indicating that lower PLF was associated with lower social functioning (Figure 1).

In our analysis, we examined eight correlations: MMN and P3a, two gamma ASSR measures (evoked power and PLF) vs. two functional measures (GF: role and GF: social scores). One of these correlations, between PLF and GF: social scores (p=0.398) was significant at a p=0.05

significance level. Evoked power and PLF were themselves highly correlated (ρ=0.41, p<0.0001) as are MMN and gamma evoked power (r=-0.45, p<0.05) and MMN and P3a (r=-0.36, p<0.05). Because these variables were not independent, a Bonferroni correction for multiple tests would not be warranted.

6.6. Discussion

The present study investigated relationships between MMN, P3a gamma ASSR and symptom outcome and real-world function in antipsychotic-naïve, help-seeking patients at CHR for psychosis. None of the ERPs differed between CHR patients and healthy controls. In patients, MMN and P3a did not correlate with any of the outcome measures, whereas lower gamma ASSR PLF correlated with lower social functioning, but not with role functioning. This result suggests a role for gamma synchrony deficits in real-world impairment at the earliest stages of the schizophrenic disease trajectory, based on the view that a range of cognitive processes necessary for effective everyday function rely on this synchrony (Green, Kern, & Heaton, 2004).

Our results are not consistent with previous findings of MMN and P3a relationships with baseline and outcome measures in CHRs (Bramon et al., 2008; Koshiyama et al., 2018b), (Özgürdal et al., 2008; Van Der Stelt, Lieberman, & Belger, 2005). Tang et al. (2019) recently found CHRs who converted had lower P300 than those who did not convert and were more like the controls participants (van Tricht et al., 2010). Similarly, Kim, Lee, Yoon, Lee, and Kwon (2018) found the MMN to be reduced in those CHR whose did not remit compared to the CHRs who did remit, and the only predictor of conversion was a larger MMN, and Hamilton et al. (2019) found P3b, but not P3a as a predictor of conversion. One explanation for this is that our particular population might not be as severely impaired due to sample differences, as CHR is a heterogenous diagnosis. Therefore their MMN and P3a would resemble that of the controls.

In contrast to the relation between gamma ASSR and social functioning, no association between ASSR and academic/occupational role functioning was detected. This may be because role functioning is a less specific phenotype for neural synchrony deficits associated with schizophrenia risk, consistent with some reports that social, but not role functioning, predicts

conversion to psychosis in CHR patients (Addington et al., 2017; Cannon et al., 2008; Cornblatt et al., 2012).

A strength of this study was CHR patients' antipsychotic-naïve status. This may account for the lack of differences between patients and controls, in contrast with MMN, P3a and gamma ASSR deficits found in previous studies of CHR patients who were not antipsychotic-naïve. Limitations of our study include its relatively small sample size, and the lack of conversion to psychosis over time. Replication studies with larger samples are needed to validate the association between gamma ASSR and social functioning.

Table 6.1. Demographic, neuropsychological, and clinical characteristics of the study sample (means with standard deviations in parentheses).

	Healthy control participants ***n* = 30**	**Clinical high-risk patients** ***n* = 45**
Age (years)	22.07 (3.1)	20.76 (3.4)
Sex	18 female, 12 male	18 female, 27 male
Handedness	27 right, 3 left	41 right, 4 left
Parental socioeconomic status (Blishen, Carroll, & Moore, 1987)	51.47 (13.9)	49.80 (14.1)
Years of Education*	15.34 (1.7)	13.84 (2.7)
National Adult Reading Test (Nelson & Willison, 1991) estimated premorbid verbal IQ	109.59 (5.8)	108.60 (9.3)
Structured Interview for Psychosis-Risk Syndromes (McGlashan, Walsh, & Woods, 2014)		
Positive Scale Total	–	10.58(3.4)
Negative Scale Total	–	12.73 (4.6)
Disorganized Scale Total	–	5.51 (3.1)
General Scale Total	–	9.53 (4.1)

*Patients differed significantly from controls, $p = 0.04$

Table 6.2. Mean values for MMN, P3a and gamma (40-Hz) auditory steady-state response (ASSR) and functional measures at electrode site Fz (standard deviations in parentheses).

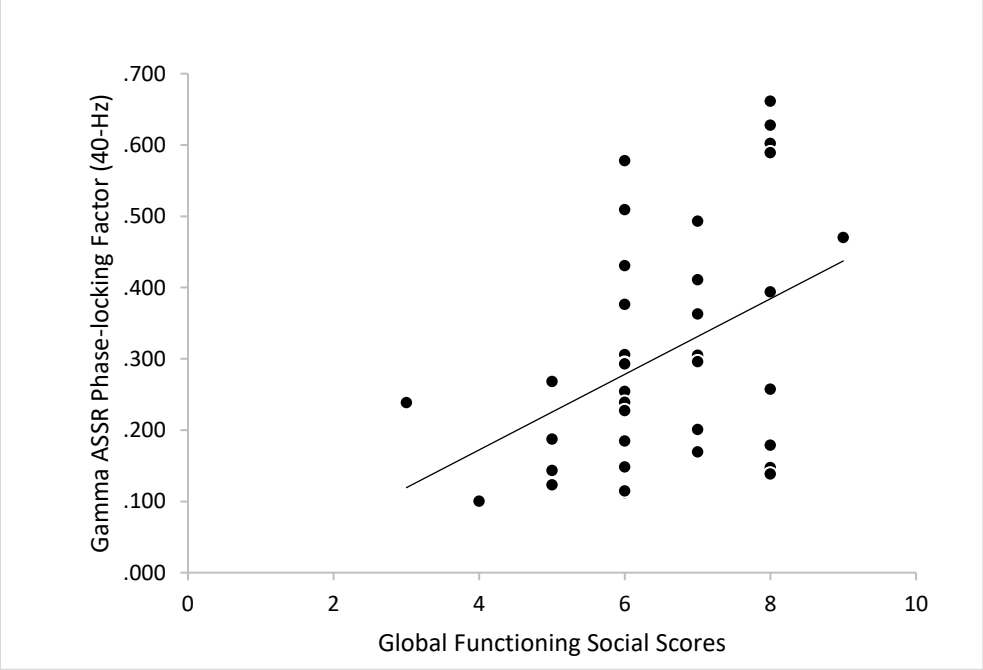
	Healthy control participants	**Clinical high-risk patients**
MMN	-4.92 (2.2)	-5.12 (2.3)
P3a	3.8 (2.81)	2.57 (2.9)
Gamma ASSR evoked power	0.74 (1.38) *n* = 30	1.34 (1.38) *n* = 44
Gamma ASSR phase-locking factor	0.29 (0.19) *n* =30	0.36 (0.21) *n* = 45
Global Functioning: Social Score	–	6.34 (1.3) *n* = 44
Global Functioning: Role Score	–	5.98(1.6) *n* = 44

Table 6.3. Spearman correlation coefficients ρ between gamma (40-Hz) auditory steady-state response (ASSR) and functional measures, in clinical high-risk patients.

	Global Functioning: Social Score	Global Functioning: Role Score
Gamma ASSR evoked power	0.139	-0.105
Gamma ASSR phase-locking factor	0.398*	-0.08
MMN	-0.283	-0.012
P3a	0.071	0.093

*p = 0.008

Figure 6.1. Scatterplot of gamma (40-Hz) auditory steady-state response (ASSR) phase-locking factor at electrode site Fz vs. Global Functioning: Social scale scores in clinical high-risk patients.



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Chapter 7

General Discussion

The identification of those at high risk for schizophrenia and their symptomology, level of functioning, cognitive abilities, and neurophysiological impairments, are imperative in the determination of who will convert to a psychotic disorder over time. We looked at a group of patients at clinical high risk for psychosis to determine whether the N400 event-related potential was deficient as it is in schizophrenia, and whether it could predict conversion to a psychotic disorder in 2 years. Participants performed computerized tasks to elicit an N400, MMN, P3a ERPs and gamma oscillations. CHR status, symptoms, functioning, and psychosis state were assessed at baseline, year 1 and year 2, and the relationship of these baseline and outcome measures to the N400 were examined. We faced several limitations with this study, specifically high attrition for the follow up assessments and a low rate of conversion to a psychotic disorder in the study sample, and consequently our main hypothesis could not be tested. However, we identified key findings about the N400 in the CHR group at baseline, and an effect of the N400 on functioning and positive symptoms over time. Based on the literature, we expected to find a significant decrease in the N400 semantic priming effect in CHRs compared to controls, due to larger than normal N400 amplitudes to related targets, across both SOAs. We also aimed to replicate past findings of deficient MMN and P3a ERPs and gamma evoked power and phase-locking factor in the high-risk group compared to controls.

With a sample of 20 in each group, we found a significant difference in the N400 amplitudes between controls and CHRs at the long SOA. In Experiment One there was no significant difference in the semantic priming effect of each group, but there was a Group x Target x SOA interaction, where there was a significant difference between unrelated and related amplitudes in controls, but no difference in the patient group. We found a similar result with a larger sample size at 47 CHRs and 25 controls, where there was a significant difference in the N400 priming effect at the long SOA at $p=0.035$. While the patient group did not have a significantly larger N400 amplitude to related stimuli as previously hypothesized, these results suggest that these individuals may be impaired in using meaningful context to initiate activation of related concepts in semantic memory, in a time intervals over 300 ms (Kiang & Gerritsen, 2019). As observed in schizophrenia patients, those at high risk might also have difficulty processing the relationships between stimulus and events within the context of their

environment, and this could lead to stimuli being perceived as unusually significant. For example, an individual with schizophrenia may believe an actor on television is speaking directly to them, and thus react to this significant message. To a lesser degree, an individual at high risk might hear a song on the radio and believe for a moment that it was playing directly for them. Healthy individuals, compared to these patients, have more of a difference in N400 amplitudes in response to unrelated versus related stimuli (i.e., larger N400 priming effects), indicating that they are able to use their surrounding context to recall factors from semantic memory that demonstrate this particular instance is expected based on this context, and therefore does not have unusual significance.

Collins and Loftus (1975) describes a model of semantic memory in which concepts are nodes. When each concept node is activated by a stimulus, activation spreads to the next node and through the network to all connected nodes. As relatedness to each node decreases, the activation falls off. Two theories discussed by Wang, Cheung, Gong, and Chan (2011) describe this impairment in schizophrenia. The processing of related conditions implies that the links between related nodes are weaker, and semantic activation spreads slower from one node to another. Or, patients with schizophrenia abnormally process weak or remotely related nodes such that there are unusually strong links between them. These two processes may happen alternatively or at different (short and long) SOA time points. Failing to connect and to appropriately activate stored contextual information may generate expectancies for external stimuli. In searching for an explanation for this emerging stimuli, leads to the development of Delusional beliefs and thought disorder may evolve out of an attempt to explain this emerging stimuli (Hemsley, 2005). These delusions and disorganized speech are found to contribute to psychotic symptoms and deficient functioning in schizophrenia patients. Since we found a similar abnormal N400 effect in the CHR group as to those in schizophrenia individuals, we would expect this effect to be associated with psychotic symptoms and overall functioning. Since this is the only study to look at the N400 amplitude and priming effect in the high-risk population, further studies with larger samples are needed in separate CHR populations to replicate and progress our findings.

7.1. Outcome Measures in CHR Individuals

7.1.1. Attenuated Psychotic Positive Symptoms

In past years, it has been suggested that transition to a psychotic disorder is not the most valid method of identifying which of those at high risk will have a poor outcome (Lin et al., 2011). It may be more productive to examine functional outcome and predictors, such as symptoms and global functioning, rather than a dichotomous predictive model of converted/nonconverted. Underlying mechanisms of the N400 semantic effect have been suggested to contribute to thought disorder and delusions in schizophrenia (Kumar & Debruille, 2004) and those at high risk for schizophrenia (Kiang & Gerritsen, 2019). Thus, we would expect to see an association with these symptoms at baseline and over time in those at risk. This was not the case in our sample. However, we found that N400 semantic priming effects predicted change in total positive symptoms as measured by the SIPS (including unusual thought content and disorganization scores), paranoia/suspiciousness scores and perceptual abnormalities scores over 2 years. Those who had a deficient N400 priming effect had less improvement in these attenuated psychotic symptoms over 2 years than those who had a more normal priming effect. Total SIPS positive symptoms of unusual thoughts, paranoia, grandiosity, perceptual abnormalities, and disorganization are shown to have difficulty resolving over time in those CHR individuals who are unable to maintain a contextualization process of meaningful stimuli in their environment. We found no correlations with positive symptoms and the N400 amplitudes or effect, meaning that it is the improvement of symptoms over time that is associated with the N400 priming effect.

7.1.2. Functioning

With a sample of 35 CHR patients we found an association with the short SOA and role functioning. A smaller N400 priming effect was related to a decrease in functioning in those at high risk. This association was again demonstrated as a function of time over 2 years in a population of 47 CHR individuals, where the functioning in role capacity improved less over time in those with attenuated N400 priming effect at the short SOA than those with a larger N400 effect. The short SOA priming effect is thought to be attributed mainly to early automatic semantic activation. Therefore, CHRs who have deficiencies in this early activation demonstrate the greatest failing with functioning (Lepock et al., 2019). Impairments in role functioning cause

emotional and financial distress on patients, their families, and society. It is thought that cognition can account for 20-60% of the variance in these functional outcomes (Lee et al., 2019), especially those in a role capacity, and these short SOA deficits of automatic semantic activations may mediate this variance. Social and role functioning may be associated with different aspects of neurocognition in CHR samples, explaining the inconsistencies in our findings of relationships to social and role functioning (Lin et al., 2011).

Social disability and functioning may be an early biomarker of schizophrenia, and is highly correlated with the illness' financial costs (Lin et al., 2011). Jackson et al. (2014) found that reduced N400 amplitudes were associated with social functioning in schizophrenia patients. Impaired social functioning has been found to be a predictor of transition to a psychotic disorder in CHR patients (Cannon et al., 2016). We found correlations between the N400 priming effect at the long SOA and social functioning scores and change in scores at one year follow up. A smaller N400 effect was associated with a lower score in social functioning after the first year, and smaller increase in change from baseline to year one. We also found that the smaller N400 priming effect had a smaller improvement in social functioning over time from one and two years. The GAF, a widely used global scale to measure symptom severity and functioning of those at high risk for psychosis, is thought to be too confounded with symptoms to properly assess developmentally specific functioning (Cornblatt et al., 2007; Lo Cascio et al., 2017). This study was able to establish a distinction between CHR patients with poor functional outcome to those who experience better outcomes over 2 years, demonstrating that it is beneficial when studying the CHR population to focus on outcome variables more than just psychosis transition.

7.2. Comorbidity

For exploratory purposes, we investigated comorbidity of pathologies in our study population. 94% of our CHR sample had at least one comorbid disorder at baseline as measured by the Structural Clinical Interview for DSM-IV (SCID). Depressive disorders were the most common at 57%, followed by anxiety disorders at 13%. Depression and anxiety were also the predominant disorders of those followed up at one and two years. These findings replicate the findings of (Lim et al., 2015) who found comorbidities of depression and anxiety in their CHR sample at one year, which is concordant with other CHR findings. Comorbidity has been associated with lower function in high-risk states (Fusar-Poli et al., 2013), suggesting that it

could compromise the individuals' ability to cope with real world situations. Like our sample, Lim (2015) found no difference in comorbidity to those who converted, suggesting it may only be associated with greater functional impairment. Treatment of these comorbidities to those at high risk may help to increase their ability to cope and decrease their functional impairment. We were unable to test the comorbidity of those who were lost to follow up for 1 and 2 years. It is possible that their comorbid illnesses worsened over this time, causing the participants to be unreachable.

7.3. Other Event-Related Potentials

We found an effect of gamma ASSR and social functioning in our CHR population, but no other ERPs tested were found to be significantly abnormal. Multiple studies have found the MMN and P300 to be deficient in the prodrome, and some predicted conversion, providing evidence for possible biomarkers of this state. Our goal was to combine these measures to increase the predictive power of these ERPs in conjunction with the N400 effect to determine whether these neurophysiological tests would prove more effective at determining conversion together than individually. Unexpectedly, neither MMN, P3a or gamma ASSR was deficient in the high-risk group compared to the healthy controls. This finding could be representative of our sample and low conversion rate, as CHR patients who convert show an abnormal in MMN and P3a amplitudes vs those CHRs who do not (Bodatsch et al., 2011; Hamilton et al., 2019). Although contrary to most of the literature, our findings are similar to that of Atkinson et al. (2017) who found no significant differences in the MMN and the P3a amplitudes in their CHR group compared to controls. This CHR sample had a low conversion rate of 10%, and the authors speculate that a higher population of converters would have been needed to see a difference in the ERPs between the groups. Only two previous studies have shown a significant difference of gamma in CHR patients and controls, (Koshiyama et al., 2018; Tada et al., 2016), and this area needs to be researched further.

7.4. Limitations

We encountered several limitations when carrying out this study. Although our baseline recruitment was 47 participants, due to attrition, we were only able to assess 30 at year 1 and 18

at year 2. The Focus on Youth Psychosis Prevention Clinic at the Centre for Addiction and Mental Health follows patients for 6 months, contributing to loss to follow-up at years 1 and 2. At year 2 the dropout rate was 49%, which was higher than anticipated. In addition, there were only three participants who converted to a psychotic disorder from baseline over 2 years. The conversion rates of 8.7% and 7.1% of all participants followed at year 1 and year 2 respectively, is lower than the convention of 30% conversion over 2-3 years (Cannon et al., 2008). There are a number of possibilities why our sample did not convert to schizophrenia, which add to the trend of general decreasing transition rates. Although antipsychotic-naïve at baseline, many of our patients might have undergone some form of treatment post baseline. This included medication such as antidepressants, low dose antipsychotics, and psychiatric intervention. This treatment could have prevented or delayed psychosis onset. Our participants could have been influenced by *Lead Time Bias*, where the earlier the detection of high-risk symptoms could result in a delayed psychosis onset or transition prevention. Another possibility is *The Dilution Effect*, where those who are help seeking but are not at high-risk are referred to services because of prodrome criteria and clinics becoming more well-known (Fusar-Poli et al., 2013). Hartmann et al. (2016) found that because of this, earlier CHR cohorts (1995-2000) may have presented a greater number of symptoms than later CHR cohorts (2000-2006), and this has contributed to the declining transition rate.

Psychosis risk criteria also have the potential to lead to false positive cases. We used the widely used and validated Structured Interview for Psychosis-Risk Syndromes (SIPS) to assess our participants for the CHR state. However, being at high risk is a continuous state, and one person may be more at risk that others in the same cohort. There are other measures used in psychosis conversion studies, the CAARMS and SPI-A, and these assessments may be measuring different symptoms underlying the prodromal phase. One cohesive measurement might be useful for future high-risk research, so that the high-risk population is assessed with the same criteria in order to decrease false positive cases. This study followed its participants for 2 years. Many studies have used a 3 year or more follow up timeline to measure conversion to psychosis, and it is a possibility that we would see a higher rate of conversion over 2 years. Also, a few studies have found that some schizophrenia patients experience a prodrome like syndrome that resolves, only to then develop full blown schizophrenia sometime later (Fusar-Poli et al., 2013).

Because of the low number of conversions in our sample, we were unable to run a

survival curve prediction analysis of the N400 and time to conversion. Our sample size was too small to run a cox regression analysis of the predictor variables in follow up. Therefore, we were unable to confirm our original hypothesis about the N400 being a predictor of conversion, combined with other predictors of MMN, P3a and gamma ASSR.

To our knowledge, this is the first study to find an association with the N400 priming effect and symptom and functioning change over time in CHR patients; however, there are a number of facets of the study that were limitations. High risk was assessed at baseline with the SIPS, using a generic cut off score to determine status. However, due to the low conversion rate of our subjects, it might have been more effective to set a higher cut off score in the SIPS with stricter parameters to ensure participants had more high-risk symptoms. However, this would have decreased our recruitment numbers and/or increased our recruitment time. Secondly, social and role functioning was assessed at baseline and follow up for the CHR participants but not for controls. Had we measured functioning for our healthy group, we would have been able to compare the two groups at baseline and follow up and assess the difference in the association between the N400 and functioning in both groups. This would affirm our results in demonstrating the relationship as being exclusive to high-risk individuals. Finally, our participants were antipsychotic-naïve at baseline for the ERP task and EEG recording; however, it is unknown if any participants started taking medication or participated in therapy within the two years post baseline. We would have been able to integrate this information when assessing the amelioration of symptoms over time for the CHR group, and would have benefited our finding that the N400 at the long SOA predicted symptoms over time in the high-risk group.

7.5. Conclusions

We hypothesized that in CHR participants we would find the N400 priming effect to be deficient compared to healthy controls, either by a significantly larger (more negative) amplitude to related stimuli, significantly smaller (less negative) amplitude to unrelated stimuli, or both. We found in Experiment One, with a sample of 20 CHR and 20 HC, at the long SOA for controls, the N400 amplitude was larger for unrelated than related targets, whereas for patients there was no difference in N400 amplitude between these conditions. As hypothesized, CHR patients have abnormalities in activating related concepts in long-term semantic memory. At a larger sample of 47 CHR participants and 25 HC, there was a significant difference in the

semantic priming effect at the long SOA, demonstrating that although we did not find a difference between the amplitudes of related and unrelated stimulus, the difference between the two for CHRs was significantly smaller. These findings continue to support our primary hypothesis: that those at high risk for psychosis process stimuli differently and are unable to maintain activation of meaningful concepts over a longer time interval. We also hypothesized that the N400 would be related to cognitive, role, and social functioning in those at high risk at baseline. For our population of 35 CHR participants, we found that the N400 at the long SOA was correlated with lower cognitive function as measured by the MCCB, and at the short SOA a decline in role functioning. This low cognitive functioning confirmed our hypothesis and is to be expected in a CHR population that is defined by low cognitive abilities.

Whereas we did not find an association with social functioning and the N400 at baseline, there was a relationship at follow up. We hypothesized that we would find a negative correlation with the N400 and functioning at one and two years follow up, and positive relationships with psychotic and disorganized symptoms. Although not all baseline CHRs were assessed at follow up, we found a negative correlation with the long SOA and social functioning at one year and the change of social functioning from baseline to one year. Those at high risk with N400 priming effects that were more negative had higher scores of social functioning at year one, and greater change of functioning over this year.

Although we were not able to confirm our hypothesis that the N400 would predict conversion in those at high risk, our findings do show an effect of the N400 on symptoms and functioning over time. We were able to demonstrate that those individuals with a more abnormal (less negative) N400 priming effect at the long SOA had less improvement in psychotic symptoms and social functioning, compared to those that had more negative priming effects. We did not find a specific correlation with disorganized speech or thought disorder as originally hypothesized. Had the study continued to follow up the participants past the two-year mark, we may have found those with more deficient symptoms and functioning, and with less negative N400 priming effects did go on to develop schizophrenia. Therefore, with more testing, the N400 ERP could be added to a number of predictor values used to determine which CHRs will demonstrate more severe deficient outcomes in symptoms, cognition and functioning, and which may eventually go on to convert to a psychotic disorder. Electrophysiological measures used to test the N400 are relatively inexpensive and reliable. This research could contribute to the development of ERP models and the discovery of biomarkers used to help predict psychosis in

the high-risk state.

7.6. Future Directions

Our study used the N400 to study CHR individuals' abnormalities in processing meaningful context. From this work emerges several questions that need to be answered before the N400 is seen as a legitimate prodromal biomarker. It would be ideal to continue to assess those CHR patients in this study longitudinally, to increase the sample size for associations with functioning and psychotic symptoms, as well as to increase the conversion rate in this sample. A conversion rate closer to the norm of 30% would allow us to test the N400, along with other ERPS, as a predictor variable to determine its influence on conversion.

In the future, it would be useful to measure the N400 effect not only at baseline but at the follow up time points as well. This would enable the N400 to be assessed as an effect of time, as well as any relationships between symptoms and functioning as it may fluctuate. In CHR research, is it common to assess those who remit from CHR symptoms vs those who do not. It would be interesting to test the N400 on those at ultra-high risk for psychosis (high cut-off scores on the SIPS), and to assess them longitudinally to determine conversion to and remission from high-risk symptoms. Previous findings have found significant differences in the MMN and P3a in those CHRs who remitted vs those who do not (Kim, Lee, Yoon, Lee, & Kwon, 2018), in some cases their ERPs resemble those of healthy controls (Tang et al., 2019). Remission and its associated symptoms could be another method to assess the N400 in those at risk, without having to rely on conversion as an outcome measure.

Schizophrenia is a debilitating disease of which the underlying causes and mechanisms are still widely unknown. Although it is a general consensus that there is a prodromal period of time before the first psychotic episode where one experiences attenuated symptoms, a decline in cognition and functioning, there is still much to be learned about this stage and how its diagnoses can directly affect conversion. There are many individuals at the high-risk state who will not go on to develop schizophrenia or a psychotic disorder, but who continue to suffer with these symptoms. A portion of this population will recover over time with no treatment. Research into the CHR state is imperative not only for the understanding of schizophrenia, but also for the treatment of these young individuals who endure attenuated and brief psychotic symptoms that greatly affect their teenage years and young adulthood. Our particular sample had a low

conversion rate; however, our participants still had difficulties with functioning in a school or work setting, socially with family and friends, they suffered from paranoia and hallucinations and they endorsed depressive episodes and anxiety disorders. By using neurophysiological methods, including the N400 and gamma ASSR, we may be able to determine which of those at high risk will have the most severe outcomes and will therefore benefit from treatment and support the most. The N400 effect as an example of how we process meaningful stimuli and integrate them into context, may help us shed light on the cognitive mechanism of symptoms such as cognitive decline and disorganized speech. Our findings from this study could be useful in developing an algorithm including multiple ERP biomarkers in conjunction with clinical symptom and functional measures, as a predictor of not only conversion to psychosis but also of remission from the clinical high-risk state.

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