# INVESTIGATING CONCURRENT AND LONGITUDINAL ERP-SYMPTOM RELATIONSHIPS AMONG RISK FOR PSYCHOSIS

by

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*In dedication to the host of family, friends, teachers, and animals who have inspired personal growth throughout life.*

*To my family who may have never fully understood what this was all about, but supported and encouraged me anyway.*

*To my friends, near and far, for filling my life with joyful memories, my soul with peace, my heart with love, and my stomach with wine. For being there to laugh a little louder, smile a little bigger, and cry a little harder.*

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# ABSTRACT

Cognitive impairments in schizophrenia (SZ) include abnormalities in executive function, attention, and semantic processing. Event-related potentials (ERPs) are used as neurophysiological measures of cognitive impairment that have been shown to map onto symptom dimensions of psychotic disorders, such as schizophrenia. While much research exists on schizophrenia, less is understood about the longitudinal relationships between ERPs and symptom dimensions among individuals at risk for psychosis. Of published work in risk samples, most have been cross-sectional, leaving clinical inferences regarding longitudinal patterns non-specific. The current study aimed to bridge this gap by recording ERPs (P300, ERN, N400) across a battery of tasks within a single risk sample, and measured positive, negative, and disorganized symptom severity via the Multidimensional Schizotypy Scale (MSS). Participants exhibiting psychosis-risk were recruited from the community (N=60), and completed a baseline and 6-month follow-up assessment (n=29). The primary goal of the baseline assessment aimed to replicate ERP-symptom dimension relationships observed in the SZ literature. Effect sizes for P300-positive and ERN-negative relationships were observed to be in the same directionality as noted in the clinical SZ literature. While not statistically significant, the small effects suggest that P300 and ERN may be similarly effected by presence of positive and negative symptoms, respectively. By contrast, N400, however, was found to have an effect size directionality opposite to that reported in the literature. This finding is consistent with mixed presentation of disorganized symptoms in clinical SZ populations. The follow-up assessment aimed to examine the relationship of symptom dimensions over time in a single at-risk sample, and leveraged ERPs as potential prospective predictors of worsening of symptoms. As expected, baseline symptoms prospectively predicted corresponding symptoms at follow-up. However, only N400 amplitude at baseline correlated with disorganized symptoms at follow-up, and no ERP prospectively predicted corresponding symptom dimensions at follow-up. Overall, examining the relationship between multiple ERPs and symptom dimensions in a single sample and via a longitudinal design is a novel addition to the literature. Future research will be necessary to clarify the use of ERPs as neural biomarkers to identify and predict symptom severity over time, ultimately reducing subjectivity in clinical diagnosis and treatment.

# INTRODUCTION

## The Psychosis Continuum

While psychosis reflects a loss of contact with reality, it is not unique to any one diagnosis. Specifically, psychosis is a set of symptoms that are serious but non-specific. There are many reasons that one may be experiencing psychosis, including a diagnosis of schizoaffective disorder, substance induced psychosis, or schizophrenia. Individuals formally diagnosed with psychotic disorders represent only a portion of the total phenotypic continuum of psychosis, with a larger proportion made up of individuals who are at risk for psychosis and experience subthreshold psychotic experiences (Eaton et al., 1991; Johns et al., 2002; Kelleher & Cannon, 2011; Konings et al., 2006; Peters et al., 1995; Raine, 1991; Raine et al., 1994; Tien, 1991; Verdoux et al., 1998). The dichotomous model of psychosis (i.e. idea that one has the presence or absence of psychosis) has been replaced given decades of research indicating that psychotic symptoms exist on a continuum. The extreme ends of the continuum are characterized by individuals meeting diagnostic criteria for a psychotic disorder, and healthy individuals who experience psychosis-like phenomena. Over the past few decades, researchers have investigated this population and have referred to these individuals by several terms, including clinical high risk (Cornblatt et al., 2007), schizotypy (Eckblad & Chapman, 1983), and psychosis proneness (van Os et al., 2009), among others. Given the small proportion of the population who meet diagnostic threshold for psychosis, the continuum may conceivably be comprised of mostly "healthy" individuals (van Os et al., 2009).

The notion of the psychosis continuum is not novel. Paul Meehl (1962) proposed a taxonomy model where he posited the relationship between schizotaxia, schizotypy, and schizophrenia varied minimally given their phenotypic expressions. A few decades later, Chapman and Chapman (1984) reported that non-clinical individuals who experience perceptual aberrations and other psychotic experiences were vulnerable to transitioning to a psychotic disorder. Followed up over a 25-month period, the authors reported that, of the high-scoring participants during the initial interview, 3 of the 162 individuals had received treatment intervention for psychosis. More recently, in the US National Comorbidity Survey, 28% of individuals endorsed psychosis-screening items (Kendler, 1996), while 7% met criteria for formal psychotic disorders. Recent literature has reported a median prevalence of 5-8% of the general population experiencing

psychotic-like experiences (i.e. subthreshold symptoms in the absence of illness; Kelleher & Cannon, 2011a), and these rates are even higher in adolescents (Laurens et al., 2007; Poulton et al., 2000; Spauwen et al., 2003).

Among adolescents, studies have reported intermittent and minimally distressing experiences including perceptual aberrations, persecutory ideas, grandiosity (Armando et al., 2010), hallucinations (Dhossche et al., 2002; Ruhrmann et al., 2012), as well as impairments in language, motor function, and executive function compared to healthy counterparts (Blanchard et al., 2010). Among healthy college-aged students, another study reported that brief auditory hallucinations were reported among 71% of their sample, while 39% endorsed experiences of thought broadcasting (Posey & Losch, 1983). Similar findings were supported by other studies of young adults (Barrett & Etheridge, 1992; Bentall & Slade, 1985; Launay & Slade, 1981; Young et al., 1986), and in the general adult population (Parra, 2006; Tien, 1991). Notably, The Netherlands Mental Health Survey and Incidence Study (NEMISIS), a longitudinal study of incident psychotic experiences, recruited a representative sample ($N$ = 7,076) of individuals 18 to 64 years and found that 8% of individuals with at least one psychotic experience were evaluated to have subclinical outcomes two years later (Hanssen et al., 2005). Individuals experiencing psychotic-like experiences were sixty times more likely to transition to a clinical psychotic disorder than those who did not endorse psychotic-like experiences. Other studies have investigated the prevalence of delusional ideas, or beliefs in unscientific or parapsychological phenomena. One study of note administered the Peters Delusions Inventory (PDI) to a large group of healthy adults as well as a group of patients diagnosed with psychotic disorders. Results showed that while the patients had significantly higher mean PDI scores (including distress, preoccupation, and conviction), the ranges in scores of the healthy group were almost identical to the patients (Peters et al., 1995), suggesting further evidence of a phenotypic continuum.

At-risk individuals share cognitive functioning deficits (Cannon et al., 2002; Horwood et al., 2008; Johns et al., 2004; van Os et al., 2009), etiological risk factors (Cantor-Graae & Selten, 2005; Fanous et al., 2001; Hanssen et al., 2006; Kendler et al., 1993; Linscott & Van Os, 2013; Polanczyk et al., 2010; Read et al., 2005; Vollema & Hoijtink, 2000), and even demographic characteristics (Johns et al., 2002; Laurens et al., 2008; Linscott & Van Os, 2013; Scott et al., 2005; Spauwen et al., 2004, 2006; van Os et al., 2009) with individuals diagnosed with psychotic disorders. Although, for those at risk, experiences of psychotic-like symptoms typically do not

meet comparative levels of distress or severity as those who have been formally diagnosed. Nevertheless, the presence of these experiences are risk factors for suicidal behavior (Ian Kelleher et al., 2012), other psychiatric disorders (Kelleher et al., 2012; Werbeloff et al., 2012; Yung et al., 2009), and poor functional outcomes (Rössler et al., 2007). However, one's experience of psychotic-like symptoms does not definitively imply that the individual will inevitably meet diagnostic threshold for psychosis; symptoms may be transitory and disappear over time.

While there is much research indicating risk for conferring psychosis based on premorbid endorsement of psychotic-like experiences, other work has indicated that risk may not be as clear (Addington et al., 2011). The NEMISIS study referred to above, among the individuals who endorsed psychotic-like experiences, 84% did not report these experiences when re-evaluated two years later (Manon Hanssen et al., 2005). Other estimates suggest that 16-29% of individuals at risk may transition to psychosis within two years (Cannon et al., 2016; Fusar-Poli et al., 2012; Nelson et al., 2013). Studies have found that experiences of positive symptoms among adolescents were not associated with psychotic disorders 8 years later, but rather non-psychotic psychopathology (Dhossche et al., 2002). However, this is not surprising given the high comorbidity of non-psychotic psychopathology and psychosis, as well as the interconnected mood characteristics of psychotic disorders (e.g., schizoaffective disorder versus mood disorders with psychotic features). Mood symptoms like depression are not uncommon observations among prodromal stages, and have been linked with increased risk for future conversion to a psychotic disorder (Häfner et al., 1999; Yung et al., 2003; Yung & McGorry, 1996).

While the boundary between health and illness may make conceptual sense, we know that psychiatric illnesses such as psychosis cannot be reduced to a single gene or dichotomous phenomenon. Rather, interacting causes contribute to the manifestation and phenotype of a given disease. That is, the field has yet to determine a specific pathway whereby one may confer risk for psychosis. Of those at risk, it remains unclear who will later convert to meet full diagnostic criteria, and who will remain relatively stable throughout their lifetime. Currently, much of what is known about at-risk groups are gleaned from those who are experiencing symptoms that are distressing enough to warrant help-seeking behavior and are those who may confer psychosis within a relatively short period of time. This suggests that the onset of psychotic-like experiences may have begun some time before that, but did not reach the level of distress or impairment for treatment. Given that minimizing duration of untreated illness directly relates to long term, functional

outcomes among these groups, it is essential to continue the work in identifying those at risk even before symptoms reach a distressing or impairing level. While there is clear evidence of overlapping risk factors between clinical and non-clinical groups, one of the main challenges for examining etiology of such disorders are low incident rates, limiting one's ability to examine the course of illness in large numbers across the lifetime. To this end, given the higher prevalence of psychotic-like experiences in the general population, investigating populations at elevated risk and examining symptom presence, severity, and structure may provide a useful glimpse into premorbid phase of psychotic disorders.

## Symptom Structure of Psychosis

Schizophrenia (SZ) is a severe psychotic disorder that is relatively rare, occurring in approximately 1% of the population (American Psychiatric Association, 2013). It is characterized by positive (disruption in content of thought ranging from odd beliefs to delusions, hallucinations), negative (flat affect, avolition, alogia) and disorganized (disturbances in ability to organize thoughts, speech, behavior) symptom dimensions, though these deficits fluctuate independently both within and between individuals (American Psychiatric Association, 2013; Bromet et al., 2011; Kotov et al., 2011, 2017). Negative symptoms (Kwapil, 1998; Mason et al., 2004; Piskulic et al., 2012a; Velthorst et al., 2009; Yung et al., 2005), attenuated positive symptoms, disruptions in functioning (Davies et al., 2018; Jones et al., 1993; Yung et al., 2003), and disorganized symptoms (Eslami et al., 2011; Flückiger et al., 2019) have been reported to predict conversion to a psychotic disorder. Just as SZ-related deficits can be broken into three core symptom dimensions, at-risk groups have also been shown to exhibit a multi-dimensional symptom structure (Bentall et al., 1989; Claridge et al., 1996; Flückiger et al., 2019; Gruzelier, 1996; Raine et al., 1994; Venables & Bailes, 1994; Williams, 1994), though reliable factor structure across studies has yet to be firmly established.

One avenue for incorporating a reliable and objective factor structure is through the use of neurophysiological measures that are able to detect aberrations in brain activity prior to onset of observable symptom manifestation (De Wilde et al., 2007; Rao et al., 1995; Strik et al., 1994; Turetsky et al., 1998). While decades of psychological practice have been relatively successful at diagnosing individuals experiencing pathology in the moment, symptom-based approaches may be better utilized when also accompanied with biological approaches. To this end, biological

approaches allow for more nuanced understanding of manifest illness deficits observed in behavioral and self-report measures, and may differentiate and predict those who may go on to develop pathology in the future, including SZ. A promising approach for integrating biological systems into current understanding of psychopathology is through the use of event-related potentials (ERPs). ERPs are scalp-recorded measures of neural activity with excellent temporal resolution and have been used to quantify deficits in primary domains of cognitive functioning such as executive function (Falkenstein et al., 2000; Foti et al., 2012, 2013, 2016a), attention (Ford, 1999; Gray et al., 2004; Mathalon et al., 2000; Polich & Kok, 1995), and semantic processing (Jackson et al., 2014; Kiang et al., 2008; Kutas & Federmeier, 2000; Mathalon et al., 2002; Mathalon et al., 2010) among individuals with formally diagnosed SZ.

Given that SZ is a heterogeneous disorder, at the population and individual level, ERPs are excellent tools to identify psychophysiological aberrations associated with SZ prior to onset of the disorder and may glean information regarding the pathogenesis of the disorder. In particular, the P300 is an ERP component that has been linked with positive symptoms and attentional deficits in SZ. It is a positive-going potential that is generally increased (more positive) for stimuli that are salient, novel, target, or infrequent (Ford, 1999; Gray et al., 2004; Mathalon et al., 2000; Novak & Foti, 2015; Polich & Kok, 1995; Frodl et al., 2002). The P300 reflects trait-like aberrations in SZ (Hamilton et al., 2018; Mathalon et al., 2000), and remains reduced in individuals even after relative remission (Mathalon et al., 2000; Rao, Ananthnarayanan, Gangadhar, & Janakiramaiah, 1995), though other studies have shown P300 may be sensitive to fluctuations of symptom states over the course of illness (Ford, 1999; Ford et al., 1992; Mathalon et al., 2000).

Another core cognitive deficit observed in SZ involves impairments in executive function—our cognitive control ability that allows us to monitor errors and maintain goal-directed actions. ERP studies have consistently noted blunted neural activity associated with monitoring errors on speeded reaction-time tasks. This neural component is known as the error-related negativity (ERN), is shown to track negative symptoms, and is associated with impairments of executive function (Foti et al., 2012; Hillyard & Kutas, 1983; Perez et al., 2012; Kerns, Nuechterlein, Braver, & Barch, 2008). This finding is also supported with neuropsychological literature (Ventura et al., 2009). The ERN is elicited approximately 50-100 ms following erroneous responses (Falkenstein et al., 1991; Gehring et al., 1993), and is thought to be generated from the anterior cingulate cortex (ACC). The ERN has been reliably shown to be blunted among

individuals formally diagnosed with SZ (Alain et al., 2002; Bates et al., 2002, 2004; Foti et al., 2012, 2013; Kansal et al., 2014; Kopp & Rist, 1999; Mathalon, Fedor, et al., 2002; Morris et al., 2006), other related psychotic disorders (Foti et al., 2012, 2013; Minzenberg et al., 2009), high-risk groups (Laurens et al., 2010; Perez et al., 2012), and unaffected siblings (Simmonite et al., 2012) gleaning evidence for ERP deficits that represent early markers of risk, or a vulnerability to psychosis.

Further, disorganized cognitive functioning abilities has been linked with poor performance on measures of concentration, learning, and language processing (Bilder et al., 1985; Kiang & Gerritsen, 2019; Liddle, 1987a, 1987b). Formal thought disorder, information processing abnormalities, and disorganized speech are central signs of SZ and are often observable prior to formal diagnosis of the disorder (Kircher et al., 2003; Kostova et al., 2005; Kumar & Debruille, 2004). Loosening of associations, poverty of content, and disturbances of comprehension have all been described in extant literature (Andreasen & Grove, 1986; Green & Walker, 1985; Kutas & Federmeier, 2011; Mathalon et al., 2010) and are thought to be due to dysfunction in context processing. For typically developing adults, language networks are developed based on associations that are reflected by our lexical knowledge and the information known about words and their relationships with other words. The development of these semantic networks directly affect one's ability to organize thoughts and communicate effectively. Language information is processed more efficiently as a function of semantic priming: the tendency to respond more quickly to a target when it is preceded by a semantically related prime (Neely, 1991). According to spreading activation theory, the more activated the semantic network becomes, the more efficient the brain can process incoming information. Efficiency in information processing declines as the semantic relationship between stimuli widens (Collins & Loftus, 1975). An electrophysiological analog of semantic priming is the N400 and it is largest (i.e. most negative) to unrelated (unprimed) information, slightly reduced to related information, and absent semantically matched (primed) information (Kiang et al., 2008; Kutas & Federmeier, 2011; Mathalon et al., 2010b). Studies have reported aberrations in semantic priming in SZ both in terms of N400 and also reaction times to unprimed stimuli (Kostova et al., 2005; Mathalon et al., 2002; Ryu et al., 2012).

Currently, there exists inconclusive understanding of the neurophysiology of risk for psychosis. Specifically, which illness features relate to ERPs among individuals at risk. Existing

literature is mixed regarding psychiatric outcome of risk groups, with evidence for higher rates of schizophrenia spectrum disorders (Chapman et al, 1994; Kelleher & Cannon, 2011), psychosis NOS, delusional disorder (Chapman et al, 1994), schizophreniform disorder (Poulton et al., 2000), and mood disorders with psychotic features (Chapman, 1994). Mapping specific SZ-related neurophysiological deficits may begin to explain heterogeneity among the risk spectrum and differential pathways of risk (Bentall et al., 1989; Claridge et al., 1996; Gruzelier, 1996; Raine et al., 1994; Venables & Bailes, 1994; Williams, 1994). Specifically, identifying physiologic underpinnings of those at-risk similar to those of SZ may imply individuals on the same pathological trajectory for developing SZ in the future. Alternatively, given that the symptom-related factor structure for those at risk has not been reliably established, those at risk may confer risk through qualitatively distinct mechanisms that are currently unknown. By combining ERPs and symptom measures in a multivariate way, we can potentially identify a neural profile, or pathway to illness, that may begin to make sense of the heterogeneous nature of the disorder. Ultimately, such work will provide novel insight into biomarkers for risk, which will set the baseline for understanding and predicting disease progression and establishing therapeutic and pharmaceutical interventions to address psychosis and psychotic symptoms at an earlier stage than currently possible.

# STUDY 1

The central tenet of the current study was to leverage ERPs as objective measures of temporal brain activity to identify unique psychophysiological risk factors that correlate with psychosis symptom dimensions, within a single sample. In order to translate known neural deficits in SZ to a risk group, the current study utilized a battery of well-validated ERP tasks to measure executive function, attentional resources, and language processing, within a sample of at-risk young adults. Utilizing ERPs in this way provides additional insight into potential biomarkers of pathological cognitive processes necessary for early detection and subsequent intervention of psychosis syndromes. The ability to identify individuals exhibiting subthreshold symptoms may enhance detection and further refine understanding of etiological risk factors associated with psychosis.

## Aim 1

Psychosis, and by extension schizophrenia, is heterogeneous in its development, progression, and prognosis. Part of this heterogeneity is accounted for by the multidimensional structure of the disease, including positive, negative, and disorganized symptoms (American Psychiatric Association, 2013; Kwapil & Barrantes-Vidal, 2015; Mason & Claridge, 2006). Extant literature suggests a similar symptom structure among subclinical populations. Within this symptom structure, there is consistent evidence for the existence of positive and negative dimensions of psychosis in the clinical and subclinical domain, whereas findings for a disorganized dimension have been mixed (Gruzelier, 1996; Kitamura et al., 1995; Mata et al., 2003; Vollema & Hoijtink, 2000). Among SZ, the literature has demonstrated that these dimensions have relatively specific and unique correlates with ERPs, namely P300, ERN, and N400. Similarly, symptom presence and severity is also linked with aberrations in ERP amplitude. Therefore, within the current study, ERPs are hypothesized to map on to qualitatively similar symptom dimensions to that of SZ. Specifically, the P300 will correlate negatively with positive symptoms (Ambrosino & Simonds, 2001; Ford, 1999; Higashima et al., 2003; Mathalon et al., 2000; Shenton et al., 2001), the ERN will correlate negatively with negative symptoms (Bowie et al., 2006; Foti et al., 2012; Johnson-Selfridge & Zalewski, 2001; Velligan et al., 2000) , and the N400 will correlate negatively

with disorganized symptoms (Jackson et al., 2014; Kiang et al., 2007a, 2008; Mathalon et al., 2010).

Despite our understanding of the multidimensional structure of SZ symptoms, most research to date has encompassed cross-sectional studies that are limited to *single* ERP components. Thus, there exists a gap in the literature examining associations of combinations of ERPs and illness characteristics within a single sample. This leads to the first aim of the study: We sought to calculate three sets of bivariate correlation analyses in a single sample, testing for three target ERP-symptom relationships (i.e., ERN-negative symptoms, P300-positive symptoms, N400-disorganized symptoms). Specific hypotheses are as follows:

Hypothesis 1:

1. Reduced P300 amplitude will be associated with increased MSS positive symptom severity.

2. Decreased ERN amplitude will be associated with increased MSS negative symptom severity.

3. Decreased N400 amplitude will be associated with increased MSS disorganized symptom severity.

**Aim 2**

Previous studies have largely focused on single ERP components and their univariate relationship with a corresponding symptom dimension (e.g., ERN-negative symptoms). Further, these studies typically measure a single ERP-symptom dimension pair, limiting information potentially gleaned from ERP-symptom dimension relationships within a single sample. This univariate approach is restrictive, as it assumes specificity between singular ERP-symptom dimension pairs. It is plausible that abnormal ERP patterns are associated more generally across symptom dimensions rather than discrete dimensions, indicating non-specific associations. For example, ERN may be similarly associated with positive and disorganized symptoms, as well as with negative symptoms. However, any evidence of general associations with ERPs and various symptom dimensions cannot be captured by single ERP-symptom relationships, as modeled in Aim 1. Therefore, building on Aim 1, Aim 2 examined partial correlation calculations of each ERP measure (ERN, P300, and N400) with each symptom dimension (positive, negative, and disorganized) for a total of 9 dyads. To further ensure the specificity of all described partial

correlations, Aim 2 controlled for demographic covariates (age, gender, race, ethnicity, SES, education level, lifetime history of non-psychotic psychopathology, and medication). While all ERPs and symptom dimensions may correlate with each other, it is expected that the ERP-symptom dimension pairs in Aim 1 will hold as the strongest associations, providing further evidence for the specificity of P300-positive, ERN-negative, and N400-disorganized pairings.

The current aim also examined the relationship between ERPs. Current literature has shown associations between symptoms of psychosis (Kay et al., 1988; Minas et al., 1992; Peralta & Cuesta, 1994); however, fewer studies have examined to what degree ERPs relate to each other within a single sample (Bates et al., 2002; Hamilton et al., 2018; Korostenskaja et al., 2005; Mathalon, Fedor, et al., 2002). As such, small to moderate effects were expected to be observed. The following hypotheses were examined for Aim 2:

Hypothesis 2:

1. While ERN and N400 may correlate with positive symptoms, positive symptoms will exhibit the strongest relationship with P300.

2. While ERN and P300 may correlate with disorganized symptoms, disorganized symptoms will exhibit the strongest relationship with N400.

3. While P300 and N400 may correlate with negative symptoms, negative symptoms will exhibit the strongest relationship with ERN.

4. Small to moderate associations may be observed across ERP-ERP correlations, with ERN and N400 exhibiting a positive effect, and the ERN and P300 and N400 and P300 exhibiting a negative effect.

## Aim 3

The overarching aim for this study sought to identify relationships between ERP amplitude and symptom domains within a single sample. Though extant literature among SZ populations have consistently yielded relationships among specific ERPs and symptom dimensions, similar associations have yet to be definitively identified among an at-risk sample. Aim 1 seeks to replicate that these patterns hold for an at-risk population, and Aim 2 seeks to further verify the specificity of ERP-symptom domain pairings. While bivariate and partial correlations provide insight into patterns of association, these analyses alone cannot empirically test for unique effects. Aim 3

builds upon Aim 2 by empirically testing the specificity of the ERP-symptom domain pairings of Aim 1 (i.e., P300-positive, ERN-negative, N400-disorganized). Such data would bridge the above identified gap, demonstrating that ERP-symptom dimension associations are similar between at-risk and SZ populations, while also accounting for the limitations in univariate comparisons described in Aim 2. To this end, a simultaneous multivariate regression analysis was performed with all three ERP components entered as simultaneous predictors and all three symptom dimensions entered as simultaneous outcomes, thus gaining clarity of unique ERP-symptom associations while controlling for shared variance among remaining ERPs. Through this, the following hypothesis was tested:

Hypothesis 3:

1. Controlling for N400 and ERN components, unique effects may emerge for P300 and positive symptoms.

2. Controlling for P300 and N400 components, unique effects may emerge for ERN and negative symptoms.

3. Controlling for ERN and P300, unique effects may emerge for N400 and disorganized symptoms.

## Method

### Power Analysis

Previous studies assessing psychophysiological indicators in relation to psychotic illness have identified that these relationships generally have moderate effect sizes [e.g., effects of diagnosis on ΔERN, $d$ = 0.20 - 0.48 (Foti, et al., 2016; Perlman et al., 2015)]. Additionally, in previous studies assessing semantic processing deficits among individuals diagnosed with schizophrenia spectrum disorders ($N$ = 41) and other psychotic disorders (N=48) compared to healthy controls ($N$ = 35), large effects were revealed ($d$ = 0.63 and 0.97, respectively; Jackson et al., 2014). For the current study, power and sample size were calculated using a medium effect of 0.35 in order to improve feasibility of participant enrollment. Therefore, a two-tailed test calculated in G*Power statistical software with alpha set at 0.05 revealed a sample size of 59 was required to achieve a medium effect of 0.35 and 80% power.

## Inclusion/Exclusion Criteria

Participants were deemed eligible following an initial phone screen if they fell between the ages of 18 and 35 years old, and endorsed at least one item on the screening questionnaire for the assessment of subthreshold psychotic-like experiences among a general population (i.e., Community Assessment of Psychic Experiences; CAPE). Participants were deemed ineligible if they were determined to meet criteria for lifetime history of frank psychotic disorder, severe substance use disorder within the last six months, or neurological disorder. History of frank psychotic disorder and substance abuse disorders were assessed via the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). All individuals were interviewed in detail upon arrival to the laboratory to validate eligibility for the study. Current treatment and historical disorders (other than psychotic disorder) were allowed in order to improve the feasibility of participant enrollment (see Table 1). Participants who endorsed exclusionary criteria were not included in analyses.

## Participants

A total of 60 participants were recruited from West Lafayette, IN and surrounding areas. Fliers advertising the study were distributed throughout Purdue University campus, across the community, on social media, and in the Tippecanoe County section of Craigslist. To ensure recruitment of a range of risk, fliers were distributed around community mental health establishments. Individuals who expressed interest in the study were screened using the CAPE (Stefanis et al., 2002) and three modules from the MINI (Sheehan et al., 1998) via phone. Three participants were excluded from analyses for meeting exclusionary diagnostic criteria (Psychotic disorder: $n = 1$; severe substance use disorder $n = 2$), leaving 57 participants in the final sample (see Table 1). The mean age of the sample was 22 years old; Approximately sixty-one percent of participants identified as Caucasian, 5.3% identified as African American, and 33.3% identified as multiracial, Asian, American Indian/Alaskan Native, or Native Hawaiian or Pacific Islander. Approximately 12% of participants identified as Latinx. Of 57 total participants included in analyses, only 13 did not meet diagnostic criteria for non-psychotic psychopathology.

Table 1. Demographics

| | *M* | *SD* | | | |
|---|---|---|---|---|---|
| Age | 22.8 | 4.27 | | | |
| | *n* | % | Diagnoses | *n* | % |
| Sex | | | MDD | | |
| Male | 14 | 24.6 | Current | 3 | 5 |
| Female | 42 | 73.7 | Past | 7 | 11.7 |
| Nonbinary | 1 | 1.7 | Recurrent | 20 | 33.3 |
| Race | | | Suicidality | 2 | 3.3 |
| Caucasian | 35 | 61.4 | Hypomania/mania | 2 | 3.4 |
| African American | 3 | 5.3 | Anxiety Disorders | 7 | 11.7 |
| Other | 19 | 33.3 | PTSD | 1 | 1.7 |
| Ethnicity | | | Substance Use Disorder | 3 | 5 |
| Hispanic/latinx | 7 | 12.3 | Bipolar Disorder | 1 | 1.7 |
| Non Hispanic/latinx | 50 | 87.7 | Psychotic Disorder | 1 | 1.7 |
| Medication | 13 | 22.8 | No dx | 13 | 21.7 |

**Procedures**

The study was completed in two phases: 1) 20-30 minute phone screen, 2) laboratory visit. The laboratory visit lasted approximately 4 hours and consisted of three parts: Mini International Neuropsychiatric Interview, a battery of self-report measures (described below), and an ERP recording session. Participants received $10/hour for completing the study. Funds were drawn from the author's Graduate Research Innovation Award, Krueger Awards, and through partial support from the author's two-year externally awarded fellowship (Grant # UL1TR002529 (A. Shekhar, PI), 5/18/2018 – 4/30/2023, and Grant #TL1TR002531 (T. Hurley, PI), 5/18/2018 – 4/30/2023, from the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award).

## Clinical Assessment

**Screening.** Screening evaluations were conducted via phone phone interview where all potential participants provided verbal consent to complete the CAPE and MINI modules I (Alcohol use Disorder), J (Substance Use Disorders), and K (Psychotic Disorders) to assess for inclusion and exclusion criteria. Eligible participants were invited to the lab for the second phase of the experiment.

**Lab visit.** All eligible participants were consented into the study. All participants also completed the CAPE (Kongings et al., 2006) and Multidimensional Schizotypy Scale (Kwapil et al., 2018). The CAPE was repeated for the clinical assessment, as the administration of the CAPE via phone during initial interviews (rather than private self-reporting) may impact the participants' willingness to answer honestly. Given that utilizing only self-reports does not allow for the opportunity to probe or clarify experiences, the current study included a clinician-rated MINI to assess for psychotic symptoms. Full MINI clinical interviews, ERP recordings, and self-report questionnaires were completed. All eligible participants were clinically interviewed by trained graduate personnel, whereas the EEG portion was conducted by a combination of trained research assistants and graduate-level supervisors.

**Community Assessment of Psychic Experiences.** The CAPE was developed to rate self-reported lifetime psychotic experiences in the affective and non-affective domains. The CAPE measures frequency and distress on a dimensional scale associated with positive (Cronbach $\alpha$ = 0.84), negative (Cronbach $\alpha$ = 0.81), and depressive (Cronbach $\alpha$ = 0.76) symptom experiences. The frequency score is measured on a 4-point likert scale (e.g. 'never (1)', 'sometimes (2),' 'often (3),' 'nearly always (4)'). The degree of distress associated with the experience is also measured on a 4-point scale with labels ranging from 'not distressed (1)' to 'very distressed (4)'. Measures of hypomania and disorganization were not included in the CAPE because they may not be reliably measured via self-report in the general population (Konings et al., 2006). Given that this questionnaire lacks measurement of the traditional three-factor structure of psychosis (positive, negative, disorganized) and instead measures positive, negative, and depressive dimensions, the CAPE was utilized as a screening tool to determine eligibility, and was not included in subsequent statistical analyses. The CAPE was utilized as a screening tool due to its sensitivity to assess a broad range of symptom presentation and severity.

**Mini-International Neuropsychiatric Interview.** The MINI was developed as a semi-structured interview to accurately evaluate a wide range of psychiatric disorders. It is a short instrument designed to explore 17 diagnoses. All diagnostic information is focused on present symptoms, unless lifetime symptom presence is clinically relevant to the disorder of interest. The MINI assesses for severity, disability, and difficulties better explained by physical problems. Inter-rater reliability has been shown to range from 0.88 to 1.0, and test-retest reliability between 0.76 and 0.93 (Lecrubier et al., 1998). Modules I, J, and K were utilized for the screening portion of this study, while the complete measure was utilized during assessment visit to assess for current and historical psychopathology. The MINI was utilized in this study for screening and comprehensive assessment purposes. Results were utilized for eligibility, and non-psychotic psychopathology was entered as covariates in select statistical models.

**Multidimensional Schizotypy Scale.** The MSS is a multidimensional questionnaire, included in this study due to its measurement of the current three-factor model of schizotypy including positive, negative, and disorganized dimensions (Kwapil et al., 2018). Items assess occurrence of experiences across the continuum of subthreshold psychotic-like experiences. Examples of positive dimension items include magical thinking, unusual perceptual experiences, special powers, and somatic experiences. The negative dimension tap into presence of diminished emotional expression, anhedonia, alogia, and avolition, while examples of disorganized items include confusion, disorganized speech, thought, and behavior, and cognitive slowing. Twenty-five positive, 26 negative, and 25 disorganized items are included in the scale, and are scored as the number of items endorsed. Subscales were developed based on content validity, and cross-validated with another independent sample. The subscale reliabilities range from good to excellent and are reported to be improved compared to other commonly utilized measures of schizotypal traits (e.g., Schizotypal Personality Questionnaire, Magical Ideation Scale). The results of the MSS assessment were utilized as the primary dependent variables.

**Physiological Assessment: Laboratory Tasks**

**Flankers task.** Participants engaged in a task during which an ERP known as the error-related negativity (ERN) was recorded. The ERN is a response-locked ERP that reflects activity of a neural system involved in monitoring actions and detecting errors, thus reflecting neural indices of executive function (Falkenstein, Hohnsbein, & Hoormann, 1990; Gehring et al., 1993; Hajcak et al., 2005; Simons, 2010) and has been shown to map onto the negative symptom domain of SZ. The ERN is a negative deflection in the ERP waveform that occurs approximately 100 ms after the commission of an error, and is considered a neural marker of automatic error processing (Falkenstein et al., 1991; Gehring et al., 1993). The ERN was elicited using an arrow flankers task (Eriksen & Eriksen, 1974) where each trial presented five arrows in the center of the screen. Participants were instructed to attend to the center arrow among the array of five and respond with a right click if the center arrow is pointing right and a left click if the center arrow is pointing left. The task included both congruent trials, when all five arrows point in the same direction ( >>>>> or <<<<<), and incongruent trials, when the flanking arrows point opposite of the center arrow (<<><< or >><>>). Feedback was provided block-wise throughout the task, instructing the participant to respond more quickly (for performance >90%), to respond more accurately (for performance <75%), or to keep repeating the same behavior. Prior to beginning the main task of 300 trials broken into 10 blocks, a practice block consisted of 15 trials. The total task lasted approximately 12 minutes and participants received breaks between each block.

**Picture-word task.** One factor hypothesized to underlie thinking disturbances in high-risk psychosis is abnormal or disinhibited automatic activation of semantic networks, which can be measured using an ERP known as the N400 (Spitzer, 1997), and has been shown to map onto the disorganized symptom domain of SZ (Green & Walker, 1985). The N400 is an electrophysiological analog of semantic priming and occurs approximately 400 ms after the presentation of unprimed stimuli (Kutas & Federmeier, 2011). The N400 is largest, or most negative, to unrelated information, slightly reduced to related information, and absent to semantically matched information (Kiang et al., 2008; Mathalon et al., 2010). Participants viewed 102 line drawings of objects (e.g. animals, clothing, food, transportation; Mathalon et al., 2010) and were subsequently presented with a word that either matches the drawing (match), was in the same semantic category as the drawing but not an exact match (related), or was in a category

unrelated to the picture (unrelated). Participants were instructed to utilize the left and right computer mouse buttons to indicate a match or non-match, respectively. The experiment was divided into four blocks of 102 trials each. Within each block there were 51 matched pairs, and either 25 or 26 related and unrelated picture-word pairs presented at random (balanced across blocks to total 102 in each non-match condition). Pictures were paired with different words and were used equally across trial types. Participants also completed a practice block, and will receive breaks between blocks.

**Auditory oddball task.** Participants participated in a task during which sustained attention was measured using an ERP known as the P300. The P300 reflects the relative amount of attentional resources allocated to processing a specific stimulus (Ford, 1999). The P300 is largest, or most positive, to novel, infrequent, target, or unexpected stimuli, and evidence exists to support its association with positive symptoms of SZ (Blackwood et al., 1987; Mathalon et al., 2000). Participants were presented with 400 auditory stimuli at a fixed inter-stimulus interval of 1.5 sec. Frequent tones (80% at 500 Hz; 80-dB sound pressure level, 50 ms duration with a shaped 5-ms rise and fall time) and infrequent tones (20% at 105 dB sound pressure level, 50 ms duration with a 100 μsec rise and fall time) were presented in a Bernoulli sequence held constant across subjects (Mathalon et al., 2000). Participants were asked to count the number of infrequent stimuli.

**Data recording and processing.** Continuous EEG was recorded using an ActiCap and the ActiCHamp amplifier system (Brain Products GmbH, Munich, Germany). The EEG signal was digitized at 24-bit resolution and a sampling rate of 500 Hz. Recordings were taken from 32 scalp electrodes based on the 10/20 system, with a ground electrode at Fpz. Electrodes were referenced to a virtual ground point formed within the amplifier. The electrooculogram was recorded from two auxiliary electrodes placed 1 cm above and below the left eye, forming a bipolar channel. Electrode impedances will be kept below 30 kOhms. Data was corrected for blinks and eye movements using a regression based method. Artifacts were rejected using a semi-automated procedure and visual inspection.

BrainVision Analyzer (Brain Products) was used for offline analysis. Data was rereferenced to the mastoid average and bandpass filtered from 0.01-30 Hz using Butterworth zero phase filters. For the ERN, data was segmented in order to isolate the time of interest, specifically -400 ms to 800 ms around the participant's response. The ERN was scored as the average activity

from 0-100 ms post-response at a pooling of Fz, Cz, FC1, and FC2. These poolings were compared to the baseline of each participant from -400 ms to -200 ms. Difference waves were created by subtracting ERPs on correct trials from ERPs on error trials. For the N400, EEG was segmented for each trial from -525 to 1000 ms relative to word onset (i.e. -200 to 1325 ms relative to picture onset). The N400 was time-locked to word onset, with a 200 ms pre-picture baseline to reduce the influence of ERP activity in response to pictures. The N400 was measured as the mean amplitude between 300 and 500 ms averaged across electrode sites Cz, CP1, CP2, and Pz. For the P300, EEG was segmented from -200 to 800 relative to infrequent targets. The P300 was time-locked to target onset, with a 200 ms pre-stimulus baseline. The P300 was measured as the average brain activity from approximately 300-450 ms at Pz (Perlman et al., 2015). Outliers will be determined as greater 3SD from the mean.

**Statistical Analysis**

All primary ERP analyses were conducted using difference scores (ERN: error minus correct; N400: unrelated minus match; P300: target minus standard; Luck et al., 2011). Prior to performing analyses for the specific project aims, ERP data was assessed for missing data patterns. Positive, negative, and disorganized symptom dimension scores were calculated from the Multidimensional Schizotypy Scale. Given that total symptom scores are a sum of the dimensional scores, the total score was excluded from all analyses due to multicollinearity.

**Aim 1.** The first aim of this study sought to replicate the associations between the multidimensional symptom structure of SZ and corresponding ERPs, among at-risk adults. While most studies to date have cross-sectionally examined individual ERP-symptom associations, the current aim examined relationships of combinations of ERPs and illness characteristics within a single sample. To this end, three bivariate correlations were conducted to examine effect size, direction of relationship, and significance of the ERN-negative symptom association, P300-positive symptom association, and N400-disorganized symptom associations.

**Aim 2.** While Aim 1 sought to replicate ERP-symptom relationships in an at-risk sample using bivariate correlations, this analysis limits the degree to which specificity of effects may be determined. The overall interest of Aim 2 was to further examine relationships between ERPs and symptom dimension pairs not assessed in Aim 1 (e.g., P300-disorganized, ERN-positive, N400-negative). This approach assesses the relative specificity of relationships across all 3 ERP components (ERN, P300, N400) and all three symptom dimensions (positive, negative, disorganized), ruling out the possibility that ERP amplitude is associated with general illness severity. To this end, partial correlations were calculated for each ERP-symptom dimension pair, as well as for each ERP-ERP pair. Age, gender, race, ethnicity, SES, education level, lifetime history of non-psychotic psychopathology, and medication were entered as covariates.

**Aim 3.** While bivariate and partial correlations provide insight into the patterns of association between ERP components and symptom dimensions, they cannot empirically test for unique effects of ERP-symptom relationships. This aim sought to bridge this gap by demonstrating unique effects of ERP-symptom associations, rather than associations that would support ERPs relationship with general illness severity utilizing a multivariate regression analysis. Within this model, ERN, P300, and N400 were entered as simultaneous predictors, and positive, negative, and disorganized symptoms entered as simultaneous outcome variables. This approach provides greater insight into ERP-symptom associations while controlling for shared variance among other ERP components.

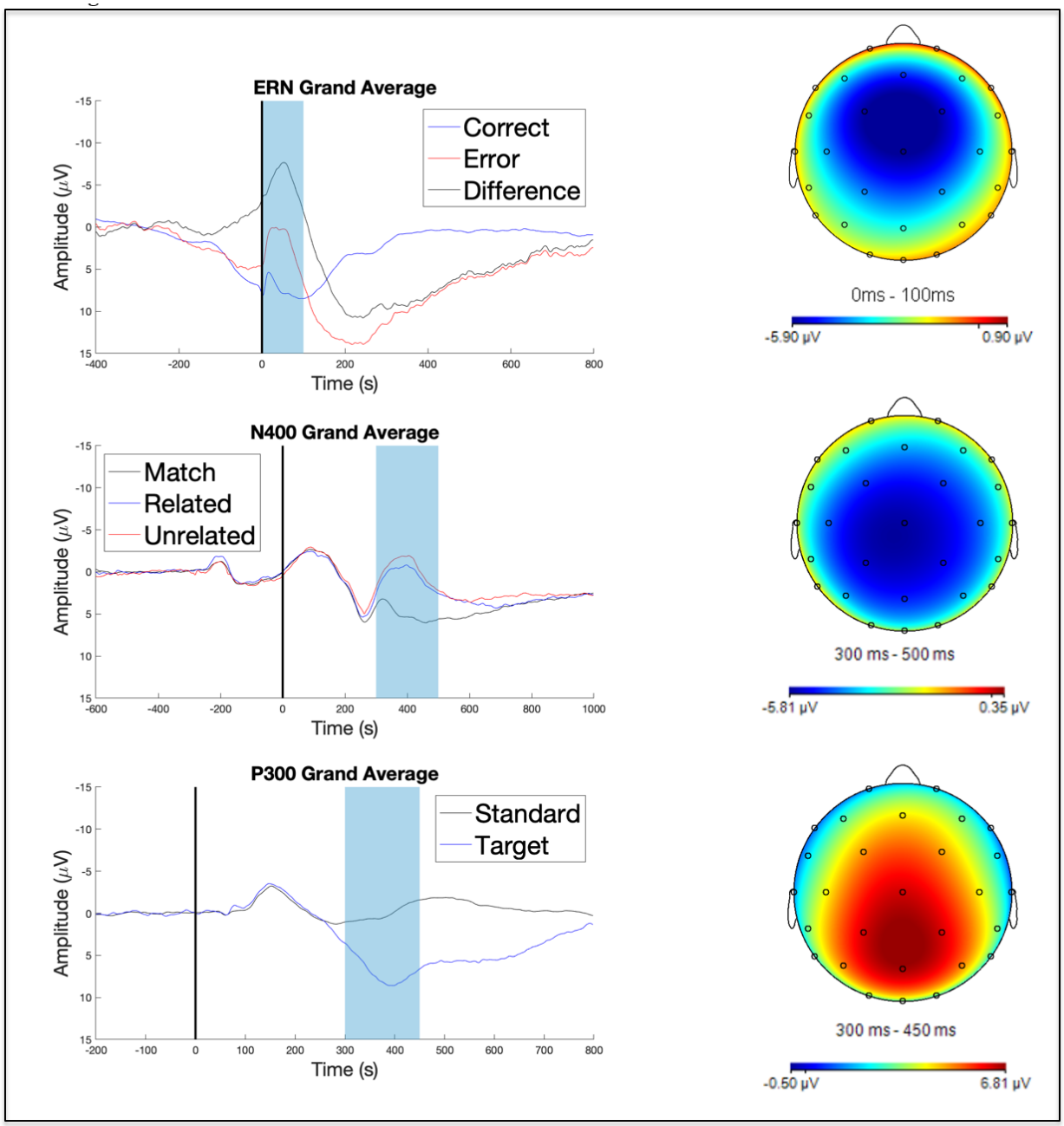
## Results

ERPs were calculated as differences scores (ERN: error minus correct; P300: target minus standard; N400: unrelated minus match; see Table 2). The mean amplitude of the ERN on error trials ($M$ = 1.96, $SD$ = 5.59) was significantly lower than the mean amplitude on correct trials ($M$ = 7.44, $SD$ = 4.10; $t(57) = -8.05$, $p < .001$) and was maximal around frontocentral sites. Similarly, P300 amplitude to target stimuli ($M$ = 6.91, $SD$ = 4.05) was significantly more positive than P300 to standard stimuli ($t(57) = 13.24$, $p < .001$; $M$ = .10, $SD$ = 1.32) and was maximal at parietal sites. Regarding N400, amplitude to unrelated stimuli was significantly larger (more negative; $M$ = -.32, $SD$ = 4.27) compared to matched stimuli ($t(57) = -11.19$, $p < .001$; $M$ = 5.0, $SD$ = 4.61) around centroparietal sites; ERP waveforms and headmaps are illustrated in Figure 1.

Table 2. ERP and Symptom Scores

| | | *M* | *SD* | | |
|---|---|---|---|---|---|
| ERPs | | | | | |
| | ΔP300 | 6.81 | 3.86 | | |
| | ΔERN | -5.48 | 5.14 | | |
| | ΔN400 | -5.67 | 2.40 | | |
| Symptoms | | *M* | *SD* | Min | Max |
| MSS | | | | | |
| | Positive | 5.61 | 6.09 | 0 | 25 |
| | Negative | 7.02 | 6.53 | 0 | 23 |
| | Disorganized | 7.77 | 7.82 | 0 | 25 |

*Note.* Top: Calculated ERP difference scores for P300, ERN, and N400. Bottom: symptom score values for each symptom domain measured via the Multidimensional Schizotypy Scale.




*Note.* Grand average waveforms and corresponding scalp topography for ERN, N400, and P300.

Figure 1. ERP waveforms and scalp topography.

Prior to performing the following analyses for the specific aims of the project, the data was assessed for missing data patterns. One outlier was identified in N400 dataset and was subsequently coded as missing data.

**Aim 1**

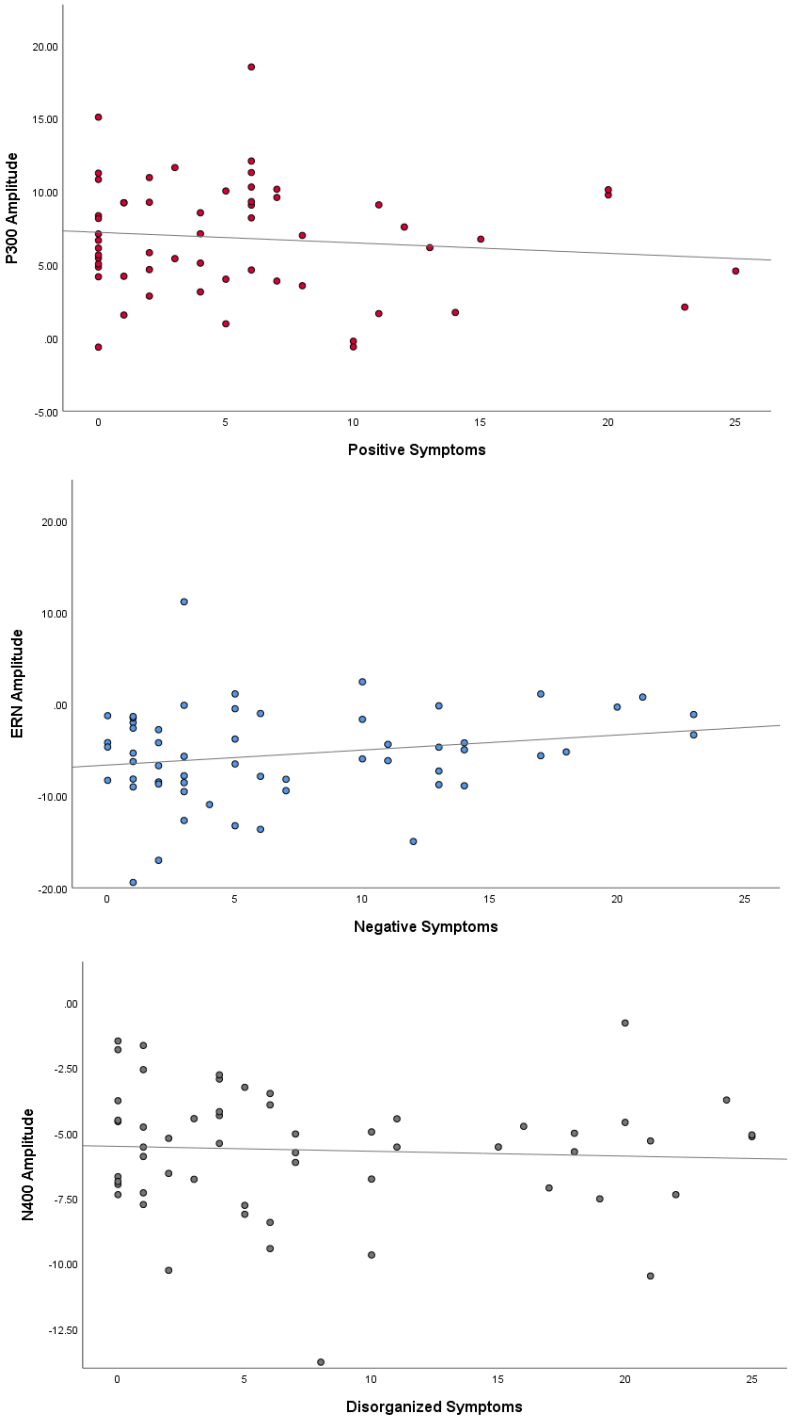
A primary interest of the current study was to examine relationships between neurophysiological functioning and symptoms among an at-risk group, given that consistent findings have yet to be established in the broader literature. Given that a reliable three-factor symptom structure has been determined among the SZ literature, current hypotheses were based on this framework: it was expected that ERPs (P300, N400, ERN) will map onto dimensions of psychosis. Specifically, a) the P300 was expected to correlate negatively with positive symptoms, b) ERN was expected to exhibit a positive relationship with negative symptoms, and c) N400 was expected to correlate positively with disorganized symptoms. To test this hypothesis, bivariate correlations were run with ERPs (P300, N400, ERN), and independent symptom dimension scores (positive, negative, and disorganized) calculated from the MSS (see Table 3). Results of these correlation analysis resulted in small, not statistically significant effects, though relationships between P300 and positive symptoms ($r$ = -0.11, $p$ = 0.40) and ERN amplitude and negative symptom severity ($r$ = 0.21, $p$ = .012) were expected directions; however, the relationship between N400 amplitude and disorganized symptoms ($r$ = -0.10, $p$ = 0.45) showed an association opposite of expected direction. These results did not support Hypotheses 1a, 1b, or 1c. Scatterplots were generated to visually reflect the relationship between each discrete ERP and their respective hypothesized symptom dimension (see Figure 2).

Table 3. Relationships Between Baseline ERPs and Baseline MSS Symptom Scores

| | P300 | ERN | N400 |
|---|---|---|---|
| Positive | -0.11 | 0.04 | -0.07 |
| Negative | .001 | 0.21 | -0.10 |
| Disorganized | -0.02 | 0.12 | -0.10 |

*Note.* Standardized zero order correlations. Baseline values.

*$p < .05$. **$p < .01$.




*Note.* Scatterplots reflecting relationship between P300 amplitude and positive symptoms, ERN amplitude and negative symptoms, and N400 amplitude and disorganized symptoms. All data was collected at baseline assessment.

Figure 2. Illustration of relationships between baseline ERPs and baseline symptom dimensions.

**Aim 2**

Partial correlations were analyzed across all 9 ERP-symptom dimension pairs, as well as each ERP-ERP pair, while controlling for covariates (age, gender, race, ethnicity, SES, education level, lifetime history of non-psychotic psychopathology, and medication; see Table 4). Here again, small effects emerged with no significant relationships found. Counterintuitively, P300 had the smallest measured effect size with positive symptoms ($r$ = -0.07, $p$ = 0.64) versus ERN and N400 ($r$ = 0.11, $p$ = .44 and $r$ = -0.18, $p$ = 0.21, respectively). ERN was measured to have the largest effect size with negative symptoms ($r$ = 0.22, $p$ = 0.14) versus P300 and N400 ($r$ = -0.04, $p$ = 0.78 and $r$ = -0.10, $p$ = .48, respectively). These results tentatively support Hypothesis 2a and 2b. Similar to Aim 1, N400 was found to have an effect in the opposite direction than expected with disorganized symptoms ($r$ = -0.13, $p$ = 0.38), ERN was found to have the largest effect size with disorganized symptoms ($r$ = 0.16, $p$ = 0.27), and P300 was found to have a negligible effect size with disorganized symptoms ($r$ = 0.004, $p$ = 0.98), not supporting Hypothesis 2c.

Table 4. Relationships Among Baseline ERPs and Symptom Dimensions

| | P300 | ERN | N400 |
|---|---|---|---|
| P300 | — | | |
| ERN | 0.36** | — | |
| N400 | -0.30** | -0.13 | — |
| Positive | -0.07 | 0.11 | -0.18 |
| Negative | -0.04 | 0.22 | -0.10 |
| Disorganized | .004 | 0.16 | -0.13 |

*Note.* Relationship between ERPs and symptom dimensions including covariates: Age, gender, race, ethnicity, SES, education level, diagnosis, medication status.

*$p$ <.05. **$p$ < .01.

For ERP-ERP pairs, significant correlations were observed. Specifically, P300 and ERN exhibited a medium positive effect ($r = 0.36$, $p < 0.01$), opposite of expected direction. P300 and N400 also exhibited a medium negative effect ($r = -0.30$, $p < 0.05$), opposite of expected direction. N400 and ERN were not found to be significantly correlated ($r = -0.13$, $p > 0.05$), with the effect in a direction opposite of expectation. While effects between P300-ERN and P300-N400 were significantly associated as hypothesized, all effects were observed to be in the opposite of expected direction, suggesting only partial support for Hypothesis 2d.

**Aim 3**

A primary strength of this study was the ability to examine relationships between multiple ERP components and symptom dimensions within a single risk sample. While correlation analyses provide insight into patterns of associations, these analyses alone cannot empirically test for unique effects. To this end, Aim 3 sought to test the specificity of ERP-symptom domain relationships from Aim 1 (ERN-negative, P300-positive, N400-disorganized), while controlling for variance shared among remaining ERP components. This analysis aimed to rule out evidence that ERPs are associated with general illness severity, but rather deficits in ERP amplitude may be unique to severity among specific symptom domains. To test this, a multivariate regression analysis was calculated with ERN, P300, and N400 entered as simultaneous predictors, and positive, negative, and disorganized symptoms entered as simultaneous outcome variables (see Table 5). Main effects of ERN ($F(3, 51) = 0.86$, $p = 0.47$) P300 ($F(3, 51) = 0.59$, $p = 0.62$), and N400 ($F(3, 51) = 0.98$, $p = 0.83$) were not statistically significant. Specifically, for positive symptoms, neither P300 ($\beta = -0.18$, $p = 0.72$), ERN ($\beta = 0.08$, $p = 0.58$), or N400 ($\beta = -0.11$, $p = 0.44$) were found to be significant effects. Although not significant, the P300 exhibited the largest effect size among all ERPs, and in the expected direction. Significant effects were not observed for negative symptoms and P300 ($\beta = -0.13$, $p = 0.42$), ERN ($\beta = 0.24$, $p = 0.11$) or N400 ($\beta = -0.08$, $p = 0.56$). Similarly, for disorganized symptoms, P300 ($\beta = -0.11$, $p = 0.47$), ERN ($\beta = 0.14$, $p = 0.35$) and N400 ($\beta = -0.10$, $p = 0.48$) we not found to hold significant effects. Interestingly, the effect size for disorganized symptoms and N400 is not distinguishably different than the effect sizes for P300 or ERN. Moreover, the direction of the N400-disorganized symptom dimension effect is opposite than expected. Taken together, these results do not support Hypothesis 3a, 3b, or 3c.

Table 5. Summary of Multivariate Regression Analyses for Baseline Assessment

| | β | 95% CI | SE |
|---|---|---|---|
| Positive Symptoms | | | |
| P300 | -0.18 | -0.47, 0.11 | 0.15 |
| ERN | 0.08 | -0.20, 0.36 | 0.14 |
| N400 | -0.11 | -0.38, 0.16 | 0.14 |
| Negative Symptoms | | | |
| P300 | -0.13 | -0.43, 0.18 | 0.15 |
| ERN | 0.24 | -0.06, 0.53 | 0.15 |
| N400 | -0.08 | -0.36, 0.20 | 0.14 |
| Disorganized Symptoms | | | |
| P300 | -0.11 | -0.40, 0.18 | 0.15 |
| ERN | 0.14 | -0.15, 0.42 | 0.14 |
| N400 | -0.10 | -0.37, 0.17 | 0.14 |

*Note.* MSS scores entered as simultaneous DV's, ERPs entered as simultaneous IV's.

*$p < .05$.

## Study 1 Discussion

Among individuals at risk for SZ, symptoms gradually increase in severity as functioning declines over time, potentially leading to a first psychotic episode and a chronic, debilitating, lifelong disease. Reducing the duration of untreated illness is one of the greatest indicators of prognosis for disorders such as SZ. Given that ERPs are concrete measures of brain functioning and are shown to map onto symptom deficits among SZ, it is plausible that ERPs may also be able to prospectively predict worsening of illness, even in the risk phase. To this end, leveraging ERPs as tools to understand the process by which someone might be at risk for SZ may elucidate psychophysiologically distinct risk markers of illness.

The primary goal of Study 1 aimed to investigate brain function and symptom dimensions in an at-risk population. To accomplish this, this study leveraged established modalities, specifically, event-related potentials and the Multidimensional Schizotypy Scale self-report questionnaire. The study first aimed to replicate the ERP-symptom dimension structure commonly observed in the SZ literature, within a single sample. Building on Aim 1, the second aim of the study investigated the relationships between all ERP and symptom combinations, while controlling for additional non-specific variance of demographic characteristics, with the goal being to further clarify specific or general relationships between ERP-symptom dyads from Aim 1. Finally, this study aimed to empirically test the relationships between symptom dimensions and all 3 measured ERPs within a single, at-risk sample, fulfilling an identified gap in the literature.

The results of Aim 1 measured effect sizes for P300-positive and ERN-negative relationships with the same directionality as seen in the clinical SZ literature (Ford, 1999; Foti et al., 2012; Perez et al., 2012). While not statistically significant, the small effects suggest that P300 and ERN may be similarly effected by presence of positive and negative symptoms, respectively. It is plausible that with a larger sample size, these effects may persist with greater magnitude. N400, however, was found to have an effect size directionality opposite to that reported in the literature (Jackson et al., 2014; Mathalon et al., 2002; Mathalon et al., 2010). While not statistically significant, these results suggest that the relationship between N400 and disorganized symptoms should continue to be scrutinized in future studies. This is also consistent with the existing literature, which has reported mixed presentation of disorganized symptoms in clinical SZ populations (Gruzelier, 1996; Kitamura et al., 1995; Mata et al., 2003; Vollema & Hoijtink, 2000). It is intuitive that these conflicting results would translate to the at-risk sample, which, by its nature, contains a smaller range of reported symptoms and aberrant ERPs, and therefore potentially limited by a lower "signal-to-noise ratio." Further, the results of Aim 1 demonstrated generally smaller effect sizes than those seen in the literature for the clinical SZ population (Foti, Perlman, Hajcak, Mohanty, Jackson, & Kotov, 2016; Perlman et al., 2015). Considering the nature of the at-risk population, likely containing a lower range and magnitude of symptom dimension severity as well as ERP aberrations, a smaller effect size might be expected. Considering that these results are not statistically significant, further evaluation and verification of the above reported results may be achieved with a further increased sample size.

The results of Aim 2 showed similar effect sizes and directionality to Aim 1. Compared to Aim 1, effect size magnitude for P300-positive symptoms was reduced, effect size magnitude for ERN-negative symptoms was effectively unchanged, and effect size magnitude for N400-disorganized symptoms slightly increased. Counterintuitively, both ERN and N400 showed larger effect sizes with positive symptoms than P300, which showed almost no association with positive symptoms. These data lend support to other studies which found almost no correlation between P300 and symptom severity (Osamu Saitoh et al., 2015; St Clair et al., 1989). However, findings from a meta-analytic study that showed P300 amplitude to be proportional to individuals symptom severity, citing individuals who have experiences brief intermittent psychotic symptoms (BLIPS) had greater reduction in P300 amplitude than those who experience other prodromal symptoms (Frommann et al., 2008; Paolo Fusar-Poli et al., 2011; Lepock et al., 2018). Given that the current sample likely has a restricted range of symptom presence and severity (i.e., fewer individuals with higher symptom scores) compared to a "true" prodromal sample, it is possible that participants in the current study may not be experiencing levels of positive symptom severity necessary to replicate this ERP-symptom dimension effect. It may be likely that the P300 does not become impaired until high levels of symptom severity. For negative symptoms, ERN effect size was largest, as expected, compared to P300 or N400. Though not significant, the size and direction of this effect is consistent among the SZ literature given that deficits in executive function (i.e., error monitoring) are among the most impaired in SZ and related disorders (Reichenberg et al., 2009). Given that disorganized symptoms and impairments in academic and role functioning have been linked with conversion to psychosis (Fusar-Poli et al., 2010; Valmaggia et al., 2013), it was hypothesized that N400 would carry links with disorganized symptoms. However, in the current sample, N400 exhibited a small effect with disorganized symptoms, and in the wrong direction (i.e., increased symptoms reflect more robust N400 amplitude). The effect size of the ERN was slightly larger to that of N400, while the P300 had a negligible relationship with this dimension. Taken together, these data suggest that, in an at-risk population, some but not all ERPs carry the strongest relationships with expected symptom dimensions. It is plausible that deficits in neural functioning may carry links with general, rather than specific, illness severity among a risk group.

Aim 3 sought to empirically examine links with symptom dimensions across ERPs. Specifically, this multivariate regression model allows for the examination of unique effects of hypothesized ERP-symptom dyads while controlling for non-specific effects of other ERPs.

Results from this aim were not statistically significant, though P300 and ERN exhibited the strongest relationship with positive and negative symptoms, respectively, and in the expected direction as hypothesized. Replicating associations from previous aims, disorganized symptoms exhibited small effects across all ERPs, with ERN exhibiting the largest effect size. The relationship between N400 and disorganized symptoms was once more in the direction opposite than expected, further denoting the need for further investigation among this symptom dimension and links with ERPs. However, it has been noted, and supported by factor structure of CAPE items, that disorganized symptoms are often difficult to reliably assess utilizing self-report methods, and have less consistent evidence to support it as a factor in an at-risk population (Kitamura et al., 1995; Lindenmayer et al., 1995; McGorry et al., 1998; Stefanis et al., 2002).

This study was one of the first to examine a battery of well-validated ERPs across symptom dimensions in a single at-risk sample. Although not significant, small effects did emerge for ERP-symptom relationships congruent with patterns hypothesized, and it is possible that the observed effects from this study may replicate and grow in magnitude with a larger sample. Given their objective utility and temporal precision, further investigation is warranted utilizing ERPs to identify biomarkers of risk. To date, many studies have focused on cross-sectional data, with questions remaining about processes that confer risk within a single sample, and how these processes may or may not fluctuate or remain stable over time. This concept serves as the primary aim for Study 2.

# STUDY 2

The long-term trajectory of psychotic-like experiences in at-risk samples is not well understood. It remains unknown whether the progression from risk to diagnosis is linear or nonlinear, and if initially expressed symptom severity is maintained over time. As established in the extant literature, there exist moderate effects between symptom severity and brain function (as measured by ERPs). Study 1 aimed to replicate these associations in a single, at-risk sample not previously explored in the literature. Presuming that these associations hold in an at-risk population, it is plausible that ERPs may be used as biomarkers to identify individuals at risk for developing SZ before illness onset, allowing the field to develop novel treatment and preventative measures.

Recent studies have shown symptom dimension severity in an at-risk population as promising indicators of early risk markers for future conversion to psychosis (Cannon et al., 2016; Vargas et al., 2021). However, the results of these studies are found to be mixed, suggesting that the role of these indicators is unclear. For example, negative symptoms have been shown to be a source of significant burden for those at risk for psychosis, with evidence suggesting higher levels of negative symptoms at baseline have an increased risk of conversion to a psychotic disorder (Valmaggia et al., 2013), while others found no association between negative symptoms and conferring psychosis (Yung et al., 2019). Another study found that the presence of negative and disorganized symptoms, but not positive symptoms, were significantly associated with conversion (Carrión et al., 2013). Studies assessing the trajectory of psychosis symptoms have ranged from six months to five years, with one study finding the estimated transition rate over a 12-month period was 21.2% in a high-risk sample (Yung et al., 1996).

This study aims to expand upon Study 1, with an overall goal of understanding potential disease progression in an at-risk population over the course of six months. A follow up period of six months was selected to increase feasibility of participant enrollment while being within the window of symptom follow up reported in the literature (Addington & Heinssen, 2012). Given that many ERP studies are cross-sectional and examine single components, Study 2 builds upon Study 1 by utilizing a short-term longitudinal approach. Specifically, Study 2 aims to examine the relationship of symptom dimensions over time in a single at-risk sample, as well as leveraging the utility of ERPs as a potential measurement tool to predict future worsening of symptoms.

**Aim 1**

Over recent decades, there has been an increased interest in the early detection of at-risk individuals, with goals to understand, predict, and prevent progression of the disease state. In order to refine detection criteria, we must further understand the long-term variability in the course of symptoms. Some studies have shown that baseline symptoms are reasonable predictors of future symptom severity disorder (Kircher et al., 2003; Kostova et al., 2005; Kumar & Debruille, 2004); however, the strength of these results have been mixed. Further, limited information exists testing this phenomenon in at-risk samples. The current aim sought to examine the strength of associations between positive, negative, and disorganized symptoms at baseline, and corresponding positive, negative, and disorganized symptom severity six months later in an at-risk sample. Further examining these links, this aim also sought to empirically test the prospective prediction of follow-up symptom severity based on symptom severity at baseline. Thus, the following hypotheses were proposed:

Hypothesis 1:

1. While other symptom dimensions may correlate, baseline positive, negative, and disorganized symptoms will exhibit the largest effects with positive, negative, and disorganized symptoms, respectively, at follow-up.

2. Controlling for other symptoms, baseline positive symptom severity will prospectively predict positive symptom severity at follow-up.

3. Controlling for other symptoms, baseline negative symptoms will prospectively predict negative symptoms at follow-up.

4. Controlling for other symptoms, baseline disorganized symptoms will prospectively predict disorganized symptoms at follow-up.

**Aim 2**

Extant literature examining psychophysiological correlates of psychotic illness have been primarily cross-sectional, leaving it unclear how neural processes relate to the course of illness (Bramon et al., 2005; Foti et al., 2016b; Kuperberg et al., 2010; Mathalon et al., 2002; McCarley et al., 1991; Perez et al., 2012; Perlman et al., 2015; Wang et al., 2011). Examining single ERP components within single studies limits the ability to draw broader conclusions regarding general

cognitive frameworks and their impact on disease progression. No study to date has examined the longitudinal links among a battery of ERPs and symptoms over time within a single sample of at-risk individuals.

The presence of ERP deficits in those at risk for developing disorders makes them a potentially useful biomarker for research on pathophysiology and treatment of these disorders. For example, the P300 is one of the most highly replicable trait markers for the disease, and reductions in P300 amplitude are observed in unaffected relatives of individuals diagnosed with schizophrenia (Friedman et al., 1986; Saitoh et al., 1984; Schreiber et al., 1991, 1992). Risk for development of schizophrenia is known to be hereditary, suggesting the P300 to be a potentially important biomarker of vulnerability for SZ (Ford, 1999). Though not conclusive, studies examining SZ have shown ERN to map onto negative symptoms (Foti et al., 2012, 2016a), the P300 to be associated with positive symptoms (Blackwood et al., 1987; Ford et al., 1994; Mathalon et al., 2000), and the N400 to carry links with disorganized symptoms (Ditman & Kuperberg, 2007; Mathalon, Faustman, et al., 2002). Thus, it was of interest to identify whether or not ERP amplitude maps onto symptom presentation at follow-up. To this end, this aim examined the relationship utilizing correlation analyses between baseline ERPs (P300, ERN, N400) and symptom severity (positive, negative, disorganized) measured six months after initial assessment while controlling for baseline symptom scores and demographic variables.

Evidence for similar patterns observed in risk groups would support neurophysiological components as potential biomarkers for risk, and will thus serve as hypotheses for the current aim:

Hypothesis 2:

1. Reduced baseline P300 amplitude will be associated with increased positive symptom severity at follow-up.

2. Decreased baseline ERN amplitude will be associated with increased negative symptom severity at follow-up.

3. Decreased baseline N400 amplitude will be associated with increased disorganized symptom severity at follow-up.

**Aim 3**

The overall aim of this study was to examine longitudinal links between symptom characteristics and neural measures of cognitive function in an at-risk sample. Further, this study

aimed to examine these links while incorporating multiple ERPs and symptom dimensions among a single sample, addressing an identified gap in the literature. Aim 1 sought to replicate associations seen in the literature between symptom presentation over time in an at-risk sample. Aim 2 sought to examine specific relationships between hypothesized ERP/symptom domains from Study 1 (i.e., P300-positive, ERN-negative, N400-disorganized), with an eye toward longitudinal prospective associations. While correlations bring about insight into patterns of association between baseline neural functioning and symptoms at follow-up, this analysis cannot prospectively predict unique effects. Aim 3 looks to bridge the gap from correlation to empirical analysis, using a multivariate model controlling for shared variance among ERPs, via the following hypotheses:

Hypothesis 3:

1. Controlling for N400 and ERN components, P300 will prospectively predict positive symptoms at follow-up.

2. Controlling for P300 and N400 components, ERN will prospectively predict negative symptoms at follow-up

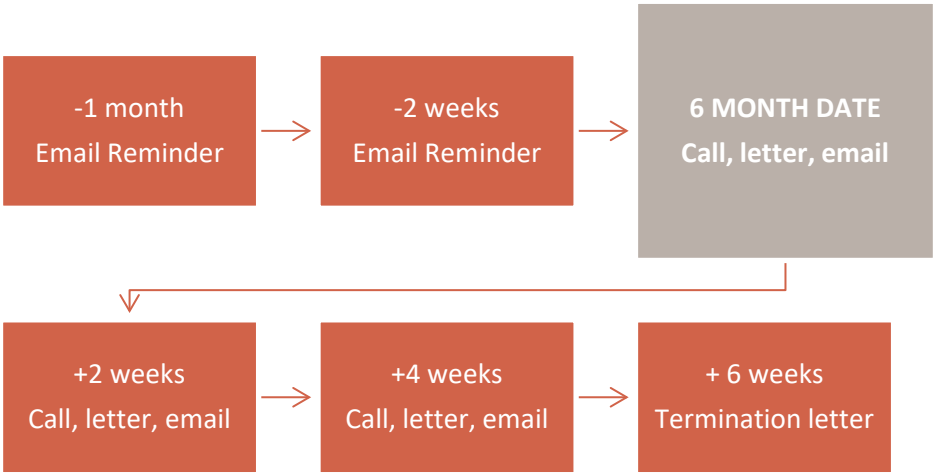
3. Controlling for ERN and P300, N400 will prospectively predict disorganized symptoms at follow-up.

## Method

### Participants

Of the 60 participants who completed baseline assessment, 42 were eligible for the six-month follow-up assessment as of May 1, 2021. Of the 42, 30 participants to date have completed the six-month follow-up (29% attrition rate). 1 participant was further removed from the study analysis, due to exclusionary diagnosis of formal psychotic disorder, resulting in a final $n = 29$ participants who have completed the study to date. No individual completed Study 2 that was not included in Study 1. Therefore, participant screening and inclusion/exclusion was identical to Study 1. Participation reminders were completed in a multi-step process (see Figure 3): One month and again two weeks prior to scheduled follow-up date, participants received email reminders of their upcoming participation in Study 2. Enrolled participants received an email with instructions (e.g., link to website) to complete a self-report survey. When participants did not complete the

follow-up questionnaire within the first week of contact, reminder emails were sent every two weeks with encouragement to complete the study. Reminders concluded 6 weeks following the participants scheduled follow-up date.




*Note*. Example timeline of participant reminders at 6-month follow-up.

Figure 3. Timeline of participant reminders at 6-month follow-up.

**Procedures**

Study 2 consisted of a one-time online self-paced questionnaire of clinical assessments to be completed at the participant's convenience. Assessments were completed via Qualtrics survey and lasted approximately 30 minutes (survey included multiple sections not included in this study). Participants received $10 for completing this portion of the study, and were entered into a drawing to win a $100 gift card at completion of data collection. Funds were drawn from accounts as described in Study 1.

**Clinical Assessment**

All participants completed the self-report MSS assessment as described in Study 1.

### Power Analysis

Given delays in data collection due to the COVID-19 pandemic, and reduction in total data points for Study 2, bivariate correlation analyses and regression analyses were calculated to examine effect sizes. At 80% power, n=29 is sufficient to detect an effect size of greater than or equal to 0.49. Follow-up data continues to be collected through October 2021 and will be included in longitudinal analyses as it becomes available.

## Data Analysis

Current as of May 1, 2021, $n$ = 30 participants have completed Study 2. One participant was excluded from analyses due to an exclusionary diagnosis of psychosis, leaving a total interim n=29. ERP data was not collected again in Study 2. Therefore, all analyses containing ERP scores were conducted utilizing Study 1 data. The ERN was scored as error minus correct, the N400 was scored as unrelated minus match, and P300 was scored as target minus standard. Positive, negative, and disorganized symptom scores were calculated from the Multidimensional Schizotypy Scale at baseline and follow-up assessment. Given that total symptom scores are a sum of the dimensional scores, the total score was excluded from all analyses due to multicollinearity.

### Aim 1

The first aim of this study sought to assess the degree to which symptom severity at baseline and follow-up were associated within a risk sample. To examine these relationships, a partial correlation analysis was run including baseline positive, negative, and disorganized symptom scores, and follow-up positive, negative, and disorganized symptom scores, respectively. This calculation controlled for covariates including age, gender, race, ethnicity, SES, education level, diagnosis, and medication status. It was hypothesized that, controlling for covariates, baseline symptom scores (e.g., baseline positive symptoms) would exhibit large effects with corresponding follow-up symptom dimensions (e.g., follow-up positive symptoms). Given expected large effects between corresponding symptom dimensions, Aim 1 also sought to empirically test the associations examined within the correlation calculation. A multivariate regression model was calculated with baseline positive, negative, and disorganized symptoms entered as simultaneous

predictors, and follow-up positive, negative, and disorganized symptoms were entered as simultaneous outcome variables.

**Aim 2**

Extant literature examining the relationship between ERPs and illness characteristics has primarily included cross-sectional analyses, typically examining single ERP components. Given inherent limitations in the ability to generalize across all neural measures and cognitive function, this aim sought to bridge this gap by examining longitudinal links among a battery of well-validated ERPs (P300, ERN, and N400) and symptom severity (positive, negative, disorganized) over the course of six months in a single sample. To examine the relationship between P300, ERN, and N400 amplitude at baseline assessment, and positive, negative, and disorganized symptom severity, respectively, at follow-up, partial correlations were calculated. To control for shared variance, baseline symptom scores, age, gender, race, ethnicity, SES, education level, diagnosis, and medication status were entered as covariates. It was expected that significant effects would emerge for P300-positive symptom, ERN-negative symptom, and N400-disorganized symptom pairs.

**Aim 3**

The third aim of this study sought to examine a battery of well-validated ERPs (P300, ERN, & N400) and their prospective predictive ability of positive, negative, and disorganized symptom dimensions over the course of six months. The goal of this aim was to gather information about potential idiosyncratic patterns of risk for conferring SZ. To test whether neural indicators of cognitive function at baseline (P300, ERN, N400) prospectively predicted hypothesized corresponding symptom severity (positive, negative, disorganized) over six months, a multivariate regression model was calculated. Specifically, P300, ERN, and N400 were entered as simultaneous predictors, and follow-up symptom data (positive, negative, disorganized) were entered as simultaneous outcomes. It was expected that baseline P300 amplitude would prospectively predict positive symptom scores at follow up, baseline ERN amplitude would prospectively predict negative symptom severity at follow-up, and baseline N400 amplitude would prospectively predict disorganized symptom scores at follow-up.

## Results

ERPs were calculated as differences scores (ERN: error minus correct; P300: target minus standard; N400: unrelated minus match). The mean amplitude of the ERN on error trials ($M$ = 1.96, $SD$ = 5.59) was significantly lower than the mean amplitude on correct trials ($M$ = 7.44, $SD$ = 4.10; $t(57) = -8.05$, $p < .001$) and was maximal around frontocentral sites. Similarly, P300 amplitude to target stimuli ($M$ = 6.91, $SD$ = 4.05) was significantly more positive than P300 to standard stimuli ($t(57) = 13.24$, $p < .001$; $M$ = 0.10, $SD$ = 1.32) and was maximal at parietal sites. Regarding N400, amplitude to unrelated stimuli was significantly larger (more negative; $M$ = -0.32, $SD$ = 4.27) compared to matched stimuli ($t(57) = -11.19$, $p < .001$; $M$ = 5.0, $SD$ = 4.61) around centroparietal sites.

Prior to performing the following analyses for the specific aims of the project, the data was assessed for missing data patterns. One outlier was identified in N400 dataset and was subsequently coded as missing data.

### Aim 1

The primary goal of Aim 1 was to replicate longitudinal correlations between baseline and follow-up symptom dimensions (positive, negative, and disorganized) across a clinically relevant time frame (six months). Based on the extant literature for SZ, it was expected that large, positive correlations would exist between symptom dimensions at baseline and their paired results at 6-months of follow up. To test this hypothesis, symptom dimension scores obtained via the MSS were analyzed via a partial correlation analysis (see Table 6). Shared sources of variance were controlled for by placing age, gender, race, ethnicity, SES, education level, diagnosis, and medication status as covariates. As a result, positive, negative, and disorganized symptoms at baseline were found to significantly correlate with their paired symptom dimension at follow up ($r$ = 0.83, $p < .001$, $r$ = 0.61, $p < 0.01$, and $r$ = 0.88, $p < 0.001$ for positive, negative, and disorganized symptom pairs, respectively).

Table 6. Relationships Between Baseline and Follow-Up Symptom Scores Baseline Symptom Scores

| | Baseline Symptom Scores | | |
|---|---|---|---|
| | Pos | Neg | Dis |
| Follow-up Symptom Scores | | | |
| Positive | 0.83*** | 0.07 | 0.03 |
| Negative | 0.14 | 0.61** | 0.45* |
| Disorganized | 0.01 | 0.41 | 0.88*** |

*Note.* Relationship between baseline and follow-up symptom dimensions, including covariates: Age, gender, race, ethnicity, SES, education level, diagnosis, medication status.

*$p < .05$. **$p < .01$. ***$p < .001$.

Given the significant associations, a multivariate linear regression was utilized to examine the predictive value of baseline symptom scores on paired dimensions at follow-up. Baseline symptom dimensions were entered as simultaneous predictors and symptom dimension scores at follow-up were entered as simultaneous outcomes (see Table 7). For positive symptoms, the overall model was significant ($F(3, 24) = 17.20$, $p < .001$) such that baseline positive ($\beta = 1.03$, $p = 0.001$) and negative symptoms ($\beta = 0.29$, $p = 0.03$), but not disorganized ($\beta = -0.10$, $p = 0.46$), predicted positive symptoms at follow-up. For negative symptoms, the overall model was significant ($F(3, 24) = 5.68$, $p = .004$). Specifically, baseline negative symptoms predicted negative symptoms at follow-up ($\beta = 0.60$, $p = .002$), while positive and disorganized symptoms did not ($\beta = 0.16$, $p = 0.38$; $\beta = 0.17$, $p = 0.32$, respectively). Lastly, for disorganized symptoms, the overall model was also significant ($F(3, 24) = 19.58$, $p < .001$) such that baseline disorganized symptoms predicted follow-up disorganized symptoms ($\beta = 0.87$, $p < .001$), while positive and negative symptoms did not ($\beta = 0.08$, $p = 0.52$; $\beta = -0.07$, $p = 0.58$, respectively). These results supported Hypotheses 1a, 1b, and 1c.

Table 7. Summary of Multivariate Regression Analyses for 6-Month Follow-Up

| | β | 95% CI | *SE* |
|---|---|---|---|
| Follow-up Positive Symptoms | | | |
| Baseline Positive | 1.09*** | 0.81, 1.37 | 0.14 |
| Baseline Negative | 0.29* | 0.02, 0.55 | 0.13 |
| Baseline Disorganized | -0.12 | -0.38, 0.13 | 0.13 |
| Follow-up Negative Symptoms | | | |
| Baseline Positive | 0.20 | -0.19, 0.58 | 0.19 |
| Baseline Negative | 0.60** | 0.25, 0.95 | 0.17 |
| Baseline Disorganized | 0.16 | -0.20, 0.51 | 0.17 |
| Follow-up Disorganized Symptoms | | | |
| Baseline Positive | 0.09 | -0.18, 0.36 | 0.13 |
| Baseline Negative | -0.06 | -0.32, 0.19 | 0.12 |
| Baseline Disorganized | 0.87*** | 0.63, 1.11 | 0.12 |

*Note.* Baseline symptoms as predictors of symptoms at follow-up.

**$p < .01$. ***$p < .001$.

**Aim 2**

Having established the relationship between symptom dimensions at baseline and follow-up, the secondary aim of the study was to examine potential associations between brain function via ERPs at baseline (P300, ERN, N400) and symptom dimensions at six-months follow-up (positive, negative, and disorganized symptom dimensions). It was expected that, controlling for covariates, reduced baseline P300 amplitude would be associated with increased positive symptom severity at follow up, decreased baseline ERN amplitude would be associated with increased negative symptom severity at follow-up, and decreased baseline N400 amplitude would be associated with increase disorganized symptom severity at follow-up.

To this end, partial correlations were run to examine the relationship between baseline ERPs (P300, N400, ERN) and dyad follow-up symptom scores (positive, negative, and

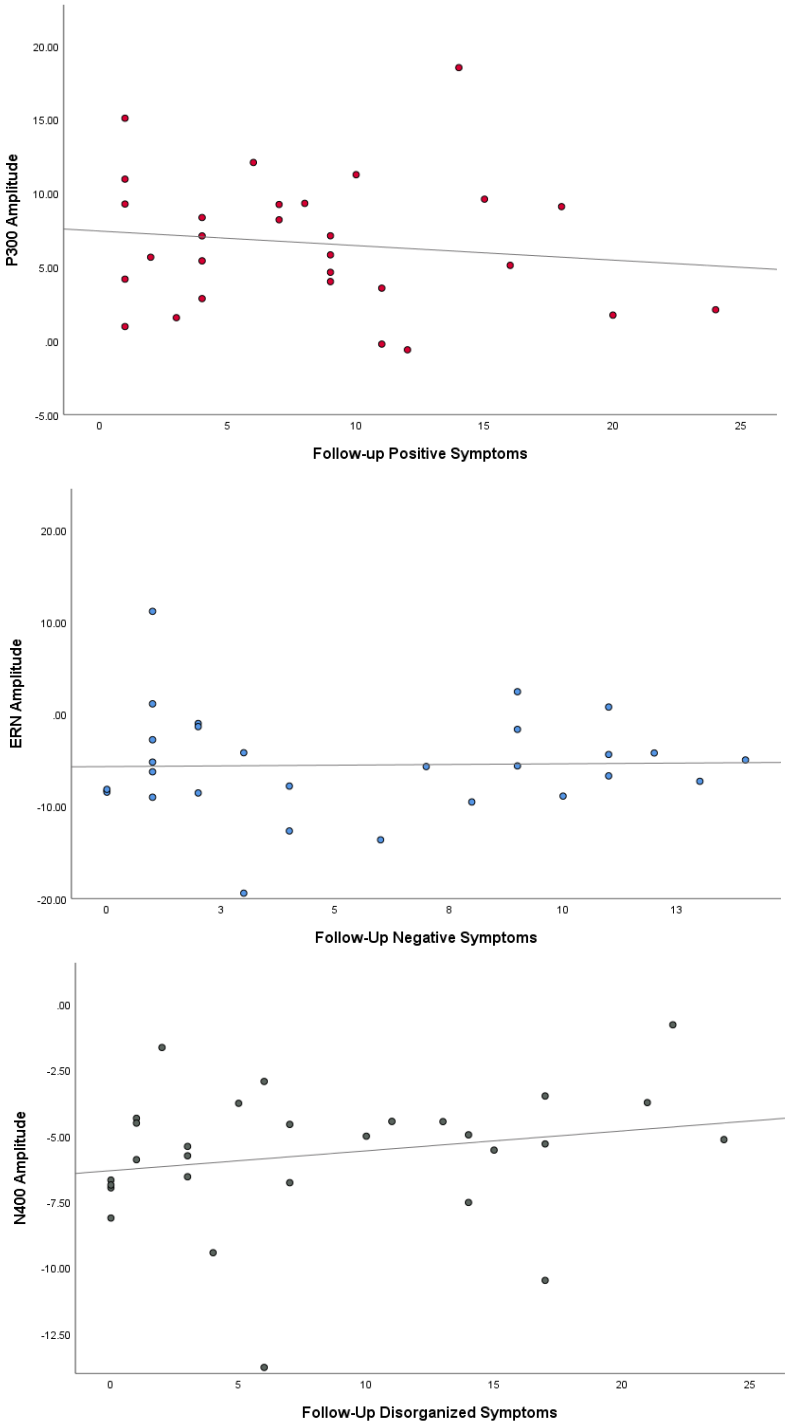
disorganized, respectively), while adjusting for baseline symptom scores and demographic covariates (see Table 8). Small, non-significant effects emerged for the P300 and positive symptoms ($r$ = 0.15, $p$ = 0.56), and ERN and negative symptoms ( $r$= -0.10, $p$ = 0.71), while a significant moderate correlation of the N400 and disorganized symptoms was observed ($r$ = 0.48, $p < 0.05$). While not statistically significant, the effect size of the P300 association with positive symptoms at follow-up had the opposite directionality than expected. Opposite directionality than expected was also observed for the ERN and negative symptom severity. Conversely, the direction of effect for the N400 and disorganized symptoms was robust and in the direction that was expected (i.e. greater symptom severity is correlated with blunted N400 amplitude). Scatterplots were generated to visually reflect the relationship between each discrete ERP and their respective hypothesized symptom dimension (see Figure 4). Together, results for P300 and ERN did not support Hypothesis 2a or 2b; however, results for the N400 supported Hypothesis 2c.

Table 8. Relationships Between Baseline ERPs and Follow-Up Symptom Measures

| | | Baseline ERPs | | |
|---|---|---|---|---|
| | | P300 | ERN | N400 |
| Follow-up Symptoms | Positive | 0.15 | -.002 | -0.16 |
| | Negative | -0.32 | -0.10 | 0.04 |
| | Disorganized | -0.31 | -0.12 | 0.48* |

*Note.* Relationship between baseline ERPs and follow-up symptom dimensions, including covariates: baseline symptom scores, age, gender, race, ethnicity, SES, education level, diagnosis, medication status.

**$p < .01$.




*Note.* Scatterplots reflecting relationship between P300 amplitude and follow-up positive symptoms, ERN amplitude and follow-up negative symptoms, and N400 amplitude and follow-up disorganized symptoms.

Figure 4. Illustration of relationships between baseline ERPs and follow-up symptom dimensions.

**Aim 3**

The overall aim of this aim was to examine longitudinal links between symptom characteristics and multiple neural measures of cognitive function in an at-risk sample, addressing an identified gap in the literature. To examine whether baseline ERPs (P300, ERN, N400) prospectively predict corresponding symptom severity (i.e. positive, negative, disorganized), a multivariate regression was calculated. Specifically, P300, ERN, and N400 were entered as simulations predictors, and MSS positive, negative, and disorganized symptoms were entered as simultaneous outcome variables (see Table 9). It was expected that, controlling for shared variance among other ERPs, the P300, ERN, and N400 would prospectively predict corresponding symptom domains at follow-up. The overall models were not significant such that the ERN ($F(3, 24) = 0.09$, $p = 0.96$), N400 ($F(3, 24) = 0.90$, $p = 0.44$), and P300 ($F(3, 24) = 0.90$, $p = 0.45$) did not predict symptoms at follow-up. Specifically, controlling for ERN and N400, the P300 did not predict positive symptom severity ($\beta = -0.15$, $p = 0.43$), controlling for P300 and N400, the ERN did not predict negative symptoms ($\beta = 0.09$, $p = 0.64$), and controlling for P300 and ERN, N400 did not predict disorganized symptoms ($\beta = 0.17$, $p = 0.53$) at follow-up. These results do not support Hypotheses 3a, 3b, or 3c.

Table 9. Summary of Multivariate Regression Analyses for 6-Month Follow-Up

| | β | 95% CI | *SE* |
|---|---|---|---|
| Positive Symptoms | | | |
| P300 | -0.15 | -0.54, 0.22 | 0.19 |
| ERN | 0.01 | -0.41, 0.41 | 0.20 |
| N400 | -0.16 | -0.74, 0.43 | 0.29 |
| Negative Symptoms | | | |
| P300 | -0.29 | -0.66, 0.08 | 0.18 |
| ERN | 0.09 | -0.30, 0.49 | 0.19 |
| N400 | -0.28 | -0.84, 0.28 | 0.27 |
| Disorganized Symptoms | | | |
| P300 | -0.22 | -0.59, 0.15 | 0.18 |
| ERN | 0.00 | -0.39, 0.39 | 0.19 |
| N400 | 0.17 | -0.39, 0.73 | 0.27 |

*Note.* Baseline ERPs as simultaneous predictors of symptoms at follow-up.

## Study 2 Discussion

The primary goal of Study 2 was to capitalize on the advantages of a longitudinal design by 1) investigating relationship of symptom dimensions over a clinically relevant time-frame of six months, and 2) examine the capability of baseline symptom dimensions and/or ERPs to prospectively predict future symptom severity. Where many studies limit analyses to single ERP components, this study examined a battery of ERP components simultaneously within a single risk sample. The goal of this study was first to investigate the association of baseline symptom dimensions with follow-up symptom dimensions, as well as calculate an empirical regression to quantitatively describe effect size and significance. Subsequently, a similar process was followed when investigating the association of baseline ERPs with follow-up symptom dimensions.

In Aim 1, baseline symptom dimensions were found to positively correlate with paired follow-up symptom dimensions, and demonstrate statistically significant effects. Further, a regression analysis demonstrated that baseline symptom dimensions prospectively predicted corresponding dimensions at follow-up. Interestingly, baseline negative symptom dimensions were also found to significantly predict follow-up positive symptoms, suggesting either a prospective predictive capability or potentially more likely a result of collinearity rather than causation. In all, these data demonstrate that, in a single at-risk sample, there is high rank-order stability between symptoms at baseline and symptoms at follow-up. This leads to logical next steps to examine if such symptoms are increasing or decreasing over time. Further work is warranted to bridge these gaps to understand the trajectory of risk.

In Aims 2 & 3, ERPs empirically known in the literature to relate with specific symptom dimensions of SZ were investigated for their association and ability to predict corresponding symptom dimensions at follow-up. Taking into account demographic covariates, only N400 and the disorganized symptom dimension at follow-up were found to correlate, and with a moderate effect size, an association that was not observed in Study 1. This finding aligns with existing literature that suggest that N400 semantic priming deficits, which map onto disorganized symptom domain, are shown to be present in individuals at clinically high risk for psychosis (Addington & Heinssen, 2012). However, as noted in Study 1, the relationship between N400 and disorganized symptoms is also contested, and these results should continue to be closely monitored. This effect did not hold upon empirically testing the N400's prospective predictive ability with disorganized symptoms.

Counterintuitively, P300-positive and ERN-negative effect sizes were found to reflect opposite directionality than expected within each respective dyad. In fact, no ERP measure was found to be a statistically significant predictor. As stated previously, it is possible that null effects may be due to insufficient power, given that the N400-disorganized symptom correlation was strong.

Together, psychophysiological measures of brain activity and cognitive function are critical to the field's understanding of psychological disease states. However, many studies have reported difficulty utilizing neurophysiological data to predict clinical states, potentially due to inherent differences among measurement tools used to assess brain function and symptom presence. Other factors contributing to this problem include the relatively stable nature of neural functioning, thus limiting the ability to map fluctuating symptom presentations within and across persons over time (Ford, 1999). While these may be plausible explanations, the number of follow-up data points was wanting, suggesting a limitation in power to detect real effects. Future work is warranted to collect data at multiple assessments (e.g., every six months for 2 years). Even so, disorganized symptoms did not correlate with N400 amplitude concurrently, in Study 1; however, controlling for covariates, N400 amplitude strongly correlated with disorganized symptoms longitudinally, suggesting promising implications for future work in a larger sample.

# GENERAL DISCUSSION

Schizophrenia is a devastating disorder that results in significant reduction in quality of life, such that persons with this disorder often have trouble living independently, performing basic tasks of daily living, and managing personal finances (Bowie & Harvey, 2006; Cardenas et al., 2008; Heinrichs et al., 2006; Patterson et al., 2001; Rocca et al., 2014). The SZ literature has characterized symptoms of SZ into three broad dimensions including positive, negative, and disorganized symptoms (American Psychiatric Association, 2013; Bromet et al., 2011; Kotov et al., 2011, 2017). However, these symptoms are often first measured after an individual has experienced their first psychotic episode and likely experienced their first treatment intervention. Thus, the etiology of SZ is still largely contested, with many arguing for the importance of examining individuals who exhibit subthreshold symptoms of psychosis, prior to onset of diagnostic threshold of a disorder.

Symptom presentation is largely heterogeneous in SZ, both within an individual over time and across individuals. For example, two people with a diagnosis of SZ may have very different symptom presentations. Alternatively, one individual diagnosed with SZ may experience waxing and waning of symptoms over their lifetime. Thus, it is plausible that similar heterogeneity is exhibited among individuals at risk for the disorder. To this end, the field has sought to examine these patterns by leveraging strengths of self-report measures, clinical interviews, and neurophysiological components, among others, to further refine the phenotype of risk.

Among SZ, much work has been conducted to investigate the utility of neural biomarkers and their relationships, or lack thereof, with clinical symptoms. However, fewer studies exist that support such relationships among an at-risk sample (for review, see Lepock et al., 2018). Of those that have been published, many have been cross-sectional, leaving clinical inferences regarding longitudinal patterns of association vague and non-specific. Considering the potential for multiple associations between neural biomarkers and clinical symptoms, there exists a substantial gap in the literature in examining multiple neurophysiological components (P300, ERN, N400) and multiple symptom dimensions within a single, at-risk sample. Such components have been well-validated among SZ but have yet to be similarly confirmed among an at-risk sample. To this end, this project aimed to examine whether similar correlations exist in a subclinical sample, and if

objective measures of neural functioning (P300, ERN, N400) have the capacity to prospectively predict future symptom severity (positive, negative, disorganized).

Study 1 aimed to examine and replicate ERP-symptom dyad associations in a single at-risk sample. By examining all three ERPs relevant to SZ and all three symptom dimensions in a single sample, this study further aimed to address the limitation of other studies, and determine any associations that may exist outside of the traditional ERP-symptom dyads (P300-positive, ERN-negative, N400-disorganized). Interestingly, these dyads did not show significant associations and exhibited small effect sizes. Previous research that has found small to moderate effect sizes in the SZ literature (Ford et al., 1999; Foti et al., 2012b; Mathalon et al., 2002) and small to large effects among studies examining clinical high risk populations (Lepock et al., 2018). Though the smaller effect size was largely unexpected, this suggests the possibility that small effects observed in Study 1 may indeed be true effects, though a significantly increased sample size would be necessary for detection. If a neural biomarker could be identified for even a small percentage of the many people who are at risk for conferring SZ, this finding would have robust clinical implications.

Given substantial literature supporting blunted neural activity in conjunction with illness state, we expected that similar trends would be observed in the current study. However, while not significant, a few associations were observed to be in the opposite direction than expected. This finding may be accounted for by several factors: 1) insufficient sample size, and 2) self-reported symptom rating may be far more variable than a "truly prodromal" sample (Fulford et al., 2014; Piskulic et al., 2012b). Among at-risk and formally diagnosed populations, this finding suggests that, in the absence of controlling for non-specific variance, relationships among ERP amplitude and symptoms may be artificially inflated. Furthermore, comorbid symptoms possibly account for unique variance among ERP amplitude, further conflating observed relationships among the interested variables.

Cross-sectional research has shown that P300 amplitude exhibits relationships with negative symptoms as well as positive symptoms (Eikmeier et al., 1992; Ford et al., 1999; McCarley et al., 1991; Mitchell et al., 1991; Pfefferbaum et al., 1980). Literature over the past 50 years or so has clarified that P300 amplitude can be utilized as a vulnerability marker of schizophrenia, as well as a marker of fluctuating clinical symptoms. For example, one longitudinal study showed that P300 tracks changes in positive symptoms such that as positive symptoms decrease, the P300 amplitude becomes more robust (Mathalon et al., 2000). These data support

our finding that, although not significant, the direction of effects in Study 1 may be suggestive of the current sample's clinical state.

Conversely, N400-disorganized symptom findings further contribute to the mixed literature regarding the ability to detect these symptoms in an at-risk sample. Studies examining 3-dimension symptom structure in clinically high-risk individuals found that positive and negative symptom domains may be relatively independent, while there is evidence that disorganized symptoms overlap with both positive and negative domains (Fonseca-Pedrero et al., 2016; Fulford et al., 2014). These findings suggest that disorganized symptoms, as they manifest in a risk sample, may be better accounted for by shared variance across positive and negative domains, further contributing to continued debate over factor structure in this population. Given that the MSS is a self-report measure, and disorganized symptoms are often difficult to assess in a risk state, it is also plausible that participants underreported disorganized symptoms, potentially explaining them away by other common experiences such as fatigue (Mark & Toulopoulou, 2016).

One of the strengths of this project was the ability to examine multiple ERP components simultaneously within a single risk sample. ERP-ERP relationships gleaned significant associations between P300 and ERN, and P300 and N400, but not ERN and N400. Interestingly, the P300-N400 correlation was moderate in size, but in opposite directionality than expected. Cross-sectionally, the literature has consistently touted blunted ERP amplitudes across illness states compared to healthy controls. Therefore, it may be reasonable to expect multiple ERPs examined together in a risk sample to fluctuate similarly. However, the amplitudes between P300 and N400 significantly fluctuated such that a decrease in amplitude in one corresponded with an amplified amplitude in the other. This finding may provide a greater degree of insight into the independent nature of these ERPs, information that cannot be gleaned from studies investigating single components.

The overall goal of Study 2 was to leverage ERPs to prospectively predict worsening of symptoms over time. Controlling for covariates, baseline positive, negative, and disorganized symptom scores significantly correlated with positive, negative, and disorganized symptom scores, respectively, six months later. In addition to these associations, baseline disorganized symptoms correlated with negative symptoms at follow-up. Across symptoms, these effects held in a regression model. Large effects emerged for identical symptom dimensions, while a moderate effect emerged for baseline disorganized and follow-up negative symptom scores. These

correlations further instill clinically-relevant confidence in the ability to prospectively predict symptom severity over a relatively short period of time. Such information could help to inform clinicians on how often to perform screening activities and under what time frame intervention may be required. We might imagine a scenario where individuals at-risk or presenting with mild symptoms may receive regular symptom assessment as a means to inform clinical treatment and prevention algorithms.

Regarding ERP-symptom relationships, and controlling for covariates, the N400 exhibited a relatively large correlation with disorganized symptoms at follow-up, a stark change from concurrent baseline associations observed in Study 1. However, this effect did not hold when testing for the prospective predictability of symptom dimensions at follow-up based on baseline ERP amplitude. Once again, it is possible that these effects are being washed out by other influences that were not controlled for in the regression model (i.e., baseline symptoms and demographic covariates). Additionally, no significant associations were observed in the partial correlation or regression model for P300 and ERN compared to longitudinal symptom dimensions. Although the N400 was not associated with concurrent symptom severity (Study 1), based on these data, it has the potential to predict symptoms longitudinally. If the relatively large effects between baseline N400 and follow-up disorganized symptoms hold in a larger sample, it is plausible that N400 could be utilized as a biomarker to prospectively predict worsening of symptoms in the relatively near future (i.e., six months). These data also reiterate that concurrent correlates are not always indicators of longitudinal predictors. Importantly, considering the likely variability inherent in a self-report measure in an at-risk sample, especially for disorganized symptoms, an objective physiological measure capable of prospectively predicting future symptom dimension severity may be instrumental in monitoring and treating individuals throughout the course of care.

## Limitations and Future Directions

As inherent in any scientific study, there exist limitations which must be identified and made transparent. Addressing of limitations allows the results to be interpreted with the appropriate context, and identifies further gaps for future work. In this series of studies, main limitations exist in the study sample, the study sample size, the lack of a control group, the assumption of ERP-symptom dimension specificity, and the duration of the longitudinal study.

Age is a primary limitation of the current study sample. The average age of participants was 22.82 with a range of 18-35 years old, with higher average age than typical risk groups (Addington et al., 2011; Addington & Heinssen, 2012; Cannon et al., 2008). Given the age of this sample, they are likely to experience greater stability in symptoms, which may impact the ability to detect associations, especially in Study 2. Beginning in late adolescents and into adulthood, "true" prodromal individuals typically experience an acute decline in functioning coupled with an acute increase in symptom severity (Addington & Heinssen, 2012). Future work should include a wider age range, potentially 12-35 years old, to fully ensure the study captures individuals within the prodromal stage. In order to assess these symptoms, future work may warrant semi-structure interviews specifically suited to assess subthreshold psychotic symptoms such as the Structure Interview for Psychosis-Risk Syndromes (SIPS), Scale of Psychosis-Risk Symptoms (SOPS) (Woods et al., 2019), or Comprehensive Assessment of at Risk Mental States (CAARMS; Oliver et al., 2018). Such interviews are specifically designed for the thorough assessment of psychosis risk, and would complement self-report measures including the CAPE and MSS. Given that the current study also recruited non help-seeking individuals from the community, there was likely variability in symptom presentation. As such, inclusion criteria for future work may include more stringent rules including meeting a particular score on a given subscale (e.g., CAPE positive scale), thus restricting the variability in symptom expression among the recruited sample and increasing resolution for detection and measurement of psychosis risk.

Other limitations of the current study include duration of the longitudinal component and lack of control group. While six-month follow-up assessments have been cited in the literature as a clinically-relevant period of time to assess changes in symptoms (Gee & Cannon, 2011), we did not expect to see much variation symptoms over this length of time. To examine nuanced fluctuations in symptoms, future work may find six-month intervals to be appropriate, and to expand the number of follow-up assessment through 2-5 years (Riecher-Rössler & Studerus, 2017). It is plausible that a participant enrolled in the current study may have converted to formal psychosis at the time of follow-up. With only self-report measures included in the follow-up data, the current study was unable to properly assess for diagnostic specificity. Future work may include ERP, self-report questionnaires, and clinical interviews at every assessment. In order to improve the feasibility of this future work, and to minimize the attrition rate, mobile EEG and telehealth methods may be appropriate.

The current study did not examine change in symptoms over six months. Correlations assessed rank-order stability and this approach did not account for change over time. Future analyses may be conducted to assess this change while accounting for relevant covariates. The current study also lacked the inclusion of a control group, where future work may compare data between a healthy and at-risk sample. However, the main aim of this project was to understand relationships between symptoms and ERP amplitude among those at-risk, negating the need for a control group.

Furthermore, the current sample size was calculated for the capability to detect medium effects, consistent with the existing literature for ERP and symptom dimension associations in SZ. Sample size was also selected to increase feasibility of participant recruitment in the allotted time-frame, and within the accessible community population. As seen in the analyses, sample size was limited, specifically for the follow-up in Study 2. Effect sizes between associations in both studies were low, likely leading to non-significance of many of the analyses. Ideally, future studies would include a rolling enrollment period lasting several years. Target enrollment would increase to several hundred, ensuring adequate power to detect effects.

Throughout decades of research, there has been a non-trivial number of articles showing evidence of ERP amplitude deficits among schizophrenia. However, while results have been mixed regarding ERP-symptom domain relationships, some evidence exists to support P300-positive, ERN-negative, N400-disorganized relationships. (Bates et al., 2002; del Re et al., 2015; Foti et al., 2016b, 2020; Jeon & Polich, 2003; Kiang et al., 2007b, 2008c; Kostova et al., 2005; Mathalon et al., 2000, 2002). Difficulties finding significant relationships in the literature between ERP components and illness characteristics may be partially explained by several factors, including a failure to report findings, failure to test relationships, and relatively ineffective assessment of symptoms (Ford, 2018). Additionally, while the field can reliably assess for components such as the P300, ERN, and N400, they are not *directly* measuring the processes of interest, including hallucinations/delusions, avolition/anhedonia, and thought disorder, respectively. Rather, ERP components reflect voltage at the scalp and may actually measure, or be conflated by, other non-specific processes. Furthermore, our ability to assess symptoms often rely heavily upon the individual's capacity to describe them, and a clinician's ability to observe and accurately report behavior. Participants may potentially misunderstand the essence of questions, or normalize an experience that may actually be a relevant symptom (i.e. interpreting a question about "feeling as

though messages through the TV or radio are meant specifically for you" as an item measuring target advertising). Furthermore, self-report measures of odd experiences may be more accurate in clinical samples given the perceived stigma of such experiences among the general population (Hanssen et al., 2003). As such, variability in such assessment may contribute to difficulty correlating neural measures and symptom ratings (Ford, 2018). It is possible that ERPs relate more specifically to sub-domains of functioning that underlie symptom dimensions rather than the dimensions themselves (Rocca et al., 2014). Lastly, given the high rate of comorbidity among individuals with severe psychiatric disorders, and the large proportion of non-psychotic psychopathology in the current sample, it is not surprising that 23% of participants reported being prescribed psychiatric medication. Given that medication has been shown to impact ERP amplitude (Demiralp et al., 2002; Umbricht et al., 1998) and alters symptom presentation, it is plausible that medications also impact the degree to which these two domains relate. Together, it is imperative that while difficult to assess, researchers continue to investigate the etiology of such chronic and impairing disorders.

To compliment information gleaned by temporal precision of ERP methods, future directions could include an expansion of units of analysis. For example, fMRI compliments ERP with excellent structural resolution, providing different information for use in identifying individuals at risk for psychosis. Cognitive and neuropsychological measures would provide insight into nuanced cognitive functioning deficits, domains that are commonly observed to be impacted by disorders such as schizophrenia (Bowie et al., 2006; Bowie & Harvey, 2006; Fioravanti et al., 2005; Lesh et al., 2011; Mohamed et al., 1999), and have been shown to map onto symptom dimensions. With the inclusion of other relevant units of analysis, statistical methods may also be expanded to examine profiles of risk for psychosis, with the goal to begin to connect these pieces in a way that allow investigators to identify pathways to symptom presentation, severity, and poor outcomes. This may ultimately lead to enhanced efforts for preventative measures and early intervention.

# CONCLUSION

Overall, this series of studies measured interesting associations in neural functioning and symptom severity in an at-risk sample. The use of multiple ERPs and multiple symptom dimensions is a novel addition to the literature, and revealed the importance in measuring and accounting for these covariates to prevent artificial inflation of reported associations. These studies begin to suggest that ERP-symptom dimension relationships may be more muted and unpredictable in an at-risk sample, though follow up studies with greater sample sizes and appropriate controls are needed to confirm this hypothesis. Additionally, this study only assessed self-report measures at follow-up, excluding repeated ERP measures and clinical interviews. It is feasible that a participant may have converted to a formal psychotic disorder at the time of follow-up. Finally, the greatest implication of this study is the demonstrated correlation between N400 and symptom severity at a clinically relevant, short-term follow-up in at-risk individuals. Though this association did not hold in the regression model, these data further strengthen the argument that neural biomarkers may be used to identify and predict symptom severity, ultimately reducing subjectivity in clinical diagnosis and treatment.

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