EXAMINING AN EVENT-RELATED BRAIN POTENTIAL INDEX OF SEMANTIC PRIMING IN CANNABIS-USING INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS

by

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Abstract

Individuals at clinical high-risk (CHR) for schizophrenia experience subthreshold symptoms of this disorder, and cannabis use further increases their risk of conversion to psychosis. To seek neurophysiological evidence that cannabis use is associated with semantic processing deficits in the CHR state, we used the N400 event-related potential (ERP) to measure semantic priming. We recorded ERPs in 15 cannabis-using and 12 non-cannabis-using help-seeking CHR individuals, and 10 cannabis-using and 15 non-cannabis-using healthy controls while they viewed related and unrelated prime-target word pairs, at a short and a long stimulus-onset asynchrony (SOA). We observed no significant differences in N400 semantic priming between the four groups, but observed a trend towards deficits at the long SOA in all CHR participants compared to all controls ($p = 0.07$). The results suggest that CHR individuals experience semantic priming deficits similar to those of schizophrenia patients but that cannabis use does not further impair this process

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Statement of Contributions

Sarah Ahmed (author): recruited participants and executed study visits, conducted data analysis and interpretation, and performed thesis write-up

Dr. Romina Mizrahi (supervisor): guidance in study design and execution, provided expertise with CHR and cannabis-using participant recruitment, provided mentorship throughout study, and guidance in thesis write-up

Dr. Michael Kiang (Program Advisory Committee member): responsible for study conception and design, provided mentorship throughout study, guidance in study execution, data analysis, results interpretation and thesis write-up

Dr. Tony P. George (Program Advisory Committee member): provided guidance and expertise on cannabis-using participant recruitment, study execution and data collection

Jennifer R. Lepock: recruited participants and executed study visits (24 of the participants completed the study prior to the start of the author's Master's program); provided guidance with analysis and interpretation of results.

Dr. Cory Gerritsen and Margaret Maheandiran: assisted with participant recruitment and study execution, and administered clinical and neuropsychological assessments.

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List of Abbreviations

2-AG	2-arachidonoylglycerol
AEA	Anandamide
APSS	Attenuated Psychotic Symptom Syndrome
BIPS	Brief Intermittent Psychosis Syndrome
CAMH	Centre for Addiction and Mental Health
CB1/CB2	Cannabinoid receptors
CBD	Cannabidiol
CHR	Clinical high-risk
CHR/C-	CHR individuals with no history of cannabis use
CHR/C+	Cannabis-using CHR individuals
COPS	Criteria of Prodromal Symptoms
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision
DSM-V	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
EEG	Electroencephalogram
ERP	Event-Related Potential
fMRI	Functional Magnetic Resonance Imaging
FYPP Clinic	Focus on Youth Psychosis Prevention Clinic
GRDS	Genetic Risk and Deterioration Syndrome
HC/C-	Healthy cannabis users with no history of cannabis use
HC/C+	Cannabis-using healthy controls
IFG	Inferior frontal gyrus
MCCB	MATRICS Cognitive Consensus Battery
MEG	Magnetoencephalogram
MTG	Left mid-posterior middle temporal gyrus
N400	Negative deflection occurring 400ms post-stimulus onset after a meaningful stimulus
PET	Positron Emission Tomography
REB	Research Ethics Board
SCID	Structured Clinical Interview for DSM
SOA	Stimulus-onset asynchrony
SOPS	Scale of Psychosis-risk Symptoms
UHR	Ultra high-risk
Δ9-THC	Delta-9-tetrahydrocannabinol

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1. Introduction

1.1. Statement of Problem

Schizophrenia is considered to be one of the most complex and severe mental illnesses, and usually begins in late adolescence to early adulthood (Charlson et al., 2018). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association [APA], 2013), the average lifetime prevalence of schizophrenia is between 0.3 to 0.7%, but there is significant variation due to race/ethnicity, geographic location and immigration status (Kahn et al., 2015; McGrath, Saha, Chant, & Welham, 2008). Alongside the distress experienced by patients and their families, the overarching health, economic and social burdens of schizophrenia are significant. Therefore, it is important to identify early signs of schizophrenia and other related psychotic disorders (Addington & Heinssen, 2012).

Between 80 to 90% of schizophrenia patients report the occurrence of subthreshold symptoms in the months and years prior to their first episode of frank psychosis (Addington & Heinssen, 2012). Research has identified this constellation of changes in cognition, behavior, perception, beliefs and attention as the clinical high-risk (CHR) or ultra-high risk state (UHR) (Yung & Nelson, 2013). Within two years of presentation to a clinical service, conversion to a frank psychotic episode is approximately 29% among this population (Kempton, Valmaggia, Mcguire, & Fusar-Poli, 2016). Furthermore, cannabis use is more prevalent among these individuals (Carney, Cotter, Firth, Bradshaw, & Yung, 2017) and it has been linked to an increase in risk of conversion to a psychotic disorder (Kraan et al., 2016). However, the neurocognitive pathways whereby cannabis may precipitate psychotic symptoms in the CHR state remain unclear. Neurophysiological biomarkers of cognitive processes have the potential for improving our understanding of these pathways. Identification of such biomarkers associated

with cannabis use in the CHR state could point to novel pharmacological and cognitive treatment targets for prevention of psychosis.

1.2. Purpose

The main purpose of this study is to contribute to a better understanding of the cognitive effects of cannabis use among those with symptoms of the clinical high-risk state. Using a neurophysiological index of semantic priming, where related words are processed more easily than unrelated words, this study aims to further delineate the cognitive changes that occur in the CHR state and how cannabis may play a role in these impairments. This study may serve a crucial role in improving our understanding about cognitive deficits experienced by CHR individuals, and how these deficits are affected by cannabis use. Furthermore, it may contribute to the vast body of research on the effects of cannabis use on conversion rates from the CHR state to a psychotic disorder, delineating the pathways and mechanisms by which this process occurs.

1.3. Schizophrenia

1.3.1. Psychopathology

Schizophrenia is defined by a diverse set of symptoms, including positive symptoms (also known as psychotic symptoms), negative symptoms and cognitive impairment (Lunn, 2017). Psychotic symptoms are characterized by a loss of contact with reality, and include delusions (fixed false beliefs), hallucinations (abnormalities in perception) and disorganized communication. An example of a delusion is an individual's belief that they are being stalked, or that the government is keeping track of their movements. They believe this without concrete evidence and attempts to bring their attention to contrasting arguments may prove to be futile. Hallucinations include seeing, hearing, smelling or tasting things that are not real. Individuals

with disorganized communication may be unable to carry on a logical conversation, or their speech may consist of words or sentence fragments that do not make sense in the given context. Negative symptoms include alogia (poverty of speech), avolition, and low mood. Cognitive impairments include deficits in attention, memory and concentration. These symptoms along with change in occupational and social functioning make up the schizophrenia syndrome (van Os & Kapur, 2009)**.** Various other mental illnesses, such as bipolar disorder, major depressive disorder and schizoaffective disorder can also include psychotic features. Psychotic disorders, including schizophrenia, that are characterized by few affective (mood) symptoms are known as non-affective psychoses (van Os & Kapur, 2009). Psychotic disorders, such as bipolar disorder with psychotic features, that consist of a high level of affective symptoms that precede the psychotic symptoms, are known as affective psychoses.

1.3.2. Disease Burden

While it is difficult to provide precise estimates of the worldwide prevalence of schizophrenia and other psychotic disorders, estimates of lifetime prevalence range between 0.40 and 0.749% (Moreno-Küstner, Martín, & Pastor, 2018; Saha, Chant, Welham, & McGrath, 2005). The annual global economic disease burden of schizophrenia is estimated to be in the range of US$94 million to US$102 billion (Chaiyakunapruk et al., 2016) due to both direct and indirect costs such as health care, lost productivity, and social services. These costs are significantly elevated in comparison to other chronic mental and physical illnesses. The largest burden falls within the 25-to-34-year age group, where individuals are normally at their highest level of economic productivity (Charlson et al., 2018). In the United States, schizophrenia patients have an increased and earlier rate of mortality than the general population, with 28.5 average years of life lost; there is also a significantly high rate of co-occurring medical illnesses

such as heart disease, liver disease, diabetes (Schoenbaum et al., 2017). Given the general severity, poor outcomes, and overall disease burden of this mental illness, it is important to find ways to identify those who are risk for developing it with the aim of preventing its onset.

1.4. Clinical High-Risk (CHR)

1.4.1. Clinical Presentation

In order to prevent schizophrenia and other psychotic disorders, we can aim to intervene in the early, prodromal stages of these illnesses. This prodromal stage is characterized as the period preceding the onset of a frank psychotic episode (Yung & McGorry, 1996). Changes in motivation, mood, cognition and the experience of attenuated psychotic symptoms such as unusual thoughts, suspiciousness and changes in perception are hallmarks of this stage (Addington & Heinssen, 2012; Figure 1). The constellation of subthreshold symptoms of psychosis led to the identification of a putative prodromal state that came to be known as the clinical high-risk (CHR) or ultra-high risk state (UHR) (Yung & McGorry, 1996). A key feature of this stage is that individuals retain insight into their symptoms and the distress it is causing.

In a typical example of the CHR state (Yung & McGorry, 1996), the individual begins worry about cars following them and friends turning against them. They begin to withdraw socially from their friends and family, to the point where it is noticeable as they avoid leaving the house for extended periods of time. They have trouble sleeping, and experience changes in their attention and concentration, which negatively affect their school grades. When alternative evidence is presented for their persecutory thinking, they are able to see how they could be misinterpreting events to come to these conclusions. We can differentiate this individual from someone experiencing a frank psychotic episode in that someone with psychosis may not

respond to alternative evidence refuting their beliefs, and may experience these persecutory ideas at a significantly greater intensity.

1.4.2. Classification of Subtypes

One of the early problems faced by researchers was the identification of false positives as belonging to the CHR syndrome, which limited the ability to predict who would convert to psychosis and to assess the effects of preventative treatment (Yung & Nelson, 2013). Contributing to this problem is the non-specific nature of many prodromal symptoms. Combining multiple risk factors, including age, clinical symptoms and functioning, to develop CHR criteria may help improve the specificity of predicting which individuals will convert to psychosis.

Yung & McGorry (1996) and Yung et al. (1998) originally identified certain subtypes of individuals at risk for developing psychosis and they can be diagnosed using the Criteria of Psychosis-risk Symptoms (COPS) which assesses the following syndromes: Brief Intermittent Psychotic Syndrome, Attenuated Psychotic Symptom Syndrome, and Genetic Risk and Deterioration Syndrome (T. J. Miller et al., 2003).

1. Brief Intermittent Psychotic Syndrome (BIPS)

The Brief Intermittent Psychotic Syndrome is characterized by frank psychotic symptoms that have occurred recently but are very brief in duration. The symptoms must have begun in the past three months and must be present at least several minutes a day, occurring at least once per month.

2. Attenuated Psychotic Symptom Syndrome (APSS)

The Attenuated Psychotic Symptom Syndrome is characterized by the presence of recent subthreshold positive symptoms in one or more of five domains (unusual thought content,

suspiciousness, grandiose ideas, perceptual abnormalities or disorganized communication) that began in the past year or are more intense than a year ago. The symptom(s) must also occur at least once per week in the past month at the current intensity. APSS is considered to be the most common presentation of the CHR state (Addington, 2013).

3. Genetic Risk and Deterioration Syndrome (GRDS)

The Genetic Risk and Deterioration Syndrome is characterized by individuals having a first-degree relative with any affective or non-affective psychotic disorder and/or meeting criteria for DSM-IV Schizotypal Personality Disorder criteria, and a functional decline of 30% from 12 months prior.

The COPS only assesses positive symptoms, therefore assessments such as the Structured Interview of Prodromal Symptoms (SIPS; Miller et al., 2003) and the Comprehensive Assessment of At-Risk Mental States (CAARMS, Yung & McGorry, 1996) are used to provide more detailed evaluation of negative symptoms, decline in social and role functioning, and sleep disturbance, alongside measuring positive symptoms. For the purposes of this study, we will be using the SIPS to evaluate for the presence of CHR symptoms, which has been validated for its predictive and diagnostic reliability (T. J. Miller et al., 2003).

1.4.3. Prevalence and Conversion Risk

As CHR criteria are based solely on those individuals who are help-seeking and access mental health care, this presents a challenge to estimating exact prevalence rates. It is possible that there are individuals who meet criteria for prodromal psychosis but whose symptom profiles have not yet been identified as they do not reach out to health care services. Regardless, the available research suggests that the prevalence ranges between 2 to 8% (Fusar-Poli et al., 2013; Schultze-Lutter, Michel, Ruhrmann, & Schimmelmann, 2017).

In terms of transition risk to a psychotic episode, an extensive meta-analysis of approximately 2500 CHR individuals found that independent of psychometric assessment used, there was a mean (95% CI) conversion risk of 18% (12%-25%) at 6 months of follow-up, 22% (17%-28%) at 1 year, 29% (23%-36%) at 2 years, 32% (24%-35%) at 3 years, and 36% (30%-43%) after 3 years (Fusar-Poli et al., 2012). An individual is considered to have transitioned to a full psychotic episode if they rate a 6 on the SIPS (highest rating, indicating symptom has reached psychotic intensity) on at least one symptom domain and this is present at a frequency of several times per week for at least one month, or in the case of severely disorganizing or dangerous symptoms, for at least one day (Yung et al., 1998). Longitudinal studies have found that 30% of CHR individuals developed psychosis within two years, 36% experienced remission of symptoms and 30% displayed limited functional recovery (Schlosser et al., 2012). Other studies have suggested that non-converters continue to exhibit a range of psychiatric and functional problems (Addington & Heinssen, 2012).

There are various risk factors that may cause one to experience CHR symptoms and/or to transition from the CHR state at a greater rate. These include stressful life events, childhood trauma in the form of psychological, physical, or sexual abuse, sexual trauma, obstetric complications, tobacco use, unemployment, migration and refugee status (Bechdolf et al., 2010; Egerton et al., 2017; Fusar-Poli, 2017; Kirkbride et al., 2017; Kraan, Velthorst, Smit, de Haan, & van der Gaag, 2015; Loewy et al., 2019; Şahin et al., 2013). Importantly, one risk factor that has become relevant today is cannabis use, especially given the prevalence of use among CHR individuals and the recent legalization of the substance in various countries, including Canada.

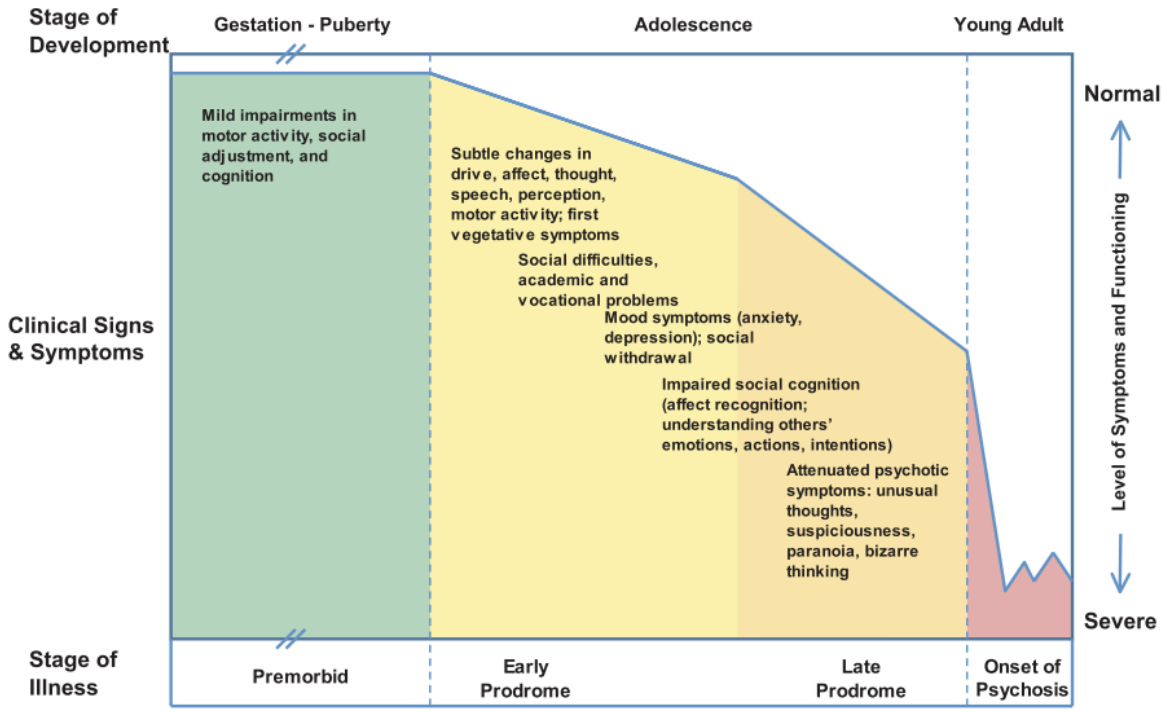

Figure 1. Clinical course of the psychosis prodrome (Addington & Heinssen, 2012).

1.5. Cannabis

1.5.1. Cannabis Prevalence

Globally, cannabis is the most commonly used psychoactive drug (The United Nations Office on Drugs and Crime [UNODC], 2019). Research suggests that approximately 3.8% of the world's population aged 15 to 64 years, which amounts to approximatively 188 million people, have used cannabis at least once in 2017 (UNODC, 2019), with the annual prevalence of use in North America amounting to 8.4% of the population. Cannabis is also the most widely used drug among youth, and use estimates are twice as high in adolescents compared to the general population. Globally, approximately 13.8 million young people (comprised mostly of students aged 15 to 16 years) have used cannabis at least once in 2017, about 5.6% of the population within this age range (UNODC, 2018).

In Canada, about 18% of the population, or 5.3 million people, aged 15 years and older reported using cannabis within the past 6 months (Statistics Canada, 2019). Use is also quite common among young people, about 30% of 15- to 24- year olds. There was an increase in cannabis use between the first quarters of 2018 and 2019, with more new users in 2019. This increase may be explained by the recent legalization of cannabis in Canada in October 2018.

1.5.2. Cannabis Constituents

Cannabis is the generic term used to describe the various psychoactive preparations of the *Cannabis* plant. Marijuana is the crude drug derived from the *Cannabis sativa* L. plant (ElSohly & Slade, 2005). Cannabis preparations are usually obtained from the female of this plant, which contains at least 750 chemicals and approximately 104 different cannabinoids (WHO, 2016), of which the three most common cannabinoid types are delta-9-tetrahydrocannabinol (Δ9-THC), cannabidiol (CBD) and cannabinol (CBN) (ElSohly & Slade, 2005). The principal psychoactive

ingredient of cannabis is Δ9-THC. Interestingly, the effects of CBD may act as an anxiolytic to counteract the psychotomimetic effects of Δ9-THC (D'Souza, 2007).

Marijuana is typically smoked in a hand-rolled cigarette or "joint", which may include tobacco (World Health Organization, 2016). A water pipe or "bong" is also another popular means of inhaling cannabis preparations. Additionally, portable, battery-powered vaporizers, including vape-pens and e-cigarettes, are devices designed to heat, vaporize and inhale cannabis (Morean, Lipshie, Josephson, & Foster, 2017; WHO, 2016) and are becoming increasingly popular. This method of inhalation is considered to be a more efficient way to ingest a variety forms of cannabis including hashish (resin) and hash oil, a waxy substance infused with Δ9-THC and dried cannabis buds. Additionally, hashish and hash oil can be consumed in the form of food products or tea.

The inhalation of cannabis by smoking or vaporization allows for maximal levels of THC to be absorbed into the blood within minutes, peaking at 15 to 30 minutes and leveling off within two to three hours (Ashton, 2001). Ninety percent of Δ9-THC is distributed to plasma and the rest to red blood cells (Sharma et al., 2017) and peak plasma concentration is attained within 3-10 minutes (Grotenhermen, 2003). Oral ingestion results in much slower absorption than inhalation of Δ9-THC from the gastrointestinal tract, and as such, the effects are only felt 30-90 minutes after consumption, peaking within two to three hours. Slower absorption results in delayed plasma peak concentrations within 60 to 120 minutes, while also being distributed to other tissues including the brain.

Because Δ9-THC accumulates in fatty tissues, it has a half-life of approximately 7 days and complete elimination may take up to 30 days (Ashton, 2001). More than 65% of the substance is excreted in feces and 25% in urine. Δ9-THC is detectable for approximately 10

hours in the urine but metabolites can be detected up to 30 days (Moeller, Kissack, Atayee, & Lee, 2017).

1.5.3. Acute Effects of Cannabis Use

The effects of cannabis consumption can be physiological, behavioral or psychiatric, and also depend on the dose, potency and individual tolerance levels. Immediate psychopharmacological effects of cannabis are associated with subjective feelings of euphoria and relaxation, or a general sense of heightened mood known as a "high" which can be induced with doses of Δ9-THC as low as 2.5mg (Ashton, 2001). This can also be accompanied by feelings of decreased anxiety, alertness and sociability. There are also associated dysphoric effects, such as severe anxiety, panic, paranoia and psychotic-like symptoms. These psychosis-like symptoms include hallucinations, depersonalization, disorientation and psychomotor agitation but is often observed in new users or due to large doses and high potency cannabis (Johns, 2001; Karila et al., 2014). Physiological symptoms include increased appetite, dry mouth, increased appetite and tachycardia. In terms of short-term effects on cognition, cannabis users have been known to display deficits in short-term memory, executive functions, performance of complex mental abilities, reaction time and motor coordination (Ashton, 2001; Karila & Reynaud, 2003; Karila, Vignau, Alter, & Reynaud, 2005; Wilkinson, Yarnell, Radhakrishnan, Ball, & Souza, 2016; Yucel, Lubman, Solowij, & Brewer, 2007).

Controlled studies using Δ9-THC have observed that in healthy controls, effects mirror positive psychotic-like symptoms such as paranoia, grandiosity, disorganized communication, hallucinations and depersonalization, and occur in a dose-dependent manner (D'Souza et al., 2004; Kaufmann et al., 2010). Additionally, Δ9-THC also has been found to induce negative psychotic symptoms, increased anxiety and cognitive deficits in working memory, verbal

fluency, attention, and decision-making (D'Souza et al., 2004; Miller, McFarland, Cornett, & Brightwell, 1977; Miller, McFarland, Cornett, Brightwell, & Wikler, 1977; Ranganathan & D'Souza, 2006). Furthermore, even when an individual is not presently intoxicated by cannabis, they may experience acute psychotic episodes, as studies have found that individuals who experienced a cannabis-induced psychotic episode were later diagnosed with a schizophrenia-spectrum disorder (Arendt, Rosenberg, Foldager, Perto, & Munk-Jorgensen, 2005; Niemi-Pynttäri et al., 2013).

1.5.4. Chronic Effects of Cannabis Use

Long-term cannabis use has been associated with a variety of outcomes. Many studies have reported that long-term use causes impairments in cognitive functioning, such as the encoding of new episodic memories, poor accuracy in decision-making (Hall & Degenhardt, 2009), and deficits in verbal learning, memory and attention (Crane, Schuster, Fusar-poli, & Gonzalez, 2013; Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003; Hall & Solowij, 1998; Schreiner & Dunn, 2012; Solowij & Battisti, 2008). Individuals who start chronically using cannabis in their adolescence are more prone to deficits in visuospatial attention, verbal fluency and inhibition compared to those who start in their adulthood (Crean et al., 2011; Curran et al., 2016). Additionally, these individuals have impaired neural connectivity in brain areas responsible for alertness, self-conscious awareness (precuneus), learning and memory (fimbria of the hippocampus) and various executive functions (prefrontal cortex) (Volkow, Baler, Compton, & Weiss, 2014). Furthermore, various clinical and preclinical studies have observed that chronic cannabis use is associated with an amotivational state, such that individuals experience reduced engagement in activities not related to drug-use, which is reflected in impaired dopaminergic reward-signaling pathways (Volkow et al., 2016).

In terms of other health effects, cannabis use has been associated with respiratory system deficits, including inflammation in large airways, and lung hyperinflation (Karila et al., 2014; Volkow et al., 2014). Chronic cannabis users also report more symptoms of chronic bronchitis, such as wheezing, coughing, and increased sputum production compared to non-users (Hall & Degenhardt, 2009; Volkow et al., 2014). Moreover, cannabis use has been associated with an increased risk of myocardial infarction, stroke, cardiac arrhythmias and transient ischemic attacks during times of use (Hall & Degenhardt, 2009; Karila et al., 2014; Volkow et al., 2014).

The main long-term, chronic effect of repeated cannabis use is cannabis dependence, which consists of the development of a variety of behavioral, cognitive and physiological phenomena. To meet criteria for this disorder, an individual must experience three of the following symptoms within the past year on the Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM-IV-TR; APA, 2000): tolerance defined by a need for markedly increased amounts of the substance to achieve intoxication or desired effect; withdrawal effects which can be adverse psychological or physiological symptoms such as nausea, headaches, lack of appetite and trouble sleeping; the substance is taken in larger amounts or over a longer period than intended; persistent desire or unsuccessful attempts to cut down on use; a great deal of time is spent in activities necessary to obtain the substance, use the substance or recover from its effects; use of the substance causes reduction in social, occupational and recreational activities; and substance use is continued despite the acknowledgement of physical or psychological problems. The updated DSM-V criteria merge both abuse and dependence disorders into a single "cannabis use disorder", and require that only two of the above symptoms must be met in the past 12 months, and are scored on severity: mild (presence of 2-3 symptoms), moderate (4-5 symptoms) or severe (6 or more symptoms) (APA, 2013). Individuals who use cannabis in their

early adolescence are at a 16% greater risk of developing cannabis dependence (Lopez-Quintero et al., 2011; Wagner & Anthony, 2007; WHO, 2016).

1.5.5. Cannabis Use in Schizophrenia Patients

Regular cannabis use has been observed to be more common among schizophrenia patients. In fact, higher Δ9-THC concentration and lower CBD concentration of cannabis consumed may increase the risk of schizophrenia, and lower the age of onset of the disorder (D'Souza, Sewell, & Ranganathan, 2009; Di Forti et al., 2014; Marconi, Di Forti, Lewis, Murray, & Vassos, 2016; Myles, Myles, & Large, 2016; Niznikiewicz, Mittal, Nestor, & McCarley, 2010; Radhakrishnan, Wilkinson, & D'Souza, 2014; van Os et al., 2002; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002). One 10-year longitudinal study of 229 patients with schizophrenia, schizophreniform or schizoaffective disorder showed that over 66% of the participants had used cannabis in their lifetime and 43% met criteria for an abuse or dependence disorder (Foti, Kotov, Guey, & Bromet, 2010). Lifetime use was associated with an earlier onset of psychosis. Current users were younger at the age at first psychiatric admission and had an earlier age at onset of symptoms. Furthermore, exposure to cannabis before baseline assessments was associated with more severe psychotic symptoms at baseline, and patterns of cannabis and psychotic symptoms seemed to covary over time.

Additionally, cannabis use has been shown to exacerbate psychotic symptoms in schizophrenia patients (Murray et al., 2017; Sewell, Ranganathan, & D'Souza, 2009). While it has been hypothesized that perhaps the reason for increased use among schizophrenia patients is that those with the disorder use cannabis to relieve symptoms, several large studies have disputed this hypothesis and shown that cannabis use precedes the onset of psychosis (Andréasson, Engström, Allebeck, & Rydberg, 1978; Fergusson, Horwood, & Swain-Campbell, 2003; Forti et

al., 2009; Ksir & Hart, 2016). One study of a Swedish national sample found that cannabis-induced psychotic disorder was a result of drug exposure in individuals at an elevated genetic risk for substance abuse and a moderately elevated genetic risk for psychosis (Kendler, Ohlsson, Sundquist, & Sundquist, 2019). Furthermore, genetic risk for psychosis predicted progression from cannabis-induced psychosis to schizophrenia. This suggests that progression to schizophrenia from a substance-induced psychotic disorder occurs in at-risk individuals who use significant amounts of cannabis, and does not occur solely due to drug exposure. Taken together, these studies suggest a complex and dynamic relationship between cannabis use and psychotic disorders, including schizophrenia. To better understand the pathway of causation, we can look to cannabis use as a risk factor for developing psychosis.

1.5.6. Cannabis Use as Risk Factor for Psychosis

One of the first studies to examine the association between cannabis use and the occurrence of a psychotic disorder was conducted by Andréasson et al. (1978), of more than 45,000 individuals, 97% of whom were male military conscripts, aged 18-20. These individuals were followed for 15 years. A strong association was observed between level of cannabis exposure at conscription and development of schizophrenia at follow-up, with a relative risk of 2.4 of developing schizophrenia in the group that reported use of cannabis at least once, when compared with non-users. There was a positive dose-dependent relationship between consumption level and increased relative risk, such that it increased to six-fold in individuals who had used cannabis more than 50 times in their life. This study controlled for juvenile delinquency, paternal alcohol use, socioeconomic status and psychiatric diagnosis at conscription. Interestingly, Zammit et al. (2002) reanalyzed this data and found that by excluding individuals who developed schizophrenia within five years of the start of the study, those who

used cannabis at least 50 times were at a 2.5 times greater risk of developing psychosis. Moreover, overall risk was reduced when controlling for IQ, disturbed behavior in childhood, psychiatric diagnosis at time of conscription, cigarette use and social integration. Finally, this registry data was analyzed at 35-years of follow up, and cannabis use was found to be a risk factor for brief psychosis and non-affective psychosis (Manrique-Garcia, De Leon, Dalman, Andréasson, & Allebeck, 2016).

Various other studies using other longitudinal cohorts around the world have observed an association between cannabis use and an increased risk of psychosis and psychotic experiences (Arseneault et al., 2002; Fergusson, Boden, & Horwood, 2015; Henquet et al., 2005; Kuepper et al., 2011; Smit, Bolier, & Cuijpers, 2004; van Os et al., 2002) and one study found that this association was greater for cannabis use than tobacco use in cigarettes (Jones et al., 2018). Another study (Jones, Calkins, Scott, Bach, & Gur, 2017) did not observe a longitudinal relationship between cannabis use and psychosis risk when controlling for confounds such as demographics, comorbid psychopathology and trauma history, and instead found that polysubstance use among cannabis users was associated with psychosis-spectrum symptoms.

Many meta-analyses have been conducted on this relationship and results have further supported a link between increased risk of psychosis and cannabis use, even when controlling for many confounds (Arseneault, Cannon, Ton, & Ay, 2004; Henquet, Murray, Linszen, & van Os, 2005; Large, Sharma, Compton, Slade, & Nielssen, 2011; Moore et al., 2007; N. Myles, Newall, Nielssen, & Large, 2012). One study found that progression from occasional to regular cannabis use has been associated with an increased risk of onset of prodromal and psychotic symptoms in first-episode patients (Compton et al., 2009). Additionally, using cannabis at a younger age is associated with earlier occurrence of psychotic symptoms compared to individuals who did not

use cannabis (Casadio, Fernandes, Murray, & Di Forti, 2011; Donoghue et al., 2014; Stefanis, Power, & Morgan, 2013), such that the age of onset of psychosis for cannabis users was 2.70 years younger than those who never used (Large et al., 2011).

To summarize, there seems to be a robust association between cannabis use and psychosis observed in multiple studies, including longitudinal analyses and meta-analyses that have controlled for various confounding factors. However, in order to better understand this relationship and account for other potential confounders, we must conduct further research that examines the effects of sampling bias, low-powered samples, overlap between psychosis-like symptoms and psychotic disorder, direction of causality, comorbid tobacco use (Compton et al., 2009) lifetime polysubstance exposure and other, unknown confounders (Gage, Munafò, Macleod, Hickman, & Smith, 2015; Gage, Zammit, & Hickman, 2013). In addition, we can look to research conducted at the prodromal stage of schizophrenia and psychotic disorders to better understand how cannabis use affects the onset and experience of psychosis-like symptoms.

1.5.7. Cannabis Use in Clinical High-Risk Individuals

Similar to schizophrenia patients, cannabis use is common among CHR individuals. This population is more than twice as likely to use cannabis in their lifetime when compared to controls, and are more than five times as likely to have a cannabis use disorder (Carney et al., 2017). Similarly, Valmaggia et al. (2014) observed that lifetime cannabis use was reported by 73.6% of their sample of UHR individuals, however, most of these individuals had stopped using cannabis because of adverse effects. An increased risk of transition to psychosis was associated with frequent use, early-onset use and continued use after clinical presentation among lifetime users. Transition rates were highest among those who started using cannabis before the age of 15 years and continued to use frequently. Corcoran et al. (2008) observed that individuals who met

for prodromal psychosis with a history of cannabis use were older than those who did not use, but did not differ in clinical measures. During times of increased cannabis use, these individuals experienced more perceptual disturbances and worse functioning and this relationship was controlled for the use of other drugs or medications. Similarly, another study observed that cannabis-using CHR individuals experienced more basic psychotic symptoms, such as thought interference and thought blockages, compared to non-cannabis users (Korver et al., 2010). In addition, frequency of cannabis use was correlated with severity of symptoms.

In a longitudinal study, Buchy et al. (2015) studied 735 CHR participants and 278 control participants at 6- and 12- month follow-ups. CHR individuals endorsed significantly higher overall cannabis use patterns, and greater lifetime prevalence and frequency of cannabis use compared to controls. CHR participants were significantly younger upon first use, but baseline substance use did not differ between CHR participants who later transitioned to psychosis and those who did not transition. CHR participants who had a psychotic clinical outcome after two years had significantly greater baseline cannabis than controls, when adjusting for overall cannabis use.

While it has been observed that lifetime cannabis use was not significantly associated with transition to psychosis, it was observed that at-risk individuals who met criteria for a cannabis abuse/dependence disorder had a greater chance (Odds Ratio: 1.75) of converting to a psychotic disorder (Kraan et al., 2015; Kristensen & Cadenhead, 2007) suggesting a dose-response relationship between cannabis use and transition to psychosis. Nicotine use was also associated with later conversion (Kristensen & Cadenhead, 2007). Interestingly, one study (McHugh et al., 2017) observed that those who experienced a history of cannabis-induced APSS were 4.90 times more likely to transition to a psychotic disorder.

To summarize, there seems to be some link between cannabis use and transition to psychosis among the CHR population. While some factors may confound this relationship, we can say with cautious confidence that this relationship exists on a dose-dependent continuum, such that earlier age of first use, the presence of cannabis abuse/dependence disorder, and increased use contribute to the exacerbation of symptoms as well as increased risk of conversion.

1.5.8. Cannabis and the Brain

In the brain, cannabinoids bind to receptors, and exist alongside endogenous ligands and enzymes that synthesize and degrade endocannabinoids. This is known as the endocannabinoid system, which was discovered when the first endogenous cannabinoids (2-Arachidonoylglycerol [2-AG] and anandamide [AEA]) were identified (Mechoulam & Parker, 2013). This system is involved in various behavioral and physiological pathways, such as pain, appetite, mood, emotion, energy metabolism, and memory (Fakhoury, 2017, for review).

Cannabinoids, including Δ9-THC but excluding cannabidiol, act as partial agonists of endogenous G-protein coupled cannabinoid receptors (CB1 and CB2). There is a high density of CB1 receptors located throughout the central nervous, namely in the prefrontal cortex, cerebellum, basal ganglia, substantia nigra, globus pallidus and hippocampus (Mechoulam & Parker, 2013; Stella, 2010), which are brain regions involved in executive functioning, motor control, learning, and short-term and long-term memory. The CB1 receptor is also located in peripheral organs such as the heart, lungs, liver and kidneys but at much lower concentrations (Fakhoury, 2017; Mechoulam & Parker, 2013). The CB2 receptor is found primarily on peripheral tissues including the spleen, tonsils and thymus, as well as in immune cells throughout the central nervous system (Mechoulam & Parker, 2013; Stella, 2010).

Δ9-THC acts as a partial agonist on both these receptors with differential outcomes, such that the physiological and behavioral effects experienced during cannabis use are attributable to binding at CB1 and anti-inflammatory effects of cannabinoids are due to binding at CB2 (Mechoulam & Parker, 2013). CB1 receptors are located on pre-synaptic GABAergic interneurons and glutamatergic principal neurons, and modulate neurotransmission by suppressing neurotransmitter release at the synaptic terminal when activated (Mechoulam & Parker, 2013; Stella, 2010).

To better understand the relationship between cannabis and psychosis, research has suggested that the answer lies within the function of the CB1 receptor and the interference of GABA neurotransmission. Δ9-THC reduces GABA release by binding to CB1 receptors located on GABAergic interneurons, which in turn, reduces the inhibition of these neurons (Cohen, Weizman, & Weinstein, 2019; D'Souza, 2007; Eggan & Lewis, 2007). Attenuation of this inhibitory signaling therefore causes reduced synchronous firing of cortical pyramidal neurons (Fortin & Levine, 2006; Hajós, Hoffmann, & Kocsis, 2008; Hájos et al., 2000), which leads to interference in various cognitive functions which depend on this synchrony. This asynchrony has been postulated as the basis for psychotic symptoms and cognitive deficits in schizophrenia (Benes & Berretta, 2001; Ford, Krystal, & Mathalon, 2007; Sherif, Cortes-Briones, Ranganathan, & Skosnik, 2018; Uhlhaas & Singer, 2010). Additionally, healthy cannabis users also display such deficits in neural synchrony, suggesting that again, symptoms displayed by regular cannabis users mirror those displayed by schizophrenia patients (Skosnik, Krishnan, Aydt, Kuhlenshmidt, & O'Donnell, 2006).

1.6. Event-Related Brain Potentials

One way we can better understand the neurophysiological underpinnings of dysfunction at the CHR state is through the technique of event-related brain potential (ERP) recordings. These recordings are measured via electroencephalography (EEG), with electrodes placed on the scalp, and reflect voltage changes over time (Luck, 2005). ERPs are believe to record the summed electrical activity of populations of neurons at the cortex known as pyramidal cells.

This electrical activity takes the form of a current that can be positive or negative depending on various factors including permeability of the cell membrane and excitatory or inhibitory inputs from other neurons (Beres, 2017; Luck, 2005). The two main types of neuronal activity are 1) action potentials, which occur when there is a rapid depolarization of a neuron from its resting state, mediated by changes in the concentration of sodium and potassium ions and 2) postsynaptic potentials, which are a result of neurotransmitter activity and synaptic activation (Luck, 2005). Compared to action potentials, which occur at a very rapid rate of about 1ms from the cell body down to the axon, postsynaptic potentials cause slower changes in membrane potentials. As such, EEGs can only record postsynaptic potentials as the change in voltage can be detected for up to 200ms, compared to the extreme speed and brevity of action potentials. This electrical activity is measured by electrodes placed on the scalp, and can be positive or negative depending on the polarity of the pyramidal cell.

Cortical pyramidal cells are oriented perpendicular to the surface of the cortex with the apical dendrite of the cell facing the outer surface, and the cell body with basal dendrites located closer to the inner white matter (Beres, 2017; Luck, 2005). If an excitatory neurotransmitter, such as dopamine, is released at the apical dendrite, changes in electrical current will yield a net negativity outside of the cell in this area. Current will also flow out of the soma and basal

dendrites, resulting in a net positivity. This results in a dipole of positive and negative electrical charges. In contrast, if the postsynaptic potential is inhibitory, this will change the polarity of the signal recorded on the scalp. Dipoles from thousands or millions neurons summed together allow for the detection of electrical activity of similarly oriented neurons. This is more likely to occur in cortical pyramidal cells, thus ERPs arise mostly from these cells.

ERPs reflect specific neural activity in response to cognitive events including stimuli (such as pictures, words, sounds) and responses, and thus help us better understand cognitive processes (Beres, 2017) such as language comprehension, attention and memory. ERPs are obtained by averaging EEG segments or epochs time-locked to the event of interest. By averaging out spontaneous brain activity unrelated to the event, we are left with the ERP that only reflects event-related activity (Figure 2). ERPs allow researchers to compare brain activity elicited by different types of events with millisecond-level temporal accuracy (Beres, 2017).

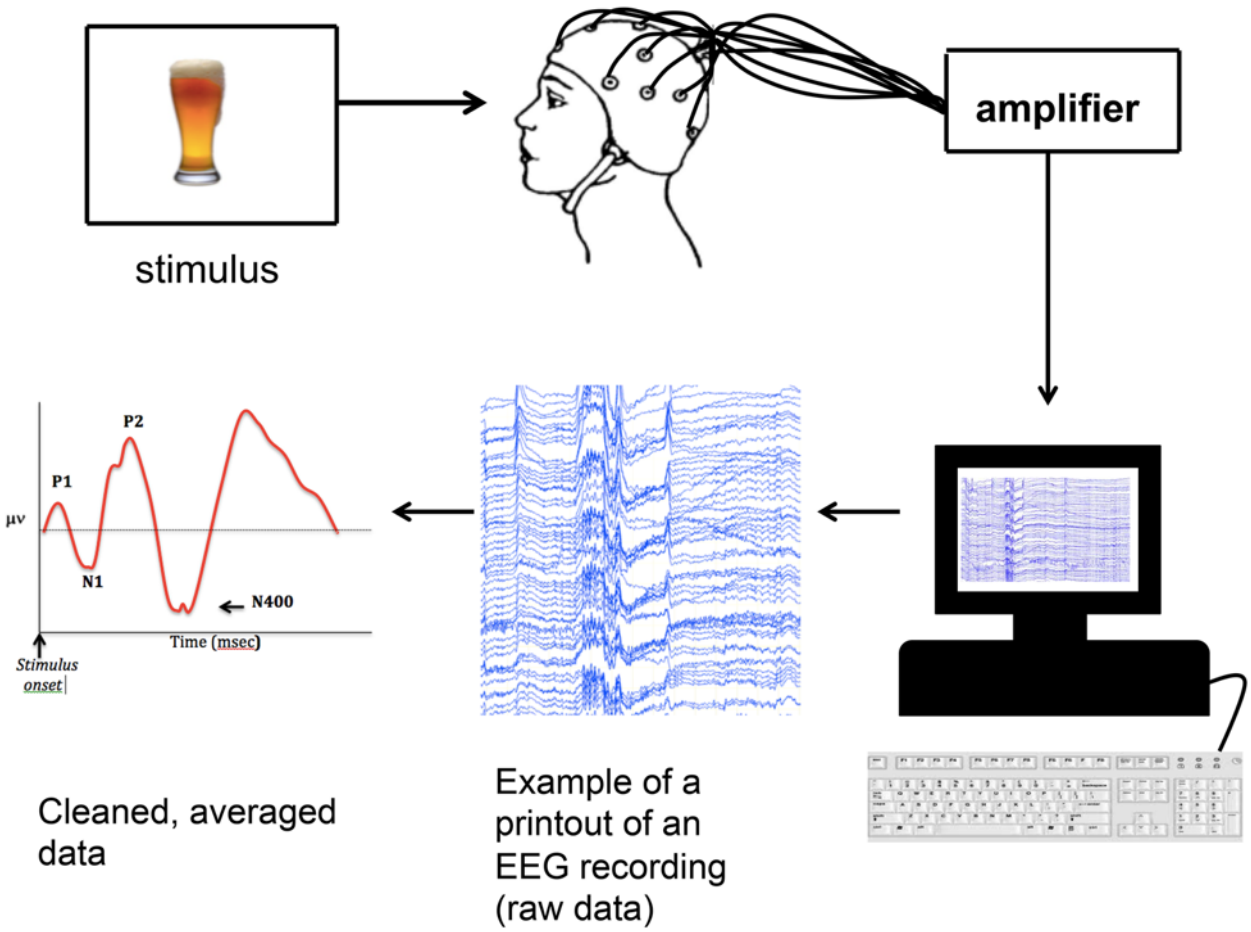

Figure 2. A typical experimental set-up to measure and record event-related brain potentials. The participant views a stimulus (in this case, a picture), their brain activity is transmitted through an amplifier and the raw EEG data is recorded. ERP data is then cleaned and averaged (Beres, 2017).

1.7. The N400 Index of Semantic Priming

One ERP waveform that has been shown to have reliable deficits in schizophrenia patients is the N400, which reflects the degree to which we can use meaningful information in our environment to predict upcoming stimuli. A significant part of what makes us human is our innate ability to continuously process immense amounts of information about ourselves, the people in our lives and stimuli in our environment (Federmeier & Kutas, 2000). We have learned from various behavioral studies that humans tend to categorize this kind of knowledge by grouping together items that are related to one another, such that the occurrence of one item brings another one to mind (Federmeier & Kutas, 2000). Our brain uses these kinds of relationships and similarities in the environment to process information more efficiently, and this is known as semantic priming. In behavioral experiments of semantic priming, it has generally been observed that participants respond quicker to target words (e.g. MOUSE) that are conceptually related to the preceding prime word (i.e. CAT) compared to unrelated target words (e.g. ARROW) (Neely, 1976). Behavioral theories posit that concepts can be represented as connected nodes in a neural network. When one encounters a meaningful stimulus such as a word, activation spreads to adjacent, semantically related nodes but not to remote, semantically unrelated nodes. This leads to facilitated semantic processing of related stimuli. One way to quantitatively measure this process is to use a neurophysiological index of semantic priming, known as the N400.

1.7.1. Characterization

The N400 is a negativity peaking around 400ms after the onset of any meaningful stimulus. However, it does not need to be absolutely negative in response to an unexpected item. Instead, it is typically observed by calculating the difference in ERP response between a context-

congruent term from an incongruent one (Kutas & Federmeier, 2011). For example, when a sentence ends in a semantically anomalous ending such as *"I take my coffee with cream and dog",* this yields a large negativity as compared to a semantically expected ending such as *"I take my coffee with cream and sugar"* (Kutas & Hillyard, 1980b). This difference is known as the N400 semantic priming effect (Kutas & Hillyard, 1980b; Figure 3). Generally speaking, the N400 is thought to represent the processing of a specific stimulus in relation to the semantic framework of the preceding context (Hagoort, Baggio, & Wlllems, 2009).

Many experiments have aimed to delineate the kinds of unexpected stimuli that elicit an N400. Indeed, such stimuli are not all equal in their responses (Hillyard & Kutas, 1983; Kutas, Van Petten, & Besson, 1988). For example, there was no N400 response observed to physically unexpected but semantically congruent sentence ending (*"I shaved off my mustache and BEARD"*) when compared to the physically expected ending (*"beard"*) (Kutas & Hillyard, 1980a).

Furthermore, N400 amplitude is highly correlated with cloze probability – that is, the degree to which individuals would choose to continue a sentence fragment with a specific word, given the preceding context (Federmeier & Kutas, 2000; Taylor, 1953). The N400 amplitude is inversely related to a word's cloze probability, where N400s were smaller to those sentence phrases with high cloze probability endings (*"The bill was due at the end of the month"*) (Kutas & Hillyard, 1984). As the "semantic fit" of a phrase increases, the overall N400 amplitude decreases (Hagoort, 2008).

Initially, the N400 was thought of as a simple tool to measure and understand language processing. However, we now understand this waveform to generally reflect the processing of meaningful relationships (Kutas & Federmeier, 2011).

N400 amplitude reductions in response to greater congruity with context is observed in sentence fragments, and also in pairs of prime-target words (Kutas & Hillyard, 1989), pictures (Holcomb & McPherson, 1994), spoken words and environmental sounds (Van Petten & Rheinfelder, 1995) and faces (Olivares, Iglesias, & Antonieta Bobes, 1999). Thus, the N400 index of semantic priming is not just a linguistic measure, but rather a tool that we can use to understand a variety of conceptual relationships

CAT (prime stimulus)…

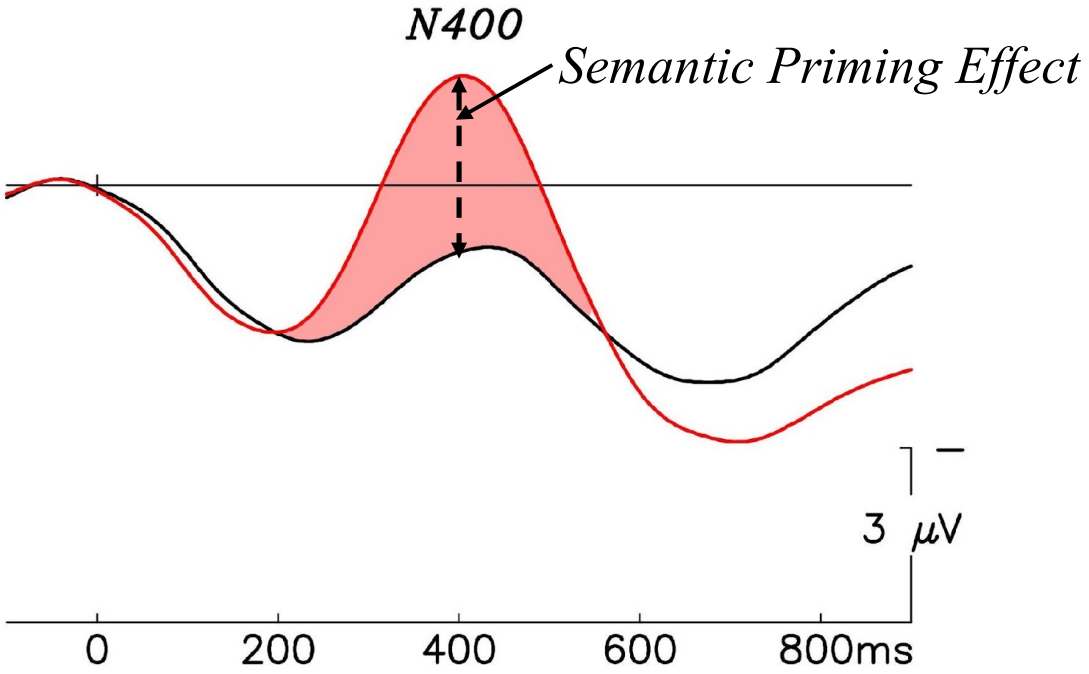

Figure 3. The N400 semantic priming effect, characterized by a difference in amplitude response to words related versus unrelated to the prime.

_____ MOUSE *(related target stimulus)*

_____ ARROW *(unrelated target stimulus)*

1.7.2. Stimulus Onset Asynchrony

There are two types of semantic priming, automatic and strategic, that co-exist on a continuum. Among other factors, they depend on the time interval between the occurrence of sequential stimuli, such as a prime word and a target word (Lau, Phillips, & Poeppel, 2008). At the occurrence of a prime stimulus, automatic priming is triggered when activation is spread automatically throughout one's network of semantic representations. This occurs at a shorter time interval between prime and target stimuli, approximately 400ms or less (Mohammad & De Lisi, 2013; Neely, 1977; Neely, Keefe, & Ross, 1989).

Strategic priming, on the other hand, reflects more conscious processes of semantic network activation. The longer time interval, usually greater than 600ms, between the prime and the target stimulus allows the subject to generate predictions of likely words that may occur and semantically match these predictions against the actual target (Becker, 1980). There does not seem to be a significant difference in N400 effect sizes between the short and long SOAs (Anderson & Holcomb, 1995; Hill, Strube, Roesch-Ely, & Weisbrod, 2002; Rossell, Price, & Nobre, 2003).

1.7.3. Functional Theories of Semantic Processing

There are various theories about the functionality of the N400, mainly based on the understanding that comprehension consists of feedforward processing, where words are first analyzed as perceptual objects, then as linguistic items during lexical processing, which then concludes in a consensus between phonological input and word recognition (Kutas & Federmeier, 2011). Upon recognition, semantic information becomes available and is then integrated with the mental representation of the sentence or discourse at hand. As such, the N400

is thought to be based in one or more of these steps within the processing cascade. There are two main theories about which process the N400 mainly reflects.

1.7.3.1. Integration View of the N400 Effect

The first theory posits that the N400 presents itself relatively late in the processing cascade, after the item is recognized**,** reflecting process of semantic integration of the present word with the working context (Brown & Hagoort, 1993; Hagoort et al., 2009; Kutas & Hillyard, 1980b). The N400 is thereby associated with processes integrating semantic information from the current item with meaningful information from multiple words that are held in one's working memory.

Specifically, Hagoort (2008) places the N400 within the so-called semantic unification process, which is one of three functional components that are part of language processing: one is *memory*, referring to the different kinds of language information stored in one's long term memory or mental lexicon, and how this information is retrieved; *unification* refers to "the integration of lexically retrieved information into a representation of multiword utterances, as well as the integration of meaning extracted from nonlinguistic modalities; this component is at the heart of the combinatorial nature of language" (p.4) ; and the *control* component converts language to action, and is carried out when a choice is to be made when faced with a language decision, either in choosing the correct language in cases of bilingualism or turn-taking during a conversation. That is, "a semantic representation is constructed that is not already available in memory" (Hagoort et al., 2009, p.20).

This solely integrative explanation for the N400 priming effect suggests that context does not play a role in how easy it is to access meaning of the stimulus in the first place. According to this theory, N400 amplitude is greater in semantically unexpected sentences because integration

is more simple and straightforward in congruent endings, whereas energy is required to process implausible endings in a way to fit discourse context or world knowledge (Lau et al., 2008). Additionally, this theory explains why less expected, but non-anomalous endings produce larger N400 responses than more expected endings but smaller responses than wholly unexpected endings, because integration is suggested to be more difficult when expectations are not met. It also explains why semantic priming results in the N400 effect, as the prime word is seen as the "context" into which the target needs to be integrated (Lau et al., 2008). This theory deserves merit in that the N400 effect reflects post-access mechanisms because it can be argued that the N400 response occurs too late to reflect lexical access (Hauk, Davis, Ford, & Pulvermu, 2006; Hauk & Pulvermu, 2004; Sereno, Rayner, & Posner, 1998).

However, contrasting views suggest that positioning the N400 late within the processing cascade does not explain the presence of N400 response to pseudowords, which are not represented in one's mental lexicon (Kutas & Federmeier, 2011).

1.7.3.2. Prediction View of the N400 Effect

Therefore, others argue that the N400 reflects processes that occur prior to word recognition and semantic access. It has been suggested that the N400 effect in fact reflects the activation of features in long-term memory that is associated with a specific lexical item (Federmeier, 2007; Federmeier & Kutas, 2000). In other words, our brains may use contextual clues to predict upcoming stimuli that are most likely, based on world knowledge and past experience. As such, the difference in N400 response to anomalous versus prediction endings does not then arise due to the anomaly itself but because predictable words that are semantically related to prime words are easier to retrieve from one's long term semantic memory (Lau et al., 2008). Contextual cues allow for the pre-activation of relevant lexical or semantic features,

making it easier to access one's lexical memory (Kutas & Federmeier, 2011). The key difference between the prediction view and the integrative view is that the prediction view does not posit any relationship between combinatorial processing and the N400, even though discourse or sentence context may provide semantic composition and in turn lead to prediction (Lau et al., 2008).

Various studies support the predictive theory of N400 semantic priming. For example, DeLong, Urbach, & Kutas (2005) created a sentence paradigm where strings ended with either "an" or "a", with target nouns ranging from highly probable to unlikely, based on cloze probability norming. They observed that strings with indefinite articles that mismatched the expected subsequent word *("The day was breezy, so the boy went outside to fly an…")* elicited larger N400s than strings with definite articles that matched the expectancy *("The day was breezy, so the boy went outside to fly a…")*. In this case, the expected word to end the sentence, based on contextual cues and world knowledge, would be *kite* to match with the article "a", however, the word "airplane" to match with the article "an" would also be plausible, albeit less likely than the previous ending. Given the fact that there is no difference in inherent meaning between the articles "a" and "an" and both should be integrated into the surrounding context to the same degree, the observed difference in N400 leads to the understanding that there is some level of prediction happening, where participants had expected the word *kite* to occur next, along with its matching article *a* based on semantic memory and world knowledge.

This also applies when unexpected sentence endings elicit smaller N400s at times when they share semantic features with the expected ending (Kutas & Federmeier, 1999). For example, after reading the phrase *"They wanted to make the hotel look more like a tropical resort. So, along the driveway they planted rows of...",* participants exhibited smaller N400 amplitudes to

pines compared to *roses*, even though both are improbable in this case, when compared to *palms.* The reason for this is that *palms* and *pines* are more semantically related to one another (both are types of trees), as compared to *palms* and *roses*. Thus, the pre-activation of the concept *palms* in predicting the ending of that sentence led to semantic network activation that made it easier for participants to process *pines* over *roses.*

Other examples involve listening to mini-stories in the Dutch language (Van Berkum, Brown, Zwisterlood, Koojiman, & Hagoort, 2005), which were truncated after the article "a", and was followed by a semantically coherent adjective whose gender suffix did or did not agree with the expected noun. In response to coherent but prediction-inconsistent adjectives, a larger N400 amplitude was observed compared to a neutral condition.

To summarize the prediction theory, we can say that the language comprehension system makes use of all information as early as it can to restrict the search in semantic memory and facilitate processing of items most likely to appear (Kutas & Federmeier, 2011). This is a predictive strategy that allows for more efficient processing when the expectation is upheld and accounts for the beneficial effects of congruent context such as faster processing, better memory and greater perceptual accuracy (Federmeier & Kutas, 2000). When the expectation is not upheld, the result is a contextual integration issue which requires more processing resources and energy. Prediction seems to be an effective comprehension strategy except when it is not as clear-cut, for example, in the case of within-category violations. In this case, the integrative strategy would be more useful to conserve resources and produce a graded response in N400 amplitude reduction.

Thus, the most recent view among the literature is that the language comprehension system employs both predictive and integrative techniques (Kutas & Federmeier, 2011). On a

neurophysiological basis, this is represented across both hemispheres, with the left hemisphere biased towards efficiency and prediction and the right hemisphere biased towards information maintenance and integration with working memory (Kutas & Federmeier, 1999).

1.7.4. Neural Basis and Localization of the N400 Semantic Priming Effect

In terms of the neural basis of the N400 semantic priming effect, amplitude reductions may be reflected in smaller post-synaptic potentials in the same neuron, activations of fewer neurons within a population, or less temporal synchrony among the eliciting neurons (Kutas & Federmeier, 2011).

Intracranial recording techniques in individuals with epilepsy may give us insight into the variety of brain regions that are co-active during the scalp-recorded N400 (reviewed in Kutas & Federmeier, 2011). These areas include the anterior medial temporal lobe (which is involved in manipulations of semantic priming, semantic congruity, repetition and recognition/verbal memory), middle, superior and inferior temporal regions, and the prefrontal region. These effects are present in both hemispheres but might be stronger in the left hemisphere. Magnetoencephalogram (MEG) studies have implicated the superior/middle temporal gyrus, temporal-parietal junction, medial temporal lobe, and with less consistency, the dorsolateral frontal cortex. As we now know, these areas are related to semantic memory storage and processes.

The N400 effect has been observed to be distributed in a centroparietal manner across the scalp, with a slight bias to the right hemisphere when visual inputs are presented (Kutas et al., 1988). As reviewed by Lau et al. (2008), a variety of studies have used functional magnetic resonance imaging (fMRI) to better understand the localization of the N400 effect. The various studies reviewed used the semantic priming paradigm (varying word pairs of semantically

unrelated and related words), mostly within the context of a lexical decision task, but also naming target and relatedness tasks. Combining the temporal sensitivity of EEG data with the spatial sensitivity of fMRI data, we can learn a great deal about localizing the N400 semantic priming effect.

There are two patterns that are revealed through fMRI studies of semantic priming. To begin, left inferior frontal effects are dependent on the SOA, such that only priming at long SOAs (>600ms) affect both anterior and posterior left ventral inferior frontal gyrus (IFG) in some studies, and in others, only part of the left IFG. The posterior left IFG is shown to be affected by reduction in activity in the semantically related condition, whereas the anterior left IFG effect was due to an increase in activity in the semantically unrelated condition.

The second pattern that is revealed is that the only area of activity that mirrors the N400 responses and shows effects of priming across both short and long SOAs and modalities is in the left mid-posterior middle temporal gyrus (MTG; Figure 4). Activation of the correct lexical item is made easier by semantic predictions in the case of long SOAs and automatic spread within a semantic network in short SOAs. Both effects which are shown within the MTG (Lau et al., 2008). Therefore, the dual activation in this area at both long and short SOAs provides us with convincing evidence that this area is robustly involved in generating the N400 effect and that the N400 priming effect involves both lexical access/integration and prediction.

To summarize, it seems that there are a variety of brain regions that are simultaneously and consecutively active during the N400 semantic priming effect, including the inferior frontal gyrus, and anterior and posterior temporal cortex. Specifically, various areas within the temporal lobe, including the middle temporal area, seem to be robustly active during both short and long interval semantic priming tasks. This suggests that this area should be of focus for future studies

of localization of the N400 semantic priming effect, to better understand neuronal architecture as well as role in cognitive function.

To conclude, the N400 index of semantic priming allows us to gain insight into the process of meaning-making at various levels, in a multimodal, context-sensitive, constructive and spatially-expanded cascade. Semantic information restricts and can also pre-activate perceptual and semantic features of oncoming stimuli in order to facilitate the processing of context-congruent information or predictions that have been made, in order to ease assimilation. This represents itself as a reduction in N400 amplitude. While no single brain region is solely responsible for this process, the N400 can still be seen as a sensitive measure of semantic processes at a psychological level.

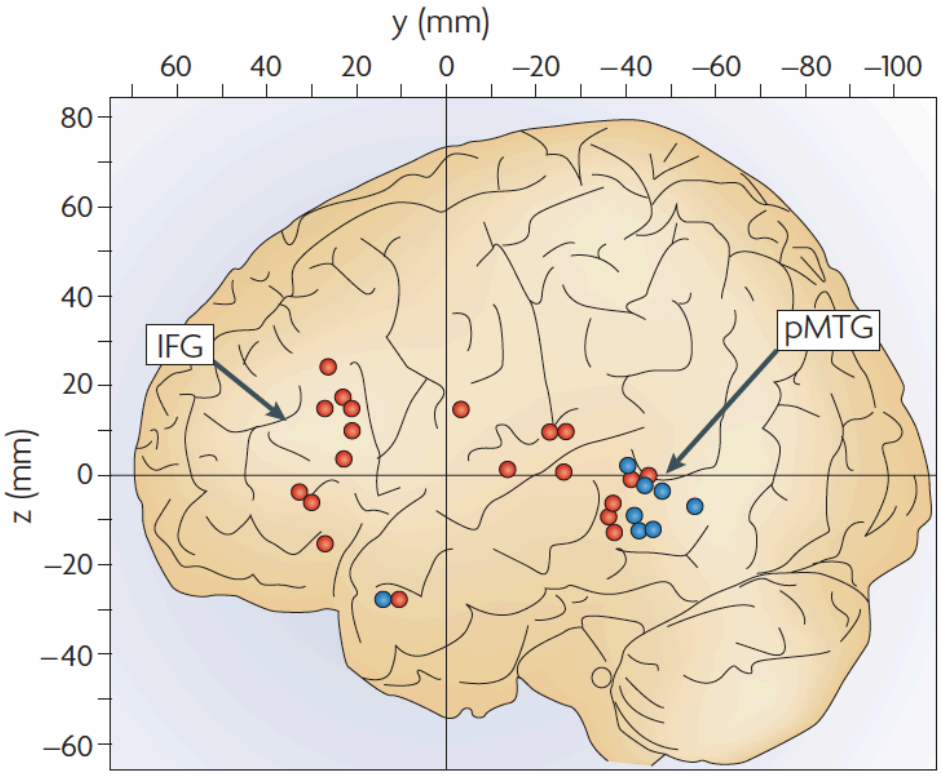

Figure 4. Visual summary of brain regions involved in the N400 semantic priming effect based on fMRI studies, including the left mid-posterior middle temporal gyrus (MTG) (Lau et al., 2008).

1.7.5. N400 Deficits in Schizophrenia

In 1911, Eugen Bleuler was the first researcher to emphasize the importance of language and communication deficits in schizophrenia (Bleuler, 1911 as cited in Besche-Richard, Iakimova, Hardy-Baylé, & Passerieux, 2014). Since then, issues in language and communication have been found in schizophrenia patients, including abnormalities in speech production, reduced sentence complexity, and poverty of speech content (Moskowitz & Heim, 2011). These problems, alongside various other symptoms such as paranoid delusions and ideas of reference, have been proposed to be caused by deficits in semantic priming. It has been suggested that issues with prediction making, a core feature of semantic processing, underlies certain symptoms of schizophrenia, including delusions, disorganized speech and behavior (Fletcher & Frith, 2009; Ford & Mathalon, 2012).

Below, we have discussed general findings of word priming paradigms, divided into the shorter and longer time intervals between stimuli. We also review studies in relatives of schizophrenia patients to consolidate the role of the N400 as a biomarker for this disorder. Select studies have been discussed in more detail.

1.7.5.1. Semantic Priming at Short SOA

Shorter SOAs are used in priming paradigms where it is necessary to study the automatic spread of activation within semantic networks (Mohammad & De Lisi, 2013). These SOAs exist at a time interval that is less than 400ms between the prime stimulus and the target stimulus. Hyperpriming refers to when the N400 signal of the target is less negative, reflecting a greater spread of automatic activation within semantic networks. Various studies have observed such an increase in semantic priming to different stimuli. Mathalon, Faustman, & Ford (2002) found that schizophrenia patients did not differ from controls in N400 amplitudes to related, primed words,

but observed hyperpriming for unrelated, non-primed words, suggesting an overly broad semantic network activation. Similarly, Mathalon, Roach, & Ford (2010) employed a task using pictures that were followed by matching or nonmatching words, and found that patients exhibited hyperpriming for non-matched, unprimed words, and hypopriming (less activation, smaller N400 amplitudes) for matched, primed words. This further suggests a deficient use of semantic context.

Additionally, schizophrenia patients have been observed to elicit smaller N400 amplitudes to incongruent endings compared to patients with bipolar disorder mania and healthy controls, reflecting an abnormal spread of automatic semantic network activation (Ryu et al., 2012).

Kreher, Goff, & Kuperberg (2009) used directly and indirectly related word pairs in explicit (make a relatedness judgement) vs. implicit (monitor filler items falling into a given category, while prime and target unconsciously passed on screen) task conditions. In the explicit task condition, schizophrenia patients had a reduced priming effect to both directly and indirectly related items, but did not display these deficits in the implicit task condition. This implies that patients are perhaps impaired on conscious tasks where they are required to make decisions about semantic relatedness, but these processes are intact when employed implicitly.

Other studies have proposed that schizophrenia patients exhibit lack of priming at the short SOA due to a minimal difference between N400 amplitudes in related versus unrelated words. For example, in medicated schizophrenia patients, no priming effect was observed due to a less negative N400 response to unrelated words, which suggests that this group displayed language abnormalities related to a lack of inhibitory processes (Niznikiewicz et al., 2010). Additionally, Kostova, Passerieux, Laurent, & Hardy-Baylé (2003) found reduction in N400

amplitudes in patients with schizophrenia with formal thought disorder in tasks with both low and high probable meaning, compared to control individuals, suggesting that these individuals are unable to benefit from contextual cues to facilitate semantic processing. In contrast, although Kostova, Passerieux, & Laurent (2005) found that schizophrenia patients also show a reduction in N400 priming effect compared to controls, this was due to negative, or greater, N400 amplitude to related words, suggesting that patients in this study were processing related words similar to the way they processed unrelated words, being unable to use meaningful cues to facilitate processing of these primed words.

Medicated patients have also been observed to have lack of priming at short SOAs, when completing priming tasks with related, non-word, and unrelated neutral targets (Laurent, Kostova, & Passerieux, 2010). Condray, Siegle, Cohen, Kammen, & Steinhauer (2003) found the priming effect to be significantly reduced for haloperidol-treated and haloperidol-free schizophrenia patients when compared with controls at short SOA. However, they observed significant priming in the haloperidol-treated group compared to the drug-free group, suggesting that medication may improve automatic activation of semantic network activation in patients. The discrepancy in these results may be due to the fact that Laurent et al.'s (2010) study consisted of patients with formal thought disorder, who may display more severe semantic priming deficits than patients without these symptoms.

A study by Besche-Richard et al. (2014) aimed to observe whether semantic priming deficits in schizophrenia were a stable cognitive feature of the disorder's psychopathology or whether these impairments were specifically related to individuals' differences in symptom severity. Administering the semantic priming task at baseline and one-year retest, they observed that schizophrenia patients were impaired behaviorally and in the N400 task compared to

controls. However, at one-year retest, behavioral semantic priming effects were still impaired in this group but N400 effects were significantly improved. This suggests N400 deficits that may not be a stable cognitive marker of schizophrenia but can be improved with treatment (in this study, antipsychotic medication) that also reduced symptoms' severity over the clinical course of the disorder.

Kiang, Christensen, Kutas, & Zipursky (2012) compared patients with schizophrenia or schizoaffective disorder and controls at both the long and short SOA. Participants were showed related, unrelated, non-words, and repeated word pairs, in a lexical decision task. They observed a graded response, as priming was observed in both groups at both SOAs, where it was greatest for repeated word pairs, then related pairs, followed by unrelated and finally non-word pairs. While there no were deficits observed at the long SOA, at the short SOA, the relatedness priming effect (difference between related response versus unrelated response) was smaller for patients than controls. This suggests that activation failed to extend normally to related concepts within semantic memory perhaps due to slower activation of related concepts or lack of inhibition to unrelated terms.

To better understand whether these N400 deficits are due to psychopathological processes in schizophrenia or was due to genetic liability, Sharma et al. (2017) used a monozygotic twin study design by comparing pairs concordant for schizophrenia/schizoaffective disorder, discordant pairs (only one twin affect by schizophrenia/schizoaffective disorder), and healthy control pairs in a lexical decision task. They observed that affected concordant twins had significantly reduced N400 direct priming compared to controls, and discordant affected twins displayed a trend for reduced direct N400 effect compared to controls. However, unaffected

twins did not differ significantly from controls, suggesting that reduced N400 effects reflect disease-specific processes and not trait liability.

1.7.5.2. Semantic Priming at Long SOA

Various studies have found that schizophrenia patients have semantic deficits at the long SOA suggesting a lack of ability to properly use context to facilitate processing (Condray et al., 2003; Hokama, Hiramatsu, Wang, Donnell, & Ogura, 2003; Matsumoto et al., 2001; Matsuoka et al., 1999).

As mentioned previously, Kiang et al. (2012) compared patients with schizophrenia or schizoaffective disorder and controls at both the long and short SOA, and observed no semantic priming deficits at the long SOA. The authors explained this discrepancy in lack of deficits at the long SOA due to the inclusion of repeated word pairs, which other studies have shown to elicit smaller than normal priming effects. This may be due to the fact that diverting individuals' attention towards recognition of word repetitions away from detecting relationships between pairs of words diminishes resources available for processing (Rugg, 1985).

Kiang, Kutas, Light, & Braff (2007) compared patients and controls, using a task with non-exemplars, low-typicality exemplars, and high-typicality exemplars as stimuli and also did not observe significant differences in amplitude responses between groups. Within patients, however, reduced N400 amplitude difference between high- and low-typicality exemplars was correlated with psychotic symptoms. This suggests that psychosis in schizophrenia may be associated with deficits in differential responses to strongly versus weakly related concepts. This finding may reflect an association of symptoms with either deficits in use of contextual cues or an overall broader spread of activation, if patients are unable to differentiate their responses to high- versus low-typicality exemplars. This correlation between priming deficits and psychotic

symptoms has also been observed in other studies (Jackson et al., 2014; Kiang, Kutas, Light, & Braff, 2008), including Debruille (2007) who observed a correlation between increased delusional symptoms and smaller N400 priming effects in less delusional versus more delusional patients. Taken together, these findings suggest that deficits in semantic priming are perhaps based in and related to the general symptoms observed within schizophrenia patients.

Using stimuli that were either directly/strongly related and indirect/weakly related, Kiang et al. (2008) studied patients at both short and long SOAs. There was no difference between SOAs but a group by target interaction was observed, such that in schizophrenia patients there was no difference in responses between unrelated, indirectly related and related stimuli. This further suggests semantic network hypoactivation in patients and an inability to use context, as responses were abnormally large to directly and indirectly related stimuli.

Kiang, Christensen, & Zipursky (2011) also looked at the role of context on the N400 priming effect, by asking participants to comment on the degree of relatedness between primes and targets in a semantic task, and then in an orthographic task, decide whether a given letter occurred in the target word. Both controls and patients had significant priming effects in both tasks, but patients had smaller N400 semantic priming effects than controls. Increased priming effects when moving from the orthographic to semantic task was present in both groups, suggesting when given a meaningful stimulus along explicit semantic processing cues, patients can use these relationships to activate related concepts even if their ability generally is somewhat diminished.

In terms of longitudinal data to test the trajectory of N400 deficits in schizophrenia, Jackson et al. (2014) compared individuals with first admission psychosis and healthy individuals. Over ten years, they observed that individuals with schizophrenia and other

psychosis had significantly reduced N400 to semantically incongruent stimuli compared to healthy participants. Schizophrenia patients did not differ significantly from patients with other psychoses, suggesting that semantic priming deficits reflect abnormalities across psychotic disorders. N400 abnormalities were not observed in individuals who recovered from psychosis when grouped by recovery status, such that those with blunted N400 semantic priming effects remained ill. This suggests that N400 deficits may reflect functioning in the real-world. However, a disproportionate amount of those who recovered were patients diagnosed with other psychotic disorders (not schizophrenia), therefore further longitudinal research needs to be conducted within individuals diagnosed with schizophrenia.

Boyd, Patriciu, McKinnon, & Kiang (2014) tested the longitudinal reliability of N400 effects, comparing performance on a lexical decision task one week apart between schizophrenia patients and controls. Semantic priming deficits were observed in schizophrenia patients due to no differences between N400 amplitudes for related and unrelated targets at both SOAs. No differences were observed between time-points suggesting that perhaps the N400 amplitude is a stable neurophysiological biomarker of semantic processing abnormalities, at least in the short-term.

1.7.5.3. Relatives of Schizophrenia Patients

Guerra et al. (2009) recruited unaffected first-degree relatives of patients with schizophrenia, patients diagnosed with schizophrenia and healthy control subjects. Significantly reduced N400 amplitude for congruent categories in a semantic matching task was found in medicated patients and relatives compared to controls, suggesting that the N400 may be an endophenotype marker.

In contrast, Kimble et al. (2000), observed that first-degree relatives did not significantly differ in their N400 amplitudes from controls, and only the schizotypy group displayed deficits. Furthermore, Kiang, Christensen, & Zipursky (2014) compared unaffected first-degree relatives, schizophrenia patients and control participants at both SOAs. Schizophrenia patients exhibited larger N400 amplitudes for related targets compared to controls and relatives, and the latter two groups did not significantly differ from one another (Figure 5). In addition, Pfeifer et al. (2012) compared siblings of patients with psychotic disorder, patients with psychotic disorder and control participants and observed no between-group differences at both SOAs. These studies are in contrast to Guerra et al. (2009), which suggests that N400 deficits may only be a biomarker for schizophrenia. This discrepancy may be because Guerra et al. (2009) used picture stimuli, and the deficits may only be shared when elicited by pictorial but not linguistic stimuli, as they may reflect different processing modalities that are indeed impaired in relatives of schizophrenia patients.

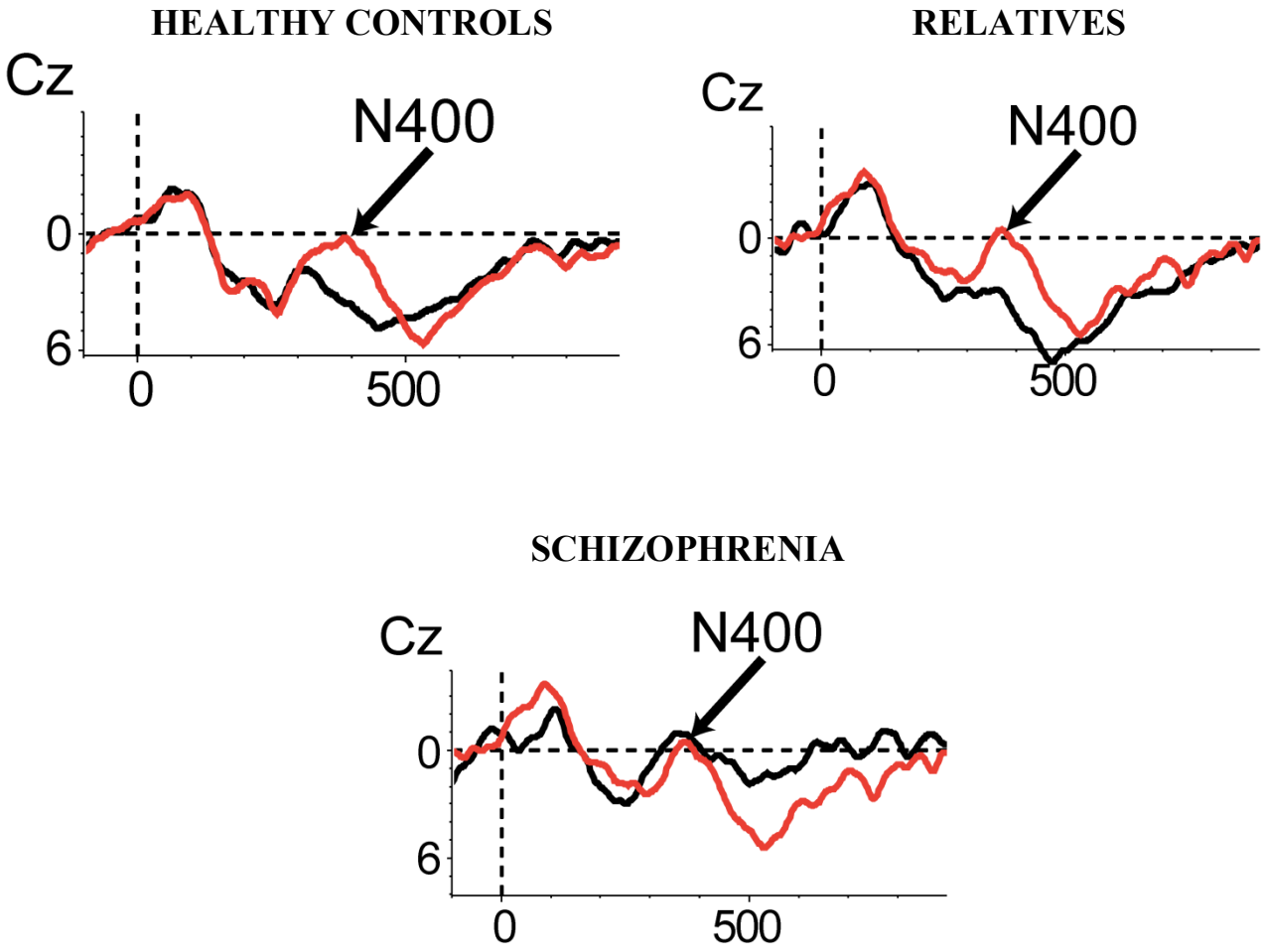

Figure 5. Results from Kiang et al. (2014) demonstrating deficits in semantic priming in schizophrenia patients, compared to healthy controls and non-affected first-degree relatives of individuals with schizophrenia.

1.7.6. N400 Deficits in Clinical High-Risk Individuals

To better understand the development and pathogenesis of these N400 deficits within the schizophrenia population, a recently published paper from our lab examined the N400 in CHR individuals (Lepock et al., 2019). It was hypothesized that CHR individuals would exhibit deficits similar to those of schizophrenia patients, with smaller N400 semantic priming effects compared to healthy controls due to larger than normal N400 amplitudes to related targets.

Twenty CHR individuals and 20 healthy controls completed the N400 task, viewing prime words followed by a target word that was either a related word, unrelated word or a pronounceable non-word in a lexical decision task. Across groups, N400 amplitudes were larger for unrelated than related targets, but there was no overall group effect or a group by target interaction. However, there was a group by target by SOA interaction, revealing that at the long SOA (750ms), CHR individuals had no difference in N400 amplitudes to unrelated vs. related targets, whereas this difference was present in controls, with N400 amplitudes being larger in the unrelated target responses compared to the related targets.

These results were consistent with the hypotheses of the authors, such that the semantic priming effects indexed by the N400 waveform were smaller than normal in CHR individuals at the longer SOA but not at the short SOA. This suggests that when it comes to consciously processing meaningful stimuli by activating one's semantic memory, CHR individuals are impaired when the interval between stimuli is longer, but this ability is retained over shorter intervals, which represent more automatic processes of semantic network activation.

While we did not see any differences in Target responses between groups, perhaps due to small sample size, it would be useful to know at which target (unrelated or related) we see the anomaly in CHR participants. If these results are indeed similar to schizophrenia patients, then

we should see a greater N400 amplitude in response to related stimuli, leading to the deficit in overall semantic priming. This would suggest that like schizophrenia patients, CHR individuals process related stimuli as if they were unrelated, implying that their ability to access their semantic memory and integrate contextual information is compromised.

1.7.7. N400 and Cannabis Use

To date, there has been only one study looking at the effects of cannabis use on the N400. Kiang and colleagues (2013) compared the N400 responses at the long SOA (750ms) between cannabis users (using an average of one joint of cannabis per week) and non-users (not using cannabis within the past year).

Using the self-rated Schizotypal Personality Questionnaire, which measures schizotypal traits corresponding to those in the DSM-IV (including odd behavior, delusional thinking and ideas of reference), they predicted that cannabis users would exhibit greater levels of delusion-like ideation compared to non-users. In addition, they hypothesized that cannabis users would exhibit larger than normal N400 responses to related targets compared to non-users, and therefore, smaller overall N400 semantic priming effects. This would correspond to previous research that has stated that frequent cannabis-using healthy individuals are at risk of developing psychosis-like experiences (Rössler et al., 2007; van Os et al., 2002). By extension, the researchers hypothesized that this is due to an interference in their ability to activate related concepts in their semantic memory following meaningful stimuli.

In line with previous research, cannabis users in this study had higher delusion-like ideation compared to non-users. Contrary to their main hypothesis, however, cannabis users exhibited smaller N400 amplitudes overall to related and unrelated targets. As such, this group's semantic priming effects did not differ significantly from the non-users. Furthermore, smaller

N400 amplitudes to both related and unrelated target stimuli were correlated with higher levels of delusion-like ideation in the cannabis group. This implies that cannabis users are impaired in their semantic processing abilities but in a different way from schizophrenia patients, perhaps reflecting differences in endocannabinoid pathway signalling leading to different effects exerted on cortical pyramidal neurons.

2. Study Rationale

In the present study, we aim to understand how cannabis use affects semantic priming deficits in the CHR state. We aim to compare CHR individuals with healthy controls, and further divide these groups based on cannabis use. This will yield four groups: healthy controls with no history of cannabis use (HC/C-), healthy controls who are regular cannabis users (HC/C+), CHR individuals with no history of cannabis use (CHR/C-) and CHR individuals who are currently or past regular cannabis users (CHR/C+).

Given that cannabis use has been observed to cause psychosis-like symptoms in healthy controls, and has been shown to both exacerbate symptoms in CHR individuals and increase risk of conversion to psychosis, studying the effects of this substance are crucial to further our understanding of the pathophysiology of this disorder. Semantic priming, indexed by the N400 event-related brain potential, has been hypothesized to underlie symptoms of schizophrenia such as disorganized communication and unusual thought content. Semantic priming occurs when an individual is able to activate contextually related items in long-term semantic memory, which facilitates processing of corresponding stimuli. Deficits in semantic priming could lead to individuals processing contextually related concepts as if they were unrelated, or vice versa. This may underlie disorganized speech, where individuals are unable to convey their thoughts in a logical sequence, as well as unusual thought content such as ideas of reference, where patients may perceive an unusual amount of significance in certain environmental stimuli.

Taken together, studying the effects of cannabis use on semantic priming in the CHR state could help us understand how these deficits contribute to conversion risk. If we find evidence that cannabis use impairs semantic priming in CHR participants, this would support future research to examine whether semantic priming is an additional risk marker for conversion

to a psychotic disorder in this population. This could aid in efforts to target treatment efforts to those most at risk in order to prevent a frank psychotic episode.

As described above, there are two contrasting theories about which semantic processing system the N400 reflects: an integrative view and a predictive view. The integrative view posits that we access the meaning of the present stimulus from semantic memory and then integrate it with contextual information held in working memory. The predictive view posits that we use contextual information held in working memory to pre-activate related information semantic memory. Given the importance of working memory and semantic memory access in both integrative and predictive strategies, we aimed to explore whether deficits in these cognitive domains would correlate with reduced N400 semantic priming deficits, consistent with a situation in which the former contributes to the latter. If so, this could provide support for novel treatment options targeting the improvement of these cognitive skills.

We also aim to explore whether severity of attenuated psychotic symptoms, specifically unusual thought content and disorganized communication, correlated with deficits in semantic processing, as observed in schizophrenia patients. As mentioned previously, deficits in these symptoms and in semantic processing may share the same neuropathology. By observing whether they are indeed correlated in CHR individuals, and whether they are both worsened by cannabis use, we can better understand the neurophysiological basis of symptoms at the CHR state.

Altogether, this study aims to test the hypothesis that cannabis contributes to semantic processing deficits at the CHR state, and whether these deficits correlate with symptoms and cognitive deficits that could share underlying pathology. This study may improve our

understanding of the relationships between cannabis use, CHR status, and semantic processing and could eventually inform development of better treatments for CHR individuals.

3. Aims and Hypotheses

3.1. Primary Aims

Our overall aim was to examine the effects of cannabis use on the N400 semantic priming effect in individuals at clinical high-risk for psychosis. We aimed to test for differences between four groups: healthy control individuals, healthy cannabis users, CHR individuals who have never used cannabis, and cannabis-using CHR individuals.

1) We aimed to test for differences in mean N400 amplitudes to related and unrelated word targets following a prime stimulus, at short and long SOAs
2) We aimed to compare N400 semantic priming effects between the above four groups, at short and long SOAs

3.2. Exploratory Aims

1) We aimed to test whether N400 semantic priming effects are correlated, at either SOA, with cognitive measures involved with the general processes of semantic processing: working memory and verbal fluency, for each of the 4 participant groups.
2) We aimed to test whether semantic priming effects at the short and long SOA are correlated with psychotic symptoms: unusual thought content (SIPS P1) and disorganized communication (P5), which are symptoms that have been correlated with semantic priming deficits in previous studies of schizophrenia patients.

3.3. Primary Hypotheses

1) We expect that cannabis-using CHR participants will have the smallest (least negative) N400 amplitudes to related and unrelated targets, given the cumulative deficits of the CHR state (similar to those of schizophrenia patients) and cannabis use, followed by non-cannabis using CHR participants, then cannabis-using controls and finally, healthy controls.
2) We expect that semantic priming effects will be smallest in cannabis-using CHR participants, followed by non-cannabis using CHR participants, then cannabis-using controls and finally, healthy controls, who should display the greatest semantic priming effects

3.4. Exploratory Hypotheses

3) Correlate N400 semantic priming effects and cognitive scores
    a. We expect that the most impaired group, that is, the cannabis-using CHR participants will show the strongest correlations between working memory scores and N400 semantic priming effects, with lower working memory scores correlating with smaller N400 semantic priming effects, because CHR participants' working memory deficits may contribute to semantic priming deficits.
    b. We expect that the most impaired group, that is, the cannabis-using CHR participants, will show the strongest correlations between verbal fluency scores and N400 semantic priming effects, with lower verbal fluency scores correlating with smaller N400 semantic priming effects, because CHR participants' semantic

memory access deficits (as indexed by verbal fluency deficits) may contribute to semantic priming deficits.

4) Correlate N400 semantic priming effects and psychotic symptoms
    a. We expect that both cannabis-using CHR and non-cannabis-using CHR groups will show correlations between P1 scores and N400 semantic priming effects, with the strongest association (higher scores correlate with smallest differences between unrelated and related terms) in the cannabis-using CHR group, reflecting cumulative effects of cannabis on the CHR state.
    b. We expect that both cannabis-using CHR and non-cannabis-using CHR groups should show correlations between P5 scores and N400 semantic priming effects, with the strongest association (higher scores correlate with smallest differences between unrelated and related terms) in the cannabis-using CHR group, reflecting cumulative effects of cannabis on the CHR state.

4. Methods

4.1. Participants

Participants consisted of four groups: healthy participants who never used cannabis (HC/C-), healthy participants who were regular cannabis users (HC/C+), clinical high-risk participants who never used cannabis (CHR/C-) and clinical high-risk participants who were present or former regular cannabis users (CHR/C+). We included past users in the last group as we anticipated that this population would be difficult to recruit in the given timeframe. Potential issues are discussed in the limitations section.

This study was partially retrospective in nature, and data that had been collected for a different study were analyzed for the present study. Thirty-eight participants, including 11 participants in the CHR/C+ group, had completed the other study prior to the start of recruitment for the present thesis. This led to missing data on some assessments that were only included for participants recruited during the timeframe of this thesis.

4.1.1. Clinical High-Risk Participants

Participants aged 16 to 35 were included in this study. CHR participants were help-seeking patients who had been referred to the Focus on Youth Psychosis Prevention (FYPP) Clinic at the Centre for Addiction and Mental Health (CAMH). CHR participants were included if they met criteria of prodromal symptoms (COPS) based on the Structured Interview for Prodromal Symptoms (SIPS; Miller et al., 2003). We rated Positive Symptoms on scales P1-P5 of the Scale of Psychosis-risk Symptoms (SOPS) found within the SIPS.

4.1.2. Healthy Control Participants

Healthy control participants were recruited from the community using advertisements on bulletin boards and websites approved by the CAMH Research Ethics Board (REB). Cannabis-

using participants underwent a preliminary email and phone screen to determine eligibility and cannabis use history.

4.2. Psychological Assessments

All participants were screened for Axis I disorders in the Diagnostic and Statistical Manual (DSM-IV) using the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 2002). Exclusion criteria for all participants were as follows: diagnosis of DSM-IV substance dependence or abuse in the last six months (except for cannabis and nicotine); current or past neurological condition; having learned English after age 5; visual or hearing impairment; and the presence of a reading disability.

Additionally, healthy control participants were excluded if they met for any past or current DSM-IV Axis I diagnosis, had a first-degree relative with a psychotic disorder or if they were currently taking any psychotropic medication. CHR participants were excluded if they received past or current antipsychotic treatment.

4.3. Cognitive Assessments

To estimate verbal IQ, we used the National Adult Reading Test (O'Carroll, Dunan, Murray, Ebmeier, & Goodwin, 1992). Furthermore, we used the MATRICS Consensus Cognitive Battery (MCCB; Kern et al., 2011) to characterize cognitive function across multiple domains, including processing speed, attention/vigilance, verbal and nonverbal working memory, verbal learning, verbal fluency/category fluency, reasoning/problem solving and social cognition.

To estimate parental socioeconomic status, we used the 1981 Canadian index (Blishen, Carroll, & Moore, 1987). To ensure patients' capacity to provide informed consent, we used the

University of California, San Diego Brief Assessment of Capacity to Consent (UBACC; Jeste et al., 2007) as a screening tool for possible impaired decisional capacity.

To assess global functioning across social and role domains, we used the Global Functioning: Role and Global Functioning: Social scales (Cornblatt et al., 2007). These scales have been validated for use in CHR populations and assess the level of social and role functioning of the individual at the lowest level of functioning in the past month (referred to as "current functioning"), and lowest and highest level of functioning over the last year.

The Global Functioning: Role scale assesses an individual's performance in school, work, or as a homemaker, if applicable. Ratings are based on age-appropriateness, as well as demands of the role, level of independence of the individual, degree of support required to function and overall performance in their primary role.

The Global Functioning: Social scale assesses an individual's quantity and quality of relationships, including those with peers and family. It also assesses level of peer conflict, age-appropriate intimate relationships, and relationships with family. Ratings are based on age-appropriate social contacts and degree of interactions outside the family, focusing especially on social withdrawal and isolation.

4.4. Assessing Cannabis and Other Substance Use

All participants were assessed for cannabis use in the past month using the Timeline Followback Method (Sobell, Brown, Leo, & Sobell, 1996). To gain an understanding of participants' cannabis use history, they completed the Substance Dependence and Abuse Module of the SCID-IV and Drug History Questionnaire (Sobell, Kwan, & Sobell, 1995). For our HC/C+ and CHR/C+ groups, we included participants who had been using at least 3 grams of cannabis per week and/or met for a cannabis dependence disorder on the DSM-IV within the past 12

months. In the CHR/C+ group, those who met for a past cannabis dependence disorder were also included. Additionally, cannabis-using participants completed a rapid qualitative urine toxicology screen for amphetamine, barbiturates, benzodiazepines, phencyclidine, cocaine, methamphetamine, methadone, opiate, tricyclic antidepressants and Δ-9-THC (Rapid Response Multi-Drug Test Panel, BTNX Inc.) at the time of the study. Participants were excluded if they tested positive for any substance other than cannabis. The cutoff to test positive for cannabis was 50ng of Δ9-THC/mL of urine. We calculated total exposure in grams by adding up participants' total cannabis use. For the HC/C- and CHR/C- groups, participants were included only if they indicated that they had never used cannabis in their lifetime.

We used the Fagreström Test for Nicotine Dependence, a validated assessment that has been found to be a reliable measure in schizophrenia (Weinberger et al., 2007), to assess for nicotine dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). A score of 4 indicates nicotine dependence, while a score of 6 or higher indicates severe nicotine dependence.

4.5. N400 ERP Procedure

4.5.1. Stimuli and task

We used the same ERP procedure and statistical analyses as those used by Kiang et al. (2014) and Lepock et al. (2019)**.** The stimuli included 80 related (e.g., METAL–STEEL) and 80 unrelated (DONKEY–PURSE) prime-target word pairs. For each related pair, the target stimulus was among words most commonly given as associates to the prime stimulus by participants in the University of South Florida word association norms (Nelson, McEvoy, & Schreiber, 1999). For each unrelated pair, prime and target were not normally associated to one another. Across these conditions, targets and primes were matched for mean length and log-transformed frequency (Francis & Kucera, 1982).

Additionally, stimuli included 160 word–nonword prime-target pairs (DRESS–ZORES), with targets that were pronounceable nonwords. No word occurred more than once among the stimuli. The 320-trial stimulus list included all prime-target pairs in a fixed randomized order, in four blocks of 80 trials each. The list had two versions, each one administered to half the participants, in which the order of prime-target SOAs across blocks was counterbalanced. In version A, SOA was 300ms in blocks 1 and 2, and 750ms in blocks 3 and 4; in version B, the order of SOAs was reversed (Figure 6).

Participants were seated 100 cm from a video monitor on which stimuli were centrally presented, in yellow letters on a black background, with each letter subtending on average 0.36° of visual angle horizontally, and up to 0.55° vertically. Each participant was presented with the stimulus list, with short rest breaks between each block. Trials consisted of: (a) row of preparatory fixation crosses for 500ms; (b) blank screen for 250ms; (c) prime word for 175ms; (d) blank screen for 125ms (in 300ms SOA trials) or 575ms (in 750ms SOA trials); (e) target for 250ms; (f) blank screen for 1250ms; (g) prompt Yes or No? until participants responded via button-press; and (h) blank screen for 3000ms until onset of the next trial. At the prompt, participants were required to press one of two buttons, positioned under their right and left thumbs. The button indicating "Yes" signaled that prime and target were related; the button indicating "No" signaled that they were not. Assignment of buttons was divided equally among participants, counterbalanced across the two stimulus list versions.

4.5.2. Electroencephalographic Data Collection and Analysis

Participants were tested in the Cognitive Neurophysiology Laboratory at CAMH, using methods previously established by Kiang and colleagues (Kiang et al., 2012, 2011). During these tasks, continuous EEG was recorded using an actiCHamp amplifier (Brain Products, Gilching,

Germany), from 32 active Ag/AgCl electrodes embedded in a cap (actiCAP System, Brain Products) at sites approximately equally spaced across the scalp, positioned according to a modified International 10–20 System (Fp1-Fp2-F7-F3- Fz-F4-F8-FC5-FC1-FC2-FC6-T7-C3-Cz- C4-T8-TP9-CP5-CP1-CP2-CP6-TP10-P7-P3-Pz-P4-P8-PO9-O1-Oz-O2-PO10; Figure 7). Electrode impedances were kept below 25 kΩ. The EEG was referenced online to FCz, and continuously digitized at 500 Hz.

Blinks and eye movements were monitored via electrodes placed on the supraorbital ridge and infraorbital ridge of the left eye, and on the outer canthi of both eyes. Offline, the EEG was re-referenced to the algebraic mean of the mastoids, and bandpassed at 0.25–60 Hz for N400 analyses. Continuous data were algorithmically corrected for eyeblink artifact (Makeig, Jung, Bell, Ghahremani, & Sejnowski, 1997). Individual trials containing artifacts due to eye movement, excessive muscle activity or amplifier blocking were rejected offline by visual inspection before time-domain averaging. ERPs were computed for epochs from 100ms pre-stimulus to 900ms post-stimulus. For each participant, separate ERP averages were obtained for trials with related and unrelated targets at each SOA. The N400 semantic priming effect was defined as the mean voltage of the difference wave obtained by subtracting the average for related trials from the average of unrelated trials, from 300 to 500ms post-stimulus onset, consistent with previous methods (Federmeier & Kutas, 2005; Kiang, Prugh, & Kutas, 2010; Mclaughlin, Osterhout, & Kim, 2004).

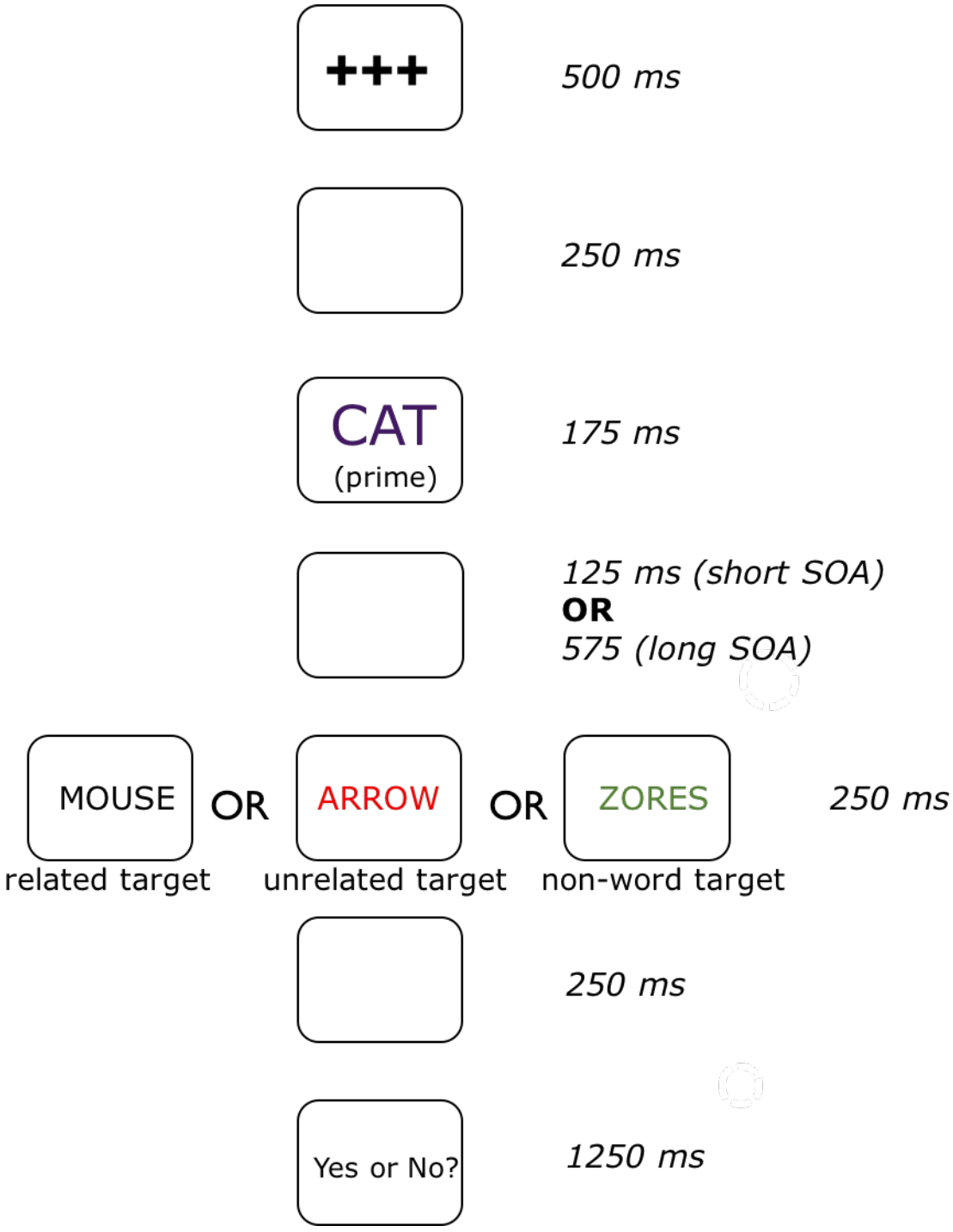

Figure 6. Overview of the N400 semantic priming task.

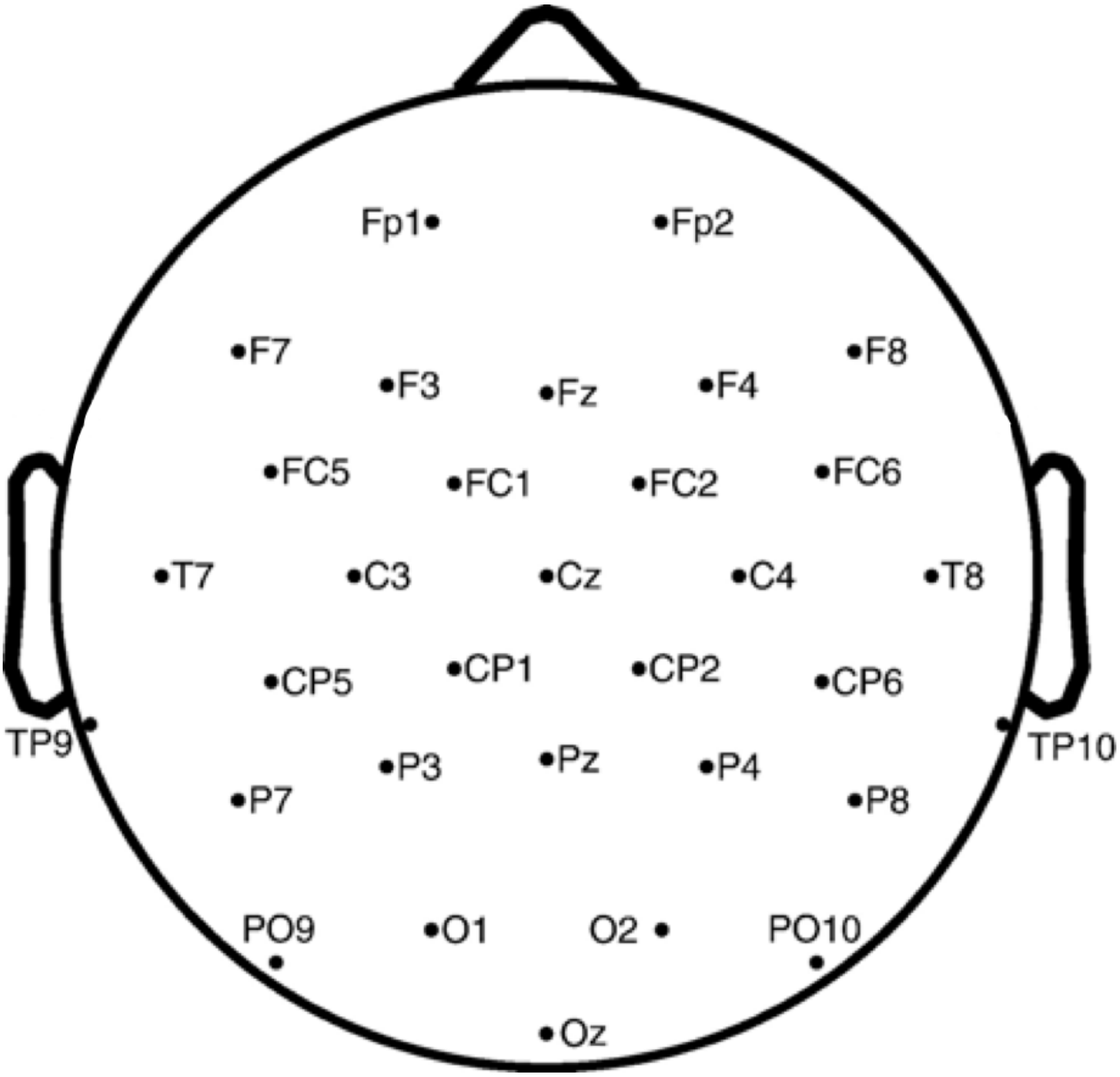

Figure 7. Schematic diagram of the 32-electrode array.

4.6. Statistical Analyses

Using statistical analyses software package SPSS (version 22.0; IBM, Armonk, NY, USA), repeated-measures analyses of variance (ANOVAs) in a general linear model were calculated. We calculated percentage of correct responses using the repeated-measures ANOVA, with group (HC/C- vs. HC/C+ vs. CHR/C- vs. CHR/C+) as between-subject variable and target (related vs. unrelated vs. nonword) and SOA (short vs. long) as within-subject variables. All *p*-values calculated are two-tailed.

N400 mean amplitude was analyzed with a repeated-measure ANOVA, with group (HC/C- vs. HC/C+ vs. CHR/C- vs. CHR/C+) as between-subject variable, and target (related vs. unrelated), SOA (short vs. long) and electrode (31 levels, all electrodes) as within-subject variables. Amplitude of N400 semantic priming effects were calculated in a repeated measures ANOVA with group (HC/C- vs. HC/C+ vs. CHR/C- vs. CHR/C+) as between-subject variable, and SOA (short vs. long) and electrode (19 levels, corresponding to a contiguous array of bilateral sites, where N400 effects are typically most prominent centered on the centroparietal region [Federmeier & Kutas, 2000]: FC1, FC2, Cz, C3, C4, CP1, CP2, CP5, CP6, Pz, P3, P4, P7, P8, PO3, PO4, Oz, O1, and O2) as within-subject variables.

For our exploratory analyses, we used Pearson's (parametric for normally distributed data) and Spearman's (nonparametric for non-normally distributed data) pairwise correlation coefficients to calculate relationships between N400 semantic priming effects at site Cz (at both short and long SOAs) vs. verbal working memory, verbal fluency, SOPS P1 and P5 (CHR participants only). We used the MATRICS Letter-Number Span task to measure verbal working memory. This orally administered task required participants to mentally reorder strings of letters and numbers and repeat them to the administrator. To measure verbal fluency (also known as

category fluency), we used the Category Fluency: Animal Naming task, where participants are required to name as many animals as possible in the span of 60 seconds. To compare correlation coefficients, we used Fisher's r-to-z transformations. All *p*-values are two-tailed.

5. Results

5.1. Participant Characteristics

A portion of the participant inclusion for this study was retrospective in nature. Participants who had already completed the study procedures prior to the start of the author's thesis were included if they met criteria for their respective group. 10 HC/C+ and 4 CHR/C+ participants were actively recruited by the author for the purpose of this thesis. In the end, this led to the inclusion of 15 non-cannabis using healthy control participants (HC/C-; mean age: 22.60 ± 3.96), 10 cannabis-using healthy controls (HC/C+; mean age: 25.50 ± 2.95), 12 non-cannabis using CHR participants (CHR/C-; mean age: 20.00 ± 1.71) and 15 cannabis-using CHR participants (CHR/C+; mean age: 21.87 ± 2.59) in the final analysis. 11 of the CHR/C- group and 10 of the HC/C- were included in the analyses of Lepock et al., (2019).

Age was significantly different between the HC/C+ and CHR/C- groups ($p < 0.05$), such that HC/C+ were older than CHR/C-. Other than that, there were no significant differences in the other demographic variables (Table 1). We were able to collect FTND data for 28 participants. Among the CHR/C+, one of these participants met for mild nicotine dependence, and one met for severe dependence. One of the HC/C+ participants did not complete the FTND but further questioning revealed that they were a heavy cigarette smoker and may meet for nicotine dependence.

One CHR/C+ participant was taking 2mg daily of Abilify (aripiprazole) at the time of the study and was previously taking 5mg daily for two weeks. This participant was included in the study as this dose of aripiprazole is considered to be below therapeutic level according to antipsychotic equivalency tables (Leucht et al., 2014; Patel, Arista, Taylor, & Barnes, 2013; Riva & Di Sciascio, 2015) and as assessed by their attending psychiatrist.

		Healthy Non-Cannabis Using Control (HC/C-)	Healthy Cannabis-Using Controls (HC/C+)	Non-Cannabis Using CHR (CHR/C-)	Cannabis-using CHR (CHR/C+)		
	n	15	10	12	15		
	Age	22.60 ± 3.96	25.50 ± 2.95	20.00 ± 1.71	21.87 ± 2.59	F = 6.415	***p* = 0.001 (HC/C+ vs. CHR/C- : p < 0.0001)***
Sex	M	6	5	6	12	X = 5.379	*p* = 0.128
	F	9	5	6	3		
	Parental SES[1]	50.90 ± 15.16	45.95 ± 14.54	47.23 ± 17.01	50.13 ± 8.51	F = 0.349	*p* = 0.790
	Years of Education	15.33 ± 1.95	15.10 ± 2.18	14.00 ± 1.91	13.67 ± 2.38	F = 2.036	*p* = 0.121
	NART Verbal IQ Score[2]	109.18 ± 5.45	107.75 ± 8.66	110.19 ± 4.24	110.87 ± 7.87	F = 0.483	*p* = 0.696
Handedness	L	1	1	1	1	X = 0.126	*p* = 0.988
	R	14	9	11	14		
	FTND[3]	N/A (n = 0 completed)	0.33 ± 1.00 (n = 9 completed)	0 (n = 6 completed)	1.54 ± 1.98 (n = 13 completed)		

Table 1. Summary of demographic variables for participants (mean ± SD). [1]Parental Socioeconomic Status. [2]National Adult Reading Test Verbal IQ Score. [3]Fagerstrom Test of Nicotine Dependence

5.2 Cannabis Use

Among the non-cannabis using participants in the HC/C- and CHR/C- groups, no subject endorsed using cannabis in their lifetime. All current cannabis users were using a minimum of three grams a week for the past year. 10 HC/C+ completed the urine drug screen but because of the partial retrospective nature of this study, we were able to collect qualitative urine drug screen data for only 4 CHR/C+ at the time of the study. These individuals all had a positive urine drug screen for only cannabis and no other illicit drug. The average age of initiation of cannabis was estimated at 16.70 ± 3.09 for HC/C+ and 15.33 ± 2.19 for the CHR/C+, and did not differ significantly between both groups. Moreover, mean total amount of cannabis exposure was approximately 2179.18 ± 1741.59 grams for HC/C+ and 929.89 ± 839.56 for CHR/C+ grams. The homogeneity of variance assumption was not met (Levene's test, $p = 0.049$), so the adjusted two-tailed p-value for the independent samples t-test revealed no significant differences between groups ($p > 0.05$; Table 2).

Nine HC/C+ participants met criteria for current cannabis dependence disorder. Seven CHR/C+ participants met for current dependence, and seven met for past dependence, of which three were in full sustained remission. Among those who met for past dependence in the CHR/C+ group, three individuals were still using cannabis in the past month.

Two CHR/C+ participants were in sustained full remission for alcohol dependence for the past 12 months. One HC/C+ participant had used LSD within the past 30 days.

		Healthy Non-Cannabis Using Control (HC/C-)	Healthy Cannabis-Using Controls (HC/C+)	Non-Cannabis Using CHR (CHR/C-)	Cannabis-using CHR (CHR/C+)		
	n	15	10	12	15		
Cannabis Use	Total Lifetime Exposure (grams)	0	2179.18 ± 1741.59	0	929.89 ± 839.56	t = -2.111	$p = 0.057$[a]
	Age of first use	-	16.70 ± 3.09	-	15.33 ± 2.19	t = -1.296	$p = 0.208$
	Cannabis Dependence Disorder (DSM-IV)	-	9 current	-	7 current, 8 past		

Table 2. Summary of participants' cannabis use history.
[a] Significance after adjusting for unequal variances (Levene's test for equality of Variances: $p < 0.05$).

5.3. Clinical and Neuropsychological Assessments

None of the healthy control participants met criteria for current or past Axis I disorders, including major depressive disorder or any anxiety disorders. The CHR groups did not significantly differ on any of the scores for Positive Symptoms on the SIPS ($p > 0.05$) or social or role functioning scales ($p > 0.05$; Table 3).

On the MATRICS battery of neuropsychological tests (Table 4 and 5), the omnibus ANOVA revealed significant differences for only the nonverbal working memory domain (Wechsler Memory Scale – third edition; $p = 0.006$). Post-hoc tests revealed differences between HC/C- vs. CHR/C- (Tukey's HSD, $p = 0.027$) and HC/C- vs. CHR/C+ (Tukey's HSD, $p = 0.008$)

		Healthy Non-Cannabis Using Control (HC/C-)	Healthy Cannabis-Using Controls (HC/C+)	Non-Cannabis Using CHR (CHR/C-)	Cannabis-using CHR (CHR/C+)		
	n	15	10	12	15		
SOPS[1]	P1	-	-	3.92 ± 0.900	2.87 ± 0.743	F = 1.244	$p = 0.275$
	P2	-	-	3.00 ± 1.414	2.20 ± 1.373	F = 0.804	$p = 0.378$
	P3	-	-	0.58 ± 1.730	0.53 ± 0.990	F = 0.230	$p = 0.635$
	P4	-	-	3.25 ± 1.485	2.47 ± 1.642	F = 0.389	$p = 0.539$
	P5	-	-	1.33 ± 1.497	2.47 ± 1.457	F = 0.344	$p = 0.563$
Global Functioning	Global Functioning Role	-	-	6.00 ± 1.348	5.21 ± 1.888	F = 0.237	$p = 0.631$
	Global Functioning Social	-	-	6.33 ± 1.303	6.07 ± 1.328	F = 1.696	$p = 0.205$

Table 3. Summary of participants' clinical characteristics. [1]SOPS – Scale of Psychosis-Risk Symptoms.

	Test	**Healthy Non-Cannabis Using Control (HC/C-)**	**Healthy Cannabis-Using Controls (HC/C+)**	**Non-Cannabis Using CHR (CHR/C-)**	**Cannabis-using CHR (CHR/C+)**		
MATRICS	TMT	47.80 ± 7.903	38.50 ± 11.247	47.08 ± 10.335	42.27 ± 12.606	F = 1.995	$p = 0.127$
	BACS	55.73 ± 14.538	45.60 ± 11.108	44.75 ± 11.323	48.53 ± 12.546	F = 2.112	$p = 0.111$
	HVLT-R	49.87 ± 8.839	52.10 ± 8.672	49.50 ± 10.086	47.27 ± 7.667	F = 0.622	$p = 0.604$
	WMS*	60.73 ± 8.771	56.10 ± 7.593	50.75 ± 9.294	49.80 ± 9.291	F = 4.721	**$p = 0.006$ (HC/C- vs. CHR/C-: $p = 0.027$; HC/C- vs. CHR/C+: $p = 0.008$)***
	LNS	53.40 ± 9.272	52.70 ± 10.220	50.58 ± 7.751	47.20 ± 7.063	F = 1.518	$p = 0.222$

Table 4. Summary of participants' neuropsychological assessment results (t-scores, standardized for age and gender). TMT - Trail Making Test; BACS - Brief Assessment of Cognition in Schizophrenia (BACS): Symbol Coding; HVLT - Hopkin's Verbal Learning Test – Revised; WMS - Wechsler Memory Scale, Third Edition; LNS - Letter Number Span.
*$p < 0.05$

	Test	**Healthy Non-Cannabis Using Control (HC/C-)**	**Healthy Cannabis-Using Controls (HC/C+)**	**Non-Cannabis Using CHR (CHR/C-)**	**Cannabis-using CHR (CHR/C+)**		
MATRICS	NAB Mazes	49.33 ± 12.315	45.90 ± 13.102	51.08 ± 6.417	48.73 ± 9.550	F = 0.446	$p = 0.721$
	BVMT-R	49.07 ± 9.982	52.00 ± 7.102	46.25 ± 9.057	45.80 ± 10.496	F = 1.067	$p = 0.372$
	Category Fluency	52.00 ± 11.421	49.70 ± 7.273	51.83 ± 9.833	49.70 ± 7.273	F = 0.197	$p = 0.898$
	MSCEIT	51.60 ± 11.867	44.80 ± 12.145	51.08 ± 8.806	45.40 ± 11.287	F = 1.360	$p = 0.266$
	CPT	47.60 ± 10.232	47.10 ± 9.758	37.67 ± 12.010	42.07 ± 10.236	F = 2.441	$p = 0.076$
	Composite Score	51.33 ± 11.223	47.60 ± 9.442	46.17 ± 8.601	44.00 ± 10.316	F = 1.392	$p = 0.257$

Table 5. Summary of participants' neuropsychological assessment results (t-scores, standardized for age and gender), continued. NAB Mazes – Neuropsychological Assessment Battery Mazes; BVMT - Brief Visuospatial Memory Test-Revised; MSCEIT - Mayer-Salovey-Caruso Emotional Intelligence Test; CPT - Continuous Performance Test.

5.4 Electrophysiological Data Analysis

5.4.1. Behavioral Data

The participants' mean correct response rates in the lexical decision task are shown in Table 6. The high correct response rates indicate that generally, participants were attending to the stimuli and task. There was no group effect [$F(3,48) = 0.554$, $p = 0.648$]. There was a target effect, [$F(2,47) = 7.801$, $p = 0.001$], indicating that across all groups, the correct response rate was higher for related targets than for unrelated and nonword targets. There was no target x group effect [$F(6,96) = 0.502$, $p = 0.805$].

5.4.2. N400 Amplitude and Semantic Priming Effect

For all four groups at short and long SOAs, mean values for N400 amplitudes to related and unrelated targets (across 31 electrodes), and mean N400 semantic priming effect (across 19 electrodes) are presented in Table 7. Grand average ERPs at the central electrode Cz are shown at short and long SOA for all four groups in Figures 8 and 9.

As age was significantly different between groups, it was added as a covariate to the repeated measures ANOVA. However, it did not have a significant effect on the model ($p = 0.564$) so we have reported the following statistics without adding Age as a covariate.

Across all groups, mean N400 amplitudes were smaller (less negative) for related targets than unrelated targets [target effect: $F(1,33) = 24.312$, $p < 0.0001$]. However, across all 31 electrodes, we observed no overall group effect [$F(3,48) = 0.015$, $p = 0.998$] or group x target interaction [$F(3,48) = 1.279$, $p = 0.292$], indicating the N400 amplitudes to unrelated and related targets did not significantly differ between groups.

In terms of the semantic priming effect (unrelated N400 amplitude minus related N400 amplitude), there was no overall effect of group across 19 electrodes [$F(3,48) = 1.362$, $p =$

0.266)] or group x SOA interaction F(3,48) = 2.070, p = 0.177)], indicating no differences in N400 priming effects between the four groups.

Analyses of Cohen's effect sizes (*d;* Tables 8 and 9) showed that that we may have been underpowered to observe differences in semantic priming effects between CHR/C+ and the other three groups at the short SOA (CHR/C+ vs. HC/C-: d = 0.434251; CHR/C+ vs. HC/C+: d = 0.881996; CHR/C+ vs. CHR/C-: d = 0.53621) and between HC/C- and the other two CHR groups at the long SOA (HC/C- vs CHR/C-: d = 0.725905; HC/C- vs CHR/C-: d = 0.63318), even in the absence of significant statistical differences. Generally, these values are considered to be medium-to-large effect sizes (Wuensch, 2015). Additionally, at the long SOA, the effect size between HC/C- and HC/C+ was small (d = 0.290632), as was the effect size between CHR/C- and CHR/C+ (d = 0.181376)*,* suggesting that cannabis did not affect semantic priming effects.

To take these exploratory analyses one step further, we examined whether N400 semantic priming effects would differ if we collapsed our four groups into two groups, that is, comparing all CHR individuals (n=27) versus all control participants (n=25). We observed a trend towards a group difference [F(1,50) = 3.437, p = 0.070)] such that CHR individuals were more impaired at the long SOA, with a smaller semantic priming effect (Figures 10 and 11).

Age and years of education were significantly different between these two groups, as healthy control participants were older and had more years of education than CHR individuals. Adding these variables as covariates to our analyses yielded a p-value of 0.147 for the overall group effect, however neither of these covariates themselves had any significant effect on the model (age: p = 0.147; years of education: p = 0.168).

SOA	Target	**Healthy Non-Cannabis Using Control (HC/C-)**	**Healthy Cannabis-Using Controls (HC/C+)**	**Non-Cannabis Using CHR (CHR/C-)**	**Cannabis-using CHR (CHR/C+)**
Short SOA	related	0.987 ± 0.034	0.993 ± 0.012	0.988 ± 0.020	0.978 ± 0.045
	unrelated	0.967 ± 0.051	0.985 ± 0.017	0.981 ± 0.030	0.967 ± 0.052
	non-word	0.983 ± 0.018	0.976 ± 0.031	0.941 ± 0.105	0.943 ± 0.090
Long SOA	related	0.980 ± 0.037	0.995 ± 0.011	0.985 ± 0.031	0.987 ± 0.021
	unrelated	0.973 ± 0.045	0.978 ± 0.018	0.965 ± 0.067	0.967 ± 0.041
	non-word	0.982 ± 0.033	0.959 ± 0.052	0.960 ± 0.062	0.957 ± 0.090

Table 6. Percentage of correct lexical-decision responses by group, target condition and SOA (mean values, with standard deviation).

SOA		**Healthy Non-Cannabis Using Control (HC/C-)**	**Healthy Cannabis-Using Controls (HC/C+)**	**Non-Cannabis Using CHR (CHR/C-)**	**Cannabis-using CHR (CHR/C+)**
Short SOA	related	-0.676 ± 0.583	0.133 ± 0.714	-0.495 ± 0.652	-1.125 ± 0.583
	unrelated	-1.089 ± 0.556	-1.375 ± 0.681	-1.347 ± 0.622	-1.603 ± 0.556
	semantic priming effect	-0.395 ± 0.363	-1.558 ± 0.444	-0.957 ± 0.405	-0.502 ± 0.363
Long SOA	related	0.749 ± 0.614	-0.023 ± 0.752	0.082 ± 0.687	0.613 ± 0.614
	unrelated	-0.813 ± 0.639	-1.136 ± 0.783	-0.216 ± 0.715	0.179 ± 0.639
	semantic priming effect	-1.489 ± 0.434	-1.203 ± 0.531	-0.280 ± 0.485	-0.427 ± 0.434

Table 7. N400 mean amplitudes to related and unrelated targets, and mean N400 semantic priming effect (mean ± standard error of the mean).

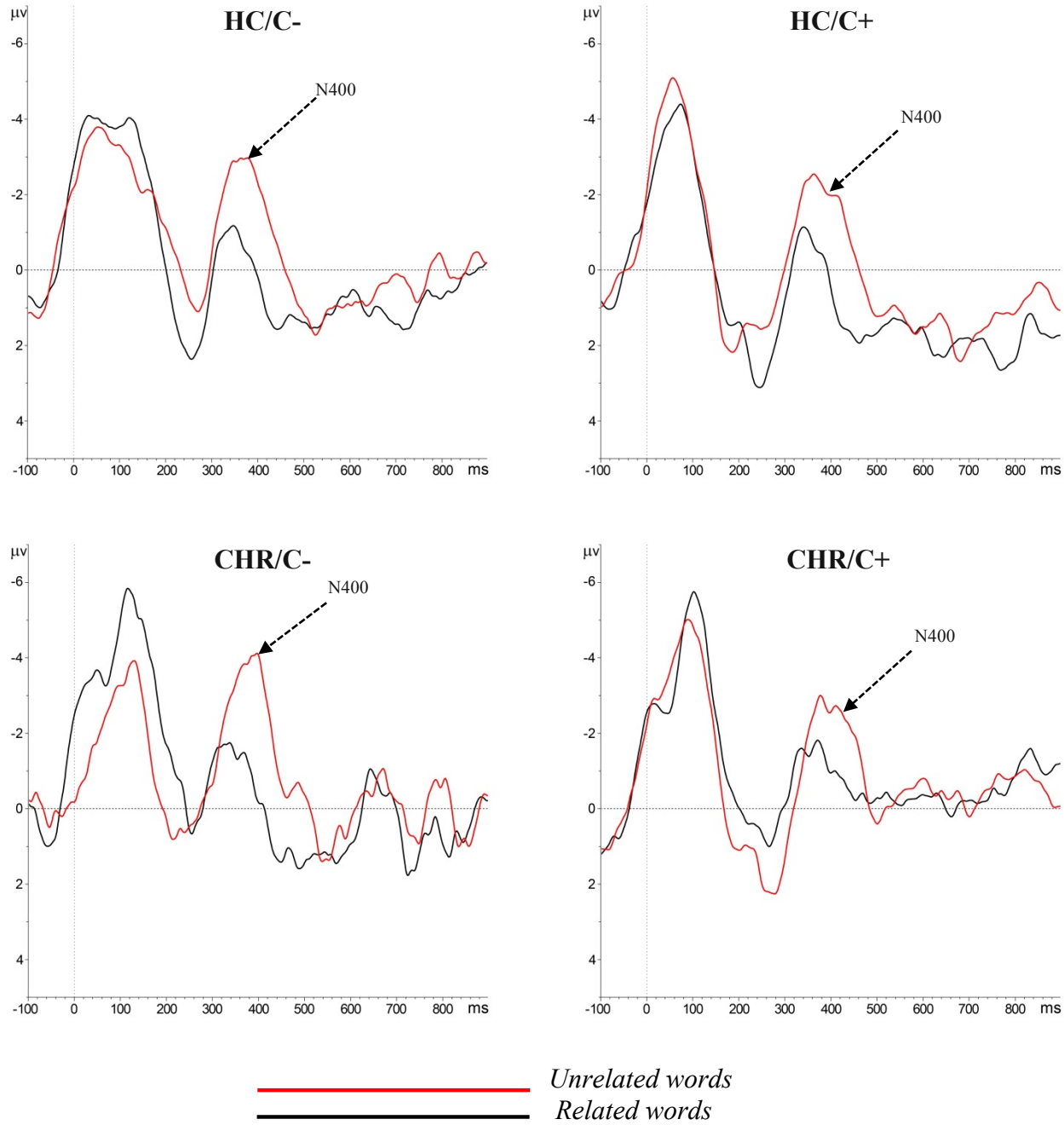

Figure 8. Grand average ERPs to unrelated (red line) and related (black line) words at midline central electrode Cz at the short SOA. Time (ms) is plotted on the x-axis and voltage (μv) is plotted negatively upward on the y-axis. No significant differences were observed between groups.

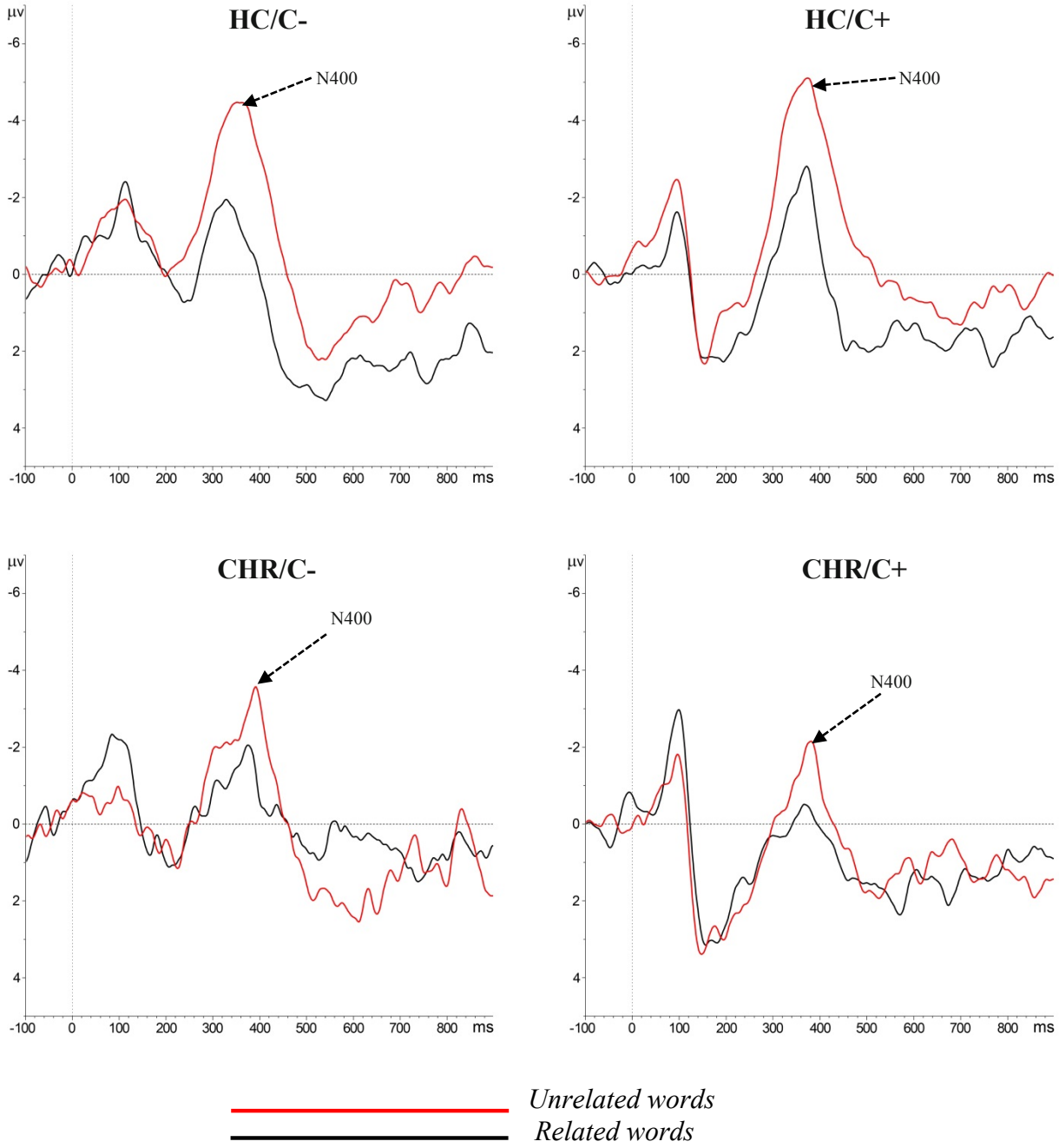

Figure 9. Grand average ERPs to unrelated (red line) and related (black line) words at midline central electrode Cz at the long SOA. Time (ms) is plotted on the x-axis and voltage (μv) is plotted negatively upward on the y-axis. No significant differences were observed between groups.

Cohen's *d*

short SOA				
	HC/C-	**HC/C+**	**CHR/C-**	**CHR/C+**
HC/C-	-	0.401027	0.205423	**0.434251**
HC/C+	0.401027	-	0.109654	**0.881996**
CHR/C-	0.205423	0.109654	-	**0.53621**
CHR/C+	0.434251	0.881996	0.53621	-

Table 8. Summary of effect sizes for differences in N400 semantic priming effects between groups at the short SOA.

Cohen's *d*

long SOA				
	HC/C-	**HC/C+**	**CHR/C-**	**CHR/C+**
HC/C-	-	0.290632	**0.725905**	**0.63318**
HC/C+	0.290632	-	0.433608	0.304675
CHR/C-	0.725905	0.433608	-	0.181376
CHR/C+	0.63318	0.304675	0.181376	-

Table 9. Summary of effect sizes for differences in N400 semantic priming effects between groups at the long SOA.

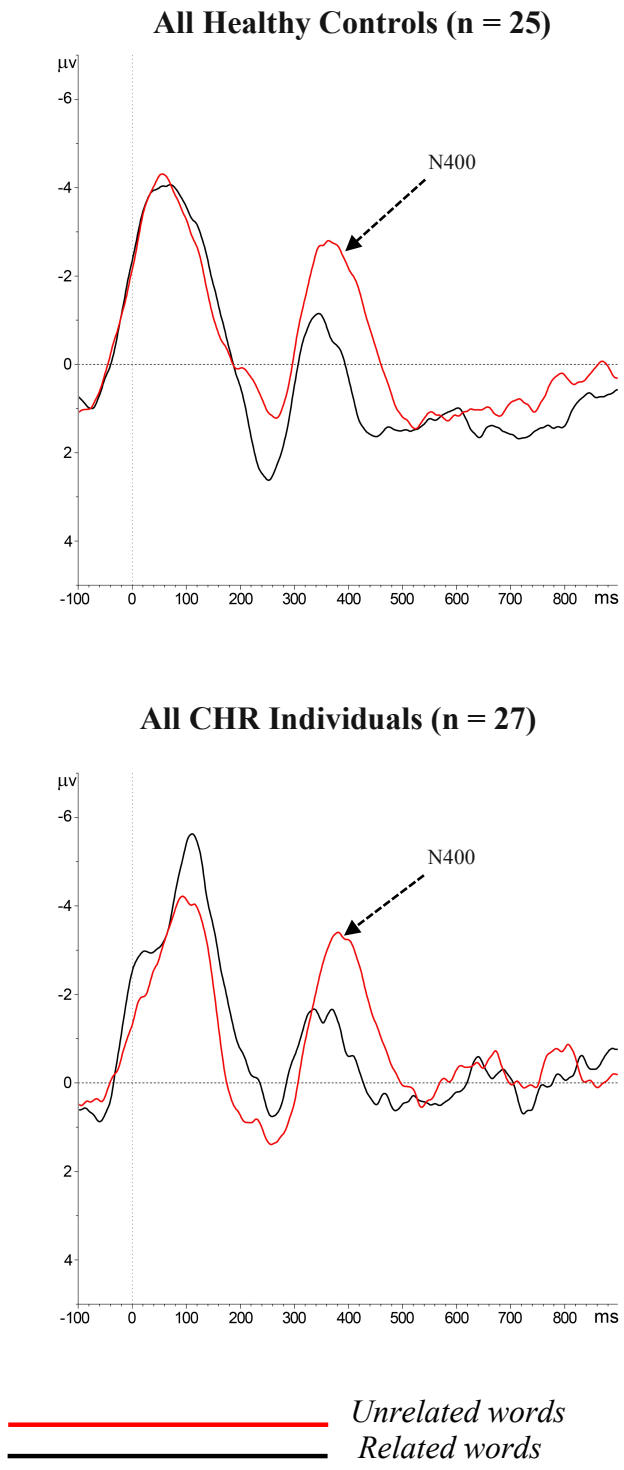

Figure 10. Grand average ERPs to unrelated (red line) and related (black line) words at midline central electrode Cz at the short SOA. Time (ms) is plotted on the x-axis and voltage (μv) is plotted negatively upward on the y-axis.

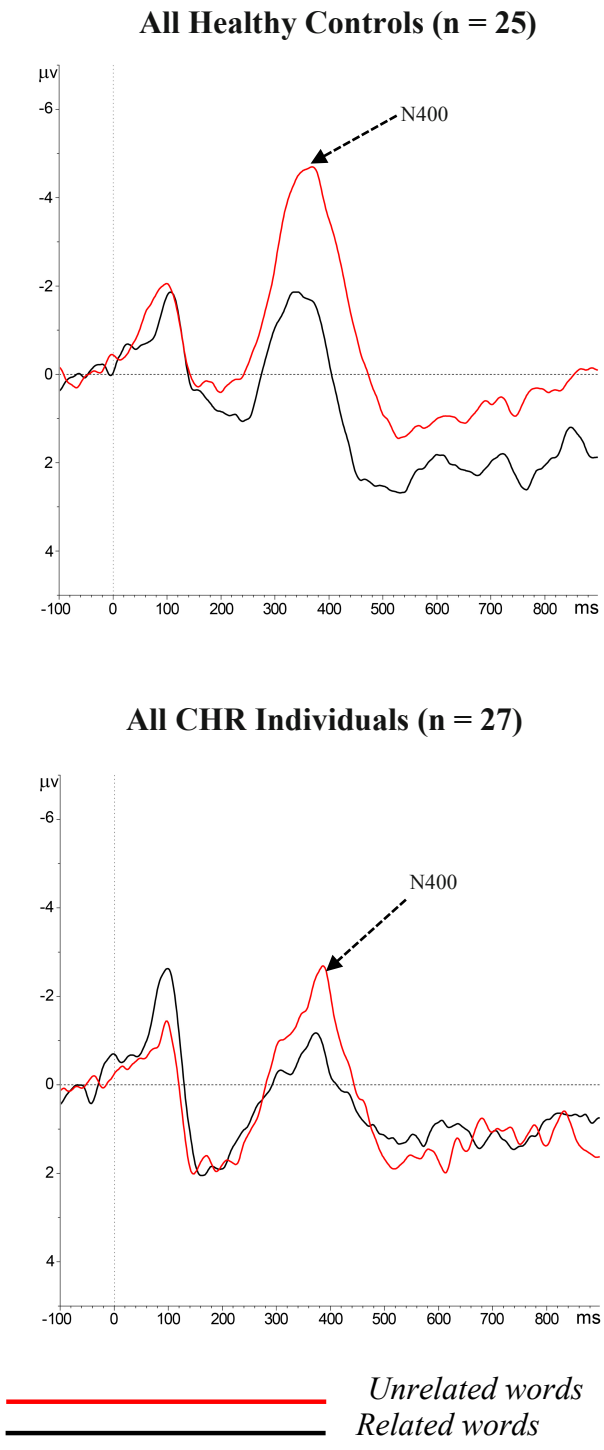

Figure 11. Grand average ERPs to unrelated (red line) and related (black line) words at midline central electrode Cz at the long SOA. Time (ms) is plotted on the x-axis and voltage (μv) is plotted negatively upward on the y-axis.

5.5. Exploratory Correlations

5.5.1. MATRICS Working Memory and Verbal Fluency Domains

Working memory and verbal fluency t-scores were standardized for age and educational norms. We observed a significant positive Pearson correlation between verbal working memory t-scores and the semantic priming effect at the short SOA for the HC/C- group ($r = 0.675$, $p = 0.006$), such that higher scores on the working memory task were associated with smaller N400 semantic priming effects (Figures 12 and 13). We observed no other correlations with verbal working memory scores at either SOA for any of the other groups ($p > 0.05$; Table 10). To determine whether differences correlation coefficients were significant between groups, we used Fisher's r-to-z transformation. We observed a significant difference in correlation coefficients between the HC/C- and CHR/C- group ($p = 0.034$) and the HC/C- and CHR/C+ group at the short SOA ($p = 0.0032$).

We observed a significant negative Pearson correlation between verbal fluency t-scores and the semantic priming effect at the long SOA for the CHR/C+ group only ($r = -0.554$, $p = 0.032$), such that higher scores on the verbal fluency task were associated with larger N400 semantic priming effects (Figures 14 and 15). We observed no other correlations with working memory scores at either SOA for any of the other groups ($p > 0.05$; Table 11). Furthermore, we observed no significant differences in correlation coefficients between CHR/C+ and any of the other groups.

5.5.2. SOPS P1 and P5 Domains

Spearman's nonparametric correlations were used for the correlations between N400 semantic priming effect and SOPS scores, given the non-normal distribution of the latter scores (Tables 12 and 13). In both patient groups, there was no correlation between SOPS P1 (unusual

thought content; Figures 16 and 17) and P5 (disorganized communication) and semantic priming effect at the short and long SOA (Figures 18 and 19).

	MATRICS Verbal Working Memory Score							
	Healthy Non-Cannabis Using Control (HC/C-)		**Healthy Cannabis-Using Controls (HC/C+)**		**Non-Cannabis Using CHR (CHR/C-)**		**Cannabis-using CHR (CHR/C+)**	
	r	*p*	r	*p*	r	*p*	r	*p*
N400 Short Effect @ Cz	0.675	0.006**	0.281	0.432	-0.114	0.725	-0.367	0.178
N400 Long Effect @ Cz	0.233	0.403	-0.370	0.293	-0.028	0.932	0.105	0.708

Table 10. Pearson correlations between MATRICS verbal working memory domain T-scores (Letter-Number Span task) and semantic priming effect at both short and long SOAs.
**$p < 0.01$

	MATRICS Verbal Fluency							
	Healthy Non-Cannabis Using Control (HC/C-)		**Healthy Cannabis-Using Controls (HC/C+)**		**Non-Cannabis Using CHR (CHR/C-)**		**Cannabis-using CHR (CHR/C+)**	
	r	*p*	r	*p*	r	*p*	r	*p*
N400 Short Effect @ Cz	-0.018	0.950	-0.451	0.191	0.010	0.976	-0.554	0.032*
N400 Long Effect @ Cz	0.099	0.724	-0.386	0.271	0.458	0.135	0.004	0.990

Table 11. Pearson correlations between MATRICS verbal fluency domain T-scores (Category Fluency task) and semantic priming effect at both short and long SOAs. We observed a significant correlation between the semantic priming effect at the short SOA and verbal fluency scores for the CHR/C+ group.
*$p < 0.05$

	N400 Short Effect @ Cz			
	Non-Cannabis Using CHR (CHR/C-)		Cannabis-using CHR (CHR/C+)	
	r	*p*	r	*p*
SOPS P1	0.454	0.138	0.127	0.651
SOPS P5	- 0.238	0.457	0.104	0.713

Table 12. Spearman's correlations between SOPS P1 and P5 scores and semantic priming effect at the short SOA. We observed no significant correlations in either of the CHR groups.

	N400 Long Effect @ Cz			
	Non-Cannabis Using CHR (CHR/C-)		Cannabis-using CHR (CHR/C+)	
	r	*p*	r	*p*
SOPS P1	- 0.417	0.177	0.019	0.946
SOPS P5	0.094	0.771	- 0.353	0.196

Table 13. Spearman's correlations between SOPS P1 and P5 scores and semantic priming effect at the long SOA. We observed no significant correlations in either of the CHR groups.

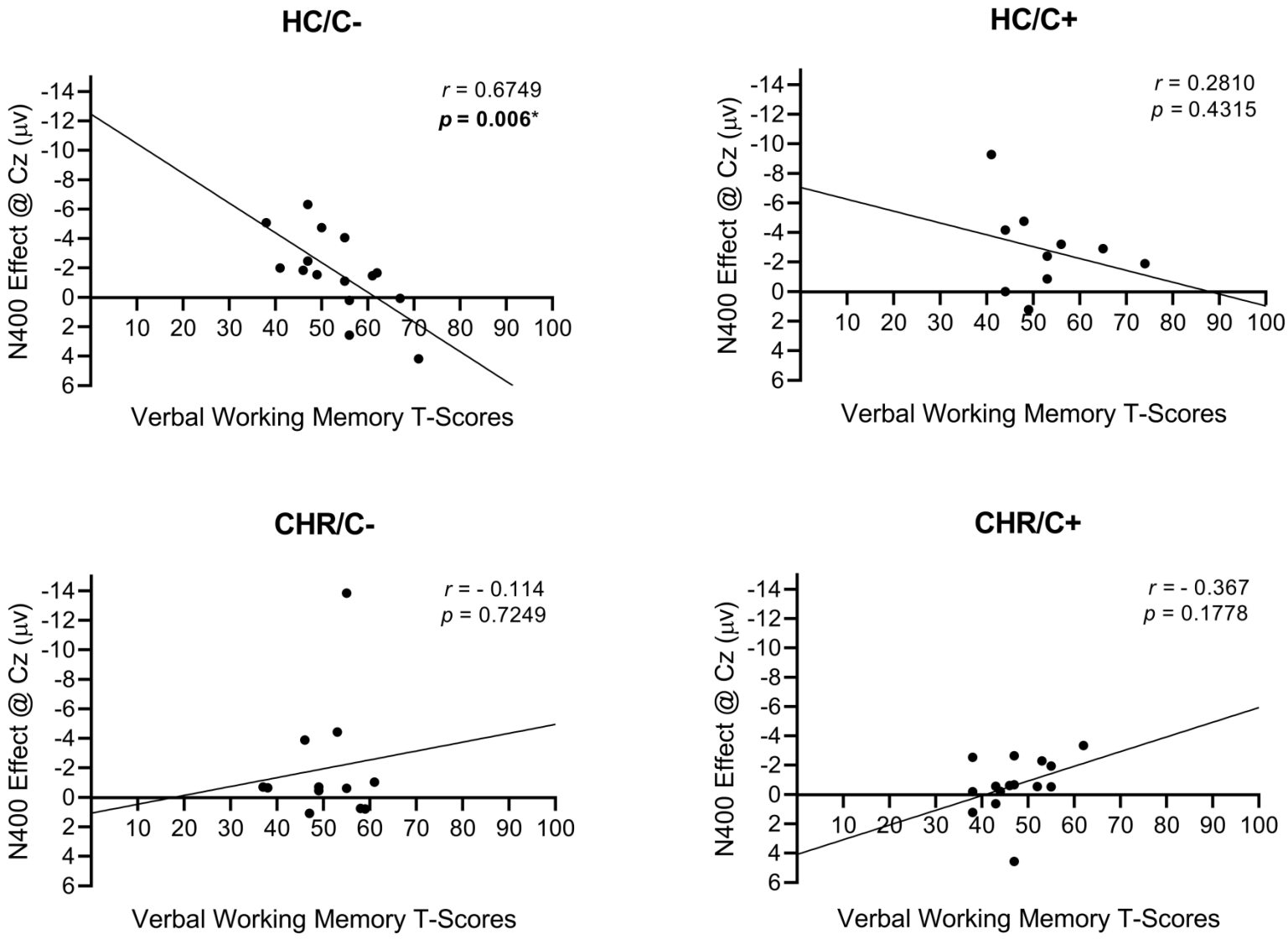

Figure 12. Correlations between verbal working memory t-scores (Letter-Number Span) and N400 semantic priming effect at the short SOA.

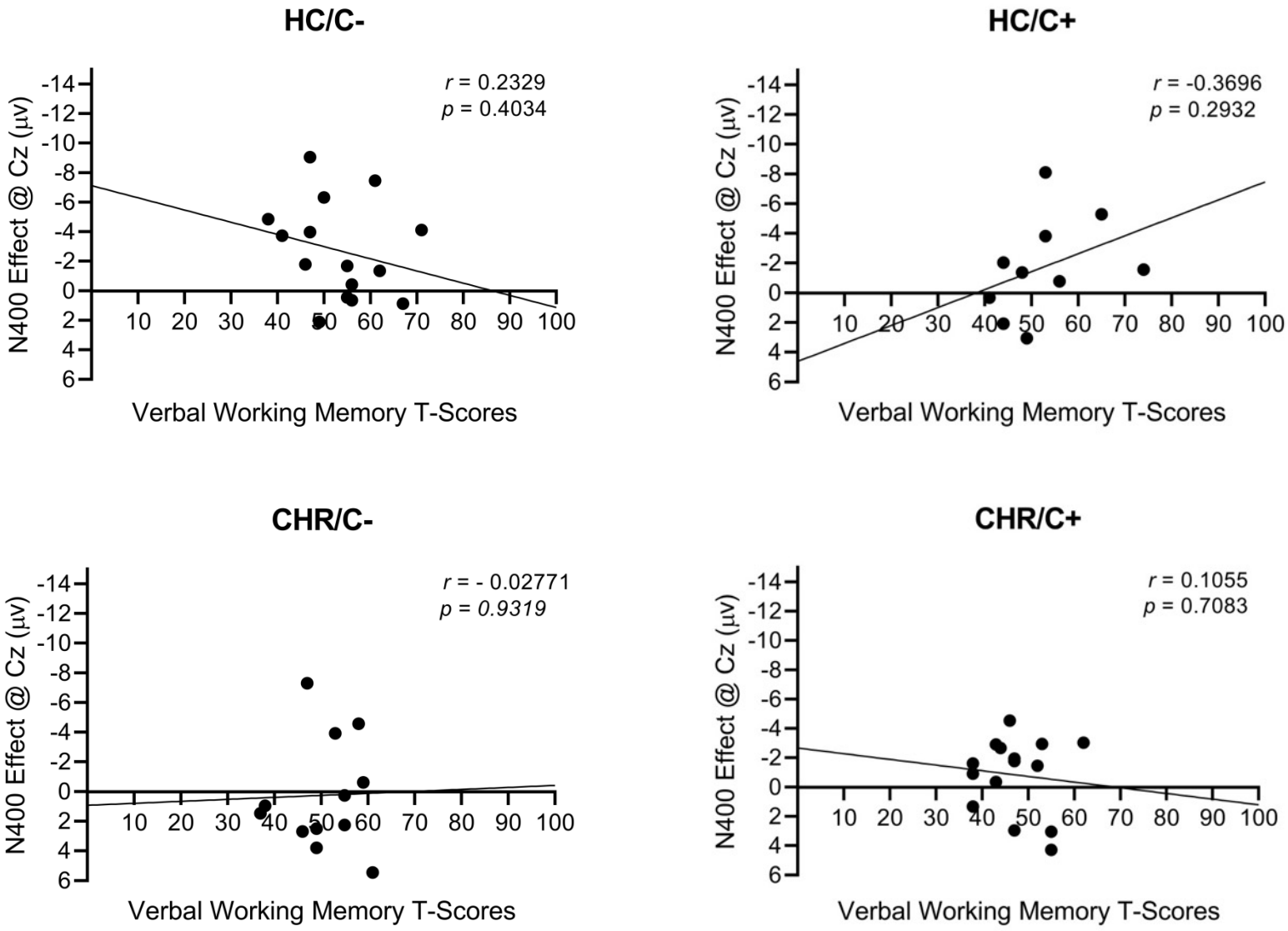

Figure 13. Correlations between verbal working memory t-scores (Letter-Number Span) and N400 semantic priming effect at the long SOA.

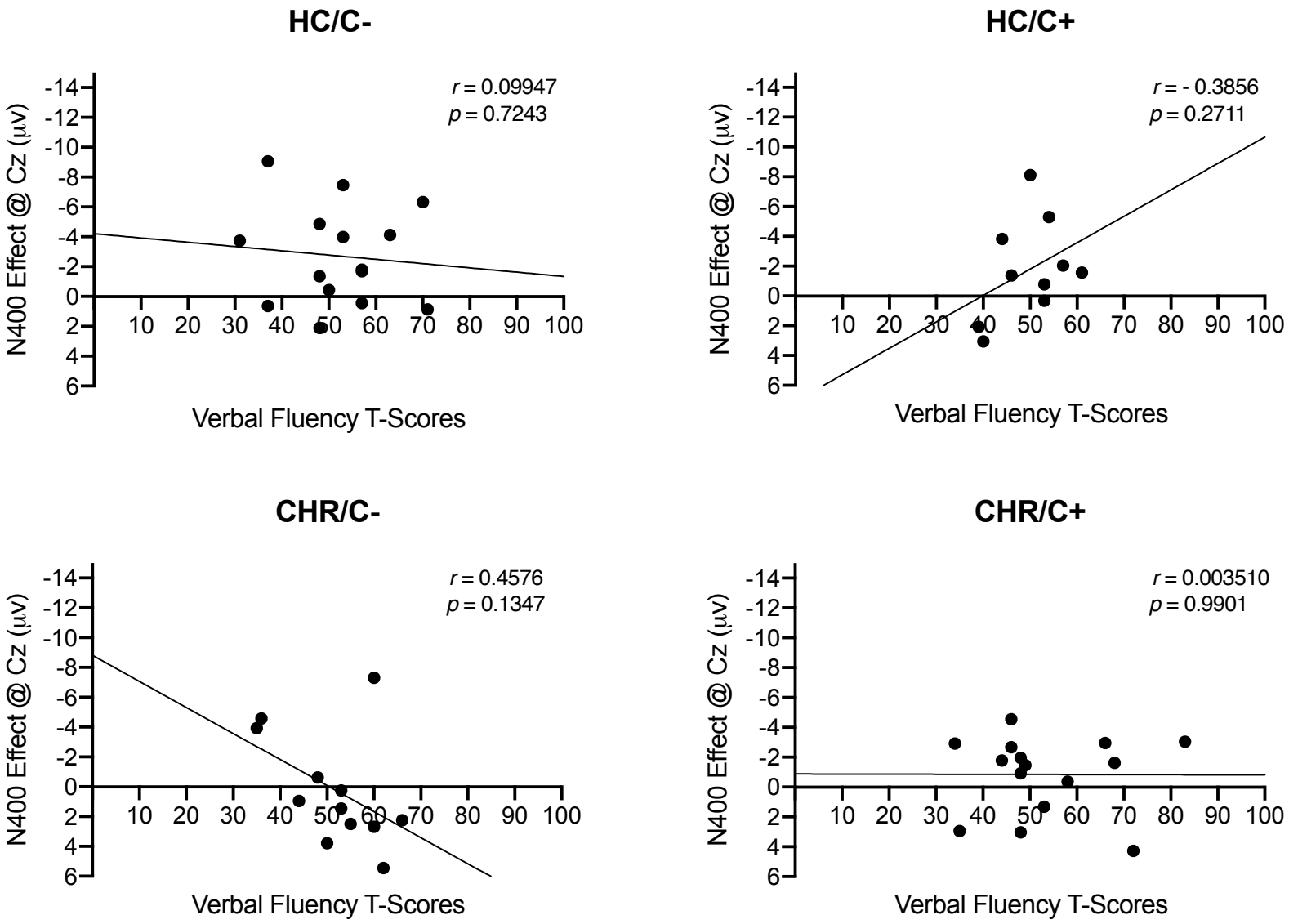

Figure 14. Correlations between verbal fluency t-scores (Category Fluency – Animal Naming) and N400 semantic priming effect at the short SOA.

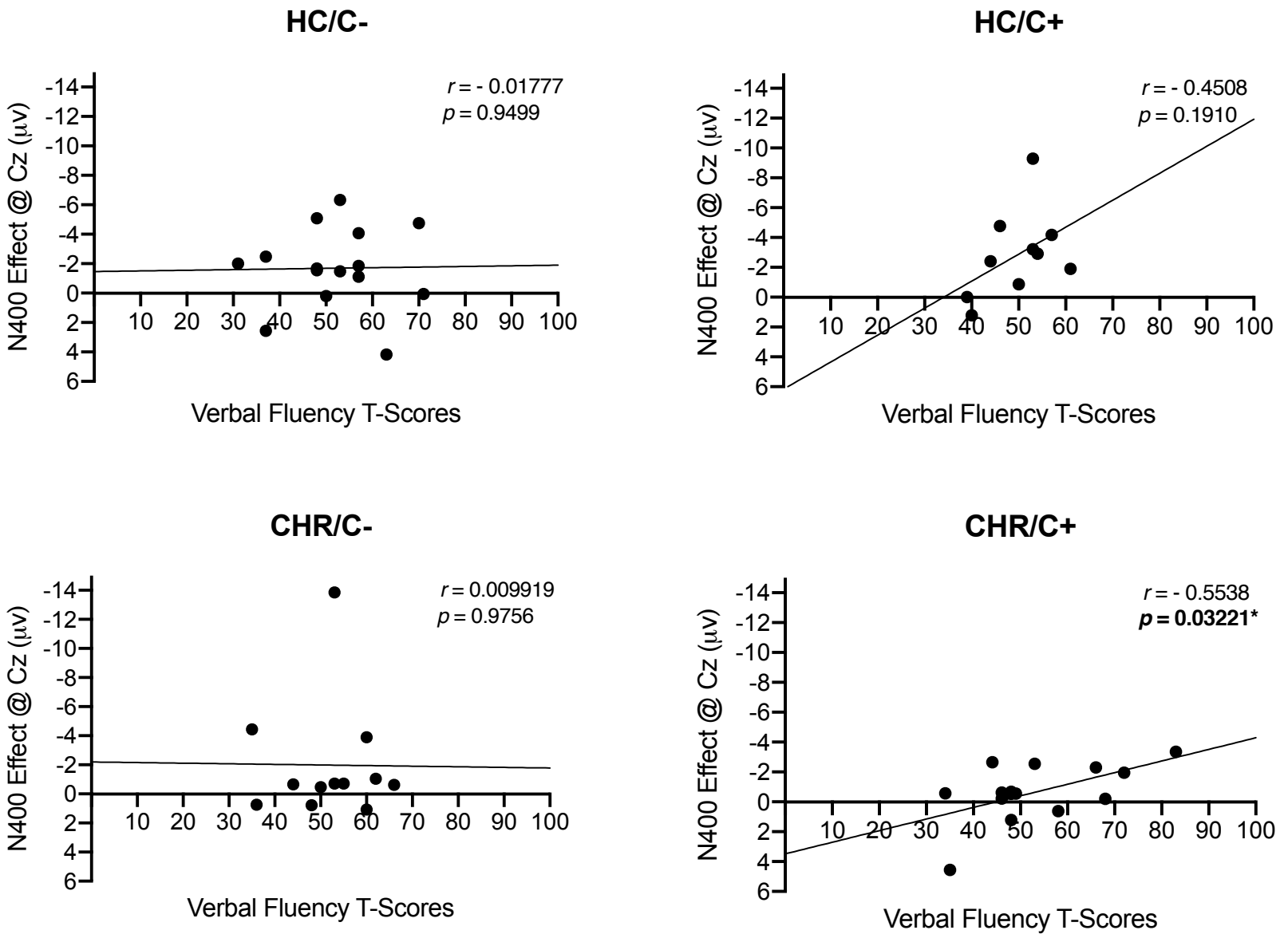

Figure 15. Correlations between verbal fluency t-scores (Category Fluency – Animal Naming) and N400 semantic priming effect at the long SOA.

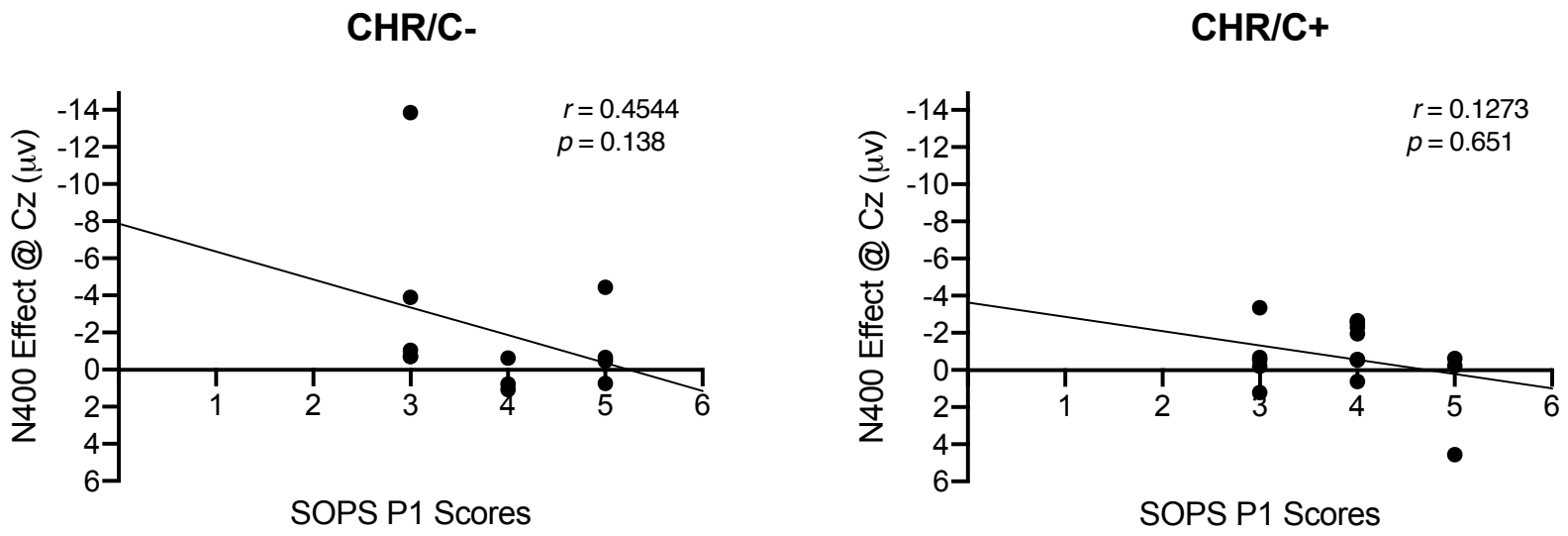

Figure 16. Correlations between SOPS P1 scores (Unusual Thought Content) and N400 semantic priming effect at the short SOA.

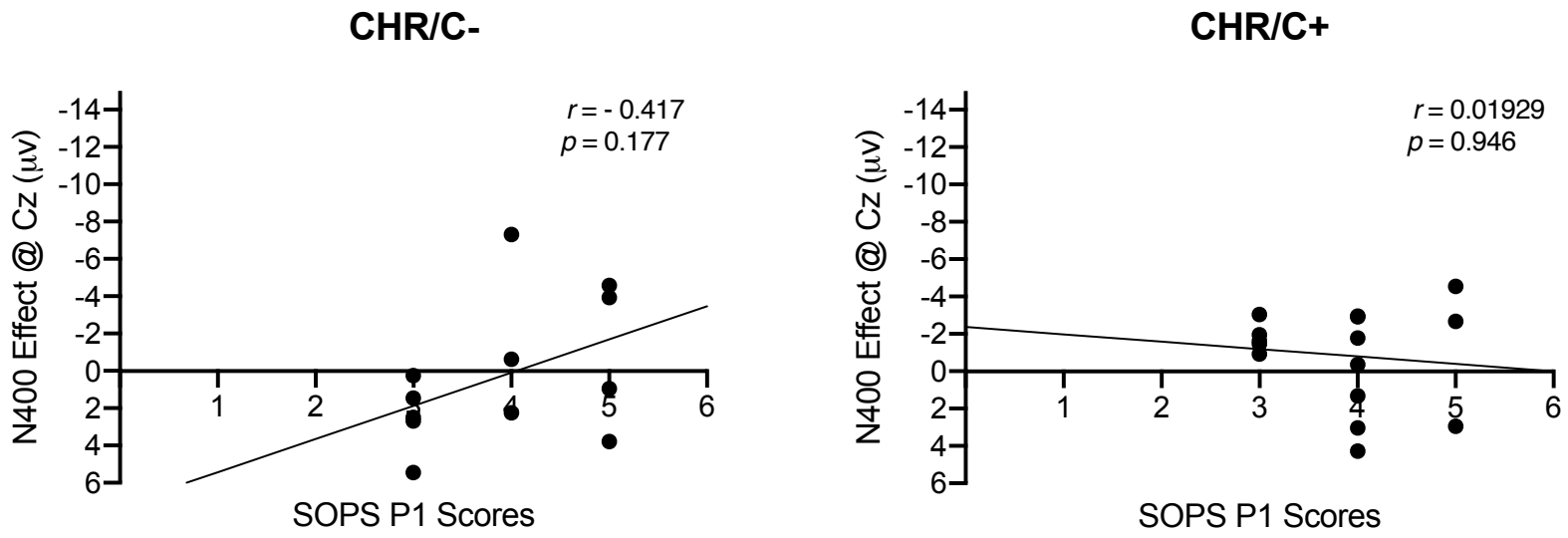

Figure 17. Correlations between SOPS P1 scores (Unusual Thought Content) and N400 semantic priming effect at the long SOA.

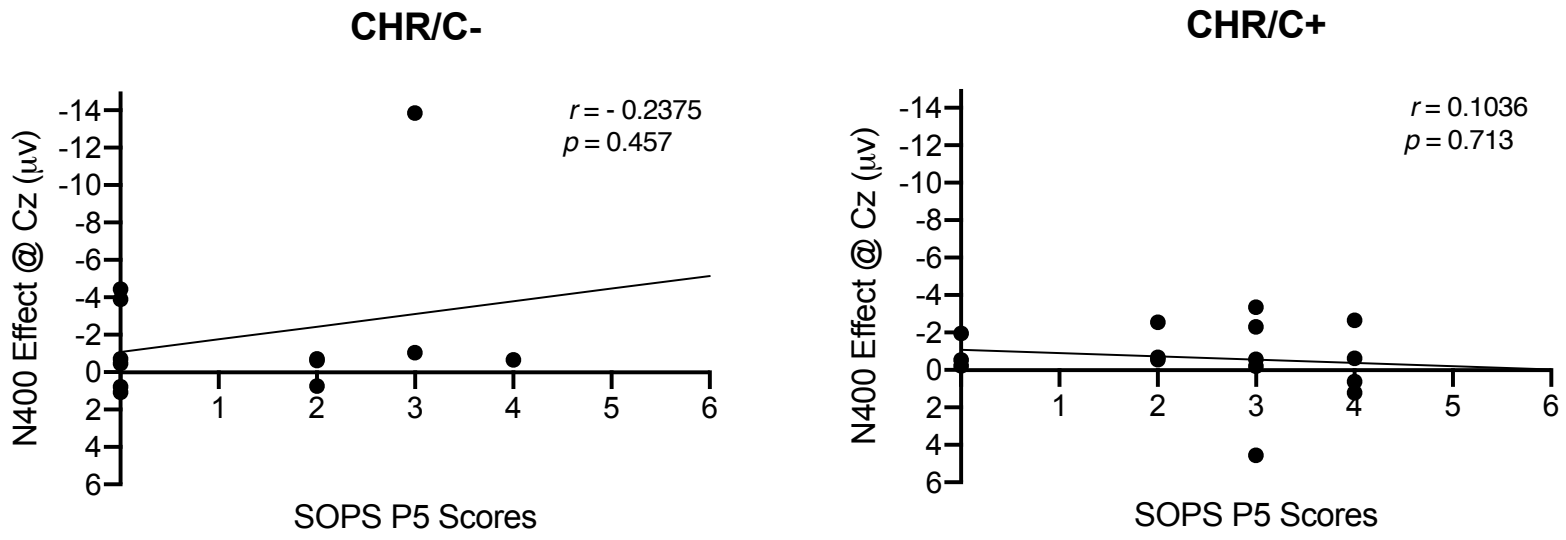

Figure 18. Correlations between SOPS P5 scores (Disorganized Communication) and N400 semantic priming effect at the short SOA.

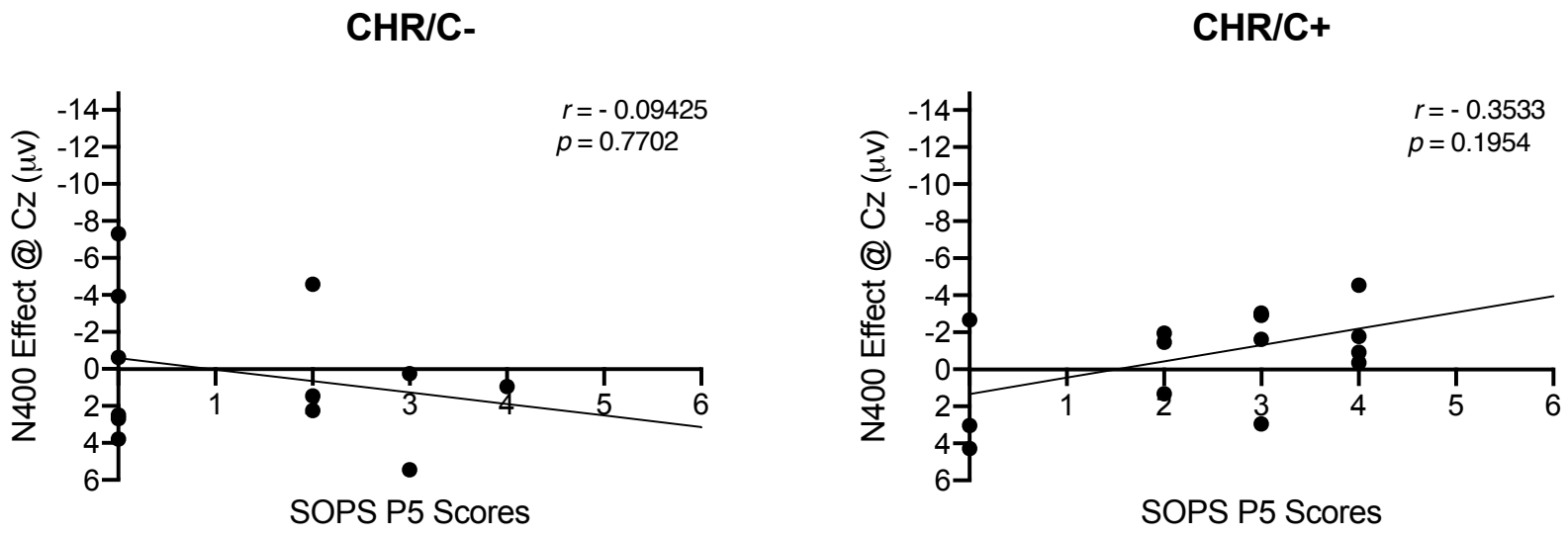

Figure 19. Correlations between SOPS P5 scores (Disorganized Communication) and N400 semantic priming effect at the long SOA.

6. Discussion

In this study, we aimed to better understand the effects of cannabis use on individuals at clinical high-risk for psychosis by using an N400 ERP index of semantic priming. We hypothesized that we would observe deficits in a graded fashion, such that cannabis-using CHR individuals would be the most impaired, followed by non-cannabis using CHR individuals, then healthy cannabis users and finally, non-cannabis-using healthy controls, who would exhibit normal semantic priming effects. However, our results did not support this hypothesis, as we observed no significant differences between any of these four groups in N400 amplitudes to related or unrelated targets, or N400 semantic priming effects at either SOA.

6.1. Effects of Cannabis Use on the N400 Semantic Priming Effect

When looking at our effect sizes for these analyses, we observed that we were likely underpowered to observe differences between cannabis-using CHR individuals and the other three groups at the short SOA. Our analyses revealed that this group may be the most impaired in semantic priming effects at the short SOA. At the long SOA, we observed the largest effect size between non-cannabis-using healthy controls and both CHR groups. When we collapsed our four groups into two larger groups based on diagnosis, there was a trend towards CHR participants being more impaired than controls, such that CHR individuals had smaller semantic priming effects than controls at the long SOA, regardless of cannabis use. Finally, we observed small effect sizes between the two healthy groups and between the two CHR groups at the long SOA. Thus, although we found no significant differences in N400 semantic priming between our groups, a study with a larger sample size might have shown results similar to those of Lepock et al., (2019), where we would have observed that all CHR individuals had smaller than normal semantic priming effects over longer intervals, with cannabis use not further impairing either of

these groups. In addition to this, over shorter intervals between meaningful stimuli, cannabis-using CHR participants may be more impaired than the other groups, suggesting a negative effect of cannabis use at least on automatic semantic network activation.

Our results, and those of Lepock et al. (2019), parallel those seen in the preponderance of research on N400 semantic priming in schizophrenia. Generally, schizophrenia patients exhibit deficits in semantic processing at both short and long SOAs, suggesting an inability to use contextual information to facilitate processing of meaningful stimuli (Condray et al., 2003; Hokama et al., 2003; Kiang et al., 2012, 2011, 2008; Kreher et al., 2009; Matsumoto et al., 2001; Matsuoka et al., 1999; Niznikiewicz et al., 2010; Ryu et al., 2012). The results of the present study, alongside those of Lepock et al. (2019), suggest that CHR individuals exhibit deficits in semantic priming similar to those of schizophrenia patients. This implies that the onset of these semantic priming deficits follows a similar trajectory to the onset of psychotic-like symptoms, indicating that N400 measures of semantic processing may reflect neurophysiological mechanisms of psychopathology of psychotic disorders.

Our main exploratory observation was that there was a trend towards a significant difference between CHR individuals and healthy controls in semantic priming effect at the long SOA, regardless of cannabis use history. This is in contrast to the only other study of N400 semantic priming effects in healthy cannabis users (Kiang et al., 2013), which observed a semantic over-activation of related, unrelated and nonwords targets leading to smaller (less negative) amplitudes to these stimuli, but no semantic priming deficits. The authors postulated that this could be explained by a trend towards a general increase in the amplitude of positive post-N400 waveform, which may have overlapped with the N400 epoch. This late positivity occurs when attempts are made to reanalyze and revaluate stimuli when they differ from what

was predicted. As such, cannabis users in this study may have made stronger or more unlikely predictions for the upcoming target word, and when confronted with actual target, a positivity would occur there was a mismatch in expectations. We did not observe such differences between our cannabis-using and non-using healthy control groups, and this may depend on our cannabis-using groups relatively higher years of education and older age compared to Kiang et al.'s sample. Our healthy cannabis users may have had similar capabilities compared to non-using controls, as their real-world functioning may have been more similar to this group, allowing them to make stronger semantic predictions.

Comparing healthy cannabis users and non-users, one behavioral study employed a lexical decision task to measure semantic priming using reaction times without the N400 ERP by testing participants on two separate occasions (Morgan, Rothwell, Atkinson, Mason, & Curran, 2010). The first session measured effects 15 minutes after smoking and the second session measured sub-acute effects of cannabis when participants were drug-free for 24 hours. The main finding was that cannabis users exhibited hyperpriming at the short SOA when under the influence of cannabis compared to being drug-free and also had greater priming than controls at the long SOA when unintoxicated. This suggests that acute cannabis intoxication leads to abnormalities in automatic semantic priming, and abstinence leads to less abnormalities in priming at the long SOA. These results suggest that cannabis has some similarities in the occurrence of hyperpriming at the short SOA observed in schizophrenia patients (Kreher et al., 2009; Mathalon et al., 2002, 2010; Ryu et al., 2012).

In our study, at the short SOA, we observed large effect sizes between our cannabis-using CHR group and the other three groups, suggesting that this group was more impaired than the others but our small sample size did not allow for us to significantly detect these differences. Our

participants did not exhibit hyperpriming, and instead we observed smaller semantic priming effects at shorter prime-target intervals. Our results still support the notion that cannabis use causes some degree of impairment at the short SOA, especially in CHR individuals. In contrast at the long SOA, cannabis use did not further impair semantic priming in either of our groups, which is similar to the results of Morgan et al. (2010), suggesting that controlled semantic network activation is not negatively affected by long-term cannabis use. Of course, because the aforementioned study used behavioral outcome measures of semantic priming (reaction times), it is not directly analogous to our results using the N400 ERP index, which provides neurophysiological data on semantic processing. This may explain why we did not see the same deficits in our sample of healthy cannabis users as Morgan et al. (2010). It is worth noting that the N400 may provide more sensitive and direct indices of semantic priming compared to behavioral measures (Kuperberg, Kreher, & Ditman, 2010), as discrepancies in results between these two measures have been previously observed (Besche-Richard et al., 2014).

Taken together, the results of the aforementioned studies suggest that cannabis use robustly causes some level of abnormalities in semantic priming reaction times. One reason we may not have observed such results in our study was that our sample was neither acutely intoxicated or abstinent for 24 hours. Our participants may have been in an intermediate state of intoxication, such that the majority had used within the past 12 hours but by this time, the effects of intoxication had worn off but they were also not completely abstinent, so the effects were not negligible either. This confound may have prevented us from seeing any differences within this group when compared to the non-using group.

Our results may be further explained by the differential effects of cannabinoids, especially Δ9-THC. Research has shown that cannabinoids affect the dopaminergic system,

which is spread throughout the prefrontal cortex (PFC) and temporal lobe (Bloomfield, Ashok, Volkow, & Howes, 2016). Δ9-THC binds to CB1 receptors in the endocannabinoid system, which, alongside reducing GABAergic inhibition in cortical pyramidal neurons, also increases the neurotransmission of dopamine in areas such as the PFC and temporal lobe (Bloomfield et al., 2016). This may improve or regulate semantic priming effects as indexed by the N400 at the long SOA, or could in turn, interfere with the balance of this system, and cause deficits that we observed at the short SOA. It is widely understood that either too much or too little dopaminergic activity in the PFC is associated with impairments in executive functions. However, we cannot go beyond speculation of pharmacological basis of our results, given that we did not directly measure dopaminergic activity in our participants.

Taken together, our results suggest that at shorter time intervals, automatic semantic network activation may be impaired in cannabis-using CHR, perhaps due to the additive deficits caused by the CHR syndrome and long-term cannabis use. This suggests that more basic processes involved at shorter prime-target intervals, such as working memory and recognition, may be impaired in CHR, and this impairment is further exacerbated by cannabis use, which has been observed previously in healthy controls (Radhakrishnan et al., 2014). However, at longer time intervals reflecting more conscious use of contextual information, we did not see deficits due to cannabis use in either our healthy control group or our CHR group. The implies that controlled semantic processing is not negatively affected by long-term cannabis use, and only diagnosis (healthy versus CHR) caused the deficits we observed.

6.2. Exploratory Findings

We aimed to explore correlations between semantic priming effects and working memory and verbal fluency to better understand the processes involved in semantic processing. We

hypothesized that we would see strongest correlations in our most impaired groups, based on the premise that working memory and verbal fluency contribute to semantic priming. As such, we hypothesized that these correlations would be strongest among the cannabis-using CHR group.

In contrast with our first hypothesis, we observed a significant correlation between greater verbal working memory capacity and smaller semantic priming effects at the short SOA in the healthy, non-cannabis-using group. In line with our hypothesis, we observed a correlation between greater verbal fluency and larger semantic priming effects at the long SOA, in the cannabis-using CHR group only.

Working memory and semantic priming effects have been previously found to positively correlate with each other in healthy individuals (Gunter, Jackson, & Mulder, 1995). Using congruent versus incongruent words in their sentence contexts, Gunter et al. (1995) observed that in conditions requiring high working memory load, individuals with greater working memory capacity exhibited larger N400 congruency effects compared to those with lower working memory capacity. This suggests that working memory performance is associated with activation of semantically related concepts, and that deficits in working memory capacity may lead to deficits in efficiently processing meaningful information.

We observed the opposite relationship in our healthy non-cannabis-using control group, where greater scores on a verbal working memory task were associated with smaller N400 semantic priming effects at the short SOA. One reason for this discrepancy may be due to the difference in paradigms, as Gunter et al. (1995) used congruent and incongruent words within a sentence paradigm, whereas we employed a prime-target word-pair task. Additionally, our task did not require an explicit need for working memory resources because our prime-target stimuli were presented in rapid succession, with less of a requirement of reading and comprehension

skills than that of Gunter et al. (1995). To our knowledge, there are no other studies that have examined the relationship between verbal working memory and N400 semantic priming in healthy individuals using a word-pair paradigm; thus, further research is required to determine whether our finding is more generally replicable.

Research comparing performance on verbal working memory tasks in CHR individuals versus healthy controls has found that overall, the former group is significantly impaired when compared to the latter (Bora et al., 2014; Fusar-Poli et al., 2012; Hauser et al., 2017; Giuliano et al., 2012; Zheng et al., 2018). In healthy-cannabis users, both short-term and long-term use has been associated with deficits in working memory (Bhattacharyya & Schoeler, 2013; Cohen et al., 2019; Ranganathan & D'Souza, 2006; Solowij & Battisti, 2008; Vo, Schacht, Mintzer, & Fishman, 2014). While we did not observe any significant differences in verbal working memory scores between any of our groups due to small sample sizes, it is worth noting that the literature provides evidence that both individuals at the CHR state and cannabis users are impaired in their working memory capacity. This may provide evidence that targeting the improvement of this cognitive ability may be a useful treatment option in CHR individuals to prevent conversion to psychosis, as schizophrenia patients have also been found to exhibit severe deficits in working memory (Forbes, Carrick, Mcintosh, & Lawrie, 2009). Further research is required to better understand how deficits in semantic priming may be related to deficits in working memory, and the effect of cannabis use on this relationship.

Moreover, we observed greater verbal fluency scores correlating with better semantic priming effects at the long SOA only in the CHR/C+ group. This test of verbal fluency, or category fluency, measures the ability to generate conceptually related items. Plausibly, this is related to semantic priming as indexed by the N400, where individuals facilitate processing by

preactivating related concepts in semantic memory. Previous studies in healthy controls found that better scores in verbal fluency tasks were correlated with larger semantic priming effects. For example, Federmeier, McLennan, De Ochoa, & Kutas (2002) employed a task where participants listened to sentences ending with expected words, unexpected words from same semantic category or unexpected words from a different category. Half the contexts were highly constraining; high constraint sentences referred to those where there was a single, highly probable ending, and low constraint sentences referred to those that had at least one preferred ending, but a wide range of possible endings that were close competitors. They found that individual variation within the older group was explained by scores on a verbal fluency task. Specifically, older adults who were successful in generating more category members elicited larger N400 reductions to within-category violations in high vs. low constraint texts. A similar finding was observed in the younger group.

We did not observe any significant differences in verbal fluency across any of the groups. This is consistent with findings from previous studies that cannabis-using and non-using healthy individuals do not differ on tests of verbal fluency (Bogaty, Lee, Hickie, & Hermens, 2018; Crean et al., 2011) although other studies have found that acute administration of Δ9-THC causes deficits in verbal fluency (D'Souza et al., 2004). However, CHR individuals perform worse on these tasks compared to controls (Hauser et al., 2017; Hwang et al., 2019) and performance on this task has been shown to be a reliable associate of conversion status (Hauser et al., 2017). Those CHR individuals who do not convert to a psychotic episode and remit exhibit no differences when compared to controls on tasks of verbal fluency (Lee et al., 2014). In fact, as CHR symptoms improve in this subset of the population, their performance on verbal fluency tasks also improves over time. In contrast, CHR individuals who continue to experience

attenuated psychotic symptoms experience a decline in verbal fluency. The strong correlation we found between semantic priming effects and verbal fluency in the cannabis-using CHR group, suggests that these two processes share an underlying mechanism that is impaired in this group.

Finally, we aimed to see whether symptoms such as delusions and disorganized communication correlated with deficits in CHR. Contrary to our hypotheses, we did not observe any significant correlations in either CHR group. As studies like those of Kiang et al. (2013) observed that healthy cannabis users exhibited N400 abnormalities that correlated with schizotypal symptoms, we also expected that we would see similar results to a greater degree in our cannabis CHR group. However, our findings do not support the hypothesis that semantic priming deficits underlie psychosis-like symptoms in CHR patients.

7. Strengths of the Study

Regardless of the fact that we observed negative findings that did not corroborate our hypotheses, there are several strengths of this study that should be considered. Firstly, we had four groups in our design that allowed us to understand the effects of cannabis use on the N400 priming effect in CHR individuals. By having two healthy control groups and two CHR groups, both of which are divided based on their cannabis use, we were able to make relatively robust conclusions based on our findings. Additionally, we ensured that our non-cannabis using groups had never used cannabis, as opposed to being occasional users. Having a clean sample within this group and ensuring that none of these individuals had used cannabis in the past month removed the possibility of a potential confounder. The fact that our cannabis groups consisted of people who used a significant amount of cannabis and most of whom also met for cannabis dependence gave us a way to study the chronic effects of cannabis.

Furthermore, when we collapsed our four groups into two larger groups based only on CHR versus healthy status, our results corroborated those of Lepock et al. (2019) even with the addition of participants not used in the original sample. This further supports the notion that CHR individuals experience deficits in processing meaningful stimuli similar to those of schizophrenia patients.

One of the main strengths of our study is the use of electroencephalographic event-related brain potentials. ERPs have a good temporal resolution, giving us a real-time window into cognitive pathways of meaning processing during a continuous EEG recording. Additionally, the N400 ERP task has an advantage of not being affected by motor reaction times which may be a potential confound in patient populations.

8. Limitations

We experienced several limitations in this study that may have prevented us from observing significant results. Firstly, we had four groups with small sample sizes and the low power of the statistical analyses may have prevented us from detecting potential differences between groups, if they even existed.

Additionally, our cannabis-using CHR group was very heterogeneous such that it included both past and present cannabis users. This may have confounded our results in that the past users may have been more similar to non-cannabis using CHR, and this would have confounded any effects we observed in the CHR/C+ by making this group more “normal”. This heterogeneity was due to the difficulty in recruiting present cannabis-using CHR, so it was an unavoidable limitation given the timeframe of this project.

Because of the partial retrospective nature of this study, we had missing data for a few of our participants for various assessments, including nicotine use as well as recent urine drug

screen data. Although we had data within the past month of cannabis use, it would have made us more confident if we had urine drug screen results. Additionally, while we accounted for some of the missing data on nicotine use and addiction in participants by cross-referencing with data collected from other studies, empirical data collected at the time of our experiment would have made our results more valid and reliable.

Although the differences were not statistically significant, our cannabis groups did vary in their total cannabis exposure, such that the healthy cannabis-using group had greater mean exposure than cannabis-using CHR. This may have been because the control group was older than the CHR group, although this was not statistically significant, and increased cannabis exposure would make sense due to this difference. We also were unable to account for precise data on acute exposure for all of our cannabis-using participants. If we would have been able to account for this, we could better understand any potential acute effects of cannabis on the N400 semantic priming task and performance.

Additionally, not all of our cannabis-using participants met criteria for a cannabis dependence disorder. To better understand psychological and functional dependence we could use other assessments such as the CUDIT-R (Adamson et al., 2010) which gives us better insight into functional symptoms of cannabis use, in conjunction with the Timeline Followback Method and the SCID-IV. Moreover, our urine drug screen panel was not as sensitive as some other panels that are currently available, which give us more detailed, qualitative results on Δ9-THC content and by extension, recency of use.

Age was significantly different between our groups such that the cannabis-using CHR group was older than the non-cannabis using CHR group. While we did not observe any effects of age in the overall analyses, age does influence the N400 such that older age accounts for

semantic priming deficits. Older age may also account for differences (although non-significant) in cannabis exposure, which is another potential confound. By controlling for all demographic variables, we can avoid the potential complications confounds may bring to the analysis.

Finally, the greatest limitation we encountered was that our study was cross-sectional in nature. A longitudinal methodology may have provided us with more conclusive information about the relationship between cannabis use and semantic priming in CHR individuals and how this relates to conversion risk. Administering the N400 task across various points in time may have also provided us with more information on whether semantic priming is a stable biomarker or whether it is dynamic and can change depending symptom severity and global functioning.

9. Conclusions

In summary, we aimed to observe the effects of cannabis use on the N400 index of semantic priming in individuals at clinical high-risk for psychosis to better understand the trajectory of this disorder on the schizophrenia spectrum and factors that may exacerbate these deficits. Overall, we found that CHR patients exhibited a trend towards smaller N400 semantic priming effects than controls at a relatively long (750-ms) prime-target SOA. We did not, however, observe any differences in overall N400 amplitudes or semantic priming effects between our four groups consisting of healthy control participants and CHR participants, which were further divided into regular cannabis users and non-users. We believe that we were underpowered to see smaller semantic priming effects in our cannabis-using CHRs at short (350-ms) prime-target SOA, as we observed medium-to-large effect sizes across comparisons with the other three groups. Furthermore, we observed an exploratory association in non-cannabis-using healthy controls between larger semantic priming effects and reduced working memory, and smaller semantic priming effects and lower verbal fluency in cannabis-using CHR individuals.

This suggests that cannabis use may make unique contributions to cognitive measures of semantic fluency in this group. Further research is required to better understand the effects of cannabis use on the association of verbal working memory and semantic priming effects in CHR individuals.

10. Future Directions

Given the plethora of research in schizophrenia patients alongside the relatively new research in CHR individuals, future studies using the N400 should seek to include comparisons between healthy controls, CHR, and first-episode psychosis individuals, with a cannabis-using group and non-using group within each of these cohorts. Recruiting a sufficiently powered sample in each group will allow for us to better understand the trajectory of N400 deficits within the schizophrenia spectrum.

Furthermore, conducting studies with the same methodology in various sites across the world would be interesting as this would permit us to account for confounds such as sampling bias based on geographic location and as well as urbanization.

To better understand the effects of cannabis on conversion rates to psychosis as well as the longitudinal reliability of the N400, we could have participants return at one-, two- and three-year follow-up assessments. We may be able to contribute to research on how cannabis use increases risk of conversion among CHR individuals by providing novel findings about whether this is reflected in their N400 semantic priming responses. This would also be valuable in contributing to a potential algorithmic calculation of psychosis risk if we were to combine it with other putative risk factors (Cannon et al., 2016), including other ERP measures, such as the MMN and P300 (Atkinson, Michie, & Schall, 2012; Bodatsch et al., 2011; Lepock et al., 2018). As such, future studies should seek to better elucidate the effects of cannabis use in disorders on

the schizophrenia spectrum. With the lack of research in this area, it would be valuable to learn more about which ERPs and the associated processes are affected and what these potential impairments look like when combining cannabis use and schizophrenia/CHR status.

In addition, to gain a more sensitive and quantitative analysis of urine Δ9-THC content, we could use urine drug panels such as NarcoCheck that would allow us to obtain exact amounts of cannabis metabolites in participants' urine, allowing us to control for recent intoxication.

Future studies should also study the acute vs. abstinent effects of cannabis on the N400 index of semantic priming. The N400 task requires attention, memory and efficient information processing, which are abilities affected by acute and chronic cannabis use. If we could better understand what the effects of cannabis are on this ERP, we may be better equipped to answer questions related to which brain regions are involved in this process as well as which neurotransmitters may be involved. Moreover, the effects of other commonly-used substances, such as nicotine, alcohol, and cocaine, should be further elucidated in their effects on the various ERPs.

Research should also seek to combine ERPs with other imaging techniques, such as Positron Emission Tomography, which would allow us to understand neuropharmacological pathways associated with cognitive event-related potentials. Combining PET with the temporal sensitivity of ERPs would allow for a more cohesive insight into deficits related to language processing in cannabis users on the schizophrenia spectrum, and may improve on our knowledge about specific pathways by which cannabis affects symptoms and functioning in psychotic disorders.

11. References

Addington, J. (2013). Identifying a treatable psychosis-risk cohort. *Canadian Journal of Psychiatry*, *58*(1), 3–4. https://doi.org/10.1177/070674371305800102

Addington, J., & Heinssen, R. (2012). Prediction and Prevention of Psychosis in Youth at Clinical High Risk. *Annual Review of Clinical Psychology*, *8*, 269–289. https://doi.org/10.1146/annurev-clinpsy-032511-143146

American Psychiatric Association. (2000). Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. DSM-IV-TR. In *American Journal of Critical Care*. https://doi.org/10.1176/dsm 10.1176/appi.books.9780890420249.dsm-iv-tr

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders (5th Edition). In *American Journal of Psychiatry*. https://doi.org/10.1176/appi.books.9780890425596.744053

Anderson, J. E., & Holcomb, P. J. (1995). Auditory and visual semantic priming using different stimulus onset asynchronies: an event-related brain potential study. *Psychophysiology*, *32*(2), 177–190.

Andréasson, S., Engström, A., Allebeck, P., & Rydberg, U. (1978). Cannabis and Schizophrenia: A Longitudinal Study of Swedish Conscripts. *Lancet*, *2*(8574), 1483–1486.

Arendt, M., Rosenberg, R., Foldager, L., Perto, G., & Munk-Jorgensen, P. (2005). Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases. *The British Journal of Psychiatry : The Journal of Mental Science*, *187*, 510–515. https://doi.org/10.1192/bjp.187.6.510

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T. E. (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ (Clinical Research Ed.)*, *325*(7374), 1212–1213. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12446537%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC135493

Arseneault, L., Cannon, M., Ton, J. W. I. T., & Ay, R. M. M. (2004). Causal association between cannabis and psychosis: examination of the evidence. *British Journal of Psychiatry*, *184*, 110–117.

Ashton, H. C. (2001). Pharmacology and effects of cannabis a brief review. *British Journal of Psychiatry*, *178*, 101–106. https://doi.org/10.1192/bjp.178.2.101

Atkinson, R. J., Michie, P. T., & Schall, U. (2012). Duration Mismatch Negativity and P3a in First-Episode Psychosis and Individuals at Ultra-High Risk of Psychosis. *Biological Psychiatry*, *71*, 98–104. https://doi.org/10.1016/j.biopsych.2011.08.023

Bechdolf, A., Thompson, A., Nelson, B., Cotton, S., Simmons, M. B., Amminger, G. P., … Yung, A. R. (2010). Experience of trauma and conversion to psychosis in an ultra-high-risk (prodromal) group. *Acta Psychiatrica Scandinavica*, *121*(5), 377–384. https://doi.org/10.1111/j.1600-0447.2010.01542.x

Becker, C. A. (1980). Semantic context effects in visual word recognition : An analysis of semantic strategies. *Memory & Cognition*, *8*(6), 493–512.

Benes, F. M. & Berretta, S. (2001). GABAergic Interneurons : Implications for Understanding Schizophrenia and Bipolar Disorder. *Neuropsychopharmacology*, *25*(01), 1–27.

Beres, A. M. (2017). Time is of the Essence: A Review of Electroencephalography (EEG) and Event-Related Brain Potentials (ERPs) in Language Research. *Applied Psychophysiology Biofeedback*, *42*(4), 247–255. https://doi.org/10.1007/s10484-017-9371-3

Besche-Richard, C., Iakimova, G., Hardy-Baylé, M. C., & Passerieux, C. (2014). Behavioral and brain measures (N400) of semantic priming in patients with schizophrenia: Test-retest effect in a longitudinal study. *Psychiatry and Clinical Neurosciences*, *68*(5), 365–373. https://doi.org/10.1111/pcn.12137

Bhattacharyya, S., & Schoeler, T. (2013). The effect of cannabis use on memory function: an update. *Substance Abuse and Rehabilitation*, 11. https://doi.org/10.2147/sar.s25869

Blishen, B., Carroll, W., & Moore, C. (1987). The 1981 socioeconomic index for occupations in Canada. *The Canadian Review of Sociology and Anthropology*, *24*(4), 465–488.

Bloomfield, M. A. P., Ashok, A. H., Volkow, N. D., & Howes, O. D. (2016). The effects of Δ9-tetrahydrocannabinol on the dopamine system. *Nature*, *539*(7629), 369–377. https://doi.org/10.1038/nature20153

Bodatsch, M., Ruhrmann, S., Wagner, M., Müller, R., Schultze-Lutter, F., Frommann, I., … Brockhaus-Dumke, A. (2011). Prediction of Psychosis by Mismatch Negativity. *Biological Psychiatry*, *69*, 959–966. https://doi.org/10.1016/j.biopsych.2010.09.057

Bogaty, S. E. R., Lee, R. S. C., Hickie, I. B., & Hermens, D. F. (2018). Meta-analysis of neurocognition in young psychosis patients with current cannabis use. *Journal of Psychiatric Research*, *99*(June 2017), 22–32. https://doi.org/10.1016/j.jpsychires.2018.01.010

Bora, E., Lin, A., Wood, S. J., Yung, A. R., Mcgorry, P. D., & Pantelis, C. (2014). Cognitive deficits in youth with familial and clinical high risk to psychosis: A systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, *130*(1), 1–15. https://doi.org/10.1111/acps.12261

Boyd, J. E., Patriciu, I., McKinnon, M. C., & Kiang, M. (2014). Test-retest reliability of N400 event-related brain potential measures in a word-pair semantic priming paradigm in patients with schizophrenia. *Schizophrenia Research*, *158*(1–3), 195–203. https://doi.org/10.1016/j.schres.2014.06.018

Brown, C., & Hagoort, P. (1993). The Processing Nature of the N400 : Evidence fiom Masked Priming. *Journal of Cognitive Neuroscience*, *5*(1), 34–44.

Buchy, L., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., McGlashan, T. H., Perkins, D. O., … Addington, J. (2015). Substance use in individuals at clinical high risk of psychosis. *Psychological Medicine*, *45*(11), 2275–2284. https://doi.org/10.1017/S0033291715000227

Cannon, T. D., Yu, C., Addington, J., Bearden, C. E., Cadenhead, K. S., Cornblatt, B. A., … Al., E. (2016). An Individualized Risk Calculator for Research in Prodromal Psychosis. *Am J Psychiatry*, *173*, 980–988. https://doi.org/10.1176/appi.ajp.2016.15070890

Carney, R., Cotter, J., Firth, J., Bradshaw, T., & Yung, A. R. (2017). Cannabis use and symptom severity in individuals at ultra high risk for psychosis: a meta-analysis. *Acta Psychiatrica Scandinavica*, *136*(1), 5–15. https://doi.org/10.1111/acps.12699

Casadio, P., Fernandes, C., Murray, R. M., & Di Forti, M. (2011). Neuroscience and Biobehavioral Reviews Cannabis use in young people : The risk for schizophrenia. *Neuroscience and Biobehavioral Reviews*, *35*, 1779–1787. https://doi.org/10.1016/j.neubiorev.2011.04.007

Chaiyakunapruk, N., Chong, H. Y., Teoh, S. L., Wu, D. B.-C., Kotirum, S., & Chiou, C.-F. (2016). Global economic burden of schizophrenia: a systematic review. *Neuropsychiatric Disease and Treatment*, 357. https://doi.org/10.2147/NDT.S96649

Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., Scott, J. G., … Whiteford, H. A. (2018). Global epidemiology and burden of schizophrenia: Findings from

the global burden of disease study 2016. *Schizophrenia Bulletin*, *44*(6), 1195–1203. https://doi.org/10.1093/schbul/sby058

Cohen, K., Weizman, A., & Weinstein, A. (2019). Modulatory effects of cannabinoids on brain neurotransmission. *European Journal of Neuroscience*, 1–24. https://doi.org/10.1111/ejn.14407

Compton, M. T., Kelley, M. E., Ramsay, C. E., Pringle, M., Goulding, S. M., Esterberg, M. L., … Walker, E. F. (2009). Pre-Onset Substance Use and Age At Onset. *Am J Psychiatry*, *166:11*(November), 1251–1257.

Condray, R., Siegle, G. J., Cohen, J. D., Kammen, D. P. Van, & Steinhauer, S. R. (2003). Automatic Activation of the Semantic Network in Schizophrenia : Evidence from Event-Related Brain Potentials. *Biological Psychiatry*, *54*, 1134–1148. https://doi.org/10.1016/S0006-3223(03)00699-1

Corcoran, C. M., Kimhy, D., Stanford, A., Khan, S., Walsh, J., Thompson, J., … Malaspina, D. (2008). Temporal association of cannabis use with symptoms in individuals at clinical high risk for psychosis. *Schizophrenia Research*, *106*(2–3), 286–293. https://doi.org/10.1016/j.schres.2008.08.008

Cornblatt, B. A., Auther, A. M., Smith, C. W., Zinberg, J., Bearden, C. E., & Cannon, T. D. (2007). Preliminary Findings for Two New Measures of Social and Role Functioning in the Prodromal Phase of Schizophrenia. *Schizophrenia Bulletin*, *33*(3), 688–702. https://doi.org/10.1093/schbul/sbm029

Crane, N. A., Schuster, R. M., Fusar-poli, P., & Gonzalez, R. (2013). Effects of Cannabis on Neurocognitive Functioning : Recent Advances , Neurodevelopmental Influences , and Sex Differences. *Neuropsychology Review*, *23*, 117–137. https://doi.org/10.1007/s11065-012-9222-1

Crean, R. D., Tapert, S. F., Minassian, A., MacDonald, K., Crane, N. A., & Mason, B. J. (2011). Effects of chronic, heavy cannabis use on executive functions. *Journal of Addiction Medicine*, *5*(1), 9–15. https://doi.org/10.1097/ADM.0b013e31820cdd57

Curran, H. V., Freeman, T. P., Mokrysz, C., Lewis, D. A., Morgan, C. J. A., & Parsons, L. H. (2016). Keep off the grass? Cannabis, cognition and addiction. *Nature Reviews Neuroscience*, *17*(5), 293–306. https://doi.org/10.1038/nrn.2016.28

D'Souza, D. C. (2007). Cannabinoids and psychosis. *International Review of Neurobiology*, *78*, 289–326. https://doi.org/10.1080/09540260902782802

D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. Te, … Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis. *Neuropsychopharmacology*, *29*(8), 1558–1572. https://doi.org/10.1038/sj.npp.1300496

D'Souza, D. C., Sewell, R. A., & Ranganathan, M. (2009). Cannabis and psychosis/schizophrenia: Human studies. *European Archives of Psychiatry and Clinical Neuroscience*, *259*(7), 413–431. https://doi.org/10.1007/s00406-009-0024-2

Debruille, J. B. (2007). The N400 potential could index a semantic inhibition. *Brain Research Reviews*, *56*(2), 472–477. https://doi.org/10.1016/j.brainresrev.2007.10.001

DeLong, K. A., Urbach, T. P., & Kutas, M. (2005). Probabilistic word pre-activation during language comprehension inferred from electrical brain activity. *Nature Neuroscience*, *8*(8), 1117–1121. https://doi.org/10.1038/nn1504

Di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S. A., … Murray, R. M. (2014). Daily Use, Especially of High-Potency Cannabis, Drives the Earlier Onset of Psychosis in

Cannabis Users. *Schizophrenia Bulletin*, *40*(6), 1509–1517. https://doi.org/10.1093/schbul/sbt181

Donoghue, K., Doody, G. A., Murray, R. M., Jones, P. B., Morgan, C., Dazzan, P., … Maccabe, J. H. (2014). Cannabis use , gender and age of onset of schizophrenia : Data from the ÆSOP study. *Psychiatry Research*, *215*, 528–532. https://doi.org/10.1016/j.psychres.2013.12.038

Egerton, A., Howes, O. D., Houle, S., McKenzie, K., Valmaggia, L. R., Bagby, M. R., … Mizrahi, R. (2017). Elevated Striatal Dopamine Function in Immigrants and Their Children: A Risk Mechanism for Psychosis. *Schizophrenia Bulletin*, *43*(2), 293–301. https://doi.org/10.1093/schbul/sbw181

Eggan, S. M., & Lewis, D. A. (2007). Immunocytochemical Distribution of the Cannabinoid CB 1 Receptor in the Primate Neocortex : A Regional and Laminar Analysis. *Cerebral Cortex*, *17*, 175–191. https://doi.org/10.1093/cercor/bhj136

ElSohly, M. A., & Slade, D. (2005). Chemical constituents of marijuana: The complex mixture of natural cannabinoids. *Life Sciences*, *78*(5), 539–548. https://doi.org/10.1016/j.lfs.2005.09.011

Fakhoury, M. (2017). Role of the Endocannabinoid System in the Pathophysiology of Schizophrenia. *Molecular Neurobiology*, *54*(1), 768–778. https://doi.org/10.1007/s12035-016-9697-5

Federmeier, K. D. (2007). Thinking ahead : The role and roots of prediction in language comprehension. *Psychophysiology*, *44*, 491–505. https://doi.org/10.1111/j.1469-8986.2007.00531.x

Federmeier, K. D., & Kutas, M. (2000). Electrophysiology reveals semantic memory use in language comprehension. *Trends in Cognitive Sciences*, *4*(12), 463–470. https://doi.org/10.1016/S1364-6613(00)01560-6

Federmeier, K. D., & Kutas, M. (2005). Aging in context : Age-related changes in context use during language comprehension. *Psychophysiology*, *42*, 133–141. https://doi.org/10.1111/j.1469-8986.2005.00274.x

Federmeier, K. D., McLennan, D. B., De Ochoa, E., & Kutas, M. (2002). The impact of semantic memory organization and sentence context information on spoken language processing by younger and older adults: an ERP study. *Psychophysiology*, *39*(2), 133–146. https://doi.org/10.1017/S0048577202001373

Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2015). Psychosocial sequelae of cannabis use and implications for policy : findings from the Christchurch Health and Development Study. *Social Psychiatry and Psychiatric Epidemiology*, *50*, 1317–1326. https://doi.org/10.1007/s00127-015-1070-x

Fergusson, D. M., Horwood, L. J., & Swain-Campbell, N. R. (2003). Cannabis dependence and psychotic symptoms in young people. *Psychological Medicine*, *33*, 15–21.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (SCID-I/P, 11/2002 revision). In *for DSMIV*. https://doi.org/M

Fletcher, P. C., & Frith, C. D. (2009). Perceiving is believing : a Bayesian approach to explaining the positive symptoms of schizophrenia. *Nature Reviews Neuroscience*, *10*(48–58). https://doi.org/10.1038/nrn2536

Forbes, N. F., Carrick, L. A., Mcintosh, A. M., & Lawrie, S. M. (2009). Working memory in schizophrenia : a meta-analysis. *Psychological Medicine*, *39*, 889–905. https://doi.org/10.1017/S0033291708004558

Ford, J. M., Krystal, J. H., & Mathalon, D. H. (2007). Neural Synchrony in Schizophrenia: From Networks to New Treatments. *Schizophrenia Bulletin*, *33*(4), 848–852. https://doi.org/10.1093/schbul/sbm062

Ford, J. M., & Mathalon, D. H. (2012). Anticipating the future : Automatic prediction failures in schizophrenia. *International Journal of Psychophysiology*, *83*, 232–239. https://doi.org/10.1016/j.ijpsycho.2011.09.004

Forti, M. Di, Morgan, C., Dazzan, P., Pariante, C., Mondelli, V., Marques, T. R., … Murray, R. M. (2009). High-potency cannabis and the risk of psychosis. *British Journal of Psychiatry*, *195*, 488–491. https://doi.org/10.1192/bjp.bp.109.064220

Fortin, D. A., & Levine, E. S. (2006). Differential Effects of Endocannabinoids on Glutamatergic and GABAergic Inputs to Layer 5 Pyramidal Neurons. *Cerebral Cortex*, *17*(1), 163–174. https://doi.org/10.1093/cercor/bhj133

Foti, D. J., Kotov, R., Guey, L. T., & Bromet, E. J. (2010). Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization. *American Journal of Psychiatry*, *167*(8), 987–993. https://doi.org/10.1176/appi.ajp.2010.09020189

Francis, W. N., & Kucera, H. (1982). *Frequency analysis of English usage.* Boston: Houghton Mifflin.

Fusar-Poli, P. (2017). The clinical high-risk state for psychosis (CHR-P), Version II. *Schizophrenia Bulletin*, *43*(1), 44–47. https://doi.org/10.1093/schbul/sbw158

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., … Yung, A. (2013). The psychosis high-risk state: A comprehensive state-of-the-art review. *Archives of General Psychiatry*, *70*(1), 107–120. https://doi.org/10.1001/jamapsychiatry.2013.269

Fusar-Poli, P., Deste, G., Smieskova, R., Barlati, S., Yung, A. R., Howes, O., … Borgwardt, S. (2012). Cognitive Functioning in Prodromal Psychosis. *Archives of General Psychiatry*, *69*(6), 562–571. https://doi.org/10.1001/archgenpsychiatry.2011.1592

Gage, S. H., Munafò, M. R., Macleod, J., Hickman, M., & Smith, G. D. (2015). Cannabis and psychosis. *The Lancet Psychiatry*, *2*, 380. https://doi.org/10.1016/S2215-0366(15)00108-X

Gage, S. H., Zammit, S., & Hickman, M. (2013). Stronger evidence is needed before accepting that cannabis plays an important role in the aetiology of schizophrenia in the population. *F1000 Medicine Reports*, *5*(2), 1–5. https://doi.org/10.3410/M5-2

Grant, I., Gonzalez, R., Carey, C. L., Natarajan, L., & Wolfson, T. (2003). Non-acute (residual) neurocognitive effects of cannabis use : A meta-analytic study. *Journal of TheInternational Neuropsychological Society*, *9*, 679–689.

Grotenhermen, F. (2003). Pharmacokinetics and Pharmacodynamics of Cannabinoids. *Clinical Pharmacokinetics*, *42*(4), 327–360.

Guerra, S., Ibáñez, A., Martín, M., Antonieta, M., Reyes, A., Mendoza, R., … Valdes, M. (2009). Brain and Cognition N400 deficits from semantic matching of pictures in probands and first-degree relatives from multiplex schizophrenia families. *Brain and Cognition*, *70*, 221–230. https://doi.org/10.1016/j.bandc.2009.02.004

Gunter, T. C., Jackson, J. L., & Mulder, G. (1995). Language, memory, and aging: An electrophysiological exploration of the N400 during reading of memory-demanding sentences. *Psychophysiology*, *32*(3), 215–229. https://doi.org/10.1111/j.1469-8986.1995.tb02951.x

Hagoort, P. (2008). The fractionation of spoken language understanding by measuring electrical and magnetic brain signals. *Philosophical Transactions of the Royal Society B*, *363*, 1055–

1069. https://doi.org/10.1098/rstb.2007.2159
Hagoort, P., Baggio, G., & Wlllems, R. M. (2009). Semantic unification. In *The Cognitive Neurosciences, 4th ed.* (pp. 819–835). Cambridge, MA, US: Massachusetts Institute of Technology.
Hajós, M., Hoffmann, W. E., & Kocsis, B. (2008). Activation of Cannabinoid-1 Receptors Disrupts Sensory Gating and Neuronal Oscillation : Relevance to Schizophrenia. *Biological Psychiatry*, *63*(11), 1075–1083. https://doi.org/10.1016/j.biopsych.2007.12.005
Hájos, N., Katona, I., Naiem, S. S., Mackie, K., Ledent, C., Mody, I., & Freund, T. F. (2000). Cannabinoids inhibit hippocampal GABAergic transmission and network oscillations. *European Journal of Neuroscience*. https://doi.org/10.1046/j.1460-9568.2000.00217.x
Hall, W., & Degenhardt, L. (2009). Adverse health effects of non-medical cannabis use. *The Lancet*, *374*(9698), 1383–1391. https://doi.org/10.1016/S0140-6736(09)61037-0
Hall, W., & Solowij, N. (1998). Adverse effects of cannabis. *The Lancet*, *352*, 1611–1616.
Hauk, O., Davis, M. H., Ford, M., & Pulvermu, F. (2006). The time course of visual word recognition as revealed by linear regression analysis of ERP data. *NeuroImage*, *30*, 1383–1400. https://doi.org/10.1016/j.neuroimage.2005.11.048
Hauk, O., & Pulvermu, F. (2004). Effects of word length and frequency on the human event-related potential. *Clinical Neurophysiology*, *115*, 1090–1103. https://doi.org/10.1016/j.clinph.2003.12.020
Hauser, M., Zhang, J. P., Sheridan, E. M., Burdick, K. E., Mogil, R., Kane, J. M., … Correll, C. U. (2017). Neuropsychological test performance to enhance identification of subjects at clinical high risk for psychosis and to be most promising for predictive algorithms for conversion to psychosis: A meta-analysis. *Journal of Clinical Psychiatry*. https://doi.org/10.4088/JCP.15r10197
Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. O. (1991). The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction*, *86*(9), 1119–1127.
Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Wittchen, H.-U., & van Os, J. (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ (Clinical Research Ed.)*, *330*(7481), 11. https://doi.org/10.1136/bmj.38267.664086.63
Henquet, C., Murray, R., Linszen, D., & van Os, J. (2005). The Environment and Schizophrenia : The Role of Cannabis Use. *Schizophrenia Bulletin*, *31*(3), 608–612. https://doi.org/10.1093/schbul/sbi027
Hill, H., Strube, M., Roesch-Ely, D., & Weisbrod, M. (2002). Automatic vs . controlled processes in semantic priming — differentiation by event-related potentials. *International Journal of Psychophysiology*, *44*, 197–218.
Hillyard, S. A., & Kutas, M. (1983). Electrophysiology of cognitive processing. *Annual Review of Psychology*, *34*, 33–61. https://doi.org/10.1146/annurev.ps.34.020183.000341
Hokama, H., Hiramatsu, K., Wang, J., Donnell, B. F. O., & Ogura, C. (2003). N400 abnormalities in unmedicated patients with schizophrenia during a lexical decision task. *International Journal of Psychophysiology*, *48*, 1–10. https://doi.org/10.1016/S0167-8760(02)00156-3
Holcomb, P. J., & McPherson, W. B. (1994). Event-related brain potentials reflect semantic priming in an object decision task. *Brain and Cognition*. https://doi.org/10.1006/brcg.1994.1014

Hwang, W. J., Lee, T. Y., Shin, W.-G., Kim, M., Kim, J., Lee, J., & Kwon, J. S. (2019). Global and Specific Profiles of Executive Functioning in Prodromal and Early Psychosis. *Frontiers in Psychiatry*, *10*(May), 1–8. https://doi.org/10.3389/fpsyt.2019.00356

J. Giuliano, A., Li, H., I. Mesholam-Gately, R., M. Sorenson, S., A. Woodberry, K., & J. Seidman, L. (2012). Neurocognition in the Psychosis Risk Syndrome: A Quantitative and Qualitative Review. *Current Pharmaceutical Design*. https://doi.org/10.2174/138161212799316019

Jackson, F., Foti, D., Kotov, R., Perlman, G., Mathalon, D. H., & Proudfit, G. H. (2014). An incongruent reality: The N400 in relation to psychosis and recovery. *Schizophrenia Research*, *160*(1–3), 208–215. https://doi.org/10.1016/j.schres.2014.09.039

Jeste, D. V., Palmer, B. W., Appelbaum, P. S., Golshan, S., Glorioso, D., Dunn, L. B., … Kraemer, H. C. (2007). A new brief instrument for assessing decisional capacity for clinical research. *Archives of General Psychiatry*. https://doi.org/10.1001/archpsyc.64.8.966

Johns, A. W. (2001). Psychiatric effects of cannabis. *British Journal of Psychiatry*, *178*, 116–122.

Jones, H. J., Gage, S. H., Heron, J., Hickman, M., Lewis, G., Munafò, M. R., & Zammit, S. (2018). Association of combined patterns of tobacco and cannabis use in adolescence with psychotic experiences. *JAMA Psychiatry*, *75*(3), 240–246. https://doi.org/10.1001/jamapsychiatry.2017.4271

Jones, J. D., Calkins, M. E., Scott, J. C., Bach, E. C., & Gur, R. E. (2017). Cannabis Use, Polysubstance Use, and Psychosis Spectrum Symptoms in a Community-Based Sample of U.S. Youth. *Journal of Adolescent Health*, *60*(6), 653–659. https://doi.org/10.1016/j.jadohealth.2017.01.006

Kahn, R. S., Sommer, I. E., Murray, R. M., Meyer-Lindenberg, A., Weinberger, D. R., Cannon, T. D., … Insel, T. R. (2015). Schizophrenia. *Nature Reviews Disease Primers*, *1*, 15067. Retrieved from https://doi.org/10.1038/nrdp.2015.67

Karila, L., & Reynaud, M. (2003). [Cognitive disorders and chronic use of cannabis]. *Annales de medecine interne*, *154 Spec N*, S58-64.

Karila, L., Roux, P., Rolland, B., Benyamina, A., Reynaud, M., Aubin, H.-J., & Lançon, C. (2014). Acute and long-term effects of cannabis use: a review. *Current Pharmaceutical Design*, *20*(25), 4112–4118. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24001294

Karila, L., Vignau, J., Alter, C., & Reynaud, M. (2005). [Acute and chronic cognitive disorders caused by cannabis use]. *La Revue du praticien*, *55*(1), 23–29.

Kaufmann, R. M., Kraft, B., Frey, R., Winkler, D., Weiszenbichler, S., Backer, C., … Kress, H. G. (2010). Acute psychotropic effects of oral cannabis extract with a defined content of Delta9-tetrahydrocannabinol (THC) in healthy volunteers. *Pharmacopsychiatry*, *43*(1), 24–32. https://doi.org/10.1055/s-0029-1237397

Kempton, M. J., Valmaggia, L., Mcguire, P., & Fusar-Poli, P. (2016). Speed of Psychosis Progression in People at Ultra-High Clinical Risk: A Complementary Meta-analysis. *JAMA Psychiatry*, *72*(6), 2015–2016. https://doi.org/10.1001/jamapsychiatry.2015.0094.Author

Kendler, K. S., Ohlsson, H., Sundquist, J., & Sundquist, K. (2019). Prediction of Onset of Substance-Induced Psychotic Disorder and Its Progression to Schizophrenia in a Swedish National Sample. *American Journal of Psychiatry*, (9), appi.ajp.2019.1. https://doi.org/10.1176/appi.ajp.2019.18101217

Kern, R. S., Gold, J. M., Dickinson, D., Green, M. F., Nuechterlein, K. H., Baade, L. E., …

Marder, S. R. (2011). The MCCB impairment profile for schizophrenia outpatients : Results from the MATRICS psychometric and standardization study. *Schizophrenia Research*, *126*, 124–131. https://doi.org/10.1016/j.schres.2010.11.008

Kiang, M., Christensen, B. K., Kutas, M., & Zipursky, R. B. (2012). Electrophysiological evidence for primary semantic memory functional organization deficits in schizophrenia. *Psychiatry Research*, *196*(2–3), 171–180. https://doi.org/10.1016/j.psychres.2012.02.026

Kiang, M., Christensen, B. K., Streiner, D. L., Roy, C., Patriciu, I., & Zipursky, R. B. (2013). Association of abnormal semantic processing with delusion-like ideation in frequent cannabis users: An electrophysiological study. *Psychopharmacology*, *225*(1), 95–104. https://doi.org/10.1007/s00213-012-2800-3

Kiang, M., Christensen, B. K., & Zipursky, R. B. (2011). Depth-of-processing effects on semantic activation deficits in schizophrenia: An electrophysiological investigation. *Schizophrenia Research*, *133*(1–3), 91–98. https://doi.org/10.1016/j.schres.2011.08.002

Kiang, M., Christensen, B. K., & Zipursky, R. B. (2014). Event-related brain potential study of semantic priming in unaffected first-degree relatives of schizophrenia patients. *Schizophrenia Research*, *153*(1–3), 78–86. https://doi.org/10.1016/j.schres.2014.01.001

Kiang, M., Kutas, M., Light, G. A., & Braff, D. L. (2007). Electrophysiological insights into conceptual disorganization in schizophrenia. *Schizophrenia Research*, *92*(1–3), 225–236. https://doi.org/10.1016/j.schres.2007.02.001

Kiang, M., Kutas, M., Light, G. A., & Braff, D. L. (2008). An event-related brain potential study of direct and indirect semantic priming in schizophrenia. *American Journal of Psychiatry*, *165*(1), 74–81. https://doi.org/10.1176/appi.ajp.2007.07050763

Kiang, M., Prugh, J., & Kutas, M. (2010). An event-related brain potential study of schizotypal personality and associative semantic processing. *International Journal of Psychophysiology*, *75*(2), 119–126. https://doi.org/10.1016/j.ijpsycho.2009.10.005

Kimble, M., Lyons, M., Donnell, B. O., Nestor, P., Niznikiewicz, M., & Toomey, R. (2000). The Effect of Family Status and Schizotypy on Electrophysiologic Measures of Attention and Semantic Processing. *Biological Psychiatry*, *47*, 402–412.

Kirkbride, J. B., Hameed, Y., Ioannidis, K., Ankireddypalli, G., Crane, C. M., Nasir, M., … Jones, P. B. (2017). Ethnic Minority Status, Age-at-Immigration and Psychosis Risk in Rural Environments: Evidence from the SEPEA Study. *Schizophrenia Bulletin*, *43*(6), 1251–1261. https://doi.org/10.1093/schbul/sbx010

Korver, N., Nieman, D. H., Becker, H. E., van de Fliert, J. R., Dingemans, P. H., de Haan, L., … Linszen, D. H. (2010). Symptomatology and neuropsychological functioning in cannabis using subjects at ultra-high risk for developing psychosis and healthy controls. *The Australian and New Zealand Journal of Psychiatry*, *44*(3), 230–236. https://doi.org/10.3109/00048670903487118

Kostova, M., Passerieux, C., Laurent, J.-P., & Hardy-Baylé, M. C. (2003). An Electrophysiologic Study: Can Semantic Context Processes Be Mobilized in Patients With Thought-Disordered Schizophrenia? *Canadian Journal of Psychiatry*, *48*(9), 615–623.

Kostova, M., Passerieux, C., & Laurent, J. (2005). N400 anomalies in schizophrenia are correlated with the severity of formal thought disorder. *Schizophrenia Research*, *78*, 285–291. https://doi.org/10.1016/j.schres.2005.05.015

Kraan, T., Velthorst, E., Koenders, L., Zwaart, K., Ising, H. K., Van Den Berg, D., … Van Der Gaag, M. (2016). Cannabis use and transition to psychosis in individuals at ultra-high risk: Review and meta-analysis. *Psychological Medicine*, *46*(4), 673–681.

https://doi.org/10.1017/S0033291715002329
Kraan, T., Velthorst, E., Smit, F., de Haan, L., & van der Gaag, M. (2015). Trauma and recent life events in individuals at ultra high risk for psychosis: Review and meta-analysis. *Schizophrenia Research*, *161*(2–3), 143–149. https://doi.org/10.1016/j.schres.2014.11.026
Kreher, D. A., Goff, D., & Kuperberg, G. R. (2009). Why all the confusion? Experimental task explains discrepant semantic priming effects in schizophrenia under "automatic" conditions : Evidence from Event-Related Potentials. *Schizophrenia Research*, *111*, 174–181. https://doi.org/10.1016/j.schres.2009.03.013
Kristensen, K., & Cadenhead, K. S. (2007). Cannabis abuse and risk for psychosis in a prodromal sample. *Psychiatry Research*, *151*(1–2), 151–154. https://doi.org/10.1016/j.psychres.2006.10.001
Ksir, C., & Hart, C. L. (2016). Cannabis and Psychosis: a Critical Overview of the Relationship. *Current Psychiatry Reports*, *18*(2), 1–11. https://doi.org/10.1007/s11920-015-0657-y
Kuepper, R., Van Os, J., Lieb, R., Wittchen, H. U., Höfler, M., & Henquet, C. (2011). Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 Year follow-up cohort study. *Bmj*, *342*, 1–8. https://doi.org/10.1136/bmj.d738
Kuperberg, G. R., Kreher, D. A., & Ditman, T. (2010). What can Event-related Potentials tell us about language, and perhaps even thought, in schizophrenia? *International Journal of Psychophysiology*, *75*(2), 66–76. https://doi.org/10.1016/j.ijpsycho.2009.09.005
Kutas, M., & Federmeier, K. D. (1999). A Rose by Any Other Name: Long-Term Memory Structure and Sentence Processing. *Journal of Memory and Language*, *41*, 469–495.
Kutas, M., & Federmeier, K. D. (2011). Thirty years and counting:Finding meaning in the N400 compent of the event related brain potential(ERP). *Annual Reviews Psychology*, *62*, 621–647. https://doi.org/10.1146/annurev.psych.093008.131123.
Kutas, M., & Hillyard, S. A. (1980a). Event-related brain potentials to semantically inappropriate and surprisingly large words. *Biological Psychology*, *11*(2), 99–116. https://doi.org/10.1016/0301-0511(80)90046-0
Kutas, M., & Hillyard, S. A. (1980b). Reading between the lines: Event-related brain potentials during natural sentence processing. *Topics in Catalysis*, *11*(2), 354–373. https://doi.org/10.1016/0093-934X(80)90133-9
Kutas, M., & Hillyard, S. A. (1984). Brain potentials during reading reflect word expectancy and semantic association. *Nature*, *307*(5947), 161–163. https://doi.org/10.1038/307161a0
Kutas, M., & Hillyard, S. A. (1989). An electrophysiological probe of incidental semantic association. *Journal of Cognitive Neuroscience*, *1*(1), 38–49. https://doi.org/10.1162/jocn.1989.1.1.38
Kutas, M., Van Petten, C., & Besson, M. (1988). Event-related potential asymmetries during the reading of sentences. *Electroencephalography and Clinical Neurophysiology*, *69*, 218–233.
Large, M., Sharma, S., Compton, M. T., Slade, T., & Nielssen, O. (2011). Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Archives of General Psychiatry*, *68*(6), 555–561. https://doi.org/10.1001/archgenpsychiatry.2011.5
Lau, E. F., Phillips, C., & Poeppel, D. (2008). A cortical network for semantics: (de)constructing the N400. *Nature Reviews. Neuroscience*, *9*(12), 920–933. https://doi.org/10.1038/nrn2532
Laurent, J., Kostova, M., & Passerieux, C. (2010). N400 and P300 modulation as functions of processing level in schizophrenia patients exhibiting formal thought disorder. *International Journal of Psychophysiology*, *75*, 177–182. https://doi.org/10.1016/j.ijpsycho.2009.10.001
Lee, T. Y., Shin, Y. S., Shin, N. Y., Kim, S. N., Jang, J. H., Kang, D.-H., & Kwon, J. S. (2014).

Neurocognitive function as a possible marker for remission from clinical high risk for psychosis. *Schizophrenia Research*, *153*(1–3), 48–53. https://doi.org/10.1016/j.schres.2014.01.018

Lepock, J. R., Mizrahi, R., Korostil, M., Bagby, R. M., Pang, E. W., & Kiang, M. (2018). Event-related potentials in the clinical high-risk (CHR) state for psychosis: A systematic review. *Clinical EEG and Neuroscience*, *49*(4), 215–225. https://doi.org/10.1177/1550059418755212

Lepock, J. R., Mizrahi, R., Korostil, M., Maheandiran, M., Gerritsen, C. J., Drvaric, L., … Kiang, M. (2019). N400 event-related brain potential evidence for semantic priming deficits in persons at clinical high risk for psychosis. *Schizophrenia Research*, *204*, 434–436. https://doi.org/10.1016/j.schres.2018.08.033

Leucht, S., Samara, M., Heres, S., Patel, M. X., Woods, S. W., & Davis, J. M. (2014). Dose equivalents for second-generation antipsychotics: the minimum effective dose method. *Schizophrenia Bulletin*, *40*(2), 314–326. https://doi.org/10.1093/schbul/sbu001

Loewy, R. L., Corey, S., Amirfathi, F., Dabit, S., Fulford, D., Pearson, R., … Vinogradov, S. (2019). Childhood trauma and clinical high risk for psychosis. *Schizophrenia Research*, *205*, 10–14. https://doi.org/10.1016/j.schres.2018.05.003

Lopez-Quintero, C., Perez de los Cobos, J., Hasin, D. S., Okuda, M., Wang, S., Grant, B. F., & Blanco, C. (2011). Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug and Alcohol Dependence*, *115*(1–2), 120–130. https://doi.org/10.1016/j.drugalcdep.2010.11.004

Luck, S. J. (Steven J. (2005). An introduction to the event-related potential technique. In *CEUR Workshop Proceedings*.

Lunn, B. (2017). Schizophrenia. *Psychiatry by Ten Teachers, Second Edition*, 102–113. https://doi.org/10.1201/9781315380612

Makeig, S., Jung, T.-P., Bell, A. J., Ghahremani, D., & Sejnowski, T. J. (1997). Blind separation of auditory event-related brain responses into independent components. *Proceedings of the National Academy of Sciences*, *94*(20), 10979 LP – 10984. https://doi.org/10.1073/pnas.94.20.10979

Manrique-Garcia, E., De Leon, A. P., Dalman, C., Andréasson, S., & Allebeck, P. (2016). Cannabis, psychosis, and mortality: A cohort study of 50,373 Swedish men. *American Journal of Psychiatry*, *173*(8), 790–798. https://doi.org/10.1176/appi.ajp.2016.14050637

Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-Analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin*, *42*(5), 1262–1269. https://doi.org/10.1093/schbul/sbw003

Mathalon, D. H., Faustman, W. O., & Ford, J. M. (2002). N400 and Automatic Semantic Processing Abnormalities in Patients With Schizophrenia. *Archives of General Psychiatry*, *59*, 641–548.

Mathalon, D. H., Roach, B. J., & Ford, J. M. (2010). Automatic semantic priming abnormalities in schizophrenia. *International Journal of Psychophysiology*, *75*, 157–166. https://doi.org/10.1016/j.ijpsycho.2009.12.003

Matsumoto, K., Matsuoka, H., Yamazaki, H., Sakai, H., Kato, T., Miura, N., & Nakamura, M. (2001). Impairment of an event-related potential correlate of memory in schizophrenia : effects of immediate and delayed word repetition. *Clinical Neurophysiology*, *112*, 662–673.

Matsuoka, H., Matsumoto, K., Yamazaki, H., Sakai, H., Miwa, S., Yoshida, S., … Ueno, T.

(1999). Lack of Repetition Priming Effect on Visual Event-Related Potentials in Schizophrenia. *Biological Psychiatry*, (46), 137–140.
McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: A concise overview of incidence, prevalence, and mortality. *Epidemiologic Reviews*, *30*(1), 67–76. https://doi.org/10.1093/epirev/mxn001
McHugh, M. J., McGorry, P. D., Yung, A. R., Lin, A., Wood, S. J., Hartmann, J. A., & Nelson, B. (2017). Cannabis-induced attenuated psychotic symptoms: Implications for prognosis in young people at ultra-high risk for psychosis. *Psychological Medicine*, *47*(4), 616–626. https://doi.org/10.1017/S0033291716002671
Mclaughlin, J., Osterhout, L., & Kim, A. (2004). Neural correlates of second- language word learning : minimal instruction produces rapid change. *Nature Neuroscience*, *7*(7), 703–704. https://doi.org/10.1038/nn1264
Mechoulam, R., & Parker, L. A. (2013). The endocannabinoid system and the brain. *Annual Review of Psychology*, *64*, 21–47. https://doi.org/10.1146/annurev-psych-113011-143739
Miller, L. L., McFarland, D., Cornett, T. L., & Brightwell, D. (1977). Marijuana and memory impairment: effect on free recall and recognition memory. *Pharmacology, Biochemistry, and Behavior*, *7*(2), 99–103. https://doi.org/10.1016/0091-3057(77)90191-5
Miller, L. L., McFarland, D., Cornett, T. L., Brightwell, D., & Wikler, A. (1977). Marijuana: Effects on free recall and subjective organization of pictures and words. *Psychopharmacology*. https://doi.org/10.1007/BF00497857
Miller, T. J., Mcqlashan, T. H., Rosen, J. L., Cadenhead, K., Ventura, J., Mcfarlane, W., … Woods, S. W. (2003). Prodromal Assessment With the Structured Interview for Prodromal Syndromes and the Scale of Prodromal Symptoms : Predictive Validity, Interrater Reliability, and Training to Reliability. *Schizophrenia Bulletin*, *29*(4), 703–716.
Moeller, K. E., Kissack, J. C., Atayee, R. S., & Lee, K. C. (2017). Clinical Interpretation of Urine Drug Tests: What Clinicians Need to Know About Urine Drug Screens. *Mayo Clinic Proceedings*, *92*(5), 774–796. https://doi.org/10.1016/j.mayocp.2016.12.007
Mohammad, O. M., & De Lisi, L. E. (2013). N400 in schizophrenia patients. *Current Opinion in Psychiatry*, *26*(2), 196–207. https://doi.org/10.1097/YCO.0b013e32835d9e56
Moore, T. H., Zammit, S., Lingford-Hughes, A., Barnes, T. R., Jones, P. B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet*, *370*(9584), 319–328. https://doi.org/10.1016/S0140-6736(07)61162-3
Morean, M. E., Lipshie, N., Josephson, M., & Foster, D. (2017). Predictors of Adult E-Cigarette Users Vaporizing Cannabis Using E-Cigarettes and Vape-Pens ABSTRACT. *Substance Use & Misuse*, *52*(8), 974–981. https://doi.org/10.1080/10826084.2016.1268162
Moreno-Küstner, B., Martín, C., & Pastor, L. (2018). Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. *PLoS ONE*, *13*(4), e0195687. https://doi.org/10.1016/j.schres.2018.07.031
Morgan, C. J. A., Rothwell, E., Atkinson, H., Mason, O., & Curran, H. V. (2010). Hyper-priming in cannabis users: A naturalistic study of the effects of cannabis on semantic memory function. *Psychiatry Research*, *176*(2–3), 213–218. https://doi.org/10.1016/j.psychres.2008.09.002
Moskowitz, A., & Heim, G. (2011). Eugen Bleuler's Dementia praecox or the group of schizophrenias (1911): a centenary appreciation and reconsideration. *Schizophrenia Bulletin*, *37*(3), 471–479. https://doi.org/10.1093/schbul/sbr016

Murray, R. M., Englund, A., Abi-Dargham, A., Lewis, D. A., Di Forti, M., Davies, C., … D'Souza, D. C. (2017). Cannabis-associated psychosis: Neural substrate and clinical impact. *Neuropharmacology*, *124*, 89–104. https://doi.org/10.1016/j.neuropharm.2017.06.018

Myles, H., Myles, N., & Large, M. (2016). Cannabis use in first episode psychosis : Meta-analysis of prevalence , and the time course of initiation and continued use. *Australian and New Zealand Journal of Psychiatry*, *50*(3), 208–219. https://doi.org/10.1177/0004867415599846

Myles, N., Newall, H., Nielssen, O., & Large, M. (2012). The Association between Cannabis Use and Earlier Age at Onset of Schizophrenia and other Psychoses: Meta-analysis of Possible Confounding Factors. *Current Pharmaceutical Design*. https://doi.org/10.2174/138161212802884816

Neely, J. H. (1976). Semantic priming and retrieval from lexical memory: Evidence for facilitatory and inhibitory processes. *Memory & Cognition*, *4*(5), 648–654. https://doi.org/10.3758/BF03213230

Neely, J. H. (1977). Semantic priming and retrieval from lexical memory: Roles of inhibitionless spreading activation and limited-capacity attention. *Journal of Experimental Psychology: General*, *106*(3), 226–254. https://doi.org/10.1037/0096-3445.106.3.226

Neely, J. H., Keefe, D. E., & Ross, K. L. (1989). Semantic priming in the lexical decision task: roles of prospective prime-generated expectancies and retrospective semantic matching. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *15*(6), 1003–1019.

Nelson, D. L., McEvoy, C. L., & Schreiber, T. A. (1999). The University of South Florida Word Association, Rhyme and Word Fragment Norms. Retrieved from http://w3.usf.edu/FreeAssociation/Intro.html

Niemi-Pynttäri, J. A., Sund, R., Putkonen, H., Vorma, H., Wahlbeck, K., & Pirkola, S. P. (2013). Substance-induced psychoses converting into schizophrenia: A register-based study of 18,478 Finnish Inpatient cases. *Journal of Clinical Psychiatry*, *74*(1), e94–e99. https://doi.org/10.4088/JCP.12m07822

Niznikiewicz, M., Mittal, M. S., Nestor, P. G., & McCarley, R. W. (2010). Abnormal inhibitory processes in semantic networks in schizophrenia. *International Journal of Psychophysiology*, *75*(2), 133–140. https://doi.org/10.1016/j.ijpsycho.2009.10.006

O'Carroll, R., Dunan, J., Murray, C., Ebmeier, K. P., & Goodwin, G. M. (1992). Selecting controls for schizophrenia research studies : the use of the national adult reading test (NART) is a measure of pre- morbid ability. *Schizophrenia Research*, *8*, 137–141.

Olivares, E. I., Iglesias, J., & Antonieta Bobes, M. (1999). Searching for face-specific long latency ERPs: A topographic study of effects associated with mismatching features. *Cognitive Brain Research*, *7*(3), 342–356. https://doi.org/10.1016/S0926-6410(98)00038-X

Patel, M. X., Arista, I. A., Taylor, M., & Barnes, T. R. E. (2013). How to compare doses of different antipsychotics: a systematic review of methods. *Schizophrenia Research*, *149*(1–3), 141–148. https://doi.org/10.1016/j.schres.2013.06.030

Pfeifer, S., Schiller, N. O., Os, J. Van, Riedel, W. J., Vlamings, P., Simons, C., & Krabbendam, L. (2012). Electrophysiological correlates of automatic spreading of activation in patients with psychotic disorder and first-degree relatives. *International Journal of Psychophysiology*, *84*, 102–112. https://doi.org/10.1016/j.ijpsycho.2012.01.017

Radhakrishnan, R., Wilkinson, S. T., & D'Souza, D. C. (2014). Gone to pot-a review of the association between cannabis and psychosis. *Frontiers in Psychiatry*, *5*(MAY), 1–24.

https://doi.org/10.3389/fpsyt.2014.00054
Ranganathan, M., & D'Souza, D. C. (2006). The acute effects of cannabinoids on memory in humans : a review. *Psychopharmacology*, *188*, 425–444. https://doi.org/10.1007/s00213-006-0508-y
Riva, M. A., & Di Sciascio, G. (2015). Aripiprazole: from pharmacological profile to clinical use. *Neuropsychiatric Disease and Treatment*, 2635. https://doi.org/10.2147/ndt.s88117
Rossell, S. L., Price, C. J., & Nobre, A. C. (2003). The anatomy and time course of semantic priming investigated by fMRI and ERPs. *Neuropsychologia*, *41*, 550–564.
Rössler, W., Riecher-Rössler, A., Angst, J., Murray, R., Gamma, A., Eich, D., … Ajdacic, V. (2007). Psychotic experiences in the general population : A twenty-year prospective community study. *Schizophrenia Research*, *92*, 1–14. https://doi.org/10.1016/j.schres.2007.01.002
Rugg, M. D. (1985). The Effects of Semantic Priming and Word Repetition on Event-Related Potentials. *Psychophysiology*. https://doi.org/10.1111/j.1469-8986.1985.tb01661.x
Ryu, V., Kyoon, S., Yeon, R., Ae, J., Ha, K., & Cho, H. (2012). Differential alteration of automatic semantic processing in treated patients affected by bipolar mania and schizophrenia: An N400 study. *Progress in Neuropsychopharmacology & Biological Psychiatry*, *38*, 194–200. https://doi.org/10.1016/j.pnpbp.2012.03.009
Saha, S., Chant, D., Welham, J., & McGrath, J. (2005). A systematic review of the prevalence of schizophrenia. *PLoS Medicine*, *2*(5), e141. https://doi.org/10.1371/journal.pmed.0020141
Şahin, S., Yüksel, Ç., Güler, J., Karadayi, G., Akturan, E., Göde, E., … Üçok, A. (2013). The history of childhood trauma among individuals with ultra high risk for psychosis is as common as among patients with first-episode schizophrenia. *Early Intervention in Psychiatry*, *7*(4), 414–420. https://doi.org/10.1111/eip.12022
Schlosser, D. A., Jacobson, S., Chen, Q., Sugar, C. A., Niendam, T. A., Li, G., … Cannon, T. D. (2012). Recovery from an at-risk state: Clinical and functional outcomes of putatively prodromal youth who do not develop psychosis. *Schizophrenia Bulletin*, *38*(6), 1225–1233. https://doi.org/10.1093/schbul/sbr098
Schoenbaum, M., Sutherland, J. M., Chappel, A., Azrin, S., Goldstein, A. B., Rupp, A., & Heinssen, R. K. (2017). Twelve-Month Health Care Use and Mortality in Commercially Insured Young People with Incident Psychosis in the United States. *Schizophrenia Bulletin*, *43*(6), 1262–1272. https://doi.org/10.1093/schbul/sbx009
Schreiner, A. M., & Dunn, M. E. (2012). Residual Effects of Cannabis Use on Neurocognitive Performance After Prolonged Abstinence : A Meta-Analysis. *Experimental and Clinical Psychopharmacology*, *20*(5), 420–429. https://doi.org/10.1037/a0029117
Schultze-Lutter, F., Michel, C., Ruhrmann, S., & Schimmelmann, B. G. (2017). Prevalence and clinical relevance of interview-assessed psychosis-risk symptoms in the young adult community. *Psychological Medicine*, *48*, 1167–1178. https://doi.org/10.1017/S0033291717002586 LK - http://AD4MH3SR7V.search.serialssolutions.com?sid=EMBASE&issn=14698978&id=doi:10.1017%2FS0033291717002586&atitle=Prevalence+and+clinical+relevance+of+interview-assessed+psychosis-risk+symptoms+in+the+young+adult+community&stitle=Psychol+Med&title=Psychological+medicine&volume=48&issue=7&spage=1167&epage=1178&aulast=Schultze-Lutter&aufirst=Frauke&auinit=F.&aufull=Schultze-Lutter+F.&coden=&isbn=&pages=1167-1178&date=2018&auinit1=F&auinitm=

Sereno, S. C., Rayner, C. A. K., & Posner, M. I. (1998). Establishing a time-line of word recognition : evidence from eye movements and event-related potentials. *NeuroReport*, *9*, 2195–2200.

Sewell, R. A., Ranganathan, M., & D'Souza, D. C. (2009). Cannabinoids and psychosis. *International Review of Psychiatry*, *21*(2 SPEC. ISS.), 152–162. https://doi.org/10.1080/09540260902782802

Sharma, A., Sauer, H., Hill, H., Kaufmann, C., Bender, S., & Weisbrod, M. (2017). Abnormal N400 Semantic Priming Effect May Reflect Psychopathological Processes in Schizophrenia: A Twin Study. *Schizophrenia Research and Treatment*, *2017*. https://doi.org/10.1155/2017/7163198

Sherif, M. A., Cortes-Briones, J. A., Ranganathan, M., & Skosnik, P. D. (2018). Cannabinoid – glutamate interactions and neural oscillations : implications for psychosis. *European Journal of Neuroscience*, *48*, 2890–2902. https://doi.org/10.1111/ejn.13800

Skosnik, P. D., Krishnan, G. P., Aydt, E. E., Kuhlenshmidt, H. A., & O'Donnell, B. F. (2006). Psychophysiological Evidence of Altered Neural Synchronization in Cannabis Use : Relationship to Schizotypy. *Am J Psychiatry*, *163*(10), 1798–1805.

Smit, F., Bolier, L., & Cuijpers, P. (2004). Cannabis use and the risk of later schizophrenia : a review. *Addiction*, *99*, 425–430. https://doi.org/10.1111/j.1360-0443.2004.00683.x

Sobell, L. C., Brown, J., Leo, G. I., & Sobell, M. B. (1996). The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. *Drug And Alcohol Dependence*, *42*, 49–54.

Sobell, L. C., Kwan, E., & Sobell, M. B. (1995). Reliability of the Drug History Questionnaire (DHQ). *Addictive Behaviors*, *20*(2), 233–241.

Solowij, N., & Battisti, R. (2008). The Chronic Effects of Cannabis on Memory in Humans : A Review. *Current Drug Abuse Reviews*, *1*(1), 81–98.

Statistics Canada. (2019). *National Cannabis Survey, first quarter 2019*.

Stefanis, N. C., Power, B. D., & Morgan, V. A. (2013). Age at Initiation of Cannabis Use Predicts Age at Onset of Psychosis : The 7- to 8-Year Trend. *Schizophrenia Bulletin*, *39*(2), 251–254. https://doi.org/10.1093/schbul/sbs188

Stella, N. (2010). Cannabinoid and Cannabinoid-Like Receptors in Microglia , Astrocytes , and Astrocytomas. *Glia*, *58*, 1017–1030. https://doi.org/10.1002/glia.20983

Taylor, W. L. (1953). "Cloze Procedure": A New Tool for Measuring Readability. *Journalism Bulletin*, *30*(4), 415–433. https://doi.org/10.1177/107769905303000401

The United Nations Office on Drugs and Crime (UNODC). (2019). *Cannabis and Hallucinogens 2019*.

Uhlhaas, P. J., & Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. *Nature Reviews Neuroscience*, *11*(2), 100–113. https://doi.org/10.1038/nrn2774

UNODC. (2018). *World Drug Report 2018 - Booklet 2 - Global Overview of drug demand and supply*. https://doi.org/10.18356/bdc264f4-en

Valmaggia, L. R., Day, F. L., Jones, C., Bissoli, S., Pugh, C., Hall, D., … McGuire, P. K. (2014). Cannabis use and transition to psychosis in people at ultra-high risk. *Psychological Medicine*, *44*(12), 2503–2512. https://doi.org/10.1017/S0033291714000117

Van Berkum, J. J. A., Brown, C. M., Zwisterlood, P., Koojiman, V., & Hagoort, P. (2005). Anticipating Upcoming Words in Discourse : Evidence From ERPs and Reading Times. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *31*(3), 443–467.

https://doi.org/10.1037/0278-7393.31.3.443
van Os, J, Bak, M., Hanssen, M., Bijl, R. V, de Graaf, R., & Verdoux, H. (2002). Cannabis use and psychosis: a longitudinal population-based study. *American Journal of Epidemiology*, *156*(4), 319–327. https://doi.org/10.1093/aje/kwf043
van Os, Jim, & Kapur, S. (2009). Schizophrenia. *The Lancet*, *372*, 635–645.
Van Petten, C., & Rheinfelder, H. (1995). Conceptual relationships between spoken words and environmental sounds: event-related brain potential measures. *Neuropsychologia*, *33*(4), 485–508.
Vo, H. T., Schacht, R., Mintzer, M., & Fishman, M. (2014). Working memory impairment in cannabis- and opioid-dependent adolescents. *Substance Abuse*, *35*(4), 387–390. https://doi.org/10.1080/08897077.2014.954027
Volkow, N. D., Baler, R. D., Compton, W. M., & Weiss, S. R. B. (2014). Adverse Health Effects of Marijuana Use. *New England Journal of Medicine*. https://doi.org/10.1056/nejmra1402309
Volkow, N. D., Swanson, J. M., Evins, A. E., DeLisi, L. E., Meier, M. H., Gonzalez, R., … Baler, R. (2016). Effects of cannabis use on human behavior, including cognition,motivation, and psychosis: A review. *JAMA Psychiatry*, *73*(3), 292–297. https://doi.org/10.1001/jamapsychiatry.2015.3278
Wagner, F. A., & Anthony, J. C. (2007). Male-female differences in the risk of progression from first use to dependence upon cannabis, cocaine, and alcohol. *Drug and Alcohol Dependence*, *86*(2–3), 191–198. https://doi.org/10.1016/j.drugalcdep.2006.06.003
Weinberger, A. H., Reutenauer, E. L., Allen, T. M., Termine, A., Vessicchio, J. C., Sacco, K. A., … George, T. P. (2007). Reliability of the Fagerstrom Test for Nicotine Dependence, Minnesota Nicotine Withdrawal Scale, and Tiffany Questionnaire for Smoking Urges in Smokers with and without Schizophrenia. *Drug And Alcohol Dependence*, *86*, 278–282. https://doi.org/10.1016/j.drugalcdep.2006.06.005
WHO. (2016). *The health and social effects of nonmedical cannabis use*. Chapter 1. Retrieved from https://www.who.int/substance_abuse/publications/cannabis_report/en/index3.html
Wilkinson, S. T., Yarnell, S., Radhakrishnan, R., Ball, S. A., & Souza, D. C. D. (2016). Marijuana Legalization : Impact on Physicians and Public Health. *Annual Review of Medicine*, *67*, 453–466. https://doi.org/10.1146/annurev-med-050214-013454
Yucel, M., Lubman, D. I., Solowij, N., & Brewer, W. J. (2007). Understanding drug addiction: a neuropsychological perspective. *Australian and New Zealand Journal of Psychiatry*, *41*(957–968).
Yung, A. R., & McGorry, P. O. (1996). The prodromal phase of first-episode psychosis: Past and current conceptualizations. *Schizophrenia Bulletin*, *22*(2), 353–370. https://doi.org/10.1093/schbul/22.2.353
Yung, A. R., & Nelson, B. (2013). The ultra-high risk concept - A review. *Canadian Journal of Psychiatry*, *58*(1), 5–12. https://doi.org/10.1177/070674371305800103
Yung, A. R., Phillips, L. J., McGorry, P. D., McFarlane, C. A., Francey, S., Harrigan, S., … Jackson, H. J. (1998). Prediction of psychosis. *British Journal of Psychiatry*, *172*(S33), 14–20. https://doi.org/10.1192/s0007125000297602
Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I., & Lewis, G. (2002). Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ (Clinical Research Ed.)*, *325*(7374), 1199. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12446534%0Ahttp://www.pubmedcentral.nih.gov/art

iclerender.fcgi?artid=PMC135490
Zheng, W., Zhang, Q. E., Cai, D. Bin, Ng, C. H., Ungvari, G. S., Ning, Y. P., & Xiang, Y. T. (2018). Neurocognitive dysfunction in subjects at clinical high risk for psychosis: A meta-analysis. *Journal of Psychiatric Research*, *103*(May), 38–45. https://doi.org/10.1016/j.jpsychires.2018.05.001