PHENOMENOLOGICAL MARKERS OF FUTURE PSYCHOSIS: THE ROLE OF CANNABIS

by

Gabriel Brooks

B.A., The University of British Columbia, 2012

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF ARTS

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Psychology)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

August 2016

Abstract

Cannabis use is a known risk factor for the development of psychosis, although the precise nature of this relationship is unclear. The phenomenological experiences associated with cannabis use vary dramatically, and for some resemble certain features of psychosis. We hypothesized that individuals who report particularly unusual experiences associated with cannabis use demonstrate similar electrophysiological patterns to those who score high on schizotypal personality traits. The Cannabis Experiences Questionnaire (CEQ) and the Schizotypal Personality Questionnaire (SPQ) were used to measure these experiences and traits. A sample of 97 individuals were placed into one of five groups: high CEQ scorers (High CEQ), high SPQ scorers (High SPQ), high CEQ and SPQ scorers (High on Both), average CEQ and SPQ scorers (Average Users), and average SPQ non-users (Average Non-Users). Participants completed a visual task in which they indicated whether they saw a face embedded within a static field. Electroencephalography was used to measure the neural response to the stimuli. The N170 event-related potential (ERP) was used to measure perceptual encoding of the stimulus. The High SPQ and High on Both groups elicited significantly reduced N170 ERPs compared to the average groups. The High CEQ group demonstrated significantly reduced N170 ERPs compared to Average Non-Users. None of the high scoring groups significantly differed in N170 ERP response from each other. No interaction was detected between trial-type and group, although group differences in laterality were robust and consistent across trial types. Replicating past research, the CEQ and SPQ scales moderately correlated with each other. We propose that the detected attenuated N170 ERP demonstrated by the high scoring groups is a manifestation of an underlying shared cognitive vulnerability.

Preface

This thesis is an original intellectual product of the author. It was conducted within the Clinical and Cognitive Neuroscience Laboratory at the University of British Columbia. In collaboration with my supervisor, Dr. Colleen Brenner, I identified and developed the research question, study design, data collection, and data analysis. This study was approved by the UBC Clinical Research Ethics Board, and is associated with approval number H13-01599, under the name "FIN Study".

Table of Contents

List of Tables

List of Figures

Acknowledgements

I would like to thank my project supervisor, Dr. Colleen Brenner, for her steadfast support and insight throughout the course of this project. I would also like to thank the research assistants who volunteered with the Clinical and Cognitive Neuroscience Lab over the last two years: Maggie, Chris, Louie, Sam, Aisha, Swetha, Spencer, and Ryley. I'm also grateful to both Dr. Paul Hewitt and Dr. Todd Handy, who volunteered to sit on my committee and also provided valuable direction for this project.

I wish to thank the Faculty of Arts and the Psychology Department, who provided financial support for this project. I would also like to thank Guenter and Diane Stahl, who provided funding via the Michael W. Stahl Memorial Graduate Scholarship award.

I want to thank my parents, friends, and colleagues for their steadfast support throughout the last two years. Finally, I wish to thank Negar Jalali, my partner in life, for her continual support, help, and encouragement spanning from early days of the graduate school application process to the hours before my Master's defense.

Phenomenological Markers of Future Psychosis: The Role of Cannabis

Cannabis is the most widely consumed illicit substance in Canada, as reported by The Canadian Centre on Substance Abuse (CCSA). The usage rates in 2014 were approximately 20.3% of youth (aged 15-24) and 8.4% of adults (CCSA, 2014). This constitutes approximately 10.2% (or 3.5 million individuals) of the Canadian population. Similar percentages are found in the United States (Substance Abuse and Mental Health Services Administration, 2013). Furthermore, the last few decades have seen a trend toward acceptance for both medicinal and recreational cannabis use. Laws surrounding consumption of this substance have become increasingly relaxed in Canada, while some American states have legalized recreational use. This changing landscape has created a new market, effectively increasing the availability of persecution-free access to the substance (Penn, 2013; Kilmer, 2014).

As acceptance and social tolerance of this substance increases, so does the importance of understanding the risks and benefits of its usage. Of the potential hazards, one prominent area of investigation is the link between cannabis use and psychosis. The typical age of onset of schizophrenia is early-to-mid-twenties for males and late twenties for females (American Psychiatric Association, 2013). Interestingly, the age-range associated with the highest cannabis consumption rate, 18-to-24, coincides with the most likely age of onset for schizophrenia (Roterman & Langlois, 2012). Furthermore, introduction to cannabis during adolescence seems to be associated with increased risk for later psychotic episodes resulting in hospitalization (Malone, Hill, & Rubino, 2010; Galves-Buccollini et al., 2012; Bagot, Milin, Kaminer, 2015). A retrospective study conducted on data from a Swedish cohort found that participants who endorsed greater than fifty lifetime uses were six times more likely to develop schizophrenia (Andreasson et al., 1987). After potential confounding variables (e.g. social background) were

controlled for, cannabis continued to remain an independent risk factor (Andreasson et al., 1987). However, causality could not be determined from this dataset. In fact, much of the extant literature exploring the relationship between cannabis and psychosis is correlational in nature, and the causative direction continues to be a topic of debate.

To further explore this association, Arseneault and colleagues (2002) used data from the Dunedin Multidisciplinary Health and Development Study in an attempt to decipher possible causative associations between cannabis use and psychosis. This dataset began collection in 1972-73 and comprises of 1037 individuals with a retention rate of approximately a 95%. Information was collected every two years until age 15, and then approximately twice a decade onwards. These researchers found that cannabis use beginning at age 15 was associated with a four-fold increase in likelihood of a schizophrenia or schizophreniform diagnosis, and an almost seven-fold rise to experience some psychotic symptoms (Arseneault et al., 2002). Arseneault and colleagues' concluded that marijuana may play a causal role in psychotic development. However, when individuals that demonstrated symptoms of psychosis (specific symptoms unspecified) at age 11 were controlled for, the heightened risk for psychotic disorders was no longer significant. This result could also be due to the subsequent loss of statistical power, as only 29 individuals were classified as users by age 15. Furthermore, heavy cannabis users (at least twice a week) that had a concurrent psychotic diagnosis showed a correlation between age of first use and first hospitalization, such that earlier use was followed by an earlier hospitalization for psychotic symptoms (approx. 7.0 $\pm$4.3 years after first use; Galves-Buccollini et al., 2012). More recently, a meta-analysis concluded that adolescent cannabis use is a significant predictor of future psychotic symptoms, where the quantity of use is associated with the severity of symptoms (Bagot, Milin, Kaminer, 2015).

Does Cannabis Cause Psychosis?

While the findings presented here may indicate that cannabis use is a risk factor for future psychosis, a causative role between these variables has not been established. Research examining this link has often been obfuscated by a variety of factors. Broadly speaking, these have been: (1) legal and methodological issues, such as the administration of cannabis to study participants, (2) the opportunity for missed symptoms or diagnoses due to the expanse of time between initial use and future psychotic development, (3) the low base rate of psychotic development in the general population, and (4) the presence of confounding variables in a heterogeneous psychotic population. This question of causation may be best answered with longitudinal data, however the expense of this kind of research has instead led to retrospective analyses of existing data. Despite these difficulties, there has been considerable effort to elucidate the mechanisms behind this relationship. Support for the hypothesis that cannabis consumption causes later psychosis has come from three primary findings. First, psychosis associated with the drug has shown dose-dependence (Hafner, 2005; Moore et al., 2007; Ongur, Lin, & Cohen, 2009; Large et al., 2011). Greater consumption of cannabis is associated with increased risk for psychosis. Second, there is evidence for the temporal precedence of the drug (Henquet et al., 2004; Stefanis, et al. 2013). That is, in those cases where an individual both uses cannabis and develops a psychotic disorder, cannabis use almost always occurs first. Finally, there also appears to be a degree of specificity within the relationship (Ksir & Hart, 2016). This has been found in both directions, where other drugs do not appear to correlate with future psychotic development as strongly, or at all, and cannabis has not been found to be a risk factor of other mental disorders (Arseneault et al., 2002; Moore et al., 2007).

Dose-dependent effects between two variables are sometimes indicative of a causal role. In a review of several longitudinal studies, Hafner (2005) found that psychotic symptoms consistently increased with the quantity of cannabis consumed. Within this analysis, the odds ratio (*OR*) of the likelihood to experience psychosis with any history of cannabis use, compared to baseline, ranged from 1.31 to 2.3. However, when adjusted to only include those classified as frequent users, *OR*s spanned from 3.1 to 4.1. Similar findings were present in the aforementioned Swedish cohort study, where the heaviest users (>50 times) were approximately 50% more likely to develop schizophrenia, compared to those who reported using 11-50 times (Zammit et al., 2002). Miettunen et al. (2008) conducted a similar study on data from an adolescent cohort in northern Finland. Consistent with the above, the quantity of endorsed prodromal symptoms of psychosis was positively associated with cannabis use (OR = 2.24 to 3.46). Another systematic review conducted by Moore et al. (2007) found a consistent trend of dose-dependent effects (adjusted *OR* = 2.09) for both psychotic experiences and clinically diagnosed psychotic disorders. The results from these studies suggest that the relationship between cannabis use and future psychotic episodes strengthens as usage increases. Although, despite the notion that dose-dependence can suggest a causative role, it does not necessarily inform the direction of the association.

To elucidate the direction of a possible relationship, it is important to establish temporal precedence (Shadish et al., 2002). To address this, a retrospective study reviewed the drug history of several individuals who had developed psychosis (Stefanis, et al. 2013). These authors found the age of first use was linearly related to the onset of psychotic episodes, as operationalized by hospital records. There was an average period of 7.85 (*SD* = 6.2) years between first use of cannabis and subsequent psychosis. This was found to be consistent across

several ages of first use, suggesting no significant interaction between initial consumption and the development of psychosis. This led Stefanis et al. (2013) to suggest a possible "cumulative toxic effect" from cannabis use, with the precise mechanism yet to be determined. Similarly, Ferdinand et al. (2005) found that cannabis use which preceded the development of psychosis imbued individuals with an *OR* of 2.81 for the future development of a psychotic disorder. Additional support for temporal precedence comes from Henquet et al. (2005), who also used an existing longitudinal dataset (the Early Developmental Stages of Psychopathology Study). After controlling for several variables (e.g. other drugs, depression), this group found that (a) cannabis use was associated with an increased risk of psychosis among those aged 14-24, and (b) that this relationship was much stronger for individuals who demonstrated a predisposition for psychosis. This was defined as a score above the 90th percentile on the "paranoid ideation" and "psychoticism" SCL-90-R (a self-report symptom checklist) subscales at baseline assessment. Specifically, the risk for psychotic symptoms in users was 21% for those who were not predisposed and 51% for those who were. This contrasted sharply to the reported risk for non-users, which was 15% and 26% respectively (Henquet et al., 2005). Combined, this data suggests that cannabis use is associated with future psychosis, and the probability may be even greater for those who are classified as particularly vulnerable to psychotic episodes. Following the research on dose-dependence, if Stefanis et al.'s (2013) assertion of a toxic effect of cannabis is correct, then these findings suggest that psychosis-prone individuals may be especially sensitive to these cumulative toxins.

If cannabis is progressively increasing an individual's propensity for psychotic episodes, then it becomes crucial to determine the mechanism. It has been suggested that the drug may sensitize the dopamine system (Howes et al., 2004) via delta-9-tetrahydrocannabinol's (THC)

interaction with the mesolimbic dopaminergic system (Dean, Bradbury, & Copolov, 2003). THC is known to induce short-term psychotic experiences in healthy participants (Kenis, Rutten, & vas Os, 2010). Furthermore, it is well documented that intermittent exposure to either a pharmacological or environmental stimulus can increase the system's reactivity to a stimulus (Lieberman, Sheitman, & Kinon, 1997). If cannabis can be considered one of these stimuli, then such sensitization of the dopaminergic system is possible. Indeed, animal models support this theory as repeated exposure to THC increases psychomotor activation in rat models (Gorriti et al., 1999; Caloni et al., 2000). The most common age range (18 to 25) for the onset of psychosis also coincides with significant neural development. Another study found a differential impact of THC on the mesolimbic dopaminergic system, dependant on the developmental stage of rats (Pistis et al., 2004). Adolescent rats, unlike adults, demonstrated enduring behavioral changes after repeated exposure to cannabinoids. Interestingly, these rats displayed substantial individual variance to the paradigm, some exhibited heightened sensitivity, whereas others showed tolerance to the substance (Pistis et al., 2004). Thus, if it is true that dopaminergic sensitization can happen in cannabis-using humans, then subsequent psychotic triggers may be expected to disproportionately impact this subgroup.

The sensitization hypothesis may also apply to mechanisms outside of an exogenously stimulated dopaminergic system. For example, childhood trauma has been associated with a heightened sensitivity to stress, resulting in a possibly increased risk of psychosis (Glaser et al., 2006; Lardinois et al., 2011). Additionally, time spent in an urban environment has been associated with increased negative thoughts and paranoid thinking, possibly due to the sensitisation of threat beliefs (Ellett et al., 2008). These findings are consistent with a review of the seemingly disparate risk factors associated with the development of psychosis (Collip et al.,

2008). These authors integrated the evidence surrounding many of these variables, and suggested a mediation model. It was proposed that environmental risk factors (e.g. trauma, prenatal environment) could interact with genetic or epigenetic factors, and lead to greater psychological (i.e. cognitions) or physiological (i.e. dopamine) sensitivity (Collip et al., 2008). Ultimately, the cumulative impact of these variables might cause some people to be especially prone to the development of psychosis. If cannabis is a causal factor, these already high-risk individuals may more readily demonstrate psychotic symptoms after prolonged use.

Finally, the specificity of the relationship between two variables can often inform the interpretation of causation. Arseneault et al., (2002) found that early cannabis use did not confer an increased risk of depression, and use of drugs other than cannabis was not associated with an increased risk of psychosis. This is consistent with Moore and colleagues (2007), who saw mixed results between cannabis use and depression, with most *ORs* in the range of 0.77 to 1.59. However, Ksir and Hart (2016) argued that the development of psychosis may not be specific to cannabis. They provided evidence that suggested increased cannabis use is found in other mental health populations, such as depression, anxiety, and bipolar disorder. Furthermore, cannabis use often coincides with other drug use, such as tobacco (Rabin, Giddens, & George, 2014). Taken together, the parameters that outline the uniqueness of this relationship requires continued clarification. However, as Ksir and Hart (2016) state, if there is not a specific relationship between cannabis use and the development of psychosis, it is still possible that a variety of substances, including cannabis, may increase the likelihood of psychosis in vulnerable individuals.

The aforementioned obstacles of legality, the latency between initial use and future psychosis, the low base rate of psychotic disorders in the general population, and the difficulty of

controlling extraneous variables that are present in this field of research have often required compromise in study design. Most commonly, this has involved a retrospective examination of longitudinal data that was not ideally suited to provide insight into the cannabis-psychosis relationship (Hall and Degenhardt, 2009). As a result, many of the studies reviewed above contained heterogeneous formatting, making comparison difficult. These differences in data formats required a certain amount of subjective decision making when comparing the statistical results. For example, psychosis was sometimes operationalized as the number of symptoms displayed, rather than development of a disorder. More commonly, it was defined as the number of medically reported psychotic episodes, or admission to a hospital setting for a psychotic disorder. The latter two do not necessarily coincide with a formal diagnosis, and only the first method is likely to detect individuals that had untreated psychotic experiences. As a consequence, this could have led to an underestimate of the prevalence of psychotic tendencies in the cannabis using population. The question of specificity is complicated as well, because precise data on drug use other than cannabis is often lacking (Arseneault et al., 2002; Fergusson, Horwood, & Swain-Campbell, 2003). Finally, those studies which compare differing usage rates may be inherently confounded. It is possible that a percentage of "low" users (e.g. lifetime use of 1-10) could experience particularly aversive effects of the drug, and may self-exclude from future use.

There has yet to be a longitudinal study with the appropriate foresight and sensitivity to clearly illuminate the nature of the cannabis-psychosis relationship. Such a design might include measures of premorbid psychosis, formal diagnoses of schizophrenia spectrum disorders, and more accurately detail the degree of cannabis consumption, as well as the type. Despite this, it is clear that not all cannabis users develop psychosis. Nor do all individuals who develop psychosis

have a history of cannabis use (Arseneault et al., 2004). Thus, it is neither a sufficient, nor necessary ingredient in the development of this disorder. However, when both variables are present, cannabis use typically precedes psychosis, an earlier age of first cannabis use is associated with an earlier age of onset of psychosis, more cannabis use is associated with more severe psychotic symptoms, and these relationships persist when potentially confounding variables such as upbringing, employment, and prior psychotic symptoms are controlled for (Arseneault et al., 2004; Henquet et al., 2004; Moore et al., 2007; Stefanis et al., 2013).

Alternative Explanations of the Association

Despite the suggestion of a dose-dependent association in the above longitudinal studies, not all evidence has supported the hypothesis that cannabis causes psychotic disorders. An Australia-wide analysis compared cannabis consumption over several decades, via percentage of the population that reported use, to the prevalence rate of schizophrenia over the same time period (Degenhardt, Hall, & Lynskey, 2003). The rate of Australian cannabis use increased from approximately 22% to 33% throughout the 1980s to 2000s. Based on this, the mathematical models used by these authors predicted that there should be at least a percentage increase in schizophrenia. Yet, the incidence rate of schizophrenia remained around the national average of 1% (Degenhardt, Hall, & Lynskey, 2003). Although, it should be noted their analysis was narrow, as it did not include recorded psychotic experiences or non-schizophrenic diagnoses. Furthermore, this design could only detect incidences of schizophrenia that would otherwise have not occurred.

It is possible that the drug could act as a catalyst in high risk individuals, hastening their development of schizophrenia or worsening the symptoms, without increasing the overall number of diagnoses (Malone, Hill, & Rubino, 2010). There is some support for this, individuals

with schizophrenia who use cannabis demonstrate more psychotic symptoms and have a worse prognosis than those who do not (Hall, Degenhardt, & Teesson, 2004). Linszen et al. (1994) tracked 94 psychotic patients and assessed their symptoms monthly. The 24 patients that used cannabis exhibited significantly more positive symptoms of psychosis, and there was also evidence for a dose-dependent effect. This remained significant after the authors adjusted for other drug use and premorbid adjustment (Linszen et al., 1994). A longitudinal study was conducted, where participants that displayed early symptoms of psychosis were tracked over a two-year period (Corcoran et al., 2008). Cannabis use significantly interacted with time, and was associated with a greater incidence rate of perceptual disturbances. No significant results were found in a between groups (users vs. non-users) comparison at baseline. Thus, these results are suggestive of an exasperation effect of cannabis on psychotic experience (Corcoran et al., 2008). However, it should be noted this effect does not exclude a causative role of cannabis in the development of a psychotic disorder.

A "self-medicating" hypothesis should also be considered as an alternative, where those who engage in cannabis use do so to lessen the discomfort of pre-existing subthreshold psychotic experiences. However, the evidence for this is sparse. First, it is not immediately consistent with the findings of temporal precedence. To resolve this discrepancy, premorbid psychosis would have to influence cannabis use, on average, for several years before individuals exhibited diagnostic symptoms and a diagnosis is made (Stefanis et al., 2013). This is substantially longer than the median duration of untreated psychosis, 60 weeks (range 16-130 weeks), that was reported in a recent study (Schultze-Lutter et al., 2015). It is also unclear whether the self-medication hypothesis can account for the possibly specific relationship between cannabis use and future psychosis. It could be that incipient psychosis leads individuals to use drugs that

produce effects congruent with their early symptomology. However, other substances that produce acute psychotic-like states, such as amphetamine and cocaine, are not associated with as much risk of future psychosis (Phillips, McKeown, & Sandford, 2009). To test the likelihood that the experience of psychosis leads to cannabis use, Fergusson, Horwood, & Ridder (2005) constructed two reciprocal causal structural equation models. Using data from the Christchurch Health and Development Study (CHDS), their results indicated that the self-medication direction of causality was not statistically significant, and that a more probable model was one of cannabis use causing subsequent psychotic symptoms. Ferdinand and colleagues (2005) analyzed the data from a 14-year follow-up of the "Zuid-Holland" study. Consistent with previous literature, they found that cannabis was a risk factor for the development of psychosis (*OR* = 2.81). However, these authors also noted that symptoms of psychosis was predictive of subsequent cannabis use (*OR* = 1.70). Thus, the self-medication model is not entirely without some support. These authors suggested that a causal relationship in both directions could exist, or that uncontrolled residual variables may modulate both cannabis use and psychosis (Ferdinand et al., 2005).

Several factors have been suggested as a potential cause for psychotic symptoms, while also influencing cannabis use. For example, it is common for schizophrenia and addiction to coincide (Hong et al., 2011). This could result from a shared vulnerability between these two variables (Batel, 2000; George, 2008). The neural physiology associated with schizophrenia may also increase the probability of tobacco addiction (George, 2008). Zullino et al. (2010) found that individuals with schizophrenia show an approximate six-fold increase in nicotine use, compared to the general population, and two 18-month follow up studies reported evidence for the temporal precedence of tobacco use. Both addiction and schizophrenia have been associated with reduced grey matter volume, which also negatively correlates with impulsivity (Schiffer et al.,

2010). Furthermore, addiction, cannabis, and schizophrenia have all been associated with the dopamine opioid neurotransmission systems (Batel, 2000). Thus, there are several possibilities where a shared vulnerability could manifest.

There is also evidence for the cannabis-psychosis relationship to be driven by independent genetic factors. McGuire et al. (1995) found that those who experienced acute psychotic-like states after cannabis use were more likely to have a family history of schizophrenia. Additionally, individuals at a genetic risk for psychosis also experience greater psychotic symptoms in response to cannabis use (Degenhardt & Hall, 2002; Rutten, van Os, & Kenis, 2010). There is evidence that a variation in the catechol-O-methyltransferase (COMT) gene coincides with increased sensitivity to the psychotic effects of THC (Henquet et al., 2006). Caspi et al. (2005) argued that a polymorphism in the COMT gene interacts with cannabis use in adolescence, but not adulthood, to predict future experiences of psychosis. However, COMT has not been reliably associated with the development of schizophrenia (Fan, 2005). More likely, COMT may act as a moderator for the development of psychosis when in the presence of other, yet to be defined, genes (Henquet et al., 2008). More research is required to determine if COMT, in combination with other genes, independently promotes both psychosis and cannabis use, or if it moderates the impact of cannabis on future psychosis (van Winkel & Keupper, 2014).

Although the current evidence leans toward a causative role of cannabis in the development of future psychosis, this relationship requires substantially more study. Complicating matters, many of the alternative hypotheses are not mutually exclusive, and a bi-directional causal relationship is possible. Furthermore, both the dopaminergic system and the endocannabinoid systems are associated with psychosis, and activated during cannabis use (Kuepper et al., 2010; Gupta et al., 2014). Therefore, it is possible that an underlying

vulnerability could exist in one or both of these systems that independently increase the risk of psychosis and cannabis use. There is also indication that some individuals are more inclined to experience the psychotic effects of cannabis, perhaps because of a shared susceptibility to both these experiences and psychosis (Degenhardt & Hall 2002). A subset of this group may be more likely to report experiences congruent with a diagnosis of a psychotic disorder. Ultimately, this could lead certain people to more readily seek out treatment and receive subsequent diagnoses (Ernst, 2002). Since the above studies primarily relied upon diagnosis or hospital admission, this may inflate the reported association between cannabis and future psychosis. Yet, even in the most conservative interpretation, cannabis use remains a clearly demonstrated risk factor for future psychotic symptoms and diagnoses. Therefore, research aimed at elucidating the subset of cannabis users most at risk for psychosis, regardless of the precise associative mechanisms, is of vital importance.

Neurochemistry of Psychosis and Cannabis

There is substantial support for the role of dopamine in schizophrenia (Volavka, Davis, Ehrlich, 1979; Laruelle, Kegeles, & Abi-Dargham, 2003; Ellenbroek, 2005). This evidence has, in part, come from the intersection of schizophrenia and pharmacology (Ellenbroel, 2005). Many antipsychotic treatments function in a similar way, by blocking dopamine D_2 receptors (Seeman, 2013). It is also known that psychostimulants increase dopamine levels while producing psychotic-like experiences (Hiroshi, 2002; Seeman, 2013). Amphetamine-induced psychosis and schizophrenia both produce deficits in attentional inhibition, thought to be caused by heightened dopamine neurotransmission (Asnafi et al., 2013). Further examples of the similarities between certain dopamine heightening drugs and the positive symptoms of schizophrenia include: paranoid beliefs, altered perception, and thought distortions (Murray et al., 2013). In fact, the

administration of drugs that influence the dopamine system has become the primary means to simulate schizophrenia in animal models (Milind, Renu, & Sushila, 2013). Thus, an aberration in the dopaminergic systems may represent a potential neural vulnerability to psychosis.

Presynaptic neurotransmitter binding sites have become a particular area of interest in the investigation of the dopaminergic abnormalities present in schizophrenia (Howes et al., 2012). Elevated pre-synaptic striatal dopamine has been consistently found in schizophrenic patients, via radiolabeled L-dopa administration (Howes et al., 2007; Fusar-Poli, 2009). Baseline synaptic dopamine levels, dopamine synthesis capacity, and dopamine release were demonstrated to have an association with schizophrenia (Howes et al., 2012). Furthermore, most antipsychotic medications target the D_2 receptor of the post-synapse, rather than pre-synaptic mechanisms (Howes et al., 2012). The authors suggest that this may explain the relatively high rate of unsuccessful antipsychotic medications.

Cannabis use has been shown to involve both dopamine and endocannabinoid receptors (Gupta et al., 2014). The cannabinoid receptor, CB_1, is also located presynaptically (Malone, Hill, Rubino, 2010). The primary psychoactive ingredient in cannabis is THC, and it is one of the few known exogenous metabolites that influence our endogenous cannabinoid receptors (Shrivastava et al., 2014). According to Malone, Hill, & Rubino (2010) neurotransmitter activity on the post-synapse appears to release endocannabinoids, these neurotransmitters travel across the synapse in a retrograde direction and couple onto CB_1 receptors. This inhibits further neurotransmitter release and acts as a regulator (Shrivastava et al., 2014). Interestingly, THC was not found to significantly alter the amount of dopamine release in the striatum in a sample of recreational cannabis users (Stokes et al., 2009). However, cannabinoids also increase extracellular dopamine through cannabinoid receptors located on certain dopaminergic neurons

(Gardner, 2005). Therefore, there is evidence that cannabis does, at least partially, involve some of the same neural systems as schizophrenia and psychosis.

Shared Phenomenological Experience

Much less research has focused on the similarities between the phenomenological experiences associated with cannabis and psychosis. The subjective experiences associated with cannabis use vary dramatically, and for many individuals do not resemble psychosis at all (Barkus et al., 2006). However, a significant minority of users do report psychotic-like perceptions and sensations, such as delusional thinking, auditory hallucinations, and paranoia. (Barkus et al., 2006). These same experiences overlap with several "positive symptoms" of schizophrenia (American Psychiatric Association, 2013). Barkus and Lewis (2008) attempted to explain the occurrence of these symptoms within a subgroup of cannabis users. The authors had non-clinical participants complete both the Cannabis Experiences Questionnaire (CEQ) and the Schizotypal Personality Questionnaire (SPQ). The SPQ asks about perceptions and experiences often associated with schizotypal personality disorder, and a higher score is indicative of greater schizotypal personality traits (Raine, 1991). Those who endorsed high levels of psychotic-like experiences while using cannabis also tended to score higher on the SPQ (Barkus & Lewis, 2008). The authors suggested that this may be a population at a particularly high risk for future psychotic episodes. There were no differences in average SPQ scores between users and non-users, suggesting that cannabis use by itself does not lead to higher schizotypy, but that unusual experiences while using cannabis may be related.

This correlation has also been demonstrated during cannabis intoxication, rather than assessments of past experiences. A study by Mason et al. (2008) attempted to examine the relationship between schizotypy and cannabis use in a naturalistic setting. These researchers

received ethics approval to allow cannabis using participants to smoke a standard "joint" before administration of the SPQ and the Psychotomimetic States Inventory (PSI). The PSI is a measure of current schizotypal symptomology. Mason and colleagues (2008) found significantly elevated levels of psychotic experiences after consumption for the users who scored high on the SPQ, compared to users that scored low on the SPQ, and both non-using groups. This suggests that cannabis and psychosis may at least partially share neural processing networks that lead to psychosis-like experiences. Thus, perhaps those who have overly sensitized, or vulnerable, networks are more likely to have psychotic-like experiences with cannabis use.

Exploring this Relationship

While preliminary data suggests a possible link between the symptoms of psychosis and unusual experiences during cannabis use, the neural mechanisms of these phenomena have yet to be thoroughly investigated. Electroencephalography (EEG) allows examination of the patterns of neural network processing, providing high temporal resolution of neural functioning following stimulus presentation. Attenuated early event-related potential (ERP) amplitudes are thought to reflect reduced perceptual encoding. For example, the P100 ERP (an electrically positive inflection approximately 100 milliseconds after a stimulus) is thought to reflect low level perceptual encoding and response to visual stimuli (Luck, 2005). P100 deficits have been reported in both schizophrenia (Haenschel & Linden, 2011) and those who score high on schizotypal traits (Koychev et al., 2010). It appears that cannabis users may share some of these deficits, demonstrating reduced memory, attention, and concentration (Crane et al., 2012). The negative 170 millisecond (N170) ERP has repeatedly been shown to play a role in facial perception and emotion (Heisz, 2006; Lissa, 2014). N170 ERPs tend to demonstrate the greatest amplitude when healthy adults are shown facial stimuli (Luck & Kappeman, 2012; Almeida et

al., 2014). Facial emotions have also been found to modulate this ERP (Lynn & Salisbury, 2008; Brenner et al., 2014; Brenner et al., 2016). Wild & Busey (2004) demonstrated that highly visible faces elicit greater N170s than low contrast faces, and that these ERPs are elicited when facial stimuli are believed to have been presented, regardless of whether they were actually presented.

However, this process is complex, and several factors influence the amplitude of the N170 ERP. Greater N170 ERPs may be evoked when healthy adults try to perceive inverted, as compared to upright face stimuli (Sadeh & Yovel, 2010). This is thought to be due to the recruitment of additional cognitive resources in the perception of such faces, perhaps from more general object recognition areas of the cortex (Epstein et al., 2005; Sadeh & Yovel, 2010). Repeated exposure to unattended facial stimuli has been shown to demonstrate habituation, and reduce the N170 amplitude over time (Heisz, Watter, & Shedden, 2006; Feng, Lou, & Fu, 2013). Furthermore, the load placed upon working memory has been seen to inversely impact N170 amplitude (Morgan et al., 2008). In addition to face-nonspecific cortical regions, some of these divergent findings may be accounted for by a model that introduces cognitive-mediation (i.e. top-down processing; Bentin & Golland, 2002). Under this premise, visual perception of a face may be augmented by stochastic activity in higher-order processes (Wild & Busey, 2004). Overall, this may suggest that it is also possible that amplification can occur as a result of stimulus expectation.

The depth of knowledge surrounding the N170 ERP make it a potentially useful measure of shared deficits between cannabis users and individuals who demonstrate symptoms of psychosis. Individuals with schizophrenia show reduced N170 ERP amplitudes in response to facial stimuli (Lynn & Salisbury, 2008; McCleery et al., 2015; Tso et al., 2015). Lynn & Salisbury (2008) found that schizophrenic patients failed to show N170 amplitude moderation by

facial expression, or right hemisphere bias in processing, compared to controls. Schizophrenic patients also failed to demonstrate the aforementioned tendency for greater N170 ERPs in response to inverted faces (Tsunoda et al., 2012). Unlike controls, schizophrenic patients were not found to elicit greater N170 responses for face stimuli, compared to images of trees (Maher et al., 2015). Furthermore, these deficits in ERP amplitude have been positively associated with the quantity or endorsed clinical symptoms or severity of social dysfunction (Lynn & Salisbury, 2008; Kirihara et al., 2012). Similar findings have been reported across numerous additional publications. Although reduced N170 amplitudes are most commonly reported, the ERP abnormalities associated with schizophrenia have displayed other distortions. A subgroup of individuals with schizophrenia, those who exhibit paranoid delusions and more readily feel threatened, demonstrate greater N170 responses to fearful facial expressions (Lee et al., 2010; Tso et al., 2015). Finally, N170 deficits have also been found in a sample of people related to diagnosed schizophrenics (Ibanez et al., 2011). This suggests that cortical firing in response to face discrimination tasks may be a feasible marker of vulnerability.

Although schizotypy has not received the same level of study as schizophrenia, a number of studies have reported ERP aberrations compared to controls. Batty and colleagues (2014) found reduced N170 amplitudes in response to inverted faces among schizotypal populations. Schizotypal individuals also displayed diminished P100, but not N170, ERPs in response to a visual paradigm (Koychev et al., 2010). Although the N170 did not display attenuation in this study, it could have been the result of non-face stimuli employed in the task. Oestreich et al. (2015) measured the N170 in response to auditory stimuli. These authors reported that it is common for healthy controls to demonstrate N170 suppression in response to self generated, but not externally generated, stimuli. Those who scored high on the SPQ exhibited significantly less

attenuation than low scorers. While not a visual task, the results of high scorers was consistent with findings from schizophrenic samples (Ford et al., 2001). Combined, these results suggest that people who do not have a diagnosis, but score high on self-report measures of schizotypy, may act as a suitable proxy for individuals with schizophrenia in research designs that target cortical functioning.

The extant literature examining cannabis use or cannabinoids, in relation to the N170 ERP was scarce. Skosnik and colleagues (2006) found that cannabis users demonstrated decreased 20Hz EEG power and signal-to-noise in a steady state auditory task, and that this was negatively correlated with SPQ scores. This suggested that they may have had reduced signal strength or auditory synchronization (Skosnik, et al., 2006). Cannabis users and non-users classified as ultra-high risk for psychosis demonstrated similar P300 attenuations (van Tricht et al., 2013). Cannabis users have also shown abnormal event-related potentials in response to a variety of stimuli. In a study where cannabis users were provided either placebo cigarettes, or THC containing cigarettes, THC ingestion was associated with a decrease in P300 & N400 ERP amplitude (Ilan et al., 2005). The authors stated these reductions were suggestive of impaired working memory and perception of novelty, respectively. Troup et al. (2016) detected a dose-dependent relationship between cannabis consumption and P300 reduction on an emotional recognition task, as compared to non-users. Conversely, Skosnik and colleagues (2008) found heighted P300 amplitudes in cannabis users for both visual oddball and affective categorizations tasks, in response to negative affective trait words. Interestingly, individuals with schizophrenia often show diminished P300 responses to affective stimuli (Bramon et al., 2004). Skosnik et al. (2008) suggested that cannabis may be most similar to the experiences elicited by the positive

symptoms of the schizophrenic spectrum (i.e. hallucination and delusion), as compared to negative symptoms (i.e. paranoia and attentional deficits).

Despite the possibility that certain cannabis-induced phenomenological experiences and psychotic symptoms are the result of shared or similar neural systems, there has been no investigation to determine if these share similar neural firing patterns. Such findings may help to delineate a subset of the cannabis using population who may be at a higher risk for the development of psychosis. Identifying these individuals may ultimately provide valuable preventative public health information. The present study seeks to contribute to this issue by using psychophysiological methods. First, we sought to determine if particularly unusual experiences during cannabis use are predictive of schizotypy, thereby replicating the results found by Barkus & Lewis (2008). Then, we employed ERP analysis in an attempt to determine whether those who score high on unusual cannabis experiences (using the CEQ) and high schizotypal scorers (using the SPQ) exhibit similar neural deficits.

In the current study we have used a visual paradigm that requires participants to indicate whether a face was present or absent within a Gaussian static field. Our stimuli are loosely based off those used by Wild and Busey (2004). We have recorded the electrophysiology elicited by these stimuli, and have conducted comparisons across five groups. These include participants (1) high in schizotypal endorsements, (2) high in unusual cannabis experiences, and (3) high in both of the former. We have two control groups (4) average SPQ and CEQ scoring cannabis users, and (5) average SPQ scoring non-users. From this, we hypothesize that participants high in schizotypy will show weaker N170 responses toward face-present stimuli, than either control group. Following previous literature, this would suggest that their perceptual neurocognitive pathways are compromised. Furthermore, we expect the false-positive responses (i.e. endorsed a

face in a static-only image) of healthy controls to exhibit a greater N170 amplitude than those high on schizotypy. This would be indicative of greater neural efficiency during top-down processing. Finally, as compared to high SPQ scorers, we anticipate that those who score high on the CEQ will display similar patterns of the N170 response. This hypothesis is based on the assumption that the same neural pathways are involved, with similar deficits in neural integrity producing particularly unusual experiences with cannabis and more schizotypal experiences. Presently, we believe we are the only research team to investigate the electrophysiological correlates between the phenomenology of cannabis use and schizotypal personality traits. If these associations are found to exist, then the user's experience of cannabis may be able to act as a marker for neural vulnerability to psychosis.

Methodology

Study Objectives

(1) To examine whether participants high in schizotypy or high in unusual experiences with cannabis (the experimental groups) demonstrate electrophysiological differences in response to visual facial stimuli, as compared to average cannabis users and non-users (the control groups). **(2)** To determine whether these responses represent identifiable differences in the integration of sensory (bottom-up) and cognitively-mediated (top-down) neural activity. **(3)** To evaluate whether the experimental groups demonstrate similarity in their predicted differences from the control groups.

Research Design

This study was a quasi-experimental between groups multifactorial design. The first trait, schizotypy, was operationalized through the Schizotypal Personality Questionnaire (SPQ). The SPQ asks participants about experiences, thoughts, and perceptions that often correspond with schizotypal behavior and personality (Raine, 1991). We were interested in the potential differences between those who endorse high schizotypy, as compared to average scorers on the SPQ. We defined a high score as equal to or above the 75^{th} percentile. To assess our second trait, the phenomenological experiences associated with cannabis use, we administered the Cannabis Experiences Questionnaire (CEQ). The CEQ is a self-report questionnaire that assesses thoughts, perceptions, and sensations attributed to consumption of cannabis. We separated high and average CEQ scorers with the 75^{th} percentile.

Electroencephalography data collection occurred during the presentation of visual stimuli. These stimuli comprised of 480 Gaussian generated static images in greyscale, displayed

on a CRT Monitor with a 60 Hz refresh rate. A face embedded within the static, also in greyscale, was present in 320 of these images. Of those trials that contained faces, 160 were male and 160 were female. Half of the faces were considered "high visibility", while the remainder were considered "low visibility", with visibility defined as the transparency level of the images in Adobe® Photoshop®. Highly visible images were set to 95% transparency (only 5% of the face was visible), and low visibility images were set to 97% transparency. Based on pilot data, high visibility trials produced a hit rate of approximately 70%, and low visibility trials elicited a hit rate of approximately 40%. The remaining 160 images contained only visual static (see appendix 1 for image examples). A consistent visual angle was maintained for all images across participants, at 5.922 degrees.

For each trial participants responded, by button press, whether they believed stimulus was visual static only, or whether a face was located within the static. This created four trial-response combinations (henceforth, trial-types): (1) correct noise-only endorsements (correct rejections), and (2) incorrect noise-only endorsements (misses), and (3) Correct face-present endorsements (hits), (4) incorrect face-present endorsements (false-positives). The average event-related potentials (ERPs) for each group associated with hits provided an indication of their relative sensory encoding of face stimuli. The average ERP for false-positives allowed us to examine the relative effect of cognitive processes on ERP amplitudes between groups.

Study Procedure

Participants. Written informed consent was obtained from all participants, in accordance with UBC ethics. Participants were recruited through three avenues: (1) the Psychology Department's Human Subject Pool (HSP) system to collect an undergraduate sample in exchange for course credit, (2) paid undergraduate volunteers, and (3) paid participants from the

community. For sources (1) and (2), participants first completed an online survey for HSP credit. This was used to screen for the four primary participant groups: (1) Those who scored high on the SPQ (the "High SPQ" group), (2) those who scored high on the CEQ (the "High CEQ" group), (3) those who scored average on both questionnaires (the "Average Users" group), and (4) those who did not endorse past or present cannabis use and also scored low on the SPQ (the "Average Non-User" group). Those that fell within one of the above groups were contacted via email and invited to participate in the EEG portion of the study. Source (3) was recruited through ads and flyers placed throughout the community, in addition to the UBC paid psychology study website. These participants completed a brief (10 minute) phone screen that contained a short-form version of the SPQ and CEQ, constructed specifically for this design (see appendix 2). Eligible community volunteers completed the SPQ and CEQ in the laboratory, to establish group placement. Both methods of data collection led to the creation of a fifth group, participants that scored high on both the SPQ and CEQ (the "High on Both" group). All participants were either awarded course credit or $10 an hour for participation.

Participants had to be between 18-55 years old, had 20/40 corrected vision or better, and were capable of reading and understanding English. Participants were excluded if they had a history of diagnosed neurological disorder, seizures, or stroke. Participants that reported a serious head injury coupled with loss of consciousness for five minutes were also omitted. Individuals judged to have complicated histories of comorbid drug use were also excluded for participation. Some participants (n = 3) were excluded due to poor quality of electrophysiological data (i.e. high impedance).

In total, usable data was collected from ninety-seven participants. They were divided between the groups as follows: High CEQ (n = 19), High SPQ (n = 19), Average-User (n = 24), Average Non-User (n = 20), and High on Both (n = 15).

EEG System. We used a 32 electrode site EEG system. During recording, impedances were below a 5-kOhm. Recording took place in a dark, quiet room. A common average reference was employed during recording and data was sampled at 1000Hz (Brainvision Quickamp).

Task Administration. Participants were provided with instructions by the research assistant, and four practice trials were given with feedback. The research assistant then probed for any remaining ambiguity, and clarified the task as necessary. Participants were instructed to respond "1" if they perceived a face and "2" if they did not perceive a face. All responses were made with the participant's dominant hand. The duration of the task was approximately 40 minutes.

Measures

Demographics. Standard demographic information was obtained using an in-house questionnaire. Variables that were collected included: sex, age, handedness, ethnicity, level of education completed, parental education level, command of the English language, recent alcohol or drug use (within 24h), smoking habits, caffeine use, current diagnoses and medication.

Schizotypal Personality. Schizotypal personality was measured using the Schizotypal Personality Questionnaire (SPQ; Raine, 1991). This is comprised of 74 self-report questions. Moderate criterion validity (0.68) and high test-retest reliability (0.82) have been demonstrated for the SPQ (Raine, 1991). Exploratory analyses that use the SPQ as a continuous variable for comparison with EEG amplitudes was calculated.

Cannabis Experiences. The Cannabis Experiences Questionnaire (CEQ) was used to assess unusual experiences during or after marijuana use. The CEQ is a self-report scale that measures three aspects of cannabis use; the frequency of pleasurable, psychotic-like, and after-effect experiences of the drug. Scores in the 75th percentile or higher on any of these sub-scales allocated the participant to the High CEQ group. A score below the 75th percentile on every scale allocated the participant in the Average User group. This is a relatively new scale, designed by Barkus and colleagues (2006), which currently lacks studies reporting its reliability and validity. Therefore, Cronbach's alpha for the total score and for each subscale score was reported at the end of the *Statistical Procedure* subsection in the results section.

Behavioral & Electrophysiological Recording. Stimuli were presented with E-Prime 2.0 software of Psychology Software Tools (2013). The rate of correct face-present endorsements, incorrect face-present endorsements, correct noise-only endorsements, and incorrect noise-only endorsements was recorded, as well as the response time for each trial. Only trials where the participant responded within 5000ms were analyzed. This was done to increase the probability that responses were the result of believed perception, rather than deliberate guesses.

Electrophysiological activity was recorded with Brain Vision Recorder 2.0 software of Brain Products (2015). The electrode sites were baseline corrected, ocular corrected using the Gratton-Coles method (Gratton, Coles, & Donchin, 1983), and filtered between 1.0 and 30.0Hz. This data was segmented and sorted into the above four trial-types. Each segment began 100ms pre-stimulus and ended 900ms post-stimulus. Within the resulting segments, epochs were automatically rejected if they exceeded ±100μV. ERPs were produced by averaging the segments corresponding to the four trial-types within each participant. Consistent with the

literature, we peak-picked N170 ERPs from the P7 and P8 sites (Luck & Kappman, 2012). This was defined as the greatest negative inflection between 100-270ms after stimulus onset.

Initial Power Analysis

This study's primary analysis involved the differences in EEG activity between groups. Unfortunately, we could find no study that used similar stimuli to compare these groups. Tsunada et al. (2012) examined the differences in N170 amplitude elicited from 15 control and schizophrenic participants, and found a standard effect size of $d = 1.36$ for upright faces. Batty et al. (2014) investigated the differences in N170 ERPs between participants that were either high or low in schizotypy, and found an effect size of $d = 0.33$. The lower effect size of Batty and colleagues may have been partially due to the use of a median split to divide their sample. The present study has used the 75^{th} percentile to divide the groups. Thus, we anticipate the High SPQ group to exhibit greater deficits than those in the study by Batty and colleagues.

From these studies, we had predicted that our experiment would produce a Cohen's *d* between 0.33 and 1.36 for face-present trials. As we expected our effect sizes to be somewhat greater than the minimum listed, the midpoint of these two values, 0.85, was used in our power analysis. Using this value, a two-tailed *p-value* of .05, and a targeted power of 0.75, our optimal sample size was 21 to detect a difference, between conditions.

Results

Participant Demographics

A total of 97 volunteers participated in this study, with a mean age of 23.93 years (SD = 8.35 years). Of these, 43 were recruited through off-campus advertising or a paid studies listing (mean age = 28.37, SD = 10.05). The remaining 54 were recruited through the University of British Columbia's human subject pool (HSP; mean age = 20.39, SD = 4.09). Sixty-one participants identified as female and 36 as male. Fifty people described themselves as Caucasian, 41 as Asian, four as Hispanic, one as Aboriginal, and one as Black. Ten participants said they had experienced a mood disorder in the past. Via phone-screen or in-lab interview, each of these participants was determined to either be in remission, lack a professional diagnosis, or be absent of core symptoms. Four participants stated the experience of a "serious head injury", however, upon interview, no symptoms associated with such an injury (i.e. vomiting, loss of focus) were reported, nor was any detriment to daily functioning endorsed. Furthermore, none of these participants were certain they had suffered a concussion. An additional six participants claimed to have lost consciousness for a period longer than five minutes. In each case, these reports did not appear to be due to trauma or medical condition (e.g. one participant claimed loss of consciousness after cannabis use).

Thirty-three participants described themselves as non-users of cannabis, 18 as past users, and 46 as current users. The frequency of cannabis use endorsed by this sample was: 7.2% = "only once or twice"; 2.1% = "about once a year"; 10.3% = "a few times each year"; 8.2% = "about once/twice a month"; 5.2% = "about once a week"; 13.4% = "more than once a week"; and 19.6% = "everyday". Forty participants claimed expenditure of greater than $4.00 per week on cannabis. Participants were asked to estimate their total cannabis use history, this had a range

Table 1: *Frequency of Non-Cannabis Drug Use*

Additional Substances Used	Number of Participants	Median Frequency of Use Endorsement
Tobacco	22	"Twice a Week"
Alcohol	69	"Two to Three Times a Month"
Hallucinogens	18	"One or Two Times in the Past Year"
Amphetamines	6	"One or Two Times in the Past Year"
Cocaine	11	"One or Two Times in the Past Year"
Barbiturates	1	"One or Two Times in the Past Year"
Opiates	2	"One or Two Times in the Past Year"
Tranquilizers	2	"Three to 11 Times in the Past Year"
Ecstasy/MDMA	18	"One or Two Times in the Past Year"

of 2 to 1,000,000 uses. When outliers were removed from this variable, there was a mean of 408.43 uses (SD = 695.95, median = 62.50). The mean age of first use was 16.31 years. Table 1 provides a listing of additional drugs endorsed by this sample, as well as the median endorsed statement of frequency.

Group status was determined by score on the Cannabis Experiences Questionnaire (CEQ), and the Schizotypal Personality Questionnaire (SPQ). Nineteen participants were placed within the High CEQ group, with a total mean CEQ score of 132.10 (SD = 24.77). The mean age was 26.00 (SD = 9.01), with a range of 18 to 47, and a gender distribution of 10 females. These participants had a mean score of 28.00 on the CEQ "after-effects" subscale, 52.26 on the "paranoid-dysphoric" subscale, and 51.84 on the "pleasurable" subscale. Ten of these participants were recruited through the HSP system. Five High CEQ participants endorsed cigarette use, and eight indicated previous use of additional illicit substances. Sixteen of these

volunteers said that they used cannabis at least once a month, with a median frequency statement of “more than once a week”. The total mean SPQ score of this group was 13.79 (SD = 7.05).

Nineteen individuals had scores consistent with the High SPQ group, with a mean total SPQ score of 35.68 (SD = 7.07). The mean age of this group was 19.42 (SD = 1.43), with a range of 18 to 24. Sixteen of these participants were recruited through the HSP system, and 16 were female. One person endorsed cigarette use, and four stated previous use of additional illicit substances. Six indicated cannabis use of at least once a month, with a median endorsed frequency statement of “more than once a week”. For those that used cannabis, the mean total CEQ score was 108.33 (SD = 18.46).

Fifteen people met criteria for the High on Both group. Eight of these participants were female, and nine were recruited through the HSP system. Their mean age was 24.20 (SD = 7.98), with a range of 18 to 44. The mean total CEQ score for this group was 150.07 (SD = 25.80), 32.01 on the after effects subscale, 65.13 on the paranoid dysphoric subscale, and 52.87 on the pleasurable subscale. Their mean SPQ score was 35.80 (SD = 8.18). Eleven participants said they used cannabis at least once a month, with a median frequency statement of “more than once a week”. Eight endorsed use of additional illicit drugs.

The Non-User Group consisted of 20 participants. Fifteen of these participants were female, and 12 were recruited through the HSP system. Their mean age was 23.30 (SD = 7.49), with a range of 18 to 45. This group had a mean total SPQ score of 11.05 (SD = 7.69). None of these participants reported cigarette use, nor did any report a history with non-cannabis illicit substances.

Table 2: *Participant Demographics by Group*

	High CEQ	**High SPQ**	**High on Both**	**Average Non-User**	**Average User**
Group Size	19	19	15	20	24
Mean Age *(SD)*	26.00 *(9.01)*	19.42 *(1.43)*	24.20 *(7.98)*	23.30 *(7.49)*	26.21 *(10.71)*
Sex Distribution	10 Female; 9 Male	16 Female; 3 Male	8 Female; 7 Male	15 Female; 5 Male	13 Female; 11 Male
Recruitment Method	10 HSP; 9 Community	16 HSP; 3 Community	9 HSP; 6 Community	12 HSP; 8 Community	7 HSP; 17 Community
Mean SPQ Score *(SD)*	13.79 *(7.05)*	35.68 *(7.07)*	35.80 *(8.18)*	11.05 *(7.69)*	11.71 *(5.95)*
Mean CEQ Score *(SD)*	132.10 *(24.77)*	108.33 *(18.46)*	150.07 *(25.80)*	N/A	93.50 *(17.56)*
Median Cannabis Use Statement	"more than once a week"	"more than once a week"	"more than once a week"	N/A	"about once or twice a month"

Note: Not all High SPQ participants used cannabis, the CEQ mean score and median usage statement do not include High SPQ non-users.

Twenty-four participants were classified Average Users. Thirteen of these participants were female, and seven were recruited through the HSP system. Their mean age was 26.21 (SD = 10.71), with a range of 18 to 51. The total mean CEQ score for this group was 93.50 (SD = 17.56), with a mean score of 20.20 on the after effects subscale, 36.67 on the paranoid dysphoric subscale, and 36.63 on the pleasurable subscale. Their total mean SPQ score was 11.71 (SD = 5.95). Fourteen volunteers in this group stated a usage rate of at least once a month, with a

median frequency statement of "about once or twice a month". Seven reported the use of additional illicit drugs.

Statistical Procedure

The mixed model ANOVA used to analyze the data used two within-subject factors, as well as a between-subject factor. The within-subject factors were electrode site laterality (electrode site P7 on the left side, and electrode site P8 on the right side) and the trial-response pattern (henceforth trial-type). Electrode sites P7 and P8 are located above the occipito-temporal cortex, and often produce the largest N170 ERP amplitudes in response to facial stimuli (Luck & Kappman, 2012). The between-subject factor was the participant's group categorization. All reported results from the Mixed ANOVA include the partial-eta squared effect size (η_p^2). Furthermore, pairwise comparisons were used to determine the principle factors responsible for detected significant differences. Cohen's *d* was calculated for significant pairwise comparisons. Morris and Deshon's (2002) equation 8 was used to correct for dependence between means, where necessary.

Prior to the main analyses, outlier ERP amplitudes were determined for each trial-type at the P7 and P8 electrode sites. Amplitudes greater than three standard deviations above or below the interquartile range for each group were considered outliers and were excluded from analyses. Participant exclusion also occurred if any of the four trial-types consisted of less than 20 trials. Furthermore, average ERPs that consisted of 20 or more trials, but had a visually indistinguishable N170 peak were also excluded.

Pearson's bivariate correlations were calculated between three potentially confounding variables (age, sex, and recruitment method) and the four trial-types for each electrode site. This

resulted in a Bonferroni adjusted significance value of $p = .0125$. None of these variables were significantly correlated with N170 ERP amplitudes for any trial-type at either electrode site (all p's > 0.013). Therefore, covariates were not included in the ANOVAs.

The CEQ is a new questionnaire and lacks the same reliability and validity testing as the SPQ. Therefore, Chronbach's alphas were calculated for the total CEQ score and each subscale. This analysis included all individuals that participated in the CEQ pre-screen ($n = 586$). The overall scale (Total CEQ) consists of 55 items ($\alpha = .914$). The paranoid-dysphoric subscale consists of 25 items ($\alpha = .918$), the pleasurable subscale consists of 16 items ($\alpha = .893$), and the after-effects scale is comprised of 12 items ($\alpha = .910$). Thus, the Total CEQ scale, and each of the subscales, demonstrated a high degree of reliability. Cronbach's alpha was also calculated for the Total SPQ score ($\alpha = .931$), and the high reliability reported previously was replicated in this sample.

Statistical Analyses

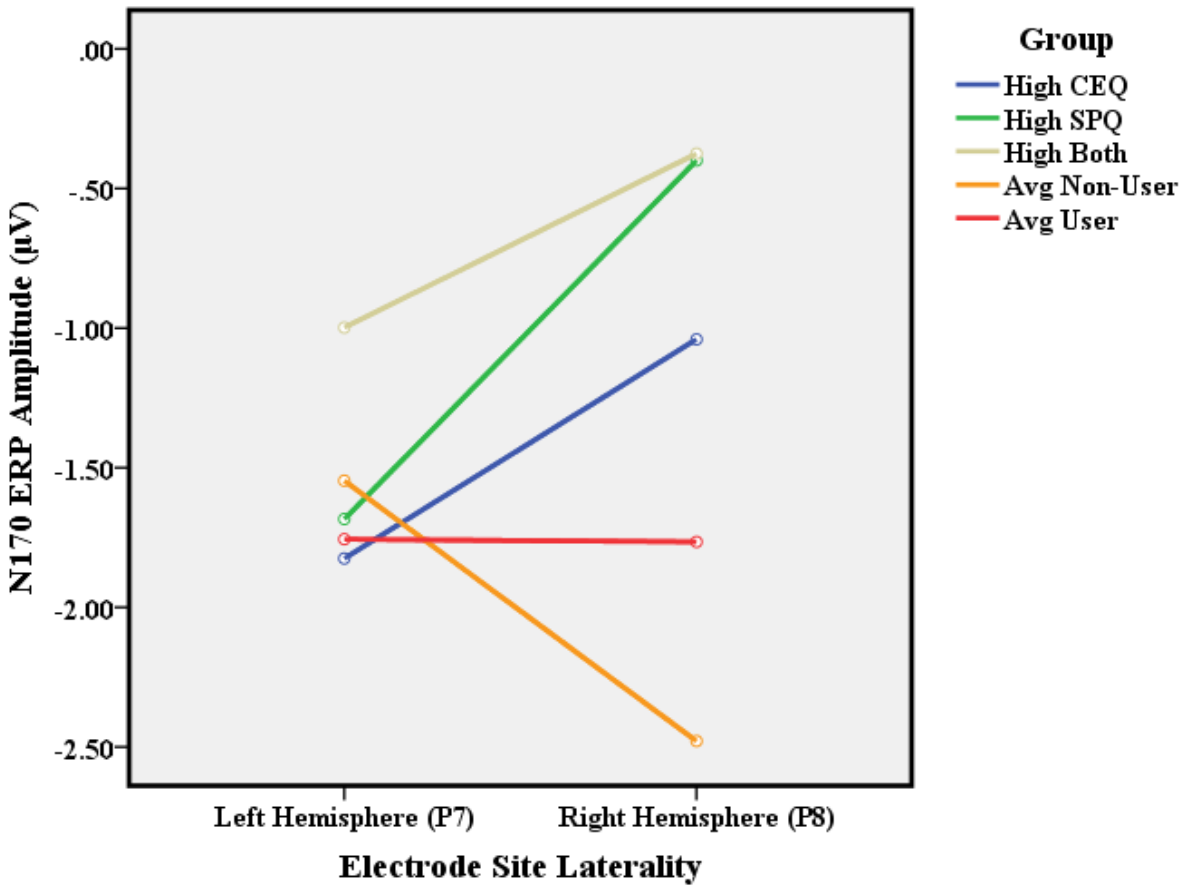
The initial omnibus Mixed ANOVA that was employed included laterality, trial-type, and participant group. Mauchly's test revealed that the assumption of sphericity had been violated for the comparisons of trial-type ($X^2(5) = 16.30$, $p = .006$), and laterality by trial-type ($X^2(5) = 20.14$, $p = .001$). Greenhouse-Geisser estimates were used to correct for this ($\varepsilon = 0.880$ and $\varepsilon = 0.809$ respectively). With the Greenhouse-Geisser adjustment, there was a main effect of laterality, $F(1.00, 64.00) = 4.07$, $p = .048$, $\eta_p^2 = .06$, and a main effect of trial-type, $F(2.64, 168.96) = 7.96$, $p = .002$, $\eta_p^2 = .08$. A pairwise comparison of trial-types revealed reduced N170 amplitude for incorrectly endorsed face-present trials compared to both correctly endorsed ($p = .001$, $d = 0.47$) and incorrectly endorsed noise-only trials ($p < .001$, $d = 0.49$). There was also a

significant interaction between laterality and group, $F(4.00, 64.00) = 5.14$, $p = .001$, $\eta_p^2 = .24$ (see figure 1). No main effect of group was found, $F(1.00, 64.00) = 1.80$, $p = .14$, $\eta_p^2 = .10$. In consideration of the main effect of laterality and an interaction between laterality and group, this initial analysis was split into two additional Mixed ANOVAs, where the right and left sites were analyzed independently.

The second Mixed ANOVA focused on trial-types elicited by the P7 electrode site (left side). There was a main effect of trial-type, $F(2.55, 168.03) = 3.08$, $p = .037$, $\eta_p^2 = .05$, indicating reduced amplitudes evoked by incorrectly endorsed face-present trials, compared to correctly ($p = .003$, $d = 0.37$) and incorrectly endorsed noise-only trials ($p < .002$, $d = 0.44$). There was no significant interaction between trial-type and group for the P7 site, $F(10.18, 168.96) = .86$, $p = .569$, $\eta_p^2 = .05$. Nor was there for group, $F(4, 66) = .67$, $p = .61$, $\eta_p^2 = .04$.

The third Mixed ANOVA was identical to the previous using data from electrode site P8. There was a main effect of trial-type, $F(2.48, 159.00) = 4.82$, $p = .005$, $\eta_p^2 = .07$, indicating that smaller N170 ERPs were associated with incorrectly endorsed face-present trials, compared to both noise-only trials (correct: $p = .006$, $d = 0.38$; incorrect: $p = .002$, $d = 0.41$). Furthermore, incorrectly endorsed noise-only trials elicited a greater average N170, as compared to correctly endorsed face-present trials ($p = .041$, $d = 0.27$). No interaction was found between group and trial-type, $F(9.94, 159.00) = .86$, $p = .164$, $\eta_p^2 = .08$. Unlike the previous analyses, a main effect of group was found for the P8 electrode site, $F(4, 64) = 3.92$, $p = .007$, $\eta_p^2 = .20$ (see figure 2). A

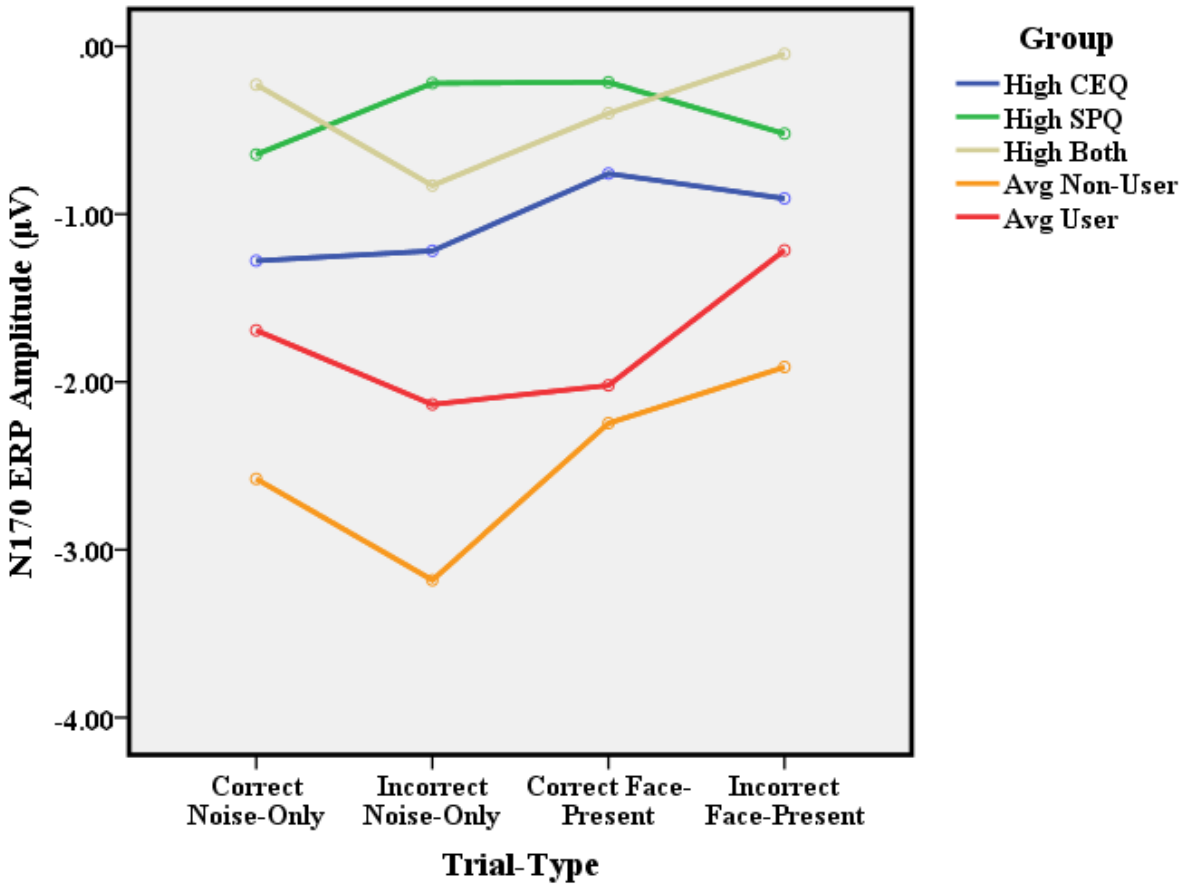
Figure 1: *Group by Laterality Interaction*



Note: The omnibus Mixed ANOVA detected a group by laterality interaction, where N170 ERP amplitude significantly differed between hemispheres for the High CEQ (p = .036), High SPQ groups (greater P7; p = .002), and the Average Non-User group (greater P8; p = .013). No significant differences between the left and right hemisphere was detected for the Average User (p = .979) and High on Both groups (p = .171).

series of pairwise comparisons indicated this effect was the result of average cannabis users eliciting significantly greater N170 ERPs, compared to the High SPQ group (p = .034, d = 0.84) and High on Both group (p = .045, d = 0.84). Furthermore, non-using controls had significantly larger N170 ERPs than all experimental conditions (High CEQ: p = .022, d = 0.88; High SPQ: p = .002, d = 1.28; High on Both: p = .003, d = 1.28).

Figure 2: *Main Effect of Group at P8*

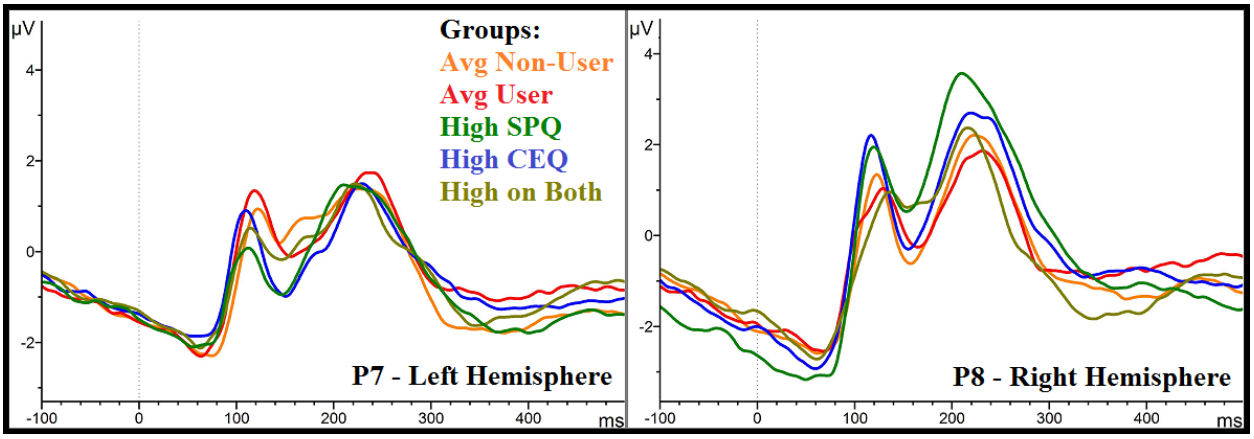


Note: The P8 Mixed ANOVA detected a main effect of group. The two control groups demonstrated significantly greater N170 ERPs, as compared to the High SPQ and High on Both groups. Furthermore, Average Non-Users demonstrated significantly greater ERPs, as compared to the High CEQ group.

Combined Experimental Group Analyses

A pair of secondary analyses were conducted on a dataset that merged those participants who scored high on both the SPQ and CEQ with the High SPQ and again with the High CEQ group. This was calculated to address the small sample size of each group independently, and as further exploratory investigation of the effect of unusual experiences while using cannabis and experiencing schizotypal traits. Although this procedure increased the power of each analysis, it

Figure 3: *Grand Average ERPs by Group*



Note: Grand average ERPs by group where a significant difference was detected between the Average Non-User group and High SPQ, High on Both, and High CEQ groups at P8, and not at P7. Significant differences were detected between Average Users and the High SPQ and High on Both Groups at P8, but not P7.

also prohibited a meaningful comparison between the augmented group and the unaltered experimental group. Thus, these comparisons were only conducted against the two control groups (e.g. Augmented High SPQ group vs. Average User group vs. Average Non-User group).

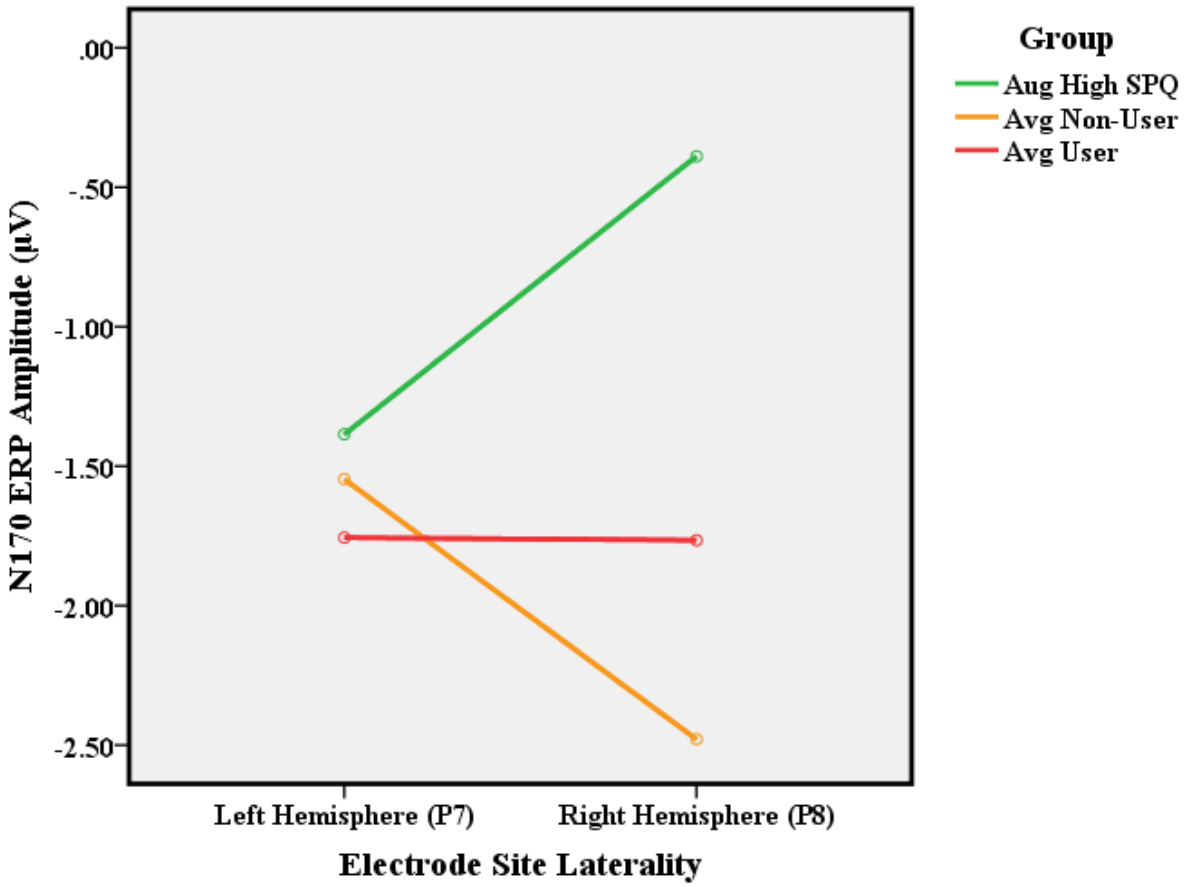
Augmented SPQ Group Analysis. This omnibus Mixed ANOVA conducted on the augmented SPQ dataset included laterality, trial-type, and participant group. Mauchly's test revealed that sphericity had been violated for trial-type ($X^2(5) = 17.54$, $p = .004$), this was corrected for with a Greenhouse-Geisser adjustment ($\varepsilon = 0.85$). Sphericity was also violated for the laterality by trial-type interaction and subsequently corrected ($X^2(5) = 24.08$, $p < .000$; $\varepsilon = 0.74$). This dataset did not exhibit a main effect of laterality, $F(1.00, 51.00) = .01$, $p = .928$, $\eta_p^2 = .00$, but did show a main effect of trial-type, $F(2.54, 129.44) = 5.67$, $p = .002$, $\eta_p^2 = .10$. The interaction between laterality and group, $F(2.00, 51.00) = 8.03$, $p = .001$, $\eta_p^2 = .24$, remained (see figure 4). Unlike the primary analysis, this Mixed ANOVA also produced a main effect of group,

$F(2, 51) = 3.48$, $p = .039$, $\eta_p^2 = .12$. Pairwise comparisons revealed the main effect of trial-type was due to incorrectly endorsed face-present trials eliciting significantly reduced N170 ERPs when contrasted with all other trial-types (correct noise: $p = .001$, $d = 0.47$; incorrect noise: $p < .000$, $d = 0.49$; correct face: $p = .010$, $d = 0.30$). The main effect of group was elicited by non-using controls exhibiting significantly more pronounced ERPs when contrasted with the augmented SPQ group ($p = .019$, $d = 0.81$). Again, this analysis was split into two separate Mixed ANOVAs due to the presence of an interaction between laterality and group.

The second Mixed ANOVA was conducted on the P7 site, and followed the same parameters that were applied to this analysis on the previous dataset. The assumption of sphericity was violated ($X^2(5) = 18.41$, $p = .002$), and corrected ($\varepsilon = 0.81$). No outcomes were found to be significant. The results were as follows for trial-type, $F(2.44, 129.08) = 2.66$, $p = .063$, $\eta_p^2 = .05$, trial-type by group interaction, $F(4.87, 129.08) = 1.06$, $p = .386$, $\eta_p^2 = .04$, and group, $F(2, 53) = .15$, $p = .862$, $\eta_p^2 = .01$.

The third Mixed ANOVA analyzed N170 ERPs elicited by the P8 site. Similar to previous analyses, the assumption of sphericity was found to be violated ($X^2(5) = 26.09$, $p < .000$), and corrected with a Greenhouse-Geisser adjustment ($\varepsilon = 0.748$). A main effect of trial-type, $F(2.24, 114.37) = 5.88$, $p = .003$, $\eta_p^2 = .10$, and a main effect of group was found, $F(2, 51) = 7.11$, $p = .002$, $\eta_p^2 = .22$. No trial-type by group interaction was detected, $F(4.49, 114.38) = 1.58$, $p = .177$, $\eta_p^2 = .06$. Pairwise comparisons suggested the trial-type main effect was due to significantly reduced N170 ERPs elicited from incorrectly endorsed face-present trials, as

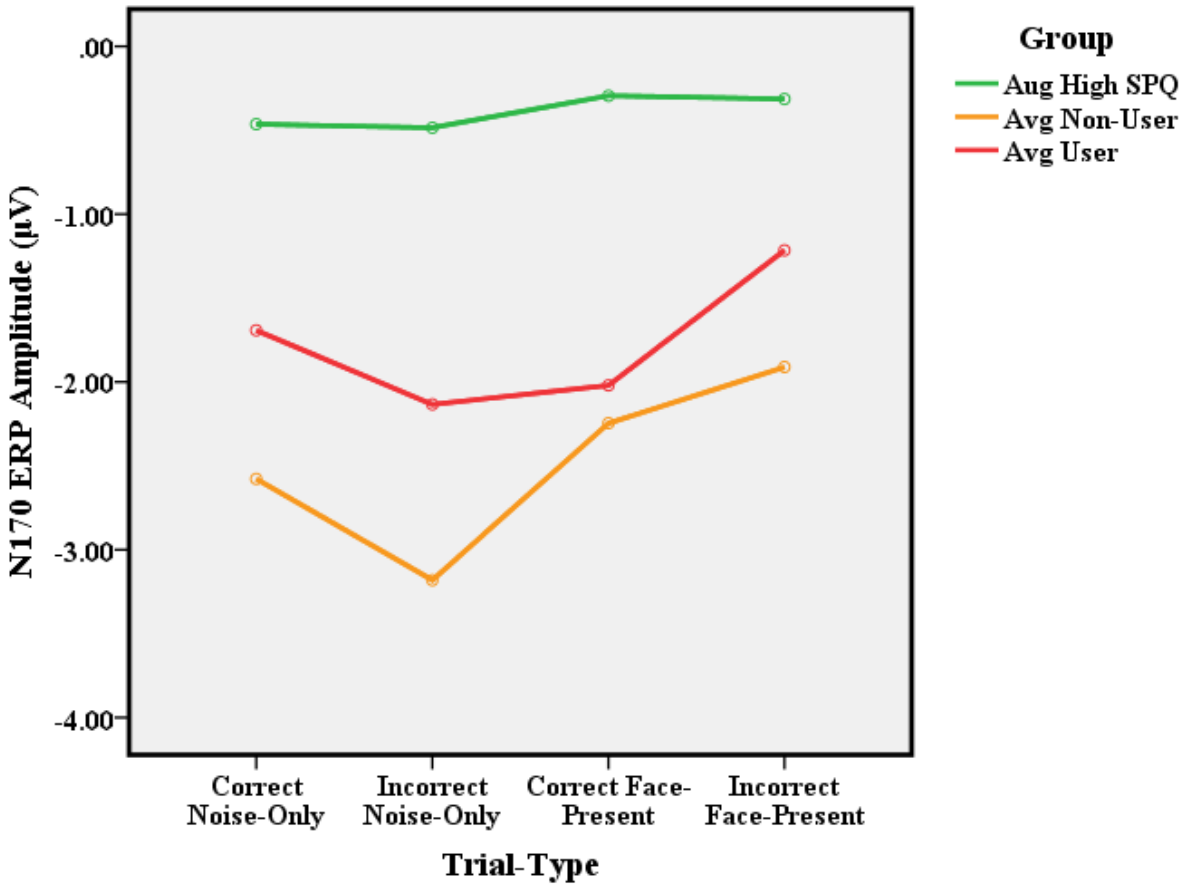
Figure 4: *Group by Laterality Interaction (Augmented SPQ Dataset)*



Note: The omnibus Mixed ANOVA conducted on the augmented SPQ dataset detected a group by laterality interaction. N170 ERP amplitude significantly differed between hemispheres for the Augmented High SPQ group (greater P7; $p = .002$) and the Average Non-User group (greater P8; $p = .017$). No significant differences between the left and right hemisphere was detected for the Average User ($p = .980$).

compared to all other trial-types (correct noise: $p = .002$, $d = 0.41$; incorrect noise: $p < .001$, $d = 0.44$; correct face: $p = .009$, $d = 0.31$). The main effect of group (see figure 5) was the result of significantly smaller N170 ERPs produced by the augmented High SPQ scoring group, as compared to both average users ($p = .019$, $d = 0.80$) and non-using controls ($p = .001$, $d = 1.21$).

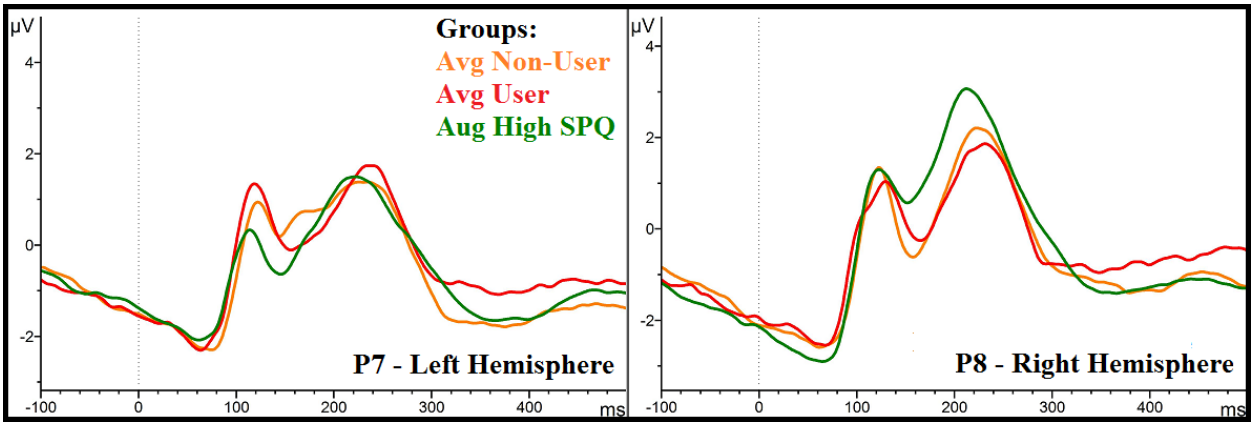
Figure 5: *Main Effect of Group at P8 (Augmented SPQ Dataset)*



Note: The P8 Mixed ANOVA conducted on the augmented SPQ dataset detected a main effect of group. N170 ERP amplitude for the High SPQ group was significantly attenuated, as compared to both control groups. No significant difference was detected between Average Users and Average Non-Users.

Augmented CEQ Group Analysis. The omnibus Mixed ANOVA conducted on the augmented CEQ dataset included laterality, trial-type, and participant group. Similar to previous analyses, Mauchly's test revealed that sphericity had been violated for trial-type ($X^2(5) = 14.41$, $p = .013$) and laterality by trial-type interaction ($X^2(5) = 19.97$, $p = .001$), these violations were adjusted for ($\varepsilon = 0.87$ & $\varepsilon = 0.79$, respectively). Similar to the augmented SPQ group, this dataset

Figure 6: *Grand Average ERPs by Group (Augmented SPQ)*

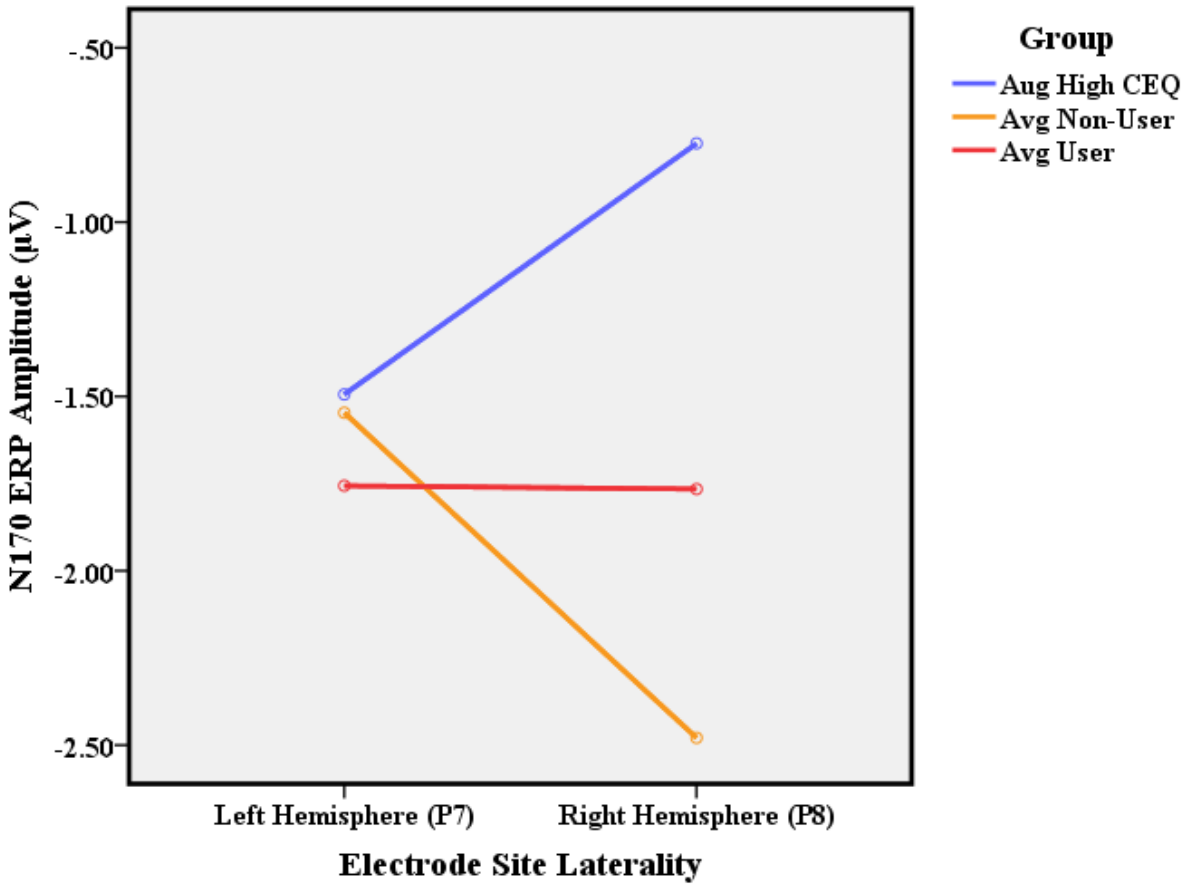


Note: The grand average ERPs by group (augmented SPQ) that demonstrate a statistically significant difference between the control groups and the augmented High SPQ group at P8, but not at P7.

indicated there was no main effect of laterality, $F(1.00, 53.00) = .15$, $p = .699$, $\eta_p^2 = .00$, but a main effect of trial-type and a laterality by group interaction ($F(2.60, 137.86) = 7.38$, $p < .000$, $\eta_p^2 = .12$; $F(2.00, 53.00) = 6.68$, $p = .003$, $\eta_p^2 = .20$). The main effect of group was not significant, $F(2, 53) = 1.89$, $p = .162$, $\eta_p^2 = .07$. Pairwise comparisons indicated the main effect of trial-type was consistent with the augmented SPQ dataset, where incorrect face-present trials demonstrated significantly smaller ERPs (correct noise: $p < .000$, $d = 0.52$; incorrect noise: $p < .000$, $d = 0.62$; correct face: $p = .004$, $d = 0.36$). Following the previous two sets of analyses, this Mixed ANOVA was split by laterality into two separate ANOVAs. Each were bound by the same parameters of prior analyses.

Analysis of the P7 site indicated that sphericity was violated ($X^2(5) = 19.47$, $p = .002$), and was therefore Greenhouse-Geisser adjusted ($\varepsilon = 0.79$). No main effect of group, or trial-type

Figure 7: *Group by Laterality Interaction (Augmented CEQ Dataset)*



Note: The omnibus Mixed ANOVA conducted on the augmented CEQ dataset detected a group by laterality interaction. N170 ERP amplitude significantly differed between hemispheres for the Augmented High CEQ group (greater P7; $p = .012$) and the Average Non-User group (greater P8; $p = .012$). No significant differences between the left and right hemisphere was detected for the Average User ($p = .979$).

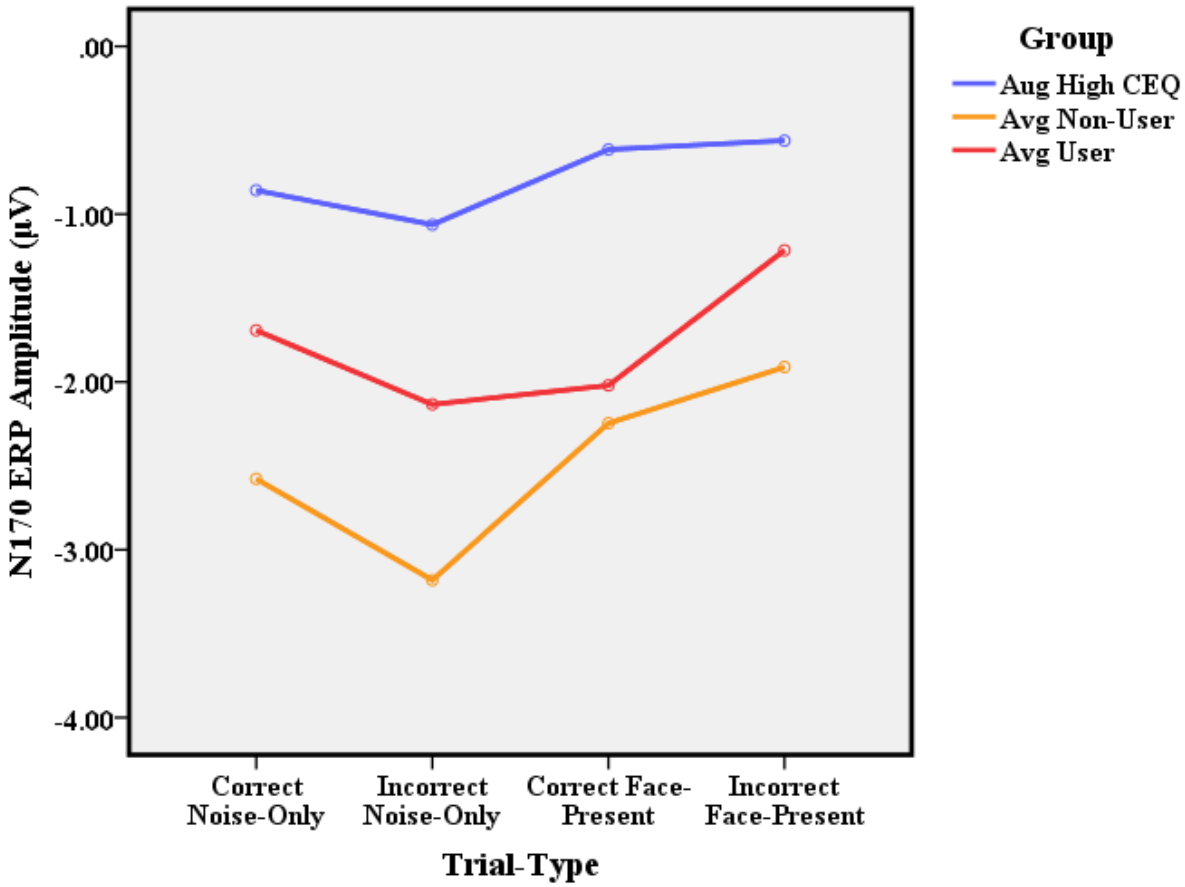
by group interaction was detected ($F(2, 53) = .15$, $p < .860$, $\eta_p^2 = .01$; $F(4.74, 125.73) = 6.68$, $p = .003$, $\eta_p^2 = .20$). However, a main effect of trial-type was detected, $F(2.37, 125.73) = 3.54$, $p = .025$, $\eta_p^2 = .06$. This was determined to be the result of reduced N170 ERPs elicited by incorrectly endorsed face-present stimuli (correct noise: $p = .007$, $d = 0.40$; incorrect noise: $p < .000$, $d = 0.55$; correct face: $p = .025$, $d = 0.29$).

The analysis of the P8 electrode site on this dataset revealed a violation of sphericity ($X^2(5) = 22.34$, $p < .000$). This was adjusted with Greenhouse-Geisser ($\varepsilon = 0.80$). Main effects were detected for trial-type ($F(2.41, 127.63) = 7.37$, $p < .000$, $\eta_p^2 = .12$) and group ($F(2, 53) = 4.72$, $p = .013$, $\eta_p^2 = .15$). The effect of trial-type was attributed to reduced N170 ERPs in response to incorrectly endorsed face-present stimuli, as compared to all other trial-types (correct noise: $p = .002$, $d = 0.43$; incorrect noise: $p < .000$, $d = 0.53$; correct face: $p = .008$, $d = 0.32$). In addition to this, a significant difference was also found between correctly endorsed face-present trials and incorrectly endorsed noise-only trials, where the former was associated with reduced ERPs ($p = .030$, $d = 0.31$). The main effect of group was determined to be elicited by larger N170 ERPs from the non-using control group, as compared to the augmented High CEQ group ($p = .004$, $d = 1.00$; see figure 8).

SPQ and CEQ Bivariate Correlations

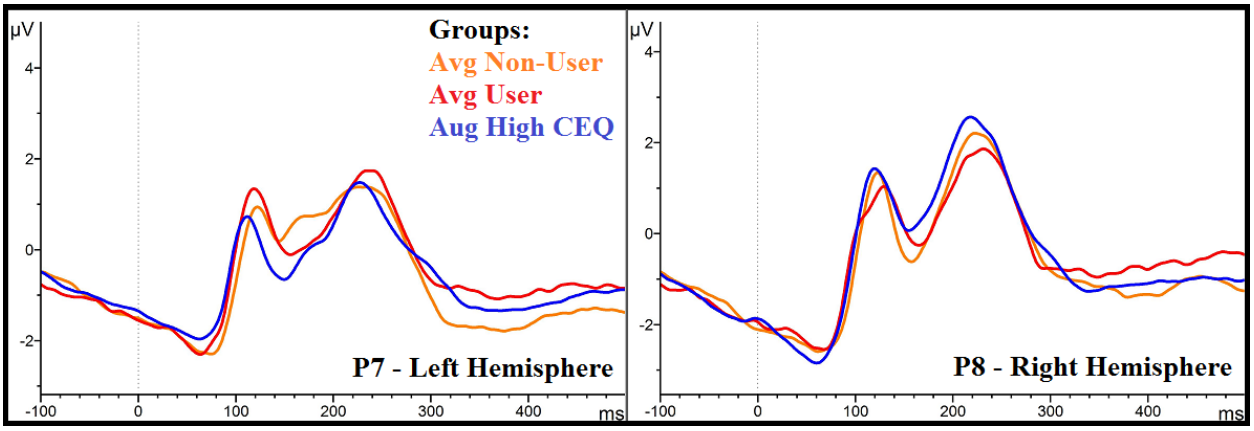
Results below a *p*-value of .05 were detected between P8 amplitudes and total SPQ score for trials where a face was perceived. Similar results were detected between P8 amplitudes and total CEQ score. This indicated that higher SPQ and CEQ scores were associated with smaller N170 amplitudes. However, none of these remained significant once a Bonferroni adjustment of the critical value to $p = .013$ (see table 3). When comparing the two self-report measures (SPQ and CEQ) a significant correlation was detected between total scores ($r = .413$, $p = .001$). The total SPQ score was also found to significantly correlate with the after-effects ($r = .317$, $p = .011$) and paranoid-dysphoric ($r = .416$, $p = .001$) CEQ subscales, but not the pleasurable subscale ($r = .264$, $p = .035$) after a Bonferroni adjustment (critical value of $p = .013$).

Figure 8: *Main Effect of Group at P8 (Augmented CEQ Dataset)*



Note: The P8 Mixed ANOVA conducted on the augmented CEQ dataset revealed a main effect of group. N170 ERP amplitude for the High CEQ group was significantly attenuated, as compared to the Average Non-User group. The High CEQ group also demonstrated a trend of reduced N170 ERP amplitude, as compared to the Average User group (p = .081, d = 0.57).

Figure 9: *Grand Average ERPs by Group (Augmented CEQ)*



Note: The grand average ERPs by group (augmented CEQ) that demonstrate a statistically significant difference between Average Non-Users and the augmented High CEQ group at P8, but not P7.

Table 3: *Pearson's Bivariate Correlations by Site and Trial-type*

	Correct Noise-Only	**Incorrect Noise-Only**	**Correct Face-Present**	**Incorrect Face-Present**
SPQ Total – P7	*r* = -.102 *p* = .387	*r* = -.010 *p* = .931	*r* = .122 *p* = .302	*r* = -.296 *p* = .123
SPQ Total – P8	*r* = .174 *p* = .144	*r* = .249 *p* = .039	*r* = .231 *p* = .053	*r* = .124 *p* = .299
CEQ Total – P7	*r* = -.174 *p* = .238	*r* = .011 *p* = .941	*r* = .044 *p* = .768	*r* = -.019 *p* = .897
CEQ Total – P8	*r* = .192 *p* = .191	*r* = .273 *p* = .070	*r* = .317 *p* = .030	*r* = .260 *p* = .075

Note. Correlations between ERP amplitudes for each trial-type and the total SPQ and total CEQ scores. Bonferroni adjustment $p < 0.013$.

Discussion

We sought to determine: **(1)** whether participants that scored high on schizotypal traits (via the SPQ) or participants that scored high on cannabis experiences (via the CEQ) displayed electrophysiological deficits, as compared to average cannabis users and non-users; **(2)** to evaluate whether the experimental groups were similar in the ways in which they deviated from the control groups; **(3)** whether these differences are identifiable in both the integration of top-down and bottom-up processing; and finally **(4)** this study also attempted to replicate the results of Barkus & Lewis (2008), where SPQ and CEQ scores were found to moderately correlate.

Hypothesis Evaluation

Hypotheses 1 & 2. We hypothesized that individuals who scored high on schizotypy and individuals that scored high on cannabis experiences would demonstrate reduced N170 event-related potentials, as compared to our control groups. We also anticipated that the experimental groups would demonstrate similar reductions. As stated in the results, the right hemisphere (P8) demonstrated a main effect of group, where High SPQ, High CEQ and High on Both groups exhibited smaller N170 amplitudes compared to the Average Non-Users. This was also true for the High SPQ and High on Both, compared to Average Users groups. These differences were associated with large effect sizes; where Cohen's *d* ranged from 0.88 to 1.28. Furthermore, the augmented CEQ dataset demonstrated a trend of reduced N170 ERPs for the Augmented High CEQ group, compared to the Average User group ($p = .081$, Cohen's $d = 0.57$). None of the experimental groups significantly differed from each other in the P8 analysis ($p = .319$), suggesting similarity in this detected N170 ERP deficit. Thus, our initial findings support the first two hypotheses.

The reduced N170 ERP associated of the High SPQ group is consistent with previous literature in which similar deficits were reported in both schizotypy and schizophrenia (e.g. Batty et al, 2014; Maher et al., 2015). Furthermore, the deficits associated with high schizotypy, as measured by the SPQ, are not limited to the N170 ERP. Reduced amplitudes have been found across several markers of early processing, such as the P50 and P100 ERPs (Koychev et al., 2010; Park et al., 2015). Schizotypal samples have also displayed impairments in attention modulated processes, such as increased duration to allocate maximal attention to a non-face stimulus (Fuggetta, Bennett, & Duke, 2015). The deficits associated with schizotypy are also similar, but of a lesser magnitude, to those found in schizophrenia (Tsunada et al., 2012). Thus, the cognitive deficiencies that produce these amplitude reductions do not appear to be specific to face perception, but rather may impact a broader spectrum of perceptual processing. Similarly, it is possible that the N170 deficits exhibited by the High SPQ group in the current study represent faulty integration of sensory and cognitive processes of perception during this task.

The reduced N170 ERPs by the High CEQ group is a novel finding. To our knowledge, no other group has investigated ERPs in those who report unusual cannabis experiences. As a result of the presence and direction of our detected effect between Average Non-Users and the High CEQ group, but not Average Users, we propose that a cognitive vulnerability may underlie these unusual experiences. While these results require replication and further study with functional imaging, the similarity between the High CEQ, High SPQ, and High on Both group's ERPs may represent a common cognitive vulnerability affecting perceptual processing. This deficit may mediate both schizotypal traits and proneness to unusual cannabis experiences. Furthermore, these results also tentatively argue that cannabis use coupled with particularly unusual experiences, but not necessarily the consumption of cannabis itself, is associated with

these potential cognitive deficits. This is somewhat bolstered by a trend toward significance between average cannabis users and those with unusual experiences in the augmented CEQ analysis. However, this analysis is exploratory and these initial inferences require further study.

Hypothesis 3. We further hypothesized that group differences would interact with a particular trial-type. Specifically, we hypothesized that the High SPQ and High CEQ groups would exhibit greater N170 ERP reduction for the correct noise-only, correct face-present, and incorrect face-present trial-types, compared to the incorrect noise-only trial-type. This hypothesis was rooted in the hallucinatory experiences, and increased endorsement of false-positives, associated with schizotypy (Grant et al., 2014; Yu, Zaroff, & Bernardo, 2015). However, we failed to reject the null-hypothesis, as no group by trial-type interactions were found in any of the analyses.

Hypothesis 4. Finally, we sought to replicate the results from Barkus and Lewis' 2008 study, which found a significant correlation between the Schizotypal Personality Questionnaire and the Cannabis Experiences Questionnaire. Our results were consistent with Barkus and Lewis (2008), in that the total scores for the Schizotypal Personality Questionnaire and the Cannabis Experiences Questionnaire were significantly, positively correlated (r = .413). Furthermore, we also replicated their pattern of results within the CEQ subscales. This association was strongest with the paranoid-dysphoric subscale (r = .416), followed by the after-effects subscale (r = .317), and no significant correlation was found with the pleasurable subscale (r = .264). These findings reinforce the notion that schizotypal traits are moderately associated with cannabis induced unusual (or particularly vivid) experiences. An abundance of literature has associated higher SPQ scores with proneness to psychosis and cognitive deficits (Nelson et al., 2013). Therefore, unusual cannabis experience may also be indicative of these vulnerabilities. This argument is

further supported by our results described in the evaluation of hypotheses 1 and 2; in which we found that both groups showed reduced ERPs compared to the control groups, and they did not significantly differ from one another. We also note that our sampling methods may have artificially reduced this correlation, as we actively sought participants that were in the 75th percentile of one scale, but below the 75th percentile in the other.

Additional Findings

Laterality. The initial Mixed ANOVA, which included laterality, trial-type, and participant group, yielded a consistent main-effect of laterality. The left hemisphere (P7 site) produced significantly larger N170 ERPs (mean difference = -0.350 microvolts). This effect seems to go against the consensus within the literature, where N170 ERPs have consistently displayed larger amplitudes in the right hemisphere when evoked by face stimuli (e.g. Rossion et al., 1999; Krombholz, Schaefer, & Boucsein, 2007; Luck & Kappeman, 2012). Some insight into this inconsistency is provided by the interaction between groups and laterality. As seen in *Figure 1*, Average Non-Users exhibited the expected pattern of N170 ERP right hemisphere dominance, Average Users and the High on Both displayed no hemispheric bias, and the High SPQ and High CEQ groups had significantly stronger left side ERPs. Subsequent Mixed ANOVAs conducted on the augmented SPQ and CEQ datasets revealed a significant laterality by group interaction (see figures 4 & 7). Again, this was the result of Average Non-Users eliciting significantly larger N170 ERPs in the right hemisphere (as expected), with the augmented experimental group exhibiting the opposite pattern of laterality.

There is some literature that may account for this inversion of laterality. Unlike controls, patients with schizophrenia did not show right side bias in a facial expression processing task (Salisbury, 2008). As reported in a recent meta-analysis, a lack of right side laterality for the

N170 has often, but not always, been found in samples of individuals with schizophrenia (McCleery et al., 2015). Although this may explain our results for the High on Both group (which showed no hemispheric bias), it does not fully explain the detected P7 dominance for the other two experimental groups. Onitsuka and colleagues (2006) found that N170 amplitude strength was positively correlated with right, but not left, posterior fusiform gyrus volume for individuals with schizophrenia. If symptoms related to schizophrenia are associated with disproportionately reduced right posterior fusiform gyrus volume, then this difference could result in significantly reduced right side N170 amplitudes, rather than strengthened left N170 ERPs. Since the High SPQ and High CEQ group did not significantly differ, and showed the same reversed laterality, they may share similar underlying neural deficits in relation to this task.

Our analyses of group differences associated with each electrode site provide cautious support this model. We found no main effect of group across all P7 (left side) analyses, suggesting the experimental and control groups ERPs were equally strong. Crucially, each P8 (right side) analysis demonstrated a group difference in the expected direction (see figures 2, 5, & 8). While there are currently no studies that report on this specific location with respect to schizotypy, several have associated schizotypal personality with reduced temporal cortex volume (e.g. Hazlett et al., 2008; Goldstein et al., 2009). Alternatively, these results may also suggest a reorganization of neural functioning, in response to a common right lateralized deficit (possibly visualized in figures 3, 6, and 9). If true, the lack of any hemispheric bias in the High on Both group could indicate a compounded neural deficit, where such compensation was not possible. Although no detected effect was found, Figure 3 demonstrates a pattern of activity consistent with this. A specific prediction regarding laterality was not made a priori. Due to the exploratory nature of these analyses, we encourage further exploration of this group by laterality interaction.

Future examination should include structural and functional imaging of the posterior fusiform gyri, and subsequent neural network modelling to fully investigate this hypothesis.

Trial-Type. A main effect of trial-type was found in all analyses conducted throughout the study, with the exception of the P7 site in the augmented SPQ dataset. Within the primary dataset (i.e. contrasting all five groups), face-present trials that were endorsed as noise-only consistently produced significantly smaller N170 ERPs, as compared to correctly and incorrectly endorsed noise-only trials. Each primary analysis also demonstrated a trend toward smaller ERPs for incorrect face-present trials, as compared to correct trials of the same type (*p*-values ranged between .069 and .124). As reported, the Augmented SPQ and CEQ datasets did find a significant main effect between these two trial-types. These findings may indicate a large cognitive influence on the N170 ERP, as discussed further in the paragraphs below.

Our task included faces that were of "high" and "low" visibility, with the latter being harder to detect and resulting in more misses. Unfortunately, we were precluded from conducting a comparison of high and low faces, due to low trial count and small group sample sizes. Rather, we combined our high and low face trials together. This resulted in a greater proportion of low faces in the incorrect face-present trial-type. High visibility faces were found to elicit a greater N170 ERP than low visibility faces in Wild & Busey's (2004) study. Subsequently, through the integration of sensory information, we would expect our correct face-present trials to elicit a greater N170 (as occurred in the augmented analyses), if only due to a greater proportion of high visibility faces. Ultimately, in our present analysis, this meant no meaningful comparison between the two face-present trial-types can be made. However, this did not impact contrasts between noise-only and face-present trials.

As stated, we consistently found significantly smaller N170 ERPs associated with incorrect face-present trials, as compared to either correct or incorrect noise-only trials. Interestingly, bottom-up processing should predict the opposite direction of effect, where the mere presence of a face should elicit a greater response. There are a few possible explanations for this. First, it could be that in the construction of our stimuli, the addition of grey-scale faces to grey-scale Gaussian noise darkened the overall stimulus, resulting in a weaker ERP. However, we used the same face stimuli as Wild & Busey (2004), who did find larger N170 ERPs associated with faces. Relative to the static background, our stimuli were substantially decreased in visibility. It is possible the reduced visibility of faces in our stimuli led to a trend of reduced N170 in response to face-present trials. However, pilot testing indicated these faces were perceptible to the majority of participants, thus this alone would not explain the reduced amplitude. Furthermore, from the bottom-up processing perspective, this should only reduce the amplitude, not invert the direction of the effect (Dering et al., 2011; Eimer, 2011).

Second, these results could be the effect of cognitive-mediation of stimuli (top-down processing). The primary finding of Wild & Busey (2004) was significantly increased amplitude for noise-only trials that were mistaken for faces, as compared to noise only trials mistaken for words. They argued that this suggested higher-order processing (the expectation of a face or stochastic activity) influencing early visual processing (the N170). Furthermore, increased N170 ERPs have been elicited from inverted face orientations, although schizophrenic patients failed to demonstrate this (Sadeh & Yovel, 2010; Tsunoda et al., 2012). This suggests additional resources, increasing the overall amplitude, may be recruited when the stimulus is not readily identifiable. The present study provided participants with instructions that asked them to “do their best to determine if a face is present”. It is possible that this had the effect of increased

focus (and cognitive resource) when faces were not readily identifiable (i.e. the noise-only trials). Thus, this cognitive-mediation may have increased amplitudes not only for false-positives, but also correctly endorsed noise trials.

Bivariate Correlations. We did not find any significant correlations between the SPQ or CEQ and trial-type amplitude, after a Bonferroni adjustment was applied. However, prior to this correction SPQ total score correlated with both incorrect noise-only and correct face-present trials in the predicted direction. Specifically, N170 amplitudes were smaller (less negative) for perceived faces, but not for perceived noise as SPQ total score increased. Similar results were present for high CEQ scores, although not as robust for incorrect noise-only endorsements (see *Table 3*). Of note, these correlations involved the total CEQ score, rather than the measures subscales. Barkus and Lewis (2008) found that the SPQ correlated most strongly with the paranoid-dysphoric subscale of the CEQ, while not significantly correlating with the pleasurable subscale. In consideration of this, we conducted additional bivariate correlations between the paranoid-dysphoric subscale and P8 amplitudes. This resulted in significant correlations for perceived faces in noise-only and face-present trials (See Appendix 3). Once a Bonferroni correction was applied, the correlation between P8 amplitude for correct face-present trials and the paranoid-dysphoric subscale was no longer significant. Although these results did trend in the expected direction, no claim of a significant association between these self-report measures and N170 ERP amplitude can be made. However, future research should focus on the paranoid-dysphoric subscale of the CEQ using larger samples.

Further Limitations

The topic of this study, an investigation of the similarities of particular traits and experiences, prohibited the use of random assignment. Thus, this study is ultimately quasi-experimental and correlational in nature. It cannot address the issue of causation in the cannabis-psychosis relationship. However, this was not the intent of the study. Rather, this study explored whether a common vulnerability might exist between high scorers on schizotypy and those who have particularly unusual experiences associated with cannabis use. While this study is the first attempt to address this question, it is beholden to several limiting factors.

Our methodology for participant recruitment was devised to boost the effect size of group differences. As referenced in our initial power analysis, a prior study used the median split to determine the high and low categories for schizotypy (Batty et al., 2014). That study produced an effect size $d = 0.33$ between groups. In an attempt to increase effect size, we recruited individuals above the 75^{th} percentile for the High SPQ and High CEQ groups. Although this method produced the desired result, with a group effect ranging from $d = .88$ to $d = 1.28$, it substantially complicated and slowed recruitment. Overall, this limited our sample size for each group. The nature of the phenomena under study further impacted sample size of the experimental groups. Due to the moderate correlation that been found between the SPQ and CEQ, participants that scored high on both scales could not be allocated to either the High SPQ and High CEQ groups. This led to the creation of the High on Both group, but reduced the overall sample within the experimental groups. Once exclusionary criteria were applied to the sample, the groups were between 20-to-50% below goal. It is possible, were we to have met the group target of 21 some of the detected trends would have reached significance. Low sample size also impacted our ability to control for the variable usage rate across groups. The High CEQ and

High on Both groups had a median frequency statement that suggested greater overall use, compared to Average Users (see table 2). While the reduced ERPs associated with these groups are interpreted as an underlying neural deficit, we cannot rule out the possible impact of different consumption rates.

This study also focused on a single event-related potential, the N170, in relation to a face perception task. Although our results may suggest the presence of a cognitive/perceptual vulnerability, our methodology does not allow precise inferences of the nature or specific location of this deficit. Without analysis of earlier, sensory driven ERP components, it is also unclear if this deficit is primarily the result of compromised sensory encoding, or reduced attentional mediation of expected stimuli. Furthermore, we cannot be certain the detected N170 ERP attenuations in both the High SPQ and High CEQ groups share a common cause. Thus, inferences made from this study should be seen as exploratory in nature.

Concluding Thoughts

This study was the first to examine the association between cannabis experiences and an indicator of neural integrity, specifically the N170 event-related potential. Consequently, we are also the first research group to examine the similarities between schizotypal personality and cannabis experiences with electroencephalography. This study demonstrates that the initial association detected by Barkus and Lewis (2008) may go beyond the behavioral responses made on the Schizotypal Personality Questionnaire and the Cannabis Experience Questionnaire. Rather, our results suggest this relationship may be mediated by cognitive vulnerability present in both of these groups. However, the precise origin of this deficit remains unclear.

This study makes no attempt to address causality. Many of the previously discussed hypotheses regarding the cannabis-psychosis relationship may act as a causative agent in this association. A primary goal of this endeavor was to determine whether particularly unusual experiences may act as a phenomenological marker of future psychosis. The experience or endorsement of schizotypal traits does not constitute a psychotic disorder. However, several studies have suggested that a "schizophrenia spectrum" exists, and schizotypy resides on this spectrum (Cochrane, Petch, & Pickering, 2012; Barrantes-Vidal et al., 2013). In a systematic review, Nelson et al. (2013) concluded that schizotypy and schizophrenic disorders are intrinsically related. Accordingly, schizotypy is seen as a risk factor for psychotic disorders (Lyons et al., 1995; Delawalla et al., 2006). If it is true that cannabis related experiences (not simply cannabis use) are the product of a neural vulnerability that also produces schizotypal personality traits, then these experiences may act as a viable indicator for future psychotic episodes. We recommend further exploration to verify and further illuminate the specific mechanisms of this relationship.

References

Almeida, P. R., Ferreira-Santos, F., Vieira, J. B., Moreira, P. S., Barbosa, F., & Marques-Teixeira, J. (2014). Dissociable effects of psychopathic traits on cortical and subcortical visual pathways during facial emotion processing: An ERP study on the N170. *Psychophysiology*, *51*(7), 645-657. doi:10.1111/psyp.12209

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

Andreasson, S, Allebeck, P, Engstrom, A, Rydberg, U. (1987). Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet*, *2*(8574): 1483-6.

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: British Medical Journal*, *325*(7374), 1212-1213. doi:10.1136/bmj.325.7374.1212

Arseneault, L., Cannon, M., Witton, J., & Murray, R. M. (2004). Causal association between cannabis and psychosis: Examination of the evidence. *The British Journal of Psychiatry*, *184*(2), 110-117. doi:10.1192/bjp.184.2.110

Asnafi, S., Sharifi, V., & Tehranidoost, M. (2013). Negative priming in amphetamine psychosis. *Psychiatry Research*, *210*(1), 263.

Barkus, EJ, Lewis, S. (2008). Schizotypy and psychosis-like experiences from recreational cannabis in a non-clinical sample. *Psychological Medicine*, *38*(9): 1267-76.

Barkus, EJ, Stirling, J, Hopkins, BS, Lewis, S. (2006). Cannabis-induced psychosis-like experiences are associated with high schizotypy. *Psychopathology*, *39*: 175-8.

Barrantes-Vidal, N., Gross, G. M., Sheinbaum, T., Mitjavila, M., Ballespí, S., & Kwapil, T. R. (2013). Positive and negative schizotypy are associated with prodromal and schizophrenia-spectrum symptoms. *Schizophrenia Research, 145*(1-3), 50-55. doi:10.1016/j.schres.2013.01.007

Bentin, S., & Golland, Y. (2002). Meaningful processing of meaningless stimuli: The influence of perceptual experience on early visual processing of faces. *Cognition, 86*(1), B1-B14. doi:10.1016/S0010-0277(02)00124-5

Bramon, E., Rabe-Hesketh, S., Sham, P., Murray, R. M., & Frangou, S. (2004). Meta-analysis of the P300 and P50 waveforms in schizophrenia. *Schizophrenia Research,70*(2), 315-329. doi:10.1016/j.schres.2004.01.004

Canadian Centre on Substance Abuse. (2014). Canadian drug summary: Cannabis. Ottawa, ON: CCSA.

Caspi, A., Moffitt, T. E., Cannon, M., McClay, J., Murray, R., Harrington, H... Craig, I. W. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: Longitudinal evidence of a gene X environment interaction. *Biological Psychiatry, 57*(10), 1117-1127. doi:10.1016/j.biopsych.2005.01.026

Cochrane, M., Petch, I., & Pickering, A. D. (2012). Aspects of cognitive functioning in schizotypy and schizophrenia: Evidence for a continuum model. *Psychiatry Research,196*(2-3), 230. doi:10.1016/j.psychres.2012.02.010

Collip, D., Myin-Germeys, I., & Van Os, J. (2008;2007;). Does the concept of "sensitization" provide a plausible mechanism for the putative link between the environment and schizophrenia? *Schizophrenia Bulletin, 34*(2), 220-225. doi:10.1093/schbul/sbm163

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), 286-293. doi:10.1016/j.schres.2008.08.008

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), 286-293. doi:10.1016/j.schres.2008.08.008

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*(2), 117-137. doi:10.1007/s11065-012-9222-1

Dean, B., Bradbury, R., & Copolov, D. L. (2003). Cannabis-sensitive dopaminergic markers in postmortem central nervous system: Changes in schizophrenia. *Biological Psychiatry*, *53*(7), 585-592. doi:10.1016/S0006-3223(02)01545-7

Degenhardt L., Hall W., & Lynskey, M. (2003). Testing hypotheses about the relationship between cannabis use and psychosis. *Drug and Alcohol Dependence*, *71*(1), 37-48. doi:10.1016/S0376-8716(03)00064-4

Delawalla, Z., Barch, D. M., Fisher Eastep, J. L., Thomason, E. S., Hanewinkel, M. J., Thompson, P. A., & Csernansky, J. G. (2006). Factors mediating cognitive deficits and psychopathology among siblings of individuals with schizophrenia. *Schizophrenia Bulletin,32*(3), 525-537. doi:10.1093/schbul/sbj082

Dumas, P., Saoud, M., Bouafia, S., Gutknecht, C., Ecochard, R., Daléry, J., ... d'Amato, T. (2002). Cannabis use correlates with schizotypal personality traits in healthy students. *Psychiatry Research*, *109*(1), 27-35. doi:10.1016/S0165-1781(01)00358-4

Ellett, L., Freeman, D., & Garety, P. A. (2008). The psychological effect of an urban environment on individuals with persecutory delusions: The camberwell walk study. *Schizophrenia Research,99*(1), 77-84. doi:10.1016/j.schres.2007.10.027

Epstein, R. A., Higgins, J. S., Parker, W., Aguirre, G. K., & Cooperman, S. (2006). Cortical correlates of face and scene inversion: A comparison. *Neuropsychologia, 44*(7), 1145-1158. doi:10.1016/j.neuropsychologia.2005.10.009

Ernst, E. (2002), Does regular cannabis use cause schizophrenia? *Focus on Alternative and Complementary Therapies, 7*(4), 334.

Feng, C., Luo, Y., & Fu, S. (2013). The category-sensitive and orientation-sensitive N170 adaptation in faces revealed by comparison with chinese characters. *Psychophysiology,50*(9), 885-899. doi:10.1111/psyp.12067

Ferdinand, R. F., Sondeijker, F., van der Ende, J., Selten, J., Huizink, A., & Verhulst, F. C. (2005). Cannabis use predicts future psychotic symptoms, and vice versa. *Addiction, 100*(5), 612-618. doi:10.1111/j.1360-0443.2005.01070.

Fergusson, D. M., Horwood, L. J., & Ridder, E. M. (2005). Tests of causal linkages between cannabis use and psychotic symptoms. *Addiction, 100*(3), 354-366. doi:10.1111/j.1360-0443.2005.01001.x

Fergusson, D., Horwood, L., & Swain-Campbell, N. (2003). Cannabis dependence and psychotic symptoms in young people. *Psychological Medicine, 33*(1), 15-21. doi:10.1017/S0033291702006402

Ford, J. M., Mathalon, D. H., Kalba, S., Whitfield, S., Faustman, W. O., & Roth, W. T. (2001). Cortical responsiveness during talking and listening in schizophrenia: An event-related brain potential study. *Biological Psychiatry, 50*(7), 540-549. doi:10.1016/S0006-3223(01)01166-0

Friese, B., & Grube, J. W. (2013). Legalization of medical marijuana and marijuana use among youths. *Drugs: Education, Prevention and Policy, 20*(1), 33-39. doi:10.3109/09687637.2012.713408

Fuggetta, G., Bennett, M., & Duke, P. (2015). An electrophysiological insight into visual attention mechanisms underlying schizotypy. *Biological Psychology, 109*, 206-221. doi:10.1016/j.biopsycho.2015.06.007

Galvez-Buccollini, J. A., Proal, A. C., Tomaselli, V., Trachtenberg, M., Coconcea, C., Chun, J., ... Delisi, L. E. (2012). Association between age at onset of psychosis and age at onset of cannabis use in non-affective psychosis. *Schizophrenia Research, 139*(1-3), 157. doi:10.1016/j.schres.2012.06.007

Gardner, E. L. (2005). Endocannabinoid signaling system and brain reward: Emphasis on dopamine. *Pharmacology, Biochemistry and Behavior, 81*(2), 263-284. doi:10.1016/j.pbb.2005.01.032

Giakoumaki, SG. (2012). Cognitive and prepulse inhibition deficits in psychometrically high schizotypal subjects in the general population: Relevance to schizophrenia research. *Journal of International Neuropsychological Society, 18*(4): 643-56.

Glaser, J., van Os, J., Portegijs, P. J. M., & Myin-Germeys, I. (2006). Childhood trauma and emotional reactivity to daily life stress in adult frequent attenders of general practitioners. *Journal of Psychosomatic Research, 61*(2), 229-236. doi:10.1016/j.jpsychores.2006.04.014

Goldstein, K. E., Hazlett, E. A., New, A. S., Haznedar, M. M., Newmark, R. E., Zelmanova, Y... Siever, L. J. (2009). Smaller superior temporal gyrus volume specificity in schizotypal personality disorder. *Schizophrenia Research,112*(1), 14-23. doi:10.1016/j.schres.2009.04.027

Gorman, D. M., & Charles Huber, J. (2007*).* Do medical cannabis laws encourage cannabis use? *International Journal of Drug Policy, 18*(3), 160-167. doi:10.1016/j.drugpo.2006.10.001

Gratton, G., Coles, M. G. H., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology, 55*(4), 468-484. doi:10.1016/0013-4694(83)90135-9

Gudjonsson, G. H. (1984). A new scale of interrogative suggestibility. *Personality and Individual Differences, 5*(3), 303-314. doi:10.1016/0191-8869(84)90069

Gudjonsson, G. H. (1987). A parallel form of the gudjonsson suggestibility scale. *The British Journal of Clinical Psychology, 26*(Pt 3), 215.

Gupta, S., Cahill, J. D., Ranganathan, M., & Correll, C. U. (2014). The endocannabinoid system and schizophrenia: Links to the underlying pathophysiology and to novel treatment approaches. *The Journal of Clinical Psychiatry,75*(3), 285.

Haenschel, C., & Linden, D. (2011). Exploring intermediate phenotypes with EEG: Working memory dysfunction in schizophrenia. *Behavioural Brain Research, 216*(2), 481-495. doi:10.1016/j.bbr.2010.08.045

Häfner., H. (2005). Psychosis and cannabis. *Revista De Psiquiatria Clinica, 32*(2) doi:10.15190/S0101-60832005000200001

Hall, W., & Degenhardt, L. (2009). Adverse health effects of non-medical cannabis use. *The Lancet, 374*(9698), 1383-1391. doi:10.1016/S0140-6736(09)61037-0

Hall, W., & Weier, M. (2015). Assessing the public health impacts of legalizing recreational cannabis use in the USA. *Clinical Pharmacology & Therapeutics, 97*(6), 607-615. doi:10.1002/cpt.110

Hall, W., Degenhardt, L., & Teesson, M. (2004). Cannabis use and psychotic disorders: An update. *Drug and Alcohol Review, 23*(4), 433-443. doi:10.1080/09595230412331324554

Hall, W., Degenhardt, L., & Teesson, M. (2004). Cannabis use and psychotic disorders: An update. *Drug and Alcohol Review, 23*(4), 433-443. doi:10.1080/09595230412331324554

Hazlett, E. A., Buchsbaum, M. S., Haznedar, M. M., Newmark, R., Goldstein, K. E., Zelmanova, Y... Siever, L. J. (2008). Cortical gray and white matter volume in unmedicated schizotypal and schizophrenia patients. *Schizophrenia Research, 101*(1), 111-123. doi:10.1016/j.schres.2007.12.472

Heisz, J. J., Watter, S., & Shedden, J. M. (2006). Progressive N170 habituation to unattended repeated faces. *Vision Research, 46*(1), 47-56. doi:10.1016/j.visres.2005.09.028

Henquet, C., Krabbendam, L., & Spauwen, J. (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ*: *British Medical Journal*, *330*(7481): 11.

Henquet, C., Murray, R., Linszen, D., & van Os, J. (2005). The environment and schizophrenia: The role of cannabis use. *Schizophrneia Bulletin, 31*(3): 608-612.

Howes, O. D., Kambeitz, J., Kim, E., Stahl, D., Slifstein, M., Abi-Dargham, A., & Kapur, S. (2012). The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Archives of General Psychiatry, 69*(8), 776.

Howes, O. D., McDonald, C., Cannon, M., Arseneault, L., Boydell, J., & Murray, R. M. (2004). Pathways to schizophrenia: The impact of environmental factors. *The International Journal of Neuropsychopharmacology, 7*(S1), S7-S13. doi:10.1017/S1461145704004122

Huizink, A. C., & Mulder, E. J. H. (2006). Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. *Neuroscience and Biobehavioral Reviews, 30*(1), 24-41. doi:10.1016/j.neubiorev.2005.04.005

Ibáñez, A., Riveros, R., Hurtado, E., Gleichgerrcht, E., Urquina, H., Herrera, E.. . Manes, F. (2012). The face and its emotion: Right N170 deficits in structural processing and early emotional discrimination in schizophrenic patients and relatives. *Psychiatry Research, 195*(1-2), 18-26. doi:10.1016/j.psychres.2011.07.027

Ilan, A. B., Gevins, A., Coleman, M., ElSohly, M. A., & de Wit, H. (2005). Neurophysiological and subjective profile of marijuana with varying concentrations of cannabinoids. *Behavioural Pharmacology, 16*(5-6), 487-496. doi:10.1097/00008877-200509000-00023

Kirihara, K., Kasai, K., Tada, M., Nagai, T., Kawakubo, Y., Yamasaki, S... Araki, T. (2012). Neurophysiological impairment in emotional face processing is associated with low extraversion in schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 37*(2), 270-275. doi:10.1016/j.pnpbp.2012.02.012

Koychev, I., El-Deredy, W., Haenschel, C., & Deakin, J. F. W. (2010). Visual information processing deficits as biomarkers of vulnerability to schizophrenia: an event-related potential study in schizotypy. *Neuropsychologia, 48*(7), 2205-2214. doi:10.1016/j.neuropsychologia.2010.04.0

Krombholz, A., Schaefer, F., & Boucsein, W. (2007). Modification of N170 by different emotional expression of schematic faces. *Biological Psychology, 76*(3), 156-162. doi:10.1016/j.biopsycho.2007.07.004

Ksir, C., & Hart, C. L. (2016). Cannabis and psychosis: A critical overview of the relationship. *Current Psychiatry Reports, 18*(2), 1-11. doi:10.1007/s11920-015-0657-y

Kuepper, R., Morrison, P. D., van Os, J., Murray, R. M., Kenis, G., & Henquet, C. (2010). Does dopamine mediate the psychosis-inducing effects of cannabis? A review and integration of findings across disciplines. *Schizophrenia Research, 121*(1), 107-117. doi:10.1016/j.schres.2010.05.031

Lardinois, M., Lataster, T., Mengelers, R., van Os, J., & Myin-Germeys, I. (2011). Childhood trauma and increased stress sensitivity in psychosis. *Acta Psychiatrica Scandinavica,123*(1), 28-35. doi:10.1111/j.1600-0447.2010.01594.x

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. doi:10.1001/archgenpsychiatry.2011.5

Le Pelley, M. E., Schmidt-Hansen, M., Harris, N. J., Lunter, C. M., & Morris, C. S. (2010). Disentangling the attentional deficit in schizophrenia: Pointers from schizotypy. *Psychiatry Research, 17*6(2), 143-149. doi:10.1016/j.psychres.2009.03.027

Lee, S., Kim, S., Kim, E., & Bae, S. (2010). Event-related potential patterns and gender effects underlying facial affect processing in schizophrenia patients. *Neuroscience Research, 67*(2), 172-180. doi:10.1016/j.neures.2010.03.001

Lieberman, J. A., Sheitman, B. B. & Kinon, B. J. (1997). Neurochemical sensitization in the pathophysiology of schizophrenia: Deficits and dysfunction in neuronal regulation and plasticity. *Neuropsychopharmacology, 17*(4), 205-229. doi:10.1016/S0893-133X(97)00045-6

Linszen, D. H., Dingemans, P. M., & Lenior, M. E. (1994). Cannabis abuse and the course of recent-onset schizophrenic disorders. *Archives of General Psychiatry,51*(4), 273-279. doi:10.1001/archpsyc.1994.03950040017002

Linszen, D. H., Dingemans, P. M., & Lenior, M. E. (1994). Cannabis abuse and the course of recent-onset schizophrenic disorders. *Archives of General Psychiatry,51*(4), 273-279. doi:10.1001/archpsyc.1994.03950040017002

Luck, S. J., & Kappenman, E. S. (Eds.). (2012). *Oxford handbook of event-related potential components*. New York: Oxford University Press.

Lynn, S. K., & Salisbury, D. F. (2008). Attenuated modulation of the N170 ERP by facial expressions in schizophrenia. *Clinical EEG and Neuroscience, 39*(2), 108.

Lyons, M. J., Toomey, R., Faraone, S. V., Kremen, W. S., Yeung, A. S., & Tsuang, M. T. (1995). Correlates of psychosis proneness in relatives of schizophrenic patients. *Journal of Abnormal Psychology, 104*(2), 390-394. doi:10.1037/0021-843X.104.2.390

MacCoun, R. J., Reuter, P., & Ebrary Academic Complete (Canada) Subscription Collection. (2001). *Drug war heresies: Learning from other vices, times, and places*. New York: Cambridge University Press.

Maher, S., Mashhoon, Y., Ekstrom, T., Lukas, S., & Chen, Y. (2016). Deficient cortical face-sensitive N170 responses and basic visual processing in schizophrenia. *Schizophrenia Research, 170*(1), 87.

Malone, D. T., Hill, M. N., & Rubino, T. (2010). Adolescent cannabis use and psychosis: Epidemiology and neurodevelopmental models. *British Journal of Pharmacology, 160*(3), 511-522. doi:10.1111/j.1476-5381.2010.00721.x

Mason, O., Morgan, C. J. A., Dhiman, S. K., Patel, A., Parti, N., & Curran, H. V. (2009). Acute cannabis use causes increased psychotomimetic experiences in individuals prone to psychosis. *Psychological Medicine, 39*(6), 951-956. doi:10.1017/S0033291708004741

Miettunen, J., Tormanen, S., Murray, G. K., Jones, P. B., Maki, P., Ebeling, H... Veijola, J. (2008). Association of cannabis use with prodromal symptoms of psychosis in adolescence. *The British Journal of Psychiatry,192*(6), 470-471. doi:10.1192/bjp.bp.107.045740

Milind, P., Renu, K., & Sushila, K. (2013). Non-behavioral models of psychosis. *International Research Journal of Pharmacy, 4*(8), 89-95. doi:10.7897/2230-8407.04815

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. *The Lancet, 370*(9584), 319-328. doi:10.1016/S0140-6736(07)61162-3

Morgan, H. M., Klein, C., Boehm, S. G., Shapiro, K. L., & David E. J. Linden. (2008). Working memory load for faces modulates P300, N170, and N250r. *Journal of Cognitive Neuroscience, 20*(6), 989-1002. doi:10.1162/jocn.2008.20072

Morris, S. B., & DeShon, R. P. (2002). Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. *Psychological Methods,7*(1), 105-125. doi:10.1037//1082-989X.7.1.105

Murray, R. M., Paparelli, A., Morrison, P. D., Marconi, A., & Di Forti, M. (2013). What can we learn about schizophrenia from studying the human model, drug-induced psychosis? *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 162*(7), 661-670. doi:10.1002/ajmg.b.32177

Nelson, M. T., Seal, M. L., Pantelis, C., & Phillips, L. J. (2013). Evidence of a dimensional relationship between schizotypy and schizophrenia: A systematic review. *Neuroscience and Biobehavioral Reviews, 37*(3), 317-327. doi:10.1016/j.neubiorev.2013.01.004

Oestreich, L. K. L., Mifsud, N. G., Ford, J. M., Roach, B. J., Mathalon, D. H., & Whitford, T. J. (2015). Subnormal sensory attenuation to self-generated speech in schizotypy: Electrophysiological evidence for a 'continuum of psychosis'. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology, 97*(2), 131-138. doi:10.1016/j.ijpsycho.2015.05.014

Öngür, D., Lin, L., & Cohen, B. M. (2009). Clinical characteristics influencing age at onset in psychotic disorders. *Comprehensive Psychiatry, 50*(1), 13-19. doi:10.1016/j.comppsych.2008.06.002

Onitsuka, T., Niznikiewicz, M. A., Spencer, K. M., Frumin, M., Kuroki, N., Lucia, L. C... McCarley, R. W. (2006). Functional and structural deficits in brain regions subserving face perception in schizophrenia. *The American Journal of Psychiatry, 163*(3), 455-462. doi:10.1176/appi.ajp.163.3.455

Park, H., Lim, V., Kirk, I., & Waldie, K. (2015). P50 sensory gating deficits in schizotypy. *Personality and Individual Differences, 82*, 142-147. doi:10.1016/j.paid.2015.03.025

Palali, A., & Ours, J. C. (2015). Distance to cannabis shops and age of onset of cannabis use. *Health Economics, 24*(11), 1483-1501. doi:10.1002/hec.3104

Pistis, M., Perra, S., Pillolla, G., Melis, M., Muntoni, A. L., & Gessa, G. L. (2004). Adolescent exposure to cannabinoids induces long-lasting changes in the response to drugs of abuse of rat midbrain dopamine neurons. *Biological Psychiatry, 56*(2), 86-94. doi:10.1016/j.biopsych.2004.05.006

Rabin, R.A., Giddens, J.L., & George, T.P. (2014). Relationship between tobacco and cannabis use status in outpatients with schizophrenia. *Am J Addict, 23*(2):170–5.

Raine, A. (1991). The schizotypal personality questionnaire (SPQ): A scale for the assessment of schizotypal personality based on DSM–III–R criteria. *Schizophrenia Bulletin, 17,* 555– 564.

Reitan, R. M. (1958). Validity of the trail making test as an indicator of organic brain damage. *Perceptual and Motor Skills, 8*(3), 271-276. doi:10.2466/pms.1958.8.3.271

Rossion, B., Delvenne, J., Debatisse, D., Goffaux, V., Bruyer, R., Crommelinck, M., & Guérit, J. (1999). Spatio-temporal localization of the face inversion effect: An event-related potentials study. *Biological Psychology, 50*(3), 173-189. doi:10.1016/S0301-0511(99)00013-7

Rotermann, M., & Langlois, K. (2015). Prevalence and correlates of marijuana use in canada, 2012. *Health Reports, 26*(4), 10.

Rutten, B. P. F., van Os, J., & Kenis, G. (2010). The environment and schizophrenia. *Nature, 468*(7321), 203-212. doi:10.1038/nature09563

Sadeh, B., & Yovel, G. (2010). Why is the N170 enhanced for inverted faces? an ERP competition experiment. *Neuroimage, 53*(2), 782-789. doi:10.1016/j.neuroimage.2010.06.029

Salthouse, T. A. (2011). What cognitive abilities are involved in trail-making performance? *Intelligence, 39*(4), 222-232. doi:10.1016/j.intell.2011.03.001

Schiffer, B., Müller, B. W., Scherbaum, N., Forsting, M., Wiltfang, J., Leygraf, N., & Gizewski, E. R. (2010). Impulsivity-related brain volume deficits in schizophrenia-addiction comorbidity. *Brain: A Journal of Neurology,133*(10), 3093-3103. doi:10.1093/brain/awq153

Schultze-Lutter, F., Rahman, J., Ruhrmann, S., Michel, C., Schimmelmann, B. G., Maier, W., & Klosterkötter, J. (2015). Duration of unspecific prodromal and clinical high risk states, and early help-seeking in first-admission psychosis patients. *Social Psychiatry and Psychiatric Epidemiology, 50*(12), 1831-1841. doi:10.1007/s00127-015-1093-3

Seeman, P. (2013). Schizophrenia and dopamine receptors. *The Journal of the European College of Neuropsychopharmacology, 23*(9), 999.

Shadish, W., Cook, T., and Campbell, D. (2002). Experimental and Quasi-Experimental Designs for Generilized Causal Inference Boston: Houghton Mifflin.

Shrivastava, A., Johnston, M., Terpstra, K., & Bureau, Y. (2014). Cannabis and psychosis: Neurobiology. *Indian Journal of Psychiatry, 56*(1), 8. doi:10.4103/0019-5545.124708

Skosnik, P. D., Park, S., Dobbs, L., & Gardner, W. L. (2008). Affect processing and positive syndrome schizotypy in cannabis users. *Psychiatry Research, 157*(1-3), 279-282. doi:10.1016/j.psychres.2007.02.010

Skosnik, PD, Krishnan, GP, Aydt, EE, Kuhlenshmidt, HA, O'Donnell, BF. (2006). Psychophysiological evidence of altered neural synchronization in cannabis use: relationship to schizotypy. *American Journal of Psychiatry, 163*(10), 1798-1805. doi:10.1176/ajp.2006.163.10.1798

Stefanis, N. C., Dragovic, M., Power, B. D., Jablensky, A., Castle, 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. doi:10.1093/schbul/sbs188

Substance Abuse and Mental Health Services Administration. (2013). National survey on drug use and health: summary of national findings. Rockville, MD: SAMHSA.

Troup, L. J., Bastidas, S., Nguyen, M. T., Andrzejewski, J. A., Bowers, M., & Nomi, J. S. (2016). An event-related potential study on the effects of cannabis on emotion processing: E0149764. *PLoS One, 11*(2) doi:10.1371/journal.pone.0149764

Tso, I. F., Calwas, A. M., Chun, J., Mueller, S. A., Taylor, S. F., & Deldin, P. J. (2015). Altered attentional and perceptual processes as indexed by N170 during gaze perception in schizophrenia: Relationship with perceived threat and paranoid delusions. *Journal of Abnormal Psychology, 124*(3), 519-531. doi:10.1037/abn0000056

Tsunoda, T., Kanba, S., Ueno, T., Hirano, Y., Hirano, S., Maekawa, T., & Onitsuka, T. (2012). Altered face inversion effect and association between face N170 reduction and social dysfunction in patients with schizophrenia. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 123*(9), 1762-1768. doi:10.1016/j.clinph.2012.01.024

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. doi:10.1093/aje/kwf043

van Tricht, M. J., Harmsen, E. C., Koelman, Johannes H T M, Bour, L. J., van Amelsvoort, T. A., Linszen, D. H... Nieman, D. H. (2013). Effects of cannabis use on event related potentials in subjects at ultra high risk for psychosis and healthy controls. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology, 88*(2), 149-156. doi:10.1016/j.ijpsycho.2013.03.012

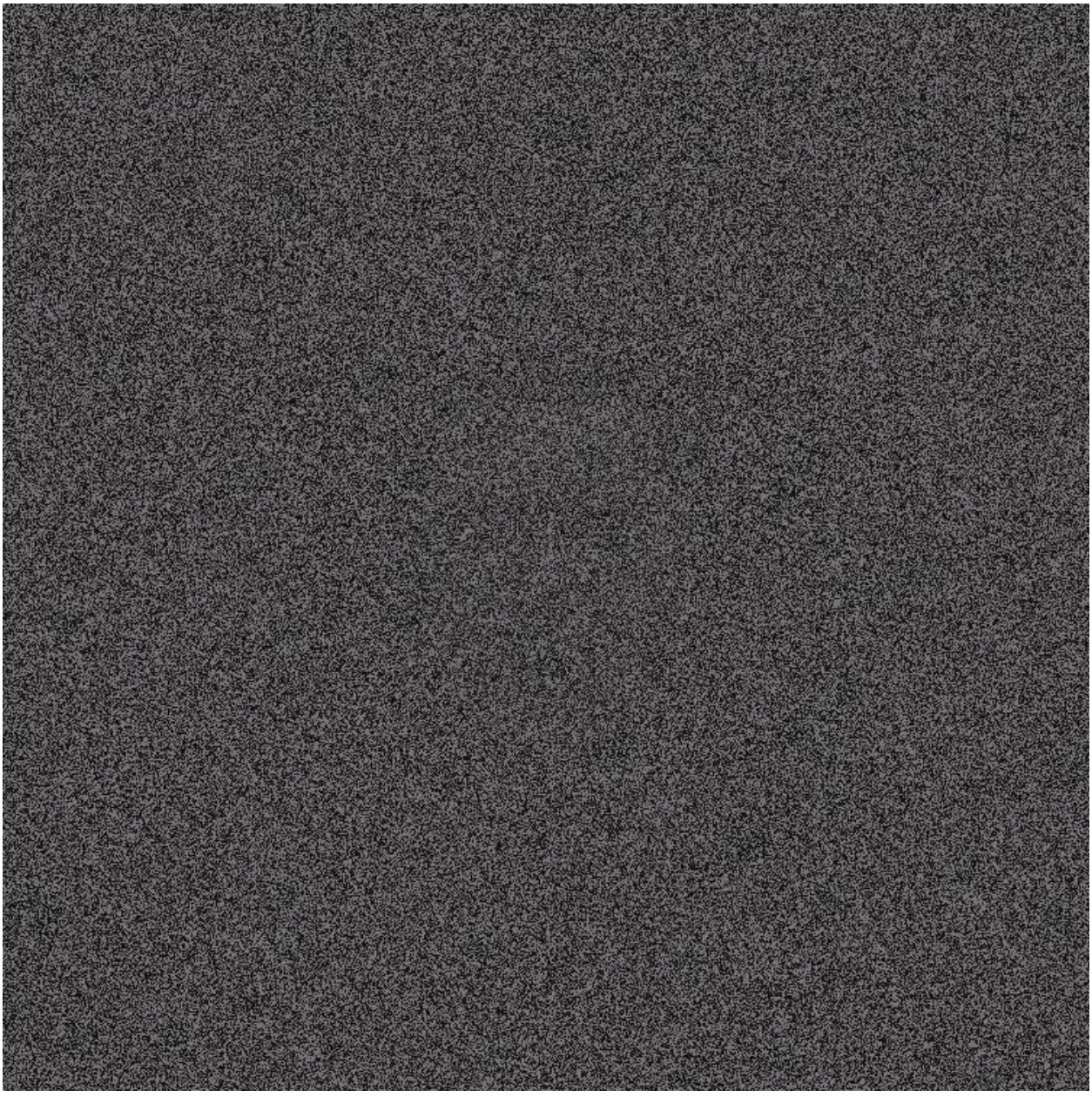
Wild, H.A., & Busey, T. A. (2004). Seeing faces in the noise: stochastic activity in perceptual regions of the brain may influence the perception of ambiguous stimuli. *Psychonomic Bulletin & Review, 11*(3), 475-481. doi:10.3758/BF03196598

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: British Medical Journal*, 325(7374), 1199-1201. doi:10.1136/bmj.325.7374.1199

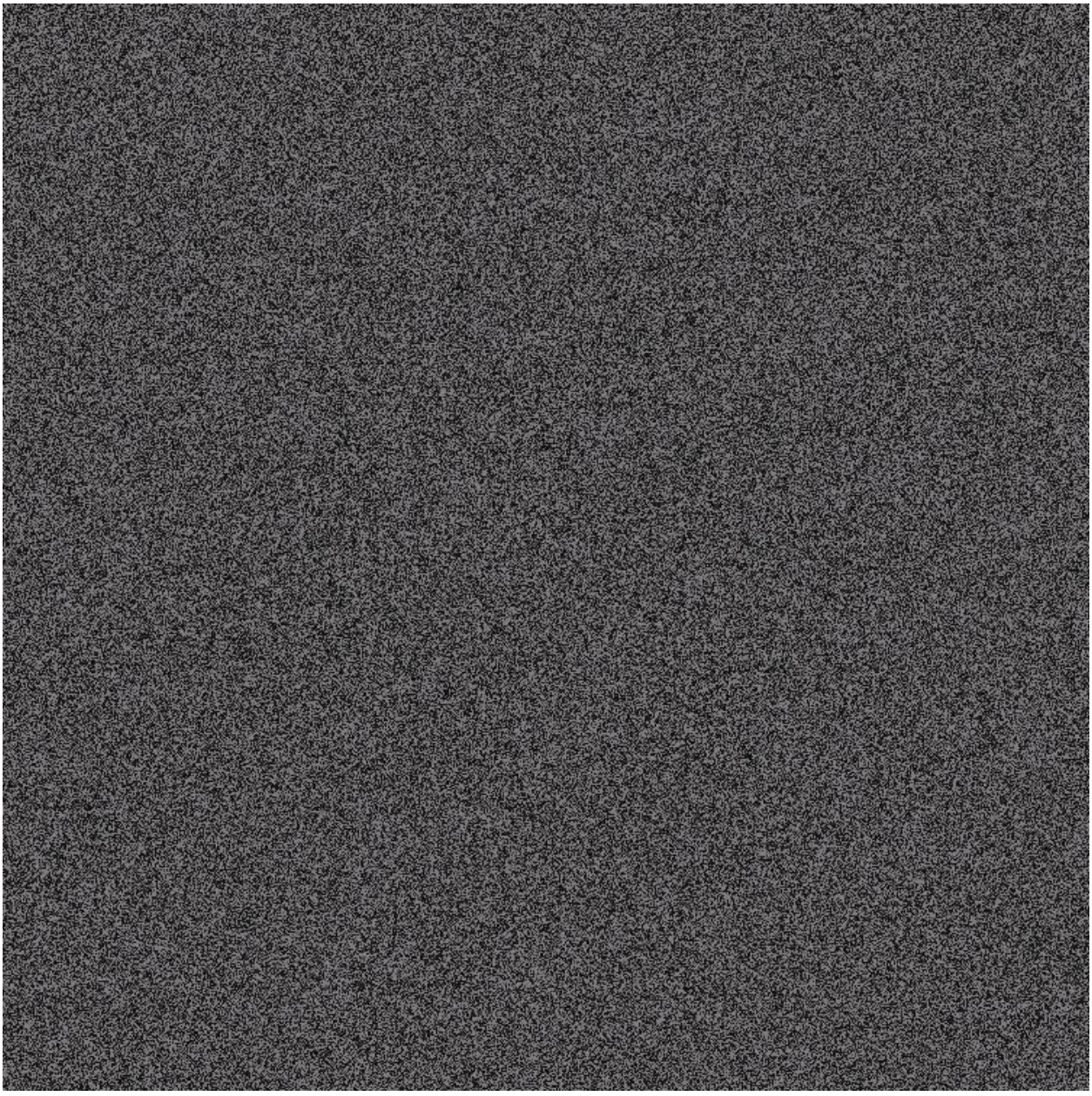
Zullino, D. F., Manghi, R., Rathelot, T., Khan, R., & Khazaal, Y. (2010). Cannabis causes schizophrenia? so does nicotine. *Addiction Research & Theory, 1*8(6), 601-605. doi:10.3109/16066359.2010.489999

Appendices

Appendix 1: Stimulus Examples



Appendix 1a: Image of a face-present trial-type.



Appendix 1b: Image of a noise-only trial-type.

Appendix 2: Phone Screen for Community Participants

FIN and TT Telephone Script

Hi, thank you for your interest in our study. Let me tell you a little about our study first to see if you are interested in participating, and then I will ask you a few brief questions to determine your eligibility.

This study is run by the Clinical and Cognitive Neuroscience Lab of Dr. Colleen Brenner through the UBC Department of Psychology. We are interested in the perceptual and neurological correlates of cannabis use and personality.

The study is composed of one session. You will be asked to come to the laboratory at UBC and answer a series of questions about yourself, your personality and your experiences. You will also be asked to complete some tests of cognition, memory and attention. Finally, you will have an EEG (or brainwaves) recorded while you are looking at things on a computer screen or hearing sounds over headphones. The entire session will take approximately 3 hours. You will be paid $10 an hour for your participation.

Does this sound like something you are interested in?

If **NO**: Ok, thank you for your time and please don't hesitate to contact us again if you change your mind.

If **YES**: Great, before we schedule an appointment I would like to ask you a few questions to determine your eligibility; is this O.K. with you?

If **NO**: I'm afraid we're unable to proceed without some general information about your eligibility. (If still not willing to answer eligibility questions) Thank you for your time and please don't hesitate to contact us again if you change your mind.

If **YES**: Please note that all the answers you provide are strictly confidential and will only be used to determine your eligibility in the study. Once we're done and your eligibility is determined, your answers to these questions will be destroyed and no permanent record of your responses will be kept.

Proceed with questions on next page:

1) How did you find out about our study?

2) How old are you? _____

3) Is English you primary language?_____
   If NO: How many years have you been communicating in English? _____

Do you have any difficulty understanding written materials presented in English such as books, magazines or the newspaper?_____

4) Do you have any difficulties with your eye sight? _____

5) Do you have any difficulties with your hearing? _____

6) Have you ever had a serious head injury or lost consciousness for more than 5 minutes?
   _____
   _____

   IF YES: did you have a concussion or any post-concussive symptoms such as: headaches, trouble with concentration, blurred vision, ringing ears, dizziness or vertigo?
   _____
   _____

7) Have you ever been diagnosed with a neurological disorder or a condition that might affect neurological functions such: epilepsy, seizures, meningitis, stroke, thyroid problems, hypoglycaemia or diabetes?

_____

_____

8) Do you think you have, or have you ever had a learning disorder?

_____

_____

IF THINKS THEY HAVE: Why do you think you have _____? What symptoms do/did you have?_____

_____

Were you ever formally diagnosed with _____? _____

9) Do you think you have, or have you ever thought you had a serious mental illness such as schizophrenia, bipolar disorder, major depression, or serious anxiety related issues)?

_____

_____

IF THINKS THEY HAVE: Why do you think you have _____?

What symptoms do/did you have?_____

_____

Were you ever formally diagnosed with _____? _____

_____

10) Are you currently seeking psychological treatment for any reason? Yes No

IF YES: What (in general) are you currently seeking treatment for? _____

_____

What kind of treatment are you receiving (meds, counselling, etc.)?_____

_____

How long have you been receiving treatment? _____

_____

11) Have you EVER sought treatment for a psychological problem in the past? Yes No
IF YES: What (in general) did you seek treatment for? _____

_____

What kind of treatment did you receive (meds, counselling, etc.)? _____

_____

12) Are you currently taking any prescription medication or undergoing treatment for any medical conditions? Yes No
IF YES: What illness are you being treated for? _____

What treatment are you receiving (list medications and treatment): _____

_____

13) Approximately how much alcohol do you drink on a regular basis? _____
_____

IF MORE THAN 3 IN ONE SITTING: How long have you been drinking this amount?
_____
_____

14) Was there ever a time in your life when you drank more than you do now? Yes No

IF YES: When was that? _____
_____

How much were you drinking then? _____

15) Do you use recreational drugs on a regular basis?
_____

IF YES: What do you use? _____
_____

How much/often do you use _____? _____
_____

How long have you been using this amount? _____
_____

16) Was there ever a time in your life when you used more drugs than you do now?
Yes No

IF YES: When was that? _____
_____

What were you using then? _____
_____

How much were you using then? _____

17) Have you ever received treatment for drug or alcohol use? Yes No

IF YES: When & for how long were you in treatment? _____
_____

What were you in treatment for?

_____

Questions from SPQ:

(1) Have you often mistaken objects or shadows for people, or noises for voices? **Yes No**
(2) Do other people see you as slightly eccentric or odd? **Yes No**
(3) Are you certain that you are being talked about behind your back? **Yes No**
(4) Do you prefer to keep to yourself? **Yes No**
(5) Are you poor at expressing your true feelings because of the way you talk and look? **Yes No**
(6) Have you ever noticed a common event or object that seemed to be a special sign for you? **Yes No**
(7) Do you feel that you have to be on guard even with friends? **Yes No**
(8) Do you sometimes feel that other people are watching you? **Yes No**
(9) Are your thoughts sometimes so strong that you can almost hear them? **Yes No**

Number of SPQ Questions Endorsed: **/9**

Questions from CEQ:

Do you or have you ever used cannabis? **Yes No**

[If YES]

For the following questions please reply with:

(1) Rarely or Never, (2) From Time to Time, (3) Sometimes Yes & Sometimes No, (4) More often than Not, or (5) Almost Always or Always.

How often do you have or have you had the following experiences while smoking cannabis?

(1) Feeling Happy
(2) Enhanced Perceptual Awareness
(3) Able to Understand the World Better
(4) Losing your sense of Reality
(5) Feeling Relaxed
(6) Feeling More Creative
(7) Rapid Flow of Thoughts
(8) Feeling Full of Ideas

How often have you had the following experiences after smoking cannabis?

(9) Not Wanting to do Anything
(10) Feeling Generally Slowed Down Physically

If **eligible**: Thank you for answering those questions. You are eligible to participate in the study and we'd like to schedule your first appointment.

If **ineligible**: Thank you for answering those questions. I'm afraid that you are not eligible to participate in this study, however new studies are started in our laboratory fairly regularly. Would you be willing for us to keep your information on file and contact you if a study for which you are eligible becomes available?

If **NO**: Ok, thank you again for calling and have a nice day.

If **Yes**: Great, we will contact you in the future if another study becomes available for which you are eligible. Thank you for calling and have a nice day.

Appendix 3: Additional Pearson's Bivariate Correlations

	Correct Noise-Only	**Incorrect Noise-Only**	**Correct Face-Present**	**Incorrect Face-Present**
CEQ Paranoid-Dysphoric – P8	*r* = .186 *p* = .194	***r* = .370** ***p* = .012**	*r* = .329 *p* = .024	*r* = .253 *p* = .083

Note. Four ad-hoc correlations were run between the P8 amplitude for each trial-type and the CEQ paranoid-dysphoric subscale. Pearson's correlation coefficients and associated *p*-values are provided. Incorrect noise-only trials remained significantly correlated with the CEQ paranoid-dysphoric scale, after a Bonferroni adjustment of $p = .013$.