The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, the thesis entitled:

Biased attentional processing associated with concurrent disorders: an event-related potential study

submitted

the degree of

in

Tanisse Chanel Maureen Epp

Master of Science

Neuroscience

in partial fulfilment of the requirements for the degree of Master of Science in Neuroscience

Examing Committee:

Dr. Christian Schütz, Psychiatry, UBC

Supervisor

Dr. Catharine Winstanley, Psychology, UBC

Supervisory Committee Member

Dr. Rebecca Todd, Psychology, UBC

Supervisory Committee Member

Dr. Stanley Floresco, Psychology, UBC

Additional Examiner

Additional Supervisory Committee Members:

Dr. Olav Krigolson, Medical Science, UVic

Supervisory Committee Member
Abstract

Background: Several studies have shown that substance use disorders are characterized by an enhanced attention processing of substance and substance-related cues, with lower attentional processing of non-substance-related affective cues. Additionally, previous research has shown that attentional processing, within addiction, is malleable and can reverse from enhanced processing of substance cues to pleasant cues following prolonged abstinence. This study examines the neural processing of stimulant, pleasant, and stimulant relative to pleasant cues in individuals with a concurrent diagnosis of mental health and substance use disorders (i.e., concurrent disorders) compared to controls using event-related potentials (ERPs).

Methods: Within in-patient individuals with concurrent disorders (n = 33) and a control group (n = 32), we studied the P300 amplitude elicited by stimulant (stimulant – neutral), pleasant (pleasant – neutral), stimulant relative to pleasant (stimulant – pleasant) cues. Additionally, individuals completed surveys and tasks to examine the implications of diagnoses, self-reported craving, cognitive function, and affect.

Results: The results indicate that in-patient participants with concurrent disorder display a larger P300 difference wave for stimulant and pleasant cues, which remained significant after controlling for age, ethnicity, and working memory, compared to controls.

Conclusions: These findings suggest that larger P300 amplitudes for stimulant and pleasant cues may be explaining emotional dysregulation within concurrent disorders. Together these findings suggest that non-invasive electrophysiological measures, such as EEG, may be used within future research to investigate the differences in concurrent disorder, mental health, and substance use disorders alone, necessary for identifying shared processes among these disorders.
Lay Summary

Greater attention to drug and pleasant cues may be a neural marker for concurrent disorders and the potential emotional dysfunction associated with the disorder. This study uses electroencephalography (EEG) to measure brain activity in response to pictures of stimulant drugs, pleasant, and neutral objects. We found that individuals with concurrent disorders show greater attention to drug and pleasant stimuli compared to those without a mental health or substance use disorder diagnosis. Together these results suggest the utility of EEG for its potentially valuable and effective measure for clinically relevant markers such as disorder susceptibility, severity, and treatment efficacy within concurrent disorders.
Preface

All of the work presented henceforth was conducted within the Behavioural Reward Affect and Impulsivity Neuroscience (B.R.A.I.N.) laboratory at the University of British Columbia, Point Grey campus, Vancouver, British Columbia and the Red Fish Healing Centre for Mental Health and Addiction, Coquitlam, British Columbia. All projects and associated methods were approved by the University of British Columbia’s Research Ethics Board [certificate # H21-01451] and the British Columbia Mental Health and Substance Use Services Research Committee and Data Access Committee. None of the text of the dissertation is taken directly from previously published or collaborative articles.

The EEG recording programming, signal processing, and data extraction code, described in Section 2.3.2, was created by M. Hammerstrom, K. Boere, and O. Krigolson.

I, Tanisse, was involved in and led all methods described in this thesis. Specifically, I was responsible for all major areas of concept foundation, ethics applications and reporting, data collection and analysis, and manuscript composition. H. Ranote and K. Klassen were involved in the early conceptual framework. A. Turcott, C. Holt-Robinson, N. Hussain Ramadhan, C. Lee, K. Realina, A. Lail, A. Lehal, and S. Soleymani were involved in data collection. J. Booth and L. Schmidt were involved in study coordination. C. Schütz was the supervisor on this project and was involved throughout the project in concept formation and manuscript edits.
# Table of Contents

Abstract ............................................................................................................................. iii
Lay Summary.................................................................................................................... iv
Preface .............................................................................................................................. v
Table of Contents ........................................................................................................... vi
List of Tables .................................................................................................................. viii
List of Figures ................................................................................................................. ix
Acknowledgements ......................................................................................................... x
Dedication ......................................................................................................................... xi

## 1 Introduction ................................................................................................................. 1
  1.1 Substance Use Disorders .................................................................................... 1
  1.2 Mechanisms Underlying Substance Use Disorders ........................................... 2
  1.3 Attentional Capturing Hypotheses ..................................................................... 4
  1.4 Electroencephalography ..................................................................................... 5
  1.5 P300 and Substance Use Disorders .................................................................... 7
  1.6 P300 and Mental Health Disorders ..................................................................... 8
  1.7 P300 and Drug Craving ..................................................................................... 8
  1.8 Aims .................................................................................................................... 10

## 2 Methods ....................................................................................................................... 11
  2.1 Study Design ....................................................................................................... 11
  2.2 Participants ......................................................................................................... 11
  2.3 Measures ............................................................................................................. 13
    2.3.1 Stimuli and Experimental Paradigm .............................................................. 13
    2.3.2 EEG Recording and Signal Processing ......................................................... 13
    2.3.3 Treatment- and Medical-Related Measures for In-Patient Participants .......... 15
    2.3.4 Demographics ............................................................................................ 16
    2.3.5 Premorbid Intelligence Quotient ................................................................... 17
    2.3.6 Working Memory ....................................................................................... 17
    2.3.7 Positive and Negative Affect ....................................................................... 18
    2.3.8 Craving ....................................................................................................... 18
  2.4 Procedures ............................................................................................................. 18
  2.5 Statistical Analysis .............................................................................................. 19

## 3 Results ........................................................................................................................ 20
  3.1 Between Control and In-Patient Analyses ........................................................... 20
3.1.1 Demographics ............................................................................................................. 20
3.1.2 Cognitive Functioning ............................................................................................... 21
3.1.3 Affect ........................................................................................................................ 21
3.1.4 Exploratory P300 Amplitude Correlation Analysis .................................................. 21
3.1.5 Analysis of Variance for P300 Wave Difference Across Group-Type .......................... 22

3.2 Exploratory In-Patient Group Analyses ....................................................................... 23
3.2.1 Demographics ........................................................................................................... 23
3.2.2 Substance Use and Craving ....................................................................................... 23
3.2.3 Exploratory Multiple Linear Regression for P300 Difference Waves ....................... 23

4 Discussion .......................................................................................................................... 24
4.1 Lower P300 Amplitude Differential to Stimulant Cues Relative to Positive Cues in Those with Concurrent Disorders Compared to Controls ............................................. 24
4.2 Larger P300 Amplitude Differentials to Stimulant and Pleasant Cues in Those with Concurrent Disorders Compared to Controls ............................................................... 25
4.3 No Predictors for P300 Amplitude Differentials Amongst In-Patient Participants .......... 26
4.4 Significant Correlation Between Self-Reported Craving and P300 Amplitude for Pleasant Cues ................................................................................................................ 27
4.5 Limitations .................................................................................................................... 28
4.6 Future Directions .......................................................................................................... 30

5 Conclusion .......................................................................................................................... 31

Bibliography .......................................................................................................................... 36
List of Tables

Table 1. Summary of demographics, cognitive functioning, affect, and P300 differentials for both in-patient and control participants. 35
List of Figures

**Figure 1.** An example of a single trial of the task. In this example, the image shown is from the stimulant-related cue type. After presentation of the picture, four questions are prompted followed by crosshairs. ................................................................. 32

**Figure 2.** EEG ERP waveforms by control and in-patient samples between -200 ms to 1000 ms for stimulant, neutral, and positive cues. A) EEG ERP waveform for control participants. B) EEG ERP waveform for in-patient participants. ................................................................. 33

**Figure 3.** Bar graphs of P300 differentials between control and in-patient samples for pleasant (relative to neutral), drug (relative to neutral) and the drug – pleasant direct contrast. *p < 0.05, ***p < .001. ................................................................. 34
Acknowledgements

I would like first to thank my supervisor, Dr. Christian G. Schütz, for his continuous support and guidance throughout this project. I am forever grateful that you entrusted me with this incredible project and allowed me to experience such a unique research environment. In addition, I am very grateful to my committee members (Dr. Olav Krigolson, Dr. Catharine Winstanley, and Dr. Rebecca Todd) for sharing their time, guidance, and expertise. Thank you!

With that, it is necessary to acknowledge that this thesis would not have been possible without the incredible research assistants who worked hard and meticulously to collect data for this study: Achint Lail, Anesha Lehal, Alyssa Turcott, Curtis Holt-Robinson, Chaehyeon Lee, Kaycee Realina, Noor Hussain Ramadhan, and Shayan Soleymani. Thank you, team, for your time and commitment to this study is sincerely appreciated! Furthermore, I would like to thank our project coordinator, Laura Schmidt, for her unwavering assistance, help, and comfort throughout the process.

Additionally, the emotional support I received for this project was a key component to its completion, and for that, I would like to thank my fellow master’s student; Karling, my family; Dave, Maureen, Michelle, Wayne, Brody, Brayden, and Tyanna, and my loving husband; Adam. Each of you supported me in many different ways, all of which I am eternally grateful for. Thank you!

Finally, research, in general, is only possible with volunteer participants who give their time to science. Thank you!
Dedication

To my brother, Brody – our hours of storytelling and discussing the details of a long-ago past fundamentally inspired my passion for research. You are my hero!
1 Introduction

1.1 Substance Use Disorders

Substance use disorders (SUDs) have developed into a global epidemic (Volkow, 2020), creating a significant burden worldwide. The SUD crisis has created costs for individual societies and the global economy (Degenhardt et al., 2018; Rehm and Shield, 2019), on the medical system due to its high propensity for relapse and overdose (Koob, 2011), its association with poorer health outcomes (Degenhardt et al., 2018), and its role in premature and preventable mortalities (Martinez et al., 2020). Additionally, the rate of comorbid diagnosis of SUDs with mental health disorders (i.e., concurrent disorder) is increasing (Hakobyan et al., 2020). Compared to SUDs alone, concurrent disorders cause more morbidity and mortality (Hakobyan et al., 2020). Due to the complexity and multimorbid nature of concurrent disorders, it is largely underdiagnosed and undertreated (Hakobyan et al., 2020). Additionally, research within this field is underdeveloped, leading to significant gaps in our understanding of the complex disorder.

One of the significant challenges within this population is the degree of heterogeneity within diagnoses. For instance, there is a difference in prevalence and frequencies among different concurrent disorders. Approximately 25% of individuals with anxiety or major depressive disorder will have an overlapping SUD (Regier et al., 1990; Conway et al., 2006), while 50% of individuals with bipolar disorder or schizophrenia will have a co-occurring SUD (Khan, 2017). Additionally, the prevalence of a particular comorbidity is associated with the severity of the disorder, which contributes to increased vulnerability to multimorbidity, social marginalization, and stigmatization (Todd et al., 2004). While the mechanisms underlying the development and maintenance of concurrent disorders are currently limited, a better
understanding of the shared neurology and overlapping risk factors with SUDs can contribute to a potential understanding of the underlying mechanisms of concurrent disorders.

1.2 Mechanisms Underlying Substance Use Disorders

SUDs are among the most prevalent psychiatric disorders (Witkiewitz et al., 2022). The Diagnostic and Statistical Manual for Mental Disorders, 5th edition (DSM-5) describes cognitive, behavioural, and physiological symptoms that signify when an individual continues to use despite significant substance-related problems (American Psychiatric Association, 2013). Symptoms can range from mild to severe depending on the number of symptom criteria endorsed and fall under four main criteria: impaired control over substance use, social impairment, risky use, and pharmacologic criteria (American Psychiatric Association, 2013). Examples of impaired control over substance use include consuming the substance in larger amounts for extended periods than intended and experiencing craving (a pressing desire to use the substance; American Psychiatric Association, 2013). Social impairment symptoms include impairments to fulfill major obligations to work, school or home; or continuing to use despite adverse social or interpersonal consequences (American Psychiatric Association, 2013). Risky use criteria include using in unsafe environments or using despite exacerbated physical or psychological problems (American Psychiatric Association, 2013). Lastly, pharmacological criteria include tolerance (using higher doses to achieve the desired effect) and withdrawal (American Psychiatric Association, 2013).

A primary goal of research is to understand the mechanisms and factors that contribute to the development and maintenance of SUDs. This has led to identifying complex systems and factors that play crucial roles, such as genetics, cognition, and environmental factors (Gelernter and Polimanti, 2021; Heilig et al., 2021; Rawls et al., 2021; Ray and Grodin, 2021). These
findings have identified distinct psychological constructs of the disorder, including alterations in reward processing (Luijten et al., 2017), salience attribution (Zilverstand and Goldstein, 2020), inhibitory control (Luijten et al., 2014; Le et al., 2021), and executive functioning (Quaglieri et al., 2020). All contributing to the distinct behavioural characteristics associated with addiction, such as craving, compulsive drug-taking, habitual drug-seeking, and relapse (Zilverstand and Goldstein, 2020; Ceceli et al., 2022).

One of the prominent models used to describe the processes and the behavioural features proposes that SUDs are a form of a chronic relapsing disorder (Koob and Volkow, 2010). This chronic relapsing disorder describes patterned drug-taking behaviour that progresses from impulsive to compulsive in a three-stage cycle: 1) binge/intoxication, 2) withdrawal/negative affect, and 3) preoccupation/anticipation (Koob and Volkow, 2010). This patterned drug-taking is characterized by attentional abnormalities, where attention is directed to drugs and drug-related cues at the expense of other reinforcing cues. This attentional bias within SUDs has been described by Dr. Rita Goldstein and colleagues (2002, 2011, 2017), suggesting that, as a result of classical conditioning from repeatedly pairing drug use and drug cues, attention is directed towards these cues later on becoming motivationally salient through this characteristic habitual use. It is proposed that attention bias towards drug cues influences drug-seeking behaviour, which is associated with increased craving (Rosse et al., 1997; Franken et al., 2000; Field et al., 2013) and relapse susceptibility (Cox et al., 2002; Waters et al., 2003; Carpenter et al., 2006; Marissen et al., 2006). Additionally, it has been identified that abstinence from drug use improves cognitive and affective functioning, including attentional bias (Garavan et al., 2013) — suggesting that attentional bias within addiction are malleable. While these theories have dominated the attentional bias field of addiction research, there has been debate surrounding
theories describing the mechanisms behind attentional capturing within attentional research alone (Luck et al., 2021).

1.3 Attentional Capturing Hypotheses

From the perspective of attentional researchers, there is evidence for two major yet competing theories within attentional capturing, specifically the stimulus-driven accounts of attention and the contingent involuntary orienting hypothesis (Luck et al., 2021). The stimulus-driven accounts of attention theory suggest that certain physically salient stimuli (distinctive of a stimulus’s physical property) will automatically drive visual attention, even when it is irrelevant to the task at hand (Jonides and Yantis, 1988; Theeuwes, 1993). In contrast, the contingent involuntary orienting hypothesis suggests that a stimulus only captures attention if it is a result of implicit encouragement favouring it (Folk et al., 1992). After decades of dispute between these opposing theories, a consensus on two main properties of attention capturing has been identified. Expressly, both of these theories agree that: 1) salient stimuli automatically capture attention, and 2) there is also the ability for attention to a salient stimulus to be prevented (Luck et al., 2021). Thus, salient stimuli play a critical role in capturing attention, such that identifying the sources of salient stimuli is necessary to consider.

Todd and Manaligod (2018) highlight four salient sources that can contribute to attentional capturing: statistical learning, semantic associations, reward, and affective salience. Within the scope of addiction, it can be hypothesized that the first stages (i.e., binge and intoxication) could result from attention to rewarding salience sources that guide drug use (Chelazzi et al., 2013; Anderson, 2015). In this example, the rewarding salience associated with using drugs for their euphoric effects contributes partially to driving behaviour through this captured attention toward rewarding salient cues. In contrast, within the later stages of addiction,
withdrawal/negative reinforcement and preoccupation/anticipation, attention is captured through negative affective salience, as the goal of drug use during these last stages of addiction is primarily driven to avoid pain (both physical and emotional; Todd and Manaligod, 2018). Within this example, the stimulus is thought to evoke a greater degree of psychological or physiological arousal related to avoiding withdrawal, and thus attentional processes are guided toward these stimuli.

Attention bias has been thoroughly researched using behavioural measures such as Stroop task (Williams et al., 1996), dot-probe task (Eysenck et al., 1987), visual search task (Bravo and Nakayama, 1992), and attentional blink test (Shapiro et al., 1997). Behavioural measures of attention bias are typically based on reaction time or accuracy in tasks which require participants to respond to different types of stimuli because of this, behavioural measures of attention bias are easy to administer and analyze and are widely used and well validated in various populations, making it easier to compare results across studies (Cisler and Koster, 2010). With that, behavioural measures rely on inferences from behaviour to determine attention allocation and can be influenced by factors unrelated to attention bias, such as general response speed or motor skills, this using an objective measure of attention bias could provide more direct measures and are less susceptible to demand characteristics and confounding factors (Cisler and Koster, 2010). Thus, using objective measures of attention bias could contribute to the neurological underpinnings associated with concurrent disorder development and maintenance.

1.4 Electroencephalography

Electroencephalography (EEG) is a technique used to measure neurophysiological brain activity and has been used to measure attentional processes objectively. EEG electrodes placed on or near the scalp record continuous changes in electrical potentials in the brain (Teplan,
When EEG is time-locked to specific events (like the presentation of a cue), the resulting positive and negative voltage changes over time are referred to as event-related potentials (ERPs; Brandeis and Lehmann, 1986). ERPs index the postsynaptic potential activity when numerous cortical pyramidal neurons in the same orientation discharge synchronously. ERPs reflect a range of cognitive processes as distinguished by the distinct timing, polarity, and response to experimental manipulations (Skrandies, 1990). For instance, the “P300”, a positive ERP component, peaks between 300 to 800ms post-stimulus onset and is commonly regarded as an index of attentional processes, thought to be reflecting a “contextual updating” process, in the context of passively viewing stimuli (Polich, 2007; Littel et al., 2012). The context updating theory suggests that after the initial processing of the stimuli, evaluations of whether this stimulus is similar to a previous stimulus occur through working memory (Polich, 2007). If the stimulus is determined to be the same, the current mental model of the stimulus is maintained within the memory stores. If a new stimulus is detected as a different stimulus, attentional processes are evoked to update the stimulus representation in working memory and result in the P300 (Polich, 2007). The stimuli in these passive viewing paradigms typically consist of pleasant, neutral, and substance-related cues. It is suggested that individuals who have active substance use disorder will allocate more attentional resources to substance-related visual stimuli than pleasant (emotionally provocative images that generate high valence and arousal, images include nudity) and neutral stimuli (neutral images that have neutral valence and arousal, images include household items; Lang et al., 1997; Franken et al., 2008).

Additionally, the P300 can be further discriminated into the P3a and P3b subcomponents (Polich, 2007). The P3a is thought to originate from stimulus-driven frontal mechanisms and is associated with attention related to novelty and emotional processes (Polich, 2007). The P3b
originates from neuronal firing in the temporal-parietal region and is associated with attention relating to updating working memory (Polich and Criado, 2006). Furthermore, P3a and P3b have distinct topographic amplitude distributions reflecting differences with response time, as the P3a engages in focal attention, leading to the memory's context maintenance (the P3b; Polich, 2007). Given the range of complex attentional processes the P300 provides, the specific measures of frontal and temporal-parietal activity (Polich, 2007), and the importance of the frontal and temporal-parietal activity within addiction (Dang et al., 2022), provide ration as to why the P300 could provide a valuable measure of attentional bias specific to SUDs.

1.5 P300 and Substance Use Disorders

Due to the ability of the P300 to provide an objective measure of complex attention processes, previous research has used the P300 to emphasize attentional biases to substance-related cues in individuals with SUDs (for a review, see: Littel et al., 2012). This attentional bias has been demonstrated through an increased P300 amplitude to substance-related stimuli compared to neutral stimuli in individuals with alcohol use disorder (Genkina and Shostakovich, 1983; Herrmann et al., 2000; Namkoong et al., 2004; Petit et al., 2013, 2015; Kroczeck et al., 2018), tobacco use (Warren and McDonough, 1999; Littel and Franken, 2007a, 2011, 2012; Minnix et al., 2013; Cheng et al., 2016; Mashhoon et al., 2018), cannabis use disorder (Wölfling et al., 2008), cocaine use disorder (Franken et al., 2008; Dunning et al., 2011), methamphetamine use disorder (Haifeng et al., 2015), opioid use disorder (Lubman et al., 2007), and heroin use disorder (Franken et al., 2003; Lubman et al., 2008; Yang et al., 2015; Shahmohammadi et al., 2016; Motlagh et al., 2017). Additionally, previous research has suggested that attentional bias to drug cues changes with abstinence, as actively abstinent individuals, show a bias toward pleasant cues instead of drug cues (Parvaz et al., 2017). Together, these findings suggest that attentional
bias, measured by EEG within SUDs, is a potentially useful and effective measure for clinically relevant markers such as susceptibility, severity, and treatment efficacy.

1.6 P300 and Mental Health Disorders

Attentional biases are not limited to individuals with SUDs. Due to many psychiatric disorders having neurocognitive deficits, the P300 has been used to examine neural function implicated in the psychopathology of various mental health disorders. Previous research has shown larger P300 amplitude to emotionally provocative cues, such as pleasant or negative cues, compared to neutral in generalized anxiety disorder (for a review, see; Botelho et al., 2023). In contrast, some studies have identified a lower P300 amplitude to emotionally provocative stimuli compared to neutral stimuli in obsessive-compulsive disorder (Thomas et al., 2013), panic disorder (Windmann et al., 2002), and major depressive disorder (Nandrino et al., 2004). Some studies have even shown a lower P300 amplitude to all cues (neutral and emotionally provocative) in individuals with schizophrenia compared to controls (Turetsky et al., 2007; Shah et al., 2018), suggesting that patients may be implementing a conscious strategy to minimize the impact of affective processing (Windmann et al., 2002; Turetsky et al., 2007). Due to the lack of consistency within these findings, it is unclear whether the P300 is linked to specific features of psychiatric disorders or is a more general neural marker of broad neural and behavioural characteristics of these disorders, as some have suggested enhanced and lower attentional biases (Santopetro et al., 2021).

1.7 P300 and Drug Craving

Drug craving is a pervasive and measurable characteristic of substance use disorders (Hasin et al., 2013). It has remained a fundamental interest in research and treatment (Ekhtiar et al., 2022), as indicated by its inclusion as a criterion for SUDs in the DSM-5 (American
A wealth of empirical data and anecdotal reports highlight the direct involvement of craving in contributing to SUD maintenance (for a review, see: Sayette et al., 2000). Craving is primarily associated with the third stage of addiction (the preoccupation and anticipation phase) and has been identified to significantly contribute to relapse and overdose (Seo and Sinha, 2014). With that, there is still uncertainty and debate in the conceptualization and operationalization of drug craving (Kozlowski and Wilkinson, 1987; Pickens and Johanson, 1992; Drummond et al., 2000; Weiss et al., 2003; Paliwal et al., 2008; Perkins, 2009). One barrier to understanding craving and its contribution to substance use patterns has been the need for more consensus on its construct and measurement (Sayette et al., 2000). Although there have been numerous developments in self-reported craving measures, the lack of consensus for a standardized measure and overall understanding of foundational constructs has led to inconsistencies in the concept of craving (for reviews, see: Rankin et al., 1979; Kozlowski and Wilkinson, 1987; Pickens and Johanson, 1992; Altman et al., 1996; Verheul et al., 1999). This has led researchers to identify a potential objective measure of craving. One model has characterized craving as patterned attentional responses to drug-related cues (Field et al., 2009). With prolonged drug use, a sensitization of drug 'wanting' or drug craving leads to the heightened attentional salience of the drug-related cues (Robinson and Berridge, 1993). This potential association between drug craving and attentional bias has led researchers to utilize the P300 to identify a potential relationship. An unpublished systematic review by our lab suggests different associations between craving and P300 amplitude for different drug types (Epp et al., 2023). With that, the use of the P300 as a quantifiable marker of craving through attentional bias processing has not been identified in individuals with concurrent disorders. Utilizing a potential objective measure of craving within the concurrent disorder
population may have implications for identifying patterns of severe craving and, thus, when an individual is at risk for relapse.

1.8 Aims

One area of ERP research that has yet to be explored is whether individuals with concurrent disorders show differentiated cue-induced P300 response than controls, of which our study is the first. The primary aim of this study is to identify a difference in P300 amplitude for stimulant, pleasant, and stimulant relative to pleasant cues between individuals with co-occurring SUDs and mental health disorders and controls. We hypothesize that the in-patient sample will have an enhanced P300 difference wave to stimulant cues relative to pleasant. We also investigate a few exploratory secondary aims to help guide future research in this area. For instance, we aim to examine associations between P300 amplitudes for stimulant, pleasant, and stimulant relative to pleasant cues and self-reported craving. We hypothesize a positive correlation between self-reported craving and the P300 difference wave for stimulant cues. Lastly, we aim to explore potential predictors for attentional bias within a sub-sample of the participants, particularly the in-patient participants. We hypothesize that diagnoses, time in treatment, substance use frequency, and craving will predict a larger P300 amplitude to stimulant cues. These findings will contribute to the limited research of concurrent disorders generally. However, they will also contribute to a greater understanding of ERPs in psychopathology research for SUDs and psychiatric disorders and their potential to prospectively predict changes in the progressions and maintenance of these disorders.
2 Methods

2.1 Study Design

This cross-sectional study is a sub-study within a longitudinal research study which began on February 16th, 2022 and is currently ongoing. Ethical approval was obtained from the University of British Columbia Clinical Research Ethics Board (H21-01451). In addition, approval was obtained to conduct this study within a Provincial Health Services Authority facility, specifically the Red Fish Healing Centre for Mental Health and Addiction, by the British Columbia Mental Health and Substance Use Services Research Committee and Data Access Committee. All participants provided ongoing informed consent, and the study was conducted per the Declaration of Helsinki.

2.2 Participants

The sample comprises 33 in-patients at the Red Fish Healing Centre for Mental Health and Addiction, diagnosed with a co-occurring mental health disorder and substance use disorder and 32 controls with no current psychiatric or substance use disorder diagnosis. While typical brain-behaviour studies have a sample size of 25 participants per group, recent findings have found that this sample size produces results that are significantly underpowered with inflated effect sizes and replication failures (Marek et al., 2022). With that, it is also important to acknowledge the limitations of research within specific populations. For instance, this study is based on a limited in-patient treatment population, with a maximum amount of beds available for patients, providing limitations to the sample size obtained. Given the sample size obtained (n = 65), an expected medium effect size of .5, and p < .05 (Cohen, 1992), lends to a power of .51 and should be a consideration within the implications of the results.
In-patient participants were recruited within the Red Fish Healing Centre for Mental Health and Addiction, where they were receiving treatment for their concurrent disorder. Control participants were community volunteers recruited virtually through social media posts (including Facebook, Twitter, Instagram, and LinkedIn), University of British Columbia Psychology Paid Research Studies postings, and Craigslist. In-patient participants were included in the study if they were a client at the Red Fish Healing Centre for Mental Health and Addiction, a participant enrolled in an additional study (Reducing Overdose and Relapse: Concurrent Attention to Neuropsychiatric Ailments and Drug Addiction (ROAR CANADA); H19-00846), the participant understood the purpose of the study, and deemed safe to participate by the Patient Care Committee (i.e., currently stable in the facility and not at risk for violence). Potential participants were required to be enrolled in the ROAR CANADA study to participate in the current study as ROAR CANADA participants had agreed for researchers to access medical charts, which allowed for the identification of admission dates and diagnoses. In-patient participants were informed that by consenting to participate in the current study, they were also consenting to collect and use medical charts and other records obtained through ROAR CANADA in this study. For controls, those 19 years or older, who could speak and read English, understood the purpose of the study, had no history of head trauma, and had no current diagnosis of psychiatric or substance use disorder were eligible to participate. The history of head trauma was determined using the Ohio State University Traumatic Brain Injury Identification Method (Corrigan and Bogner, 2007). For psychiatric and substance use disorder identification, the Mini-International Neuropsychiatric Interview Screener was used (Sheehan et al., 1998).
2.3 Measures

2.3.1 Stimuli and Experimental Paradigm

Ninety colour pictures (30 neutral, 30 pleasant, and 30 stimulant-related) served as stimuli. Neutral and pleasant pictures were selected from the International Affective Picture System, which had neutral and pleasant valence, respectively (Lang et al., 1997). Stimulant-related pictures were previously used by Dunning et al. (2011), Moeller et al. (2012), and Parvaz et al. (2017). These stimulant-related pictures consisted of pictures of stimulant drugs, individuals using stimulants, and stimulant-related paraphernalia, obtained through freely available online sources and adapted from videos of stimulants used in a previous study (Volkow et al., 2006). All pictures were randomly presented for 3000 milliseconds, followed by four questions: “Rate how much you like stimulants in response to this picture.,” “Rate how much you want stimulants in response to this picture.”, “Rate how much you like this picture.” and “Rate your emotional response to this picture.”. All participants rated the same images and responded to the same questions using a one to nine Likert scale as part of the experimental task, as shown in Figure 1.

2.3.2 EEG Recording and Signal Processing

The event-related potential was recorded by collecting EEG data from a CGX EEG Dev Kit (500 Hz sampling rate, no onboard data processing; CGX, San Diego, USA). We used four electrodes attached to the participant’s scalp at locations analogous to TP9 and TP10 following the standard 10-20 electrode placement system, with FPz and Fp2 acting as a reference and ground, respectively. EEG data were recorded using LSL’s LabRecorder software (https://github.com/sccn/labstreaminglayer) and were streamed to LabRecorder using CGX’s native acquisition software (https://www.cgxsystems.com/software). More specifically, the CGX
acquisition software allows for creating an LSL “stream” that transits incoming EEG data directly to LSL LabRecorder. Event markers were inserted into the EEG data stream being recorded with LabRecorder using the LSL MATLAB toolbox (https://github.com/labstreaminglayer/liblsl-Matlab). This method sends event markers directly from MATLAB in an LSL “stream” merged with the EEG data being streamed to LabRecorder. LSL uses the timing stamps of each device at a low level to align the various signals to achieve temporally accurate event markers (see documentation at https://github.com/sccn/labstreaminglayer for more detail). LSL inserts event markers directly from the MATLAB experiment into corresponding time points in the data. Importantly, this means that in the event, markers were inserted after the delay of Bluetooth data transmission, which introduced a known timing delay.

Data were processed offline in MATLAB using EEGLAB (Delorme & Makeig, 2004) and custom code (www.https://github.com/krigolson). As our analysis was focused on the two posterior Dev Kit electrodes (TP9, TP10) that were already referenced appropriately at the time of recording to electrode FPz, we did not re-reference the continuous EEG data. Continuous EEG data were filtered with a dual pass Butterworth filter with a passband of 0.1 Hz to 30 Hz, then a 60 Hz notch filter.

After filtering, epochs of data from 200 ms before to 800 ms after stimulus onset were extracted from the continuous EEG data and baseline corrected using the 200 ms preceding stimulus onsets (Fig. 2). An artifact rejection algorithm was implemented, and segments with an absolute difference of more than 60 µV were discarded. These segments were averaged for each condition in each session. Next, we observed no differences between TP9 and TP10, so we averaged these channels together for each session, generating grand average ERPs. Finally, we
averaged the individual waveforms to create average conditional waveforms. Peak component latencies and amplitudes for the P300 components were quantified by finding the maximal voltage amplitudes between 250 ms and 600 ms on the grand average concatenated difference waves (Krigolson et al., 2017, 2021). Hereafter, P300 amplitudes are referred to as pleasant (i.e., pleasant – neutral) and stimulant (i.e., stimulant – neutral) differentials. Moreover, differentials for the stimulant pictures relative to the pleasant pictures were also created, as done previously (Lubman et al., 2007; Moeller et al., 2012; Parvaz et al., 2017), as a parameter of attention bias to two salient reinforcers. Using stimulant relative to pleasant differentials utilizes responses to non-drug affective stimuli as an influential gauge of the motivational relevance of cues across the groups (Versace et al., 2012).

2.3.3 Treatment- and Medical-Related Measures for In-Patient Participants

2.3.3.1 Diagnosis

Diagnosis for in-patient participants was obtained through medical charts, in which psychiatrists diagnosed clients of Red Fish Healing Centre for Mental Health and Addiction upon admission to the facility. Both mental health and substance use disorder diagnoses were obtained through medical charts. Given the complexity and heterogeneity in diagnosing psychiatric disorders, this study used broad diagnosis categories within the analysis. In particular, diagnoses included categories such as psychotic spectrum disorders (schizophrenia, schizoaffective disorder, psychotic disorder, and substance-induced psychotic disorder), mood disorders (depression, bipolar disorder, and substance-induced mood disorder), anxiety/stress-related disorders (generalized anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder), and neurodevelopmental disorders (fetal alcohol syndrome and attention-deficit hyperactivity disorder). A particular substance, such as alcohol use disorder,
cocaine use disorder, methamphetamine use disorder, opioid use disorder, and cannabis use disorder, characterizes SUDs.

2.3.3.2 Days in Treatment

In-patient participants' days in treatment were obtained by calculating the difference in the session date by the date of admission, obtained through medical charts examination.

2.3.3.3 Drug Use Frequency

Drug use in the in-patient sample was obtained through the Maudsley Addiction Profile (MAP) questionnaire, precisely the total number of days used within a month within the “substance use” domain (Marsden et al., 1998). The MAP is a highly reliable and validated questionnaire (Barbieri, 2003) that is a 60-item self-reported questionnaire with four domains: substance use, health risk behaviour, physical and psychological health, and personal social functioning (Marsden et al., 1998). Within this study, the question used to obtain drug use frequency was acquired by identifying the total number of days using substances within the last month before intake. In-patients answered this question among ten substance types: alcohol, heroin, illicit methadone, illicit benzodiazepines, cocaine powder, crack cocaine, amphetamines (methamphetamine), cannabis, fentanyl, and others. Only amphetamines (methamphetamine) scores were used in this study.

2.3.4 Demographics

Demographics for the total sample were obtained through a self-reported questionnaire that addresses demographic factors such as age, gender, and ethnicity. Age was acquired by asking, “What is your current age?”. Gender was acquired by asking, “How would you identify your gender identity,” which had the following options: male, female, transsexual transgender, genderqueer, two-spirit, female-to-male, male-to-female, intersex, unsure, questioning, other,
and prefer not to answer. Additionally, ethnicity was obtained by asking, “Which population group do you most identify with?” and the following options were available for selection: White/European ancestry, Black/African ancestry, East Asian (e.g., Chinese, Japanese, Korean, Mongolian), South Asian (e.g., Indian, Pakistani, Afghan, Bangladeshi), Southeast Asian (e.g., Vietnamese, Thai, Cambodian, Malaysian, Indonesian, Filipino), Middle Eastern/West Asian (e.g., Iraqi, Iranian, Syrian, Turkish, Egyptian, Kuwaiti, Lebanese, Qatari), First Nations/Inuit/Metis, Pacific Islander (e.g., Hawaiian, Samoan, Fijian), more than one population group, and other.

2.3.5 Premorbid Intelligence Quotient

Testing premorbid functioning has become crucial in clinical research where the patient's baseline functioning is unavailable. Premorbid functioning allows us to identify any cognitive decline due to injury or illness. The Test for Premorbid Functioning (TOPF) was developed to revise the Wechsler Test of Adult Reading to be used along with demographic data to predict memory and intellectual performance (Wechsler, 2001, 2009; Reale-Caldwell et al., 2021). It is composed of 70 words that have irregular English pronunciations (Wechsler, 2009). To obtain the premorbid intelligence quotient, participants read the words out loud to the researcher, and the number of correct pronunciations is scored. It is widely used and validated for direct comparison with the Wechsler Test of Adult Reading (Wechsler, 2001).

2.3.6 Working Memory

The NIH-Toolbox List Sorting Working Memory Test (Weintraub et al., 2013) is part of the NIH-Toolbox Cognitive Battery (Gershon et al., 2010) that acquires a measure of working memory. This test shows the participant stimuli of an animal or fruit category. These stimuli are presented sequentially visually and then orally in series ranging from two to eight items. The task
is to verbally repeat the stimulus sequence according to the objects-relative size from smallest to largest. The test looks at the total number of correct sequence repetitions, and within this study, the total score is age corrected. This test takes approximately seven minutes to complete. It has been demonstrated to have convergent validity, construct validity, and excellent test-retest reliability (Gershon et al., 2010).

2.3.7 Positive and Negative Affect

Positive and negative affect was measured in all participants using the International Positive and Negative Affect Schedule-Short Form (PANAS-SF; Thompson, 2007). The PANAS-SF was developed after the 20-item International Positive and Negative Affect Schedule (Karim et al., 2011). This task now consists of 10 items that quantify participants' positive and negative traits. Ranking items on an interval scale of one to five, where one is "Very slightly or not at all," two is "A little," three is "Moderately," four is "Quite a bit," and five is "Extremely" in which the participant experiences that emotion over the past week. The PANAS-SF has been demonstrated to have high internal reliability and cross-cultural validity (Thompson, 2007; Karim et al., 2011).

2.3.8 Craving

Craving in all participants was measured through a self-reported Likert scale. Before the exposure of cues, participants were asked, “Rate how much you want stimulants at this moment.”. The Likert scale was between zero and nine, where zero represented the least, and nine represented the most.

2.4 Procedures

This cross-sectional study includes 65 identifying males and females (33 in-patient participants and 32 controls). Potential participants were given the consent form to determine if they would like to participate. After discussing the major key aspects of the study, the consent
form was signed by both parties (the research assistant and the participant), each receiving a copy. Consented participants were then screened for eligibility for their respective groups. If the participant was deemed eligible, they completed two study sessions and received a $10 gift card as remuneration after completion of each session, for a total of $20.

During the first session, participants completed survey- and questionnaire-based assessments. Participants then completed cognitive assessments, including the TOPF and the NIH-Toolbox List Sorting Working Memory Task. Approximately one week later, participants completed the second session. This session included the baseline craving Likert scale and the baseline PANAS questionnaire. The participants were then asked to swab their foreheads and their mastoids. Then the participants were connected to the EEG headset and began the EEG picture task, which began with a trial run followed by the actual task, which takes approximately 25 to 30 minutes to complete.

2.5 Statistical Analysis

First, to identify between-group differences, Chi-square tests, student t-tests, or independent 2-group Mann-Whitney U tests (depending on normality) were used to examine any statistically significant differences. This was done for P300 difference waves, age, gender, ethnicity, TOPF scores, NIH-Toolbox List Sorting Working Memory scores, and PANAS scores between controls and in-patient participants. To control for multiple comparisons, a Bonferroni correction was used to identify statistical significance (Bonferroni, 1936). An exploratory correlation analysis for the association between the P300 difference waves for stimulant, pleasant, and stimulant relative to pleasant cues was conducted against craving between the two groups Kendall's Tau-b correlation. Significance was determined using a $p < .05$. 
A 2 (group; control or in-patient) x 3 (difference waves; stimulant, pleasant, and stimulant relative to pleasant) ANCOVA was conducted to identify whether there is a main effect of difference waves between the groups, as indicated by a $p < .05$. If there was a significant main effect for these analyses, covariates that were indicated as significantly different between the control and in-patients were used to control for these factors.

Multiple linear regression was conducted to investigate predictors of attentional bias within the subgroup of in-patient participants to predict difference waves by diagnosis and substance use. For each model, a Bonferroni correction will be used for multiple comparisons (Bonferroni, 1936). Assumptions of linearity, multicollinearity, independent residuals, homoscedasticity, normally distributed residuals, and biases influencing the model were checked and corrected. Outliers were identified and removed if they exceeded 1.5 times the interquartile range. Data analysis was conducted using RStudio (RStudio, Version 2022.07.2+576, PBC, Boston, MA).

3 Results

3.1 Between Control and In-Patient Analyses

3.1.1 Demographics

Table 1 lists the descriptive statistics for the sample involved in this study. Of the 65 participants who completed the survey, 51% ($n = 33$) are in-patients at the Red Fish Healing Centre for Mental Health and Addiction with concurrent SUD and mental health disorder diagnoses. In contrast, the other 49% ($n = 32$) were recruited from online advertisements and had no current SUD or mental health disorders. The in-patient sample had a mean age of 37.3 years (SE = 0.3), while the control sample had a significantly different mean age of 29.2 (SE = 0.5; $U = 240, p < .001$). There were no significant differences between our sample’s gender distribution
as 59.4% of each group were male (n = 19, p = 1.0), and the remaining were female (in-patient: n = 14, 43.8%, control: n=13, 40.6%; p = .85). Gender-diverse data was collected but cannot be analyzed outside of male- and female-identifying individuals due to the small sample size. For ethnicity, we collected data on White/European ancestry (in-patient: n = 12, control: n = 8; p = .37), Black/African ancestry (in-patient: n = 2, control: n = 0; p = .16), Asian ancestry (in-patient: n = 0, control: n = 22; $X^2(1, n = 22) = 22.0, p < .001$), Middle Eastern ancestry (in-patient: n = 1, control: n = 0; p = .32), Indigenous ancestry (in-patient: n = 10, control: n = 0; p = .0016), and other ancestries (in-patient: n = 8, control: n = 2; p = .06).

3.1.2 Cognitive Functioning

For pre-morbid functioning, the control group showed higher scores on the TOPF ($M = 45.6$, SE = 0.4) compared to the in-patient sample ($M = 35.9$, SE = 0.4; $p = .01$), although after Bonferroni corrections this was not significant. In contrast, the control group showed a significantly higher working memory capacity ($M = 103.6$, SE = 0.1) in comparison to the in-patient sample ($M = 83.5$, SE = 0.1; $t(57) = 5.8, p < .001$).

3.1.3 Affect

There were no significant differences in the sample’s positive affect ($p = .89$). Specifically, the in-patient population had a mean score of 15.1 (SE = 0.3) compared to the mean of 15.0 (SE = 0.2) within the control sample. Additionally, the in-patient population had a higher negative affect score ($M = 10.3$, SE = 0.4) than the control population ($M = 8.2$, SE = 0.2; $p = .03$), although, after Bonferroni corrections, this did not remain significant.

3.1.4 Exploratory P300 Amplitude Correlation Analysis

As a preliminary and exploratory analysis, we conducted a Kendall’s Tau-b correlation on whether the P300 difference waves for stimulant cues, pleasant cues, and stimulant relative to
pleasant correlated with self-reported wanting. As a result, there is a significant correlation between pleasant cues and self-reported wanting ($r = 0.2, p = .048$), in which a greater amplitude to pleasant cues is correlated with a higher craving score. In contrast, we found no significant correlations between the P300 difference wave for stimulant and self-reported wanting ($p = .16$) or between stimulant relative to pleasant cues and self-reported wanting ($p = .27$).

### 3.1.5 Analysis of Variance for P300 Wave Difference Across Group-Type

One-way ANCOVAs were conducted to determine a statistically significant difference between the control and in-patient group for stimulant, pleasant, and stimulant relative to pleasant (stimulant – pleasant) cues. There is a significant effect of group type on the difference wave for stimulant cues ($F(1,44) = 5.7, p = .02$), pleasant cues ($F(1,41) = 25.5, p < .001$), and stimulant relative to pleasant cues ($F(1,41) = 6.3, p = .02$). This main effect did remain significant after Bonferroni correction and controlling for age, working memory, and ethnicity for stimulant cues ($F(1,33) = 12.5, p = .0012$) and for pleasant cues ($F(1,31) = 21.0, p < .001$). Alternatively, there is no significant main effect of group type on stimulant relative to positive cues after Bonferroni correction and controlling for age, working memory, and ethnicity ($p = .38$). Follow-up analysis revealed that compared with controls, in-patient participants showed a larger P300 amplitude for stimulant cues (stimulant – neutral; control: $M = -0.9, SE = 2.2$, in-patient: $M = 0.4, SE = 4.3$; $t(40) = -2.4, p = .02$), and pleasant cues (pleasant – neutral; control: $M = -1.7, SE = 1.2$, in-patient: $M = 0.9, SE = 1.4$; $U = 54, p < .001$). In addition, controls have a significantly larger P300 amplitude for stimulant relative to pleasant cues (stimulant – pleasant; control: $M = 1.1, SE = 1.6$, in-patient: $M = -0.1, SE = 11.1$; $t(34) = 2.4, p = .02$) then in-patients (Fig. 3).
3.2 Exploratory In-Patient Group Analyses

3.2.1 Demographics

The in-patient participants have various diagnoses, with the largest of those diagnosed with a psychotic spectrum disorder (93.1%, n = 27), followed by anxiety disorder (44.8%, n = 13), mood disorder (34.5%, n = 10), personality disorder (34.5%, n = 10), and neurodevelopmental disorder (20.7%, n = 6). Regarding SUD diagnosis, the more prevalent diagnosis is stimulant use disorder (89.7%, n = 26), followed by tobacco use disorder (75.9%, n = 22), opioid use disorder (72.4%, n = 21), cannabis use disorder (55.2%, n = 16), and alcohol use disorder (42.3%, n = 11). Due to the time variability in treatment prior to completing the study, days in treatment were calculated by subtracting the date of the session completed and the admission date. The mean days in treatment at the time of the EEG session was 58.1 days ± 56.9.

3.2.2 Substance Use and Craving

Given the prevalence of stimulant use disorder, substance use frequency was determined by previous 30-day use of stimulants. The average in this in-patient subgroup was 11.8 days (SE = 1.1). Craving, as measured by self-reported wanting of stimulant drugs, had a mean of 2.0 (SE = 1.3) on a 10-point scale.

3.2.3 Exploratory Multiple Linear Regression for P300 Difference Waves

Multiple linear regression was conducted to determine statistically significant predictors for the P300 difference wave for stimulant minus neutral, pleasant minus neutral, and stimulant minus pleasant cues. The first model uses psychiatric diagnoses as potential predictors of difference waves which revealed no significant psychiatric disorder diagnosis predicting stimulant, pleasant, or stimulant relative to pleasant cues (all p’s > .06). The second model uses
SUD diagnoses as potential predictors of difference waves which revealed no significant substance use diagnosis as a predictor for stimulant, pleasant, or stimulant relative to pleasant cues (all $p$’s > .03). The third model looks at craving, previous month use of methamphetamine and days in treatment as potential predictors of difference waves revealing no significant predictors of any of the differential waves (all $p$’s > .1).

4 Discussion

The findings of this study help contribute to the development of literature on concurrent disorders by providing a characterization of the attentional biases, diagnoses, substance use, cognitive function, craving, and affect compared to individuals without mental health or SUD diagnoses. Additionally, the findings of this study contribute to the limited understanding of whether EEG ERPs could be used as a potential neural marker for attentional biases in concurrent disorders. Most notably, this study highlights that in-patients with a concurrent disorder diagnosis have a lower P300 difference wave for stimulant cues in relation to pleasant cues than controls. These results may contribute to the potential utility of EEG as a measure for clinically relevant markers such as abstinence, treatment efficacy, and disorder susceptibility within concurrent disorders.

4.1 Lower P300 Amplitude Differential to Stimulant Cues Relative to Positive Cues in Those with Concurrent Disorders Compared to Controls

According to the incentive-sensitization theory of addiction, individuals with SUDs show excessive reactivity to drug and drug-related stimuli and diminished response to non-drug stimuli (Robinson and Berridge, 1993). This research is expanded with recent research indicating that initially, there is significant attention allocation to drug-related cues in comparison to pleasant cues, but following long periods of abstinence or significant reductions in drug use, the direction
of attentional bias reverses (Parvaz et al. 2017; Zhang et al., 2021). In support of these findings, this thesis suggests that in-patients with concurrent disorders display a lower P300 amplitude differential to stimulant cues relative to positive cues than controls. Although, these findings should be considered alongside the attenuation of the significant main effect after controlling for age, ethnicity, and working memory capacity. While our study did not look at changes in attention longitudinally, it can be presumed that these findings correspond with previous research that abstinence or prolonged drug relief, can cause a reversal in attentional bias to drug cues, as in-patient participants in this study were actively in treatment and had therefore been undergoing drug abstinence.

Previous research indicates that individuals who show a greater reversal toward pleasant cues over drug-related reported reduced cravings (Parvaz et al., 2017). While those who showed increased attention to drug cues had increased craving scores and were at greater risk for relapse (Field et al., 2009; Zhang et al., 2021). Therefore, these findings speak to the diverse utility of EEG ERPs in which changes in attentional bias from stimulant to pleasant cues during treatment may be a meaningful and valuable measure of treatment efficacy and abstinence within in-patient populations, including those with concurrent disorders. A future direction to contribute to these findings would be identifying factors contributing to the degree of reversal toward pleasant cues and how this may impact treatment adherence and success.

4.2 Larger P300 Amplitude Differentials to Stimulant and Pleasant Cues in Those with Concurrent Disorders Compared to Controls

Previous research has used the P300 to emphasize attentional biases to substance-related cues relative to neutral cues in individuals with various SUD diagnoses (for a review, see: Littel et al., 2012). In accordance, this study found that individuals with concurrent disorders had a
larger P300 differential to stimulant cues relative to neutral cues than controls. These findings further support the theories suggesting that, as a result of classical conditioning from pairing repeated drug use and drug cues, attention is directed towards these cues as a form of attention bias through the characteristic habitual use patterns present in SUDs and concurrent disorders.

Furthermore, this study found a larger P300 differential to pleasant cues relative to neutral cues in the in-patient participants compared to controls. This finding suggests that cognitive biases may be extended across various emotionally provocative stimuli, including affective and drug cues (Dunning et al., 2011; Oliver et al., 2016). This highlights the necessity of utilizing responses to non-drug affective stimuli to gauge the motivational relevance of cues in general (Versace et al., 2012). As such, observing a difference between stimulant and neutral stimuli is insufficient to conclude that brain responses to stimulant cues are aberrant (Versace et al., 2012). Furthermore, identifying an attentional bias to both stimulant and pleasant cues in in-patient participants requires that we effectively gauge attentional relevance to cues in general, which we have done by comparing stimulant cues relative to pleasant cues, as mentioned previously.

4.3 No Predictors for P300 Amplitude Differentials Amongst In-Patient Participants

We looked at variables such as diagnoses, substance use, treatment length, and craving to identify predictors for the P300 difference wave for stimulant, pleasant, and simulant minus pleasant cues. Our findings showed no predictors of P300 amplitude differentials. These findings should be considered along with those underpowered by the limitations of a small sample size. With that, it is clear from previous research across psychiatric and SUD research that diagnoses can have varying impacts on attentional bias due to the heterogeneity of underlying processes. Future research outlining the differences between diagnoses and combinations of diagnoses and
their effects on the attentional bias would contribute significantly to our currently limited understanding.

Furthermore, very few studies have identified whether substance use frequency is associated with changes in P300 amplitude. Of these few studies, Yuan and colleagues (2022) found a positive correlation between P300 amplitude and alcohol use duration in a cohort of individuals with alcohol use disorders. These findings correspond with theories suggesting that significant attention allocation is due to the pairing of drug cues after chronic and repetitive use. Due to the limited sample size and underpowered analyses, this exploratory finding should be addressed in future research to designate whether the P300 amplitude is not only associated with abstinence length but also sensitive to recent drug frequencies and diagnoses.

4.4 Significant Correlation Between Self-Reported Craving and P300 Amplitude for Pleasant Cues

Whether craving is reflected within the attentional bias associated with the P300 amplitude has been debated within research (see: Epp et al., 2023). To add to the current research in this field, we found a significant correlation between pleasant cues and self-reported wanting, in which a greater amplitude to pleasant cues is correlated with a higher craving score. In contrast, this study did not find a significant correlation between stimulant cues or stimulant relative to pleasant cues, which contradicts previous research (Namkoong et al., 2004; Littel and Franken, 2007b; Franken et al., 2008; Henry et al., 2014; Mashhoon et al., 2018; Brown et al., 2020). It has been suggested that associations between craving and P300 amplitude may be substance-dependent, given the contradictions in results between studies, although these contradictions may also be related to the lack of standardized measure for craving and inconsistencies in the concept of craving (Kozlowski and Wilkinson, 1987; Pickens and
Johanson, 1992; Drummond et al., 2000; Weiss et al., 2003; Paliwal et al., 2008; Perkins, 2009). Additionally, due to the limited sample size and underpowered analyses within this thesis, these exploratory findings should be considered alongside its limitations and addressed in future research to designate whether craving is associated with the attentional biases captured by the P300 amplitude.

4.5 Limitations

Some limitations should be taken into consideration within this study's findings. Firstly, it should be noted that this study is exploratory, given its sample size, underpowered analysis, and heterogeneity between the groups. For instance, there is a high degree of differences in the demographics between the in-patient and control samples. These differences are a product of the recruitment method, which unforeseeably contributed to differences in demographics such as ethnicity and age. Concerning demographic differences within the in-patient and control samples, most ethnicities were comparable across groups. However, there were a higher proportion of Indigenous individuals in the in-patient sample and Asian individuals in the controls sample. A higher proportion of Indigenous individuals in the in-patient sample correspond with findings from a systematic review from 2017 stating that rates of mental health and SUDs among Indigenous peoples in Canada are higher than those found in the general population (Nelson and Wilson, 2017). It is vital to acknowledge historical and cultural differences contributing to both ethnicities' prevalence and stigmatization of mental health and SUDs (Nelson and Wilson, 2017). In addition, while there are no differences in gender between the groups, there is a significant difference in mean age between the in-patient and control groups. Specifically, the in-patient sample is significantly older than the control sample. Current research shows that older individuals exhibit a smaller P300 amplitude over the midline, central,
and parietal locations (Polich, 2007; Ashford et al., 2011), even when considered healthy, indicating average cognitive decline across time affects P300 responses (Polich, 2007). By adding covariates in our models, we accounted for ethnicity and age as potential influencing factors within our analyses. Age- and ethnicity-matching would be favourable to eliminate these potentiating factors in future research. Unfortunately, due to time constraints, this study could not recruit controls after in-patients to age and ethnicity match.

Additionally, given the heterogenous nature of concurrent disorder diagnoses, the amount of differentiating factors that may contribute to a change in P300 amplitude are significantly challenging to control. With that, this study control for factors such as length of time in treatment. Within the in-patient population, individual length within the treatment and, thus, length of abstinence from substances differs. New research has identified an inverted u-shaped curve designating a change in ERP responses to drug-related cues over an abstinence period from one month to one year in individuals with cocaine use disorder (Parvaz et al., 2016). While this work used the late positive potential (an ERP from 400 – 2000 ms following a stimulus), these findings suggest an incubated effect that describes a potential temporal change in motivational attention to cues over abstinence. While it has yet to be completed within the P300, these findings may also be found within affective attention. Thus, we added the difference in treatment time as a covariate in a model to delineate any potential impacts treatment time has on the P300 response. Additionally, given this study's low power and multiple comparisons, research using larger samples is needed to replicate and extend all sub-sample and correlational analyses with higher statistical power.
4.6 Future Directions

Concurrent disorders are overwhelmingly overlooked in mental health and SUD research. This study contributes to a limited amount of research aimed at characterizing the population of individuals with concurrent disorders. It is one of the first to address using the P300 amplitude to measure of attention bias within this disorder. While much of this work is exploratory, given the sample size and limited ability to generalize the findings, this work provides a foundation for future research in this area. For instance, it would be of great interest to the field to identify differences in individuals with concurrent disorders compared to matched diagnoses for mental health disorders and SUDs. These findings would significantly contribute to our understanding of the mechanisms underlying concurrent disorders and to what degree it is related to either mental health or substance use.

Furthermore, limited research is dedicated to drug-use frequency and its association with P300 amplitude. Research aimed at characterizing this relationship would significantly contribute to our understanding of differences in drug-use severity and potentially its ability to predict treatment outcomes and potential relapse occurrences. Within this aim to contribute to our understanding of treatment outcomes and relapse vulnerability, it would be interesting to investigate whether there is an association between craving and the P300 amplitude. If, for instance, a relationship is found, we may be able to use the P300 amplitude as an objective measure of severity and adapt treatment programs that utilize this information within an individual’s care plan.

This study is ongoing to map the longitudinal changes in P300 amplitude over five months. This study aims to identify a pattern in P300 that may contribute to our understanding of the neural changes that occur during abstinence and use this information to create treatment plans.
that utilize periods in which an individual is most at risk for relapse or overdose. Additionally, this exploratory study identified other ERPs of interest when looking at ERP data outside of the P300. For instance, as seen in Figure 2, the N200 may be an ERP of interest or other markers that may contribute to a better understanding of the underlying mechanisms of concurrent disorders.

5 Conclusion

Individuals with concurrent disorders have a significantly larger P300 amplitude to stimulant and pleasant cues compared to controls. These findings correspond with previous research that SUDs show a characteristic larger P300 to drug cues compared to controls, which may be a similar characteristic in concurrent disorders, in addition to a larger P300 to pleasant cues which might indicate emotional dysregulation associated with co-occurring SUDs and mental health disorders. These findings should be considered with limitations on the low power within its analyses, between-group differences, and the size of the samples. Future research should aim to replicate and extend the analyses of this thesis but also contribute to identifying longitudinal differences in P300 and other ERP amplitudes in age-, ethnicity-, and diagnosis-matched samples.
Figure 1. An example of a single trial of the task. In this example, the image shown is from the stimulant-related cue type. After the presentation of the picture, four questions are prompted, followed by crosshairs.
Figure 2. EEG ERP waveforms by control and in-patient samples between -200 ms to 1000 ms for stimulant, neutral, and positive cues. A) EEG ERP waveform for in-patient participants. B) EEG ERP waveform for control participants.
Figure 3. Bar graphs of P300 differentials between control and in-patient samples for stimulant (relative to neutral), pleasant (relative to neutral) and the drug – pleasant direct contrast. *p < 0.05, ***p < .001. Error bars represent standard deviation.
### Table 1. Summary of demographics, cognitive functioning, affect, and P300 differentials for both in-patient and control participants.

<table>
<thead>
<tr>
<th></th>
<th>In-Patients (n = 33)</th>
<th>Control (n = 32)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)(^\text{a})</td>
<td>37.3 ± 0.3</td>
<td>29.2 ± 0.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Male</td>
<td>19 (59.4%)</td>
<td>19 (59.4%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14 (43.8%)</td>
<td>13 (40.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12 (37.5%)</td>
<td>8 (25.0%)</td>
<td>.37</td>
</tr>
<tr>
<td>Black</td>
<td>2 (6.3%)</td>
<td>0 (0%)</td>
<td>.16</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0%)</td>
<td>22 (68.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>1 (3.1%)</td>
<td>0 (0%)</td>
<td>.32</td>
</tr>
<tr>
<td>Indigenous</td>
<td>10 (31.3%)</td>
<td>0 (0%)</td>
<td>.0016</td>
</tr>
<tr>
<td>Other</td>
<td>8 (25.0%)</td>
<td>2 (6.3%)</td>
<td>.06</td>
</tr>
<tr>
<td><strong>Pre-morbid Functioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOPF(^\text{a})</td>
<td>35.9 ± 0.4</td>
<td>45.6 ± 0.4</td>
<td>.01</td>
</tr>
<tr>
<td><strong>NIH Toolbox List Sorting Working Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>List Sorting Task(^b)</td>
<td>83.5 ± 0.1</td>
<td>103.6 ± 0.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Positive and Negative Affect (I-PANAS-SF)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive Affect</td>
<td>15.1 ± 0.3</td>
<td>15.0 ± 0.2</td>
<td>.89</td>
</tr>
<tr>
<td>Negative Affect(^a)</td>
<td>10.3 ± 0.4</td>
<td>8.2 ± 0.2</td>
<td>.03</td>
</tr>
<tr>
<td><strong>P300 Amplitude Differentials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulant Cues</td>
<td>0.4 ± 4.3</td>
<td>-0.9 ± 2.2</td>
<td>.02</td>
</tr>
<tr>
<td>Pleasant Cues(^d)</td>
<td>0.9 ± 1.4</td>
<td>-1.7 ± 1.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stimulant - Pleasant Cues</td>
<td>-0.1 ± 11.1</td>
<td>1.1 ± 1.6</td>
<td>.02</td>
</tr>
</tbody>
</table>

\(^{a}\)Mann-Whitney U Test

\(^{b}\)Age-corrected

TOPF = Test of Pre-morbid Functioning. I-PANAS-SF = International Positive and Negative Affect Survey – Short Form
Bibliography


