

**Neurocognitive Examination of Attentional Bias and Inhibitory Control Alterations in  
Prescription Opioid Dependence**

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### Abstract

Prescription opioid (PO) abuse is a growing public health concern worldwide as evidenced by an increasing number of opioid-related hospital admissions with a striking lack of research examining the neural basis underlying cognitive symptomatology. Drugs of abuse, through their impact on the dopaminergic system, are thought to disrupt the cognitive network regulating impulse control and incentive salience through inhibition of goal-oriented behaviour and drug-induced attentional biases. The objective of the present study is to examine neurocognitive processes in PO abusers (vs. healthy controls) by relying on the enhanced temporal resolution (1ms) of event-related potentials (ERPs) to track information processing abnormalities associated with cognitive control. In a naturalistic clinical study, 16 patients actively using prescription opioids and 16 healthy controls (matched for age, gender, educational level and smoking status) were assessed using a Go/NoGo and cue reactivity paradigm. Analysis revealed no significant differences in N2 or P3 amplitude, measures of inhibitory control, between groups after successful NoGo trials and no significant differences in ERN or Pe amplitude, measures of error processing, between groups after unsuccessful NoGo trials. Cue reactivity analysis of attention-related ERP components in patients demonstrated significantly ( $p < 0.005$ ) smaller P2 amplitudes, indexing the commencement of attentional processing, for drug pictures compared to neutral and affective pictures. Furthermore, stimulus type did not significantly modulate LPP amplitudes, indexing sustained attention, in patients however arousal ratings for drug pictures were positively correlated with LPP amplitudes in patients. These ERP results of altered cognitive control and incentive salience suggest the neural mechanisms underlying these cognitions are affected by chronic opioid abuse. Investigating the cognitive abnormalities experienced by PO abusers is an important factor in understanding the neural correlates of substance abuse and in predicting successful outcomes to ensure the best chance at long-term recovery for addicted individuals.

## Table of Contents

<b>1.0 Introduction.....</b>	<b>1</b>
<b>1.1 Background and Context.....</b>	<b>1</b>
<b>1.2 Neural Processing in SUD .....</b>	<b>3</b>
<b>1.3 Impulse Control.....</b>	<b>5</b>
<b>1.4 Attentional Bias .....</b>	<b>6</b>
<b>1.5 Cognitive Biomarkers for Impulsivity.....</b>	<b>8</b>
1.5.1 Event-Related Potentials (ERPs).....	10
1.5.2 N200 (N2).....	10
1.5.3 P300 (P3) .....	12
<b>1.6 Cognitive Biomarkers for Attentional Bias .....</b>	<b>13</b>
1.6.1 P200 (P2) .....	14
1.6.2 Late Positive Potential (LPP) .....	17
<b>2.0 Objectives and Hypotheses .....</b>	<b>19</b>
<b>3.0 Methods.....</b>	<b>20</b>
<b>3.1 Study Participants.....</b>	<b>20</b>
<b>3.2 Procedure .....</b>	<b>21</b>
<b>3.3 Cognitive Tasks .....</b>	<b>23</b>
3.3.1 Go/NoGo Paradigm .....	23
3.3.2 Cue Reactivity Paradigm .....	24
<b>3.4 ERP Recording/Processing.....</b>	<b>26</b>
3.4.1 Go/NoGo ERPs.....	27
3.4.2 Cue Reactivity ERPs .....	28
<b>3.5 Statistical Analysis.....</b>	<b>28</b>
<b>4.0 Results .....</b>	<b>30</b>
<b>4.1 Go/NoGo Paradigm .....</b>	<b>30</b>
4.1.1 Response (Incorrect NoGo) Locked ERPs .....	30
4.1.1(a) ERN Amplitude and Latency .....	30
4.1.1(b) Pe Amplitude and Latency .....	31
4.1.2 Stimulus Locked ERPs .....	31
4.1.2(a) N2 Amplitude and Latency .....	33
4.1.2(b) P3 Amplitude and Latency.....	34
4.1.2(c) N1 Amplitude and Latency – Exploratory Findings .....	35
4.1.2(d) P2 Amplitude and Latency – Exploratory Findings.....	35
4.1.3 Correlations .....	36
4.1.4 Behavioural Data .....	36
<b>4.2 Cue Reactivity Paradigm.....</b>	<b>37</b>
4.2.1 P2 Amplitude and Latency .....	38
4.2.2 LPP (300-600 ms).....	38
4.2.3 Picture Ratings.....	41
4.2.3(a) Valence Ratings.....	42
4.2.3(b) Arousal Ratings .....	43
4.2.3(c) Personal Association Ratings .....	44
4.2.3(d) Craving Ratings in Patients .....	45

4.2.4 P2 and Picture Ratings Correlations .....	46
4.2.5 LPP and Picture Ratings Correlations .....	46
4.2.6 N1 Amplitude and Latency – Exploratory Findings .....	47
4.2.7 P1 Amplitude and Latency – Exploratory Findings .....	48
<b>4.3 Questionnaire Data .....</b>	<b>48</b>
<b>5.0 Discussion.....</b>	<b>50</b>
<b>5.1 Patient Sample and Demographics .....</b>	<b>50</b>
<b>5.2 Go/No Go and Impulse Control .....</b>	<b>54</b>
<b>5.3 Cue Reactivity and Attentional Bias .....</b>	<b>56</b>
<b>5.4 Limitations .....</b>	<b>61</b>
<b>6.0 Conclusion .....</b>	<b>63</b>
<b>7.0 References .....</b>	<b>64</b>

## **1.0 Introduction**

### **1.1 Background and Context**

Prescription opioid (PO) abuse is classified by the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) as a substance use disorder (SUD), ranging from mild to severe based on presenting symptomology (American Psychiatric Association, 2013). Due to the increasing rate of inappropriate prescribing and dispensing of prescription opioids, Ontario is currently facing a major public health crisis (Lutz & Kieffer, 2013), and admissions to substance use treatment programs for PO abuse have doubled from 2004-2009 (Canadian Centre on Substance Abuse, 2013). Furthermore, deaths due to opioids in Ontario have increased from 1991 to 2010 by 242%, and nearly 1 out of every 8 deaths among adults aged 25-34 in 2010 was opioid related (Gomes et al., 2014). Opioid abuse is linked to patient morbidity and infectious diseases (i.e. hepatitis C, HIV), resulting in a significant financial and emotional burden to families and health care systems. One of the most challenging caveats of opioid abuse is the astonishingly high relapse rate among treatment programs, where services range from solely pharmacological to strongly psychologically-based, with the most successful programs incorporating components from each discipline (Sigmon et al., 2013). Although the primary focus of these programs is preventing relapse and teaching harm-reduction strategies, over 50% of patients dropout of treatment and shortly thereafter relapse (Marhe et al., 2013). Identifying predictors of successful treatment outcomes is an important focus of addiction studies and recent studies suggest that neurocognitive measures (compared to self-report measures) are one of the most accurate predictors of relapse (Kosten et al., 2006; Marissen et al., 2006, Marhe et al., 2013). Unfortunately, there is a substantial lack of studies examining the neurocognition underlying prescription opioid abuse, where previous research has primarily focused on alcohol

(Berking et al., 2011; Stavro, Pelletier & Potvin, 2013), cocaine (Filmore & Rush, 2002; Jovanovski, Erb & Zakzanis, 2005; Aharonovich et al., 2006; Woicik et al., 2009), methamphetamine (Simon et al., 2000; Sim et al. 2001; Scott et al., 2007) and heroin dependence (Ornstein et al., 2000; Pau, Lee & Shui-fun, 2002; Franken, Stam, Hendriks & van den Brink, 2003; Redish, Jensen & Johnson, 2008).

Although heroin is pharmacologically classified as an opioid, it is important to differentiate between these two types of substance use disorders because their characteristics differ significantly. Adult PO abusers (compared to heroin abusers) are more likely to be young, Caucasian, more socially stable, report a shorter duration of use, engage in less intravenous (IV) use and overall use less drugs (Redish et al., 2008; Stacy & Wiers, 2010; Field & Cox, 2008; Goldstein & Volkow, 2011). Based on research by Moore and colleagues (2007), individuals who solely abused prescription opioids (vs. heroin-only abusers) were more likely to complete treatment (59% vs. 30%), remained in treatment longer (21.0 vs. 14.2 weeks) and had a higher percentage of opioid-negative urine samples (56.3% vs. 39.8%), suggesting PO abusers seek treatment earlier and tend to have a greater number of successful outcomes. Upon examination of neurocognitive deficits in heroin-dependent populations, previous literature reveals abnormal executive dysfunction (Hester & Garavan, 2004), impulse control (Lee & Pau, 2002, Fu et al., 2008) and attention (Pau, Lee & Chan, 2002). Evidence of cognitive processing abnormalities in heroin abusers can provide insight into possible deficits experienced by PO abusers, however a direct comparison cannot be concluded without a sufficient analysis of neurocognitive process in prescription-opioid populations.

## 1.2 Neural Processing in SUD

The opioid system is widely distributed throughout brain circuitry in addiction and involves interactions between their receptors (mu, delta and kappa) and their endogenous opioid peptides ( $\beta$ -endorphin, enkephalins and dynorphins) (Lutz & Kieffer, 2013; Koob & Volkow, 2010). Upon mu receptor activation, the mesolimbic dopaminergic reward pathways are activated and mediate pleasure derived from opioids, non-opioid drugs and natural stimuli (i.e. food and sex). Although these receptors are distributed among a large number of brain structures, the mesolimbic dopaminergic reward pathway primarily originates in the ventral tegmental area (VTA) where dopamine-rich cell bodies project and primarily terminate into the neighbouring nucleus accumbens (NAc), but also have axonal terminal projections to the amygdala, prefrontal cortex (PFC) and hippocampus (Adinoff, 2004). The direct reward and reinforcing effects of opioids are clearly demonstrated by examining the anatomy of the VTA in preclinical behavioural studies where the direct injection of morphine into the rodent VTA produced vigorous reinforcing effects as measured by self-administration (Bozarth and Wise, 1981; Stewart, 1984; Wang, You and Wise, 2012) and conditioned place preference (CPP) paradigms (Bozarth, 1987; Shippenberg and Herz, 1987, Olmstead and Franklin, 1997; Oliva and Wanat, 2016). Similarly in humans, Wanigasekera and colleagues (2012) have demonstrated that noxious stimulation during opioid administration in healthy subjects lead to functional magnetic resonance imaging (fMRI) activations in the VTA, in addition to the nucleus accumbens (NA) and in the orbitofrontal cortex (OFC). After prolonged use of opioids, PO-dependant patients displayed bilateral volumetric loss in the amygdala and significant decreases in functional connectivity in the NAc and amygdala (Upadhyay et al., 2010). Gray matter volume decreases in the amygdala were also observed in chronic-pain subjects, compared to healthy controls,

undergoing daily morphine exposure for one month (Younger et al., 2011) with dose-dependent alterations (i.e. individuals consuming a higher dose of morphine experienced the greatest gray matter loss).

The increased dopamine activity during opioid consumption promotes continued substance use and marks the beginning of the addiction cycle (Contet, Kieffer & Berfort, 2009; Le Mercer, Becker & Berfort, 2009). Repeated exposure leads to tolerance and resulting adaptive brain mechanisms compensate by reducing dopamine responsiveness to opioid stimulation, which results in the need to increase dosage to achieve similar opioid response. Prolonged use ultimately results in brain abnormalities that cause physiological dependence (using substances to avoid withdrawal symptoms) and psychological dependence (intense cravings and compulsive drug intake) (Kosten & George, 2002). There are several neurobiological and neurocognitive models of addiction that propose different aetiologies of abuse, however they all acknowledge marked deficits in both cognitive processes (Figure 1) and their underlying neurotransmitter systems (Duka, Crombag & Stephens, 2011; Franken, 2003; Morgenstern et al., 2013).

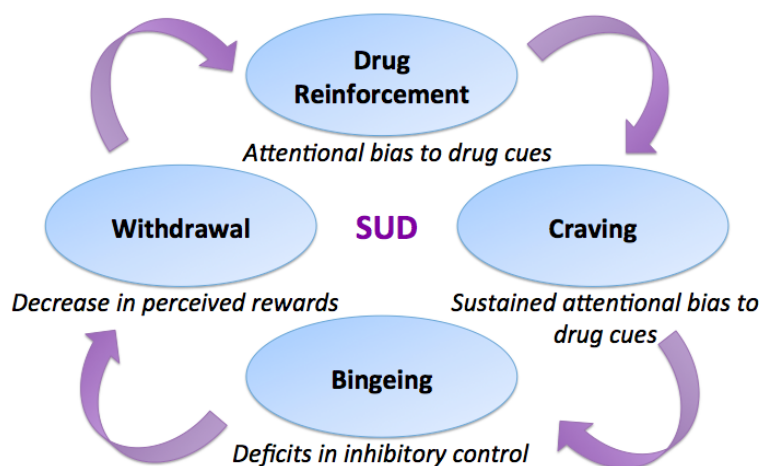


Figure 1. Neurocognitive effects observed at different stages of substance use disorder.

### 1.3 Impulse Control

Deficits in other cognitive processes are also evident in SUD, including inhibitory control, a predominately frontal executive function essential for suppressing impulses. Neurocognitive models suggest that in SUD individuals, there is a lack of emotional, cognitive and behavioural inhibition, which makes it difficult for them to resist substance consumption, especially in the presence of drug-related stimuli (Jentsch & Taylor, 1999; Bechera, Dolan & Hinds, 2002; Goldstein & Volkow, 2002; Dawe, Gullo & Loxton, 2004). The prefrontal-cingulate network composed of the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC) and basal ganglia, is thought to be the primary target of recurrent substance use that disrupts the dopaminergic release in these brain regions (Goldstein & Volkow, 2002; Braver et al., 2001; Lee et al., 2001). When abnormalities are present in the structure and function of these areas, multiple facets of impulse control are greatly affected as demonstrated by Chudasama and colleagues (2003) where lesions in the ACC lead to a reduction in discriminative accuracy and OFC lesions promoted preservative responding in the 5-choice serial reaction time task. Similarly, lesions in the nucleus accumbens core (Cardinal et al. 2001) significantly affected the animal's ability to choose a larger delayed reward over an immediate small/poor reward, often referred to as impulsive choice or behaviour.

Clinical and preclinical studies have also provided strong evidence supporting reduced striatal dopamine signalling and D2 receptor levels in SUD as having a direct impact on impulsivity and potentially acting as a biomarker to predict future drug self-administration (Trifilieff and Martinez, 2014). Animal studies (Piazza et al., 1989; Poulos, Le and Parker, 1995; Perry et al., 2005; Dalley et al., 2007) sub-grouped rodents based on their performance on behavioural paradigms (i.e. discounting preferences or premature responses on attentional task),

into low-impulsive and high-impulsive groups and observed a significant reduction in striatal D2 receptor binding in the high-impulsive group and behaviourally, the high-impulsive group consumed a larger amount of drugs and acquired drug self-administration quicker compared to the low-impulsive group. More recent findings by Besson and colleagues (2013) also suggest there is evidence that decreased striatal D2 receptor binding in impulsive animals is related to decreased NAc and VTA messenger ribonucleic acid (mRNA) expression and drug exposure leads to a greater decrease in striatal mRNA expression. Volkow and colleagues conducted positron emission tomography (PET) imaging studies to replicate similar findings in humans where the activity of the OFC and ACC were examined in relationship to striatal D2 receptor numbers and revealed that in addicted patients, there was a strong positive correlation between the number of D2 receptors and activity in the OFC and ACC, where SUD patients demonstrated lower levels compared to controls (Volkow et al., 1993; Volkow et al., 1997). Other neuroimaging studies have expanded on these findings to support the idea that low striatal D2 receptor binding in non-addicted individuals can be predictive of the development of SUD (Davidson et al. 1993, Volkow et al. 2002, Casey et al., 2014) and that high striatal D2 receptor binding may serve as a marker for resilience in those with a family history of SUD (Volkow et al. 2006a, Volkow et al. 2006b).

#### **1.4 Attentional Bias**

Incentive salience is most often described as the cognitive attribute of “wanting” in response to a rewarding stimulus by means of an incentive motivational process (Robinson and Berridge, 2008). According to the incentive sensitization theory, in SUD sensitization of the mesolimbic dopaminergic system occurs due to repetitive drug use, which leads to an increase in

incentive salience, creating an attentional bias to drug-related stimuli (highly valued reinforcers) in SUD individuals (Robinson & Berridge, 1993). As a result, these individuals automatically direct their attention to substance-related stimuli, leading to subjective cravings and possible relapse, regardless of the length of previous abstinence (Franken, 2003). Ultimately, this pathological motivation for drugs, combined with poor executive control over behaviour, is at the centre of SUD symptomology (Robinson and Berridge, 1993).

The primary emphasis of this theory is placed on the sensitization process that occurs in dopaminergic signalling pathways in key brain structures, more specifically the NAc and amygdala. During conditioned place preference paradigms in rodents, animals are trained to associate a certain “place” with drug administration and later, when they are given the option between two places, they usually return to the environment they associate with drug administration (Adinoff, 2004). In studies where amygdala ablation occurs (Hiroi and White, 1991; Meil and See, 1997), rodents forget this association, however the reinforcing effect induced by the drug administration remains apparent. Similarly, neuroimaging studies in opioid- (Upadhyay et al., 2010) cocaine- (Grant et al., 1996; Childress et al., 1999; Breiter et al., 2001; Kilts et al., 2001), alcohol- (Courtney, Ghahremani and Ray, 2015) and nicotine-addicted (Due et al., 2002; Franklin et al., 2007) individuals demonstrate limbic system activation during cue exposure to drug-related stimuli.

Important cellular and molecular mechanisms occurring in the NAc are essential in guiding the explanation of directed and sustained attention towards drugs and drug related stimuli during the binge/intoxication phase ultimately leading to chronic drug administration and increased risk of relapse. Repetitive drug intake leads to an extracellular release of dopamine, which begins inducing changes in intracellular processes almost immediately after consumption,

by altering protein synthesis at the messenger and transcription level. Both D1 and D2 receptors are found in the mesolimbic pathway but have different effects once activated by opioid consumption. D1 receptors activate membrane G proteins, which activate the adenylyl cyclase pathway, increasing cyclic adenosine monophosphate (cAMP) production whereas D2 receptors inhibit this pathway and reduce cAMP production (Adinoff, 2004). Long-term D2-induced decreases in intracellular cAMP levels caused by chronic drug use are also thought to lead to an increase in drug administration (Self and Nestler, 1995; Nestler, 2004). At the transcription level, immediate early gene (IEG) transcription factors such as the Fos family, are rapidly induced after acute exposure to opioids and other substances (Ziolkowska et al., 2012). One transcription factor in particular  $\Delta$ FosB, accumulates in the ventral striatum, amygdala and PFC and this increase in  $\Delta$ FosB expression has been shown to increase sensitivity to the rewarding effects of opioids (Kelz and Nestler, 2000; Zachariou et al., 2006). It has even been proposed that  $\Delta$ FosB acts as a “molecular switch” (Nestler, Barrot and Self, 2001) since  $\Delta$ FosB is responsible for the gradual conversion of acute drug responses to stable long-term adaptations and changes in behavioural neuroplasticity even after drug use has terminated (Hyman, Malenka and Nestler, 2006).

### **1.5 Cognitive Biomarkers for Impulsivity**

Laboratory measurements of impulsivity and response inhibition using paradigms such as the Stroop, Flanker and Go/NoGo tasks have demonstrated greater cognitive and behavioural inhibitory failure in SUD individuals compared to healthy subjects (Goldstein et al., 2001; Lubman, Yocel & Pantelis, 2004). During the Go/NoGo task, participants must respond to a frequent “Go” stimulus and withhold responses to an infrequent “NoGo” stimulus, where the

high frequency of Go trials yields a prepotent response, conflicting with the need to withhold responses for NoGo trials (Falkenstein, Hoormann and Hohnsbein, 1999; Nieuwenhuis et al., 2003). Frontal activation during “NoGo” trials is larger than during “Go” trials, which is presumed to represent the inhibitory control required to suppress active responding (Sokhadze et al., 2008). Successful NoGo trials are associated with two brain event-related potentials (ERPs): (1) N200 (N2), an early fronto-central negative component occurring 200-400 ms post-stimulus and (2) P300 (P3), a later parietal-central positive component occurring 400-600 ms post-stimulus and is larger than the predominantly parietal P3 observed during Go trials (Kok et al., 2004). The N2 is believed to be generated in the ACC and right OFC and inferior frontal gyrus (IFG) regions, representing an early, top-down inhibition mechanism (Huster et al., 2010; Nieuwenhuis et al., 2003; Bokura, Yamaguchi & Kobayashi, 2001). Similarity P3 is produced by activity in the ACC/OFC (Dimoska, Johnson & Barry, 2006; Strik et al., 1998), reflecting a later processing component where actual motor inhibition occurs within the premotor cortex (Kok et al., 2004, Dimoska, Johnson & Barry, 2006, Band & Boxtel, 1999). Incorrect responses to NoGo stimuli generate a fronto-central ERP in the ACC called error-related negativity (ERN), which occurs around 50-80 ms after making a response error and is believed to signal the initial automatic error detection process (Bernstein, Scheffers & Coles, 1995; Falkenstein et al., 1991), followed by a parieto-central positive wave (Pe) which occurs 300 ms after an incorrect response, signalling conscious awareness of error processing (Wessel, Danielmeier & Ullsperger, 2011; Nieuwenhuis et al., 2001, Overboek, Nieuwenhuis & Redderinkhof, 2005; Ridderinkhof et al., 2009).

### **1.5.1 Event-Related Potentials (ERPs)**

Neurobiological insights into cognitive functioning and processing can be improved by using electroencephalography (EEG)-derived event-related potentials (ERPs), which are brief (1-1000 ms), neuroelectric small voltage (<20uv) responses that typically occur milliseconds following presentation of discrete stimuli (Luck et. al., 2011), consisting of a sequence of positive and negative voltage peaks or components, each reflecting specific mental operations. ERPs are derived via a signal averaging procedure and the two essential measurable aspects of the ERP waveform, amplitude and latency, reflect the strength or extent of neural activation (i.e. the strength of a process), and timing of a cognitive process, respectively (Friedman & Johnson, 2000). ERP components are classified by latency and consist of early (< 400ms) exogenous components (i.e. their amplitudes depend on the physical properties of the stimulus) or late endogenous components (i.e. their amplitudes are determined by the psychological significance of the stimulus and the manner in which it is processed) (Nandrino, Massioui & Everett, 1996).

### **1.5.2 N200 (N2)**

The N2 component is elicited early in the stages of cognitive processing and indexes a top-down mechanism required to inhibit the automatic tendency to respond (Falkenstein, 2006; Kaiser et al., 2006), referred to as response inhibition. It has also been proposed that the N2 ERP indexes conflict detection mechanisms (Falkenstein, 2006; Lijten et al., 2014; Lijten, Kleinjan and Franken, 2016; Nieuwenhuis et al., 2003) where the conflict caused by simultaneous activations of two competing response tendencies leads to increased ACC activity (Donkers and van Boxtel, 2004). FMRI and PET imaging studies utilizing the go/no-go paradigm have provided support for the role of the ACC (Blasi et al., 2006; Carter et al., 1998; Elliot et al.,

2000; Kiehl, Liddle and Hopfinger, 2000; Rubia et al., 2000) and OFC/IFG regions (Buchsbaum et al., 2005; Garavan, Ross and Stein, 1999; Hazeltine et al., 2003; 2000) in response inhibition. More specifically, hypoactivity in the ACC, OFC and IFG regions is pronounced in SUD individuals (de Ruiter et al. 2012; Galvan et al. 2011; Kaufman et al., 2003; Nestor et al. 2011; Tapert et al. 2007) compared to healthy controls, suggesting that reduced dopaminergic neurotransmission may lead to behavioural alterations in inhibitory control mechanisms (Luijten et al., 2014).

Studies examining ERPs during response inhibition tasks in SUD individuals have shown alterations in NoGo N2 amplitudes (Luijten et al., 2014, Bauer, 2002). Luijten and colleagues (2014) conducted a systematic review of ERP studies investigating inhibitory control and error processing in SUD populations and found that the majority of studies observed a reduction in NoGo N2 modulation in substance-dependant groups compared to a control group. In nicotine-dependent individuals, NoGo N2 amplitudes have been reduced compared to controls (Buzzell et al. 2014; Luijten et al., 2011), with similar results in alcohol-dependant (Pandey et al. 2012) and cocaine-dependent groups (Sokhadze et al. 2008).

However, one of the studies included in the review measured NoGo N2 amplitudes in heroin-dependent (HD) individuals and observed no group differences between the HD group and control group (Yang et al., 2009). Similarly, Kamarajan and colleagues (2005) measured N2 amplitudes in a Go/NoGo task administered to alcohol-dependent individuals and Evans and colleagues (2009) measured N2 amplitudes in a nicotine-dependent group and both studies did not observe a significant change in N2 modulation between groups.

### 1.5.3 P300 (P3)

The P3 component is elicited later in the stages of cognitive processing (compared to the earlier N2 ERP) and is believed to represent the actual inhibition of the motor system in the premotor cortex during Go/NoGo paradigms (Luijten, Kleinjan and Franken, 2016). Additional evidence suggests that the P3 ERP arises from a large network of cortical generators, indexing inhibitory, attentional and working memory processing mechanisms (Kok et al., 2004; Polich, 2007; Roche et al., 2004) and as such, the NoGo-P3 has also been interpreted as an index of attentional engagement due to the low probability of the NoGo stimuli compared to Go stimuli (Kok, 2001; Polich, 2007). The NoGo-P3 component has greater anterior localization with activation of the left lateral OFC, compared to the Go-P3 which is mainly located in the medial part of the parietal cortex (Bokura, Yamaguichi and Kobayashi, 2001) and therefore the NoGo-P3 is usually more pronounced at frontocentral sites (Fallgatter and Strik, 1999; Kiefer et al., 1998).

P3 literature from Go/NoGo paradigms administered to SUD populations is mixed, as some evidence is provided to suggest NoGo-P3 amplitudes are reduced in addicted individuals, whereas other data demonstrates that no P3 differences exist between clinical groups and healthy controls. In a study examining inhibitory control in cocaine-dependent individuals, participants completed a flanker task with NoGo elements and results revealed that the SUD group (compared to healthy controls) had significantly smaller NoGo-P3 amplitudes, suggesting hypoactivity in higher-level executive motor control in cocaine dependence (Sokhadze et al., 2008). Evans and colleagues (2009) found reduced NoGo-P3 amplitudes in overnight nicotine-deprived smokers compared to non-smokers and similar findings were observed in alcohol-dependant individuals who demonstrated smaller NoGo-P3 amplitudes compared to healthy

controls in a similar Go/NoGo paradigm (Kamarajan et al., 2005). These findings are consistent with the theory that NoGo-P3 amplitudes are lowered in SUD populations, reflecting hypoactivity of the PFC resulting in frontal disruption of the inhibitory mechanisms that control drug seeking behaviours.

However, these findings were not replicated in other SUD studies examining response inhibition through administration of a Go/NoGo task. Yang and colleagues (2009) studied NoGo-P3 in abstinent heroin abusers and matched healthy controls and found no significant differences between groups for both NoGo-P3 amplitude and latency. Similarly, nicotine-dependant individuals completing a response inhibition paradigm did not show any differences in their NoGo-P3 amplitudes compared to controls (Buzzell et al., 2014; Luijten et al., 2011), suggesting that motor inhibition, indexed by the NoGo-P3 may not be as affected in SUD as other measures of cognitive control.

Previous literature on N2 and P3 markers in SUD populations must be interpreted with caution as Go/NoGo task paradigms can vary greatly across studies and differing NoGo stimuli probability (i.e. high NoGo probability) may result in cognitive changes (i.e. low inhibitory requirements) which ultimately affect the ERP amplitudes (Fallgatter et al., 1998; Kamarajan et al., 2005). Both NoGo-N2 and NoGo-P3 are possible time-sensitive markers of cognitive control and represent different time points throughout response inhibition and require further examination in prescription opioid dependence.

## **1.6 Cognitive Biomarkers for Attentional Bias**

Cue reactivity (CR) (Carter and Tiffany, 1999) is a phenomenon based off of classical conditioning theory, which occurs when opioid addicted individuals are exposed to drug-related

cues (i.e. images of opioids, images of individuals consuming opioids) and has been shown to reliably induce self-reported craving and physiological responses (Bloom et al, 2013). Cue-related drug craving can be explained through our incentive salience system (Robinson & Berridge, 1993), where it's believed that through their effects on the DA system, drugs of abuse sensitize our incentive salience evaluation of drug cues, tagging them as having a higher motivational value compared to neutral cues (Bloom et al. 2013). The resulting sensitization is displayed behaviourally as a preferential attention towards drug cues (vs. neutral cues) in PO-addicted individuals. Real-time tracking of the spatiotemporal processing deficits in SUD individuals can be performed by utilizing the enhanced (millisecond) temporal resolution of ERPs to index neural systems of attention and provide an assessment of cue reactivity induced alterations in attentional processing of PO-related cues. The P200 (P2) component represents the initial processing of the task relevance (i.e. motivational value) of the stimulus and generally commences 150-200 ms post stimulus onset (Bloom et al. 2013). The late positive potential (LPP) indexes the commencement of attentional processing towards salient stimuli followed by a sustained processing mechanism to facilitate memory encoding and storage (Hajcak and Olvet, 2008; Koenig and Mecklinger, 2008; Littel et al., 2012; Polich and Kok, 1995).

### **1.6.1 P200 (P2)**

An index of the DA reward system, the P2 ERP (peaking around 250-300 ms) mirrors VTA neuronal firing patterns with input to the medial frontal cortex (MFC) (Potts et al., 2006) where P2 amplitude is most positive in response to unpredicted rewards and least positive when an expected reward is not delivered (Schultz, Dayan and Montague, 1997). The P2 component represents the initial attention selection, identification of task-relevant perceptual stimuli and the

subsequent integration of motivational information in response to task-relevant stimuli (Potts et al., 2006; Schupp et al., 2006). P2 amplitude modulation is especially sensitive to the valence (and to a much lesser extent arousal) of the stimulus presented during a cue reactivity task and studies have examined the effect of cue types on P2 modulation. Larger amplitudes and shorter P2 latencies have been found in response to negative (unpleasant) stimuli compared to positive (pleasant) stimuli (Carretié et al., 2001) and neutral stimuli (Olofsson and Polich, 2007) and in a study where all three valence levels of stimuli were assessed, negative pictures elicited the largest P2 amplitudes, positive pictures elicited smaller P2 amplitudes (compared to negative stimuli amplitudes) but demonstrated larger P2 amplitudes than neutral cues and neutral pictures elicited the smallest P2 amplitudes (Delplanque et al., 2004).

The core emotional processing network is composed of the amygdala, insula, OFC and ACC as demonstrated by numerous neuroimaging studies (George et al., 2004; Lane et al., 1997; 1998; Mayberg et al. 1999; Rainville et al. 1997; Sprengelmeyer et al., 1998) and individuals with SUD have significant emotional processing deficits throughout the various stages of SUD (Diekhof et al., 2008; Goldstein and Volkow, 2011). During compulsive drug administration, addicted individuals no longer perceive the drug as pleasurable and consequently experience disruptions in their thalamo-orbitofrontal circuit, PFC and anterior cingulate affecting their ability to process emotionally-relevant stimuli (Goldstein and Volkow, 2002; 2011). This is reflected in studies where SUD patients are shown various picture types (neutral, affective and drug cues) and the subsequent changes in P2 amplitudes are measured.

The current literature shows mixed results on the effect of cue types on P2 amplitudes. Jiang and colleagues (2011) studied a group of heroin-addicted individuals and non-heroin users utilizing a visual cue reactivity paradigm containing heroin-related cues, negative emotional cues

and positive emotional cues. Results revealed that heroin abusers had significantly larger P2 amplitudes towards heroin cues (compared to positive and negative affective pictures) and heroin cues elicited larger P2 amplitudes in heroin abusers compared to controls. In a similar study conducted with a cannabis-dependent group and a non-user control group, individuals participated in a drug Stroop task where cannabis-related, negative and neutral images were presented. An early positive ERP similar to the P2 component was enhanced in the cannabis group during the drug blocks compared to the negative blocks and this effect was absent in the non-user group (Asmaro, Carolan and Liotti, 2014). However, a collection of further research has demonstrated a lack of P2 amplitude alterations in SUD patients viewing a cue reactivity paradigm. Franken (2003) presented heroin cues and neutral cues to heroin patients and controls participating in a CR task and did not find any significant group differences in P2 amplitudes and heroin patients showed no significant differences in P2 amplitudes between cue types. In a similar study with alcohol abusers, P2 amplitudes were assessed at Fz, Cz and Pz for alcohol-related pictures and neutral pictures presented to light and heavy abusers and in both addicted groups, there were no alterations in P2 amplitudes between both cue types at all assessed sites (Herrmann et al., 2001). Furthermore, in research conducted with smokers and non-smokers, P2 amplitudes were increased towards smoking-related cues (vs. neutral cues), however this effect was observed in both groups (Bloom et al., 2012). Generalizing results from the above studies is difficult since the acute drug state of the individual and the emotional relevance assigned to the cues (valence content) are important factors affecting the modulation of cognitive processing in cue-related paradigms.

### **1.6.2 Late Positive Potential (LPP)**

Sustained attention is indexed by the LPP starting at approximately 300 – 400 ms post stimulus onset (Liu et al., 2012), sustained throughout the duration of stimuli presentation (Cuthbert et al., 2000) and is enhanced following the presentation of pleasant and unpleasant visual cues (Hajcak and Olvet, 2008; Keil et al., 2002; Schupp et al., 2003). The LPP is an emotionally-modulated centroparietal ERP (Cacioppo et al., 1994; Codispoti et al., 2007; Hajcak and Nieuwenhuis, 2006, Schupp et al., 2004) generating activation across multiple dorsal and ventral cortical structures including the NAc and anterior cingulate (Engelmann et al., 2012; Sabatinelli et al., 2013). Meta-analyses have shown that there is a significant increase in LPP amplitudes (Littel et al., 2012) in response to substance-related stimuli and an increase in self-reported cravings (Singh et al., 2009) during cue reactivity paradigms. As there is no literature to date that investigates LPP alterations in a passive cue reactivity paradigm with PO-dependant individuals, studies using other SUD populations such as cocaine, nicotine, heroin and cannabis users are often relied upon when examining neural substrates in a PO-dependent population. Extensive studies conducted with nicotine-addicted individuals viewing a passive picture paradigm observed larger LPP amplitudes in response to smoking cues, compared to non-smoking cues (Littel and Franken, 2007; 2011; 2012). After presenting smokers with emotional (pleasant and unpleasant), neutral and cigarette-related cues, Versace and colleagues (2011) observed similar results where emotional and cigarette-related pictures prompted a larger positive LPP compared to neutral pictures over central and parietal sites. These findings have been replicated in abstinent heroin-dependant patients (Franken et al., 2003; Lubman et al. 2008) where larger LPP amplitudes are observed in heroin patients in response to heroin-related cues whereas in controls, no differences in LPP amplitude have been observed between stimulus

types. Furthermore, in both current (Dunning et al., 2011) and abstinent (Franken et al., 2008; Van de Laar et al., 2004) cocaine abusers, LPP amplitudes have also been shown to be enhanced in patients following presentation of cocaine-related stimuli vs. neutral stimuli.

Despite the strong evidence of enhanced cognitive processing (i.e. larger LPP amplitudes) of substance-related stimuli, some studies have failed to replicate similar findings. In a study by Jang and colleagues (2007), no significant differences were observed in LPP amplitudes between groups (smokers and non-smokers) or between stimulus types (smoking-related, antismoking and neutral) and similar research conducted in alcohol-dependant patients (Hansenne et al., 2003) found no ERP differences between groups (alcoholics and controls) in response to alcohol-related cues and neutral cues.

Strong behavioural evidence from cue reactivity paradigms demonstrate that attentional biases exist and are pronounced in prescription opioid abusers, among other SUD populations (Field & Cox, 2008, Franken et al., 2000; Lubman et al., 2000). The Desires for Drug Questionnaire (DDQ) (Franken et al., 2002), or similar assessment tools, are often used in conjunction with cue-reactivity ERP paradigms to assess acute drug craving following presentation of drug-related stimuli and the relationship between processing bias and drug craving has been examined in SUD populations (Littel and Franken, 2007). In a study where cocaine abusers were classified as “low” or “high” cravers based on their baseline DDQ score, only “high cravers” demonstrated larger LPP amplitudes to cocaine cues vs neutral cues (Franken et al, 2004) and similar results were observed in heroin abusers (Franken et al., 2003) where a significant correlation was found between post-experiment craving and mean LPP response to heroin pictures. Most of the literature supports the hypothesis that that high levels of

craving lead to enhanced attentional processing of drug-related cues (Field et al., 2006), indexed by alterations in LPP amplitudes following exposure to drug-related stimuli.

Evidence suggests that P2 and LPP amplitudes vary as a function of affective value and motivational significance of a stimulus presented during a cue reactivity paradigm. In addicted populations, drug stimuli are motivationally relevant and capture attentional resources early during the processing stages and this attentional bias is sustained throughout the presentation of the stimulus, resulting in alterations in neural substrates.

## **2.0 Objectives and Hypotheses**

The primary aim of this project is to examine the neurocognitive alterations in PO-dependent patients. It is hypothesized that (1) disruption of pre-frontal impulse control processes will occur with frequent exposure to drugs and drug-related stimuli and lead to compulsive intake and (2) sensitization of the incentive salience system will occur with repeated exposure to drugs and drug-related stimuli which will dominate the attention of PO abusers and lead to subjective cravings. ERPs will be used to assess if neural evidence exists that salience and inhibitory processes are distorted in PO abusers (compared to healthy controls). In a Go/NoGo paradigm, PO abusers are expected to demonstrate reduced response inhibition on successful NoGo trials indexed by smaller NoGo-N2 and NoGo-P3 amplitudes, compared to healthy controls and, in a cue reactivity paradigm, exaggerated salience to opioid-related stimuli (vs. affective and neutral stimuli), indexed by larger P2 and LPP amplitudes (vs. healthy controls). Secondly, Barratt Impulsivity Scale measures (BIS-11; Patton et al., 1995) will be examined for their relationship with Go/NoGo ERPs and stimulus valence and arousal ratings in the cue reactivity paradigm will be examined in relation to cue-related ERPs.

### 3.0 Methods

#### 3.1 Study Participants

Using a naturalistic study design, 16 prescription opioid-dependent patients ( $N = 11$  males, 5 females, mean age =  $27.19 \pm 1.49$ ) entering the Regional Opioid Intervention Service (ROIS) who had previously consented to an existing ROIS evaluation study, were recruited for study participation. In order to be considered, patients were required to meet the following inclusion criteria:  $\geq 16$  years of age, meet DSM-V criteria for Substance (Opioid) Use Disorder-Moderate or Severe (American Psychiatric Association, 2013), provide an opioid-positive drug screen at time of consent, be willing to be detoxed from opioids and be able to read and write in English. Exclusion criteria for patients included: actively psychotic, currently having suicidal ideation, loss of consciousness from a previous head injury, diagnosis of any neurological disorder, electroconvulsive therapy (ECT) in the past year or any other significant medical history. Current or previous psychiatric disorders were not exclusionary factors. Sixteen healthy controls ( $N = 10$  males, 6 females, mean age =  $29.75 \pm 1.88$ ) were recruited from the local community and were matched for age, gender, education level and smoking status. Exclusion criteria for controls included: current use of opioids, a history of substance abuse or any significant psychiatric, neurological or medical illness. Controls were assessed during a screening process including a complete drug urine screen and the Structured Clinical Interview for DSM-IV Non-Patient Edition (SCID-NP; First, Spitzer, Gibbon et al., 1995). All participants signed an informed consent form and the study was approved by the Research Ethics Boards at the Royal Ottawa Mental Health Center.

### 3.2 Procedure

Patients seeking opioid detoxification presented to the ROIS clinic for a health assessment visit where their current substance use was evaluated by a physician and subsequently referred to the EEG research team if they were found to be actively using primarily prescription opioids (based on a clinical interview and drug urine screen). Consent for study inclusion occurred during this initial health assessment and the EEG research session was subsequently organized before initiation of detoxification treatment. EEG testing sessions were conducted anytime between 8 am-1 pm, depending on the participants' availability, and lasted approximately 2 hours. On the day of EEG assessment, patients presented first to the ROIS clinical team and once they had completed their daily assessment, where it was confirmed that they were not in an acute state of withdrawal; they were escorted to the EEG laboratory. Upon arrival, patients were asked to document any substance use in the past 48 hours including prescription opioids, illicit drugs, marijuana, caffeine, alcohol and nicotine, followed by the administration of two questionnaires to assess both current and past substance use (Alcohol, smoking and Substance Involvement Screening Test (ASSIST), Severity of Dependence Scale (SDS)). Vital signs were collected, followed by electrode hook-up and completion of self-report questionnaires to assess impulsivity, depression, anxiety and mood; Barratt Impulsivity Scale (BIS-11; Patton et al., 1995), Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001), Generalized Anxiety Disorder 7-item scale (GAD-7; Spitzer et al., 2006). Electrophysiological recording paradigms were delivered in a fixed order for all participants starting with a 3-minute eyes-closed baseline recording (not included in this thesis), administration of the Go/NoGo task followed by the cue reactivity paradigm. Immediately after recordings, self-reports of drug cravings (using the 14-item Desire for Drug Questionnaire) (Franken et al., 2002) and stimulus

valence and arousal were acquired. At the end of the session, a vital signs assessment and clinical debriefing session were conducted (administered by an addiction counsellor, social worker or registered nurse) to ensure patient safety. Control participants presented to the EEG laboratory the day of testing where they read and signed a consent form, were given a drug urine screen and subsequently followed the same testing laboratory procedure including all self-reports as patients with the exception of a clinical debrief. Urine screens for all healthy controls were negative for amphetamines, barbiturates, benzodiazepine, cocaine, methadone, opiates & oxycodone. Results from the patient urine screens are presented below in table 1.

Table 1

*Patient substance use demographics*

Patient ID	Last Reported Use on Day of EEG (Hrs)	Days Between (+) Urine Screen and EEG (Days)	Drug Type(s)
1	17	14	Oxycodone
2	6	3	Morphine, Hydromorphone
3	2	24	Hydromorphone, Oxycodone
4	>24	4	Oxycodone
5	>24	28	Hydromorphone
6	>24	22	Oxycodone
7	2	3	Codeine, Oxycodone
8	24	4	Fentanyl
9	2	ND	Fentanyl
10	2	24	Fentanyl
11	1	0	Codeine, Morphine
12	>24	ND	Oxycodone
13	22	7	Fentanyl
14	1	7	Oxycodone
15	>24	ND	Fentanyl
16	1	4	Hydromorphone, Oxycodone

*Notes.* Patients were allowed to refuse a urine screen from the clinical team for legal reasons not originally disclosed to research team at time of consent (i.e. healthcare professional, current legal proceedings). The average time between urine screen and EEG test session was  $11 \pm 9.94$  days with a range of 0-28 days. \*ND = No Data available.

### 3.3 Cognitive Tasks

#### 3.3.1 Go/NoGo Paradigm

Based on the paradigm used by Little et al. (2012), participants completed a Go/NoGo task where they were shown a series of letters of the alphabet on a computer screen and were instructed to click by use of a computer mouse to every letter shown (Go trials) and withhold

their response for repeated letters (NoGo Trials). A total of 636 letters were divided into four blocks of 159 letters, where all letters of the alphabet were used in a randomized order with 74 (11.6%) repeated letters. Participants first practiced on 10 trials before the 4 stimulus blocks (with a 60 second rest break between each block) and were instructed to respond as quickly and accurately as possible by pressing a mouse key with their dominant hand index finger. NoGo trials were presented in an unpredictable manner by utilizing a filler in the number of intermitted Go trials and NoGo trials were never presented in succession. Each letter was presented on the screen for 700 ms, followed by a 300 ms white fixation cross on a black screen before the next letter was presented. Behavioural measures (reaction time, percentage correct and incorrect) were also recorded and analyzed.

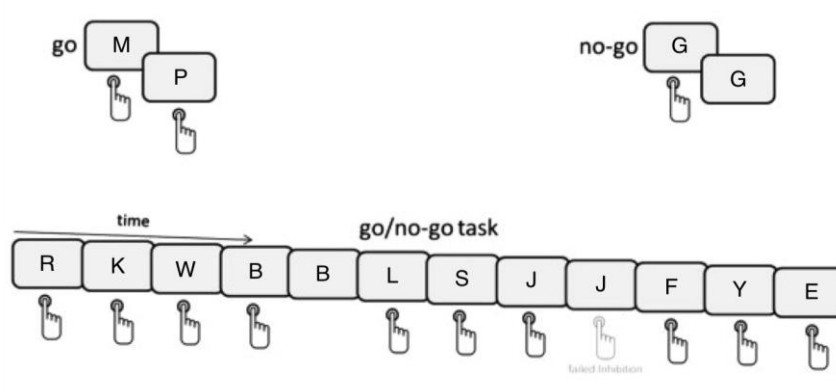


Figure 2. Schematic of the Go/NoGo paradigm. Adapted from Huster et al., 2013.

### 3.3.2 Cue Reactivity Paradigm

The visual cue reactivity paradigm was similar to the one performed by Lubman et al. (2008), which allowed for the examination of attentional bias specificity towards opioid-related vs. emotional vs. neutral stimuli. Participants were instructed to passively view each visual stimulus, which included a total of 120 pictures (40 opioid-related, 40 neutral and 40 emotional) divided into two experimental blocks consisting of 60 pictures each, with a 2 minute rest interval

between experimental blocks. Participants were first presented with 10 practice trials (consisting only of neutral filler pictures), followed by the two experimental blocks, with 3 neutral filler pictures at the beginning of both blocks before stimulus presentation. Images were displayed on the screen for 500 ms followed by a white fixation cross for 500 ms and a blank screen for 500 ms, with a 3-5 second inter-stimulus interval prior to presentation of the next fixation cross. Following completion of this task, participants rated a selection of 30 images (10 drug, 10 emotion and 10 neutral) in order to assess the valence (range from unpleasant (1)-pleasant (9)), arousal (range from calm (1)-arousing (9)), personal association (range from low (1) – high (9)) and opioid craving (0-100%) scores associated with each image type. Neutral and emotional images were chosen from the International Affective Picture System (IAPS) (Lang et al., 1999) based on their arousal and valence scores and the criteria from Lubman et al. (2008) were used to classify the pictures into three categories (neutral, emotional-positive and emotional-negative). Selected IAPS neutral pictures had an arousal score of less than 5 and a valence score between 3.3 and 6.7, positive pictures had an arousal score of more than 5 and valence score between 6.3 and 9 and negative pictures had an arousal score of more than 5 and valence score between 1.3 and 3.7. There is no known standardized inventory of opioid-related images; therefore these images were taken with the assistance of the University of Ottawa Simulation Laboratory, and based on the patient demographics of the ROIS (i.e. Approximately 50% of ROIS patients abuse opioids orally therefore 50% of the images depict oral-based drug consumption). Furthermore, the images were matched in size, quality (pixels), colour and intensity and the number of images containing human faces was matched across picture type.

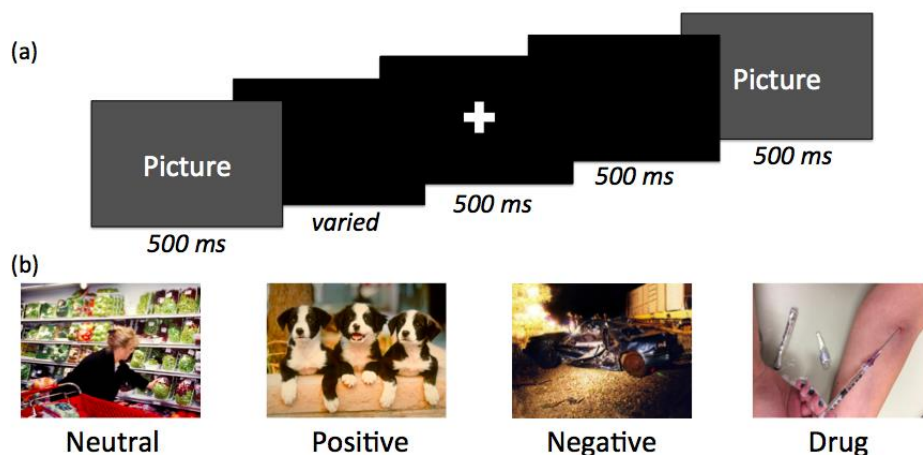


Figure 3. Cue reactivity paradigm design (a) and the four different stimuli categories (b).

### 3.4 ERP Recording/Processing

ERPs were recorded with Na/NaCl electrodes embedded in an electrode cap containing 32 different sites. Four electrodes were placed on orbital sites for bipolar recordings of vertical (VEOG) and horizontal (HEOG) electro-oculographic activity (Light, Williams, Minow et al., 2010). EEG signals were referenced to electronically linked earlobe electrodes and another electrode was positioned on the middle forehead site to serve as the ground. Electrode impedance was kept below  $5k\Omega$ . All electrical activity was recorded with the BrainVision Quickamp<sup>®</sup> (Brain Products, GmbH, Munich, Germany) amplifier and BrainVision Recorder Systems<sup>®</sup> with bandpass filter settings at 0.1-70 Hz and electrical activity was sampled at 500 Hz. BrainVision Analyzer<sup>®</sup> software was used for offline data processing and included re-filtering (0.1-35 Hz, 24 dB/oct for the Go/NoGo task; 0.15-30 Hz, 24 dB/oct for the Cue Reactivity task), stimulus-locked epoch segmentation (1000 ms post-stimulus for the Go/NoGo task, 800 ms post-stimulus for the Cue Reactivity task and 200 ms pre-stimulus for both tasks), response-locked epoch segmentation (100 ms pre-stimulus and 600 ms post-stimulus for the Go/NoGo task only), ocular



positive peak between 325-600 ms. Four midline sites of maximum amplitude (Fz, Cz, CPz and Pz) were utilized for each stimulus-locked ERP component. Amplitudes were measured in reference to the mean pre-stimulus (baseline) voltage.

### **3.4.2 Cue Reactivity ERPs**

Both the P2 and LPP components were assessed at their site of maximal amplitude (site Pz), where the maximum positive peak between 200-275 ms was quantified as the P2 ERP and the average voltage between 300-600 ms was used to index the LPP component. For exploratory purposes only, the LPP was further subdivided into 50 ms segments to track possible time-sensitive changes in ERP amplitudes over the 300 ms time course. The secondary components were defined as the maximum positive peak between 75-150 ms for the P1 ERP component and the maximum negative peak between 150-200 ms for the N1 ERP.

### **3.5 Statistical Analysis**

Two-way mixed analysis of variance (ANOVA) were performed for the ERN and Pe ERPs from the Go/NoGo task with group (controls vs. patients) as a between-subjects variable and site (Fz, Cz, CPz and Pz) as a within-subjects variable. Three-way repeated measures ANOVAs were performed for the N2 and P3 ERPs with group (controls vs. patients) as a between-subjects variable and correctness (incorrect and correct) and site (Fz, Cz, CPz and Pz) as within-subjects variables. A comparison between groups (controls vs. patients) using independent-samples t-tests was used to examine group differences in Go/NoGo behavioural measures (reaction time, % correct Go, % correct NoGo, % incorrect NoGo). Pearson correlations were computed between ERP amplitudes and scores on the second order factors of the BIS-11 questionnaire (attention, cognitive instability, motor, perseverance, self-control and cognitive complexity).

Two-way mixed ANOVAs were used to examine the P2 and LPP from the cue reactivity task with group (controls vs. patients) as a between-subjects variable and stimulus type (neutral vs. affective vs. prescription-opioid-related) as a within-subjects variable. In addition, two interaction contrasts were used to examine whether the group difference in P2 and LPP is larger when exposed to opioid-related stimuli compared to a) affective and b) neutral stimuli. For behavioural measures, two-way mixed ANOVAs were also conducted for picture valence, arousal and personal association scores with group (controls vs. patients) acting as a between-subjects variable and stimulus type (neutral vs. emotional vs. prescription-opioid-related) as a within-subjects variable. Differences in drug craving ratings between pictures types were assessed in patients only using an independent-samples t-test. Pearson correlations were also conducted between valence and arousal scores for each stimulus type and LPP amplitudes for each stimulus type (neutral, affective and drug).

Questionnaire data (GAD-7, PHQ-9 and BIS-11) was analyzed using an independent-samples t-test to examine differences in scores between patients and controls.

## 4.0 Results

### 4.1 Go/NoGo Paradigm

#### 4.1.1 Response (Incorrect NoGo) Locked ERPs

Grand averaged response-locked ERP waveforms associated with incorrect NoGo responses are shown for patients and controls in Figure 5.

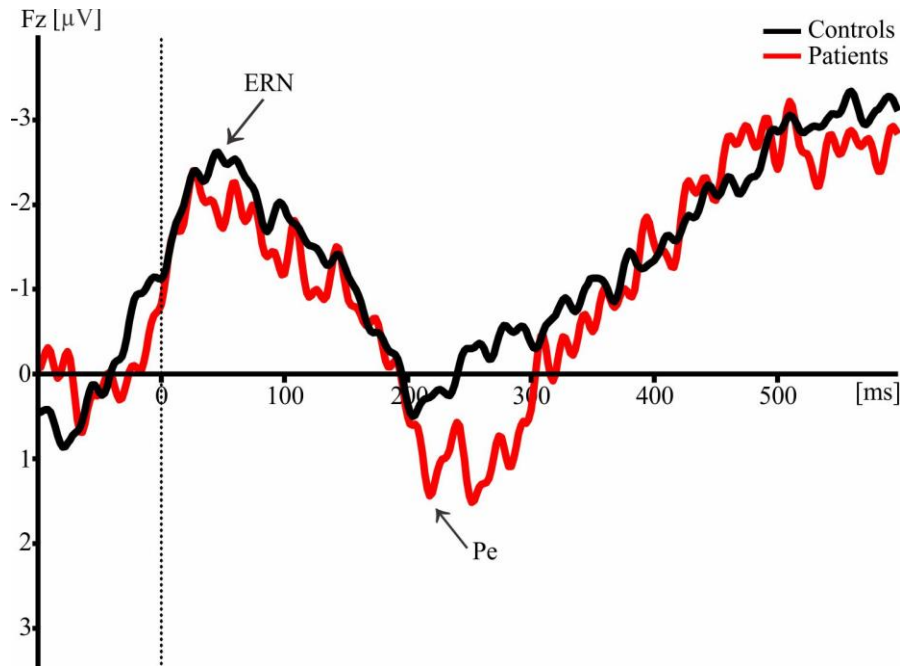


Figure 5. Response-locked grand average frontal (Fz) ERP waveforms for controls and patients associated with an incorrect NoGo response at the site of maximal amplitude (Fz).

#### 4.1.1(a) ERN Amplitude and Latency

A main site effect was observed for ERN amplitude  $F(3,90) = 24.33, p < 0.001$ . Follow-up comparisons revealed a significantly ( $p < 0.001$ ) more pronounced ERN at Fz ( $M = -3.98 \mu\text{V}$ ,  $SE \pm 0.60$ ) compared to the other three sites (Cz, CPz and Pz). Interestingly, there was a trend towards significance ( $p = 0.056$ ) for group differences, with patients ( $M = -2.05 \mu\text{V}$ ,  $SE \pm 0.33$ )

trending towards larger ERN amplitudes compared to controls ( $M = -1.14 \mu\text{V}$ ,  $SE \pm 0.33$ ). There were no significant effects found for ERN latency.

#### **4.1.1(b) Pe Amplitude and Latency**

Only a main site effect was observed for Pe amplitude  $F(3,90) = 13.01$ ,  $p < 0.001$  demonstrating significantly larger amplitudes at site Fz compared to all other analyzed sites (Cz, CPz, and Pz). Follow-up comparisons did not reveal any significant findings between groups or for group x site interactions. There were no significant effects found for Pe latency.

#### **4.1.2 Stimulus Locked ERPs**

Grand averaged stimulus locked ERP waveforms for patients and controls elicited in response to correct Go and NoGo stimuli are shown in Figure 6. Comparisons of correct and incorrect NoGo waveforms are displayed in Figure 7.

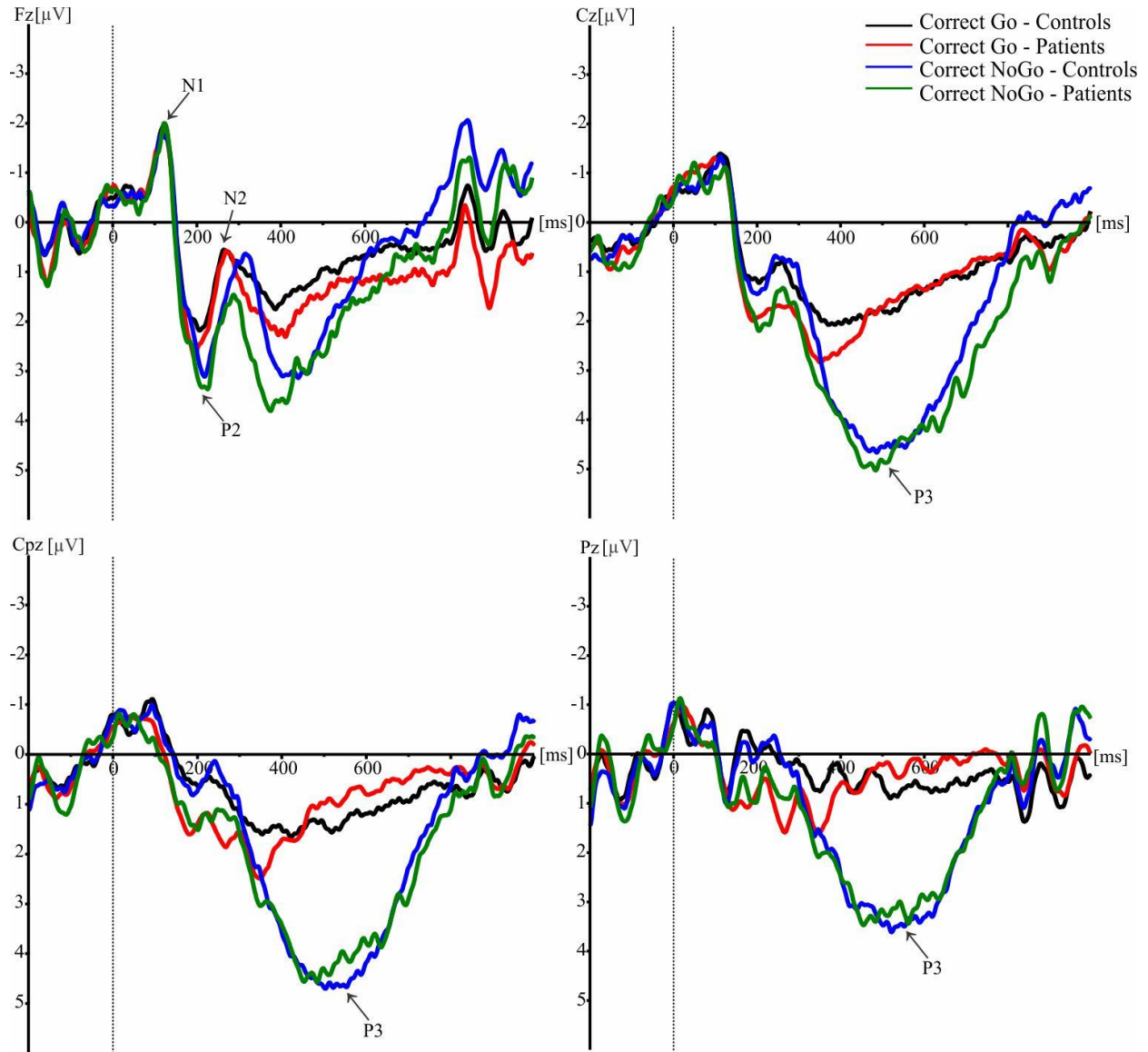


Figure 6. Grand average stimulus locked ERP waveforms elicited in response to correct Go and correct NoGo stimuli for patients and controls at sites Fz, Cz, CPz, and Pz.

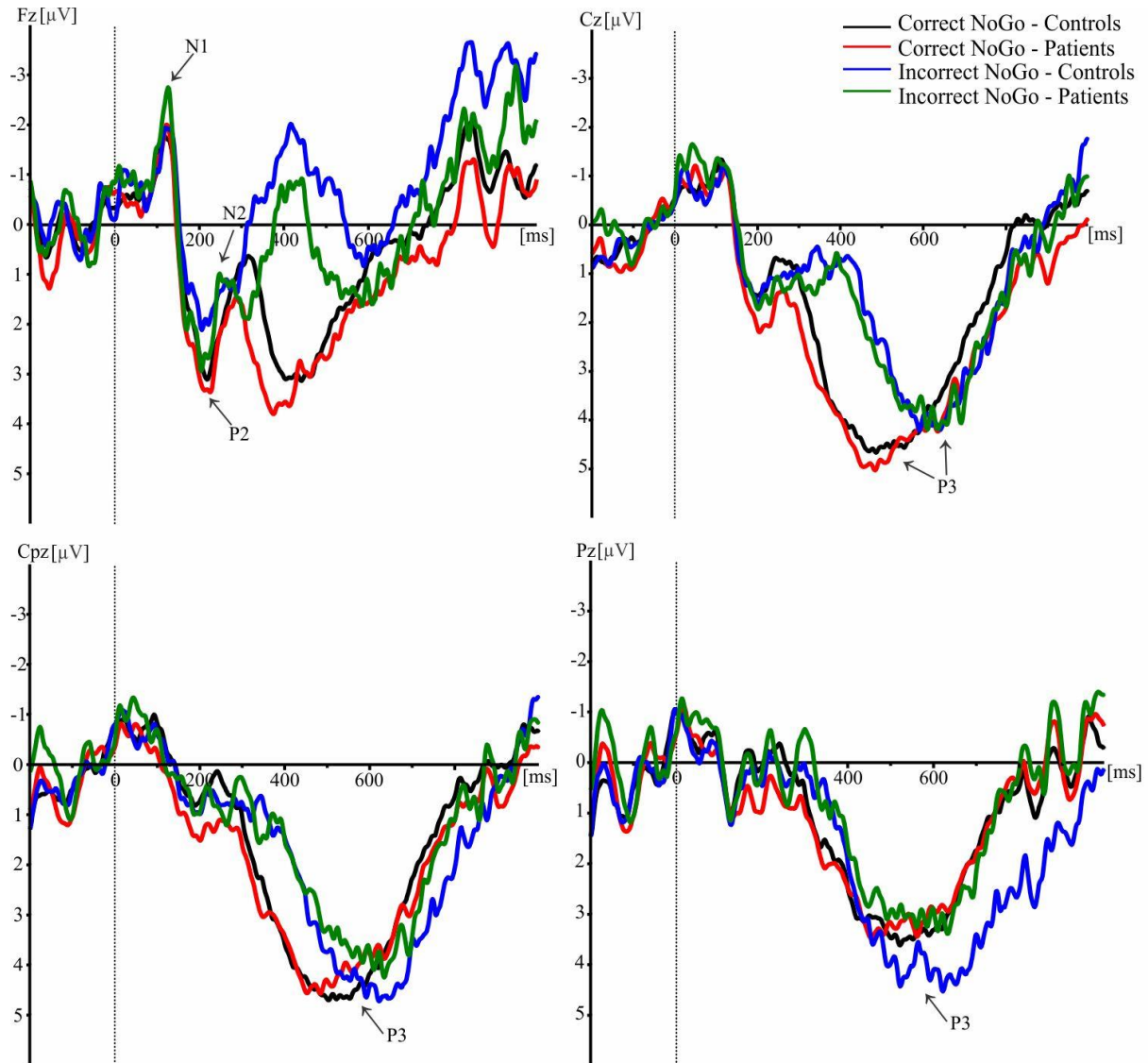


Figure 7. Grand average stimulus-locked ERP waveforms in response to correct NoGo and incorrect NoGo stimuli for patients and controls at sites Fz, Cz, CPz, and Pz.

#### 4.1.2(a) N2 Amplitude and Latency

No significant main effects were observed for N2 amplitude. Follow-up comparisons revealed significantly larger ( $p = 0.02$ ) N2 amplitude for NoGo stimuli ( $M = 0.08 \mu\text{V}$ ,  $SE \pm 0.36$ ) compared to Go stimuli ( $M = 0.66 \mu\text{V}$ ,  $SE \pm 0.23$ ) at site Cz and significantly larger ( $p = 0.04$ ) N2 amplitude for NoGo stimuli ( $M = -0.27 \mu\text{V}$ ,  $SE \pm 0.32$ ) compared to Go stimuli ( $M = 0.26$

$\mu\text{V}$ ,  $\text{SE} \pm 0.27$ ) at site CPz. No differences were observed between groups or for group x correctness. There were no significant effects for N2 latency.

#### 4.1.2(b) P3 Amplitude and Latency

There was a main correctness effect observed for P3 amplitude  $F(1,30) = 135.17$ ,  $p < 0.001$ . Follow-up comparisons revealed that P3 amplitudes were significantly larger ( $p = 0.01$ ) for NoGo stimuli ( $M = 5.26 \mu\text{V}$ ,  $\text{SE} \pm 0.38$ ) compared to Go stimuli ( $M = 2.63 \mu\text{V}$ ,  $\text{SE} \pm 0.23$ ). In patients, P3 amplitudes were also significantly ( $p < 0.001$ ) larger for NoGo stimuli ( $M = 5.46 \mu\text{V}$ ,  $\text{SE} \pm 0.54$ ) compared to Go stimuli ( $M = 2.93 \mu\text{V}$ ,  $\text{SE} \pm 0.33$ ). Similarly in controls, P3 amplitudes were significantly ( $p < 0.001$ ) larger for NoGo stimuli ( $M = 5.06 \mu\text{V}$ ,  $\text{SE} \pm 0.54$ ) compared to Go stimuli ( $M = 2.32 \mu\text{V}$ ,  $\text{SE} \pm 0.33$ ). This finding was observed at all measured sites (Fz, Cz, CPz, and Pz) for both patients and controls. There were no significant group differences for P3 amplitude.

A main correctness effect was also observed for P3 latency  $F(1,30) = 24.42$ ,  $p < 0.001$ . Follow-up comparisons revealed that P3 latency was significantly ( $p < 0.001$ ) earlier for Go stimuli ( $M = 412.31 \text{ ms}$ ,  $\text{SE} \pm 15.19$ ) compared to NoGo stimuli ( $M = 492.75 \text{ ms}$ ,  $\text{SE} \pm 11.97$ ). In controls, P3 latency was also significantly ( $p = 0.001$ ) earlier for Go stimuli ( $M = 428.88 \text{ ms}$ ,  $\text{SE} \pm 21.48$ ) compared to NoGo stimuli ( $M = 510.25 \text{ ms}$ ,  $\text{SE} \pm 16.93$ ). Similarly in patients, P3 latency was significantly ( $p = 0.002$ ) earlier for Go stimuli ( $M = 395.75 \text{ ms}$ ,  $\text{SE} \pm 21.48$ ) compared to NoGo stimuli ( $M = 475.25 \text{ ms}$ ,  $\text{SE} \pm 16.93$ ). There were no significant differences between patients and controls.

#### 4.1.2(c) N1 Amplitude and Latency – Exploratory Findings

There were no significant main effects observed and follow-up comparisons did not yield any significant differences between groups, for correctness (Go and NoGo stimulus) or group x correctness interaction effects. There were also no significant effects for N1 latency.

#### 4.1.2(d) P2 Amplitude and Latency – Exploratory Findings

Main correctness effect was observed for P2 amplitude  $F(1,30) = 7.24, p = 0.01$  in addition to a main correctness x site effect  $F(3,90) = 5.60, p = 0.01$ . Follow-up comparisons revealed that P2 amplitudes were significantly larger ( $p = 0.01$ ) for NoGo stimuli ( $M = 2.63 \mu\text{V}$ ,  $SE \pm 0.24$ ) compared to Go stimuli ( $M = 2.24 \mu\text{V}$ ,  $SE \pm 0.18$ ) and significantly ( $p = 0.02$ ) larger P2 amplitudes in patients ( $M = 2.90 \mu\text{V}$ ,  $SE \pm 0.27$ ) compared to controls ( $M = 1.97 \mu\text{V}$ ,  $SE \pm 0.27$ ). For correct Go stimuli, patients ( $M = 2.75 \mu\text{V}$ ,  $SE \pm 0.25$ ) demonstrated significantly ( $p = 0.01$ ) larger P2 amplitudes than controls ( $M = 1.74 \mu\text{V}$ ,  $SE \pm 0.25$ ) however only a trend was observed for correct NoGo stimuli, with patients ( $M = 3.06 \mu\text{V}$ ,  $SE \pm 0.33$ ) trending ( $p = 0.08$ ) larger P2 amplitudes compared to controls ( $M = 2.21 \mu\text{V}$ ,  $SE \pm 0.33$ ). In the control group, there was a significant ( $p = 0.03$ ) difference between P2 amplitude for correct Go ( $M = 1.74 \mu\text{V}$ ,  $SE \pm 0.25$ ) and correct NoGo stimuli ( $M = 2.21 \mu\text{V}$ ,  $SE \pm 0.33$ ) however this was not observed in patients. For controls, at site Fz, there was a significant ( $p = 0.01$ ) difference between P2 amplitude for correct Go ( $M = 2.80 \mu\text{V}$ ,  $SE \pm 0.31$ ) and correct NoGo ( $M = 3.71 \mu\text{V}$ ,  $SE \pm 0.43$ ) stimuli which was also observed in patients at site Fz, where P2 amplitudes were also significantly larger for correct NoGo stimuli ( $M = 4.31 \mu\text{V}$ ,  $SE \pm 0.43$ ) compared to correct Go stimuli ( $M = 3.18 \mu\text{V}$ ,  $SE \pm 0.31$ ). There were no significant effects for P2 latency.

### 4.1.3 Correlations

For correct NoGo stimuli in patients, there was a significant ( $p = 0.05$ ) positive correlation ( $r = 0.58$ ) between P2 amplitude at Cz and scores on the motor scale of the BIS-11. There was also a significant ( $p = 0.05$ ) positive correlation between P3 amplitudes at CPz and the attention ( $r = 0.51$ ) and cognitive instability ( $r = 0.62$ ) scales of the BIS-11. In controls for correct NoGo stimuli, there was a significant ( $p = 0.05$ ) positive correlation ( $r = 0.60$ ) between N1 amplitude at Fz and self-control in addition to a significant ( $p = 0.05$ ) positive correlation ( $r = 0.57$ ) between P2 amplitude at Cz and cognitive complexity.

In patients, for correct Go stimuli, there was a significant ( $p = 0.05$ ) negative correlation between N2 amplitudes at Fz and cognitive instability scores ( $r = -0.51$ ). There was a significant positive correlation ( $p = 0.05$ ) observed between P2 amplitudes at Cz for motor scores ( $r = 0.50$ ) and between P2 amplitudes at CPz and cognitive instability scores ( $r = 0.50$ ). Whereas in controls, there was a significant ( $p = 0.01$ ) positive correlation between P2 amplitude at Cz and cognitive complexity scores ( $r = 0.70$ ) on the BIS-11 and a significant ( $p = 0.05$ ) negative correlation between P2 amplitudes at Pz and perseverance scores ( $r = -0.52$ ) on the BIS-11.

No significant correlations were observed between BIS-11 scores and incorrect NoGo ERPs (ERN and Pe).

### 4.1.4 Behavioural Data

Mean and standard error for behavioural components are displayed in Figure 8. There were no significant group differences for reaction time, percent correct of NoGo stimuli and personal incorrect of NoGo stimuli.

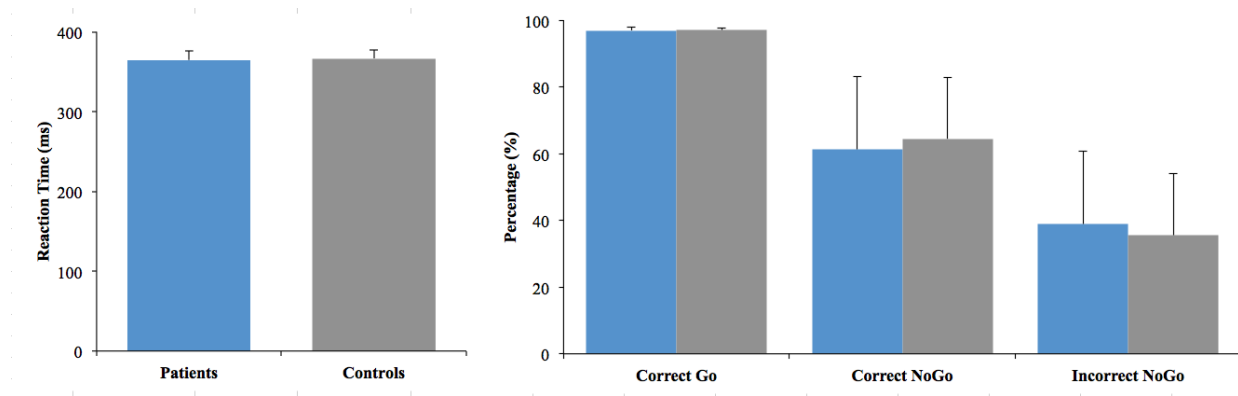


Figure 8. Mean and standard error for behavioural measures of Go/NoGo task.

### 4.2 Cue Reactivity Paradigm

Grand average waveforms elicited by neutral, affective and drug stimuli in patients and controls are shown in Figure 9 and Figure 10, respectively.

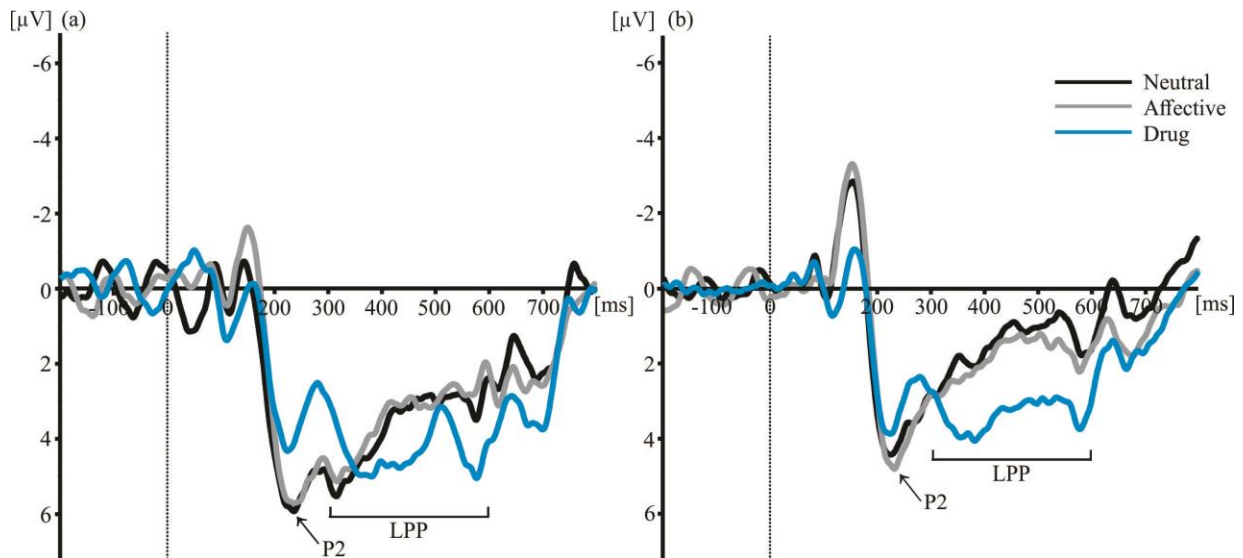


Figure 9. Grand average ERP waveforms for patients (a) and controls (b) for each picture type (neutral, affective, drug) at the site of maximal amplitude (Pz).

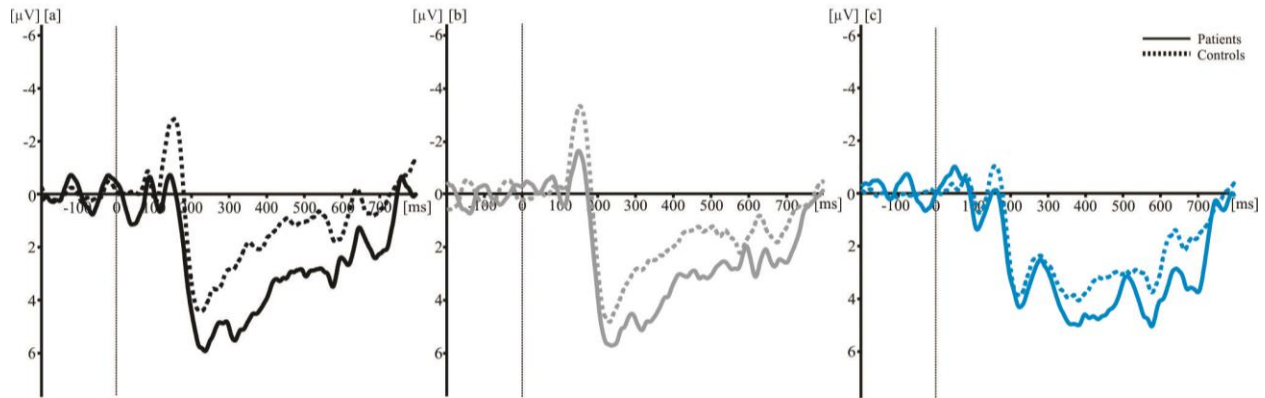


Figure 10. Grand average ERP waveforms for neutral picture stimuli (a), affective picture stimuli (b) and drug picture stimuli (c), in patients and controls at the site of maximal amplitude (Pz).

#### 4.2.1 P2 Amplitude and Latency

There was a main picture type effect for P2 amplitude  $F(2,60) = 8.61, p = 0.001$ . Follow-up comparisons revealed that P2 amplitude for drug pictures ( $M = 5.06 \mu\text{V}, SE \pm 0.57$ ) was significantly ( $p = 0.006$ ) smaller than P2 amplitude for neutral pictures ( $M = 6.22 \mu\text{V}, SE \pm 0.75$ ) and significantly smaller ( $p = 0.007$ ) than P2 amplitude for affective pictures ( $M = 6.17 \mu\text{V}, SE \pm 0.72$ ). Although neither a group effect nor a group x picture type interactions were significant, these stimulus effects were evident only in patients. In the patient group, P2 amplitude for drug pictures ( $M = 5.22 \mu\text{V}, SE \pm 0.81$ ) was significantly ( $p = 0.004$ ) smaller than P2 amplitude for neutral pictures ( $M = 6.91 \mu\text{V}, SE \pm 1.06$ ) and significantly smaller ( $p = 0.022$ ) than P2 amplitude for affective pictures ( $M = 6.56 \mu\text{V}, SE \pm 1.02$ ).

There were no significant main or interaction effects for P2 latency.

#### 4.2.2 LPP (300-600 ms)

There was a main picture type effect for LPP amplitude  $F(2,60) = 8.73, p = 0.001$ . Follow-up comparisons revealed that LPP amplitude for drug pictures ( $M = 3.83 \mu\text{V}, SE \pm 0.45$ ) was

significantly ( $p = 0.004$ ) larger compared to LPP amplitude for neutral pictures ( $M = 2.58 \mu\text{V}$ ,  $\text{SE} \pm 0.36$ ) and significantly ( $p = 0.004$ ) larger compared to affective picture LPP amplitude ( $M = 2.63 \mu\text{V}$ ,  $\text{SE} \pm 0.51$ ) across groups. Although there were no significant main group or picture  $\times$  group interaction effects, patients ( $M = 3.65 \mu\text{V}$ ,  $\text{SE} \pm 0.51$ ) demonstrated significantly ( $p = 0.006$ ) larger LPP amplitude compared to controls ( $M = 1.51 \mu\text{V}$ ,  $\text{SE} \pm 0.51$ ) for neutral pictures only.

In the control group, LPP amplitude for drug pictures ( $M = 3.35 \mu\text{V}$ ,  $\text{SE} \pm 0.64$ ) was significantly ( $p = 0.003$ ) larger compared to LPP amplitude for neutral pictures ( $M = 1.51 \mu\text{V}$ ,  $\text{SE} \pm 0.51$ ) and significantly larger ( $p = 0.014$ ) compared to affective picture LPP amplitude ( $M = 1.87 \mu\text{V}$ ,  $\text{SE} \pm 0.72$ ). In patients however, there were no significant LPP differences between the different types of pictures. Although LPP amplitude for drug pictures in patients ( $M = 4.32 \mu\text{V}$ ,  $\text{SE} \pm 0.64$ ) displayed a slightly larger mean than LPP amplitude for drug pictures in controls ( $M = 3.35 \mu\text{V}$ ,  $\text{SE} \pm 0.64$ ) the groups were not significantly different in response to these pictures or to affective pictures, they only differed in their response to neutral pictures as mentioned above.

Results for the follow-up exploratory ANOVA comparing LPP amplitude for each 50 ms interval between 300-600 ms, are displayed in Table 2 below.

Table 2

Summary of significant follow-up exploratory comparisons for 50 ms intervals of the LPP response to picture cues.

Time (ms)	Main Effects and Interactions	Between Picture Types	Between Groups	In Patients	In Controls
300-350	Picture type x Group $F(2,60) = 5.59^{**}$	NS	NP (5.22 $\mu$ V $\pm$ 0.80) > NC (2.48 $\mu$ V $\pm$ 0.80)*	D (3.93 $\mu$ V $\pm$ 0.69) < N (5.22 $\mu$ V $\pm$ 0.80)*	NS
350-400	Picture type $F(2,60) = 7.84^{***}$	D (4.42 $\mu$ V $\pm$ 0.56) > N (3.19 $\mu$ V $\pm$ 0.53)* D > A (3.16 $\mu$ V $\pm$ 0.52)**	NP (4.43 $\mu$ V $\pm$ 0.74) > NC (1.95 $\mu$ V $\pm$ 0.74)*	NS	D (3.94 $\mu$ V $\pm$ 0.79) > N (1.95 $\mu$ V $\pm$ 0.74)** D > A (2.26 $\mu$ V $\pm$ 0.73)**
400-450	Picture type $F(2,60) = 16.72^{***}$	D (4.04 $\mu$ V $\pm$ 0.56) > N (2.34 $\mu$ V $\pm$ 0.41)*** D > A (2.35 $\mu$ V $\pm$ 0.55)***	NP (3.37 $\mu$ V $\pm$ 0.58) > NC (1.32 $\mu$ V $\pm$ 0.58)*	D (4.70 $\mu$ V $\pm$ 0.76) > N (3.37 $\mu$ V $\pm$ 0.58)* D > A (3.09 $\mu$ V $\pm$ 0.77)**	D (3.39 $\mu$ V $\pm$ 0.76) > N (1.32 $\mu$ V $\pm$ 0.58)*** D > A (1.61 $\mu$ V $\pm$ 0.77)**
450-500	Picture type $F(2,60) = 13.9^{***}$	D ( $M=3.64$ $\mu$ V, SE $\pm$ 0.53) > N (2.00 $\mu$ V $\pm$ 0.38)*** D > A (2.21 $\mu$ V $\pm$ 0.54)***	NP (2.95 $\mu$ V $\pm$ 0.53) > NC (1.05 $\mu$ V $\pm$ 0.53)*	NS	D (3.09 $\mu$ V $\pm$ 0.76) > N (1.05 $\mu$ V $\pm$ 0.53)** D > A (1.33 $\pm$ 0.77)**
500-550	Picture type $F(2,60) = 4.18^*$	D (3.26 $\mu$ V $\pm$ 0.55) > N (1.88 $\mu$ V $\pm$ 0.36)**	NP (2.91 $\mu$ V $\pm$ 0.51) > NC (0.86 $\mu$ V $\pm$ 0.51)**	NS	D(2.98 $\mu$ V $\pm$ 0.78) > N (0.86 $\mu$ V $\pm$ 0.51)*
550-600	Picture type $F(2,60) = 7.68^{**}$	D (4.02 $\mu$ V $\pm$ 0.47) > N (2.21 $\mu$ V $\pm$ 0.35)*** D > A (2.21 $\mu$ V $\pm$ 0.61)*	NP (3.01 $\mu$ V $\pm$ 0.49) > NC (1.41 $\mu$ V $\pm$ 0.49)*	D (4.67 $\mu$ V $\pm$ 0.66) > N (3.01 $\mu$ V $\pm$ 0.49)* D > A (2.54 $\mu$ V $\pm$ 0.86)*	D (3.37 $\mu$ V $\pm$ 0.66) > N (1.41 $\mu$ V $\pm$ 0.49)**

Notes. Mean amplitude and standard error are noted. N = Neutral, A = Affective, D = Drug, P =

Patients, C = Controls, NS = Not significant. \* $p < .05$ , \*\* $p < .01$  and \*\*\* $p < .001$ .

A main picture type effect is present at all time intervals followed by a between group difference during all intervals where neutral LPP amplitude is larger in patients compared to controls. Drug LPP is larger than affective LPP and neutral LPP for patients during the 400-450 ms interval as well as the 550-600 ms interval. In controls, drug LPP is larger than affective LPP and neutral LPP at 350-500ms and the drug LPP remains larger than neutral LPP from 500-600ms post-stimulus onset.

### 4.2.3 Picture Ratings

Mean ( $\pm$  SE) scores for valence, arousal, personal association and drugs cravings from the picture-rating questionnaire are depicted in Table 3.

Table 3

*Mean and standard error for self-reported scores on picture rating questionnaire*

Picture Type	Group	Valence	Arousal	Personal Association	Drug Cravings
Neutral	Patient	4.94 $\pm$ 0.72	2.46 $\pm$ 1.37	3.09 $\pm$ 1.53	12.63 $\pm$ 5.59
Neutral	Control	5.68 $\pm$ 1.12	1.78 $\pm$ 0.70	3.89 $\pm$ 1.42	N/A
Affective	Patient	4.68 $\pm$ 0.80	5.78 $\pm$ 1.45	3.56 $\pm$ 1.08	13.94 $\pm$ 5.64
Affective	Control	4.89 $\pm$ 0.67	5.92 $\pm$ 1.71	3.77 $\pm$ 1.20	N/A
Drug	Patient	4.84 $\pm$ 1.82	6.37 $\pm$ 1.85	5.58 $\pm$ 1.81	40.09 $\pm$ 7.62
Drug	Control	2.70 $\pm$ 1.12	4.29 $\pm$ 2.20	1.60 $\pm$ 1.03	N/A

*Notes.* Valence, Arousal and Personal Association were rated on a scale from 1-9 and Drug Cravings were rated on a scale from 0-100%. Drug cravings in controls were not assessed.

#### 4.2.3(a) Valence Ratings

Mean ( $\pm$  SE) valence scores for each picture type are shown for patients and controls in Figure 11. There was a main picture type effect reported for mean valence ratings  $F(2,60) = 15.77, p < 0.001$ , in addition to a main picture  $\times$  group effect  $F(2,60) = 15.14, p < 0.001$ . Follow-up comparisons revealed that affective pictures ( $M = 4.78, SE \pm 0.13$ ) had a significantly ( $p = 0.048$ ) lower reported valence compared to neutral pictures ( $M = 5.31, SE \pm 0.17$ ). Reported valence for drug pictures ( $M = 3.77, SE \pm 0.27$ ) was also significantly ( $p < 0.001$ ) lower compared to reported valence for neutral pictures and significantly ( $p = 0.005$ ) lower than reported valence for affective pictures ( $M = 4.78, SE \pm 0.13$ ).

Follow-up group comparisons for picture type revealed that for neutral pictures, patients reported a significantly ( $p = 0.035$ ) lower valence ( $M = 4.94, SE \pm .24$ ), compared to controls ( $M = 5.68, SE \pm 0.237$ ) and for drug pictures, patients reported a significantly ( $p < 0.001$ ) higher valence ( $M = 4.84, SE \pm 0.38$ ), compared to controls ( $M = 2.70, SE \pm 0.38$ ).

Follow-up comparisons in controls revealed that valence scores for neutral pictures ( $M = 5.68, SE \pm 0.24$ ) were significantly ( $p = 0.034$ ) higher compared to valence scores for affective pictures ( $M = 4.89, SE \pm 0.19$ ) and significantly ( $p < 0.001$ ) higher than valence scores for drug pictures ( $M = 2.70, SE \pm 0.38$ ). There were no significant differences between reported valences for different pictures types in the patient group.

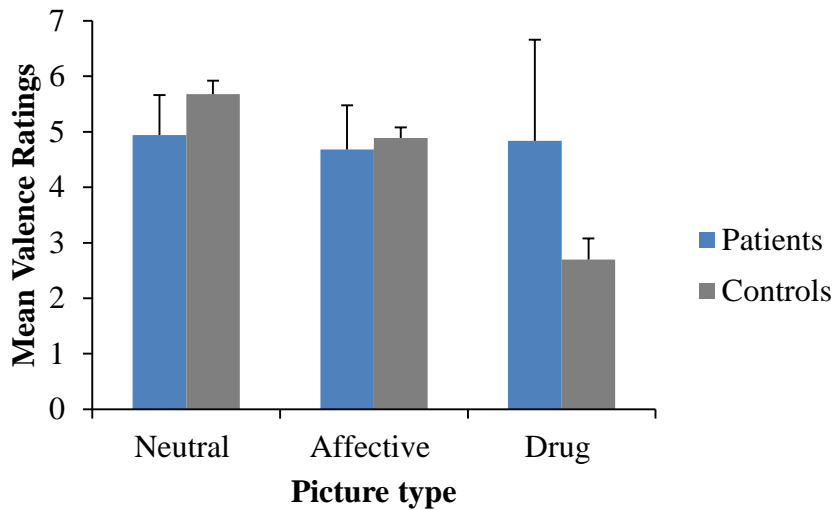


Figure 11. Mean ( $\pm$  SE) and standard error for valence scores by picture type reported in patients and controls.

#### 4.2.3(b) Arousal Ratings

Mean ( $\pm$  SE) arousal scores for each picture type are shown for patients and controls in Figure 12. There was a main picture type effect reported for arousal ratings  $F(2,60) = 87.20, p < 0.001$ , in addition to a main picture  $\times$  group effect  $F(2,60) = 6.70, p = 0.003$ . Follow-up comparisons revealed that drug pictures had a significantly ( $p < 0.001$ ) higher reported arousal rating ( $M = 5.33, SE \pm 0.36$ ) compared to reported arousal ratings for neutral pictures ( $M = 2.12, SE \pm 0.19$ ) and affective pictures had a significantly ( $p < 0.001$ ) higher reported arousal ratings ( $M = 5.85, SE \pm 0.28$ ) compared to neutral pictures ( $M = 2.12, SE \pm 0.19$ ). Follow-up comparisons between groups revealed that for drug pictures, patients reported significantly ( $p = 0.007$ ) higher arousal ratings ( $M = 6.37, SE \pm 0.51$ ), compared to controls ( $M = 4.29, SE \pm 0.51$ ). No group differences were observed for neutral or affective picture arousal scores.

Follow-up comparisons in the control group demonstrated that affective pictures ( $M = 5.92, SE \pm 0.40$ ) had significantly ( $p < 0.001$ ) higher reported arousal ratings compared to neutral

pictures ( $M = 1.78$ ,  $SE \pm 0.27$ ) and significantly ( $p = 0.001$ ) higher reported arousal ratings than drug pictures ( $M = 4.29$ ,  $SE \pm 0.51$ ). Additionally, drug pictures had significantly ( $p < 0.001$ ) higher reported arousal ratings than neutral pictures. Similarly, in the patient group, affective pictures ( $M = 5.78$ ,  $SE \pm 0.40$ ) also had significantly ( $p < 0.001$ ) higher arousal ratings compared to neutral pictures ( $M = 2.46$ ,  $SE \pm 0.27$ ) and drug pictures ( $M = 6.37$ ,  $SE \pm 0.51$ ) had significantly ( $p < 0.001$ ) higher reported arousal ratings than neutral pictures ( $M = 2.46$ ,  $SE \pm 0.27$ ), but not affective pictures.

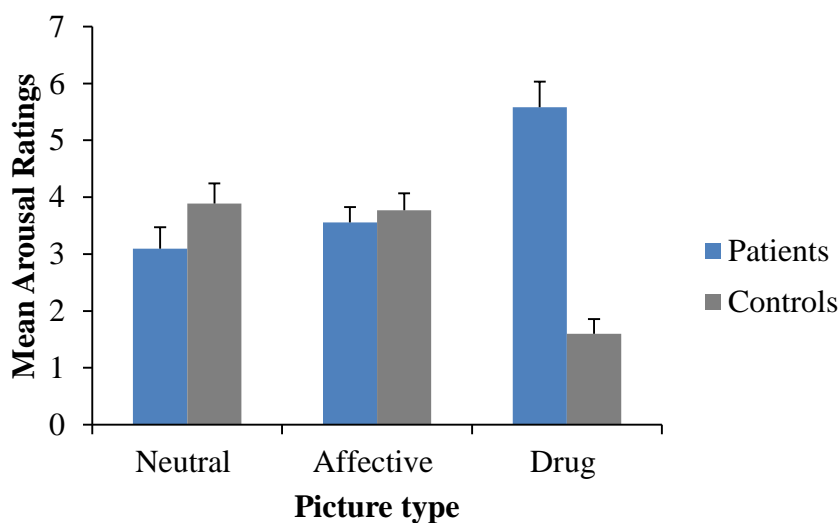


Figure 12. Mean and standard error for arousal scores by picture type reported in patients and controls.

#### 4.2.3(c) Personal Association Ratings

There was a main picture x group effect for mean personal association ratings  $F(2,60) = 49.18$ ,  $p < 0.001$ . Follow-up comparisons revealed that patients ( $M = 4.08$ ,  $SE \pm 0.27$ ) reported significantly ( $p = 0.014$ ) higher personal association to all pictures compared to controls ( $M = 3.09$ ,  $SE \pm 0.27$ ). For drug pictures, patients ( $M = 5.58$ ,  $SE \pm 0.37$ ) reported a significantly ( $p <$

0.001) higher personal association compared to controls ( $M = 1.60$ ,  $SE \pm 0.37$ ). There were no significant group differences between personal association ratings for neutral or affective pictures. In controls, drug pictures had significantly ( $p < 0.001$ ) lower personal association ratings than neutral pictures ( $M = 3.89$ ,  $SE \pm 0.37$ ) and significantly ( $p < 0.001$ ) lower personal association ratings than affective pictures ( $M = 3.77$ ,  $SE \pm 0.29$ ). Contrarily in patients, drug pictures had significantly ( $p < 0.001$ ) higher personal association ratings than neutral pictures ( $M = 3.09$ ,  $SE \pm 0.37$ ) and significantly ( $p < 0.001$ ) higher personal association ratings than affective pictures ( $M = 3.56$ ,  $SE \pm 0.29$ ).

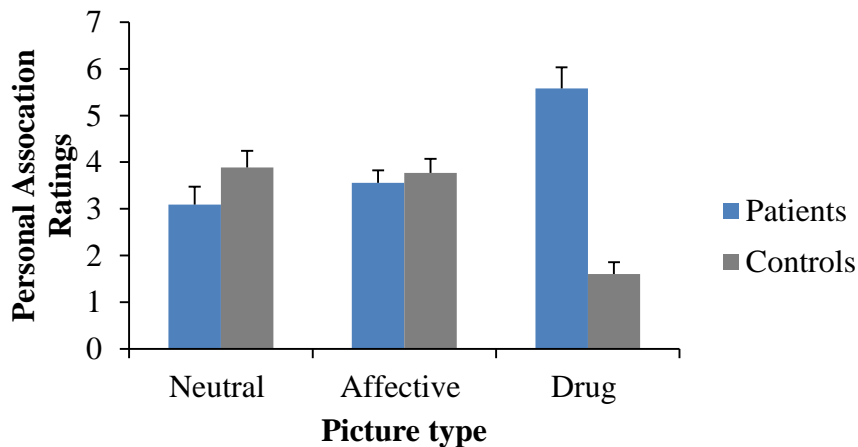


Figure 13. Mean and standard error for arousal scores by picture type reported in patients and controls.

#### 4.2.3(d) Craving Ratings in Patients

There was a main picture type effect for self-reported craving ratings in patients  $F(2,30) = 19.88$ ,  $p < 0.001$ . Patients reported significantly ( $p = 0.001$ ) higher cravings towards drug pictures ( $M = 40.09\%$ ,  $SE \pm 7.63$ ) compared to neutral pictures ( $M = 12.63\%$ ,  $SE \pm 5.59$ ) and significantly ( $p = 0.002$ ) higher drug craving ratings compared to craving ratings for affective

pictures ( $M = 13.94\%$ ,  $SE \pm 5.64$ ). No significant differences were found in patients between reported cravings towards neutral and affective pictures.

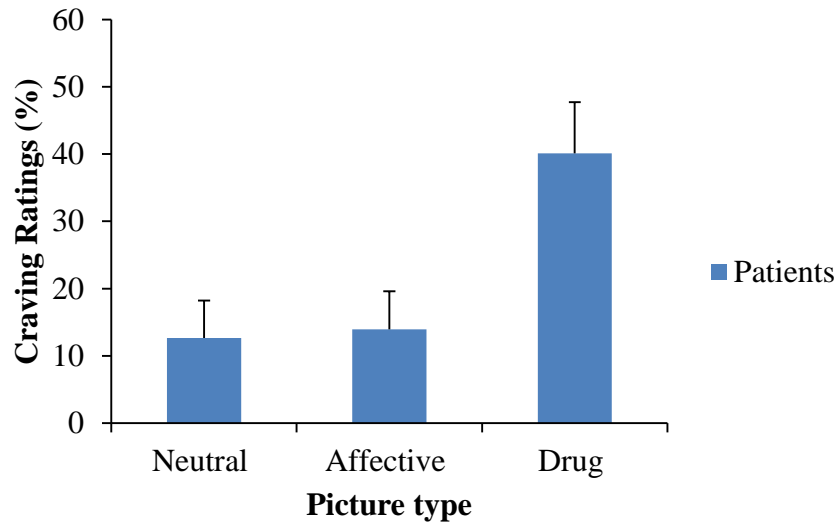


Figure 14. Mean and standard error for craving ratings by picture type reported in patients only.

#### 4.2.4 P2 and Picture Ratings Correlations

There were no significant correlations between P2 amplitude and picture ratings scales (valence, arousal, personal association and drug cravings) for patients or controls.

#### 4.2.5 LPP and Picture Ratings Correlations

A significant ( $p < 0.05$ ) positive correlation (0.50) was found between the LPP and arousal ratings for drug pictures in patients only (Figure 15). There were no significant LPP-arousal correlations found in either group for neutral and affective pictures. There were also no significant correlations between LPP amplitude and valence, personal association or drug cravings ratings for both groups.

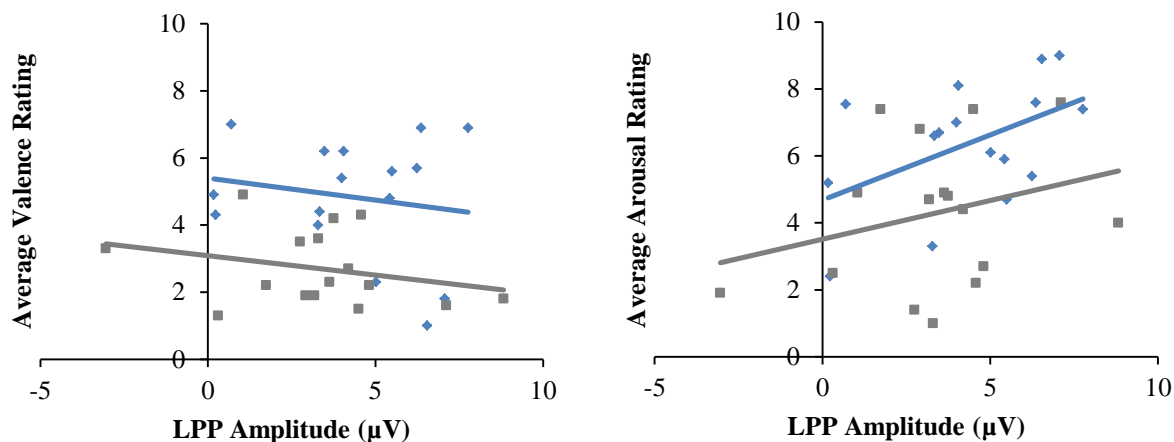


Figure 15. Correlations between LPP amplitude and average valence (a) and arousal (b) ratings for drug pictures in patients (blue) and controls (grey).

#### 4.2.6 N1 Amplitude and Latency – Exploratory Findings

There was a main picture type effect observed for N1 amplitude  $F(2,60) = 11.60, p < 0.001$ . Follow-up comparisons revealed that N1 amplitude for drug pictures ( $M = -1.41 \mu\text{V}, SE \pm 0.50$ ) was significantly ( $p = 0.006$ ) smaller than N1 amplitude for neutral pictures ( $M = -2.70 \mu\text{V}, SE \pm 0.70$ ) and significantly smaller ( $p = 0.001$ ) than N1 amplitude for affective pictures ( $M = -3.35 \mu\text{V}, SE \pm 0.78$ ). Although a picture type  $\times$  group interaction was not observed, the picture type effects were more noticeable in the control group as N1 amplitude for drug pictures ( $M = -1.91 \mu\text{V}, SE \pm 0.706$ ) was significantly ( $p = 0.029$ ) smaller than N1 amplitude for neutral pictures ( $M = -3.39 \mu\text{V}, SE \pm 0.99$ ) amplitudes and significantly smaller ( $p = 0.017$ ) than N1 amplitude for affective pictures ( $M = -3.86 \mu\text{V}, SE \pm 1.10$ ). In the patient group by contrast, N1 amplitude for drug pictures ( $M = -0.92 \mu\text{V}, SE \pm 0.71$ ) was significantly ( $p = 0.020$ ) smaller than N1 amplitude for affective pictures ( $M = -2.84 \mu\text{V}, SE \pm 1.10$ ) but not neutral pictures.

There were no significant differences for N1 latency between groups or pictures types.

#### 4.2.7 P1 Amplitude and Latency – Exploratory Findings

There was a main picture type effect observed for P1 amplitude  $F(2,60) = 4.37, p = 0.024$ . Follow-up comparisons revealed that P1 amplitude for drug pictures ( $M = 2.24 \mu\text{V}, SE \pm 0.39$ ) was significantly ( $p = 0.003$ ) larger than P1 amplitude for affective pictures ( $M = 1.42 \mu\text{V}, SE \pm 0.43$ ). A picture type  $\times$  group interaction was not shown in the analysis but in the patient group, P1 amplitude for drug pictures ( $M = 2.89 \mu\text{V}, SE \pm 0.55$ ) was significantly ( $p = 0.014$ ) larger than P1 amplitude for affective pictures ( $M = 1.91 \mu\text{V}, SE \pm 0.61$ ) and neutral picture amplitudes ( $M = 3.08 \mu\text{V}, SE \pm 0.77$ ) were significantly larger ( $p = 0.03$ ) than affective picture amplitudes. There were no significant picture type differences in the control group for P1 amplitude.

There was also a main picture type effect observed for P1 latency  $F(2,60) = 4.46, p = 0.024$ . Follow-up comparisons revealed that P1 latency for drug pictures ( $M = 118 \text{ ms}, SE \pm 4.06$ ) was significantly ( $p = 0.025$ ) later than P1 latency for affective pictures ( $M = 104 \text{ ms}, SE \pm 3.92$ ) but not for neutral pictures ( $M = 111 \text{ ms}, SE \pm 4.77$ ). Their latency differences were only seen in the patient group with P1 latency for drug pictures ( $M = 123 \text{ ms}, SE \pm 5.74$ ) being significantly ( $p = 0.014$ ) later than P1 latency for affective pictures ( $M = 102 \text{ ms}, SE \pm 5.54$ ).

#### 4.3 Questionnaire Data

Patients ( $M = 12.56, SE \pm 0.96$ ) scored significantly ( $p = 0.01$ ) higher on the attention scale of the BIS-11 than controls ( $M = 9.19, SE \pm 0.77$ ). Patients ( $M = 18.19, SE \pm 1.22$ ) scored significantly ( $p = 0.03$ ) higher on the motor scale of the BIS-11 than controls ( $M = 15.13, SE \pm 0.60$ ). Patients ( $M = 14.88, SE \pm 1.01$ ) scored significantly ( $p = 0.01$ ) higher on the non-planning (self-control) scale of the BIS-11 than controls ( $M = 11.56, SE \pm 0.683$ ). Patients ( $M = 10.75, SE \pm 1.731$ ) scored significantly ( $p < 0.001$ ) higher on the GAD 7 compared to controls ( $M = 2.50, SE \pm 0.811$ ), where a mean score of 10.75 indicates moderate anxiety and probably diagnosis of

GAD and a mean score of 2.50 indicates no symptoms of anxiety. Patients ( $M = 12.00$ ,  $SE \pm 2.12$ ) scored significantly ( $p < 0.001$ ) higher on the PHQ 9 compared to controls ( $M = 3.00$ ,  $SE \pm 0.82$ ), where a mean score of 12.00 indicated minor depression, dysthymia and major depression (mild) and a mean score of 3.00 indicates no symptoms of depression.

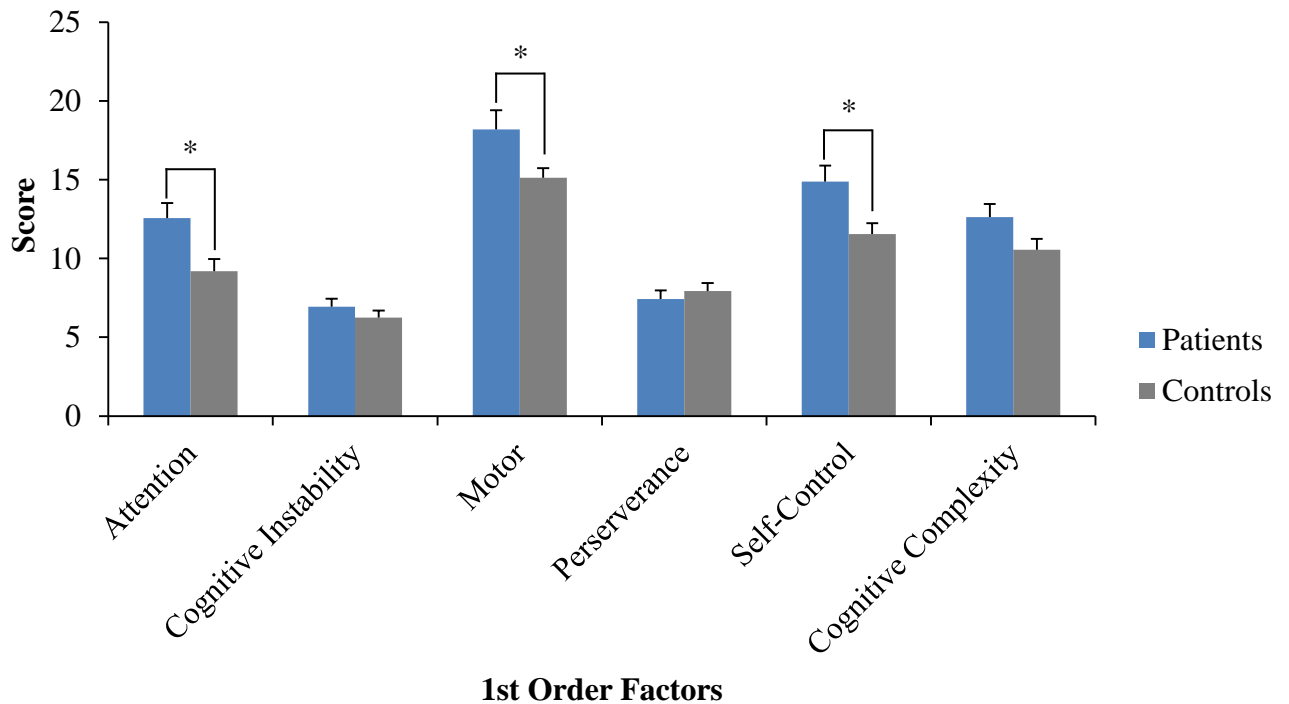


Figure 16. Mean ( $\pm$  SE) and standard error for BIS-11 self-report questionnaire in patients and controls. \*  $p < 0.05$

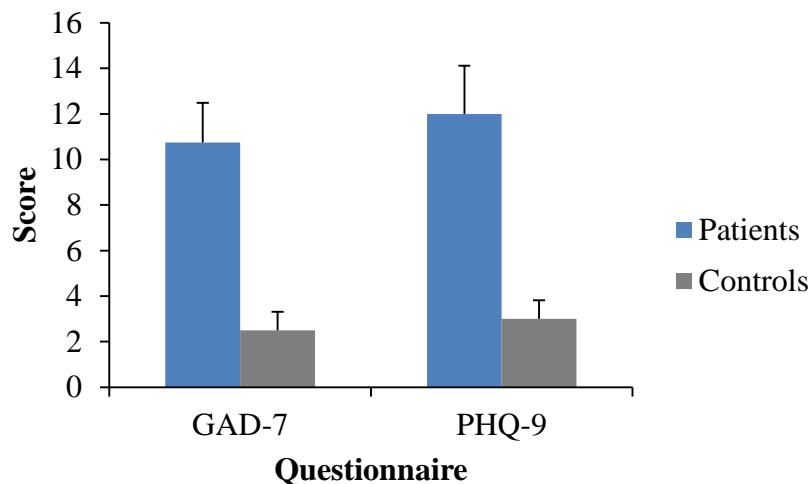


Figure 17. Mean ( $\pm$  SE) and standard error for mood and anxiety self-report questionnaires in patients and controls.

## 5.0 Discussion

The aim of the present pilot study was to examine inhibitory control and attentional bias deficits in actively using prescription opioid-dependant individuals by measuring ERP correlates of cognitive control. Inhibitory control was measured using a Go/NoGo paradigm, indexed by N2 and P3 ERPs whereas attentional bias was assessed using a cue reactivity paradigm, indexed by P2 and LPP ERPs. To date, there have been no studies of cognitive control in PO-dependant individuals.

### 5.1 Patient Sample and Demographics

Working with a SUD population has innate difficulties (i.e. reduced motivation, low commitment, etc.) that contributed to smaller recruitment numbers. After two years of patient recruitment, 18 SUD patients were successfully consented into the study and two were excluded during data analysis, therefore a total of 16 SUD patients were included into the final study

number. The total number of eligible patients consented was 45, and it was difficult motivating individuals to follow up with their planned EEG testing session. Multiple reminder strategies were utilized (i.e. booking EEG session with next clinical appointment, consenting at first clinic visit, reminder cards, etc.) and a slight increase in follow-up rates occurred after administering these strategies, however it was still a persistent recruitment issue. It is important to note that recruited individuals were actively using opioids and seeking assistance for detoxing from opioids, therefore their mindset is likely different from an individual who is actively using and does not wish to discontinue drug use. Furthermore, many studies in SUD populations examine individuals who are abstinent drug users and are consequently at a different stage in the SUD cycle compared to our actively using sample. Individuals who have recently abstained from using drugs, are likely in the “drug craving” stage of the I-RISA Syndrome of Drug Addiction proposed by Goldstein and Volkow (2002) where activation of the orbitofrontal circuit, anterior cingulate amygdala and hippocampus are heightened as the learned response is encoded linking the substance to its relative sensation and environment (Brown and Fibiger, 1993; Franklin and Druhan, 2000; Meil and See 1997; Volkow et al., 1999). Consequently, active drug users are more likely in the “drug intoxication” stage where acute and short-term drug use leads to increased dopaminergic signalling in the nucleus accumbens and other frontal regions (Goeders and Smith, 1986; Hurd and Ungerstedt, 1989; Ritz et al., 1987). The differing neurobiology between these two stages may result in varying cognitive states between individuals, therefore results from studies with abstinent users should be interpreted with caution when generalizations are made concerning actively using individuals with SUD.

With a smaller sample size, it was not possible to perform some of the analyses that may have yielded a more complete picture of neural alterations in SUD. For example, in our sample,

there was a mixed use demographic where some patients have a much longer use duration compared to others, varying drug choice (i.e. oxycodone, fentanyl, morphine, etc.), drug use pattern (i.e. swallowing, inhalation, intravenous) and time between last use and EEG testing, all differed between patients and are important factors to consider during analysis. The abuse potential liability of a prescription opioid depends on its pharmacokinetics and route of administration (Farre and Cami, 1991). In order to obtain the greatest level of euphoria (i.e. “high”), drug users will aim for the ideal ratio between blood concentration of the PO and time required for euphoria onset (Katz et al., 2011). The prescribed route of a PO will give an individual a high blood concentration ( $C_{max}$ ) and short euphoric onset ( $T_{max}$ ) and some POs can be easily abused by altering either of these two factors (i.e. taking POs above their recommended dose, altering their prescribed route of administration, etc.) (Marsch et al., 2001; Volkow et al., 1995; 2000). For example, extended-release formulations, such as fentanyl transdermal patches, are commonly tampered with in order to obtain a quicker and more intense drug high and consequently have the potential to be more potent and abused more frequently than other types of POs (Katz et al., 2011). However, some drugs such as oxycodone, hydrocodone and hydromorphone, do not differ in terms of their relative potency and abuse potential (Walsh et al., 2008). Furthermore, repeated opioid abuse induces tolerance and increases long-term neural alterations. Imaging studies in humans have demonstrated a positive correlation between reductions in D2 receptor binding and duration of opioid abuse (Wang et al., 1997; Zijlstra et al., 2008) in opioid-dependant individuals and similarly in animal models and post-modern studies, opioid gene expression in behaviour and reward brain regions were significantly altered, suggesting that the length of abuse may result in varying cognitive impairments. In future

studies, it would be valuable to stratify the sample into smaller groups based length of use and patterns of drug abuse.

Table 1 in the methods section outlines the positive urine screen results indicating which substances were being used, the time between the urine screen and EEG session and the self-reported time since last drug use and EEG session. Since the patients included in this study were actively using and seeking help to stop abusing drugs, it would have been unethical to ask for a urine screen the day of EEG testing since clinicians were concerned this would deter patients from continuing through the detoxification program. This also meant that patients could refuse a drug screen until they were in the non-using phase of treatment, when urine tests became mandatory. In order to account for this, before each EEG session patients were asked when they last used opioids and after completing the cue reactivity paradigm, individuals completed the DDQ. The DDQ is a commonly used self-report measure of drug craving and its' scales have good reliability and concurrent validity (Franken, Hendriks and van den Brink, 2002). Although it's impossible to ensure patients were forthcoming about their recent drug use, it was observed that most of the time, patients did not hesitate to answer the question as they were told that it would not be communicated with the clinical team. Self-reports of drug use have also demonstrated respectable reliability and validity to provide behavioural descriptions of drug use patterns (Darke, 1998). Upon review of the questionnaire data, the subjective state of mind of the individual can be assessed. Question 14 asks "I would accept to use opioids now if it was offered to me" where 1 indicates, "strongly disagree" and 5 indicates, "strongly agree". Only 2 patients indicated either "strongly disagree", "disagree" or "neither agree nor disagree" whereas 13 chose either "agree" or strongly agree". Similarly question 6 asks, "Using opioid would be pleasant now" where 5 patients indicated either "strongly disagree", "disagree" or "neither agree nor

disagree” and 11 patients chose either “agree” or strongly agree”. This suggests that the majority of patients had a current desire to use opioids during their EEG session, regardless of when they actually last used opioids.

Before reviewing the ERP literature, it is important to note that since limited research is available on PO abuse, studies conducted with other SUD populations are used as a guide to interpret the present results. A significant portion of the available studies are also conducted with abstinent users, which reflect a different psychological and physiological state (as previously described) than the patients included in the present study.

## **5.2 Go/No Go and Impulse Control**

N2 and P3 amplitudes were measured in patients and matched healthy controls completing a Go/NoGo paradigm designed to assess impulse control. NoGo-N2 amplitudes were significantly larger compared to Go-N2 amplitudes in both patients and controls and similarly, NoGo-P3 amplitudes were significantly larger compared to Go-P3 amplitudes in both groups, indicating the task elicited the expected neural response in both groups (Eimer, 1993). There were no observed differences between groups for both NoGo-N2 and NoGo-P3 amplitudes and behavioural measures (i.e. reaction time and response accuracy) also did not differ between groups. As presented in the introduction, there are many studies in SUD populations that did not find any ERP differences (Buzzell et al., 2014; Evans et al., 2009; Kamarajan et al., 2005; Luijten et al., 2011; Oddy and Barry 2009; Yang et al., 2009) nor behavioural effects (Buzzell et al., 2014; Lawrence et al., 2009; Luijten et al., 2014) between SUD individuals and healthy controls. Interestingly, one study assessed P3 amplitudes using a short-term memory task and found that P3 amplitudes were smaller in abstinent heroin users, but no significant differences

were found between current heroin users and healthy controls (Papageorgiou et al., 2004). Similarly, Kouri and colleagues (1996) did not observe any differences in N2 or P3 amplitude or latency between actively using drug-dependent individuals and healthy controls however, following detoxification, P3 amplitudes were significantly reduced in the drug-dependant group. These findings suggest that the acute drug state of the individual has a significant effect on the observed ERP alterations.

Specifically in the present patient group, it is possible that acute and mild opioid administration may actually stabilize an individuals' acute cognitive state and consequently their performance on cognitive assessments is similar to non-drug users. The current results are consistent with literature on opioid normalization as a result of regular drug use, where individuals perform normally without any significant impairment on neuropsychological measures (Davis et al., 2002; Grant et al., 2000; Mintzer et al., 2005; Verdejo-Garcia et al., 2004). Another possibility is that baseline ERP markers of inhibitory processing in individuals with SUD are lower than in healthy non-drug users and opioids help normalize their ERPs (Kouri, 1996). This effect is commonly observed in individuals with schizophrenia (Dulude et al., 2010), Alzheimer's (Engeland et al., 2002), cannabis users (Impey et al., 2015) and individuals with other cognitive impairments (Knott et al., 2012; 2014) whose baseline ERPs are lower than healthy controls and after acute nicotine administration, normalization of their ERPs occur. Nicotine is believed to have cognitive enhancing effects by increasing fronto-parietal-thalamic (Newhouse et al., 2004), cortical (ACC) and subcortical (NAc and amygdala) activation (Lawrence et al., 2002) by targeting nicotinic acetylcholine receptor signalling pathways (Dajas-Bailador and Wonnacott, 2004), significantly overlapping key brain regions in the dopaminergic reward system. Recent studies show that opioid and nicotinic-cholinergic neurotransmitter

systems interact whereby nicotine-modulated DA release is dependent on the opioid system and self-administration of opioids is modulated in part by the nicotinic-acetylcholine system (Britt and McGehee, 2008; Yoon et al., 2015; Xue and Domino, 2008). Furthermore, both nicotine and opioids increase extracellular DA by inducing VTA neuronal burst firing (Erhardt et al., 2002; Kiyatkin and Rebec, 2001), supporting the theory that similar neuro-alterations in signalling pathways after acute opioid and nicotine administration account for ERP similarities between both substances.

Of interest is the finding of a significant positive correlation between patient NoGo-P3 amplitude at CPz and both the attention and cognitive instability scales of the BIS-11, two first order factors encompassing the higher second order factor of “attention”. High scores on these factors is often defined as “attentional impulsiveness” and interpreted as an index of attentional control (Stanford et al., 2009). One explanation for this finding would suggest that individuals who subjectively indicate experiencing a greater level of cognitive instability ultimately employ a larger number of cognitive resources during a task requiring a high degree of attention, resulting in larger NoGo-P3 amplitudes. As NoGo stimuli are presented less frequently than Go stimuli, it has been proposed that NoGo-P3 may also index overall attentional engagement (Kok, 2001; Polich, 2007) and this interpretation is further supported by the lack of behavioural performance differences (Buzzell et al., 2014).

### **5.3 Cue Reactivity and Attentional Bias**

Attentional processing in PO-dependent individuals was assessed using a passive cue reactivity paradigm containing neutral, affective and PO-related stimuli and ERP indices of attention (P2 and LPP) were compared to matched healthy controls. In patients only, P2

amplitude was significantly smaller for drug stimuli, compared to neutral and affective pictures and no significant differences in P2 amplitudes were found between stimuli types in controls. For LPP amplitudes, between group differences were only noted for neutral stimuli, where patients demonstrated a significantly larger LPP for neutral pictures, compared to controls. In controls, LPP amplitude was larger for drug stimuli (vs. neutral and affective) but this was not observed in patients. Picture rating scales assessing valence found that patients reported a higher valence for drug pictures compared to controls and similarly reported a higher arousal rating for drug pictures (vs. controls). Controls rated affective pictures as the most arousing, followed by drug pictures and the least arousing were neutral pictures. Patients also rated affective pictures as more arousing than neutral pictures and drug pictures more arousing than neutral pictures but there were no differences in arousal ratings between drug and affective stimuli in patients. For IAPS pictures (neutral and affective), valence and arousal scores reported by patients and controls did not significantly differ from IAPS standardized rating scores. Correlational analyses revealed a significant positive correlation between drug stimuli LPP and arousal ratings for drug pictures in patients only.

Evaluating the stimuli used in this paradigm is crucial as the selection of pictures can significantly alter ERP findings (Franken et al., 2004). One limitation of the present study is that opioid stimuli were not taken from a standardized database (i.e. IAPS) therefore self-reported measures of valence and arousal of our stimuli is unknown. This is common practice in SUD studies, as the IAPS database does not have a large selection of drug stimuli, especially for prescription opioids. The stimuli selected for the present cue reactivity task was reflective of the characteristics of the SUD population in our hospital (i.e. 60% of patients abuse PO's orally, therefore 60% of PO images represent oral use) however some type of substance abuse may be

perceived differently among patients, especially for intravenous (IV) use. IV use of POs is the least common method of PO abuse (Katz et al., 2011) and is often perceived negatively among non-IV users. Another study found that PO abusers experienced greater cravings towards drug stimuli that contained the actual substance compared to drug paraphernalia (McHugh et al., 2016). Furthermore, the affective state of the participant has also been shown to be an important factor influencing individual cue-reactivity (Rees and Heather 1995). Allocating different affective values to stimuli, which may also depend on the subjective affective state of the individual, are factors that subsequently effect neurocognitive reactions (i.e. ERPs) towards drug stimuli.

Interestingly, the only significant P2 modulation occurred in patients, where drug P2 was significantly smaller than neutral P2 and affective P2. In cue-reactivity paradigms, the P2 is believed to index the initial attention selection and identification of task-relevant stimuli (Potts et al., 2006; Roberts et al., 2013; Schupp et al., 2006) and the literature is mixed as some studies have reported an increase in drug-P2 amplitude while others report no differences in P2 amplitude between stimulus types however, no studies to date show a decrease in drug P2 in SUD populations. P2 amplitude is sensitive to the emotional value assigned to a stimulus (i.e. valence) with inputs from the sensory cortex and ACC (Carretié et al., 2004). It is possible that current PO abusers may no longer perceive PO and PO-related stimuli as emotionally-relevant since they are actively seeking out detoxification assistance at the time of EEG testing and subsequently rate PO stimuli as having low emotional significance. Analysis of self-reported valence scores in our sample supports this theory as there were no significant differences in valence between stimulus types in patients and mean drug valence scores for patients was  $4.84 \pm 1.82$ , indicating a “neutral” assessment. Therefore, the current mental state of the PO abuser

likely affects the emotional valence assigned to the stimuli and ultimately influences P2 modulation.

Patients did not demonstrate the predicted LPP response to drug stimuli and controls demonstrated a sustained enlargement of drug LPP compared to neutral and affective LPP however, there were no significant differences in drug LPP between groups. The absence of effects in patients could have been caused by a lack of power, as the sample size in each group only included 16 participants and it may have also been influenced by the current motivation and affective state of the patients as these individual differences have been demonstrated to have an effect on late ERP components (Littel et al., 2012). Therefore, the assumption can be made that individuals who are highly motivated to seek out drugs for consumption, will differ in LPP amplitude compared to individuals that are not highly motivated and these individuals are likely healthy non-drug users but could also be PO abusers whose drug craving has already been satisfied. The present correlational analyses support this theory as a significant positive relationship was observed between LPP amplitude and drug stimuli arousal ratings in patients therefore patients who reported higher arousal scored towards PO stimuli also had larger LPP amplitudes. Patients also rated drug stimuli as more arousing and expressed greater personal association towards drug cues compared to neutral cues, however, patients did not rate drug pictures as being more pleasant (higher valence) than neutral pictures. The lack of differential valence scores is reflected in the ERP data as no significant differences were observed between drug LPP and neutral/affective LPP. The current drug use state of the individual is likely influencing these results since they are actively using prescription opioids and may not perceive substances as overly pleasant or unpleasant as their drug craving has been satisfied.

Although there were no significant correlations between LPP amplitude and scores of the GAD-7 and PHQ-9, patients mean scores on both questionnaires indicate moderate anxiety and mild-major depressive symptomology, consistent with reports of high co-morbidity rates of anxiety and mood disorders in SUD (Goldner et al., 2014; Strain, 2002). Affective state has demonstrated a strong ability to modulate LPP amplitude, with studies showing a reduction in LPP amplitudes in depressed (Pelosi et al., 2000; Proudfit et al., 2015; Shestyuk et al., 2005; Weinburg et al., 2016) and anxious (MacNamara et al., 2011) individuals and a reduced ability to process emotionally relevant stimuli (Clark and Watson, 1991; Dichter and Tomarken, 2008; Foti et al., 2010; Proudfit et al., 2015; Weinburg et al., 2016; Wexler et al., 1994). Furthermore, hypoactivation in the prefrontal cortex, especially dorsolateral and dorsoventral brain regions, is a predominant feature of major depressive disorder (MDD) (Kimbrell et al., 2002; Rigucci et al., 2012). The ACC and DLPFC, two crucial brain regions in the dopaminergic reward pathway, have also shown decreased activity in MDD (Pandya et al., 2012), whereas hyperactivation of these areas occur in SUD, therefore PO use may be a compensatory mechanism in depressed PO-abusers to increase dopaminergic signalling in affected brain regions.

Jang and colleagues (2007) observed similar findings where the effect of stimuli was not significant in smokers and argue that baseline ERPs, especially later components such as the P300 and LPP, are on average 5  $\mu$ V smaller than non-smokers (Anokhin et al., 2000). Although no similar studies have been conducted in PO-dependant populations, due to the overlapping neurocircuitry of nicotine and opioids, it may be deduced that similar effects are likely seen in PO-abusers, where their baseline ERPs are smaller than non-drug users, resulting in a reduced effect of stimuli on LPP amplitude. The enhanced processing of drug cues by controls can be explained by literature demonstrating an increase in the P300 component in response to both

pleasant and unpleasant stimuli with drug cues being encoded as unpleasant in non-user populations (Hajcak et al., 2010). Drug stimuli may be perceived as novel to non-users and subsequently increase LPP modulation in PO-naïve individuals.

Another unpredicted finding in patients was the absence of LPP enhancement towards affective pictures compared to neutral pictures. Lubman and colleagues (2008) also found no ERP enhancement towards affective stimuli and proposed that in SUD, individuals may experience a reduced sensitivity to rewarding and affective stimuli. One potential contributing factor is the high scores of depression in the present study sample as individuals with depressive symptomology demonstrate a reduced ability to process emotionally relevant stimuli, as previously discussed. Particularly in our picture set, positive and negative affective pictures were included together as emotionally salient stimuli and may have subsequently collapsed ERP effects. Data from studies comparing negative (unpleasant) and positive (pleasant) stimuli have demonstrated enhanced attentional processing towards negative cues compared to positive cues (Smith et al., 2003) and is further supported by neuroimaging studies showing greater amygdala activation towards negative (vs. positive and neutral) pictures (Straube et al., 2008).

#### **5.4 Limitations**

The present results may have implications for prescription opioid use disorder; however there are several study limitations to consider. First, the naturalistic study design has inherent restrictions, as some important factors could not be controlled, such as the time between last PO use and EEG session, co-morbid mental health disorders and current medications. Of particular concern is the varied time between most recent drug use and EEG recording since the duration ranges from a couple hours to more than 24 hours. Ensuring a positive drug urine screen the

morning of the EEG session would help reduce any drug confounds and future studies should include this procedure in ethics proposals. That being said, it's important to ensure the patient is not excessively intoxicated where they are unable to perform any cognitive tasks. Furthermore, the sample size was relatively small and may have not generated sufficient power to allow for generalizations to the overall SUD population, therefore results should be interpreted with caution. The current population was also non-abstinent and non-withdrawal whereas most of the literature is conducted in abstinent SUD individuals and in abusers using other classes of substances (i.e. cocaine, heroin, cannabis, etc.). The lack of literature on the present sample makes it difficult to yield appropriate hypotheses and consistent results. In order to account for some variability, controls were matched on the highest numbers of factors possible including smoking status (nicotine and marijuana), education, age and gender.

To address these issues in the future, studies may wish to consider fast-acting routes of administration, such as inhalation or intravenous methods and subsequently stratify patients into drug use categories based on their drug use patterns and lifetime duration of substance use. Increasing the number of participants would yield stronger power but would also require a longer study duration to insure the appropriate sample size. Broadening the depth of the study to include various phases of SUD would also be extremely beneficial in understanding the various neurological mechanisms contributing to the different stages of SUD.

## **6.0 Conclusion**

Prescription opioid abuse is a growing epidemic in Canada with limited brain-based research on the neurocognitive consequences of sustained use. Although there were no clear alterations in incentive salience and inhibitory control mechanisms in non-abstinent PO users, correlational analysis showed unique relationships between ERPs and ratings, suggesting that there are individual differences in the way PO abuse affects the brain-behaviour relationships. Further research is required to understand the neurocognitive processes that play a role in opioid use disorder, specifically during each stage of SUD (i.e. non-abstinent, non-withdrawal, active withdrawal, sustained abstinence) and the potential for ERPs to be used as neurocognitive markers to predict successful outcomes for PO-addicted individuals.

## 7.0 References

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