Neural Correlates of Marijuana Addiction: Differences in the Processing of Drug-Related and Emotional Pictures Between Addicted Versus Healthy Controls

by
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Abstract

This project aims to understand the electrophysiology and neuropsychology of emotion and drug stimulus processing in marijuana addicts relative to healthy participants. In addition to reviewing neuroimaging findings that attempt to understand the temporal processing of emotion stimuli, current findings related to understanding the neural correlates of addiction behaviour are reviewed and the structure and function of neural regions implicated in this disorder are highlighted. This literature review provides a basis for the current study, where high density EEG is used in conjunction with a modified drug-Stroop paradigm to understand the timing of neural events that are associated with cue reactivity to salient visual stimuli. Behavioural data regarding Stroop interference produced by the various categories of stimuli used in the study and the degree of self-reported craving experienced by participants during the paradigm are examined, as well as the electrophysiological data obtained from the marijuana user and control participants.

Keywords: ERPs; Addiction; Neuropsychology; Emotion; Marijuana; Stroop
Dedication

To my committee and labmates, who helped me climb the necessary steps towards completing this exciting project.
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Introduction

Marijuana use has been on the rise in many parts of the world, and use of this substance has increased at an alarming rate particularly within North America. When the use of any illicit substance increases within the general population, cases of substance abuse and/or substance dependence are likely to increase as well. Because substance dependence places a substantial burden on many aspects of the societies that it affects, a great deal of resources have been allocated towards addiction research so that a better understanding of the psychological and biological processes inherent to its development can be identified. There have been many neuroimaging studies done using a variety of methodologies to better understand what areas of the brain contribute to the cyclical pattern of relapse and abstinence that typically entails addiction to psychoactive drugs (i.e. Volkow, Fowler, & Wang, 2003). A great deal of attention has also been given to the role of environmental stimuli in triggering relapses of substance obtaining behaviour (i.e. Goldstein et al., 2007). A growing consensus in the addiction literature states that the environment may play a major role in maintaining addiction behaviour and may actually contribute more to the addiction cycle than the chemical properties of the drugs themselves. With regard to marijuana use, this assertion is particularly concerning given that its use is becoming more and more accepted within many industrialized societies. Because the acceptance of marijuana culture is becoming more widespread, the number of cues that remind its users of the drug taking experience are also becoming more and more prevalent.

Addiction itself can be considered a multi-faceted disorder, and a number of theories have been put forward in attempts to characterize the cycle that affected individuals progress through as the severity of dependence increases. One of the most well-known theories is the incentive-sensitization model of addiction (Robinson & Berridge, 1993). In this model, it is stated that the motivation to obtain a drug of abuse increases over time (the “wanting” aspect of cognition), yet the hedonic value of the substance (the “liking” aspect) remains the same or declines as the behaviour continues.
These processes are theoretically set into motion via the process of reinforcement, and a number of stimuli in the environment can play a role in triggering the wanting/craving response in an addict. Given that pathways extending from the nucleus accumbens to the ventral tegmental area are activated when people experience the effects of recreational drugs and that the cues in the environment present during this experience become conditioned to the experience itself (Pierce & Kumarasen, 2006), neuroscientific evidence seems to support the validity of this theory of drug addiction.

Clinical Issues Related to Chronic Marijuana Use

Chronic marijuana use has been shown to affect a number of cognitive and behavioural processes. One study looked at a symptom of chronic cannabis use, namely impairment in verbal memory (Battisti et al., 2010). Given that the subsequent memory effect (SME) has been regarded as an ERP signature that indexes successful memory encoding, these researchers looked at modulations of this complex during a verbal memory task in order to establish whether reduced SME amplitudes could be used to assess impairments in memory function within cannabis users. Participants were required to list as many words as possible during a 10 second period following presentation of a random word list. When the behavioural data was analyzed, it was found that cannabis users recalled far fewer words than the control group across all categories of words presented. Related to the behavioural data were modulations of two components that make up the SME, namely the N400 and LPC components. For cannabis users, the N400 was found to be attenuated on both correctly and incorrectly recalled trials relative to the control group, and the attenuation occurred at frontal or parietal sites respectively. Overall, it appears as though poor performance on this verbal memory task was significantly associated with attenuated SME complex signatures and these deficits in functions such as memory encoding, retention, or recall can be objectively assessed using ERPs.

Research has also shown that marijuana use is associated with a number of adverse trajectories throughout development. Relative to people who do not use marijuana, chronic marijuana users were significantly more likely to participate in criminal behaviour, experience symptoms of anxiety and depression, achieve less
success within the domain of job performance, as well as have a significantly smaller chance of becoming married (Brook, Lee, Brown, Finch, & Brook, 2011). In addition to these adverse developmental trajectories, chronic use of marijuana has also been associated with higher levels of impulsivity (Gruber, Silveri, Dahlgren, & Yurgelun-Todd, 2011), poor decision making and performance on the Iowa Gambling Task (Wesley, Hanlon, & Porrino, 2011), retrieval and immediate verbal memory deficits (Takagi et al., 2011), as well as on impaired performance on neuropsychological tests of memory (Thoma et al., 2011). Given the wide range of implications for chronic use of marijuana, it is imperative that research is conducted to gain a better sense of the neural correlates of these deficits. Doing so may allow for effective clinical interventions to be devised that target specific elements of brain function. Furthermore, identifying the neural regions that show hypo- or hyperactivity when chronic marijuana users participate in various experimental tasks could allow for the implementation of pharmacological interventions that bring brain metabolism to normal levels. Although this approach is not currently being adopted, it becomes a distinct possibility for future endeavours that aim to curb rates of marijuana use globally.

Research has also suggested that many aspects of emotional processing are also affected by sustained heavy use of marijuana. For example, Ernst et al. (2010) found that substance abuse/dependence significantly predicted bias towards perceiving negative but not positive emotions in youth who were assessed in a longitudinal study. Using ERPs and a variation of the emotional Stroop task called the drug-Stroop (dStroop) task, Cane, Sharma, and Albery (2009) found that marijuana dependent participants exhibited substantial differences relative to a control group with regard to spatial and temporal characteristics of elicited ERP waveforms as well as the degree of interference caused by the presentation of the drug related words in the Stroop task. Specifically, marijuana users were found to have far more errors in their behavioural data relative to the control group for presentations of drug related words. Furthermore, research has shown that long term cannabis use can produce structural abnormalities in the amygdala (Yucel et al., 2008), which may have effects on the perception of a wide range of emotional stimuli due to the fact that this is a key structure involved in appraisal and generation of many emotional states.
Neuroimaging and Addiction

There have been a number of fMRI and PET studies that have attempted to elucidate the neural underpinnings of addiction. Van Hell et al. (2009) used fMRI to investigate differences between long term marijuana users, cigarette smokers, and healthy controls. Using a task that was designed to elicit reward anticipation via monetary incentives, it was found that long term marijuana users showed a decreased reward-related anticipatory response relative to cigarette smokers and control participants. These differences were found in the nucleus accumbens (ventral striatum) as well as within the caudate nucleus (dorsal striatum). It is well known that the nucleus accumbens is part of the so called “pleasure pathway” and is thought to be a key dopaminergic structure involved, among the other things, in the addiction cycle (Volkow, Fowler, and Wang, 2003; Schmitz, 2005). Furthermore, it has also been suggested by the previously cited researchers that the pathway projecting from the nucleus accumbens to the ventral tegmental area (VTA) may be specifically involved with the rewarding aspects of obtaining substances that individuals frequently abuse. Although the data from numerous studies has supported this assertion, the rewarding aspects of drug taking experiences do not fully capture the entire spectrum of behaviours and cognitive processes inherent to drug addiction. For instance, numerous studies have also found that stimuli in the environment play a major role in maintaining the addiction cycle, and that the abstinence syndrome associated with not obtaining the rewarding substance may not actually be a critical component of the addiction cycle. This phenomenon, often referred to as cue reactivity, has been well documented within the addiction literature. For example, Van Gucht, Van Den Bergh, Beckers, and Vansteeneewegen (2010) monitored the behaviour of a representative sample of cigarette smokers, and found that smoking was most likely to occur in specific contexts. The highest proportion of cigarette use occurred when environmental cues (ie. Being in one’s kitchen or car) were available. Based on results such as these, it appears as though drug obtaining behaviour cannot be mediated entirely by relief of the negative effects of abstinence syndrome.

Neuroimaging techniques are frequently used to explore how the brain responds to the processing of visually presented information. Because each neuroimaging
technique has its limitations, a trend in the literature has been to use different neuroimaging techniques in order to provide convergent evidence for the involvement of neural structures and the specific psychological mechanisms involved in any given research paradigm. For example, fMRI techniques are known to provide excellent spatial resolution for imaging the functioning brain, yet are poorly suited for attempting to explore brain function within the temporal domain due to the sluggish temporal course of the hemodynamic response (up to 15 sec) (see Luck, 2005). In contrast, the ERP technique is well suited for exploring the temporal characteristics of brain function due to its exquisite time sensitivity (< 1 msec), yet the spatial resolution of scalp-recorded electrical signals is coarse at best, and the localization to underlying brain generators relies on mathematically modeling the inverse problem by projecting scalp voltages into the brain via source localization procedures (ie. sLORETA, CLARA). This data can then be compared to findings obtained using either fMRI or PET, and a reasonable argument can be made to support the idea that specific cognitive operations are performed by the functioning of a subset of brain areas identified by the neuroimaging techniques. With regard to experiments using visual stimuli, this method is particularly useful as the temporal characteristics of stimulus processing and the neural regions associated with these processes can be determined, and inferences can then be made regarding the brain-behaviour relationships that arise as a result of exposure to the stimuli.

ERPs and Affective Stimulus Processing

Anterior Effects

Given that the emotional Stroop task (eStroop) can be used to explore the effect of emotional stimuli on human attention mechanisms and can be used in conjunction with electrophysiology to understand the timeline of events that occur when these stimuli are processed, this makes it an ideal task for furthering scientific understanding of addiction behaviour. Since its inception, a number of variants from the eStroop task have been devised and implemented in research designed to further investigate subjective emotion experiences in healthy as well as disordered populations. One such variant is known as the drug-Stroop task (dStroop), which can be used to elucidate findings that discriminate between addicts and healthy populations with regard to
interference effects (as illustrated by slower reaction times) and error rates in response to various categories of stimuli. Due to the nature of addiction, stimuli that are related to an addicts’ substance of preference are assumed to be especially salient to these individuals and emotionally intense, thus facilitating an increased allocation of attentional resources when these stimuli are present in either natural or laboratory settings. A study conducted by Fehr, Wiedenmann, and Hermann (2006) attempted to explore the electrophysiological counterparts of nicotine cue reactivity using nicotine consumption-related and neutral words in a dStroop task. Using nicotine addicted and non-smoking control participants, the task required that each subject report the color of the word in each trial by means of a button press. Although there were no significant differences between groups with regards to RT differences to neutral or nicotine words, several significant ERP effects were found both within and between groups. Smokers displayed a left frontal positivity within the 300-400 ms window regardless of stimulus category, and when the effects of nicotine cues were examined separately, increased right frontal lobe activity in the form of a positive going potential was observed. These results were taken as evidence for drug-cue related modulation of late occurring ERP components, which support the idea that salient cue information can successful engage attentional mechanisms and therefore enhance the processing of information that is highly relevant to individuals. According to the authors, stimuli eliciting “approach” behaviour carry an affective dimension with them, and it may be the case that the brain has evolved to process stimuli that have been associated with rewarding responses with a degree of specialization.

Lubman, Allen, Peters, and Deakin (2008) had male heroin addicts (10 of whom were on opiate pharmacotherapy and 10 who were recently detoxified) and 13 matched control participants passively view opiate-related, emotional and neutral pictures while EEG was recorded. Heroin dependence was assessed using the SDS (Severity of Dependence Scale; Gossop et al., 1995). They reported that heroin addicts displayed significantly larger P300s in response to opiate related pictures compared to other stimulus categories, and there was no difference in P300 amplitudes when other emotional stimuli were compared to neutral stimuli. In contrast, the opposite pattern was observed in the control group. Here, opiate-related pictures did not elicit larger P300s compared to other stimuli, yet larger P300s were observed when emotional pictures
were compared to neutral ones. To determine whether the P300 could be utilized as a measure of craving severity, the researchers conducted a multiple regression analysis where the P300 values were entered as a dependent variable and the BDI, SDS, HADS-Anxiety, baseline craving measures, and post-experiment craving measures were included as independent variables. It was found that baseline craving scores significantly predicted P300 amplitudes in the heroin user group, with a significant positive correlation being observed between measures of these 2 variables. Based on this study, it appears as though well studied ERP components can be used as an objective measure of mood states that have been regarded as fundamental to the diagnosis of addiction (namely craving in the present case). Behavioural measures that are collected within an experimental session can provide useful data which can be correlated to ERP component amplitudes, and can thus give researchers an indication about whether one variable predicts the occurrence of the other.

**Posterior Effects**

Using the ERP technique, researchers have also observed ERP components that are detected over posterior regions of the scalp. Dunning et al. (2011) had participants who met criteria for cocaine use disorder (CUD) view images that were either emotionally valenced, related to cocaine use, or neutral in valence and arousal (with the neutral and emotional pictures coming from the IAPS inventory), and the ERPs elicited by these pictures were compared to those seen in remitted CUD and healthy control participants. Participants who had a history of cocaine use displayed a number of significant differences in their ERP waveforms, especially with regard to the LPP component. The window that conceptualized the LPP was divided into an early (400-1000 ms) and a late LPP (1000-2000 ms) in order to better understand the cognitive processes that were occurring within these lengths of time. Previous research has suggested that the early part of LPP reflects the engagement of attention towards salient stimuli, and that the later part of the component reflects a response to the emotional salience of the stimulus (Foti, Hajcak, & Dien, 2009). For the early part of the LPP, both CUD groups showed an enhanced response to cocaine related stimuli, and these responses were not significantly different when compared to responses elicited by pleasant or unpleasant stimuli. In addition, the early LPP responses to all emotional and cocaine related stimuli were significantly larger than that seen in response to neutral
stimuli. The control participants showed a very different pattern of activation, such that the cocaine related cues elicited a very small LPP response (similar to the LPP elicited by neutral cues). However, both negative and positive pictures produced much larger responses compared to the other categories of stimuli. When the later window of the LPP was analyzed for between and within group differences, a different pattern was observed. The remitted CUD group was the only group that showed an enhanced processing for cocaine cues, and only the remitted CUD and control participants showed enhanced processing for the pleasant and unpleasant pictures. The only effects that were observed in the currently using CUD group were attenuated LPP responses to pleasant and unpleasant stimuli relative to what was seen in control subjects, and an attenuated response to cocaine cues relative to the remitted CUD group. These findings were taken as support for the idea that cocaine stimuli were a highly salient cue for the CUD groups, it was able to engage attentional mechanisms, and that current users of cocaine had deficits in processing the more elaborate properties of the salient as opposed to neutral pictures in the task when compared to the remitted and neutral groups. Given that the processing of a variety of cues could be examined using the ERP method in this cue-reactivity paradigm, the use of the ERP technique is also validated as valuable tool for understanding neural communication inherent in addiction.

Furthermore, Franken et al. (2008) found that the amplitude of the LPP was significantly positively correlated with self-reports of cocaine craving in abstinent cocaine users, which also validates the usefulness of this ERP component when assessing mood states related to drug dependence.

Other studies that have used variants of the eStroop task have also been successful for studying the neural mechanisms behind emotion processing. Van Hooff, Dietz, Sharma, & Bowman (2008) conducted an ERP study using an eStroop task where the stimuli consisted of negatively valenced or neutral words presented on a computer screen. As was expected, significant differences in RT to negative versus neutral words were observed and these were accompanied by differences in elicited ERP components. Negative words produced deflections within the 300-700 ms range that were more negative going compared to words that were categorized as being neutral (this was particularly pronounced at fronto-medial electrode sites.)
Neural Structures Implicated in Emotion Cue Reactivity

A number of neural structures have been implicated in healthy and pathological cue-reactivity to emotionally salient stimuli. A study conducted by Abler et al. (2010) suggests that the mPFC plays a fundamental role in the assessment of emotionally valenced stimuli. Using pictures from the IAPS inventory in conjunction with fMRI, these researchers found differences between groups of participants who were rated as being either high or low in their responsiveness to stimuli that elicited strong positive or negative emotions. For those people who were less likely to utilize emotion suppression strategies and were therefore highly responsive, hyperactivity was observed in the mPFC region (particularly the orbitomedial PFC). The opposite pattern was observed in the group that was deemed more likely to employ emotion suppression, with decreased metabolic activity being observed in response to the same positive and negative stimuli when these responses were compared to a neutral condition. Similar results were obtained when Liotti et al. (2000) used PET in conjunction with an experimental task that required subjects to generate feelings of sadness or anxiety driven by autobiographical memory scripts. When sadness was contrasted with a neutral condition, increased activation was observed in the left and right anterior insular cortex, as well as the subgenual anterior cingulate cortex. However, when anxiety provoking stimuli were contrasted with the neutral presentations, the right ventral insula, left OFC, and right anterior temporal cortex was found to be significantly activated. When contrasted with the latter study that implicated a role for emotion suppression in reducing the likelihood of affect related pathology, it seems as though the activity of this frontal lobe network can be modulated by cognitive control, and that factors in the environment may play a major role in determining how an individual will respond to an emotion eliciting stimulus. A role for attentional processes is also implied, given that attention is required in order for varying levels of intensity to be experienced by participants. Use of substances such as marijuana (which has been linked to deficits in attention allocation) may then result in a reduced ability to experience the full range of human emotion responsivity.

A number of studies have attempted to identify the neural regions that are affected by stimuli associated with addicts obtaining their substances of preferences. Goldstein et al. (2010) conducted an fMRI study aimed at understanding BOLD
responses to drug-cue stimuli in cocaine users and whether these responses would becoming attenuated after methylphenidate was administered. Specifically, it was hypothesized that methylphenidate administration (relative to a placebo condition) would increase activity within the ACC, a region believed to facilitate inhibitory control of behaviour. When the responses from the placebo group were examined, there was significant hypoactivation within the cdACC, indicating that conflict monitoring processes were operating at a sub-optimal level. As was expected, administration of methylphenidate improved neural functioning within this brain region and the BOLD response within the cocaine use disorder group resembled the response pattern seen within the control group. In addition to this finding, a significant reduction in frontal lobe activity was also observed, specifically within the frontal gyrus and prefrontal gyrus. This finding indicated that signaling between the ACC and frontal regions is a key element in the appraisal of drug cue information, and that the functioning of this pathway can be a target in attempts to minimize the occurrence of addiction behaviors. Furthermore, given that emotion suppression has been found to decrease cue responsivity in subjects who are at risk for anxiety and depression (ie. Liotti et al., 2000), it is possible that a failure to suppress anterior and medial frontal lobe activity in response to drug cues may be a fundamental factor in relapse for drug use (see Li & Sinha, 2008). In addition to these findings, Goldstein et al. (2009) compared chronic cocaine users to healthy matched controls in an fMRI study that gave participants monetary rewards for each correct categorization of neutral or drug related words presented to them during the task. Also, craving for cocaine was assessed prior to fMRI data acquisition as well as after the task was completed. The cocaine abusing group showed no significant differences in the behavioural component of the task when compared to the control group, although there were several significant differences in glucose metabolism in response to the presentation of these two categories of stimuli between groups. Firstly, cocaine users showed significant hypoactivational patterns in the cdACC, medial OFC, DLPFC, DMPFC, and right inferior parietal lobule when blocks of neutral stimuli were presented. However, when highly salient drug stimuli were presented, the opposite pattern of activation was observed across groups. This reversal of activation was found to be strongest at the rvACC/mOFC region of interest. Secondly, the frequency of cdACC hypoactivation was found to be strongly positively correlated to the frequency of cocaine use. Importantly, the largest hypoactivations were found when less salient stimuli
(neutral) were presented, indicating that the ACC is recruited more when emotionally relevant stimuli are present. Given that the drug related stimuli were sufficiently able to produce enhanced activation in the rvACC/mOFC region, it appears as though signaling within and beyond the ACC is affected by drug-related changes in neural communication, and that normal emotional experience may also be affected as a result of synaptic changes that occur as drug addiction progresses. Another study conducted by Vollstadt-Klein et al. (2010) found significant differences in neural activation when participants who were categorized as heavy drinkers or social drinkers viewed a series of alcohol related and neutral cues. Heavy drinkers showed enhanced activation of the dorsal striatum in response to such cues, but the social drinkers showed enhanced activation in the ventral striatum and right medial and middle frontal gyri. Furthermore, scores on the OCDS (a measure used to gauge the severity of addiction) were found to correlate with these activations. Ventral striatal activation in social drinkers was negatively correlated with high scores on the OCDS, and dorsal striatal activation was found to be positively correlated. Furthermore, differences in PFC activation were interpreted as mediating the craving responses given by participants. The increased activation of the PFC in response to drug cues could mean that top-down control was still being exercised by the social drinkers, which helped to minimize the degree of subjective craving experienced during the task. The lack of this response in the heavy drinkers indicated that this process of self-regulation was dysfunctional to one degree or the other. Given that this these PFC activations occurred in regions that are anatomically close to the anterior ACC and that past research has supported the idea that mPFC-ACC pathways are necessary for inhibitory control to be exercised (ie. Goldstein et al., 2010; Goldstein et al., 2009; Lubman, Yucel, & Pantelis, 2004; Liotti et al., 2000), it is likely that deficits in neuronal communication between these areas were present when heavy drinkers viewed stimuli of this category.

The orbitofrontal cortex (OFC) is believed to signal internally and externally cued behavior, and has also been implicated in processing emotionally salient cues in the environment regardless of stimulus modality (Scharpf, Wendt, Lotze, & Hamm, 2010). Furthermore, OFC functioning has also been suggested to play a role in a wide range of impulse control disorders (Winstanley et al., 2010). In addition, the OFC has also been implicated in present state learning which necessarily involves detecting and processing
environmental cues (ie. Tanaka et al., 2006), so it is reasonable to suggest that the functioning of this cortical region may be the link between addictions to a variety abused substances. The OFC has also been implicated as playing a role in a number of processes related to executive functioning and emotion expression, including empathy, decision making, and interpersonal behaviours (Lamm, Batson, & Decety, 2007; Beer, Knight, & D’Esposito, 2006; Beer, John, Scabini, & Knight, 2006). Research has suggested that the orbitofrontal cortex is involved in the integration of environmental stimuli and subjective thoughts and emotions (Felmingham et al., 2007), and functional neuroimaging studies have supported the notion that the OFC becomes hyperactive when addicts view stimuli that remind them of their substances of preference and that metabolic activity decreases once the craving experienced by participants is satiated (ie. Goldstein et al., 2009; Kufahl et al., 2008). One particularly striking demonstration of this was presented by Kufahl et al. (2008) in an fMRI study that had severely addicted cocaine users view messages that indicated a direct injection of cocaine was about to be administered to them intravenously. During this period of expectation, the participants exhibited increased activity in both the left and right lateral orbitofrontal cortices, as well as within the right medial OFC. When cocaine was actually being administered, the left and right lateral orbitofrontal cortices still displayed an amplified BOLD response, yet the activity in the medial OFC was found to return to baseline levels. The finding that the mOFC was hyperactive when visually presented stimuli were present replicates the findings reported by Goldstein et al. (2009), and provides evidence that the functioning of the OFC is a key factor when considering how conditioned visual stimuli in the environment are perceived by addicts. The fact that the left and right lateral orbitofrontal cortices remained active when cocaine was being administered also supports the notion that the different regions within the OFC respond to different forms of sensory stimulation related to the drug taking experience. For instance, the feeling an addict gets when administering drugs is a cue in and of itself, and the OFC has been thought to provide an online evaluation of internally generated emotional cues and external cues in the environment that are emotionally salient (Coccaro, McCloskey, Fitzgerald, & Phan, 2007; Felmingham et al., 2007; DelParigi et al., 2007). Furthermore, researchers have also found that the mOFC is particularly responsive to tactile stimulation when marijuana dependent participants touched paraphernalia that was used to self-administer marijuana, and this activation of the mOFC was not observed with neutral tactile stimuli.
(Filbey, Schacht, Myers, Chavez, & Hutchison, 2009). The fact the OFC is responsive to various forms of sensory input further suggests that this structure is a likely candidate for processing the reward value of drug cues regardless of their modality, and it likely plays a role in the conditioned response that occurs after drugs are repeatedly used in familiar contexts.

Despite the fact that this structure has been implicated in a variety of cognitive processes related to addiction behaviour and emotion appraisal, there have been no ERP studies done to further understand the temporal sequence of events that occur when addicts perceive stimuli that are drug related or emotionally valenced. By addressing this gap in the research, a better understanding of the neural communication that occurs shortly after salient stimulus presentation can be attained, and this may have significant clinical implications as the neural correlates for the automaticity of this response would be identified. By comparing these findings with results from other neuroimaging projects, a more complete understanding of the neural substrates of this disorder and how they operate to produce behaviour would be revealed. A potentially fruitful approach would be to use ERPs in tandem with techniques that allow for greater spatial resolution so that convergent evidence may be obtained through the application of different methodologies aimed at understanding the operation of a common neural substrate. Furthermore, the ERP technique is relatively inexpensive to utilize and requires far less maintenance compared to other neuroimaging techniques used in psychological research. These advantages make it a prime candidate for research on the neuropsychology of addiction, especially because this technique could be made accessible to clinicians hoping to use neuroimaging techniques to objectively assess individual clients and monitor the progress of their addiction interventions.

The current study attempts to explore differences in scalp topography between groups of heavy marijuana users and non-using control participants. The ERP technique was used in conjunction with a modified Stroop task (drug-Stroop) that incorporates marijuana stimuli as well as those that have either a positive or negative emotional valence.
Hypotheses

Regarding the behavioural component of the experimental task, our first hypothesis is that marijuana cravers will display significantly slower RTs and/or more errors while responding to the color of drug than neutral stimuli compared to the group of non-cravers. Our second behavioural hypothesis is that these behavioural effects would be specific to the drug stimuli, and will be larger than the differences elicited by emotional versus neutral stimuli.

With regard to the ERP data, our first hypothesis is that an early anterior positivity (EAP) will be observed within 250-350 milliseconds after stimulus presentation for the craver group in response to the drug blocks, and that this would not be observed when negative and positive blocks are presented. Furthermore, we believe that this ERP component will source localize to the mOFC/vmPFC on the basis of functional imaging research that suggests a role for neural networks within this region when drug cues are presented to addicts. Our final hypothesis is that an LPP effect will be elicited by presentations of affective stimuli for all groups, yet the LPP effect will be significantly greater than that seen for other stimulus categories in response to drug cues for the craver group only.
Method

The Simon Fraser University Research Ethics Board approved this experiment. All participants gave their written informed consent before participating, and received either course credit or a monetary incentive for their involvement.

Participants

13 chronic marijuana users and 15 matched control participants who had never used marijuana were recruited for this study. One marijuana user had abnormal EEG data and was excluded from the analyses, and one control participant’s behavioural data was excluded due to an unacceptably high error rate in his responses. All participants were between 18-30 years old. Marijuana users were contacted through word of mouth, and non-users were recruited through the Research Participation System used in the Psychology department at SFU. Participants were pre-screened in order to ensure that the inclusion criteria for the study were met. Suitable participants met criteria for marijuana dependence or were deemed to have never used the drug (as assessed by the C-SDS and medical screening questionnaires, see below), and did not show signs of clinical depression, anxiety, or thought disorder. In order to ensure that only the effects of consistent marijuana use were measured, participants were also screened for their use of other recreational drugs and cigarettes. Any participant who was found to show signs of comorbid substance dependence was excluded from the analysis. Furthermore, because this study employed a drug-Stroop paradigm using visual cues, participants were also excluded if they were found to be color blind or if they did not have normal or corrected to normal visual acuity. After suitability for participation was determined, suitable participants signed informed consent forms and preparation for an EEG recording commenced. All data acquisition took place at the Laboratory for Affective and Developmental Neuroscience at Simon Fraser University.
Materials

Questionnaires

Several questionnaires were administered before and after the EEG recording took place. These questionnaires are designed to assess the participant’s current medical condition, substance use, degree of cannabis dependence, and affect related pathology.

Beck Depression Inventory

The Beck Depression Inventory (Beck, Steer, & Brown, 1996) is one of the most reliable and valid measures of depression used in the field today. It has withstood the test of time, and will be used in this study to ensure that the level of depression present in participants is relatively homogenous.

State Trait Anxiety Inventory

Speilberger et al. (1970) developed the State Trait Anxiety Questionnaire (STAI) in order to assess a person’s anxiety at the moment (state) as well as their stable level of anxiety (trait anxiety). This measure was used to assess the presence of pathological anxiety in our samples.

Medical History Questionnaire

The Medical History Questionnaire was administered to participants for the purpose of assessing inclusion/exclusion criteria. This questionnaire was used to screen for normal or correct-to-normal vision, handedness, absence of present or past history of neurological or psychiatric disorders, sleep disorders, alcohol or substance abuse, and learning disabilities.

Cannabis Severity of Dependence Scale

The C-SDS is a 5 item measure that has been shown to have good reliability (test-retest coefficient (ICC): $\alpha = .88$; Martin, Copeland, Gates, & Gilmour, 2006). It has a theoretical range of 0-20, and is frequently used to screen for marijuana use (scores of 3 or more have also been found to reliably predict substance dependence). This
questionnaire was also administered in interview format in an attempt to maximize participant truthfulness.

**Fagerstrom Test For Nicotine Dependence**

The FTND (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) is a 6 item questionnaire that assesses the severity of a person’s dependence on nicotine. This questionnaire is currently the most widely used measure of nicotine addiction (Fidler, Shahab, & West, 2010), and will be used to determine whether cigarette smoking is confounded with marijuana use.

**Procedure**

After suitability for participation in this study was determined, the eligible participants were asked to come into the lab at a time that was suitable for them. Upon arrival, each participant was informed about the nature of the study and gave their written informed consent prior to beginning the experiment. Each of them filled out the Medical History Questionnaire and the informed consent forms, and answered all questions from the C-SDS. Upon completion, an electrode cap was then placed on the participant’s head and all the electrodes were attached. After cap set-up was completed, they were led to a sound-proof experimental room where EEG data was recorded from. Here, participants sat in front of a computer screen on which visual stimuli were presented. Subjects were presented with marijuana, neutral, positive, and negative stimuli, and all the data was acquired within a single recording session. After EEG data collection, participants then completed the STAI, BDI, and FTND questionnaires, were debriefed, and thanked for their involvement in the study.

**Stimuli**

Four categories of visual stimuli were presented to participants during the EEG task. There were a total of 600 stimulus presentations, with 300 stimuli being categorized as positive, negative, or drug stimuli (hereby referred to as target stimuli). The other 300 stimuli were included to balance each block of target stimuli, and were
classified as being neutral stimuli. The paradigm employed a block format, with each block consisting of 25 target stimuli and 25 neutral stimuli. Participants were also given the opportunity to take a short break after every 50 stimulus presentations. Each category of the target stimuli was presented to participants four times during the EEG session, for a total of 100 trials for each target category. All stimuli were selected at random according to a computer script that was created using the ePRIME (version 2.0) program. All positive and negative visual stimuli as well as their neutral counterparts were selected from the IAPS inventory, and the data for valence ratings were used to demarcate which stimuli should be included in the positive, negative, and neutral blocks. Some examples of the stimuli in the positive category include pictures of happy couples, people riding a roller-coaster, and pictures of kittens playing together. Some examples of the negative stimuli include pictures of wounded soldiers, people being robbed at gunpoint, scenes of poverty stricken environments, and guns being pointed at the participant. The neutral stimuli consist of pictures that received ratings around the midpoint of the range of valence scores taken from the IAPS data. Some examples of stimuli in this category include pictures of people with neutral facial expressions, pictures of furniture, and pictures of plants. For the drug stimuli, a comprehensive search using the Google images tool was conducted. Pictures that were thought to depict highly salient marijuana cues were included in the paradigm in an attempt to elicit drug craving and their neutral counterparts were selected based on the degree of similar perceptual characteristics.

Because this study employed a Stroop paradigm, each trial also included a colored square that was presented at the center of the screen. This colored square replaced the fixation cross that was present during ISI, and was red, green, blue, or yellow. Participants were required to respond via button press to each color, with a button press of 1 being the correct response for red, 2 being the correct response for green, 5 being the correct response for blue, and 6 being the correct response for yellow. In order to ensure that the participant remained attentive during the task and to minimize the occurrence of low frequency EEG artifacts, a jittered ISI was also employed (this was randomly selected from values ranging between 500-1000 milliseconds, at which time a grey fixation cross appeared on the screen). Also, each stimulus was
presented for a total of 500 milliseconds, resulting in trial time ranging between 1000-1500 milliseconds.

Figure 1. Trial Series Used in the Present Study

Rating Scales

In order to ensure that the drug-related and emotional stimuli yielded the desired subjective responses, three rating scales were presented after each block of 50 stimulus presentations asking how positive and negative they were feeling at that moment in time, and how much they were craving marijuana at that given moment. All rating scales were presented in Likert scale format, and required a 1 to 5 response by the participant.
Apparatus

EEG activity was recorded continuously from the scalp through 64 sintered Ag-AgCl electrodes embedded in an elastic cap (electrocap international), which provides very low noise, low offset voltages and very stable DC performance. Electrodes were positioned in an equiradial layout relative to the vertex (i.e., each electrode was radially equidistant from Cz, the vertex location at the scalp). Water-soluble conductive electrode gel (SignaGel) was used with no additional skin preparation, given that active electrodes would make this redundant. Two external electrodes were placed on the left and right mastoids. In order to monitor eye movement activity, four extra electrodes were placed at the corner of each eye (horizontal movements) and below the left and right eyes (vertical movements and blinks). DC offset was kept below +/- 25 mV. EEG signals were amplified between 0.16 and 100 Hz by BioSemi Active-Two amplifiers and sampled at 512 Hz (bandwidth 52 Hz). Brain electrical activity was analyzed using BESA software version 5.3. Trials contaminated by eye movements or muscle activity were rejected from the analyses based on amplitude (>120 uV). From each participant, event-related activity was selectively averaged for positive, negative, neutral, and drug stimuli, correct responses for these trials (hits), incorrect responses for these trials (misses), as well as block effects for each stimulus category. All averaging was time-locked to stimulus onset, and a baseline of -200 milliseconds was included in order to gauge the degree of electrical activity occurring prior to the onset of each stimulus. Grand-averages were then calculated for each of conditions.

In order to explore the differences for brain responses to each affective stimulus, ERP waveforms and topographical maps of grand-averages for each stimulus type were inspected and compared for latency and amplitude of peak voltage activity in the main observed components. Regions of interest (ROIs) were selected based on peak voltages and neighbouring electrodes showing similar voltage amplitudes and the windows of interest were centered around this activity. Mean voltage amplitudes in the selected time windows were then extracted and employed as a parameter in the statistical analysis of the ERP data. Mean voltage amplitudes in selected time windows were entered in a One Between (Group) Four Within (positive, negative, neutral, drug)
Repeated Measures ANOVA. Significance criterion was set at p<.05, and degrees of freedom were corrected using the Greenhouse-Geisser epsilon factor.

Source Analysis

In order to project scalp topographies into brain space, source localization techniques were employed. We utilized CLARA, which allowed for current density to be estimated and projected onto normalized MRI images of the brain. By employing this technique, neural activations elicited by the drug-Stroop paradigm could be compared with other cue-reactivity findings in the fMRI/PET literature.
Results

Demographics

In order to assess confounding effects, ANOVAs were run using data from the questionnaires given to participants. Besides the obvious differences in the C-SDS, $F(1,25)=217.78, p<.0001$, unanticipated differences were found between groups for the BDI, $F(1,25)=7.829, p=.01$, the STAI-State, $F(1,25)=6.212, p=.02$, the STAI-Trait, $F(1,25)=8.409, p=.008$, while, no significant effect was observed on the FTND. Several items on the medical history questionnaire were also analyzed in order to determine whether age, years of education, or amount of sleep the night before data collection were different between groups. Here, a significant difference for the variable age was observed ($F(1,25)=4.823, p=.038$). Mean differences for years of education and total sleep prior to data collection did not reach significance.

Table 1. Descriptive Statistics for Cravers and Non-Cravers on Test Battery

<table>
<thead>
<tr>
<th>Scale</th>
<th>Cravers Mean (SD)</th>
<th>Non-Cravers Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-SDS</td>
<td>4.67 (1.231)***</td>
<td>0 (0)***</td>
</tr>
<tr>
<td>STAI-State</td>
<td>36.33 (8.627)*</td>
<td>28.53 (7.624)*</td>
</tr>
<tr>
<td>STAI-Trait</td>
<td>41.33 (7.667)**</td>
<td>31.64 (9.137)**</td>
</tr>
<tr>
<td>BDI</td>
<td>8.42 (5.248)**</td>
<td>3.2 (4.443)**</td>
</tr>
<tr>
<td>FTND</td>
<td>0.25 (.622)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Age</td>
<td>22.33 (2.964)*</td>
<td>20.27 (1.907)*</td>
</tr>
<tr>
<td>Sleep Last Night</td>
<td>7.583 (1.379)</td>
<td>7.533 (1.3819)</td>
</tr>
<tr>
<td>Education</td>
<td>2.54 (2.251)</td>
<td>2.10 (1.168)</td>
</tr>
</tbody>
</table>

*: $p<.05$
**: $p<.01$
**: $p<.0000001$
Self-Report Scales

A-priori defined independent sample t-tests ($\alpha=.0167$) revealed that the only significant between group difference was the comparison of Drug Craving after Drug Blocks ($t(26)=5.316, p=.0001$). Within group paired-t tests ($\alpha=.0167$) showed that among cravers drug craving was greater after drug than positive blocks ($t(11)=-3.697, p=.004$). No effects approached significance in the non-cravers.

Table 2. **Descriptive Statistics for Cravers and Non-Cravers on Rating Scales**

<table>
<thead>
<tr>
<th>Scale Presentation</th>
<th>Cravers Mean (SD)</th>
<th>Non-Cravers Mean (SD)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DrugScaleAfterDrugBlock</td>
<td>2.94 (1.077)</td>
<td>1.18 (.427)</td>
<td>***</td>
</tr>
<tr>
<td>PositiveScaleAfterPositiveBlock</td>
<td>3.02 (.895)</td>
<td>3.58 (.603)</td>
<td>ns</td>
</tr>
<tr>
<td>NegativeScaleAfterNegativeBlock</td>
<td>2.42 (.900)</td>
<td>2.28 (1.25)</td>
<td>ns</td>
</tr>
</tbody>
</table>

***: $p<.0001$

Table 3. **Descriptive Statistics for Within Subjects Contrasts for Craving Scales**

<table>
<thead>
<tr>
<th>Scale Presentation</th>
<th>Cravers Mean (SD)</th>
<th>Non-Cravers Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DrugScaleAfterDrugBlock</td>
<td>2.94 (1.077)</td>
<td>1.18 (.427)</td>
</tr>
<tr>
<td>DrugScaleAfterPositiveBlock</td>
<td>2.27 (1.175)</td>
<td>1.07 (.258)</td>
</tr>
<tr>
<td>DrugScaleAfterDrugBlock</td>
<td>2.94 (1.077)</td>
<td>1.18 (.427)</td>
</tr>
<tr>
<td>DrugScaleAfterNegativeBlock</td>
<td>2.54 (1.261)</td>
<td>1.08 (.225)</td>
</tr>
</tbody>
</table>

**: $p<.001$

Drug-Stroop Data

Reaction Time Data

Given the a-priori hypothesis that there would be significant differences for RTs to drug stimuli, within group paired samples t-tests were run to determine where significant mean differences were found. After a Bonferroni correction for 3 comparisons was employed ($\alpha=.0167$) significant differences were found within the craver group for reaction times to drug versus neutral drug stimuli, ($t(11)=3.35, p=.007$), with drug stimuli
showing shorter RTs compared to their neutral counterparts. For the non-craver group, the only comparison that reached significance was the contrast between negative and neutral negative stimuli ($t(13)=3.91, p=.002$), with the negative stimuli eliciting greater RTs compared to the neutral negative stimuli (see Figure 3).

**Error Analysis**

A-priori defined paired t-tests Bonferroni-corrected for 3 comparisons ($\alpha =.0167$) showed that the contrast of Positive versus Neutral Positive errors reached significance within both the cravers and non-cravers ($t(11)=-5.75, p<.001$ and $t(13)=-6.74, p<.0001$ respectively). An a-priori defined independent samples t-test also revealed a significant group difference for errors to Drug stimuli ($t(24)=2.31, p=.03$, see Figure 2).

*Figure 2. Errors for Cravers and Non-Cravers*
Figure 3.  
**RT to Stimuli for Cravers and Non-Cravers (Correct Responses Only)**

**ERP Analysis**

Grand-averages were computed for both the marijuana craver groups and the control group for each category of stimulus. Upon inspection, we determined the electrode sites and windows of time where data would be extracted from.

**EAP Effect (250-350 ms)**

Data was extracted from the left hemisphere electrode sites A4, A5, A6, A10, A11, A12, and A13 due to the observation that significant differences in ERP component amplitude were seen over the left frontal region. These channels were grouped to form a single region of interest (ROI), and the overall mean for this region was used in our analysis of this effect. To further explore the data, restricted ANOVAs were then computed for each of the groups using Block and Stimulus as variables for the repeated measures test. For the craver group, the main effect of Block was highly significant,
F(2,10)= 12.897, p=.002. For the non-craver group, the only effect that reached significance was the Block x Stimulus interaction, F(2,13)=6.139, p=.013. Because a significant interaction was observed, we proceeded to break down this interaction using a series of contrasts of means.

To better understand this main effect, additional analyses were conducted using Bonferroni corrected t-tests (corrected $\alpha=0.167$ for 3 comparisons, see Figures 4 and 5). Within the craver group, t-tests revealed a significant effect for Drug Block versus Negative Block component amplitudes, t(11)=-3.756, p=.003, as well as Drug versus Positive block component amplitudes, t(11)=-4.157, p=.002. Here, the Drug block amplitudes were more positive in mean amplitude compared to the Negative and Positive blocks (-3.13 versus -.4.55 and -3.13 versus -4.48 respectively). The equivalent block contrasts in the control group were far from significant (for all, $p>.08$).

For the control group, only the within block comparison of Positive Hits versus Neutral Positive Hits reached significance, t(14)=3.831, p=.002. In this case, the Positive Hits were more positive in mean amplitude when compared with the Neutral Positive Hits (-1.54 versus -3.00 respectively). No other comparisons came close to reaching significance (for all, $p>.05$).
Figure 4. EAP and LPP Amplitudes By Channel and Group

Figure 5. EAP (250-350 ms) Mean Amplitudes For Cravers and Non-Cravers by Stimulus
**LPP Effect (350-550)**

Based on our observations of the posterior scalp electrical activity, we extracted data from electrodes A30, A31, and A32 and combined these 3 locations to form a single region of interest. A 1 between 3 within ANOVA was run in order to investigate whether significant main effects or interactions were observed within our groups. A significant main effect of Stimulus was observed, F(5,21)=6.078, p=.001, as well as a significant ROI x Group interaction (F(1, 25)=6.065, p=.021. No other main effects of interactions reached significance.

In order to break down these effects, Bonferroni corrected contrast t-tests were run in order to determine where significant mean differences occurred. No significant mean differences were observed with the dependent and independent samples t-tests when family wise error rates were controlled for.

**Source Analysis**

In order to estimate the neural generator of the EAP effect within the craver group, the CLARA source localization procedure within BESA 5.3 was implemented for the mean electrical activity within the 250-350 ms window. The results of this procedure produced a depiction of mOFC/vmPFC activity (see Figure 6 below).
Figure 6. CLARA Source Localization for the EAP 250-350 ms Effect
Discussion

In this study, we explored whether participants who met criteria for marijuana dependence processed positive, negative, and drug stimuli differently from healthy controls. We used a modified Stroop task (drug-Stroop) to assess the degree of interference elicited by these various stimulus categories, and we had participants rate how positive and negative they felt after each block of stimuli. We found significant effects for the behavioral component of the task, as well as a significant ERP effect within the 250-350 ms time window (which we labeled the L AP effect). Furthermore, our source analysis procedure localized the activity to the mOFC/vmPFC region.

Questionnaire Data

The analysis conducted on data obtained from our screening battery indicated that people who frequently use marijuana display higher state and trait anxiety, as well as higher levels of depression. It may be the case that people who are dependent on marijuana are using the drug as a psychological tool to cope with either these higher levels of negative emotionality or adverse environmental conditions, and past research suggests that this is a plausible explanation for the maladaptive drug use (Hampton, Halkitis, & Mattis, 2010). It was not clear from this study whether higher levels of anxiety or depression caused drug use, or whether these affective states are a side effect of chronic marijuana use. Furthermore, it was not statistically sensible to assess the possibility that subjects’ anxiety and depression levels confounded the results given the small sample size of the current project. Future studies should attempt to solve the previously mentioned directionality problem, possibly by means of conducting a longitudinal study that encompasses a significant portion of adolescent development. Furthermore, future large sample studies will allow for a more meaningful assessment of the influence of the previously mentioned confounding factors.
Rating Scale Analysis

We included rating scales in the ERP paradigm in order to assess mood states after each block of stimulus presentations. Not surprisingly, the marijuana cravers reported the highest subjective craving after drug blocks, thus supporting the notion that exposure to drug cues increases craving for frequent drug users. This finding is consistent with evidence that suggests that environmental stimuli that have been conditioned to the drug taking experience can trigger drug taking behaviours (ie. Goldstein et al., 2007; Gucht, Van Den Bergh, Beckers, and Vansteenwegen, 2010), and the craving that is produced by the stimuli may be satisfied after obtaining the drug of choice. By satisfying this craving, it can be argued that a reward was obtained, especially after a pleasurable mood state is experience by the user. Following this logic, orbitofrontal cortex function may play a role in determining the course of action the individual takes, given that it has been suggested to appraise the appetitive value of internally versus externally generated affective cues (Felmingham et al., 2007) and that its metabolism increases when drug stimuli are presented to addicts and decreases once the drug of choice in administered to these same people (ie. Goldstein et al., 2009; Kufahl et al., 2008). Given that the OFC also becomes hyperactive when drug cues are presented to addicts in experimental tasks (ie. Scharpf, Wendt, Lotze, & Hamm, 2010; Goldstein et al., 2007), this may also be a key region affected by the increased wanting process mentioned in the incentive sensitization model of drug addiction occurs as drug taking behavior continues (Robinson & Berridge, 1993).

dStroop Data

Our first hypothesis that cravers will display significantly slower RTs and/or more errors to drug stimuli relative to the control group was only partially supported. While more errors were incurred by the cravers in response to drug than neutral stimuli, the RT data indicated the unexpected finding that drug stimuli were actually processed more quickly than the neutral drug stimuli. This facilitation goes against findings obtained in other reports, as these stimuli tend to produce greater RTs or no RT difference in participants who suffer from substance use disorders (Fehr, Wiedenmann, & Hermann, 2006; Fardardi & Ziaee, 2010). For our sample, it appears as though processing for drug
stimuli was facilitated, and this facilitation was not observed for any other stimulus category. Although future studies will need to be conducted in order to determine whether this effect can be replicated, a likely interpretation is that a speed-accuracy trade-off may have emerged as an indicator of impulsive responses elicited selectively by drug stimuli in the user group. Future studies could explore this in greater detail using tasks that are designed to measure impulsivity more directly, such as inhibitory control tasks possibly including drug stimuli (a drug noGo task). This line of research appears promising given the evidence that impulsivity may contribute to relapse behaviour (ie. Fox, Bergquist, Keri, Gu, & Sinha, 2010).

With regard to the effect found in the control participants, the RT difference for negative compared to neutral stimuli makes intuitive sense and can be taken as validation that the paradigm worked correctly. Negative stimuli have been known to capture attention to a greater degree than positive stimuli or neutral stimuli (Gootjes, Coppens, Zwaan, Franken, & Van Strien, 2011), and our paradigm nicely replicated this recent finding. Furthermore, the lack of a dSTroop effect in response to negative stimulus presentations in the marijuana craver group (and the similar effects for the EAP, see below) suggest that people who are marijuana dependent may display abnormal processing for other emotional stimuli (in this case negative stimuli), and this inability to give proper attention to negative contexts may contribute to the addiction cycle. By giving insufficient attention to environmental stimuli that signal adverse consequences for the self, those who heavily use the drug may not learn that engaging in excessive drug taking behaviour is maladaptive, and may therefore continue engaging in it. It is also possible that those in the control group have more ability to pay attention to the negative consequences of drug use, and therefore abstain from use of illicit substances, and past research indicates that chronic marijuana users exhibit poor performance on neuropsychological tests that tap into the ability to learn from negative experiences (Wesley, Hanlon, & Porrino, 2011). One direction for future research would be to investigate this possibility further, as this could guide therapeutic approaches to treating addiction more generally, and it may also shed light on why subjective feelings of craving persist in light of salient consequences for engaging in heavy drug use. If clinicians could increase the addict’s ability to properly attend to negative stimuli, it is possible that
this increased awareness could help reduce to probability of relapse and increase effective self-monitoring/down-regulation.

**EAP (250-350 ms) Effect**

Our prediction that an EAP to drug stimuli would be observed within 250-350 ms for the craver group only was supported. Using a high density electrode array, we were able to obtain ERP grand-averages for each category of stimulus presented during the task. Similar to past research done in our lab (Asmaro et al., in press), we observed an early occurring positivity over the left frontal region of the scalp within a chocolate-craving group between 250-350 milliseconds after presentations of chocolate stimuli. Furthermore, source localization allowed us to estimate the generator of this electrical activity. By projecting this AP effect into brain space, we were able to conclude that this finding is consistent with functional imaging results that suggest a role for the mOFC/vmPFC in detecting drug related stimuli (Goldstein et al., 2009; Kufahl et al., 2008), and that ERPs may be useful in assessing the effects of cue reactivity. In addition, research has suggested that decreased blood flow in OFC occurs after addicts receive their drug of choice, the clinical application of ERPs as an assessment tool in clinical settings may be feasible. If clinicians use a particular therapy or pharmacological approach to help the patient recover from addiction, the success of the approach could be objectively assessed using this methodology. In this case, one might predict that OFC/vmPFC activation would not be elicited in response to drug cue presentations and that this would remain so long as the patient was successful at abstaining from substance use.

Surprisingly, we also an ERP effect within the 250-350 ms window of time for participants in the control group, although this effect occurred when ERP data for positive hits were contrasted with data corresponding to negative hits. This effect is interesting given that positive stimuli evoked more positive voltages in the non-cravers, similar to what was seen when the craver group perceived drug stimuli. Based on the ERP data, it may be the case that drug stimuli are processed by a similar neural pathway that non-users typically use to process positive emotional contexts. One theory of addiction states that the drug, via the striatal pathway, hijacks a natural pathway that
is used to modify behaviour through the process of reinforcement and learning (Kauer & Malenka, 2007). In the average person’s life, positive stimuli are used to help healthy socialization occur. Dopaminergic transmission between the mesolimbic dopamine pathway and the prefrontal cortex is one pathway that can help mediate this learning, and drugs of abuse have also been found to modulate excitatory inputs going to and from this region. Given that a greater peak amplitude was seen within the craver group when drug stimuli were compared with positive stimuli, it seems possible that abnormal functioning may be present within heavy marijuana.

Limitations and Future Directions

To our knowledge, this study was the first of its kind to utilize and high-density electrode array in combination with an addiction Stroop task and source analysis procedures with the goal of detecting region of interest activation within a sample of marijuana users. This study replicates past research done in our laboratory using cue reactivity paradigms, and the results have both scientific and clinical merit. Despite the strengths of our experimental design, several limitations can be noted. First, we did not include a sample of female participants. Although we consciously made this decision knowing that substance disorder rates tend to be higher in males as opposed to females and because of differences in brain laterality across gender, it would be important to assess whether similar electrophysiological markers of addiction could be observed within females despite the fact that their left and right hemispheres are more symmetrical. Also, it would be interesting to note whether craving scores over the course of the paradigm would be more likely to change when between group comparisons are made for male and female marijuana users. Second, although our sample size was comparable to other studies reported in the literature, some of the effects that failed to reach significance may have become significant had we achieved a greater sample size and therefore more power to reject the null hypotheses of there being no effect between or within our groups. Doing so may have allowed for us to observe an effect for the late positive potential (LPP), which has frequently been reported in previous studies in the addiction and emotion literature. Lastly, ethics at Simon Fraser University made it difficult for us to recruit marijuana users in the
community because we could only do so via word of mouth (posters, advertisements on social networking sites, and other means of recruitment were strictly prohibited). Future studies may wish to collaborate with more large scale projects in order to have better access to the marijuana dependent population. Furthermore, because the drug-Stroop paradigm is a relatively new adaptation of the classic Stroop, replication of the results will be needed in order to have more confidence in the robusticity of the findings obtained in this study.

The findings obtained from this study could benefit greatly from replication. It would be very useful to conduct a similar study using a completely different sample in order to determine whether the AP effect and Stroop effects could be found again. It would also be useful to create a modification of this paradigm for use within an fMRI setting in order to provide more concrete evidence for the role of the OFC and ACC in cue reactivity or drug-Stroop tasks. Utilizing both methods simultaneously would allow for functional connectivity measures to be employed, and would therefore allow for a better understanding of the neural correlates of drug reactivity within both the spatial and temporal domains of neuroimaging. With regard to the incentive-sensitization model of addiction, future studies could attempt to demonstrate a link between the EAP and LPP ERP components and the wanting versus liking aspects of the model. By connecting these affective states directly to objectively measured ERP components, information regarding the degree to which top-down control can be exercised over subjective feelings of liking or wanting and at which stage of information processing may be elucidated. Furthermore, it would be interesting to use this same paradigm with other groups of substance users (ie. Cigarette smokers, cocaine users) to see whether these effects would be observed regardless of drug preference. It is possible that addiction to different substances would modulate effects for specific aspects of the task. By doing so, a more complete understanding of addiction may be obtained and this could guide future research in the field as well as clinical practice.
References


Appendices
Appendix A. Cannabis Severity of Dependence Scale

Cannabis Habit Assessment Scale

Please circle the mark on the line that best characterizes your cannabis using behaviour over the last 3 months.

1) Did you ever think your use of cannabis was out of control?

<table>
<thead>
<tr>
<th>Never or almost never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
</table>

2) Did the prospect of missing a smoke make you very anxious or worried?

<table>
<thead>
<tr>
<th>Never or almost never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
</table>

3) Did you worry about your use of cannabis?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a Lot</th>
<th>A great deal</th>
</tr>
</thead>
</table>

4) Did you wish you could stop?

<table>
<thead>
<tr>
<th>Never or almost never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
</table>

5) How difficult would you find it to stop or go without cannabis?

<table>
<thead>
<tr>
<th>Not difficult</th>
<th>Quite difficult</th>
<th>Very difficult</th>
<th>Impossible</th>
</tr>
</thead>
</table>
Appendix B. Medical History Questionnaire

The Neural Correlates of Marijuana Use

Medical History Questionnaire

Date

Subject #: Age: Years of Post-Secondary Education:

1) Are you wearing glasses or contacts?

2) Is your vision nearly normal, or corrected to normal if wearing glasses/contacts?

3) Are you colour-blind?

3) Are you Right-Handed or Left-Handed?

4) How you ever seen a psychiatrist or have been treated for any of the following problems:
   a) Depression
   b) Anxiety
   c) Attention-Deficit Disorder
   d) Thought disorder
   e) Other (specify)

5) Have you ever seen a neurologist or been in an emergency room for:
   a) Loss of motor or sensory function
   b) Loss of consciousness
   c) Head concussion
   d) Sleep disorder
   e) Migraines
1) Have you ever had a CT scan, MRI scan or Electroencephalogram?  
   YES  NO

6) Have you been told you have a learning disorder such as dyslexia?  
   YES  NO

7) Have you had/do you have any serious medical condition?  
   YES  NO
If yes, explain which

8) Are you currently taking any prescription medication?  
   YES  NO
   If yes, explain which

9) How many hours do you typically sleep?  
   How many hours did you sleep last night?

10) Please describe which and how many alcoholic beverages you typically have in a week:  

11) Do you use non-prescription drugs frequently?  
    YES  NO
    If yes, explain which and how often

Please rate, on a scale from 0 (not at all) to 9 (very much so) how sleepy you have been feeling during the past week:

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not sleepy</td>
<td>Very sleepy</td>
<td>Great effort to fight sleep</td>
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</tbody>
</table>
Please rate, on a scale from 0 (not at all) to 9 (very much so) how sleepy you feel now:

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<tr>
<th>0</th>
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<th>5</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
<td>Very Alert</td>
<td>Very Sleepy</td>
<td>Great effort to stay awake</td>
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<tr>
<td>Wide Awake</td>
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How tired-fatigued have you been feeling during the past week:

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<tbody>
<tr>
<td>Very little</td>
<td>Extreme fatigue; interferes with work, duties &amp; social activities</td>
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<td>No fatigue</td>
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Please rate, on a scale from 0 (not at all) to 10 (very much so) the way you are feeling now:

<table>
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<tr>
<th>Sad</th>
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<td>Anxious</td>
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<tr>
<td>Tired</td>
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<td>Relaxed</td>
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<td>Energetic</td>
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<td>Upset</td>
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<tr>
<td>Happy</td>
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Appendix C. Beck Depression Inventory

<table>
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<tr>
<th>Subject #: __________</th>
<th>Date: __________</th>
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On this questionnaire are groups of statements. Please read each group of statements carefully. Then pick out the one statement in each group which best describes the way you have been feeling in the PAST WEEK, including TODAY. If several statements in the group seem to apply equally well, check each one. Be sure to read all the statements in each group before making your choice.

1. 
   - ☐ I do not feel sad.
   - ☐ I feel sad.
   - ☐ I am sad all the time and I can’t snap out of it.
   - ☐ I am so sad or unhappy that I can’t stand it.

2. 
   - ☐ I am not particularly discouraged about the future.
   - ☐ I feel discouraged about the future.
   - ☐ I feel I have nothing to look forward to.
   - ☐ I feel that the future is hopeless and that things cannot improve.

3. 
   - ☐ I do not feel like a failure.
   - ☐ I feel I have failed more than the average person.
   - ☐ I feel I have nothing to look forward to.
   - ☐ I feel I am a complete failure as a person.

4. 
   - ☐ I get as much satisfaction out of things as I used to.
   - ☐ I don’t enjoy things the way I used to.
   - ☐ I don’t get real satisfaction out of anything anymore.
   - ☐ I am dissatisfied or bored with everything.

5. 
   - ☐ I don’t feel particularly guilty.
   - ☐ I feel guilty a good part of the time.
   - ☐ I feel quite guilty most of the time.
   - ☐ I feel guilty all of the time.

6. 
   - ☐ I don’t feel I am being punished.
   - ☐ I feel I may be punished.
   - ☐ I expect to be punished.
   - ☐ I feel I am being punished.

7. 
   - ☐ I don’t feel disappointed in myself.
   - ☐ I am disappointed in myself.
   - ☐ I am disgusted with myself.
   - ☐ I hate myself.

8. 
   - ☐ I don’t feel I am worse than anybody else.
   - ☐ I am critical of myself for my weaknesses or mistakes.
   - ☐ I blame myself all the time for my faults.
   - ☐ I blame myself for everything bad that happens.

9. 
   - ☐ I don’t have any thoughts of killing myself.
   - ☐ I have thoughts of killing myself, but I would not carry them out.
   - ☐ I would like to kill myself.
   - ☐ I would kill myself if I had the chance.

10. 
    - ☐ I don’t cry anymore than usual.
    - ☐ I cry more now than I use to.
    - ☐ I cry all the time now.
    - ☐ I used to be able to cry, but now I can’t cry even though I want to.
The Beck Inventory

Subject #: __________  Date: ______________

11. ☐ I am no more irritated now than I ever was.
   ☐ I get annoyed or irritated more easily than I used to.
   ☐ I feel irritated all the time now.
   ☐ I don’t get irritated at all by the things that used to irritate me.

12. ☐ I have not lost interest in other people.
   ☐ I am less interested in other people than I used to be.
   ☐ I have lost most of my interest in other people.
   ☐ I have lost all of my interest in other people.

13. ☐ I make decisions about as well as I ever could.
   ☐ I put off making decisions more than I used to.
   ☐ I have greater difficulty making decisions than before.
   ☐ I can’t make decisions at all anymore.

14. ☐ I don’t feel I look any worse than I used to.
   ☐ I am worried that I am looking old or unattractive.
   ☐ I feel that there are permanent changes in my appearance that make me look unattractive.
   ☐ I feel that I am ugly or repulsive looking.

15. ☐ I can work as well as before.
   ☐ It takes an extra effort to get started at doing something.
   ☐ I have to push myself very hard to do anything.
   ☐ I can’t do any work at all.

16. ☐ I can sleep as well as usual.
   ☐ I don’t sleep as well as I used to.
   ☐ I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
   ☐ I wake up several hours earlier than I used to and cannot get back to sleep.

17. ☐ I don’t get more tired than usual.
   ☐ I get tired more easily than I used to.
   ☐ I get tired from doing almost anything.
   ☐ I am too tired to do anything.

18. ☐ My appetite is no worse than usual.
   ☐ My appetite is not as good as it used to be.
   ☐ My appetite is much worse now.
   ☐ I have no appetite at all anymore.

19. ☐ I haven’t lost much weight, if any, lately.
   ☐ I have lost more than 5 pounds.
   ☐ I have lost more than 10 pounds.
   ☐ I have lost more than 15 pounds.

   [PLEASE ALSO ANSWER: I am trying to lose weight via dieting? Yes ___ No ___]

20. ☐ I am no more worried about my health than usual.
   ☐ I am worried about physical problems such as aches and pains or upset stomach or constipation.
   ☐ I am very worried about physical problems and it’s hard to think of much else.
   ☐ I am so worried about physical problems that I cannot think of much else.

21. ☐ I have not noticed any recent changes in my interest in sex.
   ☐ I am less interested in sex than I used to be.
   ☐ I am much less interested in sex now.
   ☐ I have lost interest in sex completely.
Appendix D. The Speilberger State-Trait Anxiety Index
Appendix E. The Fagerstrom Test for Nicotine Dependence (FTND)

Fagerström Test For Nicotine Dependence (FTND)

1. How soon after you wake up do you smoke your first cigarette?
   a. Within 5 minutes 3 points
   b. 6 – 30 minutes 2 points
   c. 31 – 60 minutes 1 point
   d. After 60 minutes 0 points

2. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, in the cinema, etc.?
   a. Yes 1 point
   b. No 0 points

3. Which cigarette would you hate most to give up?
   a. The first one in the morning. 1 point
   b. Any other 0 points

4. How many cigarettes/day do you smoke?
   a. 10 or less 0 points
   b. 11 – 20 1 point
   c. 21 – 30 2 points
   d. 31 or more 3 points

5. Do you smoke more frequently during the first hours after awakening than during the rest of the day?
   a. Yes 1 point
   b. No 0 points

6. Do you smoke if you are so ill that you are in bed most of the day?
   a. Yes 1 point
   b. No 0 points

The FTND has been correlated with biochemical measures of nicotine dependence including exhaled air carbon monoxide, salivary cotinine, and salivary nicotine.

The FTND has also been found to reliably predict smoking cessation.
Possible range is 0 – 10: Scores of 4 or greater indicating nicotine dependence
Scores of 6 or greater indicating severe nicotine dependence

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