

**Out of Sight Out of Mind: Do Electrophysiological
Markers Elicited by Nicotine Related Visual Cues
Predict Relapse in a Sample of Adult Smokers? A
Longitudinal Study**

by

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Abstract

Nicotine dependence is a global health problem that continues to adversely affect millions of people. In order to better understand the effects of cigarette cue-reactivity, event-related potentials (ERP) were recorded while smoking-related and neutral pictures and words were presented to abstinent smokers (who were later classified as been successful abstainers or relapsers after 1 month) and never smokers (Studies 1 and 2 respectively). To assess the effects of top-down regulation in mitigating smoking cue reactivity, Study 1 also included “Suppress” and “Express” instructions that required participants to either regulate any experienced affect or react without restraint. Study 3 utilized discriminant function analyses to explore the predictive value of data acquired in Studies 1 and 2. For Study 1, greater craving was experienced after exposure to smoking-related pictures for both groups of smokers. An early frontal EAP response was also observed in both groups of abstinent smokers after cigarette cue exposure in the “Express” condition, but this cue-related response was not observed in the successful abstainer group during the “Suppress” condition. A later posterior LPP response was larger after smoking cue exposure in the “Express” and “Suppress” conditions for successful abstainers and relapsers respectively. For Study 2, reaction times to smoking-related words were significantly slower for abstinent smokers, and a significant P2a difference was seen over the anterior scalp when all abstinent smokers were compared to never smokers and when relapsers were compared to never smokers. Lastly, Study 3 found that data from Study 1 was particularly useful for predicting which of the smokers would relapse within a 1 month period, as a model that combined ERP and questionnaire data identified relapsers and successful abstainers with 86.5% accuracy. These findings have the potential to inform researchers, therapists, and cigarette smokers about the effects of cigarette cue-exposure, and may also help facilitate successful abstinence.

Keywords: ERPs, Addiction, Nicotine, Relapse, Attentional Bias, Cue-Reactivity

Dedication

To Kanako, Batool, Kiyomi, Hiromitsu, Tom, Lahab, Gori, and Kohei. You were all with me as I took on this challenge, and I look forward to taking on many more.

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Chapter 1.

Psychopharmacology of Nicotine

1.1. Drug-Receptor Interactions

The mechanisms through which nicotine exerts its behavioral, cognitive and affective effects through ionotropic receptor interactions have been studied extensively as these processes are fundamentally tied to facilitating and maintaining the addiction cycle. Although the majority of studies done in this area have used rats and mice as subjects, some human research has also been conducted by means of positron emission tomography (PET) imaging. Animal research has shown that nicotine binds to a variety of nicotinic acetylcholine receptor subunits (nAChRs), with receptor binding at these respective sites being associated with discrete cognitive and affective changes including increased anxiety at high doses ($\alpha 7$ subunit; Pandya & Yakel, 2013), selectively enhanced auditory processing in the primary auditory cortex, ($\alpha 4\beta 2$ subtype; Metherate, Intskirveli, & Kawai, 2012), enhanced reinforcement value via increased dopamine release in ventral tegmental area (Avena & Rada, 2012; Gao et al., 2010), associations with the onset of withdrawal symptoms (increased ACh and DA levels in the nucleus accumbens; Rada, Mark, Taylor, & Hoebel, 1996; Rada, Pothos, Mark, Hoebel, 1991), and modulation of the cellular basis for memory formation (long term potentiation moderation via the $\beta 2$ and $\alpha 4\beta 2$ nAChR subunits and glutamatergic AMPA/NMDA interactions; Nakauchi & Sumikawa, 2012; Bell, Shim, Chen, McQuiston, 2011, Gao et al., 2010; Nakauchi, Brennan, Boulter, & Sumikawa, 2007). In addition to these effects, researchers have also found that nicotine administration produces motor effects, with increased locomotor activity occurring via nicotinic interactions with the $\alpha 6$ subunit (which facilitates ACh and DA release in the substantia nigra (SNc) and ventral tegmental area; Cohen et al., 2012; Drenan et al., 2010). Given the relevance of each of these processes to the state of nicotine dependence, findings obtained through the use

of animal research have helped to guide applied research and treatment of human beings, particularly with improving the nicotine user's odds of quitting the habit through pharmacological intervention and in improving cognitive deficits through nAChR and DA receptor binding (i.e. Papke, Trocmé-Thibierge, Guendisch, Al Rubaiy, & Bloom, 2011; Hutchison et al., 2004; Uzüm, Diler, Bahçekapili, Tasyürekli, & Ziyilan, 2004).

1.2. Physiological, Behavioral, and Psychological Effects of Nicotine in Humans

1.2.1. Physiological/Behavioral Effects

The behavioral, cognitive, and emotional effects of acute and chronic nicotine administration in humans have also been studied extensively. Research done with a sample of adolescent female smokers found that heart rate significantly increased after one cigarette was smoked relative to a pre-smoking condition, and that desire to smoke decreased significantly once the cigarette was consumed (Corrigall, Zack, Eissenberg, Belsito, & Scher, 2001). This finding has also been replicated in research that attempted to understand how caffeine can potentiate the reinforcing effects of nicotine, with participants having increased blood pressure (Acheson, Mahler, Chi, & de Wit, 2006; Jones & Griffiths, 2003), as well as decreased skin temperature and increased heart rate after both high and low doses (Jones & Griffiths, 2003). These effects also seem to change in a dose-dependent fashion, with quicker intake (and therefore higher concentrations) of the drug causing an increase in unpleasant physiological symptoms (including nausea, dizziness, light headedness, increased heart rate, tingling sensations, and headaches; Dallery, Houtsmuller, Pickworth, & Stitzer, 2003). Importantly, use of the partial nAChR $\alpha 4\beta 2$ agonist Varenicline (Chantix) reduced heart rate and increased positive mood in a sample of smokers who were given the drug in combination with intravenous doses of nicotine (Sofuoglu, Herman, Mooney, & Waters, 2009), indicating that partial binding at the $\alpha 4\beta 2$ receptor site can decrease physiological responsivity to nicotine while mimicking the affective outcomes of nicotine administration. Physiological research has also been able to demonstrate that frequent cigarette smokers respond appetitively to nicotine cues, as startle responses elicited by auditory startle probes were decreased when participants were viewing a nicotine stimulus (Dempsey, Cohen,

Hobson, & Randall, 2007). This finding is in line with other reports in the literature, as reductions in the startle response while participants are viewing pleasant stimuli are commonly observed across studies (i.e., Lang, Bradley, & Cuthbert, 1990). Although there is a reduction in startle response when smokers view subjectively pleasant smoking cues, there is also evidence that a prolonged stress response accompanied by psychomotor agitation is elicited when smokers are exposed to psychosocial stressors (rather than acoustic stressors), and this dysregulated response may contribute substantially to the high relapse rates observed when following smokers who attempt to quit the habit (Wardle, Munafò, & de Wit, 2011; Childs & de Wit, 2009). Work done using startle probes also found that smokers have reduced startle reflexes to loud auditory stimuli relative to non-smoking control participants at baseline, therefore showing a diminished behavioral response to these aversive cues (Orain-Pelissolo, Grillon, Perez-Diaz, & Jouvent, 2004). In contrast with regular nicotine use, behavioral observations of smokers who have been nicotine deprived show that eye gaze towards nicotine cues and self-reported craving is substantially increased relative to when they were not deprived (Kang et al., 2012; Mogg, Field, & Bradley, 2005; Field, Mogg, & Bradley, 2004). Other research that had deprived and non-deprived smokers complete a visual search task also found that nicotine intake facilitated performance, with decreased fixation times and faster reaction times (RTs) to pop-out target stimuli observed in the non-deprived group (Rycroft, Rusted, & Hutton, 2005). Research has even identified an effect of nicotine on handwriting, with decreased movement time and increased velocity being observed in a non-deprived smoking group and a non-smoking control group after low and high dose nicotine gum administration (Tucha & Lange, 2004).

Some studies have attempted to understand whether there is a gender difference regarding the reinforcing effects of nicotine. Research suggests that women may become dependent on nicotine faster than men, but that they are also more likely to seek treatment (for a comprehensive review, see Lynch, Roth, & Carroll, 2002). Using a novel paradigm where participants were awarded puffs of either their preferred brand of cigarette or a low dose cigarette (.1 mg nicotine) by finding items in an array presented on a computer monitor under standard progressive ratio reinforcement contingencies, researchers were able to conclude that women were less willing to exert increasing efforts to obtain nicotine doses compared to men (Perkins, Jacobs, Sanders, &

Caggiula, 2002). Gender effects have also been reported, with men showing increased alcohol consumption when nicotine was administered via transdermal patch whereas women consumed fewer alcoholic beverages when given the opportunity to drink (Acheson, Mahler, Chi, & de Wit, 2006). Here, men were also willing to spend more money to obtain the alcoholic beverages relative to women.

1.2.2. Psychological Effects

Studies have also suggested that nicotine binding results in a number of cognitive benefits. One study had heavy smokers come into the lab and perform a short term memory task where auditory stimuli were to be recognized from a set of previously presented tones (Houlihan, Pritchard, & Robinson, 2001). Participants were required to smoke either a “denicotinized” or a “nicotine-yield” cigarette prior to each attempt at the task. In addition to replicating the finding that heart rate increased after smoking a regular nicotine cigarette, the researchers also found that accuracy improved after smoking both types of cigarettes and that reaction time (RT) scores decreased significantly after the participants smoked the “nicotine-yield” one. This study provides evidence for the cognitive benefits that nicotine can facilitate given that a within-subjects repeated measures design was employed and the independent variable “nicotine” was precisely controlled. Furthermore, this report coincides nicely with research funded by the tobacco giant Philip Morris Inc. that showed nicotine dose-dependent facilitation for sensory ERP latencies during a pattern reversal task (Gullotta, Kuhn, von Holt, Kaegler, & Reininghaus, no date). Other research also provides evidence that certain cognitive effects are specific to nicotinic binding at receptor sites in the central nervous system and that these are not a product of withdrawal reversal. Using tasks that were designed to assess improvements in covert orienting and visual search capabilities, researchers gave heavy smokers effective doses of nicotine (.9 mg) or ineffective doses (.1 mg) (Mancuso, Lejeune, & Anseau, 2001). It was found that effective doses of nicotine significantly decreased RTs to target stimuli and that eye movements were significantly faster when stimuli were presented in the periphery of the visual field. Similarly, researchers have also found that frequent cigarette smokers show decreased RTs to invalid cue trials in modified versions of the classic Posner paradigm (which measures attention capacity), with salivary cotinine (the main metabolite of nicotine) levels being

inversely correlated with RT values (Shirtcliff & Marrocco, 2003). Similar effects for selective attention have also been observed when the classic Word-Color Stroop task was completed by smokers and non-smokers. When abstinent overnight, smokers showed longer RTs and decreased accuracy when presented with incongruent Stroop trials, yet this effect disappeared when nicotine was administered before testing (Domier et al., 2007). Gender specific benefits resulting from regular nicotine use have also been reported for attention and psychomotor speed based on data obtained from the Digit Symbol Substitution task, as well as for divided attention as assessed by the delayed matching to sample task for men and women respectively (File, Dinnis, Heard, & Irvine, 2002). Related to the effects of nicotine on various aspects of memory, Min, Moon, Ko, & Shin (2001) found that transdermal administration of nicotine to non-smoking elderly participants significantly improved scores on the Rey-Kim Memory Task (a Korean version of the Rey Auditory Verbal Learning Task), which is used to assess delayed recognition, learning slope, memory retention, and retrieval efficiency. Specifically, nicotine produced a significantly improved rate of learning as expressed by a steeper learning curve in participants who were given transdermal nicotine doses. Nicotine deprivation also appears to cause a decline in verbal working memory performance, with decreased accuracy being observed when non-smokers performed the high load condition of the auditory N-back task (Jacobsen, Mencl, Constable, Westerveld, & Pugh, 2007). Importantly, this effect was not observed when smokers were non-deprived. The positive effect of nicotine on RTs in working memory tasks, RT and accuracy in short term memory tasks, and RTs in orienting attention tasks have been further confirmed using meta-analytic techniques (Heishman, Kleykamp, & Singleton, 2010). Given the benefits of nicotine on cognition, researchers have attempted to use nicotine based ACh agonists in order to provide relief for some of the symptoms of ADHD, schizophrenia, Parkinson's disease, and aging-related disorders such as Alzheimer's Disease where deficits in attention and memory differentially contribute to the dysfunctions experienced by the patients (Kadir, Almkvist, Wall, Långström, & Nordberg, 2006; see Levin, McClernon, & Rezvani, 2006; Mansvelder, van Aerde, Couey, & Brussaard, 2006 for reviews).

1.2.3. Affective Effects

Studies that compared male and female smokers to non-smoking control groups have found that persistent smokers were more likely to experience negative mood after experimentally induced states of stress (File, Dinnis, Heard, & Irvine, 2002). After difficult cognitive tests were completed in this study, smokers were found to experience higher levels of stress, discontent, spitefulness, and rebelliousness, as well as less calmness relative to non-smokers. Related to this, research has also shown that persistent smoking causes different stress reactions between genders, with male smokers showing increased aggressive tendencies relative to females after moderate stress was experimentally induced and females reporting that they felt calmer after the stress induction only when nicotine was given at the beginning of the testing session (File, Fluck, & Leahy, 2001).

Research that examines the hedonic responses of smokers to cigarettes has been useful in predicting adherence to treatment programs as well as future smoking status. Shiffman, Ferguson, and Gwaltney (2006) found that smokers who participated in a nicotine replacement therapy program were more likely to have future lapses if they rated the hedonic experience of smoking at time of initial lapse higher and that lower hedonic ratings at time of first lapse were associated with a greater amount of time before the occurrence of a second lapse. This is a pertinent finding when taken into consideration with a report that demonstrated that smokers with higher levels of anhedonia were more likely to have positive mood experimentally induced following administration of nicotine via cigarettes, and that the increased positive mood was not observed if they consumed a denicotinized cigarette prior to mood induction (Cook, Spring, & McChargue, 2007). Partial nAChR agonists can also attenuate some of the acute effects of nicotine, creating improved mood and decreasing physiological responsivity (Sofuoglu, Herman, Mooney, & Waters, 2009). There are also indications that poorer executive functioning as indexed by delayed RTs to congruent versus incongruent positively valenced trials in a modified Simon task predict smoking cessation success at baseline (Schlam et al., 2011), thus supporting the notion that assessments of affect related cue-reactivity may be especially useful when assessing risk of relapse.

Research has also suggested that nAChR binding may cause an alleviation of negative mood. By having non-smokers who showed signs of depressive symptoms wear a high-dose (7 mg) nicotine patch, researchers were able to attenuate self-reported depressed mood when this group was compared to a placebo condition (although this effect disappeared once a lower dose patch was administered) (McClernon, Hiott, Westman, Rose, & Levin, 2006). This finding was replicated in a study that compared depressed versus never depressed smokers on measures of psychomotor speed, positive reinforcement, and positive mood (Malpass & Higgs, 2007). Although both groups reported increases in positive mood after having cigarettes, depressed patients experienced positively reinforced craving within 30 minutes after smoking whereas the non-depressed group did not show this effect. This was interpreted as indicating that depressed smokers may experience greater rewarding effects when consuming cigarettes, which may make it especially hard for them to successfully quit when abstinence attempts are made. Research looking at anhedonia produced by nicotine deprivation in a sample of smokers who had no intention of quitting also found that processing for happy faces was significantly disrupted relative to a non-deprived state, as measured by the amount of time it took them to identify the gender of the face presented to them (Leventhal et al., 2012). It may be the case that abstinence from cigarette smoking produces an overall effect of blunted affective responsiveness to emotionally valenced external stimuli, and nicotine administration reverses these effects regardless of stimulus valence (Dawkins & Powell, 2011).

Chapter 2. **Addiction Neuroimaging**

Given the intricacies involved in understanding the contributions of acute drug effects and long-term neural changes that occur with repetitive self-administration of various drugs, researchers have attempted to use neuroimaging paradigms to study addiction processes as these techniques can provide valuable insights into the brain functioning of those who pathological crave substances (i.e., Fowler, Volkow, Kassed, & Chang, 2007). Through use of techniques that help to understand the effects of drugs on the brain and the processes that maintain the addiction cycle, a better understanding of the temporal and spatial aspects of addiction related brain responses can be defined.

2.1. Addiction and fMRI

One technique that has been used extensively to illustrate the processing of drug stimuli within the brain is functional magnetic resonance imaging (fMRI). The following subsections will highlight fMRI research that attempted to define the short and long term effects of various abuse substances on pathological users as well as the processing of substance-related cues. Understanding both of these domains is especially useful given that both contribute significantly to the maintenance of addiction over the lifespan.

2.1.1. Changes in Neural Activity in Addictions

Using fMRI, researchers have been able to image activations in the brain that are unique to discrete pathological conditions involving substance consumption. Furthermore, researchers have also been able to determine that significant overlap exists across conditions ranging from obesity to heavy cocaine use. In their review, Tomasi and Volkow (2013) point out that fMRI findings suggest that a network involving midbrain dopaminergic nuclei may play a fundamental role in habit formation and reward signaling, with regions in the dorsal and ventral striatum found to be more active in

response to food and drug cues for patients who are unable to regulate their intake of these substances. Furthermore, researchers have been able to reduce the neural correlates of food cue reactivity seen in obese people as well as the motivation to view high caloric food images when the mu-opioid receptor antagonist GSK1521498 was administered before an fMRI session, and this effect may not be unique to food addiction (Cambridge et al., 2013). In another interesting approach to understanding how food addiction overlaps with drug addiction, researchers gave high body mass index (BMI) participants high caloric foods or water during fMRI scans and found that these people showed hyperactive neural responses in the medial orbitofrontal cortex (OFC), ventral tegmental area, nucleus accumbens (NAcc), insula, putamen, and caudate to the taste of high caloric food only (Filbey, Myers, & Dewitt, 2012). Similar activations have also been observed after acute cocaine administration to cocaine addicts during functional imaging scans (Kufahl et al., 2005). In addition to this, Filbey, Myers, and Dewitt (2012) found that neural activation correlated with the number of self-reported symptoms on the Binge Eating Scale, with those participants who showed more occurrences of binge eating having greater activation of the brain's dopaminergic reward centers. Sustained neural responsivity to high caloric foods has also been observed in obese participants before and after consumption of food to levels of satiety, with activation of the DLPFC and lateral OFC being observed in response to these cues after consumption in the obese group only (Dimitropoulos, Tkach, Ho, & Kennedy, 2012). Researchers have also found that those who are at high risk of pathological overeating show greater activation of the insula, OFC, caudate, and putamen after monetary receipt, indicating that structural changes in the brain's reward system may cause abnormal neural responses to rewards (see review by Burger & Stice, 2011). Greater activation of the OFC in response to high caloric food cues has also been associated with future weight gain (Stice, Yokum, Burger, Epstein, & Small, 2011). Similar to the analysis completed by Stice et al. (2011), Nestor, Hester, and Garavan (2010) also found that activations of the ventral striatum in response to cues that signaled non-drug rewards were positively associated with lifetime use of cannabis, where greater BOLD responses were related to longer and heavier lifetime usage of the drug. Overall, research that attempts to compare findings from food addiction and drug addiction literature has found a substantial degree of overlap between the two conditions, suggesting that a common pathway is activated when patients respond to stimuli they pathologically crave (see

Zhang, von Deneen, Tian, Gold, & Liu, 2011 for a review). Additionally, food addiction scores have been found to correlate with medial OFC, ACC, and amygdala activations that were elicited by the anticipated receipt of food (Gearhardt et al., 2011).

Research with samples of illicit drug users who completed various cue reactivity paradigms have produced results that mirror those found with food addiction, and many of the neural activations are similar regardless of what substance is being abused. Filbey, Schacht, Myers, Chavez, and Hutchison (2009) found that tactile stimulation of the hand with marijuana paraphernalia produced increased activation of the dACC, ventral tegmental area, insula, and amygdala relative to neutral tactile cues. Activations of the OFC and nucleus accumbens were also positively correlated with greater addiction severity, and the fact that OFC was activated by haptic stimuli suggests that this region responds to substance abuse cues regardless of stimulus modality. Similar activations of the prefrontal cortex, cingulate, and striatum to the taste of alcohol in a sample of regular drinkers have also been documented in the literature, and activations to these cues were above and beyond what was observed after other appetitive taste stimuli were administered (Filbey et al., 2008). Research that examined the neural correlates of craving in a sample of methamphetamine users who were exposed to methamphetamine cues found an increased activation of the ACC, and this was seen only after exposure to drug cues (Yin et al., 2012). It has also been suggested that individual differences in reward responsivity may be valuable predictors of addiction progression in individuals who over-consume substances of preference. Cousijn et al. (2013) found that when heavy marijuana users completed the Iowa Gambling Task during fMRI scans, there was greater activation in the right OFC, insula, and left superior temporal gyrus during the win versus loss contrasts. In addition to this indication of heightened reward responsivity in heavy marijuana users relative to control participants, a significant association was found between the amount of cannabis smoked per week and the strength of the activation in the right caudate, right insula, and right ventrolateral PFC. Similar reports of differential reward responsivity have also been obtained when samples of people addicted to gambling completed an fMRI task where they attempted to win money and avoid losses. When cues that triggered the anticipation of a gain or a loss were presented during the task, those who were pathological gamblers showed decreased activity in the caudate nucleus relative to patients with obsessive compulsive

disorder and those who were healthy controls (Choi et al., 2012). This blunted response may be predictive of risk for future problem gambling, and may also be a marker that is common across other forms of addiction. Indeed, differences in performance and neural responsivity have been found to differentiate cocaine using from non-using men, where activation of the ACC, bilateral dorsal superior frontal gyri, bilateral supramarginal gyri, and bilateral middle occipital gyri were less deactivated during successful Stop Signal Task trials in drug users (Elton et al., 2014). Furthermore, administration of dopaminergic drugs appears to improve performance on the Stroop task in a sample of long term cocaine users, where methylphenidate intake reduced errors and increased post-error slowing (Moeller et al., 2014). Similar results were reported by Goldstein et al. (2010), where subjects with cocaine use disorder showed greater activation of the cdACC in response to an oral dose of methylphenidate (which correlated with a reduction in errors committed during a cocaine Stroop task) (Goldstein et al., 2010). In addition, oral methylphenidate also reduced cocaine cue-related activation of the DLPFC, which has been shown to reduce drug-cue related OFC activation due to modulations of neural communication between these two structures (Hayashi, Ko, Strafella, & Dagher, 2013). The former finding was thought to be reflective of drug addicts becoming more cautious during the task due to pharmacological intervention. Regarding brain activations, a significant decrease in right dACC and DLPFC activity was observed in the addicts when error versus correct trial contrasts were made, and the opposite effect was observed in the control group. Research done using the drug Modafinil (a drug that is currently in clinical trials and may reduce drug-related craving) found that cocaine cue induced activations of the left OFC, ventral tegmental area, and left medial PFC disappeared following drug administration (Goudriaan, Veltman, van den Brink, Dom, & Schmaal, 2013). Also, increased activation of the ACC was correlated with reductions in self-reported cocaine craving, and a similar effect was also found when participants were told to employ self-regulation strategies (Zhao et al., 2012). Interestingly, administration of the drug bupropion was also found to reduce craving for video game playing in a sample of pathological videogamers, with increased activation of the DLPFC in response to video game cues being observed at baseline and decreases in regional activity being observed after 6 weeks of treatment (Han, Hwang, & Renshaw, 2010). Based on current findings, the dorsal and ventral striatum (which code for stimulus response learning and reward prediction), OFC (which is involved in learning reward values), and

the ACC (which is implicated in guiding action choices in response to salient stimuli) appear to be heavily involved in the maintenance and initiation of addiction, with projections from midbrain dopaminergic nuclei perhaps coordinating communication between these distinct regions (see Diekhof, Falkai, & Gruber, 2008 for a review).

Although many studies have found activations in structures such as the dACC, DLPFC, OFC, and insula after drug-cue exposure in samples consisting of men and women combined (see Parvaz, Alia-Klein, Woicik, Volkow, & Goldstein, 2011 for a review), research has also found that differences in neural activations exist between genders depending on contextual differences. Potenza et al. (2012) were interested in understanding gender differences in neural activation for stress versus drug-cue induced drug craving in chronic cocaine users. Using fMRI, they had participants read individualized scripts that described drug use and stress contexts in addition to relaxing scripts, and self-reports of current stress and craving were completed after each trial. For cocaine dependent women, greater activation during the stress condition was seen in reward circuit structures, including the DLPFC, ACC, dorsal and ventral striatum, and lateral and medial OFC. For men, activation in these structures was found to be greater for the drug versus relaxing cue contrast, indicating that a gender difference in how stress and drug cues differentially elicit drug craving. The researchers state that by understanding the gender differences in cue-related craving and relapse, more effective delivery of therapy based interventions may be facilitated and success rates may increase if important factors for relapse are being targeted by the practitioner.

2.1.2. Deficits in Cognitive Functions with Repeated Substance Abuse

Deficits in cognitive functioning that arise as a result of prolonged drug use have also been the subject of functional neuroimaging studies. One study that looked at frequent ecstasy (MDMA) users found that they had reduced neural efficiency when encoding semantic stimuli (Dutch words) relative to a control group, as activity within the bilateral posterior parietal cortex was abnormal in the drug user group although task performance was similar across the drug user and control groups (Watkins et al., 2013). Importantly, this activation was significantly positively correlated with lifetime ecstasy

use. Research done with opioid pharmacotherapy users also found that repeated drug use affected neural functioning, with control participants showing increased activity in the insula, left fusiform gyrus, left supramarginal gyrus, hippocampus, and striatum during a spatial working memory task (Bach et al., 2012). However, behavioral performance was matched across groups and it was suggested that the deficits in neural processing might have become significantly associated with task performance if the task was modified to incorporate a greater cognitive load. Conceptually similar findings have also been obtained using an fMRI compatible version of the classic Stroop task with a sample of recently abstinent methamphetamine users, where poorer performance on incongruent trials relative to controls was believed to be associated with hypoactivation of the ACC, right inferior frontal gyrus, right supramarginal gyrus, anterior insula, and motor areas in the brain (Nestor, Ghahremani, Monterosso, & London, 2011). Another study had methamphetamine users complete a word-color Stroop task, and it was found that methamphetamine abusers were disadvantaged when responding to conflict trials after they were presented consecutively (trial-to-trial adjustment; Salo, Ursu, Buonocore, Leamon, & Carter, 2009). On the other hand, the control group participants demonstrated an RT advantage to this trial sequence, and this was associated with increased activation of the right PFC (conversely, very little PFC activation was seen in the drug user group). Using a drug-Stroop task that included drug and neutral words, Moeller et al. (2012) found that abstinence from heavy cocaine use was associated with improved RTs to neutral trials as well as greater activation in midbrain (ventral tegmental area and substantia nigra) at a 6 month follow-up. This midbrain region was found to be hypoactive at baseline and resembled the activations seen in active users, yet resembled the healthy control group after the abstinence period. Research using the drug-Stroop task also found greater deactivation of the rACC/mOFC ROI for cocaine use disorder patients when brain activity during drug trials was contrasted with neutral trials (Goldstein et al., 2007), although accuracy and performance by trial type was not significantly different. Higher order executive functions also become impaired with repeated cocaine use, and researchers have shown that a hypoactivational pattern in the ACC and left insula appears when users are presented with moral dilemmas, thus indicating a reduced ability to process various aspects of the event in addition to a breakdown in moral judgment capabilities more generally (Verdejo-Garcia, 2014). This reduction in higher-order cognitive abilities is also corroborated by reports that long-term

drug use impairs behavioral monitoring by decreasing ACC activity, and interoception/self-awareness is negatively affected by changes in insula functioning (Goldstein et al., 2009b). Research that had current cocaine users complete a go/no-go task after intravenous injections of the drug also found error related activations were greater in cortical regions including the right posterior cingulate, the left inferior parietal lobule, right middle frontal gyrus, and lower in the left posterior cingulate relative to saline injection, indicating a reduced ability to apply cognitive control over behavior during the task (Garavan, Kaufman, & Hester, 2008). Given the numerous reports of ACC and prefrontal cortex involvement in suboptimal performance in cognitive tasks that tap into behavioral inhibition and executive function capabilities, the maintenance of approach behavior towards substances of abuse despite their deleterious effects on quality of life may be at least partly attributed to dysfunction of these structures (i.e., Garavan & Hester, 2007).

2.1.3. Differences in Affective Appraisal between Substance Abusers and Non-Users

A great deal of research has attempted to understand how affect-related appraisal and experience change after repeated use of addictive substances. Early experiments found that cocaine users show abnormal affective responses relative to healthy control participants when viewing happy, sad, and cocaine use videos, with decreased right middle temporal lobe activation seen during the happy tape, decreased right superior frontal gyrus and bilateral caudate activation in response to the sad tape, and increased ACC activation/craving during the cocaine use tapes (Wexler et al., 2001). When Goldstein et al. (2009c) had participants suffering from cocaine use disorder and those who were not substance users respond to differently colored cocaine related and neutral words (with each button corresponding to 1 of 4 colors), it was found that cocaine users showed a heightened affective response to these motivationally relevant cues with bilateral ventral striatum activation being seen in response to drug related words only. This activation was thought to reflect the reward value of these words, given that the ventral striatum is a key dopaminergic center in the midbrain and dopamine release is known occur when classically conditioned reward stimuli are perceived (Robinson & Berridge, 1993). Goldstein et al. (2009a) also found that regions

within the ACC were differentially activated by emotionally salient monetary rewards in patients with cocaine use disorder, where greater hypoactivation of the rvACC/mOFC during the most salient condition of the task was specific to this group, and the opposite pattern was found within the cdACC during the same condition. This pattern of activation was interpreted as reflecting a compensatory mechanism, as the hypoactivations of the rvACC/mOFC were associated with better performance during the task despite an increased desire for cocaine. Furthermore, the 2 groups performed equally well on the behavioral component of the task, which further suggested that a recruitment of compensatory mechanisms could take place and that the ACC was responsible for deploying them. Research has also found that processing of naturally pleasant stimuli becomes abnormal with continued administration of the cocaine, as hypoactivation of the dorsomedial PFC/ACC, right nucleus accumbens, caudate, and putamen is seen in addicts but not healthy control participants, therefore suggesting that continued substance abuse may hijack brain circuitry that is typically used to help people interact with naturally occurring primary reinforcers in the environment (Asensio et al., 2010).

Chapter 3: Addiction Research Using Event-Related Potentials

Relative to the vast body of research that has accumulated using fMRI, research done using electrophysiological techniques (namely event-related potentials or ERPs) has been scant. Nonetheless, interest in applying the ERP technique to the study of addictions is gaining popularity and the exquisite temporal resolution associated with ERP data helps to answer questions about the real time processing of stimuli such as drug cues. Given that fMRI cannot measure neural responses in the temporal domain with this degree of specificity, findings that are obtained using ERPs provide another part to the addiction story. When considered in tandem with functional neuroimaging findings, ERPs may help to provide a more complete picture regarding many facets of the addiction cycle.

Early evidence of the utility of ERPs for studying populations affected by drug use focused on measuring deficits in information processing while brain electrical activity was recorded. In one such experiment, researchers found that 7-to-12 year old boys who were exposed to heroin in utero showed decreased amplitude of the P200 waveform elicited by auditory tones that had a low probability of occurrence (Guo et al., 1994). Another early study found that delinquent adolescent boys who were at risk for later drug dependence showed shorter latency for the auditory N100 component when distracting white noise was presented in the background during an oddball task, and the amplitude of the P300b component was also significantly smaller for those delinquent boys who had previous drug use (Herning, Hickey, Pickworth, & Jaffe, 1989).

Based on PubMed searches, it appears that a significant gap in the publishing of ERP papers focusing on the study of addictions occurred between 1994 and 2000. More recent research beginning in the year 2000 began to focus on ERPs that were elicited by drug-related cues in various samples of substance users. Herrmann et al.

(2000) found that severely dependent alcoholics had larger P300 responses to alcohol-related words relative to controls, with the waveform being more positive for alcohol relative to neutral words at the posterior midline electrode site Pz. Despite the fact that they found a between group difference, ERP responses were recorded based on amplitudes at a single electrode site centered at the vertex of the scalp, thus restricting any detection of frontal lobe responses to the cues. Another study found similar results using samples of nicotine deprived and non-deprived smokers, where greater P300 amplitude in response to visually presented cigarette cues was found although 12 hour nicotine deprivation did not significantly modulate the amplitude of this component (McDonough & Warren, 2001). Researchers have also attempted to use ERPs such as the P300 to index abnormalities in cognitive performance, and it has been found that long-term abstinent heroin users showed reduced P300 amplitude relative to patients with obsessive-compulsive disorder and healthy controls, where ERP recording was time-locked to the anticipatory period before commencing a computerized version of the digit span forward task (Papageorgiou, Rabavilas, Liappas, & Stefanis, 2003). This reduction in amplitude was thought to suggest that working memory updating was less efficient in the abstinent drug users, and that gray matter abnormalities may have been present. Another early study that had a sample of heroin users view heroin and neutral images replicated the finding that P300 amplitude was larger for heroin related pictures compared to neutral ones, but greater modulations of a later occurring ERP component in the 400-700 millisecond range indicated that processing was enhanced for drug cues (Franken, Stam, Hendriks, & van den Brink, 2003). The finding that P300 modulations occur when addicts view pictures associated with the use of their substances of preference has also been interpreted as an indication that greater allocations of attentional resources are made towards these motivationally relevant stimuli and that this may play a fundamental role in triggering relapse (Lubman, Allen, Peters, & Deakin, 2007). Furthermore, addicts appear to show greater P300/LPP responses (250-550 ms) in response to drug images relative to negative and positive ones, yet non-users showed no difference when responses to drug and neutral images were compared (Lubman, Allen, Peters, & Deakin, 2008). ERP research has also shown that long term opiate users who were currently undergoing treatment display less reduction in P300 components elicited by auditory startle probes while viewing pleasant visual stimuli, thus indicating that these naturally occurring reinforcers fail to capture attention in the same

way that might be seen in a healthy control participant (Lubman et al., 2009). Newer research has also shown that the LPP is successfully elicited after presentations of cocaine related images for those suffering from cocaine use disorders, but that an earlier occurring component called the EPN (early posterior negativity, 200-300 ms) was also elicited by these affective cues (Dunning et al., 2011). This EPN has been reported as an anterior effect in previous studies that presented participants with craving inducing stimuli, where it was termed the EAP and was believed to localize to the OFC in a manner similar to what was seen in previously mentioned fMRI research (Asmaro et al., 2012). Therefore, ERP responses have the potential to tell us a great deal about how attention is allocated towards objects in the external world in a scale of time that the participant (or fMRI techniques for that matter) could not possibly report. Importantly, ERPs can be used to gauge the strength of these various responses and successful drug use interventions could theoretical reduce the attentional biases afforded to these conditioned stimuli. Indeed, Lubman et al. (2009) found that the amplitude of the P300 elicited via startle probe during the viewing of pleasant pictures also predicted heroin relapse at a follow-up date after the initial ERP data collection session. Greater amplitude late positive potentials to marijuana pictures have also been found to differentiate heavy marijuana users from non-using controls, although no significant correlations between LPP amplitude and self-reported craving were found (Wölfling, Flor, & Grüsser, 2008). Similar results were also obtained when researchers had samples of abstinent cocaine users and control participants view randomized cocaine and neutral images, with cocaine images producing enhanced positivities in late occurring components ranging from 700 to 4000 milliseconds (Van de Laar, Licht, Franken, & Hendriks, 2004). Importantly, this was interpreted as suggesting that drug cues were still able to engage the neural systems responsible for emotion in the abstinent cocaine user group despite the long period of abstinence, thus illustrating the power of such cues and their potential to trigger relapses.

The utility of measuring ERP responses to salient cues is further illustrated by a study that had obese and normal weight individuals view high caloric food stimuli and neutral cues while either hungry or satiated. Here, it was found that P300/LPP amplitude was reduced after satiety in the normal weight group only, yet obese participants had a larger response when hungry (Nijs, Muris, Euser, & Franken, 2010). These results, when

considered in tandem with other aforementioned research findings, provide evidence that specific ERP components can help to discriminate those who pathological crave a substance from those who simply enjoy it, and that modulations of certain components can be induced by aspects of the experiment that attempt to reduce cue reactivity. Although the majority of published studies use visual cues as target stimuli, ERP research done with auditory cues has found similar results, including greater amplitude P300 and LPP amplitudes to alcohol related sounds for detoxified alcoholics but not for controls (Heinze, Wölfling, & Grüsser, 2007), therefore providing evidence for the notion that stimuli can be classically conditioned to reward anticipation regardless of sensory modality. Remarkably, similar paradigms have also been able to assess the evoked LPP response to video game cues among casual players and those that play online games excessively, with video game cues eliciting a significantly larger LPP response for those in the excessive gaming group only (Thalemann, Wölfling, & Grüsser, 2007). Given the similarities between excessive video game playing and drug addiction, this study exemplifies the utility of using ERP paradigms to study abnormal cue processing in pathological populations, as paradigms can easily be modified to study discrete populations of addicts and to define neural responses that support the argument that two sets of maladaptive behaviors are similar in terms of how the brain responds to cues that have been classically conditioned to the different experiences of these individuals. A recent meta-analysis also appears to affirm the reliability of the P300 and LPP components being elicited by substance related pictures for substance users, with moderate to large effect sizes being observed when all identified studies were factored into the analysis (Littel, Euser, Munafò, & Franken, 2012).

A clinically relevant finding was also obtained using ERPs when cocaine dependent participants and controls were asked to respond with a left or right button press when the central letter in a letter array was either an H or an S (Franken, van Strien, Franzek, & van de Wetering, 2007). This task is known to produce errors, and differences in the error related negativity (ERN) component were found between groups. For the cocaine user group, there was a significant reduction in ERN amplitude relative to controls, which may indicate a reduced awareness of errors made during the task. This is plausible, especially given that the cocaine users had significantly more errors of omission and commission during the task. This finding could generalize to the real world,

where cocaine addicts may show decreased awareness for decision making errors, which could lead to a host of negative outcomes. Indeed, researchers have also attempted to use the amplitudes of drug-cue elicited components to predict treatment success. In one such study, abstinent drug users who failed to abstain from drug use after self-admission to a drug treatment program were found to have significantly reduced P300s to oddball stimuli in a visual discrimination task relative to former users who successfully completed the program (Wan, Baldridge, Colby, Stanford, 2010). Importantly, P3 amplitude predicted treatment outcome to a greater degree than any other questionnaire or psychophysiological index included in the study, where 76.2% of relapses were predicted by this factor alone. Similar research with cocaine addicts also replicates the methodology used by Wan et al. (2010), with LPP amplitudes significantly predicting drug choice behavior as measured by the selection to view cocaine related picture relative to positive, negative, and neutral ones (Moeller et al., 2012), although the effect was only found in drug users who had little insight into what triggered their relapses. Based on studies that attempt to use ERP components to predict real-world behavior, there appears to be considerable utility in using this technique but more work needs to be done in order to assess the validity of the procedure.

Chapter 4. **Nicotine Dependence and Functional Neuroimaging**

Although a great deal of neuroimaging research has been done with addiction processes in general, less research has been done with nicotine addiction specifically. Given that nicotine dependent subjects frequently relapse following attempts at abstinence, it is particularly important to try and understand which personal and situational factors may affect relapse occurrence, as well as how cognitive control and reductions in nicotine cue responsivity may affect the long term prospects of this population.

4.1. fMRI Research on Nicotine Addiction

Since the late 1990s, researchers have attempted to understand how the human brain responds to nicotine cues and to the drug itself, with initial findings indicating that intravenous nicotine administration caused activation of the insula, PCC and ACC, orbital, dorsal, and medial frontal lobes, nucleus accumbens, and amygdala relative to saline injection (Stein et al., 1998). fMRI research projects have been devised in attempts to understand how attitudes towards nicotine consumption may be differentially related to nicotine cue elicited neural activations. Stippekohl et al. (2012) found that nicotine users who were unhappy with their smoking habits showed increased activation in neural regions associated with appetitive cue processing relative to smokers who were content with smoking. Here, it was found that these discontent smokers showed greater activation of the amygdala, insula, and hippocampus when stimuli that represented the immediate reward of cigarettes were presented. This was believed to indicate that discontented smokers may have an increase in incentive value for cigarette cues that signal the reception of reward, and that this may be a neural foundation for the attitude-behavior inconsistency they show with regard to their smoking habit. Perhaps because the incentive value is so great, attempts at regulation fail despite the smoker

wishing they could quit the habit. When considering the incentive salience model of addiction, where liking for a drug stays the same over time yet the wanting aspect increases (Robinson & Berridge, 2003), it could also be predicted that people who have been smoking for longer periods of time throughout the lifespan may be more susceptible to this kind of hyperactive responding. Research that studied neural responsivity to nicotine cues in a sample of men who currently smoke found that when cigarette stimuli were presented, the allocation of attention towards them was associated with activation of the left PCC, right ACC, right DLPFC, bilateral insula, left inferior parietal gyrus, and right superior parietal gyrus (Kang et al., 2012). It was further determined that activations of the left and right PCC, right DLPFC, and left primary motor cortex were associated with the deployment of attention to the cigarette cues, yet activation of the left OFC and left insula were predictive of greater craving when they were correlated with QSU (which is a questionnaire that measures nicotine craving) scores.

Functional connectivity has also been studied in order to identify neural networks that appear to be involved in the processing of nicotine cues for nicotine dependent individuals, and researchers have found that a mPFC-left fronto-parietal network was activated by smoking cues smokers but not for non-smokers (Janes, Nickerson, Frederick, & Kaufman, 2012). Interestingly, the regions that these researchers used to define their mPFC and left fronto-parietal networks include many of the same structures identified by Kang et al. (2012), with activation of the insula, DLPFC, ACC, OFC, and parietal cortices being activated by the sight of cigarette cues only. Research that compared heavy smokers with problem gamblers seeking treatment and healthy controls also found that heavy smokers showed increased smoking-cue activations in the bilateral ventromedial PFC, left ventrolateral PFC, and rostral ACC in response to cigarette cues only, although former gamblers showed a similar pattern (albeit no ventromedial PFC activation) when presented with gambling cues (Goudriaan, de Ruiter, van den Brink, Oosterlaan, & Veltman, 2010). fMRI research with nicotine dependent samples has also been able to demonstrate that different activations can be elicited based on modality of stimulus presentation. Yalachkov, Kaiser, Görres, Seehaus, & Naumer (2013) compared BOLD responses to tactile cigarette cues relative to cues presented visually, with touch related activations being more pronounced in the dorsal

striatum. Activations to haptically presented cues were also positively correlated with severity of nicotine dependence as measured by the Fagerstrom Test for Nicotine Dependence (FTND). The authors note that smoking becomes a learned, automatic behavior over time, so this finding may be particularly useful for distinguishing smokers who are in the earlier stages of addiction from those that are compulsive, heavy smokers. Furthermore, the observed activation to haptically presented cues may be a useful biomarker for severity of nicotine dependence. Differences in nicotine cue-related activation have also been observed between groups of occasional and nicotine dependent smokers, with occasional smokers showing increased responsivity in the reward circuit during anticipation of a monetary reward and addicted smokers showing increased activations to cues that predicted both monetary and nicotine rewards (Bühler et al., 2010). Importantly, when the participants were deprived of nicotine the only regions to show a significant change in BOLD signal were the inferior and middle orbitofrontal cortices, the medial superior frontal gyrus, anterior cingulate gyrus, and gyrus rectus. In the deprivation condition, these activations were observed regardless of whether the stimulus was a nicotine or monetary cue. fMRI research has also suggested that bottom-up and top-down processing of nicotine cues may change when a smoker manages to successfully quit. Here, increased nicotine cue responsivity was found in the nucleus accumbens and the ACC when smokers were compared to ex-smokers (Nestor, McCabe, Jones, Clancy, & Garavan, 2011). On the other hand, ex-smokers were found to have increased activation in response to cigarette cues in the DLPFC and insula, suggesting that greater cognitive control was being utilized in order to minimize feelings of craving. The idea that improved cognitive control can blunt nicotine-cue responsivity has obvious therapeutic implications, and studies that attempt to assess differential neural functions within groups of heavy smokers during attempts at cognitive control may help to further the utility of this approach. Assessing differences in adolescent smokers may also facilitate intervention research and could also identify those who are at greater risk for later severe addiction, and research has shown that adolescents who have reduced reward responsivity in the bilateral ventral striatum during a monetary incentive delay task were more impulsive and more likely to smoke (Peters et al., 2011). The idea that decreased reward sensitivity may contribute more to the addiction cycle than impulsivity has also been a topic of debate within the literature, and the current consensus is that both concepts may contribute to the development of addiction (see

Hommer, Bjork, & Gilman, 2011). Understanding how adolescent smokers respond to nicotine cues is an emerging area of research and the need for it is especially prudent given that even light adolescent smokers (<5 cigarettes per day) show activation in the medial OFC, left ACC, bilateral PCC, and left amygdala in response to smoking cues, and this pattern closely reflects that seen in highly addicted adults (Rubinstein et al., 2011).

The effects of nicotine withdrawal have also been assessed by fMRI, and early findings indicated that smokers showed increased activation of structures including the nucleus accumbens, ventral tegmental area, and middle frontal gyrus to nicotine cues relative to neutral cues following overnight deprivation (Due, Huettel, Hall, & Rubin, 2002). Onur et al. (2012) found that overnight smoking abstinence was associated with reductions in right amygdala responsivity to fearful faces, yet no differences were observed when satiated smokers were compared to non-smokers. Furthermore, the response was found to be negatively correlated with severity of dependence, suggesting that fear stimulus processing becomes more abnormal due to nicotinic effects on neurons that communicate with amygdala structures. McClernon, Kozink, Lutz, and Rose (2009) found that 24 hour abstinence resulted in a potentiated response to pictures of nicotine related cues in regions including the right superior parietal lobule, bilateral precuneus, bilateral PCC, bilateral striatum, and left superior frontal gyrus. Importantly, once satiation occurred there were no significant differences in regional BOLD activation for nicotine and neutral cues. Differences in regional cerebral blood flow have been observed when using arterial spin labeling MRI, where increased blood flow in the inferior ACC/mOFC (a region similar to that seen in Goldstein et al., 2009a), and left OFC were found during cigarette abstinence (Wang et al., 2007). Furthermore, a decrease in blood-flow to the right PFC was seen during abstinence and this deactivation was negatively correlated with craving, (which fits in nicely with findings reported by Hayashi, Ko, Strafella, & Dagher, 2013 and Han, Hwang, & Renshaw, 2010). Despite differences that have been reported before and during abstinence, some reports suggest that neural responses to nicotine cues remain relatively stable during short term abstinence, particularly within the brain's reward structures (McClernon, Hiott, Huettel, & Rose, 2005).

In addition to the research on neural activation to nicotine cues, a number of studies have tried to decrease nicotine cue-related activations in specific neural structures and modulate neural responses that may change after effective smoking-related intervention. By giving nicotine addicted participants instructions to reappraise cigarette stimuli instead of simply processing them as a reward predictors, Zhao et al. (2012) found that the dorsal anterior cingulate cortex (dACC) was recruited during self-regulation attempts and that activation here was significantly negatively correlated with self-reported cigarette craving. In a striking demonstration of how different neural structures involved in nicotine cue processing interact, Hayashi, Ko, Strafella, and Dagher (2013) had smokers view videos that showed people engaging in smoking behavior during fMRI runs while TMS was applied to the left DLPFC. When the TMS machine was on and the participants were watching the smoking videos, significant reductions in left DLPFC, medial OFC and ventral striatum BOLD responses were observed along with significant reductions in self-reported cigarette craving. These same structures were also found to be hyperactive in response to the cues when a sham TMS procedure was applied. Based on these results, the researchers state that cue-related activation of the medial OFC could possibly be modified via upstream inactivation of the left DLPFC, which would subsequently result in reduced craving. Disruption of function in other cortical regions have also been associated with cessation of smoking, with dramatic evidence showing that ablation of the insula caused a number of long term smokers to suddenly quit the habit and importantly, they no longer felt the urge to smoke (Dani & Montague, 2007; Naqvi, Rudrauf, Damasio, & Bechara, 2007).

Reductions in activity at specific neural regions have also been observed when nicotine replacement therapies were administered to abstinent smokers, with improved executive functioning, attention, and concentration being correlated with activation changes in the OFC, cingulate cortex, and fronto-temporal/insular cortex (Cole et al., 2010). Research on cognitive control could be especially effective when paired with research that attempts to identify biological markers of nicotine addiction. For instance, Hong et al. (2009) found that functional connectivity between the dACC and striatum was indicative of severity of nicotine dependence, and that administration of nicotine increased functional connectivity between the OFC-striatum and ACC-striatum. If therapeutic approaches could alter the strength of the connectivity between these

circuits, greater treatment success may occur as a result and this could also provide a measure for therapeutic efficacy. Studies that attempted to determine whether effortful cognitive control can change nicotine-cue neural activations have also been conducted, and one study found that instructions to suppress craving caused greater activation of the left ACC, middle superior frontal gyrus, precuneus, and posterior cingulate cortex (PCC), which indicated that cognitive control mechanisms were recruited to modulate experienced craving (Brody et al., 2007). However, no reduction in self-reported craving was observed, and the researchers explained this as potentially being caused by participants paying more attention to cues in the resist trials after being told not to do so. It is worth mentioning that exercise has also been found to reduce activations in brain regions that are activated by the sight of cigarette cues, where decreases in self-reported craving and increases in the PCC and the rostral-medial frontal region were seen in response to smoking cues after exercise. However, participants who underwent a control procedure showed activation in reward regions to the same cues and no decrease in self-reported craving (Van Rensburg, Taylor, Hodgson, & Benattayallah, 2009). Evidence also supports the notion that tailored therapeutic messages may be more effective than generic statements made within therapeutic contexts for the treatment nicotine addicts. In one study, highly tailored messages elicited greater activation of the rostral medial prefrontal cortex (a region of the brain that is implicated in self-referential processing) relative to low tailored and generic statements (Chua, Liberzon, Welsh, & Strecher, 2009). In addition to showing how making a therapy personally relevant can recruit different neural regions that may facilitate the development of cognitive control over the habit, this study also demonstrated the utility of using neuroimaging techniques to create and measure individualized therapeutic approaches (which may prove highly efficacious relative to a “one size fits all” approach).

Chapter 5. Nicotine Dependence and Event-Related Potential Research

Relative to the large number of studies that have been done to understand the interaction between nicotine consumption, behaviour, and cognition using fMRI, significantly less published empirical research exists with the use of ERP technology. Nonetheless, results obtained using this technique were of significant interest to a number of major tobacco companies in the 1980s (e.g. Philip Morris, RJ Reynolds) (Wayne, Connolly, & Henningfield, 2004) and there has been a renewed interest in using this technique for nicotine research in the 21st century.

5.1. Nicotine Addiction and Drug Cueing

As was mentioned in Chapter 3, early work using the ERP technique was able to identify ERP components (namely the P300) that were larger in amplitude to cigarette versus neutral visual cues (McDonough & Warren, 2001). More recent research has found that nicotine-related words were able to elicit ERP components in a modified Stroop (nicotine Stroop) task. Here, early modulations of P1 and N1 amplitudes, greater positivities over the right frontal scalp peaking around 200 ms post-stimulus presentation, and pronounced posterior negativities to smoking words over posterior scalp sites (including reduced P300 amplitude) were seen for smokers but not non-smoking control participants (Fehr, Wiedenmann, & Herrmann, 2006). Interestingly, there were no differences in RTs or accuracy during the task despite the differential neural activity between groups. This group of researchers later detailed both smokers and non-smoker's behavioral and physiological responses during a color-matching task, where the monochromatic color of smoking related and neutral visual scenes needed to be identified (Fehr, Wiedenmann, & Herrmann, 2007). Here, it was found that smokers showed greater positivities in response to smoking cues in a time window ranging from 400-600 ms (LPP). An earlier occurring right frontal positivity was also observed

between 200-250 ms in response to the same cues. The use of ERP technology has also been useful for defining the neural responses to nicotine cues after prolonged periods of nicotine abstinence. One study had smokers, ex-smokers, and never smokers view pictures of cigarette related and neutral pictures, and it was determined that P300 and slow-positive wave amplitudes were larger for smokers relative to the other groups in response to cigarette cues, yet no difference was seen between the ex-smokers and controls (Littel & Franken, 2007). This was thought to indicate that ex-smokers show the same degree of bias towards the cigarette pictures as those who had never smoked, yet a pronounced bias towards cigarette cues was characteristic of current smokers in response to the presentation of these motivationally relevant cues. Later work with samples of cigarette smokers has further delineated how slow wave late positive potentials (LPPs) are especially sensitive to cigarette cues, with larger LPPs being observed after cigarette cue presentations relative to positive, negative, and neutral ones (Versace et al., 2011). In addition, researchers have also shown that geometric shapes that had been repeatedly paired with cigarette images were able to elicit a sustained positive potential ranging from 300-800 ms (Littel & Franken, 2012), thus indicating that cigarette cues can facilitate classical conditioning to previously neutral stimuli, therefore turning them into conditioned stimuli (CS). Research done using a task that is known to elicit the ERN and Pe (error positivity) components (the Eriksen flanker task) has also shown that smokers' neural responses to errors are different than those seen in control participants (Franken, van Strien, & Kuijpers, 2010). Although accuracy and error rates were not significantly different between groups and the ERN component was of comparable magnitude after incorrect trials, the smokers were found to have reduced amplitude Pe waveforms indicating that the errors were not as relevant to smokers and that error processing was attenuated. Research findings that describe deficits in error salience are also complemented by findings obtained using tasks that assess inhibitory control capabilities. Using a modified Go/NoGo task (smoking go/NoGo) where participants viewed cigarette and neutral cues that had differently colored borders indicating that they should respond as quickly as possible or withhold their responses, researchers found that cigarette smokers were less likely to correctly inhibit themselves during the task (Luijten, Littel, & Franken, 2011). This deficit in performance was also indexed by reductions in N2 amplitudes, which may reflect an inhibitory control deficit with obvious implications for the maintenance of cigarette

consumption. ERP research has also identified a component that is sensitive to outcomes such as gains or losses known as the ORN component (Kamarajan et al., 2009), and it has been determined that the amplitude of this component is heightened when deprived smokers view stimuli that indicate the potential for nicotine rewards in a modified gambling task (Muñoz, Anllo-Vento, del Carmen Fernández, Montoya, & Vila, 2012). Furthermore, ORN amplitudes to cues that indicated that there was potential to have a cigarette predicted desire to smoke as measured by the QSU in the nicotine deprived group only, therefore indicating that the reward value for this cue was larger than that found during states of satiety.

5.2. ERPs and Nicotinic Effects on Cognitive Processes

Researchers have used ERPs to study the direct action of nicotine on components that are commonly elicited by specific tasks. One demonstration of this approach comes from a study conducted by Shah et al. (2011). When non-smokers were given oral doses of nicotine and performed a visual search task, the N2pC component that was elicited when participants located the singleton feature that popped out from the display was greater for those participants who had greater physiological reactions to the drug (as measured by heart rate). The opposite effect was seen for those who had lower heart rate, and this was taken as an indication that cognitive effects (namely increased visuospatial attention) were not uniformly observed in the entire population. This finding nicely reflects other research that suggests nAChR binding causes improvements on tasks that require the allocation of attention (e.g. Mancuso, Lejeune, & Ansseau, 2001; Domier et al., 2007), including findings that nicotine can enhance the preconscious detection of deviant auditory stimuli as measured by the mismatch negativity component (Fisher et al., 2010; Martin, Davalos, & Kiskey, 2009). Despite pronounced changes in ERP component amplitudes in tasks that require both visual and auditory attention, behavioral results have not reflected these neural processing enhancements although a number of studies do report decreases in reaction times (see Knott et al., 2009). The enhanced cognitive abilities that some people experience may also serve to reinforce drug use or may serve as a marker for susceptibility to more severe substance abuse in later life. Related to reinforcement

susceptibility, ERP research that attempted to explore differences between male and female smokers regarding their ability to deploy attention also found that the N100 component was of larger amplitude to target trials in a spatial cueing task, but P300 amplitudes were similar for both groups (Neuhaus et al., 2009). Although this needs to be defined in further studies, gender differences that exist regarding how attention is deployed to stimuli in the external world may be important for researchers to understand, especially when considered in tandem with drug cue reactivity findings regarding the initiation of craving. Lastly, Gilbert et al. (2004) were able to show how nicotine deprivation and satiety differentially modulate affective responses to emotionally valenced stimuli, which has obvious implications when self-medicating behavior and its role in maintaining substance abuse is taken into consideration. Here, the amplitude of the frontal PN component elicited by negative stimuli was significantly larger in the abstinence condition, yet nicotine administration was found to significantly decrease its size thus reflecting a reduction in cue salience.

Cognitive research that used the ERP technique has also identified markers that indicate nicotine dependence, which may be especially useful if clinicians wish to acquire objective measurements of relapse susceptibility. Mobascher et al. (2010) conducted a large scale study of smokers and non-smokers from six institutions within Germany and found significant differences between smokers and non-smokers when EEG recordings were completed. Specifically, smokers were found to have reduced amplitude P300b global field power in response to infrequent auditory oddball stimuli relative to non-smokers, and the reduced amplitude of the P300b was believed to be an endophenotype for nicotine abuse. Importantly, heavier nicotine use was negatively correlated with reduced P300b amplitude, therefore suggesting that the amplitude of this component may distinguish those who are in need of more intensive interventions. More recent research has found that the LPP may also be a strong predictor of long term smoking abstinence. Versace et al. (2012) had participants view negative, cigarette, pleasant, and neutral stimuli while brain activity was recorded, and each subject was interviewed at a number of time points to check on whether their attempts at abstinence were successful. Smokers who were less likely to be abstinent showed decreased LPP responses to pleasant stimuli, thus supporting the idea that repeated drug use hijacks the system that responds to naturally occurring rewards. It is worth mentioning that this

effect, in addition to late positive potentials (which frequently include windows of time that demarcate the P300 components) have also been reliably observed in studies conducted by tobacco manufacturers themselves (see Panzano, Wayne, Pickworth, & Connolly, 2010). The attenuation of the P300b in smokers when they discriminated between stimuli and the use of the LPC (or LPP) in discriminating between different cigarette odors were both regarded as strong electrophysiological candidates for assessing flavor discrimination. Internal documents from these manufacturers also show that these effects were first described several decades ago and were used to guide corporate decisions regarding the marketing of tobacco products. This is especially relevant given the findings from one study that had former smokers and non-smokers complete an auditory oddball task while EEG was recorded. Here, former smokers were found to have a reduced P300 response to the deviant tone, and source localization found pronounced hypoactivations in the left DLPFC and medial OFC relative to the control group (Neuhaus et al., 2006). These findings were thought to indicate that neural responses in frontal lobe structures that facilitate cognition and adaptive behavior remain abnormal for many years after the smoker quits, and that the brain continues to behave as though it is in a nicotine deprived state for an indefinite amount of time.

Chapter 6. **Emotion Regulation**

While there have been a number of attempts to understand the neural correlates of cue-reactivity to appetitive stimuli, there have been far fewer studies that have attempted to understand the processes that are engaged when attempts at affect regulation are employed. According to Gross (2002), emotion regulation refers to the processes we use to regulate our emotions, when we experience them, and how we express them. Additionally, we distinguish between antecedent-focused strategies (which refer to processes that modulate an affective experience prior to the actual activation of an emotional response), and response-focused strategies (which modulate emotional experience after the response has already been activated). The following section will summarize some of the current findings that have been reported on in this area of research.

According to Richards and Gross (2000), our capacity to employ self-regulation strategies during day to day functioning is critical for our adaptive success. Given that emotions are powerful drivers of goal-directed behaviour, successfully managing impulses that are triggered by them also seems particularly relevant for understanding addictions and that reducing memory for perceived stimuli may help buffer smokers (and other kinds of addicts) from cue-related craving. Indeed, Richards and Gross (2000) also note that the results of a study they conducted which explicitly linked affect regulation attempts to a reduction in cognitive resources during the processing of evocative emotional cues found that affect suppression attempts impaired memory for information that was presented during a short film. It is noteworthy that attempts at affect suppression and attempts at cognitive reappraisal produced differential effects on memory, where affect suppression was found to impair memory while cognitive reappraisal did not. Despite these differential effects on cognitive processes, both emotion regulation strategies produced the desired effect of dampening emotional reactivity during the presentation of negative stimuli in this experiment. Furthermore,

Gross (1998) posits that emotion regulation strategies can be implemented early on during the generation of an emotional response, or later (after a person's subjective response tendencies have been initiated). He further notes that affect suppression strategies (which inherently deal with emotion inhibition after a response has already been elicited), tend to be implemented at the later stage. On the other hand, cognitive reappraisal (where a response to a particular situation or stimulus is effortfully construed in an alternate way), tends to be implemented early on. Although both strategies have considerable merit when the day-to-day functioning of smokers is considered, explicitly reducing their memories of cigarette-related cues could help to reduce the probability of future relapses due to its effects on explicit memory processes. With sufficient training, it is also theoretically plausible that this group could learn to suppress affect when being situated in environments where cigarette cue exposure is highly likely. Other research has also found that those who use emotion suppression strategies tend to look away from emotionally evocative cues more than those who attempt to use cognitive reappraisal (Bebko, Franconeri, Ochsner, & Chiao, 2011), which may also play a role in mitigating cue-related craving.

Researchers have also attempted to identify the neural correlates of emotion regulation using functional neuroimaging. A recently published meta-analysis found that cognitive reappraisal attempts during the presentation of emotional stimuli appear to activate regions of the brain that are linked to cognitive control, including the dorsomedial PFC, dorsolateral PFC, ventrolateral PFC, as well as parts of the posterior parietal cortex (Buhle et al., 2013). Other research has also shed light on the neural correlates of emotion suppression, with regions of the brain implicated in cognitive control (i.e., PFC and ventrolateral PFC) being activated by short films that attempted to induce negative affect in participants (Goldin, McRae, Ramel, & Gross, 2008). However, it was also found that greater amygdala and insula activation in the right hemisphere was elicited for suppress but not reappraisal attempts, and that suppress mechanisms took longer to activate (10.5-15 seconds relative to 0-4.5 seconds). Taken together, it appears as though prefrontal circuitry plays an integral role in the application of both of these strategies and that the temporal nature of their implementation may require follow-up investigation using techniques that are more suited for looking at temporal dynamics (i.e., event-related potentials).

Event-related potential studies that have attempted to explore the neural correlates of cognitive control are scarce, although some preliminary findings have been reported. Using cognitive reappraisal instructions, Hajcak & Nieuwenhuis (2006) found that the late-positive potential (LPP) response to unpleasant stimuli was significantly reduced relative to a condition where participants were simply told to attend to the stimuli. Importantly, the intensity of the participants' emotional experience was also reduced when attempts at suppression were made. Similar effects have also been reported in an experiment that had participants suppress affect while unpleasant stimuli were presented, with decreased P2 (250-350 ms) and LPP (350-600 ms) amplitudes to such cues being observed relative to a passive viewing condition (Moser, Hajcak, Bukay, & Simons, 2006). However, no effect for reappraisal was reported for LPP modulations to positive stimuli even though these stimuli were incorporated into their paradigm. Given that drug cues elicit an appetitive response for users of those substances, addressing how affect regulation interacts with the perception of craving inducing cues still needs to be explored from an ERP perspective.

Chapter 7. **Rationale for Proposed Studies**

Based on the research presented in the preceding paragraphs, it appears that cue-reactivity paradigms that utilize the ERP method can help address research questions that are related to the processing of appetitive, reward-related stimuli. Given the enormous public health burden posed by nicotine addiction and the relevance of understand how affect regulation may help to mitigate attentional bias and cue-related craving experienced by this subgroup of the population, an ERP paradigm that uniquely incorporated these elements into it could provide a great deal of information about how smokers process these cues as well as how they utilize cognitive control strategies relative to those who have never smoked before. Being able to identify people who are more at risk for relapse based on their electrophysiological responses to smoking cues as well as those who are more likely to successfully buffer themselves from cue-related craving can also be addressed using ERPs, may the components that define these responses still need to be delineated. Lastly, there appears to be heterogeneity in terms of the kinds of stimuli presented to participants during cue-reactivity paradigms (i.e., words, pictures, videos), and further investigation of how different stimuli may uniquely elicited ERP components that are specific to smoking words still needs to be explored. Study 1 attempted to investigate smoking cue-reactivity in a picture-based affect suppression task with groups of participants that met criteria for nicotine dependence and were later found to have relapsed or abstained over a 1 month period, while Study 2 attempted to determine whether these participant's ERP responses to smoking-word presentations differed across group and stimulus type.

Chapter 8. **Study 1- Introduction**

Nicotine dependence is a global issue that has created a major burden on the health of human beings worldwide. Smokers' attempts at abstinence are frequently met with failure, and studies have reported relapse rates approaching 50% less than 2 months after the initial attempt at quitting is made (i.e., Janes et al., 2010). This is especially concerning given that in 2005 alone, there were 5.4 million tobacco attributable deaths worldwide and estimates predict that up to 10 percent of deaths worldwide will be tobacco related by 2015 (Mathers & Loncar, 2006). The severity of the problem has become large enough that researchers have even begun developing vaccines in order to prevent the initiation of the habit altogether, although a recent clinical trial appears to have met little success (Tonstad et al., 2013). Given the immense difficulty cigarette smokers have when trying to achieve long term abstinence and because of the associated human and economic costs at global, national, and local levels, a great deal of research has been conducted in order to understand the neural correlates of this specific addiction in order to increase abstinence success rates.

Research has shown that the active ingredient in the cigarette (nicotine) causes profound changes at the cellular level in a number of neural regions including the ventral tegmental area, nucleus accumbens, hippocampus, hypothalamus, amygdala, and PFC via modulation of acetylcholine and dopaminergic neurotransmission (see Rosenthal, Weitzman, and Benowitz, 2011; Engelmann et al., 2012). Cellular changes in circuits involving these brain regions are thought to reinforce nicotine consumption and may lead to severe addiction, but looking at cellular level changes does not fully capture the effects of stimuli that have become associated with the drug taking experience and how they elicit conditioned responses (namely, effortful behaviour aimed at obtaining cigarettes despite efforts to abstain; see Robinson & Berridge, 1993). In order to do this, neuroimaging studies that look at drug-cue reactivity have been utilized in order to facilitate a better understanding about the neural structures involved in this response as

well as the discrete cognitive processes they support. By using paradigms such as these, a better understanding of how frontal lobe networks and their connections with more posterior cortical regions contribute to the addiction cycle may be achieved. Ultimately, results from studies such as these could improve the effectiveness of intervention techniques that are designed to help smokers successfully abstain from future nicotine abuse.

One technique that has considerable utility in addressing this area of research is the event-related potential (ERP) technique. ERPs have excellent temporal resolution (up to 1 msec; see Luck, 2005), and can detect biological markers in addicted individuals that may be useful for identifying groups that are at high risk for relapse. ERP research has revealed that pictures of substances that people crave (i.e., marijuana, chocolate, cigarettes, and cocaine) produce reliable patterns of activation when those high in trait craving view them relative to control groups that either do not use the given substances or are low in trait craving for them (Asmaro et al., 2012; Asmaro, Carolan, & Liotti, 2014; Versace et al., 2011; Dunning et al., 2011). These patterns of activation include a positive going potential over the frontal scalp occurring roughly 200-350 msec after stimulus presentation (EAP effect), as well as a more posterior positivity overlying the parietal lobes in the 400-2000 msec range (LPP effect). The clinical significance of these findings are further strengthened by observations coming from studies that used fMRI designs to measure neural reactivity within the brain while drug cues are being perceived. For example, Engelmann et al. (2012) used activation likelihood estimation in their meta-analysis of smoking-cue reactivity in fMRI paradigms and found that medial PFC and extended visual system activations were most commonly observed across all studies. Interestingly, the previously noted ERP effects were detected at regions of the scalp that overlie the neural regions cited in the Engelmann et al. meta-analysis. Despite the fact that between group differences are reliably observed when drug/substance cues are presented, little is known about how these activations predict relapse among those trying to abstain from substance use. If assessment of cue-reactivity can be explicitly linked to prospective outcomes for individuals who enter smoking cessation programs, the potential for using ERPs in clinical settings could increase substantially due to their ability to facilitate tailoring of interventions to meet the needs of specific clients and

because the maintenance and acquisition costs of the recording and analysis equipment is quite low.

The concepts of cognitive control and impulsivity have received attention in the addiction literature and both are highly relevant to smoking cessation research. Researchers have found that people who are high in trait impulsivity (and therefore lack the necessary cognitive control to regulate the automaticity of impulsive drug taking) particularly when experiencing subjective states of craving, are more likely to remain addicted in the long term (i.e., Ersche et al., 2012). Due to findings such as these, efforts have also been made to assess the impact that various cognitive strategies have in reducing self-reported craving. Using fMRI, Zhao et al. (2012) found that self-reported craving for cigarettes decreased after trials where subjects were told to regulate their emotions relative to trials where they were told to express their feelings naturally. Furthermore, data from their fMRI scans indicated that activity in the right dACC increased when “regulate” instructions appeared on screen. Based on this study, it appears as though effortful regulation of affective state stimulates activation in this neural region. It is also possible that cognitive control over conditioned responses to nicotine cues may be achieved via communication from pathways extending from the dACC. In addition to findings that were obtained through fMRI, researchers have also demonstrated that cognitive reappraisal strategies that distract participants from evaluating the pleasurable aspects of cigarette cues also diminish the amplitude of late occurring ERP components when comparisons are made with conditions that required participants to think of the appetitive value of presented stimuli (Littel & Franken, 2011). Although research on emotion regulation has been receiving a great deal of interest in the last 15 years, many of its applications are not clearly delineated, especially when neural processes that indicate that these mechanisms are being engaged are taken into consideration (Gross, 2013).

8.1. Study One- Hypotheses

Two similar sets of hypotheses were put forward for the EAP and LPP effects. First, it was predicted that a significant EAP effect would be present in both the relapser and abstinent groups but not in the never-smoker control group when instructions to

react to the stimuli without restraint were given (Express condition). Second, it was anticipated that the EAP effect in the Express condition would vary in amplitude as a function of dependence status – being larger in the relapser rather than the successful abstainer group. Third, it was hypothesized that instructions to suppress affect would produce differential results on the EAP effect as a function of dependence status—namely, that the EAP effect would be significantly reduced for the abstinent group only while the relapser group would fail to downsize the EAP effect. Similar hypotheses were formulated for the later LPP time window.

No specific predictions were made for differential effects on early and late components, although we deemed differences in EAP window to be more relevant and novel given the research focus of our laboratory on this component as index of pre-attentive bias to appetitive and abuse substances (Asmaro et al., 2012; Asmaro, Carolan, & Liotti, 2014; Asmaro & Liotti, 2014).

Chapter 9. **Study 1-Method**

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

9.1. Participants

Forty nicotine dependent participants willing to make a serious attempt at quitting smoking participated in the study procedures. The success or failure of their quit attempts was assessed over the course of a 1 month period, and the group was subsequently divided into a “successful abstinence” and “relapser” groups. In addition to having recently abstinent smokers included in the study, a group of twenty control participants who had never smoked before were also included in order to help make a more meaningful interpretation of the questionnaire, behavioural, and electrophysiological data. Out of the original sample of 40 abstinent smokers and 20 never smokers, usable ERP data was obtained from 18 relapsers (12 male, 6 female), 19 abstainers (6 males, 13 females), and 18 never smokers (7 males, 11 female). Additionally, 1 participant in the relapser group and 1 participant in the abstainer group were left-handed. 2 relapsers, 1 abstainer, and 2 never-smokers were excluded from subsequent analyses due to poor recording quality or an unacceptable numbers of artifacts in the EEG. All participants were recruited through word of mouth, the Research Participation System used in the Psychology department at SFU, and through advertisements in and around the university community. Participants were pre-screened in order to ensure that the inclusion criteria for the study were met. Suitable participants met criteria for nicotine dependence or were deemed to have never smoked (as assessed by the Fagerstrom Test for Nicotine Dependence and medical screening questionnaires, see below), were between 18-45 years old, and did not show signs of clinical depression, anxiety, or thought disorder. Any participant who was found to show

recent comorbid illicit substance use was excluded from the study. Furthermore, because visual cues were presented on a computer screen during the data collection session, 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, participants signed an informed consent form and preparation for an EEG recording commenced. Once all EEG data was collected, participants were debriefed and told when they would be contacted for a quit smoking follow-up interview.

9.2. Materials

Questionnaires. Several questionnaires were administered before and after the EEG recording took place. In addition, a standardized series of questions were presented to participants at the time of the follow-up session. The questionnaires were designed to assess the participant's current medical condition, substance usage, degree of nicotine dependence, and affect related pathology, while the follow-up interview intended to gauge whether the participant relapsed during the course of the study. No follow-up sessions were done with participants in the control group.

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 was used in this study to help determine whether levels of depression in our samples were relatively homogenous and below clinical levels. Participants were excluded from the study if they met clinical criteria for depression according to this questionnaire (score > or equal to 29).

State Trait Anxiety Inventory. Spielberger et al. (1970) developed the State Trait Anxiety Index (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. Total scores for each measure can range from 20-80, with higher scores indicating greater anxiety.

BIS/BAS. The Behavioral Inhibition System/ Behavioral Activation System (BIS/BAS) scales were initially developed by Carver and White (1994) and were

designed to assess the behavioural activation-behavioural inhibition dimension of personality. According to their factor analysis, the scales were believed to be made up of 4 subscales (BIS, BAS Drive, BAS Reward Responsiveness, and BAS Fun Seeking). Additionally, BIS scores are meant to reflect all reactions that a person may have towards the anticipation of punishment, whereas the BAS Drive, BAS Reward Responsiveness, and BAS Fun Seeking scales reflect goal persistence, positive responses in lieu of reward anticipation, and desire for new rewards respectively. Given the relevance of these concepts to substance use, these scales were included in the current study in order to provide demographic information about our groups. The scale consists of 24 items, and the minimum and maximum scores for each subscale are 4-16, 4-16, 5-20, and 7-28 respectively. Higher scores on each subscale indicate greater propensity for the participant to exhibit each characteristic.

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.

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. Scores on this measure have also been shown to strongly correlate with expired carbon monoxide measurements, which provide a biochemical method of measuring cigarette usage. This questionnaire is currently the most widely used measure of nicotine addiction (Fidler, Shahab, & West, 2010), and was used in the current study to assess nicotine dependence at the time of screening. Participants needed to have scores of 3 or higher to be included in our sample of smokers, as research has shown that this score is a strong indicator of at least a low level of dependence (Storr, Reboussin, & Anthony, 2005; Fagerstrom, Heatherton, & Kozlowski, 1992).

Quit Smoking Follow-Up Survey. In order to determine whether the abstinent smokers were able to successfully abstain from smoking for at least 1 month (31 days),

a survey instrument that could be completed during a phone-call interview or over email was created in collaboration with an expert from the MD Anderson Cancer Center in Houston, Texas (Dr. Francesco Versace; see Appendix A). The survey required participants to note whether “they had even one puff of a cigarette in the last 24 hours, last 7 days, and last 31 days”. If any cigarette smoking occurred, they were also required to report how many cigarettes they had per day and in total for each of the periods. Participants were also required to report whether they used nicotine replacement therapies (e.g. nicotine patches, nicotine gum) for each of the aforementioned periods. Once data had been acquired for all participants, determinations for instances of relapse were made based on a definition provided by the Society for Research on Nicotine and Tobacco (SRNT) where relapse was defined as a return to regular smoking after an initial abstinence period (Hughes et al., 2003).

9.3. Procedure

After suitability for participation was determined, eligible participants were asked to come to the lab at a time that was suitable for them. For smokers, the lab session also took place within 7 days of the participant making an attempt at nicotine abstinence and a minimum period of 24 hours abstinence had to be achieved in order for data collection to begin. Upon arrival, each participant was informed about the nature of the study and gave their written informed consent prior to beginning the experimental tasks (note that Studies 1 and 2 were both completed within a single session with each participant). Participants completed the Medical History Questionnaire and the informed consent forms, and were administered the FTND in interview format. Upon completion, an electrode cap was placed on the participant’s head and all the electrodes were connected. After cap set-up was completed, the participant was led to a sound-proof experimental room where EEG data was recorded. Here, participants sat in front of a computer screen on which visual stimuli were presented. Subjects viewed smoking related as well as neutral stimuli, and all EEG data was acquired within a single recording session. Participants were also given instructions to suppress or express affective responses respectively for each half of the stimulus presentations (therefore creating one “Express” and one “Suppress” condition that all stimulus presentations

could be categorized in). To help the participants do this affect regulation task properly and to standardize the procedure, the participants were told that “express” meant to react naturally to any feelings of anxiety or craving without any attempt at restraint. For the “suppress” condition, subjects were told to dampen and down-regulate any emotions and/or craving they experienced during that half of the task. After the participants completed the express and suppress conditions, they proceeded to complete experiment 2 following a short break (see Chapter 10).

9.4. Stimuli

Two categories of visual stimuli were presented to participants during this EEG task. There were a total of 400 stimulus presentations, with 200 stimuli being smoking related and 200 being categorized as neutral in valence. The paradigm employed a mini-block format, with each mini-block consisting of 10 neutral or smoking stimuli and 1 target stimulus (randomly presented images of chairs) that participants were asked to respond to with a button press (for a total of 11 stimuli per mini-block). Participants were also given the opportunity to take short breaks after each of the 11 stimulus presentations. There were a total of 40 mini-blocks throughout the experiment, with 20 of them being presented in conjunction with the “express” instructions and 20 of them being presented with the “suppress” instructions. “EXPRESS” and “SUPPRESS” mini-blocks were not intermixed. There were a total of 10 “express nicotine” mini-blocks, as well as 10 “suppress nicotine”, 10 “express neutral”, and “10 suppress neutral” ones. All stimuli were randomly presented in the E-Prime (version 2.0) program, and the presentation of either the “suppress” or “express” instructions at the beginning of the experiment were randomized to control for potential order effects. All visual stimuli as well as their neutral counterparts were selected using Google image search. Some examples of the stimuli in the smoking mini-blocks include pictures of cigarette packages, people smoking together, and pictures of burning cigarettes sitting in an ashtray. Some examples of the neutral stimuli include pictures of people with pencils in their mouths, people holding a pencil or pen, and pictures of rolling pins.

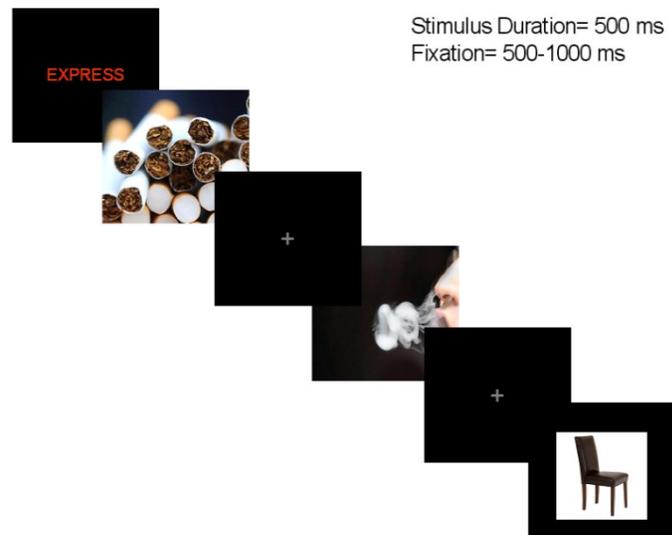
In order to ensure that the participants remained attentive during the task and to minimize the occurrence of low frequency EEG artifacts, a jittered inter-stimulus interval

(ISI) was also built into the task (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 times ranging between 1000-1500 milliseconds.

9.5. Rating Scales

In order to conduct an analysis of subjective craving throughout the task, rating scales were also presented after each mini-block. All rating scales were presented in Likert scale format, and required a 1 to 5 response by the participant, where a “1” would indicate that no craving was experienced while a “5” would indicate extreme craving.

Figure 1: Trial Series for Passive Task “Express” Condition



9.6. Apparatus

EEG activity was recorded continuously from the scalp through 64 sintered Ag-AgCl electrodes embedded in an elastic cap (electrocap international), which provided 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. Two external electrodes were placed on the left and right mastoids in order to provide a reference point for later ERP event averaging. 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 between +/- 25 millivolts. 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 μ V). From each participant, event-related activity was selectively averaged for the express nicotine, express neutral, suppress nicotine, and suppress neutral conditions. All averaging was time-locked to stimulus onset, and a baseline of -200 milliseconds was included in order to assess the degree of electrical activity occurring prior to the onset of each stimulus. Grand-averages were then calculated for each of the conditions.

9.7. Data Processing

In order to explore differential brain responses to each affective stimulus, ERP waveforms and topographical maps of grand-averages for each stimulus type were then inspected and compared for amplitude of peak voltage activity. Regions of interest (ROIs) were created based on peak voltages and neighboring electrodes showing similar voltage amplitudes with windows of interest being centered on this activity. Mean voltage amplitudes in the selected time windows (200-300 ms and 300-600 ms) were then extracted and employed as a parameter in the statistical analysis of the ERP data. For the 200-300 ms (EAP) effect, data from frontal channels AF3, F1, F3, AF4, AFz, Fz, F2, and F4 were collapsed to form a single ROI. For the 300-600 ms (LPP) effect, channels PO3, O1, Oz, POz, PO4, and O2 were collapsed to form a second ROI. Mean voltage amplitudes in these selected time windows were then entered into dependent and independent samples t-tests in order to test our a-priori hypotheses directly. Significance criterion was set at $p < .05$, and if the assumption of homogeneity of variance

was violated degrees of freedom were corrected using the Greenhouse-Geisser epsilon method.

Chapter 10. Study 1-Results

10.1. Descriptive Statistics

Pairwise contrasts were run in order to account for similarities and differences across the 3 groups we tested in the current study. As can be seen on Table 1, the groups were largely similar save for several exceptional cases. Not surprisingly, the relapsers and successful abstainers had significantly higher mean scores on the FTND relative to never smokers (for both $p < .0001$, 5.44 and 4.47 versus 0 respectively), confirming their status of nicotine dependence. Importantly, relapsers turned out to be more dependent on cigarettes than the successful abstainers when FTND scores were contrasted ($t(35)=2.721$, $p=.01$, Cohen's $d=.89$). Several group differences were also observed when relapsers were compared with control participants, namely for BAS Reward Responsivity ($t(19.55)=-2.557$, $p=.019$, Cohen's $d=.85$) and trait -Anxiety ($t(34)=3.223$, $p=.003$, Cohen's $d=1.07$). When abstainers were contrasted with controls, only the comparison for trait-Anxiety was found to distinguish the two groups ($t(35)=2.510$, $p=.017$, Cohen's $d=.83$).

Table 1: Descriptive Statistics for All Groups in the Express-Suppress Study

	Relapsers (n=18, mean, SD)	Abstainers (n=19, mean, SD)	Never Smokers (n=18, mean, SD)
<i>Questionnaire</i>			
Age	22.33(5.13)	23.47(4.48)	20.22(3.00)
FTND	5.44(1.20)	4.47(.96)	.00(0)
BASDrive	10.00(2.28)	11.11(1.79)	10.89(2.03)
BASFunSeeking	11.00(2.85)	12.05(2.86)	11.50(2.20)
BASReward	14.22(4.71)	16.63(2.95)	17.17(1.29)
BIS	18.67(4.49)	20.58(2.99)	21.44(4.10)
BECK	12.50(8.36)	11.94(7.68)	8.00(5.12)
STAIState	39.67(9.49)	37.00(9.12)	34.89(9.54)
STAITrait	48.83(12.17)	45.79(11.53)	36.83(10.08)
<i>Craving Measures</i>			
ExpressNic	3.45(.91)	3.19(.93)	1.01(.02)
ExpressNeut	2.39(.72)	2.23(.66)	1.01(.02)
SuppressNic	2.94(1.15)	2.75(.93)	1.01(.02)
SuppressNeut	1.99(.82)	1.89(.74)	1.00(.00)
<i>ERP Effects</i>			
<u>EAP200-300</u>			
EAPExpressNicotine	-5.67(3.27)	-3.56(4.55)	-6.30(4.56)
EAPExpressNeutral	-6.78(3.04)	-5.57(4.56)	-5.45(4.64)
EAPSuppressNicotine	-3.91(4.46)	-4.62(4.48)	-6.33(4.66)
EAPSuppressNeutral	-6.08(4.78)	-5.39(5.83)	-7.61(5.15)
<u>LPP (300-600 ms)</u>			
LPPEXpressNicotine	2.93(4.23)	5.94(8.71)	3.77(3.91)
LPPEXpressNeutral	2.46(7.32)	2.16(7.35)	3.02(4.75)
LPPSuppressNicotine	4.81(11.72)	4.27(7.14)	2.30(3.56)
LPPSuppressNeutral	3.08(12.41)	3.97(9.96)	1.50(3.76)

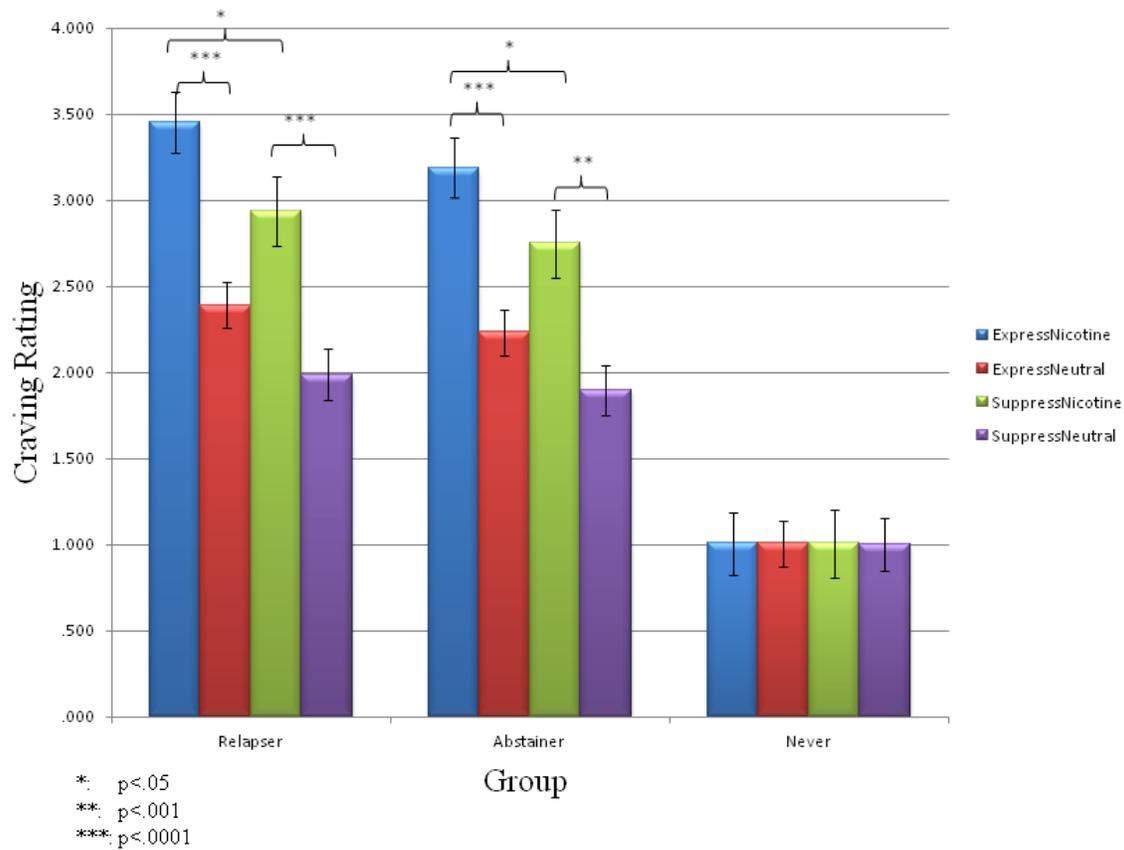
10.2. Self-Reported Craving

A 2 (Condition) x 2 (Stimulus) x 3 (Group) mixed effects ANOVA was run in order to determine if any significant main effects or interactions were present in the data. The main effect of Condition was highly significant ($F(1, 52)=13.487, p=.001, \eta^2=.206$), as were the effects of Stimulus ($F(2, 52)=52.10, p<.0001, \eta^2=.50$) and Group ($F(2, 52)=51.91, p<.0001, \eta^2=.666$). The interaction effects for Condition x Group ($F(2, 52)=3.325, p=.044, \eta^2=.113$) and Stimulus x Group ($F(2, 52)=12.87, p<.0001, \eta^2=.331$) were also highly significant. The Condition x Stimulus and Condition x Stimulus x Group interactions failed to meet significance at the $p<.05$ level.

In order to better understand our main effects and interactions, pairwise contrasts were run between and within each group. Both abstinent smoker groups (relapsers and abstainers) experienced significantly more craving than the never smokers regardless of mini-block type (neutral or nicotine) or condition (suppress versus express) (for all, $p<.0001$.) Contrasts that compared relapsers to abstainers did not reach significance (for all, $p>.05$).

When contrasts were run within each group, several significant effects were observed. Within the relapser group, self-reported craving after the express nicotine versus express neutral ($t(17)=4.754, p<.0001, \text{Cohen's } d=1.12$), suppress nicotine versus suppress neutral ($t(17)=4.987, p<.0001, \text{Cohen's } d=1.18$), and express nicotine versus suppress nicotine mini-blocks ($t(17)=2.531, p=.022, \text{Cohen's } d=.60$) was significantly different, with craving being lower in the suppress condition. The same pattern was also observed within the abstainer group, with express nicotine versus express neutral ($t(18)=5.727, p<.0001, \text{Cohen's } d=1.31$), suppress nicotine versus suppress neutral ($t(18)=3.905, p=.001, \text{Cohen's } d=.90$), and express nicotine versus suppress nicotine ($t(18)=2.532, p=.021, \text{Cohen's } d=.58$) being significantly different, albeit the mean craving ratings were not quite as high as those observed in the relapser group (see means in Table 1). No significant differences were observed within the never-smoker group (for all, $p>.05$).

Figure 2: Craving Rating Means by Group



10.3. ERP Effects

10.3.1. EAP Effect (200-300 ms)

To test the hypothesis that a significant EAP modulation would be present in the Express condition for relapsers and abstainers but not for never smokers, a 1 Between (Group) x 1 Within (Stimulus) mixed effects ANOVA was run. While the Group ($F(2,52)=.959$, $p=.39$) and Stimulus ($F(1,52)=3.195$, $p=.08$) main effects failed to reach significance, a significant Group x Stimulus interaction was observed ($F(2,52)=4.026$, $p=.024$, $\eta^2=.134$).

In order to break down this interaction effect and support our a-priori predictions, paired samples t-tests were run within each group to see if the EAP to smoking cues was more positive in amplitude. A significant planned dependent samples t-tests

determined that relapsers had a more positive going ERP response to nicotine cues relative to neutral cues ($t(17)=2.145$, $p=.047$, Cohen's $d=.51$), as did those who were classified as being successful abstainers ($t(18)=2.159$, $p=.045$, Cohen's $d=.50$). These significant differences for the EAP effect in the Express condition were also further supported by a t-test that assessed the effect in all smokers together ($t(37)=2.919$, $p=.006$, Cohen's $d=.48$) No effect was observed in the never smoker group, ($t(17)=-1.307$, $p=.209$). Therefore, both relapsers and non-relapsers showed enhanced positive going ERP deflections within this window of the EEG epoch while no difference was observed for those who had never smoked.

To test hypothesis two, i.e. that under Express instructions the EAP effect would vary in size as a function of dependence status (being greater in relapsers than abstainers), a mean EAP difference value (Cigarette minus Neutral) was computed for each participant and group, and an independent group t-test was conducted between relapsers and abstainers on the difference score. Contrary to our prediction, there was no difference in the size of the EAP effect as a function of dependence status under express instructions, ($t(27.92)=-.852$, $p=.401$).

To test the hypothesis that instructions to suppress affect would yield differential results on the EAP effect as a function of relapse or abstinence status, a 1 Between (Group) x 1 Within (Stimulus) mixed effects ANOVA was run. A significant main effect for Stimulus was observed ($F(1, 52)=10.398$, $p=.002$, $\eta^2=.167$), yet the Group main effect ($F(2, 52)=1.089$, $p=.344$) and Group x Stimulus interaction were not significant ($F(2, 52)=.877$, $p=.422$).

In order to test our a-priori hypothesis that only those who successfully abstained from smoking would be able to regulate the EAP response, paired-samples t-tests that compared the EAP to nicotine versus neutral cues were subsequently conducted (Bonferroni correction for three contrasts, $\alpha=.0167$). Only the contrast for the relapser group was significant, with greater voltage for Smoking relative to Neutral cues ($t(17)=3.367$, $p=.004$, Cohen's $d=.79$) being observed. The contrasts for the abstainer ($t(18)=.89$, $p=.385$) and never smoker groups ($t(17)=1.77$, $p=.095$) were far from significance. Based on these combined EAP results, it appears that those who abstained

from smoking were able to reduce nicotine related cue reactivity such that it resembled the response seen after neutral cue presentations. Unlike the abstainers, relapsers were unable to suppress the EAP response. In fact, while attempting to suppress they appeared to show even greater responsivity to the smoking cues.

Figure 3: Summary Figure of ERP Waveforms by Group

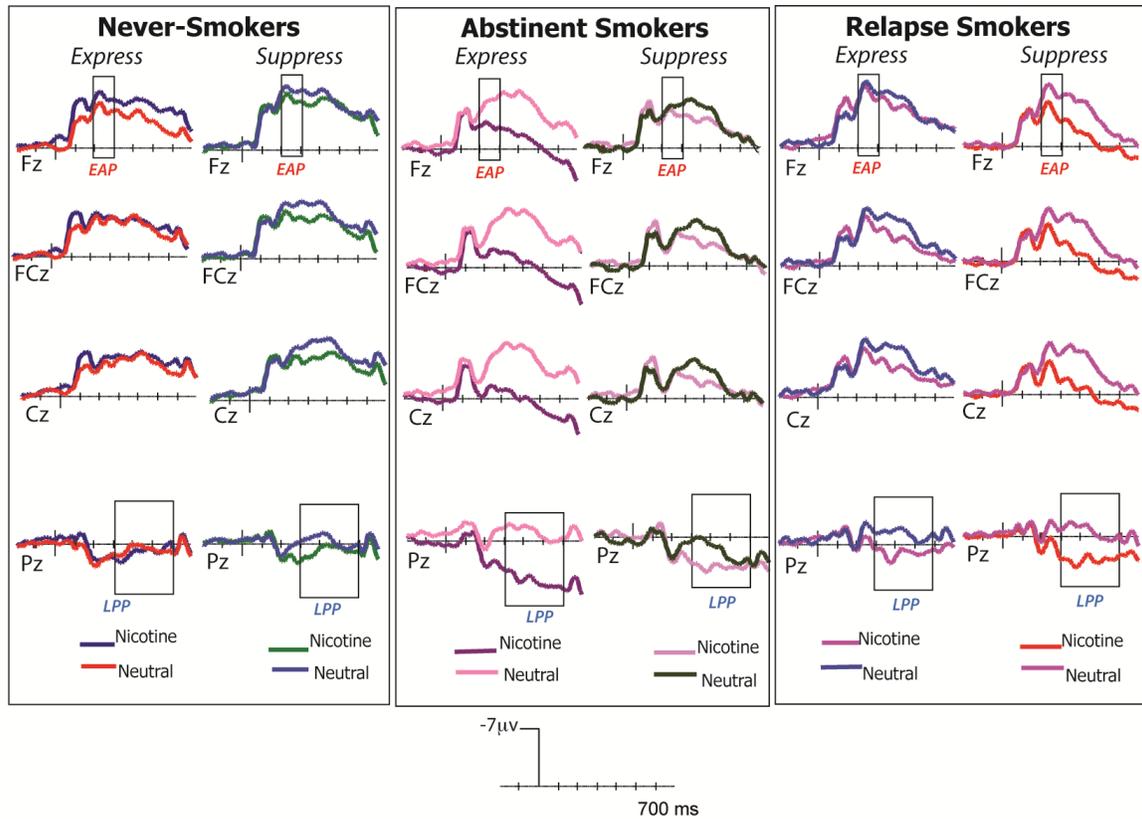
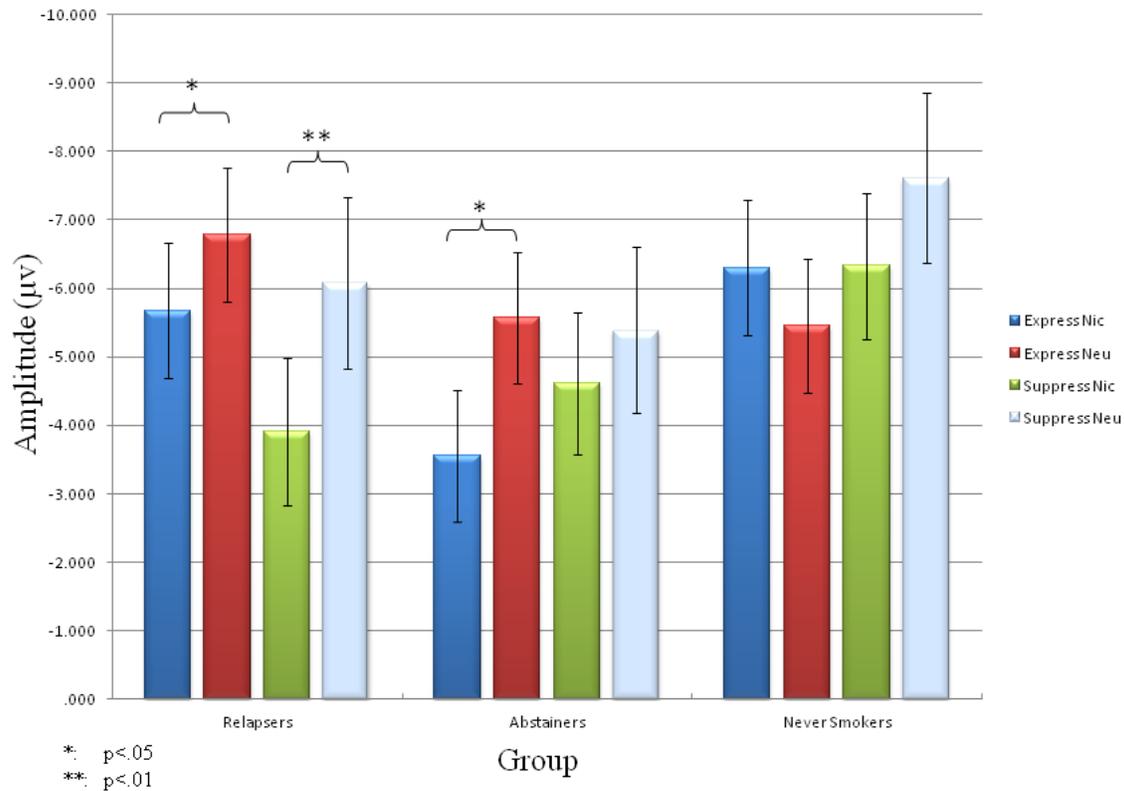


Figure 4: EAP (200-300) Mean Amplitudes by Group



10.3.2. LPP Effect (300-600 ms)

To test the hypothesis that the amplitude of the LPP elicited by cigarette versus neutral pictures would be greater for relapser and abstainers in the Express condition, a 1 Between (Group) x 1 Within (Stimulus) mixed effects ANOVA was run. While the Group main effect failed to reach significance ($F(1, 52)=.244, p=.784$), the Stimulus main effect was strong ($F(1,52)=6.857, p=.012, \eta^2=.117$). Also, the Group x Stimulus interaction trended towards significance ($F(2,52)=2.832, p=.068$).

In order to better understand these results, paired samples t-tests were subsequently conducted (Bonferroni corrected $\alpha=0.167$). A significant LPP modulation was observed for nicotine relative to neutral cues ($t(18)=3.010, p=.008, \text{Cohen's } d=.69$) in the abstainer group. No significant mean differences were observed for relapsers ($t(17)=.377, p=.711$) or never smokers ($t(17)=1.096, p=.288$). Abstinent smokers also did

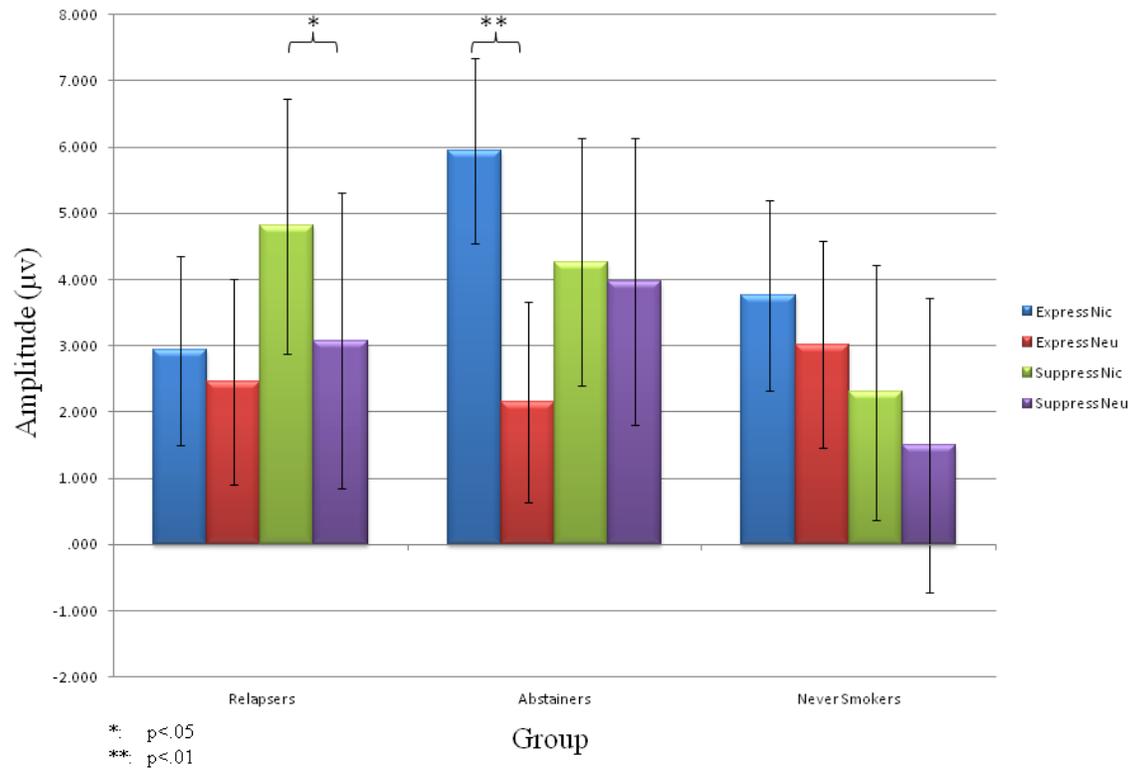
not have a greater LPP response to smoking cues compared to never-smokers ($t(53)=-.401$, $p=.69$), and relapsers were not significantly different from abstainers ($t(35)=-1.327$, $p=.193$).

To test the hypothesis that the EAP response in the Express condition would vary as a function of dependence status, an independent samples t-tests was run to compare the abstainers and relapsers. No significant mean difference was observed ($t(35)=-1.327$, $p=.193$).

To test the hypothesis that the amplitude of the LPP elicited by smoking versus neutral pictures would be reduced for the abstinent group only in the Suppress condition, a 1 Between (Group) x 1 Within (Stimulus) mixed effects ANOVA was run. No main effects or interaction effects were observed. Neither the Group ($F(2, 52)=.375$, $p=.689$) nor Stimulus ($F(1, 52)=2.949$, $p=.092$) main effects reached significance, and neither did the Group x Stimulus interaction ($F(2, 52)=.585$, $p=.561$).

Despite the fact that we did not observe any main or interaction effects, we conducted planned paired-samples t-tests within each of the 3 groups based on our a-priori defined hypotheses (Bonferroni corrected $\alpha=0.167$). Similar to what was seen with the EAP analysis, a significant difference was observed for the relapser group ($t(17)=2.715$, $p=.015$, Cohen's $d=.64$). In contrast, no significant difference was observed in the never smokers ($t(17)=.975$, $p=.343$). More importantly, there was no trace of a difference in the abstinent smoker group either ($t(18)=.241$, $p=.812$). In other words, as for the EAP, the abstainer group was able to down-regulate the LPP response to nicotine stimuli. In contrast, for the relapser group, suppression instructions led to a paradoxical increase in the salience of the smoking stimuli, marked by an inability to down-regulate the response. See Appendix B for a summary table of all Study 1 Behavioural and ERP effects.

Figure 5: LPP Mean Amplitudes by Group



Chapter 11. **Study 1-Discussion**

We confirmed that successful abstainers and those who relapsed indeed show significant ERP modulations in response to nicotine cues for the frontal EAP (200-300 msec) and the posterior LPP (300-600 msec). Our hypothesis that greater EAP reactivity to smoking cues would be present in the Express condition for the relapser and abstainer groups was supported, although only the abstainers showed a greater LPP response for smoking stimuli presented within this condition. The hypotheses that greater EAP and LPP responsivity would be observed in relapsers versus abstainers were not supported. Furthermore, our prediction that successful abstainers would be able to suppress affect to a greater extent relative to those who relapsed was supported by analyses that used the EAP and LPP data.

11.1. BAS Reward Responsivity

One interesting finding that was discovered in our analysis of the BASRewardResponsivity subscale of the BIS/BAS measure was that our relapsers' self-reported significantly less reward responsivity than the control participants. It is also notable that their scores were lower than the non-relapsers as well, although this difference only trended towards significance. Given that scores on the Reward Responsivity subscale of the BAS are thought to reflect a person's tendency to "positively respond to the anticipation or occurrence of reward" (Carver & White, 1994), it is possible that our group of relapsers may have reduced reward responsiveness and therefore may be at risk of developing and remaining addicted to nicotine as the drug engages a system that fails to be activated by natural reinforcers that are present in their everyday environments. Past research has shown that reduced responsiveness to natural rewards is frequently observed in addicted samples (Koob & Volkow, 2010), and that low hedonic capacity is a known predictor for future nicotine dependence in adolescents (Audrain-McGovern et al., 2012). Several studies have also found that reduced hedonic capacity is associated with future relapse in samples of smokers who

were making serious quit attempts (Leventhal et al., 2009; Versace et al., 2012). Our findings appear to be consistent with this past research, and this consistency also suggests that our participants were being truthful in their subjective reports of nicotine dependence and abstinence success/failure. Future research may wish to explore whether changes in BAS Reward Responsivity before and after a given therapeutic regimen are associated with improved abstinence success, as well as whether scores taken from young people prior to first experiences with cigarette smoking predict habit development at later periods in their lives.

11.2. Self-Reported Craving

Our finding that craving was significantly reduced in both groups of abstinent smokers during the “suppress” condition supports the notion that they were able to execute some level of cognitive control over their affective states, therefore potentially reducing the bottom-up effects of the nicotine cues. The fact that they were recently abstinent from nicotine yet remained able to reduce cravings in the midst of these appetitive stimuli makes this finding even more notable. This also suggests that techniques which focus on increasing self-awareness may have clinical utility when patients suffering from addiction seek treatment (e.g., Chua, Liberzon, Welsh, & Strecher, 2009). According to Robinson & Berridge (1993; 2000), drug cues have the ability to trigger craving and relapse behaviour due to the fact they have been conditioned to the drug taking event, and the presence of such cues (even if a person is unaware of them), may trigger a series of bottom-up affective processes that ultimately lead to drug taking lapses and relapses following attempts at abstinence. The learning that takes place when stimulus presentation and drug taking experiences are presented together has been empirically documented in laboratory studies where cigarette smokers learned to respond to neutral cues that predicted immediate nicotine reward (Hogarth, Dickinson, & Duka, 2003). In this study, galvanic skin response measurements also showed that the neutral stimuli were eventually able to elicit a traditional Pavlovian type response on their own, mimicking what could be expected after presentations of salient cigarette cues. Given that craving ratings were higher when our smokers viewed cigarette related stimuli in the Express condition (without restraint), our results appear to

be in-line with these perspectives. Other studies that had participants actively suppress craving have found results similar to our own, where self-reported craving for foods was kept constant or decreased relative to a condition where participants were told to not to alter their mental states during cue exposure (Alberts, Thewissen, & Middelweerd, 2013). Future research may wish to explore this in greater detail using research designs that test different groups of substance users who have received different cognitive training and/or different task instructions, as replication of our results and past findings would make them even more convincing.

11.3. ERP Effects

11.3.1. Early Amplitude Differences (EAP 200-300 ms)

The significant differences observed across our groups regarding an enhanced, early frontal response to smoking-related but not neutral cues was predicted, and is in-line with past studies that suggest the EAP effect differentiates substance users from non-users (Asmaro, Carolan, & Liotti, 2014) and those who self-report lower substance craving (Asmaro et al., 2012). Because this effect has now been identified in 3 separate studies that looked at craving for different categories of abuse substances, it seems possible that this response may be an objectively measured biological marker for trait craving. Given that the EAP is extracted from an early time window in the global EEG epoch, it is also quite probable that this component references within-group attentional biases towards salient appetitive cues. Because smoking-related attentional bias scores are also traditionally calculated by subtracting nicotine from neutral stimulus RTs in order to create a difference score (e.g., Bradley, Field, Mogg, De Houwer, 2004), this component may better represent early frontal attentional processes that are linked to observable behaviors typically involved in drug taking (i.e., attentional bias). Other researchers have shown that later occurring ERP components such as the P300/LPP waveform can be modulated by earlier occurring prefrontal events (Hajcak et al., 2010), and it is possible that EAP provides an objective measurement of attentional resource allocation that would ultimately facilitate downstream affective and cognitive appraisals of stimulus value. One potentially useful approach that could be tested in future studies

might include using neural measures of attentional bias such as the EAP to assess treatment outcomes instead of behavioural data alone, as the possibility of observing significant treatment effects is a distinct possibility.

Our finding that greater EAP-related smoking cue reactivity was observed within our relapser but not abstainer group within the Suppress condition supports the notion that this group is less likely to reduce cue reactivity relative to those who are likely to be successful at making abstinence attempts. Indeed, no significant differences in reactivity to these different stimulus categories were observed within the abstainer group within the suppress condition. This finding extends upon past research that has shown that regular drug users show enhanced neural responses to drug cues relative to never-users (i.e. Henry, Kaye, Bryan, Hutchison, & Ito, 2014), and also suggests that those who are less prone to relapse after making abstinence attempts are more likely to apply self-regulation techniques successfully. Given that the differences we report here take place in the early stages of stimulus processing, it is also possible that our relapser group exhibited greater responses towards the cigarette cues while attempting to suppress because of a greater amount of attention being afforded to these appetitive cues after awareness was directed towards their internal feeling states (e.g., Hogarth, Mogg, Bradley, Duka, & Dickinson, 2003). Past ERP studies have also found effects within a similar window of time as was used in our analysis of early effects, where smokers were found to show greater frontal P2a enhancements to nicotine cues (Bloom, Potts, Evans, & Drobles, 2013). Unlike the latter study, we were also able to discriminate between smokers and non-smokers based on their reactivity to nicotine cues, with greater amplitudes been observed when both groups of abstinent smokers were compared to never smokers. Importantly, no significant differences were observed for responses to smoking and neutral stimuli in never smokers regardless of whether these presentations occurred in the “Express” or “Suppress” conditions.

It is also notable that both groups of abstinent smokers showed greater reactivity to nicotine cues within the Express condition, and this observation also provides support for the idea that attentional bias towards drug cues can be indexed both behaviourally and physiologically, and that this cue-related bias may be related to subjective craving. Although we would not have observe significant effects within our relapser and abstainer

groups in the Express condition if Bonferroni corrected a criteria for multiple comparisons were applied, the highly significant contrast that grouped all abstinent smokers together and compared the EAP to smoking versus neutral cues supports the notion that this effect is real and not a spurious effect related to Type 1 error. Additionally, using mean differences for cue-reactivity may be informative in the case of individual assessment, where a patient is being assessed at period before or after attempts at abstinence are made. In situations like these, there would be no need to correct for multiple comparisons and any mean differences that are observed across conditions could be useful for making inferences about an individual client's reactivity to nicotine cues (and perhaps reactivity to other visually presented substance cues as well). These findings could also be taken as evidence that those who are more likely to succeed at abstinence attempts may be more able to exert cognitive control over their affective states, and may be less likely to experience cue-related craving while conscious of drug stimuli in their environments. Indeed, fMRI research that attempted to trigger craving using appetizing food cues has also found that activation increased in regions of the brain associated with executive functioning when participants were told to actively suppress craving state, while areas associated with the mediation of attentional processes were found to be less active (Yokum & Stice, 2013). Our finding that ERP effects in the 200-300 ms range could be used to distinguish neural responses to nicotine cues within groups also distinguishes our findings from those of other studies where early effects were either not observed (e.g., Littel & Franken, 2011a), or were found to occur in a P1/N1 window (e.g., Fehr, Wiedenmann, & Herrmann, 2006) when different groups of smokers were compared to non-smokers.

Given that our effect in the suppress condition disappeared for abstainers yet remained for the relapsers, it is possible that this reduction in smoking cue-related voltage amplitudes may indicate that those less prone to relapse may be able to better regulate craving by means of executive control. One potential mechanism that may facilitate this process concerns the allocation of attentional resources towards cigarette cues across conditions that tap into bottom-up versus top-down processes. Our measurements of self-reported craving support this possibility, as mean craving rating remained slightly but not significantly higher for relapsers within the suppress condition. Past research supports the notion that increased craving and neural activation is

observed when those suffering from addictions are exposed to drug cues (Chase, Eickhoff, Laird, & Hogarth, 2011), and it is possible that our findings provide an electrophysiological analogue to these functional neuroimaging findings. Notably, craving elicited by exposing cigarette smokers to nicotine-related cues appears to produce robust increases in self-reported craving (Carter & Tiffany, 1999), and this is likely to be further enhanced by recent abstinence and exposure to familiar environments where a great deal of conditioning has previously taken place (e.g. Culbertson et al., 2010; Baumann & Sayette, 2006). Ultimately, conscious control of cravings triggered by such cues may indeed be more difficult to manage for this population, and this finding may present clinicians working in the area of substance use disorders with an opportunity to reduce relapse vulnerability by understanding the neural mechanisms underlying observable drug-seeking behaviour.

11.3.2. Late Amplitude Differences (LPP 300-600 ms)

Our finding that LPP amplitudes to nicotine stimuli varied by group nicely replicates effects that have been found in past studies that looked at responses to nicotine cues in smokers and never smokers (Minnix et al., 2013; Versace et al., 2012; Littel & Franken, 2011a). However, our initial hypothesis regarding the differentiation of the relapser and abstainer groups based on LPP amplitude was not in the direction we had expected given that a larger LPP was observed in the abstainers during the “Express” condition. It is possible that members of this group found the stimuli more evocative due to subjective feelings towards cigarettes (i.e., greater fear of what may happen if smoking behaviour continues), and that this may have added affective salience to the images above and beyond possible carry-over effects that remained across blocks of nicotine and neutral images. Future research will be needed to test whether this is a factor that affects LPP responses among different subgroups of abstinent smokers. However, our prediction concerning the relapsers’ LPP response to smoking stimuli within the suppress condition was supported given that a larger LPP was seen for smoking-related but not neutral cues. Because we observed a significant mean difference for our relapser group within the suppress condition yet failed to see a similar effect in our abstainer group, it is possible that attempts at top-down cognitive control may reduce the late-occurring psychological effects of nicotine cues for those who are

more likely to abstain from smoking. This finding that top-down control reduces the amplitude of the LPP replicates what has been found in past research where the elicitation of the LPP after presentations of emotionally valenced images was reduced following reappraisal attempts (Moser, Most, & Simons, 2010; Hajcak & Nieuwenhuis, 2006). Indeed, within the suppress condition, the never-smokers had a similar non-significant LPP response when nicotine and neutral cues were contrasted, indicating that a dampening of cue reactivity occurred within this later, more conscious, window of time. Given that Littel and Franken (2011a) suggest that this late occurring effect references increased motivation towards nicotine cues by those who smoke, it is possible that abstainers are able to decrease the appetitive value of nicotine cues (thereby lessening their motivational significance), where those who are prone to relapse failed to modulate the motivational significance of nicotine cues (possibly because earlier attentional processes referenced by the EAP were not sufficiently reduced by means of effortful control). It is also possible that the earlier regulation of the EAP effect within the abstinence group reflects a decreased allocation of attentional resources towards the smoking cue, which may translate into a decreased craving response due to possible reduced cue salience. Importantly, the relapsers appeared to show a paradoxical response profile, as smoking cue reactivity increased when greater interoceptive awareness was exercised (perhaps unintentionally) due to the suppression instructions (similar to what was seen for the EAP). Based on these observations, those who are at risk of relapse may not be able to buffer the affective consequences of drug cue exposure, and efforts to do so may ultimately enhance the subjective effects of this experience. Although future studies need to be conducted in order to confirm this finding, if the effect is replicated, clinicians may be able to one day use this knowledge to their advantage when assessing relapse vulnerability and when providing treatment to those seeking to quit smoking. For example, our findings may guide those who are conducting interventions to teach patients a set of skills that allow them to effectively regulate themselves in real-world settings, perhaps by diminishing nicotine cue reactivity within a controlled clinical environment first. Although we found several within-group effects with our LPP data, no discernable between-group effects were observed. It may also be more fruitful to use physiological effects that distinguish across groups when attempting to predict vulnerability to relapse. In this case, the EAP effect may be a better biological marker for craving/addiction severity, and future studies may wish to test this using

multiple regression and discriminant function analysis techniques. If a model that uses EAP amplitude to predict self-reported craving and/or future relapse is significant while one that uses LPP amplitude is not, this could help provide additional evidence that supports this assertion. Nonetheless, our results do help to clarify this issue and could be an important initial step towards bringing laboratory techniques into settings where intervention and prevention approaches are practiced.

11.4. Clinical Relevance of ERP Effects

The current findings about the early effects of nicotine cues on the attentional system while attempts to decrease their salience are being made may be particularly useful in clinical settings. Here, clinicians wishing to make an objective assessment of an individual's susceptibility for later relapse at the time of initial assessment/admission to a treatment program could use these findings to supplement their own professional judgments on a case by case basis. Using the ERP technique to assess the presence of the EAP could also be a useful measure of therapeutic effectiveness that those working in clinical settings may wish to use in order to validate a particular therapeutic approach. Here, a reduction in amplitude of the EAP before or after treatment administration could indicate a reduction in drug cue salience, which may be associated with reduced vulnerability to relapse (Garland, Froeliger, & Howard, 2014; Marhe, Luijten, & Franken, 2014). Indeed, our sample of successful abstainers were able to reduce the impact of the smoking cues in early and late time windows, such that there were no significant differences in their ERP amplitudes when efforts to suppress affect and craving were being made. Notably, this was not true for those who relapsed, as a more positive going ERPs were recorded in the suppress condition while neutral cue responses were similar across all groups (therefore indicating that they were unable to suppress during the task). fMRI studies that had participants make attempts at affect regulation also found significant effects for regions involving the ACC and prefrontal cortices (see Sofuoglu, DeVito, Waters, & Carroll, 2013 for a review of these activations and their relationship to using cognitive enhancement to treat addiction). Although our effect may have originated from the same regions in brain space, techniques that have higher spatial resolution would be able to provide additional certainty regarding the neural structures and possible

neural networks that are involved in this response. Nonetheless, techniques such as those that employ mindfulness based strategies that enable cigarette smokers and illicit substance users to reduce the effects of attentional bias towards drug cues and associated increases in craving for drugs are a promising forms of treatment that aim to reduce relapse probability by teaching clients skills that help them refocus their attention and disengage from salient stimuli (see Garland, Froeliger, & Howard, 2014). In the case of mindfulness based interventions, the technique emphasizes processes that were also employed in the current study (i.e., instructions for participants to neutralize emotional states that were caused by cigarette cue presentations). Using ERP components like the EAP to document these changes may provide a useful glimpse into how the cigarette smoker is becoming more able to reduce the effects of substance related attentional bias and disrupt the bottom up processes that lead to increases in drug cue related craving as the implicit processes involved in these responses ultimately enter consciousness.

11.5. Strengths, Limitations, and Future Directions

Although there were a number of novel features incorporated into the current study, several limitations should be mentioned. First, the samples were primarily composed of young adults that were generally recruited near a university setting. Given that many smokers come from poorer socioeconomic (SES) regions, it is possible that a disparity between our sample and a lower-SES one in terms of years of education completed could affect interpretations of our ERP data (particularly the data in the suppress condition). Also, many heavily addicted smokers who wish to make quit attempts are older than the sample of participants we recruited. Because brain structure is known to change as age increases, it may be beneficial to replicate our results using an older sample. If the results were similar across both studies, a more compelling argument for the validity of our findings could be made, as well as their utility in predicting relapse and measuring treatment success. Furthermore, we did not screen for ethnicity and future studies may wish to assess this as it may be a variable that relates to relapse vulnerability. Finally, future studies may wish to recruit larger samples of participants and use biochemical measures to establish when nicotine products were

last used. Although we believe our participants were being truthful (based on past research and the questionnaire data we obtained), including such measures would not be unduly onerous and may provide an additional variable to use in subsequent analyses.

Despite these limitations, this appears to be the first study to combine ERP methods and a longitudinal design to understand how salient stimulus processing is affected by effortful, top-down control versus passive, bottom-up processing. We believe that our findings have important implications for those working with patients who are nicotine dependent, and can also be extended to populations experiencing problems with substance abuse and food craving more broadly. Although not perfect, the potential cost savings and portability of using high-density electrode arrays instead of expensive fMRI equipment could change the way scientists conduct research, and may increase the overall scientific output seen within the field given that more research could be done using the same amount of resources. Although our results need to be replicated, we were able to successfully demarcate early and late effects within smokers who either relapsed or abstained following an abstinence attempt, and were also able to catalogue how these two groups differed from never smokers.

Chapter 12. Study 2-Introduction

Although cigarette-related pictures have been used to elicit ERP components in groups of smokers, cigarette-related words have also been used to produce reliable effects. One common paradigm that utilizes these stimuli is the Smoking Stroop task, which is a modification of the classic Stroop (Stroop, 1935). Here, smoking related and neutral words are presented to smokers in a variety of colors, and the participant is instructed to indicate the color of the word via button press. Using this task, behavioral effects for accuracy and reaction time (RT) can be assessed, and ERP responses to the various words can also be measured if the paradigm is run while EEG is been recorded. Canamar and London (2012) found that smokers who are deprived of nicotine for one night prior to completing a Smoking Stroop task showed slower reaction times to nicotine versus neutral words, and that resumption of smoking decreased RTs to these stimuli. Furthermore, Fehr, Wiedenmann, and Hermann (2006) used nicotine and neutral words in conjunction with the ERP technique and found that a frontal positivity was elicited by the nicotine words within a 300-400 msec time range. Although they were unable to identify any significant RT effects to the nicotine words, this study nicely illustrates how the ERP technique can be used to investigate both behavioral and neural effects with responses occurring in the order of milliseconds. However, research that has used the Smoking Stroop task within ERP paradigms has been scarce. Furthermore, although behavioral effects have frequently been reported when the Smoking Stroop task is used, with nicotine words producing greater attentional bias as measured by RT in blocked tasks especially after periods of abstinence (Waters & Feyerabend, 2000; Gross, Jarvik, & Rosenblatt, 1993), other research has demonstrated that inconsistencies with this finding are not uncommon. For instance, Spiegelhalter et al. (2011) found that there was no indication of attentional bias across groups of smokers that either did not intend to quit or among those who participated in therapy.

A number of past studies have utilized emotion Stroop (eStroop) and drug-Stroop (dStroop) paradigms in order to assess the effects of attentional bias towards salient affective stimuli. Carolan, Jaspers-Fayer, Asmaro, Douglas, and Liotti (2014) were able to distinguish participants who were high in trait psychopathy from those who were low trait based on their ERP responses to positively and negatively valenced pictures in an eStroop task. Here, reductions in early (EAP 200-300 ms) and late (LPP 400-600 ms) component amplitude after affective stimulus presentation characterized those who were high in trait-psychopathy, and component amplitude in response to such cues was found to be larger for low-trait psychopathy participants. In another ERP study that used an eStroop task, it was found that people who were diagnosed with panic disorder and obsessive compulsive disorder had enhanced P1 responses to threat words, therefore illustrating that processing of threat stimuli is enhanced due to increased attentional resource allocation for both of these clinical groups relative to healthy controls (Thomas, Gonsalvez, & Johnstone, 2013). ERP studies that utilized dStroop paradigms have also identified effects that appear to differentiate substance users from non-users, where enhanced EAP (200-300 ms) amplitudes in response to marijuana cues appeared to differentiate those who were marijuana dependent from those who had never used the drug (Asmaro, Carolan, & Liotti, 2014).

An additional benefit for using smoking related words in ERP studies that assess nicotine cue reactivity is that these stimuli may uniquely elicit ERP components that would not be elicited by pictures, which may help to distinguish relapsing smokers, successful abstainers, and non-smokers from one another other. If these unique components successfully distinguish groups such as the ones previously mentioned, they may also make good candidates for biological markers that indicate relapse vulnerability. The utility of using words rather than pictures for the elicitation of various components has been demonstrated in past research (i.e. Battisti et al., 2010), and further exploration of potential biomarkers for relapse across different stimulus parameters may assist in the identification of reliable markers in ERP data.

In order to provide additional evidence for evoked brain electrical responses to nicotine and neutral words presented in a Smoking Stroop task and to extend upon the findings reported in study 1, we sampled neural responses from abstinent smokers and

never smokers and collected ERP data using a high density array of electrodes. We hypothesized that 1) abstinent smokers' reaction times (RT) in the Smoking Stroop task would be significantly greater in response to nicotine rather than neutral stimuli and that this would not be seen in never smokers, 2) That the ERPs to nicotine-related words would show significant amplitude enhancements over the frontal and posterior scalp relative to neutral words in the 150-300 msec and 300-600 msec time ranges and would be greater for relapsers compared never smokers. In order to relate our ERP findings to fMRI research more easily, source localization procedures were also carried out for the significant activations in order to assess the neural loci of the observed activity. We further hypothesized that 3) the early frontal response to nicotine cues would source localize to the PFC/ACC.

Chapter 13. **Study 2-Method**

All participants who completed Study 1 also completed Study 2. The materials, apparatus, and procedures used for Study 2 were also used in the Study 1 session, and the reader can refer to Chapter 9 for a review of what was included.

13.1. Participants

Forty nicotine dependent participants willing to make a serious attempt at quitting smoking participated in the study procedures. Due to technical issues with the EEG and computer equipment, four participants from the overall “abstinent smoker” group were dropped from the analysis. The success or failure of their quit attempts were assessed over the course of a 1 month period, and the group was subsequently divided into “abstainer” group and “relapse” groups based on whether they were able to refrain from relapsing for 1 month or not. The final sample consisted of 20 relapsers (11 male, 9 female) and 16 successful abstainers (8 male, 8 female). In addition to having cigarette smokers in the current study, a group of 20 control participants who had never smoked were also included in order to help make a more meaningful interpretation of the behavioral and electrophysiology data. One participant was dropped due to technical issues during data collection, leaving a final sample size of 19 never-smokers (7 male, 12 female). Additionally, 1 participant in the relapser group and 1 participant in the abstainer group were left-handed. All participants were between 18-45 years old, and the three groups were matched in terms of education level and alcohol/substance use. All participants were recruited through word of mouth, the Research Participation System used in the Psychology department at SFU, and through advertisements in and around the university community. Participants were pre-screened in order to ensure that the inclusion criteria for the study were met. Suitable participants met criteria for nicotine dependence or were deemed to have never smoked (as assessed by the Fagerstrom Test for Nicotine Dependence and medical screening questionnaires, see

below), and did not show signs of clinical depression, anxiety, or thought disorder. Any participant who was found to show recent comorbid illicit substance use was excluded from the study. Furthermore, since visual cues were presented on a computer screen during the data collection session, 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, eligible participants signed an informed consent form and preparation for an EEG recording commenced. Once the EEG session ended, participants were debriefed and told when the first phone call follow-up would happen.

13.2. Procedure

After experiment 1 (emotion regulation task), participants proceeded to complete experiment 2 (Smoking Stroop Task). Participants were informed about the nature of the task while they sat in front of a computer screen on which instructions and visual stimuli were presented. Subjects were presented with smoking-related and neutral words, and all the data was acquired within a single recording session. Participants were told to respond to the color of the words via button press, with each of the three colors corresponding to one of three buttons. After EEG data collection was completed, participants then completed the BIS/BAS, STAI, and BDI questionnaires, were debriefed, and then informed that they would be contacted in 1 month for the first follow-up (abstinent smokers only).

13.3. Stimuli

Two categories of word stimuli were presented to participants during this modified Stroop task. There were a total of 198 stimulus presentations, with 99 stimuli being categorized as smoking related words and 99 being categorized as neutral words. The paradigm utilized a block format, with each block consisting of 33 neutral or smoking stimuli. Participants were given the opportunity to take short breaks after each of the 33 stimulus presentations. There were a total of 6 blocks in the experiment, with 3 of them being “smoking” blocks and 3 of them being “neutral” blocks. All stimuli were randomly

presented using the E-Prime (version 2.0) program, and the presentation of either the “nicotine” or “neutral” block at the beginning of the experiment was randomized to control for potential order effects. All nicotine words as well as their neutral counterparts were selected based on a previously published study that assessed cue-reactivity in a sample of smokers. Some examples of the smoking related words were “cigarette” and “tobacco”. Examples of the neutral words were items such as “glycerin” and “pennant”. All stimuli were adopted from a previously published study that utilized nicotine and neutral words in a Smoking Stroop task (Gross, Jarvik, & Rosenblatt, 1993).

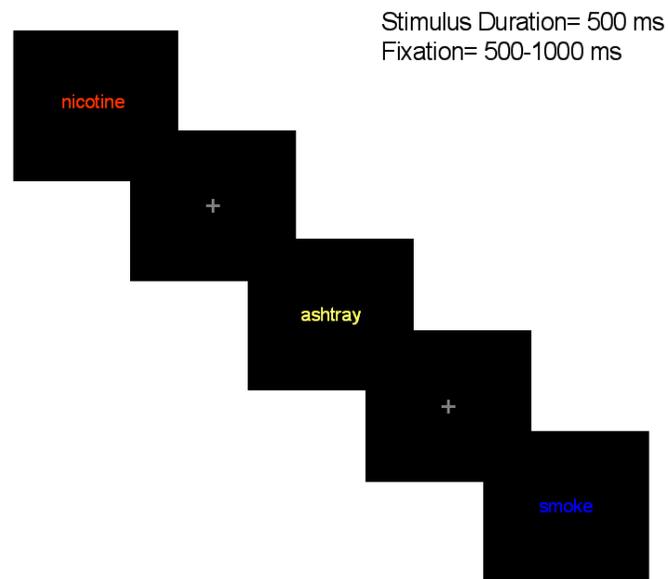
Participants were required to respond via button press to each color, with a button press of 1 being the correct response for words presented in red, 2 being the correct response for words presented in green, and 5 being the correct response for words presented in blue. In order to ensure that the participant remained attentive during the task and to minimize the occurrence of low frequency EEG artifacts, a jittered ISI was again 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 times ranging between 1000-1500 milliseconds.

13.4. Data Processing

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 then inspected and compared for latency and amplitude of peak voltage activity in the main observed components. Regions of interest (ROIs) were created based on peak voltages and neighboring electrodes showing similar voltage amplitudes with windows of interest being centered on this activity. Mean voltage amplitudes in the selected time windows (150-300 ms and 300-600 ms) were then extracted and employed as a parameter in the statistical analysis of the ERP data. For the P2a (150-300 ms) effect, data from frontal channels F1, F3, FC3, FC1, Fz, F2, F4, FC4, FC2, FCz were collapsed to form a single ROI. For the P3b/LPP 300-600 ms effect, data was extracted from channel Cz and subjected to subsequent analyses. Mean voltage amplitudes in these selected time windows were then entered into dependent and independent samples t-

tests in order to test our a-priori hypotheses directly. Significance criterion was set at $p < .05$, and if the assumption of homogeneity of variance was violated degrees of freedom were corrected using the Greenhouse-Geisser epsilon method.

Figure 6: Trial Series for Smoking Stroop Task



Chapter 14. Study 2-Results

14.1. Descriptive Statistics

We conducted pairwise comparisons in order to determine whether significant group differences existed for scores on the FTND, BASDrive, BASFunSeeking, BASReward, BIS, BECK, STAI-State, STAI-Trait measures, as well as the Age. For FTND scores, relapsers and abstainers were not significantly different from one another ($p=.212$). Furthermore, relapsers and abstainers were not significantly different from one another for any other variable we examined. However, relapsers did have significantly higher scores on the FTND relative to control participants ($p<.0001$), and not surprisingly, had higher trait anxiety as measured by the STAI-Trait ($t(37)=2.616$, $p=.013$, Cohen's $d=.84$). The abstainer group also had a significantly greater FTND score ($p<.0001$) than the never smoker group and were also significantly different in terms of age ($t(24.66)=2.744$, $p=.01$, Cohen's $d=.95$). Despite this effect, both groups were still in roughly the same developmental bracket (early adulthood).

Table 2: Descriptive Statistics for All Groups in the Smoking Stroop Study

	Relapsers (n=20, mean, SD)	Abstainers (n=16, mean, SD)	Never Smokers (n=19, mean, SD)
<i>Questionnaire</i>			
Age	22.35(4.90)	23.88(4.67)	20.16(2.99)
FTND	5.15(1.23)	4.69(.87)	.00(0)
BASDrive	10.1(2.17)	10.81(1.80)	10.63(2.09)
BASFunSeeking	11.6(2.56)	11.38(3.36)	11.37(2.48)
BASReward	14.55(4.32)	16.06(3.86)	16.58(2.71)
BIS	19.3(4.37)	20.38(3.14)	20.53(4.82)
BECK	12.95(7.97)	11.31(7.00)	8.84(5.70)
STAIState	39.9(10.00)	37.56(9.85)	35.21(9.48)
STAITrait	48.25(12.88)	45.63(11.27)	38.37(10.52)
<i>Behavioural Effects</i>			
NicRT	601.01(141.42)	617.58(104.41)	535.41(63.74)
NeutRT	573.83(102.08)	597.16(90.88)	542.97(71.34)
NicACC	90.1(8.68)	91.94(4.67)	92.11(3.14)
NeutACC	88.05(10.63)	92.00(5.88)	92.11(4.46)
<i>ERP Effects</i>			
P2a Nicotine	3.38(3.02)	2.59(2.38)	1.26(3.43)
P2a Neutral	3.11(4.34)	2.60(2.53)	.99(3.45)
P3b/LPPNicotine	7.76(5.70)	6.06(4.95)	5.65(6.52)
P3b/LPPNeutral	7.79(6.64)	6.27(5.44)	4.87(5.31)

14.2. Behavioural Effects

14.2.1. Smoking Stroop Reaction Times (RTs)

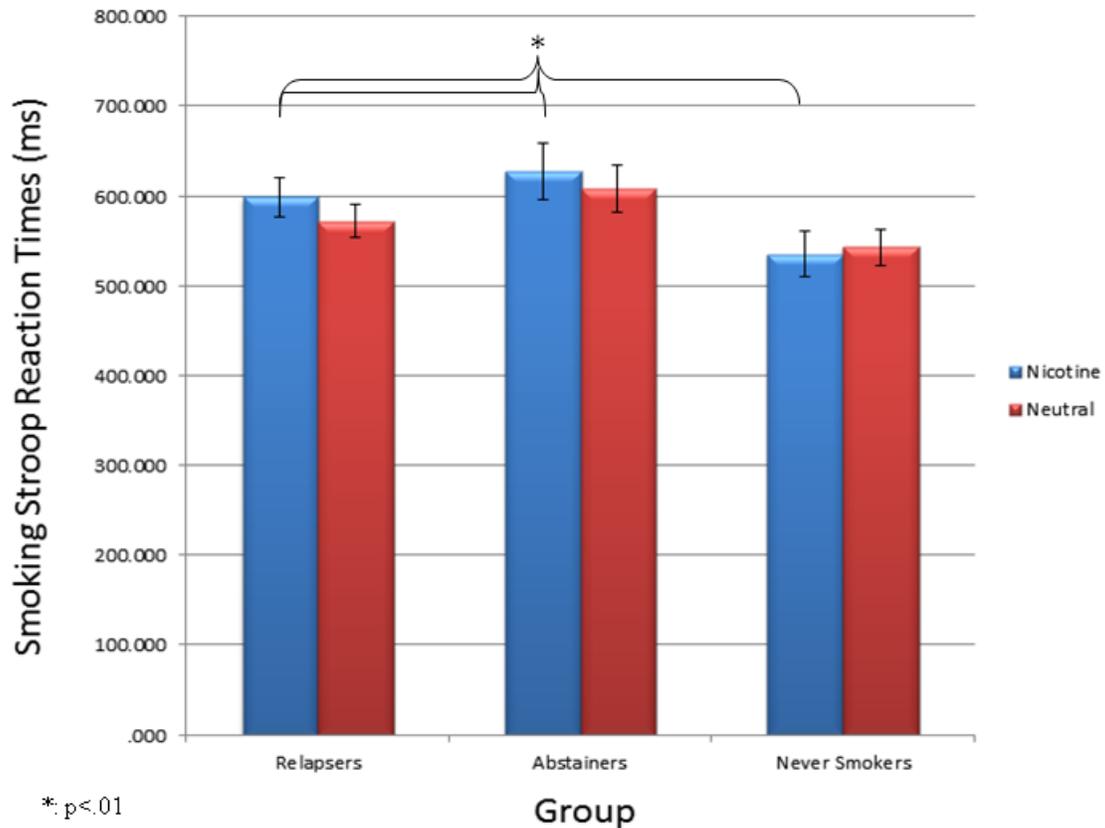
To test the hypothesis that abstinent smokers would have longer RTs to smoking related words relative to never smokers, a 1 Between (Group) x 1 Within (Stimulus) mixed effects ANOVA was run. While the Stimulus main effect was not significant ($F(1, 53)=1.080, p=.304$), the Group main effect ($F(1, 53)=4.509, p=.038, \eta^2=.078$) and the

Group x Stimulus interaction ($F(1, 53) = 3.937, p = .05, \eta^2 = .069$) were found to meet significance criteria.

In order to better understand these main and interaction effects, relapser, abstainer, and control participant reaction time data for nicotine and neutral word trials were subsequently extracted and entered into separate pairwise contrasts. Planned independent samples t-tests revealed that abstinent smokers were significantly slower than the never smokers in response to smoking words ($t(52.98) = 2.87, p = .006$, Cohen's $d = .74$). This difference was not observed for RTs to neutral words, $t(53) = 1.64, p = .11$.

While the between-group contrast was the one suggested by previous literature on the Smoking Stroop, we also conducted, on an exploratory basis, other contrasts to determine whether within group effects existed for RTs to smoking and neutral words. None of these paired-samples comparisons came close to reaching significance for the relapser ($t(19) = 1.665, p = .112$), abstainer ($t(15) = 1.327, p = .204$), or never smoker ($t(18) = -1.396, p = .18$) groups.

Figure 7: Nicotine and Neutral Trial RTs by Group



14.2.2. Smoking Stroop Accuracy

Accuracy data was entered into the same general linear model that was used for the RT analysis. No significant main effects or interactions were observed (for all, $p > .2$). All groups had high accuracy rates for our Smoking Stroop task.

Given that we also wanted to assess whether any within group effects were present in our dataset, accuracy data for nicotine and neutral word presentations were also conducted. Within the relapser group, a significant mean difference was observed ($t(19)=2.259$, $p=.036$), with the mean accuracy score for nicotine being greater (90.1 versus 88.05). However, this contrast failed to remain significant after a Bonferroni correction for Type 1 error rates was employed (adjusted $\alpha=.025$). No contrasts approached significance within the abstainer or control groups.

14.3. ERP Effects

14.3.1. P2a Effect (150-300 ms)

After ERP waveforms for neutral and nicotine words were inspected for all groups, data was extracted from a window in the epoch extending from 150 to 300 ms after stimulus onset.

To test the hypothesis that the P2a response to smoking related words would be greater for relapsers relative to never smokers, a 1 Between (Group) x 1 Within (Stimulus) mixed effects ANOVA was run. No significant effects for Stimulus ($F(1, 52)=.194, p=.661$), Group ($F(2, 52)=2.563, p=.087$) nor the Group x Stimulus interaction ($F(2, 52)=.052, p=.949$) were observed.

Because we wished to test our a-priori hypothesis regarding enhanced P2a activation to the sight of smoking words for relapsers and because the Group effect trended towards significance, independent samples t-tests were run in order to identify whether any significant differences were present (Bonferroni corrected $\alpha=.025$). First, we tested whether all smokers collectively had a greater P2a response to smoking-related words relative to never smokers, and a significant difference was observed ($t(53)=2.082, p=.042$, Cohen's $d=.57$). A significant difference was subsequently observed when the relapser group's frontal P2a response to nicotine cues was compared to the control group's responses ($t(37)=2.051, p=.047$, Cohen's $d=.66$; see Figure 4). The contrast that compared the successful abstainer group to the never smoker group failed to reach significance ($t(33)=1.307, p=.200$). While some of these contrasts met significance criteria at the .05 level, they failed to reach significance when the more conservative Bonferroni corrected α criteria were used. Nonetheless, it was also clear that the relapsers carried the effect that was found when all smokers were compared to never smokers which suggests that this effect was not related to Type 1 error.

We also ran an exploratory analysis using dependent samples t-tests to determine whether significant differences in brain reactivity to nicotine and neutral words were present within the groups. No significant differences were observed within the

relapsers ($t(19)=.360$, $p=.723$), abstainers ($t(15)=-.016$, $p=.987$), or never smokers ($t(18)=.481$, $p=.636$).

Figure 8: ERPs to Nicotine and Neutral Words by Group

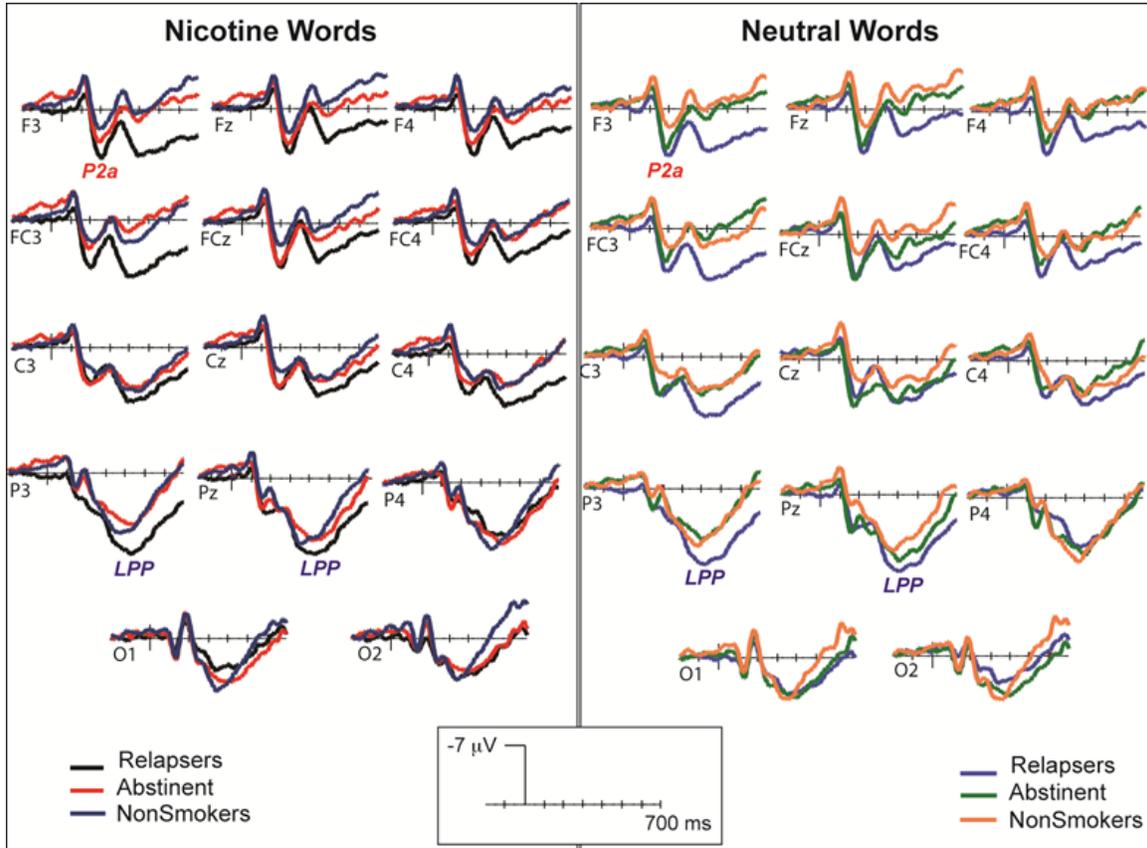
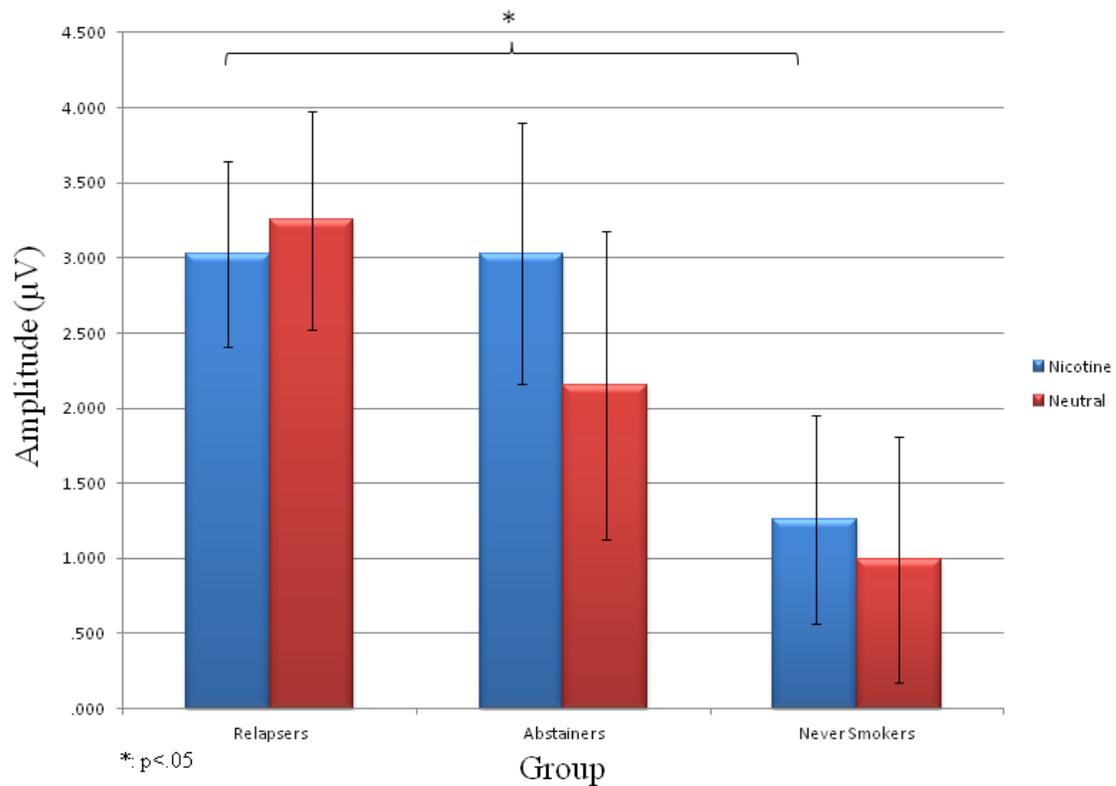


Figure 9: Bar Graph of P2a Amplitudes by Group



14.3.2. LPP Effect (300-600 ms)

LPP data from a 300-600 ms window in the EEG epoch was entered into a 1 Between (Group) x 1 Within mixed effects ANOVA. No significant Group ($F(2, 52)=1.082, p=.346$) nor Stimulus ($F(1, 52)=.093, p=.762$) main effects were observed, and the Group x Stimulus interaction effect also failed to reach significance criteria ($F(2, 52)=.274, p=.761$).

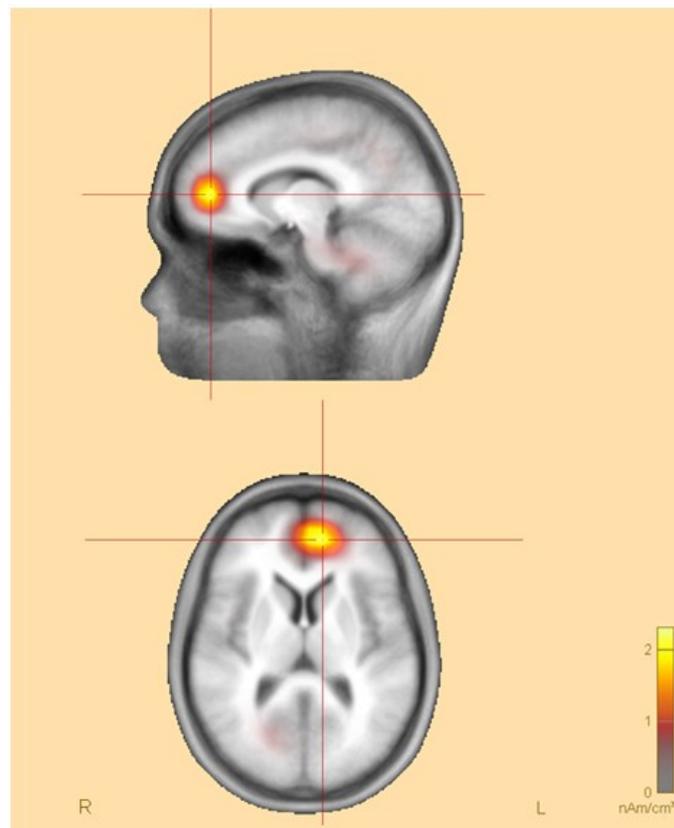
Several pairwise contrasts were then run in order to test our hypothesis that the LPP to smoking words would be larger for relapsers compared to never smokers. No significant mean differences were observed when relapsers were compared to never smokers ($t(37)=1.077, p=.289$), nor when abstainers were compared to never smokers ($t(33)=.203, p=.840$). A contrast that compared all abstinent smokers to never smokers also returned a non-significant result ($t(53)=.823, p=.414$).

As an exploratory analysis, we also tested whether there were significant effects for LPP amplitude to smoking versus neutral words within each of the 3 groups. No significant mean differences were observed for the relapsers ($t(19)=-.033$, $p=.974$), abstainers ($t(15)=-.162$, $p=.873$), or never smokers ($t(18)=.984$, $p=.338$). See Appendix C for a summary table of all Study 2 Behavioural and ERP effects.

14.4. Source Localization of the P2a Effect

Using the CLARA technique implemented in BESA 5.3, we conducted source analysis in order to estimate neural generators for the Relapsers minus Never-Smokers difference wave for Smoking words in the P2a time window (150-300 msec). As shown in Figure 5, a main source generator was found in PFC/ACC was clearly identified.

Figure 10: Source Localization of P2a to Cigarette Words (Relapsers Minus Never-Smokers)



Chapter 15. **Study 2-Discussion**

We predicted that abstinent smokers' reaction times to stimuli presented during the task would be greater after nicotine stimuli compared to those responses obtained from the never smokers. We also predicted that smokers who relapsed would show greater early and late occurring voltage enhancements to nicotine words over the frontal scalp relative to participants who had never smoked before. Finally, we hypothesized that the early frontal response to nicotine cues would source localize to the PFC/ACC. After analyzing our behavioural and electrophysiological data obtained from an early 150-300 ms window and a later 300-600 ms window, our predictions were indeed supported.

15.1. Behavioural Data

RTs to nicotine words were significantly slower when all abstinent smokers were compared to the never smokers, therefore indicating that nicotine words captured attentional resources to a greater extent than did neutral words. This finding replicates past research that used the Smoking Stroop task and found that smokers who endured overnight abstinence had significantly slower RTs when nicotine words were presented (Canamar & London, 2012). This attentional bias to nicotine cues may also be associated with relapse, as an increased salience for stimuli associated with smoking may be especially hazardous for those who have made a recent attempt at quitting as well as those who are dependent on substances of abuse more generally (see Marhe, Luijten, & Franken, 2014; Janes et al., 2010). Although we were not able to use the reaction time data to distinguish between relapsers and abstainers, future studies should be conducted using larger samples in addition to stimuli that are more naturalistic in order to better assess potential group differences. Doing so may help establish whether attentional bias to such cues is a valid predictor of abstinence success. Reaction time data could also be entered into a multiple regression model that combines questionnaire,

behavioural, and electrophysiological/functional neuroimaging data together in order to assess relapse potential.

Regarding the lack of strong accuracy effects, the possibility of a ceiling effect is a likely explanation for why the groups were not distinguished from one another (i.e. relapsers versus non-relapsers, smokers versus never-smokers). Again, null findings like these are not unheard of, as previous reports that use Smoking Stroop paradigms tend to have similar findings (e.g., Fehr, Wiedenmann, & Herrmann, 2006). Future studies may wish to use similar stimuli in a task that is more cognitively taxing, as this may help to differentiate group performance and perhaps allow for poorer accuracy rates to be recorded from recently abstinent smokers.

15.2. ERP Effects

Our hypothesis that an early positive going frontal potential (P2a) would distinguish relapsers from control participants was supported. This finding is in line with past research that used nicotine and neutral pictures in a Smoking Stroop task with smokers and non-smokers, where a P2 effect was observed in a window of time similar to ours (Bloom, Potts, Evans, & Drobles, 2013). The visual P2a is thought to reflect an enhanced allocation of attentional resources to stimuli, and because relapsers had greater P2a amplitudes relative to never-smokers, it appears as though this group is more attentive to cigarette related stimuli and perhaps more prone to cue-related lapses and relapses. A previous study that used a Smoking Stroop paradigm also interpreted effects that occurred within a similar time window as we used as potentially reflecting an increased allocation of attentional resources to such cues by smokers (Fehr, Wiedenmann, & Herrmann, 2006). Given that our group of relapsers also failed to abstain from cigarette smoking for more than 1 month after making their quit attempt, it is possible that they allocate more attentional resources towards nicotine related cues outside of the laboratory as well. Ultimately, this could contribute to increased attentional bias towards these appetitive cues and resultant increases in cigarette and substance craving (see Robinson & Berridge, 1993; Garland, Froeliger, & Howard, 2014). Because we also observed a significantly greater P2a amplitude when we combined relapsers and non-relapsers together into a single group (abstinent smokers) and compared them

to never-smokers, it appears as though the P2a component may be useful as a marker for nicotine and substance addiction more generally, and could be useful for future studies that aim to assess substance abuse/substance dependence to nicotine and other recreational drugs. Despite the fact that we also observed a significantly larger P2a to smoking-related words when we grouped all our abstinent smokers together and contrasted them with never smokers, our contrasts would not have been considered significant if Bonferroni corrected p values were used as significance criteria to control for family-wise error rates. Although the t -test that compared all abstinent smokers to never smokers suggests that the effect in the relapsers versus never smokers contrast is real and not a Type 1 error, larger sample studies should be conducted in our to confirm that this is in fact the case. Future studies may also wish to explore whether the amplitude of the visual P2a elicited by nicotine stimuli is predictive of later relapse after serious attempts at abstinence are made, as well as whether future source localization attempts can replicate our findings.

Our hypothesis that a larger amplitude LPP effect would be observed for relapsers after presentations of nicotine words was not supported by the data obtained in this study. Indeed, no significant differences across group were observed when they were compared with one another, nor when all abstinent smokers were compared to controls. One possible explanation for this originates from the nature of the task used. Specifically, participants were instructed to respond as quickly and accurately as possible to the color of the words, without actually processing the meaning of the word. This may have affected the amplitude of the LPP, thereby decreasing its amplitude as the impact of the stimulus on affective state was diminished. A recent literature review has stated that affectively relevant stimuli need to be overtly (rather than covertly) attended to in order for LPP effects to occur (Codispoti, Ferrari, & Bradley, 2007). More recent research supports this view, as studies that used images that required participants to passively attend to overtly presented stimuli successfully reported significant LPP effects (i.e., Asmaro et al., 2012; Versace et al., 2012). Taken together, past research provides plausibility for our null LPP finding, yet future studies may wish to alter task instructions so that the words become more meaningful for participants. Doing so may enable researchers to distinguish relapsers from non-relapsers or smokers from

non-smokers, and may also allow for a more naturalistic representation of everyday life to be created in the lab environment.

15.3. Limitations and Future Directions

Despite the novel nature of the current study, several limitations were noted. Perhaps the most obvious of these pertains to the sample size. Although a number of ERP studies use samples similar to our own, some effects that were marginally significant or trended towards significance may have become significant with increased power. Future studies may wish to replicate the methods used in the current study in order to assess this empirically. Also, due to the non-clinical setting used to conduct this research project, we did not use biochemical measures for assessing abstinence in our smokers, nor did we include such measures as part of our initial assessment. Although we used a widely accepted measure to determine our smokers' eligibility, having such data may have allowed for other interpretations of our data to be made, and may have helped us define our groups more accurately. Although past research suggests that substance abusers can be fairly honest about their substance usage (Del Boca & Darkes, 2005), objective measures would certainly not detract from a study of this nature. Finally, our sample used a relatively young group of males and females who were recruited from in and around the university community. These participants have higher cognitive functioning than participants who come from lower socioeconomic status neighborhoods, which may impact the generalizability of the results (especially given that cigarette smoking is more prevalent in areas such as these). This sampling issue warrants a replication of our study with participants who are older and perhaps lower in socioeconomic status being the target population. Furthermore, we did not screen for ethnicity and future studies may wish to assess this as it may be a variable that relates to relapse vulnerability.

Despite these limitations, our study provides important information about how the brains of recently abstinent smokers who later relapse or achieve successfully abstinence respond to nicotine-related words, as well as how abstinent smokers process this form of visual information. To our knowledge, this is the first study to investigate the neural correlates of nicotine and neutral word exposure in groups of smokers who

successfully abstained from smoking, those who failed to achieve longer terms of abstinence, and those who had never smoked using a high-density electrode array to record ERPs. Given that a younger sample was recruited, these results may also be especially informative for policy makers that wish to take a preventative approach to this global health problem. Young smokers are also frequently targeted by big tobacco companies, and understanding how reactivity to nicotine cues manifests itself in this population may help to inform those wishing to help intervene in this harmful behavioural pattern. Nonetheless, it would be useful if future ERP studies could replicate the procedures used in the current study given that findings obtained using this paradigm are remain quite sparse.

Chapter 16. **Study 3-Introduction**

One clinically relevant aspect of using ERPs to study smoking cue reactivity in nicotine dependent users is the ability to identify potential biomarkers that predict intervention and clinical outcomes. Iacono, Malone, and McGue (2008) state that the use of ERPs and other physiological measures for detecting endophenotypes is an area of research that is in its infancy. Using these techniques to predict relapse has received even less attention, although there are several studies that have attempted to understand how drug-cue reactivity can have predictive value for clinical outcomes (see Sinha, 2011 for an informative overview). Paulus, Tapert, and Schuckit (2005) attempted to use fMRI activations during a simple decision making task to predict relapse in a sample of methamphetamine dependent patients. By assessing the decision making processes that this 2 choice task elicited relative to a control task where subjects simply pushed a button in response to a stimulus presented on screen, the researchers determined which areas of the brain were active when cognitive resources were being utilized by the participants. It was found that activations in the right insula, right posterior cingulate, and right middle temporal gyrus were predictive of relapse in 83.3 % of the sample and abstinence in up to 90.9 % of the sample. Similar studies that were conducted using samples of alcoholics and healthy controls found that activations in the medial PFC were predictive of future relapses among alcoholics who were trying to abstain from drinking (Grusser et al., 2004). One fMRI study that looked at groups of cigarette smokers who were attempting to quit the habit also found that smoking cues differentially activated the prefrontal cortex, ACC, bilateral insula, posterior cingulate, amygdala, and parahippocampal cortex when the smoking group was compared to a healthy non-smoker control group (Janes et al., 2010). When functional connectivity analyses were conducted, it was found that decreased functional connectivity between the insula, ACC, and dorsolateral prefrontal cortex was present among smokers who failed to abstain, and this could reflect a decreased ability to apply top-down control over affective states among those vulnerable to relapse. Despite the fact that a number of

fMRI studies have been conducted in the hopes of identifying patterns of activation or deactivation that might identify addicts who are at heightened risk of relapse, there have been very few ERP studies done with the same intentions. Despite the fact that this is a new area of exploration, Anderson, Baldridge, and Stanford (2011) were able to successfully predict adherence to a drug treatment program using the amplitudes of elicited P3a (200-600 ms) activations, where decreased P3a amplitude was found to be predictive of failure to complete a 90 day intensive treatment program. Although the program was not specific to nicotine abstinence and auditory cues that were not related to drugs were used as stimuli, the use of P3a amplitude as a predictor was a more powerful predictor of treatment outcome than any other assessment measure used to screen the patients. Given the utility and flexibility of using the ERP technique in clinical settings, this is a gap in the literature that should be addressed and doing so will help to provide more information regarding the nature of drug stimulus processing and the neural correlates that predict relapse.

Using data from Study 1 and Study 2, we aimed to discriminate relapsers and abstainers from never-smokers in addition to discriminating relapsers from abstainers using questionnaire responses, behavioural effects, and ERP responses that distinguished the groups in previously reported pairwise tests on means. For Study 1 questionnaire data, it was hypothesized that BASReward Responsivity and STAI-T scores would significantly discriminate abstinent smokers from never smokers. Also, it was hypothesized that BAS Reward Responsivity, STAI-T, and FTND scores would significantly discriminate between relapsers and non-relapsers. Using Study 1 ERP data, we hypothesized that Express Nicotine EAP values would significantly discriminate between abstinent smokers and never-smokers, and between relapsers and non-relapsers. Lastly, we predicted that the inclusion of all ERP and questionnaire measures within a model that aimed to successfully predict future relapse and abstinence would accurately classify members of both groups. For analyses run using questionnaire data from Study 2, we predicted that STAI-T data would distinguish abstinent smokers from never smokers, and that this measure plus the FTND would successfully discriminate relapsers from non-relapsers. Using Nicotine RTs, we hypothesized that abstinent smokers would be distinguished from never smokers when this factor was used to predict group membership. We also predicted that P2a Nicotine amplitudes would

distinguish relapsers from never-smokers. Finally, it was hypothesized that the inclusion of all these measurements into a single model would allow for the statistically significant and accurate prediction of abstinent smokers who would go on to relapse as well as those who would successfully abstain.

Chapter 17. **Study 3-Method**

Study 3 was conducted with data that was acquired during Study 1 and Study 2. Questionnaire, behavioural, and ERP data were used as independent variables in a regression model that aimed to predict relapse and abstinence in smokers and whether both groups of smokers could be successfully distinguished from those who had never smoked.

17.1. Procedure

After Study 2 and the final questionnaires were completed, participants were informed about their first follow-up date at the end of the debriefing. The goal of the follow-up interviews was to assess whether abstinent smokers had been successful in their attempts to quit or whether they relapsed. The sample of cigarette smokers was subdivided into the “successfully abstain” or “relapse” groups. No follow-up interviews were conducted with participants who were deemed to be never smokers. Based on this categorization scheme, discriminant function analyses were run in the hopes that the participants’ group membership could be successfully predicted using individual factors and/or a larger, more inclusive model.

17.2. Data Processing

A separate series of discriminant function analyses was run using data from Study 1 and Study 2 (see “Results” section below). Variables that were useful for distinguishing groups in the previous analyses and subsequent t-tests were entered used into the discriminant analyses reported here. Each of these variables was used to discriminate relapsers, abstainers, and never smokers from one another. Separate analyses were also run with FTND scores included, as we also wanted to determine if

relapsers could be distinguished from successful abstainers based on the inclusion of this data into the model. These analyses were conducted separately due to the inappropriateness of using this measure with those who had never smoked before. Wilks' λ values were reported when these variables were used to predict group membership on their own, and χ^2 values were reported in tests of overall model success. Overall model prediction success rates were also expressed in terms of total correct predictions per sample, and in terms of group related percentages and overall model percent correct values.

Chapter 18. Study 3-Results

18.1. Discriminant Function Analysis Study 1 Data

Given that significant group differences were observed when mean amplitude values and questionnaire responses from our relapsers, abstainers, and control participants were found and because we had a-priori hypotheses pertaining to the predictive value of our ERP components, discriminant function analyses were run using the EAPExpressNicotine, EAPSuppressNicotine ExpressNicLPP and SuppressNicLPP values. Because of their potential clinical utility, the difference scores for the EAP for Nicotine minus Neutral voltage amplitudes in the Express and Suppress condition were also entered into the model. Lastly, STAI-T and BASRewardResponse questionnaire data from study 1 were also entered. After an overall analysis was completed with all three groups, a separate set of discriminant analyses were run for the relapsers and non-relapsers with the FTND included as we were interested in determining whether our ERP components and questionnaire measures would predict relapse status more or less than values obtained using this questionnaire.

18.1.1. Discriminant Function Analyses All Groups

All variables that differentiated our groups in the Study 1 analyses were entered into a discriminant function analysis in order to determine whether any of these variables could be used to successfully predict relapse, abstinence, and never smoker status. When all predictors were entered into the model, a not significant result was returned ($\chi^2(7)=11.44$, $p=.121$). The model was only able to successfully classify 12 of 18 relapsers, 7 of 19 abstainers, and 13 of 18 never smokers. The overall accuracy of the model was 58.2%. However, we proceeded to test each variable independently in order to determine if any one of them was useful in classifying members of our groups. Significant results were found for BAS Reward Responsivity (Wilks' $\lambda=.863$, $p=.02$),

STAI-T (Wilks' $\lambda=.825$, $p=.007$), and Express NicMinusNeutral EAP (Wilks' $\lambda=.866$, $p=.02$). However, EAP Express Nicotine (Wilks' $\lambda=.922$), EAP Suppress Nicotine (Wilks' $\lambda=.95$), Suppress NicMinusNeutral EAP (Wilks' $\lambda=.967$), Express Nicotine LPP (Wilks' $\lambda=.955$), and Suppress Nicotine LPP (Wilks' $\lambda=.982$) were not able to classify members belonging to our three groups significantly (for all, $p>.1$).

18.1.2. Discriminant Function Analysis Relapsers and Abstainers Only

Next, we re-examined the data using only those participants belonging to the relapsers and abstainer groups. We also included the FTND, as this measure significantly differentiated between the two groups in our Study 1 analysis. When the effects for these individual predictors were assessed separately, FTND scores were the only factor that allowed for successful discrimination between the two groups (Wilks' $\lambda=.825$, $p=.01$). 77.8% of relapsers and 57.9% of non-relapsers were successfully classified, and overall model accuracy was 67.6%. The discriminant analysis that used BAS Reward Responsivity data approached significance (Wilks' $\lambda=.909$, $p=.069$). However, data for EAP Express Nicotine (Wilks' $\lambda=.93$), EAP Suppress Nicotine (Wilks' $\lambda=.993$), Express Nicotine LPP (Wilks' $\lambda=.952$), Suppress Nicotine LPP (Wilks' $\lambda=.999$), Express NicMinusNeutral EAP (Wilks' $\lambda=.98$), Suppress NicMinusNeutral EAP (Wilks' $\lambda=.955$), and STAI-T (Wilks' $\lambda=.983$) did not successfully distinguish between relapsers and non-relapsers. However, when all factors were entered into the model together, a significant result was returned ($\chi^2(9)=19.464$, $p=.022$) and 16 out of 18 relapsers (89%) and 16 out of 19 non-relapsers (84%) were correctly classified. The overall classification rate was 32 out of 37 (86.5%).

18.2. Discriminant Analyses with Study 2 Data

As was the case with discriminant analyses conducted with data from Study 1, analyses were also run using the P2a Nicotine, LPP Nicotine, and Nicotine RT, and STAI-T data from Study 2. Once again, a separate set of discriminant analyses were also run for the relapsers and abstainers with the FTND included as we were interested in determining whether our ERP components and behavioral measures would predict

relapse status more or less than values obtained using this questionnaire and whether we could construct a model to predict relapse and abstinence accurately.

18.2.1. Discriminant Function Analyses All Groups

All variables that differentiated our groups in the Study 2 analyses were entered into a discriminant function analysis in order to determine whether any of these variables could predict relapse, abstinence, and never smoker status. When all predictors were entered into the model, a non-significant effect was found ($\chi^2(3)=1.267$, $p=.737$). However, we nonetheless proceeded to test whether these factors could distinguish the groups independently. STAI-T scores were found to classify participants significantly (Wilks' $\lambda=.875$, $p=.03$). Nicotine RTs approached significance, yet could not meet or beat the criterion level of $p=.05$ (Wilks' $\lambda=.900$, $p=.064$). The factors P2aNicotine (Wilks' $\lambda=.914$) and P3b/LPP (Wilks' $\lambda=.973$) did not approach significance (for all, $p>.09$).

18.2.2. Discriminant Function Analysis Relapsers and Non-Relapsers Only

Next, we proceeded to re-examine the data using participants from the relapsers and abstainer groups only. When the effects for individual predictors were assessed separately, all factors including Nicotine RT (Wilks' $\lambda=.996$), P2aNicotine (Wilks' $\lambda=.979$), P3b/LPPNicotine (Wilks' $\lambda=.974$), FTND (Wilks' $\lambda=.914$) and STAI-T (Wilks' $\lambda=.955$) failed to successfully classify correct group membership (for all, $p>.2$). The larger model also failed to reach significance after all factors were entered ($\chi^2(5)=2.963$, $p=.706$).

Overall, data from Study 1 was more useful than data from Study 2 in correctly classifying participants as relapsers, abstainers, or never-smokers. Notably, the Express EAP was able to discriminate successfully when all three groups were entered into the model as a dependent variable. Still, the discriminant analysis showed that FTND scores were the strongest (and only) successful predictors of relapse when never smokers were excluded from the model. However, the most interesting finding that was discovered in this analysis was the significant discrimination when all Study 1 factors were entered into a model that attempted to discriminate relapsers from non-relapsers. The model was

highly significant, and was able to predict relapse or abstinence 89% and 84% of the time respectively. See Appendix D for a summary table of all Study 3 effects.

Chapter 19. **Study 3- Discussion**

We predicted that Study 1 questionnaire data (BAS Reward Responsivity and STAI-T) and ERP voltages (Express Nicotine EAP) would significantly predict relapse, abstinence, and never smoker status when entered into the function analysis independently and when included in a more inclusive model. We further predicted that questionnaire scores (BAS Reward Responsivity, STAI-T, and FTND scores) and ERP measurements (Express NicMinusNeut EAP) would successfully discriminate between relapsers and abstainers alone and when included in an inclusive model that attempted to predict future abstinence success. Using data from Study 2, we predicted that questionnaire data (STAI-T), behavioural effects (NicRT), and ERP voltages (P2a Nicotine) would successfully distinguish relapsers, abstainers, and never smokers on their own and when included in a larger model. Lastly, we predicted that these same measurements (with the FTND included) would successfully discriminate relapsers from abstainers alone and when included in a larger model that aimed to predict abstinence success/instances of relapse. The results of our discriminant analyses partially supported our initial predictions.

19.1. Discriminant Function Analyses Study 1

The successful (and highly accurate) prediction of relapse or abstinence status when EAP Express Nicotine, EAP Suppress Nicotine, Express NicMinusNeutral EAP, Suppress NicMinusNeutral EAP, Express and Suppress Nicotine LPP, BAS Reward Responsivity, STAI-T, and FTND scores were entered into a model confirmed our hypothesis that groups could be discriminated from one another based on acquired self-report and objective physiological recordings. Furthermore, the significant prediction of group membership when all three groups were entered into the model clearly shows that the EAP effect may be a useful biological marker for substance dependence. However, the observation that the inclusion of the EAPEXpress Nicotine, EAP Suppress Nicotine,

Express NicMinusNeutral EAP, Suppress NicMinusNeutral EAP, Express and Suppress Nicotine LPP, BAS Reward Responsivity, and STAI-T scores failed to significantly discriminate relapsers, abstainers, and control participants from one another was surprising. It is possible that the inclusion of the never smokers introduced noise variance into the model, and therefore took away from its ability to discriminate between groups successfully. This possibility is supported by the fact that non-relapsers and never smokers had similar values for SuppressNicMinusNeutralEAP and BASReward Response, which could have made prediction more difficult. Indeed, once never smokers were removed from the overall model, participants were assigned to the relapse or no relapse groups nearly 90% of the time. It was also surprising that only the FTND was able to predict later relapse or abstinence status when relapsers and non-relapsers were assessed independently of never smokers, although this speaks to the reliability and validity of this measure as a test of nicotine dependence. Although we were hoping that the ExpressNicMinusNeutralEAP would also predict relapse/abstinence on its own, the fact that questionnaire data and physiological measurements could be combined in our global model to accurately predict both abstinence and relapse status after one month of initial screening may be highly informative for those wishing to assess the vulnerability of individual clients seeking treatment for a variety of addictions. Given that the presence of the EAP may reflect attentional bias that is triggered by drug cues in groups of substance users (Asmaro, Carolan, & Liotti, 2014), future research may wish to test whether a reduction in EAP amplitude is associated with reduced rates of relapse after initial measurements are taken at the beginning of a given intervention. It has been suggested that certain therapeutic approaches have been known to reduce the degree of attentional bias afforded to these salient cue categories (Garland, Froeliger, & Howard, 2014), and this consideration coupled with the fact that the FTND is not designed to test smokers who have been abstinent for longer durations certainly warrants a continued effort to identify biological markers that can be assessed using cost effective physiological measurement such as ERPs. Doing so will allow interested parties to gauge smoking cessation treatment efficacy and assess relapse vulnerability over the course of multiple time points, which may ultimately allow for greater abstinence success rates and reductions in the worldwide disease burden caused by smoking related illnesses. Given that questionnaire results can be biased by repeated measurements (i.e., Lo, Humphreys, Byrne, & Pachana, 2012) and that behavioural

measurements of attentional bias to drug cues are considered to be reliably observed effects that are significantly associated with drug craving (Field, Munafò, & Franken, 2009), objective physiological measurements may be very useful variables for cataloguing neural changes that occur within individual clients as context and vulnerability can change over time. Still, the finding that the ExpressEAP effect successfully distinguished members of our three groups supports that idea that this effect is a marker of attentional bias towards salient, craving inducing cues. This finding also supports previously published studies that reported on EAP effects, where groups of substance users were distinguished from those who either never used a substance or were low in trait substance craving (Asmaro et al., 2012; Asmaro, Carolan, & Liotti, 2014; Asmaro & Liotti, 2014).

19.2. Reward Responsivity

Another interesting finding concerned the significant prediction of group membership when BASRewardResponsivity scores were used to predict membership within all three groups. This finding is in line with past research that demonstrated that reduced hedonic capacity (the tendency to not enjoy pleasurable, rewarding activities) during adolescence was associated with an increased probability of nicotine dependency in later life (Audrain-McGovern et al., 2012) and increased probabilities of later relapse for those attempting to quit cigarette smoking (Leventhal et al., 2009). Our finding is also in line with research that suggests that reduced responding during presentations of natural rewards is a characteristic of addictions (Koob & Volkow, 2010). Inclusion of measures that attempt to assess reward responsivity at both initial assessment and after attempts at intervention may indeed provide useful information about a particular person's vulnerability to relapse, and it is possible that this characteristic is relatively universal across the spectrum of substance addictions. Given that this variable was also able to discriminate between relapsers and control participants and nearly distinguished relapsers from non-relapsers in Study 1, it is possible that the reward responsivity construct is another subject specific factor that intervention should be geared towards.

19.3. Discriminant Function Analyses Study 2 and the Overall Role of Trait Anxiety

Although we had made a number of predictions regarding the ability for questionnaire, behavioural, and ERP effects to predict relapse, abstinence, and never smoker status, global models that attempted to predict membership to these three groups or those who either relapsed or abstained were far from significant. Nonetheless, participants' scores on the STAI-T were able to significantly predict group membership when Study 1 and Study 2 data were entered into discriminant function models. This finding is in-line with past research that suggests that smokers tend to have higher levels of trait anxiety relative to those who do not smoke (Pritchard & Kay, 1993). Research that examined the subjective experiences of nicotine withdrawal in participants attempting to quit the habit also found that higher, but not lower levels of anxiety sensitivity were associated with more withdrawal symptoms when higher levels of depression were concurrently experienced (Langdon et al., 2013). Abstinent smokers with higher levels of trait anxiety may also be more likely to smoke as this facilitates relief from this unpleasant state of being (Kelley, Grant, Cooper, & Cooney, 2013). Our finding supports the notion that smoking cessation treatments that target anxiety may be useful for reducing rates of relapse. Positive results have been reported when techniques such as Brief Automated Suggestive Relaxation (BASR) were used (Frances, Tabares, & Palarea, 2012), and pharmacological approaches that target the $\alpha 4\beta 2$ nicotinic acetylcholine receptors on dopaminergic neurons may also produce clinically significant effects partly through their ability to mediate levels of reported anxiety (McGranahan, Patzlaff, Grady, Heinemann, & Booker, 2011). Future research may wish to directly test whether self-reported trait anxiety pre- and post-treatment significantly predicts abstinence success and relapse incidence, as this would provide more conclusive evidence regarding the importance of this factor when smoking cessation attempts are being made.

Despite the observation that trait anxiety scores consistently predicted group membership, both overall composite models that used Study 2 data (relapsers, non-relapsers, never smokers and relapsers/non-relapsers only) failed to reach significance. One reason for this may be due to the fact that our ERP effects were not as pronounced

as those found in Study 1. Indeed, this may be directly related to the nature of the stimuli used in our Smoking Stroop task. The words only covertly communicated the salience value of the respective targets, and were certainly not as salient as the pictures used in Study 1. It is also likely that the instructions that were given to participants in Study 2 contributed to these reduced effects. Rather, participants were explicitly told to respond to the color of the words and ignore their meanings and the speed and accuracy of their 3 choice button responses to the various colours was emphasized. However, in Study 1, participants were explicitly told to watch the images on screen while either reacting natural or attempting to actively suppress affect. Based on this, the instructions given to participants in experiment 2 may have inadvertently decreased the amount of attention allocated towards the processing of these stimuli, therefore decreasing attention related effects for the P2aNicotine and P3a/LPP response to nicotine stimuli (an effect that would not be seen in the Express condition of Study 1). Future studies may wish to replicate the results of the current study, and may wish to run discriminant analyses with data that is acquired from a paradigm that employs an emotional Stroop design with stimuli consisting of pictures rather than words (e.g., Asmaro, Carolan, & Liotti, 2014). Doing so may increase the degree of attentional bias being experienced by recently abstinent smokers, and may facilitate better discrimination between those who relapse versus those who successfully abstain over the course of a given time period. Furthermore, it is possible that our effects could have become significant if we had more power (particularly for the prediction of group based on NicRT). Although our sample size is comparable to other studies that have used functional and electrophysiological indices to predict relapse and abstinence (Anderson, Baldridge, & Stanford, 2011; Janes et al., 2010), RTs to nicotine stimuli have been found to predict later relapse (e.g. Janes et al., 2010) and replication of this effect using ERP methods could allow for additional inferences to be made regarding the combination of behavioural and physiological measurements taken from cognitively demanding tasks to predict relapse vulnerability.

19.4. Strengths, Limitations, and Future Directions

The development of techniques that use physiological measurements of factors that may predict later relapse and abstinence is still in its infancy, and the current study

helps to draw attention towards factors that may be good candidates for future clinical and experimental investigations of addiction behaviour. To our knowledge, this is the first study to take data from 2 separate drug cue-reactivity paradigms and vet them to see which kind of paradigm more successfully predicts relapse, abstinence, and never using status. Importantly, all ERP effects (EAP and LPP) that were entered into these respective models were extracted from similar windows of time across studies and were shown to be useful in uniquely characterizing our groups after separate tests on means were conducted beforehand. These results may help to guide others who wish to explore the predictive utility of functional and electrophysiological techniques within the context of addiction, and may lead to some highly insightful findings if other addiction related factors that have not yet been discovered are entered into similar discriminant analyses. Our findings also appear to replicate and extend on previous findings that suggest the EAP distinguishes between cravers and non-cravers for various substances, that trait anxiety is a relevant variable in predicting relapse and withdrawal severity in abstinent smokers, and that an individual's ability to respond to rewarding stimuli is an important clinical consideration for those wishing to prevent potential relapses for smokers attempting to quit the habit. Lastly, our findings support previously conducted psychometric evaluations of the FTND that show that the measure is a reliable and valid indicator of addiction severity (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991), which in turn is a predictor of abstinence success.

Despite the strengths of the current study, several limitations should be noted. First, the sample size for each of our groups was relatively small, and larger sample sizes would facilitate increasingly sophisticated statistical analyses that may better predict relapse and abstinence among smokers or drug users more generally. For instance, larger sample sizes would enable future researchers to utilize techniques based on logistic regression (i.e., Versace et al., 2012), which may be better suited for predicting group membership with effects that have smaller effect sizes. These measures could also facilitate mediation and moderation analysis, which would allow researchers to construct intricate models that more accurately capture the intricate nature of human addiction. Given the large number of environmental, intrapersonal, interpersonal, genetic, and drug specific factors that need to be taken into consideration by those studying this disorder, such techniques should certainly be vetted against

findings obtained using discriminant function analyses. Congruency between the two different approaches would allow for researchers to be especially confident in their findings, and may allow for the development of innovative treatment approaches that significantly reduce relapse probability and increase abstinence success. A second limitation concerns the measurement of relapse and abstinence. We used an interview and relied on participants to be honest about their quit attempts. Given the financial constraints faced by our lab regarding the acquisition of CO monitoring equipment and assays that could test for salivary cotinine levels (both of which can confirm abstinence from nicotine use) and the fact that the study was conducted in a non-clinical setting, this was a recommended choice of action. Even though biochemical measurements have their own limitations regarding their ability to detect whether someone recently smoked, these measurements could have provided additional validation for our interview results, and could have allowed us to be more confident about our groups. Future research may wish to replicate our findings while using biochemical measures such as the ones previously mentioned, as this would improve certainty about the accuracy of our participants' self-reports.

Chapter 20. **Summary**

The results of these three studies provide a unique look at smoking cue-reactivity and its associated effects on attentional bias, craving, neural responses, and how these factors can be used in tandem to identify individuals who are at risk of relapse in the early stages of smoking cessation. Using ERPs, both early and late occurring effects were found to uniquely characterize those who were later identified as relapsing within one month of initial screening, with greater nicotine cue reactivity being seen within the suppress condition of Study 1 (EAP and LPP effects), and greater Express EAP activity differentiating this group from never smokers. Importantly, this suggested that those who are prone to later relapse may not be able to suppress nicotine cue-related neural activation, which may contribute to the maintenance of the addiction cycle and the ineffectiveness of smoking cessation therapy. In contrast, those who were successful at abstaining over a one month period displayed greater LPP amplitudes to nicotine cues in the Express condition, yet this difference disappeared when attempts to suppress were made. Similar to the relapsers, an EAP effect in the Express condition also differentiated this group from those who had never smoked before, and both groups experienced more craving for cigarettes in the Express condition relative to the Suppress condition. Not surprisingly, all contrasts within the never smoker group failed to reach significance. In Study 2, it was discovered that abstinent smokers' reaction times to nicotine related words were slower when compared with the responses recorded from never smokers. However, no reliable effects for accuracy data were seen. Looking at the neural responses elicited by smoking-related words, a frontal P2a effect (150-300 ms) differentiated abstinent smokers from never smokers and also distinguished those who relapsed from those who had never smoked before. No such difference was observed between successful abstainers and never smokers, which could be taken as evidence that abstainers are less prone to nicotine cue-related attentional biases (which may ultimately affect relapse probability). No significant differences were found within or across groups for P3b/LPP responses to nicotine versus neutral words. Finally, Study 3

attempted to use discriminant function analysis and data from Studies 1 and 2 to successfully predict which participants would be later categorized as members of the relapser, abstainer, or never smoker groups. These models were run using all three groups, and within the relapser and abstainer groups respectively given that other important variables could be entered into the model if never smokers were left out. Using the data from Study 1, the global model that included all relevant variables was unsuccessful in significantly discriminating the groups, yet significance was attained when STAI-T, BASReward Responsivity, and ExpressEAP data were independently used to predict group membership. When the analysis was rerun using only relapsers and abstainers, FTND scores were the only variable that could independently predict relapse and abstinence. However, the global model was found to be extremely successful in discriminating between relapsers and non-relapsers, with an 86.5% success rate being achieved. Data from Study 2 were not as useful when discriminant function analysis was run with them, as the only significant effect that could be found when membership in all three groups was being calculated came from the STAI-T variable. When relapse and abstinence status was being predicted, only the FTND significantly predicted group membership and the global model failed to reach significance. All of these findings are in line with past research on attentional bias towards drug cues, their role in craving and relapse, and the importance of subjective factors such as reward responsivity, trait anxiety, and severity of nicotine dependence predicting abstinence success. These findings also bring attention to the utility of using biological measurements in tandem with behavioural and questionnaire data to assess patients that wish to curb their use of addictive substances, as these measures may be able to predict later relapse and abstinence in nearly 90% of cases. Biological markers that can be detected using ERPs may be especially useful, as changes in neural responses may reflect changes in cellular communication created by successful behavioural or pharmacological interventions. In addition to these becoming extremely useful as measurements of treatment effects and references for improved inhibitory control, ERP technology is relatively inexpensive and does not require the maintenance and technical expertise required for fMRI or MEG units. Although results pertaining to the importance of ERP based biological markers are not conclusive based on the results obtained in the current study, they appear to be a useful inclusion for models attempting

to predict relapse and future larger sample studies may be able to better define components of interest to addiction researchers and clinicians.

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Appendix A.

Quit Smoking Study Follow-Up Interview Template

Phone Call Follow-Up Procedure-(Participant Code Here)

Ask the following questions:

1) In the last 24 hours, did you have even one puff of a cigarette? (Y / N)

2) In the last 7 days, did you have even one puff of a cigarette? (Y / N)

-If yes, do you recall how many day(s) you smoked on? (Record exact dates).
How many did you have (per day and over the entire 7 days)?

3) In the last month, did you have even one puff of a cigarette? (Y / N)

-If yes, do you recall the number of day(s) out of the last 31 you smoked on?
How many did you have (in total and over the entire 31 days)?

Have you used any nicotine replacement therapies (i.e. The patch, nicotine gum, electronic cigarettes)?

If yes, how many units in the last 24 hours?

Last week?

Last month?

Appendix B.

Summary Table of Effects Study 1

	Effects	<i>p</i> value
<u>Behavioural Effects</u>		
<i>Craving</i>	<u>Global ANOVA</u> -Significant Condition, Stimulus, and Group main effects -Significant Condition x Group and Stimulus x Group interactions	<u>Global ANOVA</u> Condition main effect: $p < .001$ Stimulus main effect: $p < .0001$ Group main effect: $p < .0001$ Condition x Group: $p = .044$ Stimulus x Group: $p < .0001$
	<u>Contrast t-tests</u> 1) <i>Relapsers</i> : Express Nicotine > Express Neutral, Suppress Nicotine > Suppress Neutral, Express Nicotine > Suppress Nicotine 2) <i>Abstainers</i> : Express Nicotine > Express Neutral, Suppress Nicotine > Suppress Neutral, Express Nicotine > Suppress Nicotine	<u>t-tests</u> <i>Relapsers</i> Express Nic > Express Neutral: $p < .0001$ Suppress Nic > Suppress Neutral: $p < .0001$ Express Nic > Suppress Neutral: $p = .022$ <i>Abstainers</i> Express Nic > Express Neutral: $p < .0001$ Suppress Nic > Suppress Neutral: $p = .001$ Express Nic > Suppress Neutral: $p = .021$

ERP Effects

EAP (200-300 ms)

Express Condition (F-tests)

1) Significant Group x Stimulus

Group x Stimulus: $p=.024$

Suppress Condition (F-tests)

1) Significant Stimulus effect

Stimulus main effect: $p=.002$

Contrast t-tests (Express)

1) *Relapsers*: Express Nicotine > Express Neutral

Contrast t-tests (Express)

Relapsers

Express Nicotine > Express Neutral: $p=.047$

2) *Abstainers*: Express Nicotine > Express Neutral

Abstainers

Express Nicotine > Express Neutral: $p=.045$

3) *All Abstinent Smokers versus Never Smokers*: Express Nicotine > Express Neutral

All Abstinent Smokers versus Never Smokers:

Express Nicotine > Express Neutral: $p=.006$

Contrast t-tests (Suppress)

1) *Relapsers*: Suppress Nicotine > Suppress Neutral

Contrast t-tests (Suppress)

Relapsers

Suppress Nicotine > Suppress Neutral: $p=.004$

LPP (300-600 ms)

Express Condition (F-tests)

1) Significant Stimulus effect

Stimulus main effect: $p=.012$

Suppress Condition (F-tests)

No significant effects

Contrast t-tests (Express)

1) *Abstainers*: Express Nicotine > Express Neutral

Contrast t-tests (Express)

Abstainers

Express Nicotine > Express Neutral: $p=.008$

Contrast t-tests (Suppress)

1) *Relapsers*: Suppress Nicotine > Suppress Neutral

Contrast t-tests (Suppress)

Relapsers

Suppress Nicotine > Suppress Neutral: $p=.015$

Appendix C

Summary Table of Effects Study 2

	Effect	<i>p</i> values
<u>Behavioural Effects</u>		
<i>sStroop RT</i>	<u>RT Effects (F-tests)</u> Group and Group x Stimulus effects	Group main effect: <i>p</i> =.038 Group x Stimulus effect: <i>p</i> =.05
	<u>Between Group Contrast t-tests</u> 1) <i>Abstinent Smokers versus Never Smokers</i> : Nicotine RT > Neutral RT	<u>Between Group Contrast-tests</u> <i>Abstinent Smokers versus Never Smokers</i> Nicotine RT > Neutral RT: <i>p</i> =.006
	No within group mean differences	No within group mean differences
<i>sStroop Accuracy</i>	<u>Contrast t-tests</u> 1) Relapsers: Nicotine > Neutral (Failed to remain significant if Bonferroni correction applied)	<u>Contrast t-tests</u> 1) Relapsers: Nicotine > Neutral; <i>p</i> =.036
<u>ERP Effects</u>		
<i>P2a (150-300 ms)</i>	<u>P2a (F-tests)</u> No significant effects	
	<u>Between Group Contrast t-tests</u> 1) <i>Nicotine P2a</i> : Abstinent Smokers > Never Smokers	<u>Between Group Contrast t-tests</u> <i>Nicotine P2a</i> : Abstinent Smokers > Never Smokers: <i>p</i> =.042
	2) <i>Nicotine P2a</i> : Relapsers > Never Smokers	2) <i>Nicotine P2a</i> : Relapsers > Never Smoker: <i>p</i> =.047
	No within group effects	No within group effects
<i>LPP (300-600 ms)</i>	No effects	No effects

Appendix D.

Summary Table of Effects Study 3

	Overall Model	Significant Individual Variables	Wilks' λ and p values
<u>Study 1 Data</u>			
<i>Discriminant Analysis (All Groups)</i>	Not significant	1) BASReward 2) STAI-T 3)ExpressNicMinus Neut	1) BASReward: Wilks' λ =.863, p =.02 2) STAI-T: Wilks' λ =.825, p =.007 3)ExpressNicMinusNeutralEAP: Wilks' λ =.866, p =.02
<i>Discriminant Analysis (Relapsers and Abstainers Only)</i>	($\chi^2(9)$)=19.464, p =.022 -16/18 relapsers (89%) and 16/19 non-relapsers (84%) correctly classified. -Overall classification rate was 32 out of 37 (86.5%)	1) FTND	1) FTND: Wilks' λ =.825, p =.01
<u>Study 2 Data</u>			
<i>Discriminant Analysis (All Groups)</i>	Not significant	1) STAI-T	1) STAI-T: Wilks' λ =.875, p =.03
<i>Discriminant Analysis (Relapsers and Abstainers Only)</i>	Not Significant	None significant	No effects