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Where there's smoke, there's fire:

The brain reactivity of chronic smokers to anti-smoking stimuli

par

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Ce mémoire intitulé:

Where there's smoke, there's fire:
The brain reactivity of chronic smokers to anti-smoking stimuli

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Résumé

Contexte : Plusieurs études ont démontré que les indices environnementaux associés à la cigarette peuvent provoquer des envies de consommer (« *cravings* ») chez les fumeurs, ce qui nuit aux efforts d'abandon de la substance et favorise le maintien du tabagisme. Un bon nombre d'études en imagerie cérébrale ont examiné les bases neurophysiologiques de cette caractéristique clinique. Le tabagisme se caractérise aussi par l'incapacité des représentations négatives de la consommation (méfaits médicaux et sociaux) d'influencer la consommation des fumeurs. Étonnamment toutefois, très peu de travaux de recherche se sont intéressés à examiner les bases neurophysiologiques de cette insouciance envers les méfaits de la cigarette chez les fumeurs. En utilisant l'imagerie cérébrale fonctionnelle, l'objectif de cette étude était: d'examiner la réponse neurophysiologique des fumeurs chroniques à des images qui illustrent les effets négatifs de la cigarette (campagne anti-tabac); d'examiner le caractère affectif de cette réactivité utilisant des conditions contrôles (c.-à-d., images aversives non-liées au tabac et appétitives liées au tabac); d'examiner la connectivité fonctionnelle durant cette tâche entre les systèmes affectifs et exécutifs (une interaction qui peut favoriser ou entraver l'impact des évènements aversifs). **Méthodes**: 30 fumeurs chroniques ont passé une session de neuroimagerie durant laquelle ils devaient regarder des images appétitives et aversives de cigarettes, des images aversives non-reliées au tabac et des images neutres. **Résultats** : Les images aversives liés au tabagisme suscitent une plus grande activation dans le cortex médial préfrontal, l'amygdale, le gyrus frontal inférieur et le cortex orbitofrontal latéral en comparaison avec les images neutres, mais une moins grande activation dans des structures médiaux / sous-corticales comparé aux images aversives non-reliés et images

appétitives reliées aux tabac. L'activité du système exécutif présente une connectivité fonctionnelle négative avec le système affectif lorsque les images aversives sont liées au tabac, mais pas quand elles ne le sont pas. **Conclusions:** Le modèle d'activation du cerveau observé suggère qu'il y a un biais dans la réactivité des fumeurs chroniques lorsqu'ils observent des représentations négatives de la consommation du tabac. L'activité du système exécutif cérébral semble promouvoir chez les fumeurs une baisse d'activité dans des régions impliquées dans la genèse d'une réponse physiologique affective ; il s'agit d'un mécanisme qui permettrait de réduire l'impact persuasif de ces représentations des méfaits de la cigarette sur la consommation des fumeurs.

Mots clés: toxicomanie - tabac - craving - anti-tabac - aversion - neuroimagerie – connectivité fonctionnelle

Abstract

Background: Studies have shown that appetitive smoking-related stimuli trigger important cravings in smokers which promote the maintenance of smoking behavior. Neuroimaging studies have been valuable in elucidating the mechanisms underlying this clinical feature. However, another important but under-explored feature of tobacco dependence is the inability for aversive smoking-related stimuli, such as anti-smoking campaigns, to influence this craving and smoking response. Using functional magnetic resonance imaging, the goal of this study was three-fold: to examine the neurobiological response of chronic smokers when processing aversive smoking-related cues; to further characterize this response using control conditions (i.e., aversive nonsmoking-related, appetitive smoking-related cues); to examine the pattern of functional connectivity during this task between executive and affective systems that may interact in ways that promote or hinder the impact of aversive events. **Methods:** Thirty chronic smokers passively viewed aversive smoking-related, aversive nonsmoking-related, appetitive smoking-related and neutral images presented in a block design while being scanned. **Results:** Aversive smoking-related stimuli elicited significantly greater activation in the medial prefrontal cortex, amygdala, inferior frontal gyrus and lateral orbitofrontal cortex than neutral stimuli. Aversive smoking-related stimuli elicited lower activation in medial/sub-cortical structures compared to the processing of aversive nonsmoking-related and appetitive smoking cues. Executive and affective systems are negatively associated when aversive cues are smoking-related, but not when nonsmoking-related. **Conclusion:** The brain activation pattern observed suggests that chronic smokers experience an aversive response when processing aversive smoking-related stimuli, however we argue that the

latter triggers a weaker negative emotional and driving response than the aversive non-smoking-related and appetitive smoking-related cues respectively. Executive systems, activated during aversive smoking-related processing, may act to down-regulate activity in regions key to an affective and persuasive response; a mechanism that may reduce the extent to which “feeling bad” affects a change in behavior.

Key words: addiction – tobacco – craving – anti-smoking – aversion – neuroimaging – connectivity

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Liste des abréviations

ACC: anterior cingulate cortex (ACC)

ACh: acetylcholine

ADHD: Attention deficit hyperactivity disorder

BA: Broadmann area

BDI: Beck depression inventory

BIS: Behavioral Inhibition System

BIS-11: Barratt Impulsiveness Scale

BOLD: blood oxygenation level dependent

DA: dopaminergic

dmPFC: dorsomedial prefrontal cortex

DSM: diagnostic and statistical manual

FFFS: Fight–Flight–Freeze system

fMRI: functional magnetic resonance imaging

FOV: field of view

FTCQ-12: French Tobacco Craving questionnaire

FTND: Fagerström Test for Nicotine Dependence

FWHM: Full width half maximum

GABA: gamma-amino-butyric acid

IAPS: International affective picture system

IFG: inferior frontal gyrus

ISIS: International smoking image series

LOFC: lateral orbitofrontal cortex

MPFC: medial prefrontal cortex

nAChRs: nicotinic acetylcholine receptors

NAc: nucleus accumbens

OFC: Orbitofrontal cortex

PCC: Posterior cingulate cortex

PFC: prefrontal cortex

PPI: Psycho-physiological interaction

PS: Punishment sensitivity

ROI: Region of interest

SPM5: Statistical parametric mapping software

SPSS: Statistical package for the social sciences

STAI: State-trait anxiety inventory

SUD: substance use disorder

VLOFC: ventrolateral orbitofrontal cortex

VTA: ventral tegmental area

WHO: World Health Organization

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1 Introduction

1.1 Tobacco: Major public health issue

Many addictive drugs derive from natural sources and have been consumed by mankind for thousands of years. They are pharmacologically effective substances that promote repeated use via their rewarding and therapeutic properties. The psychoactive effects of tobacco were first discovered two to three millennias ago in the Americas. Since then, tobacco has become one of the most widely utilized addictive substances worldwide. Indeed, the prevalence of smoking is high. For instance, it is estimated that approximately 16.1% of Canadians (Reid, Hammond, Rynard, & Burkhalter, 2014), 19.5% of Americans (Janz, 2011; King, Dube, & Tynan, 2012) and 22% of British are smokers (Bogdanovica, Godfrey, McNeill, & Britton, 2011; Fidler et al., 2011; Gallus et al., 2011). Sm rates are even greater in low to middle income countries, reaching approximately 30% in Poland, Turkey, Ukraine and China, and as high as 39% of the population in Russia (Giovino et al., 2012; Jha et al., 2006). Globally there are over a billion smokers today and another additional billion is projected for 2030 (Peto & Lopez, 2004). The issue however is that smoking is associated with significant mortality and adult disease, and, as such, is an economic burden for societies worldwide.

1.1.1 Mortality rates associated with smoking

Tobacco is the single most preventable cause of death in the world today (WHO, 2008). The World Health Organization (WHO) reports that more than five million deaths per year are a direct result of tobacco use - a mortality rate greater than tuberculosis, HIV/AIDS and malaria combined. These rates remain significantly high in developed

countries. In Canada and the United Kingdom, it is estimated that approximately one in five deaths are attributable to tobacco smoking (Allender, Balakrishnan, Scarborough, Webster, & Rayner, 2009; Baliunas et al., 2007). In the United States, cigarette smoking kills an estimated 440,000 U.S. citizens each year— more than alcohol, illegal drug use, homicide, suicide, car accidents, and AIDS combined. In all, it is estimated that among persistent cigarette smokers (those who start in early adult life and do not give up), about 50% will eventually be killed by tobacco (WHO, 2008). Unless better understanding of the mechanisms underlying tobacco dependence and how best to treat/prevent it is reached, tobacco's annual death toll and other associated costs will continue to rise (Mathers & Loncar, 2006).

1.1.2 Negative health-related consequences of smoking

Since the first epidemiological studies linking smoking with lung cancer in the 1950s, it is now widely accepted that smoking harms nearly every organ in the body and is a significant risk factor for many adult diseases. It is well-documented that smoking substantially increases the risk of heart disease (e.g., stroke, heart attack, vascular disease, aneurysm), lung disease (e.g., chronic bronchitis, pneumonia, emphysema, asthma) and cancer (NIDA, 2012). For instance, cigarette smokers are 2–4 times more likely to develop coronary heart disease than non-smokers (MMWR, 2008). Tobacco use accounts for more than one-third of all cancer deaths, including of the mouth, pharynx, larynx, esophagus, stomach, pancreas, cervix, kidney, bladder and acute myeloid leukemia, with the most prominent being lung cancer (NIDA, 2012). Smoking increases the risk of developing lung cancer by 23 times in men and by 13 times in women (CDC, 2004).

Overall rates of death from cancer are twice as high for smokers than non-smokers and four times greater in heavy smokers than non-smokers (NIDA, 2012).

A number of other diseases are similarly linked to tobacco smoking, although these associations are typically less known. Studies have shown that tobacco smoking has harmful effects on the gastrointestinal tract (Wu & Cho, 2004), the skin (Naldi, 1998), vision (Evans, 2001), bone density (Law & Hackshaw, 1997), the risk of developing type II diabetes (Haire-Joshu, Glasgow, & Tibbs, 1999), oral health (Winn, 2001), male and female fertility, pregnancy and birth (Pasqualotto, Sobreiro, Hallak, Pasqualotto, & Lucon, 2005; Werler, Pober, & Holmes, 1985). For instance, a meta-analysis of eight cohort studies (based on 20,059 women) demonstrated that female smokers were 42% more likely to be infertile that non-smokers, which increases with severity of dependence (Augood, Duckitt, & Templeton, 1998). In addition to the direct effects of cigarettes on smokers, secondary smoking is also associated with significant disease. Inhaling second hand smoke is associated with an increased risk of lung cancer and coronary heart disease in non-smokers (IARC, 1986).

1.1.3 Economic burden of smoking

Given the burden of smoking on health, tobacco use is associated with significant economic costs for society. Smoking related-diseases typically necessitate extensive medical care, including hospitalizations, surgeries, prescriptions and doctor's visits, and thus, is a source of significant health-care costs. Between 2002 and 2005, Canada spent every year between 4.1 to 4.5 billions CAN$ per 30 million inhabitants of health care cost on tobacco-related health issues. In the United States, more than $96 billion each year of all U.S. healthcare costs are attributable directly to smoking (NIDA, 2012). In

addition to health care costs, smoking-related diseases impede an individual's ability to work. This loss of productivity is estimated to cost 12.5 billion CAN$ per year (Rehm et al., 2007) and $97 billion per year in the United States (NIDA, 2012). The economic burden of smoking per year thus adds up to approximately 16.6 CAN$ billion in Canada and more than 193 US$ in the United States. These numbers, while high, remain under-representative of the actual total costs of smoking as it does not include indirect smoking-related issues, such as burn care from smoking-related fires, medical care costs associated with disease caused by second-hand smoke and perinatal care for infants of mothers who smoke; the latter estimated to be more than $350 million per year (NIDA, 2012).

1.2 Characteristics of smokers: Who is at an increased risk of smoking?

Tobacco use typically begins in adolescence. In the United States, about 70% of adult smokers report that they had started smoking by the time they were 18 (CDC, 1994). Initiation of tobacco use in teens is not only the result of psychosocial influences, such as peer pressure, but of psychological vulnerability factors. A recent epidemiological study has shown that young adults reporting symptoms of Attention deficit hyperactivity disorder (ADHD) (i.e. impulsivity, inattention and hyperactivity) are significantly more likely to be regular smokers (Kollins, McClernon, & Fuemmeler, 2005). Similarly, conduct disorder, also marked by impulsivity issues, is associated with chronic tobacco use (Dierker, Avenevoli, Merikangas, Flaherty, & Stolar, 2001). This increased risk of tobacco use in a psychiatric population is also present in adults. While 30% of Americans report living with a psychiatric condition, they account for almost half of the cigarette consumption in the U.S. (Lasser et al., 2000). Smokers, compared to non-smokers, report

more depressive symptoms and greater life stress (van Loon, Tijhuis, Surtees, & Ormel, 2005). Consumption of tobacco products remains remarkably high among individuals with bipolar disorder and major depression with respective prevalences of 68% and 57% (Chapman, Ragg, & McGeechan, 2009; de Leon & Diaz, 2005; Diaz et al., 2009; Lambert & Hartsough, 1998; Lasser et al., 2000). The presence of other substance use issues is also highly associated with an increased likelihood of smoking behavior (Opaleye et al., 2012). More than 30% of alcohol and 50% of illicit drug users with substance abuse/dependence issues are also tobacco dependent (Grant, Hasin, Chou, Stinson, & Dawson, 2004). The most extensive comorbidity overlap however is the one that exists between smoking and schizophrenia, since, in clinical samples, the rate of smoking in patients with schizophrenia varies from 60% to as high as 90% (NIDA, 2012).

Gender and socio-economic status are also associated with trends in tobacco use. Men and Caucasians are more prone to becoming smokers than women and African-Americans respectively (Shuaib et al., 2011). In addition, tobacco consumption is more prominent in the unemployed, less educated (less than 10 years vs. more than 14) and in lower social economic classes (Helasoja et al., 2006; Opaleye et al., 2012; Shuaib et al., 2011; van Loon et al., 2005).

1.3 Tobacco Use Disorder

1.3.1 Clinical features of Tobacco Use Disorder

Tobacco Use Disorder is recognized as a medical condition in the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association. Similarly to other

addictions, it is characterized by compulsive drug seeking despite its negative effects on social, physical and/or occupational health. In the revised fourth edition of the DSM (DSM-IV-TR), it is defined by a pattern of repetitive and chronic consumption of tobacco in the last 12 months, that contains at least three of seven following criteria: (a) tolerance; signs of tolerance are a need for a markedly increased amount of nicotine to produce the desired effect or a diminished effect with continued use of the same amount of nicotine (b) withdrawal, as manifested by either the characteristic nicotine withdrawal syndrome, or nicotine (or a closely related substance) is taken to relieve or avoid withdrawal symptoms (c) nicotine is used in larger amounts or over a longer period than intended (d) the user has a persistent desire or makes unsuccessful attempts to cut down on tobacco (d) a great deal of time is spent in obtaining or using the substance (e.g., chain smoking) (e) important social, occupational, or recreational activities are reduced because of tobacco use (f) use of the substance continues despite recurrent physical or psychological problems caused or exacerbated by tobacco: for example, continuing to smoke despite diagnoses such as hypertension, heart disease, cancer, bronchitis, and chronic obstructive lung disease (APA, 2000).

A number of changes to diagnostic criteria have been made within the latest edition of the DSM, DSM-V (APA, 2013). DSM-V combines the diagnoses of substance abuse and dependence under the bracket of substance use disorder, rather than divide the two categories, as was the case in the DSM-IV-TR. The DSM-V criteria for tobacco use disorder are nearly identical to the DSM-IV-TR criteria with three exceptions. A new criterion, craving or a strong desire or urge to use a substance, has been added. In addition, the threshold for substance use disorder diagnosis is set at two or more criteria,

in contrast to a threshold of three or more. Furthermore, the criteria for DSM-V tobacco use disorder are now the same as those for other substance use disorders. Previous versions of the DSM did not include a category for tobacco abuse based on the assumption that abuse criteria were not relevant to nicotine disorders (Hughes, Higgins, & Bickel, 1994; Shmulewitz et al., 2013). However, it is now recognized that tobacco users show maladaptive patterns of smoking behavior relevant to abuse criteria, such as continued tobacco use despite increasingly widespread anti-smoking norms and policies (potentially contributing to social stigmatization of smoking and problems with others about smoking) and knowledge of the health-related problems that will result from smoking (Benowitz, 2010; Shmulewitz et al., 2011). Therefore, the DSM-IV criteria for substance abuse are new for tobacco in the DSM-V.

Tobacco use disorder is not immediately as debilitating as other addictions; for instance, it's immediate pharmacological effects do not hinder the users ability to fulfill their duties at work, home or school nor is it a significant trigger for impulsive or aggressive behavior, such as in the case of alcohol or stimulant abuse. It is, however, considered to have the strongest addictive potential; 67.5% of chronic users of nicotine will be dependent at some point in their lives, compared with 20.9% and 8.9% of chronic users of cocaine and cannabis respectively (Lopez-Quintero et al., 2011). In addition, quit rates remain low despite the availability of numerous pharmacological treatments aimed at cessation of tobacco smoking (Haas, Munoz, Humfleet, Reus, & Hall, 2004). Of the chronic smokers who attempt to quit, only 3-5% are successful without the use of nicotine replacement therapies, and no more than one-third are successful with them

(Stead, Perera, Bullen, Mant, & Lancaster, 2008). Difficulties in quitting promote continued use and thus, the detrimental effects of smoking on health and functioning.

1.3.2 Psychological effects of tobacco

Nicotine is the main addictive chemical component of tobacco and is responsible for the acute effects of smoking. It triggers a cluster of physiological, behavioral and cognitive phenomena that promotes its therapeutic effects and addictive nature. The administration of nicotine, through its stimulation of the nervous system, increases heart rate and blood pressure during the first 5 to 10 minutes; the values return to a basal level about 90 minutes after consumption (Adan & Sanchez-Turet, 1995). Its benefits include promoting feelings of alertness, improving mental acuity, while inhibiting drowsiness (Underner, Paquereau, & Meurice, 2006); reducing appetite and potentially promoting weight loss (Jorenby et al., 1996; Miyata, Meguid, Fetissov, Torelli, & Kim, 1999); causing feelings of pleasure and reward; temporary improving cognitive abilities (West, 1993). A recent meta-analysis (41 studies from 1994 to 2008) investigated the effects of acute nicotine administration compared to placebo on cognitive (working memory, episodic memory), attention and motor skills. Heishman, Kleykamp, and Singleton (2010) reported that nicotine improved the performance of smokers on a number of tasks, such as episodic short-term memory and attention/vigilance, and the speed of non-smokers on attention/vigilance, directed attention and working memory tasks, compared to placebo (Heishman et al., 2010). Interestingly, the beneficial effects of smoking seem to be reduced in non-smokers: consumption does not improve their performance per se, but increases their speed of response.

In addition, these benefits may help counter the cognitive difficulties faced by psychiatric populations, such as in schizophrenia (Newhouse, Potter, & Singh, 2004) and ADHD (Conners et al., 1996; Levin et al., 1996; Potter & Newhouse, 2008). The benefits of nicotine on the performance of schizophrenia patients has been well-documented. Nicotine administration significantly improves the performance of non-smoking patients on measures of attention, cognitive inhibition and episodic memory; these benefits were less pronounced in a non-psychiatric population (Barr et al., 2008; Jubelt et al., 2008). Nicotine has also been shown to improve filtering processes of auditory information, which are dysfunctional in schizophrenia patients (Potter, Summerfelt, Gold, & Buchanan, 2006). In the case of ADHD, nicotine administration is associated with clinician-rated global improvement of ADHD symptoms, self-reports of increased vigor and concentration, as well as better performance on measures of attention and timing accuracy (Conners et al., 1996; Potter & Newhouse, 2008).

1.4 Neurobiological mechanisms of nicotine

1.4.1 Nicotine: activation of acetylcholine receptors in the brain

Cigarettes and other smoked tobacco products rapidly deliver nicotine to the brain, about as efficiently as an intravenous injection with a syringe (Benowitz, 1996). After inhalation of cigarette smoke, nicotine reaches the pulmonary circulation and the brain within 10 to 20 seconds, thus avoiding the need for first-level metabolism (Le Houezec, 2003). This speed of absorption in addition to its increased concentration in the brain increases the addictive potency of tobacco smoking. There is also a mild “high” caused in part by the drug’s stimulation of nicotinic acetylcholine (ACh) receptors (nAChRs).

Neuronal nAChRs are ion channels comprising five membrane-spanning subunits that combine to form a functional receptor (Changeux & Taly, 2008) and include nine isoforms of the neuronal α-subunit (α2–α10) and three isoforms of the neuronal β-subunit (β2–β4) (Markou, 2008). These subunits combine with a stoichiometry of two α- and three β-, or five α7-subunits to form nAChRs (Markou, 2008); α4β2-containing and α7 homomeric receptors are the most prevalent nAChRs in the brain. Because of the wide distribution of nAChRs, administration of nicotine stimulates the release of most neurotransmitters throughout the brain, such as dopamine, serotonin, glutamate, and gamma-amino-butyric acid (GABA) (McGehee & Role, 1995). Activation of these receptors is associated with the rewarding and cognitive benefits associated with tobacco smoking.

1.4.2 Nicotine: activation of the reward system

The DSM-V recognizes that activation of the brain's reward system is central to problems arising from drug use. The euphoric feeling that people experience as a result of taking drugs may be so profound that they ignore responsibilities and disregard the negative consequences of their behavior in favor of taking the drug. Nicotine is addictive in part because of its activation of the reward pathways in the brain (Markou, 2008).

In the midbrain of mammals, interconnected brain structures are referred to as the mesocorticolimbic brain system which includes the mesolimbic pathway connecting the ventral tegmental area (VTA) to the limbic system via the nucleus accumbens (NAc), amygdala, hippocampus and medial prefrontal cortex, as well as the mesocortical pathway connecting the VTA to the frontal cortex (Roberts & Koob, 1997; Wise, 1998).

Activation of the VTA is critical to drug dependence; it is an area rich in dopaminergic (DA) neurons, a neurotransmitter involved in the motivation to approach rewards (Everitt, Dickinson, & Robbins, 2001). Nicotine binds to nicotinic acetylcholine receptors located on the DA neurons of the VTA (Clarke & Pert, 1985; Deutch, Holliday, Roth, Chun, & Hawrot, 1987), as well as on glutamatergic and GABAergic neurons that modulate these DA neurons (Mansvelder, Keath, & McGehee, 2002; Wooltorton, Pidoplichko, Broide, & Dani, 2003). Nicotine increases the firing rates of VTA DA neurons (Calabresi, Lacey, & North, 1989), leading to increased DA release in the NAc, amygdala and PFC (Imperato, Mulas, & Di Chiara, 1986), hijacking the neurobiological structures that promote feelings of reward (Brody et al., 2002; Brody et al., 2007; Childress et al., 1999; Claus, Kiehl, & Hutchison, 2011; Due, Huettel, Hall, & Rubin, 2002; Luijten et al., 2011; Volkow, Fowler, & Wang, 2004; Yalachkov, Kaiser, & Naumer, 2009). Activity in these regions are responsible for providing the incentive for drug-seeking behavior (Salamone, 1994; Salamone, Correa, Mingote, & Weber, 2003), learning about the rewarding properties of stimuli (Parkinson et al., 2001; Whitelaw, Markou, Robbins, & Everitt, 1996) and focusing attention towards a goal-directed behavior (Wise, 1998). This activation of mesocorticolimbic structures is thus responsible for users' experience of pleasure, reduced anxiety and the other rewarding effects of nicotine.

1.5 Appetitive processes in Tobacco Dependence

1.5.1 Craving in addiction research

A central concept in drug abuse research is that increased activity in the reward system

are responsible for the reinforcing effects of drugs (Di Chiara & Imperato, 1988; Koob & Bloom, 1988; Roberts & Koob, 1997). Through a learning process however, certain cues in the environment become associated with the rewarding effects of drug use, and eventually, the cues alone can drive drug-seeking behavior, making it an important mechanism underlying addictive behavior. In the context of tobacco smoking, smoking cues, such as the smell of tobacco smoke or viewing someone smoke, have been found to trigger *an appetitive response towards the act of smoking, known as cravings* (Caggiula et al., 2001). These cravings triggered by the presentation of salient smoking cues promote hastier smoking initiation and subsequent cigarette consumption (Herman, 1974).

Cravings are characterized by an intense desire to consume, a feature that is now recognized by the DSM-V as a core symptom of SUD (substance use disorder) syndromes. It is a marker for severity of tobacco dependence and the inability to quit. In a study using nationally representative samples of cigarette smokers, Goedeker and Tiffany (2008) found that increased cravings were a defining characteristic of dependent smokers compared to nondependent smokers. In addition, reports of greater craving in abstinent smokers are associated with the inability to remain abstinent and an increased rate of relapse at follow-up (Catley, O'Connell, & Shiffman, 2000; Hughes, Peters, & Naud, 2008; Killen & Fortmann, 1997; McClernon, Kozink, Lutz, & Rose, 2009; Shiffman et al., 1997).

In all, users experience a potent appetitive response when presented with drug-related stimuli that promotes self-control failure and drug seeking behavior; an important mechanism that maintains addictive behavior.

1.5.2 Craving in addiction and neuroimaging research

Because of its role in the maintenance of addictive behavior, an extensive body of work has examined the neural responses underlying this appetitive response to drug cues. Typically, the functional neuroimaging paradigms used to investigate this response expose smokers to stimuli associated with tobacco use. These appetitive smoking-related cues may be visual (pictures or videos) (Luijten et al., 2011), olfactory or gustatory (smelling or smoking) (Claus et al., 2011; Schneider, Olmstead, Franzon, & Lunell, 2001); multi-sensory drug cues may also be employed (e.g., holding a cigarette while watching audio-videos of smoking) (Brody et al., 2007; Franklin et al., 2007). Subjects may be instructed to passively experience the drug cues or, alternatively, to actively respond to these stimuli (e.g., enhance craving; suppress craving). Matched, neutral and non-drug-related stimuli in the same sensory domain are often used as control stimuli (e.g., images of hand vs. hand holding a cigarette) and allow examining the neural reactivity associated with the smoking component of the task (Chase, Eickhoff, Laird, & Hogarth, 2011; Kuhn & Gallinat, 2011).

Neuroimaging results thus far have implicated the importance of a number of regions in driving nicotine seeking behavior. A recent meta-analysis of functional magnetic resonance imaging (fMRI) studies on tobacco craving concluded that exposure to appetitive smoking-related cues, compared to neutral cues, is associated with increased activation in regions involved in perceptual processing and attention (e.g., extended visual system), self-referential processing (e.g. precuneus/posterior cingulate), planning/regulatory processes (e.g. ACC and dorsolateral PFC), emotional responding (e.g., insula), as well as the triggering of automatic conducts (e.g. dorsal striatum)

(Engelmann et al., 2012). Activation of the anterior cingulate cortex, insula and medial prefrontal cortex are believed to be particularly key to drug-seeking behavior (Naqvi & Bechara, 2009, 2010; A. Verdejo-Garcia & Bechara, 2009). Increased activity in these regions while viewing appetitive drug cues are predictive of self-reported craving and inability to quit (Brody et al., 2002; Janes, Farmer, Frederick, Nickerson, & Lukas, 2014; Janes et al., 2009; Wang et al., 2007).

In addition, specific individual states and traits appear to modulate the brain response to appetitive smoking cues. Some authors have shown that dependence severity, motivation to quit, craving and features related to addictive behavior (e.g., impulsivity) modulate prefrontal and sub-cortical activity towards smoking cues (Bourque, Mendrek, Dinh-Williams, & Potvin, 2013; Jasinska, Stein, Kaiser, Naumer, & Yalachkov, 2014; McBride, Barrett, Kelly, Aw, & Dagher, 2006; McClernon, Hiott, Huettel, & Rose, 2005; McClernon et al., 2009; Smolka et al., 2006; Wilson, Sayette, & Fiez, 2004).

In summary, neuroimaging studies have helped uncover the neurobiological mechanisms underlying smokers' appetitive response to smoking cues.

1.6 Aversive processing in Tobacco Dependence

1.6.1 Negative consequences in addiction research

Addiction is marked by an appetitive response to drug cues that promotes a greater predisposition towards drug use despite knowledge or experience with its negative value (Bechara, 2005). Indeed, while rewarding, substance use is also associated with a number of undesirable effects such as ill health, disrupted social or familial relations, social stigmatization, high drug costs for the individual and more (Dobkin & Nicosia, 2009).

Decades of research on psychosocial interventions have shown that awareness and experience with the negative consequences of drug use however are not sufficient to alter the drug seeking behavior of an addict (Chamberlain et al., 2013). Typically, when the consequences of an act are negative, the behavior tends not to be repeated. This inability for negative consequences to alter drug seeking behaviour in addiction is a defining feature of this disorder and plays a role in the maintenance of addictive behavior. Indeed, according to Campbell (2003), substance use issues should be viewed, not solely as a sensitivity to the appetitive value of using, but as a disorder of faulty volition characterized by the inability to use knowledge or experience with the negative consequences of drug consumption to promote self-control. He states that treatment will continue to achieve limited success until the mechanisms underlying this clinical feature are properly understood.

1.6.2 Risk and Punishment sensitivity in addiction

Recent research has suggested that greater propensity for risk-taking and decreased sensitivity to punishment may underlie this clinical feature (Gowin, Mackey, & Paulus, 2013; Hester, Bell, Foxe, & Garavan, 2013; Hester, Madeley, Murphy, & Mattingley, 2009; Hester, Nestor, & Garavan, 2009; Luijten, O'Connor, Rossiter, Franken, & Hester, 2013; Rossiter, Thompson, & Hester, 2012). Studies have shown that smokers are aware of the risks of smoking (Viscusi, 1999), however they continue to smoke. This suggests that smokers may be risk insensitive. Studies have indicated that compared to nonsmokers, smokers are more likely to partake in a variety of risky behaviors, whether drug or nondrug-related (Dom, D'Haene, Hulstijn, & Sabbe, 2006; Leland, Arce, Feinstein, & Paulus, 2006; Leland & Paulus, 2005). Daily smokers are less likely to wear

their seat belts (Eiser, Sutton, & Wober, 1979), tend to choose riskier occupations (Hersch & Viscusi, 1998), engage in more high-risk sexual behaviors and drug-taking than nonsmokers (Valois, Oeltmann, Waller, & Hussey, 1999). In addition, studies have found that behavioral indices of risk-taking are predictive of drug use problems and tobacco smoking in adolescents and young adults (Fernie, Cole, Goudie, & Field, 2010). These findings highlight that tobacco users are more likely to engage in risky situations in which something unpleasant may arise.

Relevant to this is their reactivity to punishment, the experience of "something unpleasant" as a result of their behavior. Studies suggest that a reduced aversive response to punishment, whether drug- or nondrug-related, may be an important mechanism underlying the propensity for risk taking and problematic substance use (Bechara, Dolan, & Hindes, 2002). Punishment sensitivity (PS) arose from the reinforcement sensitivity theory of Gray and is believed to be mediated by activity of the Fight–Flight–Freeze system (FFFS). The latter monitors the presence of danger and aversive stimuli and activates the Behavioral Inhibition System (BIS) in response to these aversive events that promotes adaptive avoidant behavior. It has been suggested that addicts are less responsive to these aversive events, and thus, Gray's BIS is not sufficiently activated in response to these negative cues to induce the behaviour to cease (Corr, 2002; Franken, Muris, & Georgieva, 2006; Yen, Ko, Yen, Chen, & Chen, 2009). Consistent with this theoretical prediction, several studies have reported associations between low punishment sensitivity and a greater propensity for substance use, including nicotine and cannabis (Knyazev, 2004; Loxton et al., 2008; Simons & Arens, 2007). Lower PS was a consistent risk factor for being a current smoker, and for number of cigarettes smoked among young

smokers (White, Young, Morris, & Lawford, 2011). This decreased sensitivity to aversive events may contribute to greater risk taking and the inability for negative consequences to modify drug behavior (de Ruiter et al., 2009; Simons, Dvorak, & Batien, 2008).

1.6.3 Aversive processing in addiction and neuroimaging research

The somatic-marker hypothesis has been proposed in order to account for the underlying neural mechanisms underlying this disregard for the negative consequences of one's behavior (Verdejo-Garcia & Bechara, 2009). It stems from observations in a group of neurological patients with prefrontal lesions that demonstrate similar impairments in judgment and decision-making seen in addiction, characterized by a tendency to choose the immediate reward, at the expense of severe negative future consequences (Damasio, 1996). It stipulates that adaptive decision-making following negative consequences depends on neural substrates that regulate emotion and feeling (Damasio, 1994). The inability for negative consequences to affect the behavior of drug users is attributed to a dysfunctional emotional processing mechanism by which a somatic aversive state does not signal the importance of consequences and thus, does not assist in selecting an advantageous response (Verdejo-Garcia & Bechara, 2009).

Studies suggest the importance of brain regions, key to an aversive response, in promoting this clinical feature. A recent meta-analysis of emotional processing suggest that increased activity in a network of regions underlie the experience of a negative emotional response: anterior cingulate cortex (ACC), insula, amygdala, ventrolateral orbitofrontal cortex (VLOFC), hippocampus, parahippocampus, dorsal striatum, rostral temporal gyri, thalamus, dorsomedial prefrontal cortex (dmPFC), secondary motor area

and thalamus (Hayes & Northoff, 2011). A few studies have found brain activation differences in these aversive regions that distinguish individuals with SUDs from healthy comparisons during the experience of negative consequences. In a study by Hester et al. (2013), abstinent cocaine dependent subjects and control participants performed a response inhibition task that measures their capacity to withhold a prepotent response to act when required to inhibit this response; missed trials resulted in significant monetary fines. Cocaine dependent subjects were found to be less sensitive to punishment, such that their capacity for inhibitory control and adapting their performance was not modulated following error despite knowing it would result in monetary loss. In addition, they showed a blunted neuronal response in the ACC, insula and prefrontal cortex to failed control attempts (errors), which was associated with this behavioral insensitivity to punishment. Similar findings have been found for other addictions (e.g., cannabis, tobacco) in the context of decreased reactivity to error, as well as punishment following error (Dong, Hu, & Lin, 2013; Hester, Nestor, et al., 2009). Reviews have highlighted decreased activity in regions important for promoting a negative emotional response (i.e., medial prefrontal cortex, insula, anterior cingulate cortex, dorsal striatum) and the processing of self-relevant material (i.e., medial prefrontal cortex) during risk and punishment in addiction (Gowin, Mackey, et al., 2013; Wesley, Hanlon, & Porrino, 2011). The few studies that have examined this response in the context of tobacco dependence report similar results. de Ruiter et al. (2009) found failure to activate the insula in a group of chronic smokers when processing negative consequences, such as monetary loss during a gambling task.

And so, the evidence thus far demonstrates that addiction is marked by a

generalized pattern of decreased reactivity to aversive events, such as negative feedback and consequences, and that this response is associated with a decreased neurobiological response specific to these tasks, compared to non-users.

1.6.4 Aversive smoking-related processing in neuroimaging research

Another interesting approach to understanding the insensitivity of smokers towards the negative consequences of smoking is to measure directly their brain reactivity when viewing these negative drug-related consequences, using aversive smoking-related cues (e.g., anti-smoking campaigns).

Countries worldwide have mandated the use of anti-smoking stimuli, such as graphic images with text on cigarette packages or televised anti-smoking campaigns, that act as aversive smoking-related cues. They are designed to evoke a negative emotional/aversive response and remind users of the negative value of smoking. These health warnings tend to illustrate the harmful consequences of smoking on quality of life and the risk of mortality, but also it's negative effects on physical appearance, its social acceptability, the perils and costs of addiction, as well as the effects of second hand smoke. The use of these messages is based on the premise that viewing the negative consequences of smoking will motivate viewers to change their behavior and will help curb their desire to smoke. As discussed previously, however, studies have shown that substance users demonstrate a pattern of hyposensitivity to negative consequences, such as monetary loss following error. In addition, one of the defining clinical features of SUDs is a decreased sensitivity to the negative consequences of drug use. Findings regarding the persuasive impact of anti-smoking campaigns have not been consistent and a number of researchers have questioned its use, particularly in the context of tobacco

dependence (Ruiter & Kok, 2005). Exposure to anti-smoking campaigns has been found to paradoxically result in increased anxiety and cravings in current smokers, rather than decreases in the desire to smoke (Gilbert, 2005; Loeber et al., 2011; Wolburg, 2003). Advertisements eliciting strong emotional responses are perceived as effective in reducing the desire to smoke in non-smokers and smokers that are planning to quit, but not in current smokers (Siegel & Biener, 2000). Similarly, greater cigarette consumption (20 or more vs. 10 or less per day) and lower motivation to quit are associated with decreases in the perception of effectiveness of these ads (Davis, Nonnemaker, Farrelly, & Niederdeppe, 2011). And so, tobacco dependence is marked by a behavioral hyposensitivity to negative consequences, whether drug or non-drug related. It is possible then that exposing dependent smokers to aversive smoking-related cues is not effective at curbing smoking behavior.

Similarly to the research conducted on negative nondrug-related consequences in addiction (e.g., monetary loss), neuroimaging research can be valuable for understanding the mechanisms underlying the behavioral hyposensitivity to negative drug-related consequences (e.g., lung cancer). It is possible that *dependent tobacco* users may present a similarly biased aversive response to anti-drug cues that limits its impact on behavior. The majority of studies using anti-drug stimuli however have not directly investigated this topic. These studies examined: whether patterns of neural activity while viewing anti-smoking stimuli can predict behavior change in *treatment seeking* smokers (Chua et al., 2011; Falk, Berkman, Whalen, & Lieberman, 2011; Jasinska et al., 2012; Wang et al., 2013); what content and format of anti-smoking campaigns, and underlying neurocircuitry, promote its persuasive impact on smokers (Langleben et al., 2009; Wang

et al., 2013); the role of self-relevant processing when viewing anti-smoking stimuli in promoting memory and behavior change in treatment-seeking smokers (Chua et al., 2011; Falk et al., 2011). Studies thus far have demonstrated that increased activity in structures key to the generation of an aversive response [i.e., Medial prefrontal cortex (MPFC), insula, ACC, lateral prefrontal cortex, amygdala] and self-relevant processing (i.e., MPFC, posterior cingulate/precuneus) is associated with greater message persuasiveness, memory for its content and can promote healthy behavior change (Chua et al., 2011; Falk, Berkman, Mann, Harrison, & Lieberman, 2010; Jasinska et al., 2012; Langleben et al., 2009; Wang et al., 2013). Greater activity in the medial prefrontal cortex, as well as precuneus, while processing anti-smoking information has been shown to predict declines in smoking behavior at one-month follow-up (Falk et al., 2011). In other words, activity in these structures while viewing the negative value of smoking may promote an increased sensitivity towards this information. Research has also highlighted that the interaction between brain regions mediates the persuasive impact of negative drug-related consequences. Ramsay, Yzer, Luciana, Vohs, and MacDonald (2013) found that a positive interaction between the inferior frontal gyrus (IFG), a region involved in executive control and emotion regulation, and activity in the amygdala and insula, regions key to a negative emotional response, promotes the persuasive impact of anti-drug health campaigns on adolescents.

Together these findings highlight a pattern of brain reactivity that potentially promotes the impact of negative drug-related information on individuals.

1.7 Limitations of previous neuroimaging research on aversive processing in addiction

The aversive neurobiological pattern underlying the hyposensitivity to negative drug-relate consequences, characteristic of dependent smokers, has not yet been specifically explored.

Most studies have focused on examining the reactivity of *treatment-seeking* smokers to anti-smoking stimuli, but not of *chronic smokers* who are not attempting to quit. Treatment-seeking smokers have been shown to be more receptive to anti-smoking information (Davis et al., 2011). Neuroimaging research has also shown that users that are motivated compared to unmotivated to quit will differ in their neurobiological response to drug cues (Wilson, Sayette, & Fiez, 2012). Thus, it is likely that the neurobiological response of treatment-seeking smokers to anti-smoking stimuli will differ from that of those less motivated to quit.

Neuroimaging studies thus far on the processing of anti-smoking stimuli examined participants' reactivity to these cues compared to neutral stimuli. To our knowledge, no study to date has included additional control conditions that could help further characterize the affective processes underlying this response. The anti-smoking stimuli used in these studies were designed to trigger an arousing and aversive response regarding one's consumption that hypothetically would hinder one's desire to smoke and motivate cessation efforts. Studies in addicts on punishment sensitivity and reactivity to the negative consequences of their behavior suggest that they may present an inadequate aversive response to these negative events. To our knowledge, no study has examined whether smokers reactivity to aversive smoking-related stimuli differs from the processing of other forms of aversive nonsmoking-related stimuli. Examining activity in the aversive system of tobacco dependent users during aversive smoking- compared to

aversive nonsmoking-related stimuli would allow to examine the presence of biases in aversive processing when drug versus nondrug-related.

From a theoretical perspective, addiction is marked by a decreased sensitivity to the negative value and a greater predisposition towards the appetitive value of using (Bechara, 2005). To our knowledge, no study has attempted to understand the neurobiological response that may underlie this greater orientation towards the appetitive compared to aversive value of smoking. Comparing stimuli depicting the appetitive versus aversive value of smoking would allow us to examine the differences between processing drug-related cues as a result of being appetitive vs. aversive, and whether a pattern emerges that can explain an addicts need to consume despite knowledge of the negative value of using.

Furthermore, studies have found that features of tobacco dependence, such as motivation to quit, dependence severity and personality traits related to addiction (e.g., impulsivity) modulate smokers' reactivity to *appetitive* smoking cues. To our knowledge, no study to date has explored whether these features similarly modulate smokers reactivity to *aversive* smoking cues.

Finally, the connectivity pattern of current drug users (e.g., chronic smokers) between frontal and affective regions during the processing of aversive drug-related stimuli has not yet been specifically explored. Connectivity between these systems has been shown to be important for promoting the persuasive impact of anti-drug information, but has only been explored in young adolescents without any substance use issues.

1.8 Purpose of our study

The neurobiological mechanisms that hinder the effects of negative drug-related consequences on addictive behavior are not fully understood. Theories and studies on negative nondrug-related consequences suggest that a pattern of problematic affective processing may underlie this clinical feature, however no study to date has explicitly examined this system's reactivity to depictions of the negative consequences of drug use, in current drug users (at least, to our knowledge). The primary purpose of this study was to use fMRI to examine the neurobiological reactivity of chronic smokers, not attempting to quit, in these regions (e.g., MPFC, precuneus, posterior cingulate cortex, ACC, insula, amygdala, parahippocampus, lateral prefrontal cortex) during the processing of aversive smoking-related stimuli. We used a set of images used by health campaigns that depict the negative value of smoking and have been found to trigger a negative emotional response in smokers and non-smokers. Our objective is to characterize the neuronal reactivity of current users to these aversive smoking-related cues and verify whether smokers demonstrate a neurobiological pattern that has been found to promote a hyposensitivity towards the negative consequences of one's behavior.

To properly characterize this response, a novel aim of this study is the inclusion of two additional control stimuli: aversive nonsmoking-related and appetitive smoking-related images. Both aversive smoking-related and aversive non-smoking-related images have been found to trigger a negative emotional response (Hammond, 2011; Lang, Bradley, & Cuthbert, 1997). Adding another aversive condition to this study would allow us to determine whether there is a bias in the aversive processing of addicts when the stimuli are drug vs. nondrug-related that may account for their decreased sensitivity to aversive

drug events. Similarly, the addition of an appetitive contrast would allow us to examine the differences between processing drug-related cues as a result of being appetitive vs. aversive, and whether a neurobiological pattern emerges that can explain the greater disposition of an addict towards the appetitive compared with aversive value of consuming. Furthermore, exploratory correlations were performed between brain activity and important clinical measures shown to moderate an addicts reactivity to drug-related cues. This will allow us to validate whether a certain pattern of activity in these affective and self-relevant brain systems during the processing of aversive smoking-related cues is associated with clinical features of addiction.

Finally, another goal of this study was to investigate the functional connectivity between frontal and affective brain regions in a group of current smokers during the processing of aversive smoking-related images, as well as examine whether there are differences in connectivity during aversive processing depending on whether the stimuli is smoking versus nonsmoking-related. These systems may interact in a manner that promotes or hinders an emotional response and its impact on behavior. Examining this interaction would allow us to investigate whether there are biases during aversive processing that may hinder the impact of aversive smoking-related stimuli on behavior.

In all, a better understanding of the neurobiological structures involved in the processing of anti-smoking stimuli will provide insight on the mechanisms underlying the decreased sensitivity to the negative value of drug consumption, an important clinical feature of tobacco and other substance dependence poorly investigated in research.

1.9 Hypotheses

We hypothesize that chronic smokers will demonstrate a brain activation pattern characteristic of aversive processing when attending to the negative value of smoking. Because of the decreased reactivity to negative consequences in addiction reported in previous neuroimaging studies, we hypothesize that chronic smokers, who are not attempting to quit, will demonstrate a similar neurobiological pattern to negative drug-related consequences. We hypothesize that chronic smokers will demonstrate a decreased affective response to aversive smoking-related cues compared to aversive nonsmoking-related cues, as viewed in self-report ratings of affect and brain reactivity during this task.

As for the comparison between appetitive and aversive drug-related processing, we hypothesize that appetitive stimuli will trigger greater activation in medial regions associated with a driving motivational response that accounts for the greater motivational power of the appetitive value of smoking, compared to its aversive value.

In addition, since a positive connectivity between frontal and affective systems during the processing of anti-drug information has been shown to promote its persuasive impact, we hypothesize that a negative interaction between these regions will be found in chronic smokers, who are not easily persuaded by anti-smoking information.

Since greater dependence severity and personality traits, such as impulsivity, promote continued use despite its negative consequences, we hypothesize that increases in these clinical measures will be associated with further decreases in aversive processing of anti-smoking stimuli in chronic smokers.

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Adrianna Mendrek contributed to the conceptualization of the project, design of the research protocol, interpretation of results and revision of the article.

Josiane Bourque contributed to the conceptualization of the project, creation of the fMRI task used in this study, recruitment of participants, data analysis and revision of the article.

Stéphane Potvin contributed to the conceptualization of the project, design of the research protocol, interpretation of results and revision of the article.

All authors have revised and approved the final version of the article.

Where there's smoke, there's fire:

The brain reactivity of chronic smokers when exposed to the negative value of smoking.

***Running title**:* Anti-smoking neural response.

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ABSTRACT

Rational: The addictive nature of smoking is characterized by responses to cigarette stimuli that significantly impede smoking cessation efforts. Studies have shown that smokers are roused by appetitive smoking-related stimuli, and their consumption tends to be unaffected by the negative value of smoking. *Purpose:* Using functional magnetic resonance imaging, the goal of this study was two-fold: to examine the brain reactivity of chronic smokers when processing the negative value of smoking using aversive smoking-related cues; to further characterize this response by comparing the latter to the processing of aversive nonsmoking-related and appetitive smoking-related cues. *Method:* Thirty chronic smokers passively viewed aversive smoking-related, aversive nonsmoking-related, appetitive smoking-related and neutral images presented in a block design while being scanned. *Results:* Aversive smoking-related stimuli elicited significantly greater activation in the medial prefrontal cortex, amygdala, inferior frontal gyrus and lateral orbitofrontal cortex than neutral stimuli. Aversive smoking-related stimuli elicited lower activation in the parahippocampal gyrus, insula and inferior frontal gyrus compared to the aversive nonsmoking-related condition, as well as lower activation in the posterior cingulate, precuneus and medial prefrontal cortex compared to appetitive smoking-related cues. *Conclusion:* The brain activation pattern observed suggests that chronic smokers experience an aversive response when processing aversive smoking-related stimuli, however we argue that the latter triggers a weaker negative emotional and driving response than the aversive non-smoking-related and appetitive smoking-related cues respectively. These fMRI results highlight potentially important processes

underlying the insensitivity to the negative value of smoking, an important characteristic of addiction.

Key words: addiction – tobacco – craving – anti-smoking – aversion – neuroimaging

1. INTRODUCTION

Smoking tobacco is one of the leading causes of disease and mortality worldwide (WHO, 2003). Despite the dangers of smoking however, use rates remain high; 19.3% of adults in the United States smoke cigarettes (B. King, Dube, Kaufmann, Shaw, & Pechacek, 2011). Additionally, 70% of smokers report a desire to quit but only 5-17% of unaided attempts are successful (Hughes et al., 2008), highlighting the addictive nature of smoking. Tobacco research can provide a better understanding of the mechanisms that maintain smoking behaviour despite its harmful effects and a desire to quit.

Addiction is characterized by responses to drug-related stimuli that significantly impede cessation efforts. Through a learning process, certain cues in the environment become associated with drug use and its rewarding value; eventually, the cues alone are sufficient to rouse the urge to consume. In the context of tobacco smoking, smoking-cues have been found to trigger cravings in smokers (Caggiula et al., 2001) and have been implicated as a precipitating factor in relapse episodes (Killen & Fortmann, 1997). A significant body of neuroimaging research has examined the neural substrates of a craving response. A recent meta-analysis of 11 functional magnetic resonance imaging (fMRI) studies on tobacco craving concluded that exposure to smoking-related cues, compared to neutral cues, is associated to increased activation in the extended visual system, the superior and middle

temporal gyri, the precuneus, the posterior and anterior cingulate gyri, medial and dorsal prefrontal cortices, the insula as well as the dorsal striatum; regions involved in learning, memory, attention, emotion, interoceptive awareness and driving motivated behaviour (Engelmann et al., 2012). The medial prefrontal cortex, anterior cingulate and insula have emerged as particularly important structures in predicting consumption following exposure to drug cues. For instance, greater activation of these structures to smoking cues is associated to greater chances of relapse (Janes et al., 2009). Neuroimaging studies have provided valuable information on the neurobiological processes that underlie a craving response and have highlighted potentially mechanisms underlying addictive behaviour.

In addition to this reactivity to drug stimuli, addiction is marked by persistent drug use despite experience or knowledge of its negative motivational value, such as its harmful effects on health or social/occupational functioning. Very few studies however have attempted to elucidate this response. In traditional learning paradigms, when the consequences of an act are negative, the action is generally not repeated. An addict however appears unable to discontinue consumption despite understanding or experience with its negative value. Campbell (2003) contends that this disregard for the negative aspects of consumption is not only a key factor in the maintenance of addiction, but its defining characteristic. He argues that addiction should be viewed as a disorder of faulty volition, an inability to use negative drug-related experiences or information for adaptive decision making and self-control, and treatment will continue to have limited success if this is not properly understood. Neuroimaging and identifying the brain regions involved in the processing of the negative motivational value of consuming can provide information on the neurobiological processes underlying this facet of addiction.

A few neuroimaging studies have began to investigate the neural substrates of this response by examining the brain reactivity of chronic drug users to negative consequences more generally. Compared to controls, addicts demonstrate decreased activation of the anterior cingulate, insula, hippocampus, parahippocampus and prefrontal cortices during the prospect, anticipation or receipt of negative feedback, such as punishment (Hester et al., 2013; Luijten et al., 2013; Patel et al., 2013; Rossiter et al., 2012). These studies however measured the neural sensitivity of this population to negative non-drug related events, namely monetary loss. Four previous fMRI studies have looked at the brain of smokers while viewing negative drug-related stimuli designed to trigger an aversive response and remind users of the adverse effects of smoking, such as televised anti-smoking commercials (Falk et al., 2011; Langleben et al., 2009) and audio/visual presentations of smoking-cessation messages (Chua et al., 2011; Jasinska et al., 2012). These studies however assessed the brain reactivity of treatment-seeking smokers, restricted analyses to limited predefined brain regions (i.e. medial prefrontal cortex, amygdala) and did not include any control conditions in order to properly characterize how smokers respond to anti-smoking stimuli. To our knowledge, no neuroimaging study to date has conducted a whole brain analysis detailing the regions involved in the processing of anti-smoking stimuli, in a group of chronic smokers, whom are not attempting to quit. A whole-brain analysis is necessary for an exhaustive understanding of the neural substrates involved in the processing of aversive drug-related stimuli and treatment-seeking smokers may differ in their sensitivity to negative depictions of their consumption. Using fMRI, the primary purpose of this study was to conduct a whole-brain analysis of how current users process aversive smoking-related

images, a set of images used by health campaigns to trigger a negative emotional response and to remind smokers of the negative value of smoking.

In order to properly characterize this response, this study included 2 additional control conditions. Indeed, a novel aim of this study was the addition of aversive non-smoking-related images. Both aversive smoking-related and aversive non-smoking-related images have been found to trigger a negative emotional response (Hammond, 2011; Lang et al., 1997). Adding another aversive condition however allows one to characterize the differences in aversive processing in addiction when the stimuli is drug vs. non-drug-related. Furthermore, from a theoretical perspective, addiction is marked by a decreased sensitivity to the negative value and a greater predisposition towards the appetitive value of using (Bechara, 2005). No fMRI study to date however has examined the processes underlying the disposition of an addict towards the appetitive vs. aversive value of consuming. An additional goal of this study was to examine the differences between processing drug-related cues as a result of being appetitive vs. aversive.

We hypothesize that chronic smokers will demonstrate a brain activation pattern characteristic of aversive processing when attending to the negative value of smoking, However, given the insensitivity to negative consequences characteristic of addiction, we hypothesize that chronic smokers, whom are not attempting to quit, will demonstrate a lower negative emotional response when processing aversive drug-related vs. aversive nondrug-related images, and lower activity in regions associated in previous research to a decreased sensitivity to aversive events (e.g., anterior cingulate, insula, hippocampus, parahippocampus, prefrontal cortices). As for the comparison between appetitive and aversive drug-related processing, we hypothesize that appetitive stimuli will trigger

greater activation in medial regions associated to a driving motivational response (e.g., medial prefrontal cortex, anterior cingulate).

Findings can shed light on the neurobiological processes that promote smoking behaviour despite exposure to its negative health consequences. This information is essential for a comprehensive understanding of addiction and can help improve smoking-cessation efforts.

2. MATERIALS AND METHODS

2.1. Participants

30 healthy smokers (15 men) were recruited through the research center and affiliated hospital, as well as using Internet advertisements. Participants were chronic smokers (between 12 and 33 cigarettes/day; mean: 19.1; SD: 5.7) not currently seeking treatment or attempting to quit, aged 18 to 55 (mean: 31.9; SD: 9.4), right-handed (97%), Caucasian (83%), with no concomitant neurological, axis I or axis II disorder; and no contra-indications for MRI. The average number of years of education was 12.9 (SD= 2.7). Participants had been smoking cigarettes for an average of 15.9 years (SD: 9.6) prior, with their first cigarette at 16.1 (SD = 3.4) years of age, and had tried quitting an average of 2.8 times (SD: 2.7). Nicotine dependence severity was assessed using the Fagerström Test for Nicotine Dependence (FTND) (Fagerstrom & Schneider, 1989), and cigarette craving with the French Tobacco Craving questionnaire (FTCQ-12) (Berlin, Singleton, & Heishman, 2010). In addition, our group was required to fill the Readiness to Quit Ladder (Abrams DB & PM., 2003). On average, participants were moderately dependent on nicotine; the mean score on the FTND was 4.2 (SD: 2.6), 3.6 (SD: 1.0) on the FTCQ-12, and 5.2 (SD: 1.4) on the Readiness to Quit Ladder (I think about quitting

smoking, but I have no plans). We administered the Beck Depression Inventory (BDI) (Beck, Steer, Ball, & Ranieri, 1996) and the State-Trait Anxiety Inventory (STAI) (Spielberger, 1983) as measures of depression and anxiety symptoms respectively. Participants were compensated for their time.

In agreement with the *Declaration of Helsinki*, written informed consent was obtained from each participant prior to the testing sessions. The study was approved by the ethics committee of the *Réseau de Neuroimagerie du Québec*.

2.2. Stimulus material

Four sets of images were created for the purposes of this study: Aversive smoking-related, Aversive non-related to smoking, Appetitive smoking-related and Neutral. For the aversive smoking-related condition, images consisted of anti-smoking images (e.g., lung cancer, smoking through the throat) used in the past from various countries around the world (e.g., Thailand, Brazil, Indonesia) to control for current habituation to Canadian anti-smoking campaigns. No text was included. Previous aversion smoking-related studies have not included an aversive control condition, and so, a preliminary study was conducted on 50 non-smokers to adequately match both sets of aversive images in valence and arousal. The two aversive conditions were designed to elicit a negative emotional response. Out of a sample of 40 images, 20 aversive smoking-related cues were selected based on participants ratings for negative valence (scores of 5 – 9 on a 9-point valence scale) and moderate arousal (scores of 4 – 6 on a 9-point activation/arousal scale) using the International Affective Picture System (IAPS) (Lang et al., 1997) rating

scale. The aversive nonsmoking-related cues utilized in this study derive from IAPS and the final 20 aversive IAPS images were individually matched for valence and arousal with the aversive smoking-related images ratings. Images were also matched in visual complexity, color, and number of faces and body parts. The 20 appetitive smoking-related pictures were selected from the International Smoking Image Series (ISIS).

The study was divided into two task-specific runs in order to avoid any spill over effects between appetitive and aversive stimuli, as well as to limit attention loss and/or signal drift. Participants first passively viewed 15 counterbalanced blocks of aversive smoking-related, aversive IAPS and neutral images (5 blocks per condition). In a second run, we introduced 10 alternating blocks of appetitive smoking-related pictures and neutral cues (5 blocks per condition). Neutral cues differed between the aversive and appetitive runs and were matched in visual complexity, color and number of faces and body parts with their respective condition. Each block was comprised of 5 experimental (aversive IAPS, aversive smoking-related and appetitive smoking-related images) or 5 neutral images, randomly presented. Blocks were separated by rest periods consisting of a 15-second blank screen with a fixation cross. Images were displayed for 4 seconds each with an inter-stimulus interval (blank screen) ranging from 0.5 to 1.5 seconds. Participants viewed a total of 25 aversive smoking-related, 25 aversive IAPS, 25 appetitive smoking-related and 50 neutral images. Stimuli were presented with E-Prime software (version 1.1).

2.3. fMRI procedure

Thirty to 40 minutes prior to fMRI scanning session, participants smoked a cigarette to minimize withdrawal effects and standardize the period of non-smoking, as well as complete a self-report questionnaire assessing smoking status and mood. While in the scanner, participants first underwent an anatomical acquisition. Prior to the following functional acquisition, the experimenter would instruct them to press a button when a picture appeared, in order to monitor their level of attention. Participants then viewed the blocks of aversive/neutral stimuli, followed by the second run of appetitive/neutral stimuli presented after a 2-min rest period. At the end of the fMRI session, participants were asked to rate the strength of felt emotion when attending to each block of aversive IAPS, aversive smoking-related and neutral images of the first task on a scale from 0 (no emotion) to 100 (strongest emotion ever experienced). Participants also rated the strength of craving experienced during presentation of appetitive smoking-related and neutral images from the second task on a scale from 0 (images elicit no desire to smoke a cigarette) to 100 (images elicit the strongest desire to smoke ever experienced).

2.4. fMRI data acquisition

We recorded blood oxygenation level dependent (BOLD) signals using a single-shot, gradient-recalled echo-planar imaging sequence [repetition time (TR)=3000 ms, echo time (TE)=30 ms, flip angle=90º, FOV=224 x 224 mm, slice thickness=3.5, slices=41, matrix size=64 x 64 voxels, voxels size=3.5 x 3.5 x 3.5 mm^3] on a Siemens TRIO MRI system at 3.0 Tesla and a 32-channel, high-resolution, transmit/receive brain volume coil for a total of 390 volumes for the entire picture-viewing task. We then registered the functional volumes to individual high-resolution co-planar anatomical images taken

during the same scanning session (three-dimensional, ultrafast gradient echo sequence; repetition time = 2300 ms, echo time = 2.98 ms, flip angle = 9, matrix size = 256 × 256 voxels, number of slices = 176, voxels size = 1.0 mm × 1.0 mm × 1.0 mm).

2.5. fMRI data analysis

We analyzed fMRI data using Statistical Parametric Mapping-5 software (SPM5: Wellcome Department of Cognitive Neurology, London, UK) according to the methods outlined by Friston (K. J. Friston, 1995). Functional images were realigned to the mean volume of the run to correct for minor head movements, high-pass filtered, spatially normalized using the standardized brain template, and spatially smoothed with a three-dimensional isotropic Gaussian kernel (8 mm FWHM) to improve signal-to-noise ratio. We used a standard peak-detection approach and the general linear model implemented in SPM5 for our statistical analyses in order to identify the dynamic cerebral changes associated with smoking aversion, non-smoking related aversion and cigarette craving, using a block design. First, we undertook a fixed-effects analysis for each participant to investigate individual brain activation maps associated with our contrasts of interest [(aversive smoking-related/aversive IAPS) versus (neutral); (aversive smoking-related) vs. (aversive IAPS); (appetitive smoking-related) vs. (neutral)]. Second-level random-effects models were implemented to investigate these contrasts in our group, using one-sample *t*-tests. Considering the dearth of fMRI studies on smoking aversion, exploratory analyses for the entire brain volume was performed. We also examined any potential differences between the contrasts [(appetitive smoking-neutral) vs. (aversive smoking-neutral)] using paired *t*-tests. A Monte Carlo corrected threshold was adopted for all

contrasts shown. Simulations were computed using AFNIs 3dClustSim (Ward, 2000). Assuming a per voxel probability threshold of p=0.001, after 10000 simulations, a cluster size of 23 contiguous resampled voxels was indicated to correct for multiple comparisons at $p<0.05$.

2.6. Behavioral data analyses

To examine demographic and self-report data, we conducted descriptive analyses with the *Statistical Package for the Social Sciences*.

3. RESULTS

3.1. Self-report analysis

The group scored 36.0 (SD: 7.8) on the STAI and 5.3 (SD: 6.1) on the BDI. Participants rated the intensity of experienced emotion when exposed to aversive smoking-related ($t=13.8$, $p\leq0.05$), aversive IAPS ($t=18.7$, $p\leq0.05$) and appetitive smoking-related images ($t=8.1$, $p\leq0.05$) as significantly greater than neutral images with average ratings of 60.4% (SD:22.0%), 68.9% (SD: 19.3%) and 48.0% (SD: 28.1%) respectively.

3.2. fMRI analysis

3.2.1. Aversive stimuli contrasts

The one-sample t-test for the contrast of aversive smoking-related images minus neutral material yielded significantly greater activations in regions of the visual association cortex and extended visual system, the temporal and parietal lobes, limbic system, lateral orbitofrontal cortex, inferior frontal gyrus (triangular part) and medial prefrontal cortex

(see Table 1). The one-sample t-test for the contrast of aversive nonsmoking-related images (IAPS) minus neutral material yielded significantly greater activations in occipital-temporal-parietal regions, the cerebellum, precuneus, thalamus, limbic system, mid cingulum, insula, caudate nucleus, gyrus rectus, medial and lateral orbitofrontal cortex, inferior frontal gyrus (triangular and opercular parts), medial superior frontal cortex, precentral gyrus and supplementary motor area (see Table 2). When contrasting the aversive smoking-related and aversive IAPS conditions, we observed significantly greater activation in the cuneus, precuneus, calcarine fissure, cerebellum, precentral gyrus, inferior frontal gyri, insula and parahippocampal region during the processing of aversive IAPS images (see Table 3) and the inferior temporal, occipital and parietal gyri during the processing of aversive smoking-related images (see Table 3).

3.2.2. Appetitive stimuli contrasts

We observed significantly greater cerebral activations in the ventral part of the anterior and posterior cingulate gyri, precuneus, medial superior frontal gyrus, superior frontal gyrus and angular gyrus as compared to neutral images (see Table 4). Assessed using a paired t-test, the comparison between the aversive smoking contrast (anti-smoking minus neutral material) versus the appetitive smoking contrast (smoking minus neutral material) revealed greater cerebral activations in the visual cortex and extended visual system, precentral gyrus and inferior frontal gyrus triangular part when processing anti-smoking images than smoking images (see Supplementary table). The precuneus, hippocampus and posterior cingulate (within the same cluster), inferior parietal, middle orbital and medial frontal superior gyrus were significantly more activated when processing

appetitive smoking related images than aversive smoking-related images (see Supplementary table).

4. DISCUSSION

Neuroimaging studies have been valuable for understanding the effects of smoking cues on smokers; the structures involved in craving and the responses that promote a disposition towards the appetitive value of smoking. This is the first study to investigate the brain reactivity of chronic smokers when exposed to the negative value of smoking using an fMRI cue reactivity paradigm. The goal of this study was twofold: first, to examine the whole brain activation pattern of chronic smokers to aversive smoking-related cues; and second, to examine brain reactivity differences as a function of processing aversive non-smoking and appetitive smoking stimuli. The brain activation patterns observed demonstrate that anti-smoking stimuli triggered an aversive response, however there was significantly less activity in regions key to aversive processing compared to the aversive non-smoking-related condition. We also found decreased activity in limbic and medial prefrontal regions compared to the processing of appetitive smoking-related cues; structures that have been shown to promote the impact of stimuli on motivation and behaviour. Together, these findings highlight structures that are hypoactive when processing aversive drug-related stimuli compared to other emotional stimuli and that may underlie the hyposensitivity to negative consequences characteristic of addiction.

The whole brain analysis revealed that responses to anti-smoking images differed from neutral cues in several areas of the occipital, parietal, temporal and cerebellar regions

associated to the processing of arousing stimuli *(Lane, Chua, & Dolan, 1999; Lang et al., 1998)*. Signal increases were evident in key frontal and limbic regions, such as the right amygdala, hippocampus, lateral orbital frontal cortex (LOFC), medial prefrontal cortex (MPFC), inferior frontal gyrus (IFG) *triangular*, a pattern consistent with previous studies on aversive processing (Hayes and Northoff, 2011). Indeed, it is likely that this activation pattern reflects the processing of anti-smoking stimuli as aversive. Images were rated as significantly more negative and arousing than neutral stimuli, and there is considerable neural overlap across the processing of aversive smoking-related and negative IAPS images; a set of normative emotional stimuli designed to elicit feelings of unpleasantness (Lang et al., 1997). Furthermore, the right amygdala and lateral OFC are more consistently activated when attending to negative than positive stimuli (Costafreda, Brammer, David, & Fu, 2008; Hayes & Northoff, 2011; Kensiger, 2006; O'Doherty, Rolls, Francis, Bowtell, & McGlone, 2001). Together, these findings suggest that when nontreatment-seeking chronic smokers are exposed to the negative value of smoking, this material is processed as unpleasant and engages structures responsible for setting the neural preconditions for negative emotions to arise (Barrett, Bliss-Moreau, Duncan, Rauch, & Wright, 2007; Lane et al., 1997; Taylor, Liberzon, & Koeppe, 2000). Our results also extend the current literature by highlighting further regions that underlie the processing of anti-drug stimuli, such as the lateral OFC and IFG; previous studies had focussed on the MPFC and amygdala as important for this task (Berkman, Falk, & Lieberman, 2011; Falk et al., 2011; Jasinska et al., 2012).

Typically, an organism will expend energy to minimize or avoid a negative emotional state, either behaviourally or via inhibitory processes, which typically engage the lateral

OFC and IFG (Hayes & Northoff, 2011; Seymour, Singer, & Dolan, 2007). The IFG is involved in the executive control of emotional processing and expression, and activation of lateral OFC is specific to the down-regulation of negative affect and the inhibition of a dominant response (Ochsner et al., 2004; Seymour et al., 2007). And so, we hypothesize that chronic smokers experience an arousing and unpleasant emotional response when attending to the negative value of their consumption which they attempt to modulate or suppress. No study to date has highlighted these regions during the processing of aversive smoking-related stimuli. Future research is needed to determine the effects of LOFC and IFG activation on the relationship between an arousing emotional response, amygdala activity and behaviour change.

Interestingly, the pattern of aversive processing observed for the anti-smoking condition was less extensive than during the processing of aversive nondrug-related stimuli. Structures activated during the aversive smoking condition were similarly observed during the processing of aversive nonsmoking-related images. These findings are expected given that the aversive smoking and nonsmoking-related images were carefully matched in arousal and valence using the ratings of a group of 50 non-smokers, and both were designed to trigger a negative emotional response. Yet, there was significantly greater activity during the aversive processing of nondrug-related than drug-related stimuli in the insula, parahippocampal gyrus, precuneus and inferior frontal gyrus (triangular part and operculum); a pattern of activation for aversive IAPS images replicated in previous studies (Kensiger, 2006; Lane et al., 1997). These regions are core to aversive processing (Hayes & Northoff, 2011) and, are involved in the arousal and visceral response associated to the processing of negative stimuli (Colibazzi et al., 2010;

Naqvi & Bechara, 2009, 2010; T. D. Wager et al., 2004; T.D. Wager & Barrett, 2004). Increases in insular and parahippocampal activity is associated to greater psychological distress (Jarcho, Berkman, & Lieberman, 2011) and subjective ratings of negative affect and valence (Blood, Zatorre, Bermudez, & Evans, 1999; Chua, Gonzalez, Taylor, Welsh, & Liberzon, 2009). Furthermore, these regions have emerged as important driving forces of behavior (Jarcho et al., 2011; Krawitz, Fukunaga, & Brown, 2010; Palminteri et al., 2012). Hypoactivation of these structures to negative feedback has been reported in drug users and is associated to a behavioral insensitivity to punishment (Hester et al., 2013; Patel et al., 2013). On the other hand, increased activity in the insula to health campaigns promoting behavior change (e.g., avoid skin cancer by using sunscreen) reflects a sensitivity to its message and predicts subsequent behavior (e.g., increase in use) (Falk, Berkman, et al., 2010). Given these findings, we argue that activation of these structures during the aversive nonsmoking-related condition but not during the aversive smoking-related condition suggests that current smokers experience a limited affective reaction and exhibit a diminished neural sensitivity to negative stimuli when drug-related. This dampened reactivity is interesting given the insensitivity to the negative value of consumption characteristic of addiction. We argue that lower activity in these limbic and prefrontal regions are consistent with this clinical feature and may underlie this insensitivity. While speculative, activation of these structures may be essential for favoring the impact of negative drug-related stimuli on behavior.

The contrast between aversive and appetitive smoking-related conditions highlights another process that may limit the effects of negative drug-related stimuli on behavior. Exposure to appetitive smoking-related images compared to neutral triggered significant

activation in the ventral part of the anterior cingulate, posterior cingulate gyri/precuneus, medial prefrontal cortex, superior frontal gyrus and angular gyrus in a group of non-treatment-seeking chronic smokers. Activation of these structures to smoking stimuli is commonly reported and is believed to underlie cue-elicited urges (Engelmann et al., 2012). In general, appetitive stimuli activated more medial regions, while aversive stimuli (smoking-related or not) activated more lateral regions; a pattern reported in previous research (Kensiger, 2006; O'Doherty et al., 2001). Appetitive smoking-related images triggered activation in the anterior cingulate cortex, and when contrasting the latter to the aversive smoking-related condition, the MPFC and posterior cingulate/precuneus were significantly more activated during the appetitive condition. These structures are involved in cognitive processes, such as the processing of self-relevant stimuli (Falk et al., 2011; Jarcho et al., 2011; Lieberman, 2010), and are believed to play a key role in motivation and goal-oriented behavior (Walter, Abler, Ciaramidaro, & Erk, 2005). Indeed, activity in these regions has been shown to predict cue-oriented behavior, whether the stimuli is aversive or appetitive. Falk et al. (2011) found that greater activity in the MPFC and precuneus/posterior cingulate while viewing anti-smoking TV commercials predicted greater declines in smoking at one-month follow-up, in a group of heavy smokers enrolled in a smoking-cessation program. Similarly, Sinha and Li (2007) found that increased MPFC and posterior cingulate activity during the processing of craving images predicted subsequent relapse and amount of drug used at a 3-month follow-up in a group of abstinent alcoholics. It is possible then that while both smoking and anti-smoking cues trigger MPFC activity, greater activity in this region, as well as activity in other medial regions such as the anterior cingulate and precuneus/posterior cingulate, when processing

appetitive smoking stimuli may account for the greater disposition in addiction towards appetitive than aversive drug-related stimuli. It is possible that greater medial activation may be valuable for promoting the sensitivity of users to the negative value of their consumption. Indeed, hyporesponsiveness of the MPFC during the processing of negative consequences (e.g., wrong answer, monetary loss) in the context of a previously rewarding response has been observed in addiction and hyporesponsiveness or damage of this region is associated to riskier/poorer decision making (Bechara, 2005; de Ruiter et al., 2012). Future research could uncover ways to improve the sensitivity of smokers to aversive smoking-related stimuli and examine whether these medial structures mediate this response.

5. Conclusion and Limitations

Our study gives a more detailed description of the regions involved in the processing of aversive drug cues than previous studies and contributes to further understanding of this response. Our findings suggest that chronic smokers exhibit an aversive response when processing reminders of the negative value of smoking. This study however found that compared to aversive nondrug-related processing, aversive drug-related stimuli triggers a lower negative emotional response. We found hypoactivation in frontal and limbic regions important for aversive processing and that promote the effects of negative stimuli on behaviour. This suggests that addiction is characterized by a biased processing of aversive stimuli when it depicts the negative consequences of using.

In addition, addiction has been theorized as a hypersensitivity to reward and hyposensitivity to its negative value. We add to this literature by demonstrating that appetitive processing engages medial frontal and sub-cortical structures while aversive

processing engages more lateral prefrontal regions. These medial structures are key to self-relevant processing and a motivational response, whether the stimuli is appetitive or aversive. It is possible then that greater activation of these regions for appetitive but not aversive drug-related stimuli may underlie this greater orientation towards the former, promoting addictive behaviour.

In all, we argue that despite eliciting an aversive response, being exposed to the negative value of using does not elicit the emotional and cognitive reactivity that promote sensitivity towards this form of stimuli and its effects on behaviour. Hypoactivity in important regions (i.e,, ACC, insula, parahippocampus, IFG, MPFC, PCC, precuneus) during the processing of anti-drug cues may underlie the insensitivity to the negative value of consumption, characteristic of addiction. Future studies on the efficiency of health advertisement campaigns or the decreased sensitivity of addicts to negative consequences may benefit by investigating activity in these regions during these tasks.

The interpretation of our results, while interesting, is hypothetical and more research is needed to verify the ideas put forth. For instance, future studies could investigate whether activation in the regions hypothesized as important for promoting sensitivity to the negative value of consuming predict behavioural measures, such as the ability to resist cravings or successful abstinence. Future work will also benefit by addressing the limitations of this study. Our aversive conditions (smoking-related and nonsmoking-related) were carefully matched in valence and arousal using the ratings of a group of 50 non-smokers in a preliminary study. The chronic smokers in this study however reported the aversive IAPS images as slightly more aversive (68% vs. 60%) and thus, may account for the dampened aversion-related brain reactivity observed for the anti-smoking

condition. Still, these ratings may also be a result of the diminished sensitivity of chronic smokers to the aversive value of smoking. In addition, the negative images utilized for this study were selected for moderate arousal as to result in an interpretable pattern of brain activity. Our findings are thus limited to the processing of moderately arousing depictions of the negative value of smoking; it is possible that more severe health campaigns, such as the one's currently used in the United States, elicit stronger reactivity in chronic smokers. Future research should examine the reactivity of chronic smokers to aversive smoking-related images and aversive IAPS images, rated as similarly negative and arousing by current users. Similarly, without the use of a control group, it is difficult to conclude that smokers exhibit a dampened aversive response to the negative value of smoking. The goal of this study was to investigate the processing of aversive smoking-related stimuli compared to the processing of its appetitive value and non-smoking-related aversive stimuli, within a group of chronic users. Future studies will benefit by adding a control group and examining brain reactivity differences while processing these emotional cues as a function of smoking status (i.e., non-smoker, treatment seeking group and nontreatment seeking group). Furthermore, few studies have directly compared the processing of the appetitive and aversive properties of the same stimuli. Given the distinct qualitative nature of the two, as well as the greater tendency for aversive stimuli to elicit an arousing response (Lane et al., 1997), the latter two conditions may not have been ideally matched in the intensity of felt emotion (e.g., negative emotion, craving). Future research may benefit from comparing the aversive and appetitive drug-related processing of deprived users, as this state is associated with a heightened response to drug-related stimuli (McClernon et al., 2005). In addition, a full-factorial design, such as

including an appetitive non-smoking-related condition, would have allowed us to further characterize emotional processing in addiction and its interaction with drug-relevancy (e.g., appetitive vs. aversive valence; drug vs. non-drug related). Future studies may contribute to a greater understanding of reward/aversive processing in addiction by adding this additional condition.

Ultimately, more research is needed on the mechanisms underlying the limited effects of negative consequences on consumption, a defining characteristic of addiction poorly investigated in research. This will help improve the theoretical understanding of this disorder and pinpoint useful strategies for improving treatment and health campaigns.

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Conflict of Interest

Over the last 3 years, SP has received funding, not related to the current work, from Eli Lilly, Pfizer and Servier Institutes. The authors declare no conflict of interest.

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TABLES

Table I. Cerebral activations during viewing of aversive smoking-related images (relative to neutral images). R = Right; L = Left; BA = Brodmann area; masked at 0.001, Monte Carlo corrected at .05.

Brain region	R/L	BA	MNI coordinates			Z-score	Voxels
			x	y	z		
Inferior occipital / middle temporal	L	19	-46	-70	-14	7.76	2005
Fusiform / inferior occipital	R	37	46	-60	-18	6.61	1063
Supramarginal	R	2	63	-24	38	5.73	65
Middle occipital / superior occipital / inferior parietal	R	39	32	-70	32	4.74	193
Amygdala	R	21	35	0	-28	4.63	94
Inferior frontal triangular part	L	46	-52	35	14	4.47	74
Inferior orbitofrontal	L	11	-38	35	-14	4.03	66
Medial superior frontal / superior frontal	L	10	-4	60	32	4.01	51

Table 2. Cerebral activations during viewing of aversive nonsmoking-related images (relative to neutral images). R = Right; L = Left; BA = Brodmann area; masked at 0.001, Monte Carlo corrected at .05.

Brain region	R/L	BA	MNI coordinates			Z-score	Voxels
			x	y	z		
Calcarine/ Lingual	R/L	18	0	-91	-7	7.22	8725
Cerebellum	L	--	-21	-74	-14	6.80	387
Fusiform / inferior occipital	R/L	37	42	-60	-21	6.22	270
Superior temporal/ middle temporal	R/L	21	-60	-60	7	5.25	171
Gyrus Rectus	R/L	10	0	46	-18	5.08	95
Amygdala	R/L	--	-24	-4	-14	4.99	165
Middle occipital/superior occipital/ inferior parietal	R/L	31	28	-74	24	4.94	216
Frontal superior medial	R/L	8	-4	56	32	4.93	265
Thalamus	R/L	--	21	-28	0	4.87	154
Insula	R	--	28	18	-18	4.61	137
Inferior orbitofrontal	R/L	47	-35	21	-18	4.54	251
Supramarginal	R/L	40	-60	-32	42	4.47	121
Precentral	R	6	38	-4	42	4.25	135
Caudate nucleus	R/L	--	10	7	14	4.24	170
Thalamus	R/L	--	-21	-14	0	4.17	241
Posterior cingulate/precuneus	R/L	23	-4	-63	18	4.03	79
Inferior frontal triangular part	R/L	46	46	35	4	3.98	136
Mid cingulum	L		-4	-18	42	3.81	31
Parahippocampal	R/L	35	-18	-35	-10	3.74	224
Inferior frontal opercular part	R/L	9	-46	10	21	3.68	64
Suppl. Motor area	R	6	10	10	66	3.29	55

Table 3. Cerebral activation differences between aversive nonsmoking-related and aversive smoking-related conditions, R = Right; L = Left; BA = Brodmann area; masked at 0.001, Monte Carlo corrected at .05.

Paired *t*-tests	Brain region	R/L	BA	MNI coordinates			Z-score	Voxels
				x	y	z		
Aversive smoking – Aversive IAPS	Inferior occipital/inferior temporal	R/L	37	-42	-66	-10	4.55	131
	Inferior parietal	R/L	40	56	-60	42	3.73	42
Aversive IAPS – Aversive smoking	Calcarine/ cuneus	R/L	18	-4	-94	14	7.45	3475
	Cerebellum	L	--	-10	-42	-56	4.98	90
	Parahippocampal	R	35	24	-42	-10	4.23	24
	Precuneus	R/L	7	7	-52	56	3.83	110
	Inferior frontal *opercular part*	R	13	42	18	10	3.49	43
	Inferior frontal *triangular part*	R	44	46	21	7	3.45	54
	Precentral	R	6	42	-4	46	3.41	29
	Insula	R	13	38	32	4	3.23	43

Table 4. Cerebral activations during viewing of appetitive cigarette images (relative to neutral images). R = Right; L = Left; BA = Brodmann area; masked at 0.001, Monte Carlo corrected at .05.

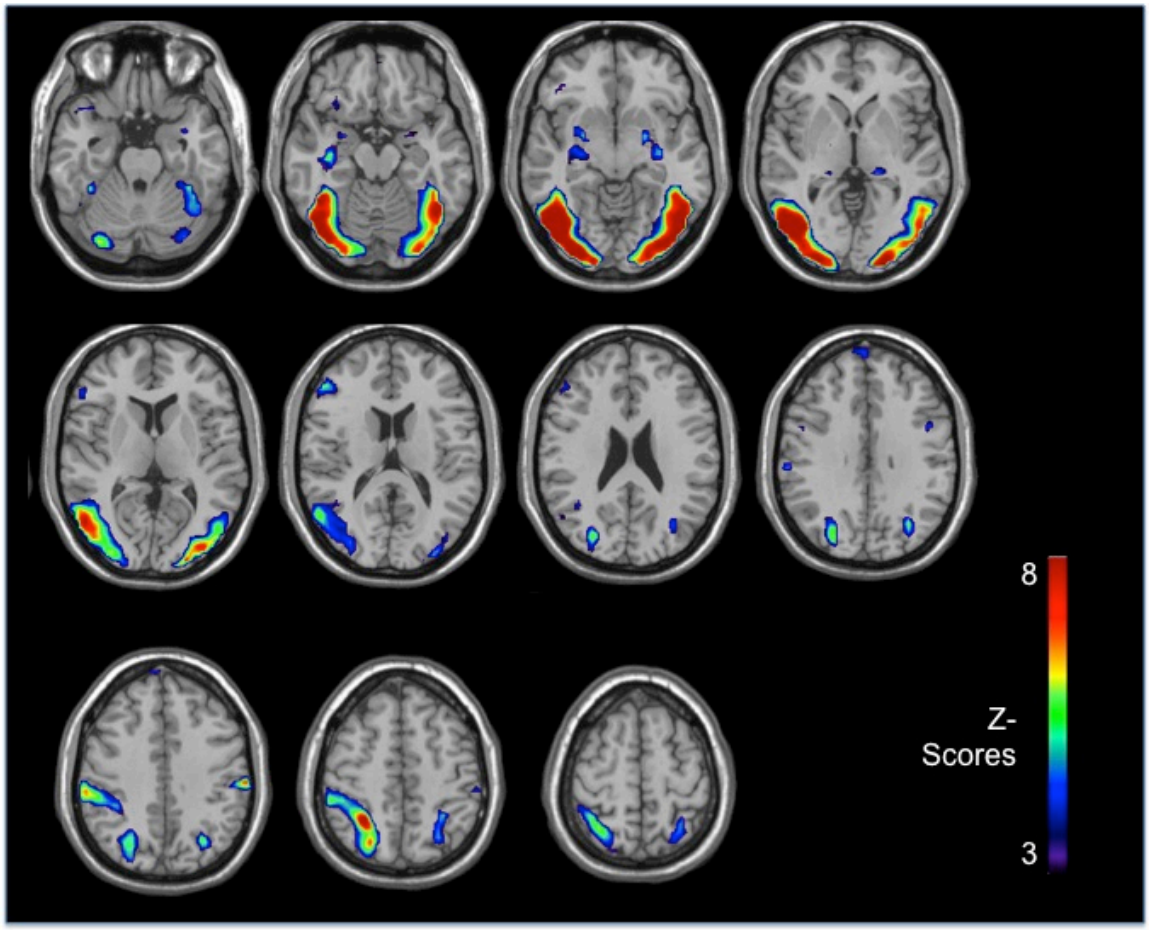
Brain region	R/L	BA	MNI coordinates			Z-score	Voxels
			x	y	z		
Anterior cingulate	R/L	24	7	38	0	3.90	332
Superior frontal	L	9	-14	46	38	3.37	24
Medial superior frontal	R	10	14	66	10	3.31	24
Posterior cingulate	L	31	-4	-52	32	3.27	94
Angular	R/L	39/40	-49	-66	42	3.19	49

Supplementary Table. Cerebral activations revealed by paired *t*-tests which contrast appetitive smoking images minus neutral ones with aversive smoking images minus neutral ones. R = Right; L = Left; BA = Brodmann area; masked at 0.001, Monte Carlo corrected at 0.05.

Paired *t*-tests	Brain region	R/L	BA	MNI coordinates			Z-score	Voxels
				x	y	z		
Appetitive - aversive	Precuneus	R	7	14	-63	32	3.87	26
	Hippocampus / posterior cingulate / calcarine	L	--	-21	-42	10	3.84	48
	Inferior parietal	R	40	56	-60	42	3.73	42
	Superior frontal / middle orbitofrontal	L	10	-24	60	0	3.58	63
	Superior frontal	R	10	24	60	7	3.53	28
Aversive - appetitive	Inferior temporal /inferior occipital / calcarine	L	19	-49	-63	-10	6.40	1866
	Inferior temporal / inferior occipital / calcarine	R	37	49	-56	-14	5.93	1481
	Cerebellum	L	--	-21	-66	-52	4.31	36
	Precentral	R	9	46	4	32	3.67	36
	Triangular inferior frontal	L	46	-52	32	21	3.35	30
	Precentral	L	6	-42	-4	42	3.20	26

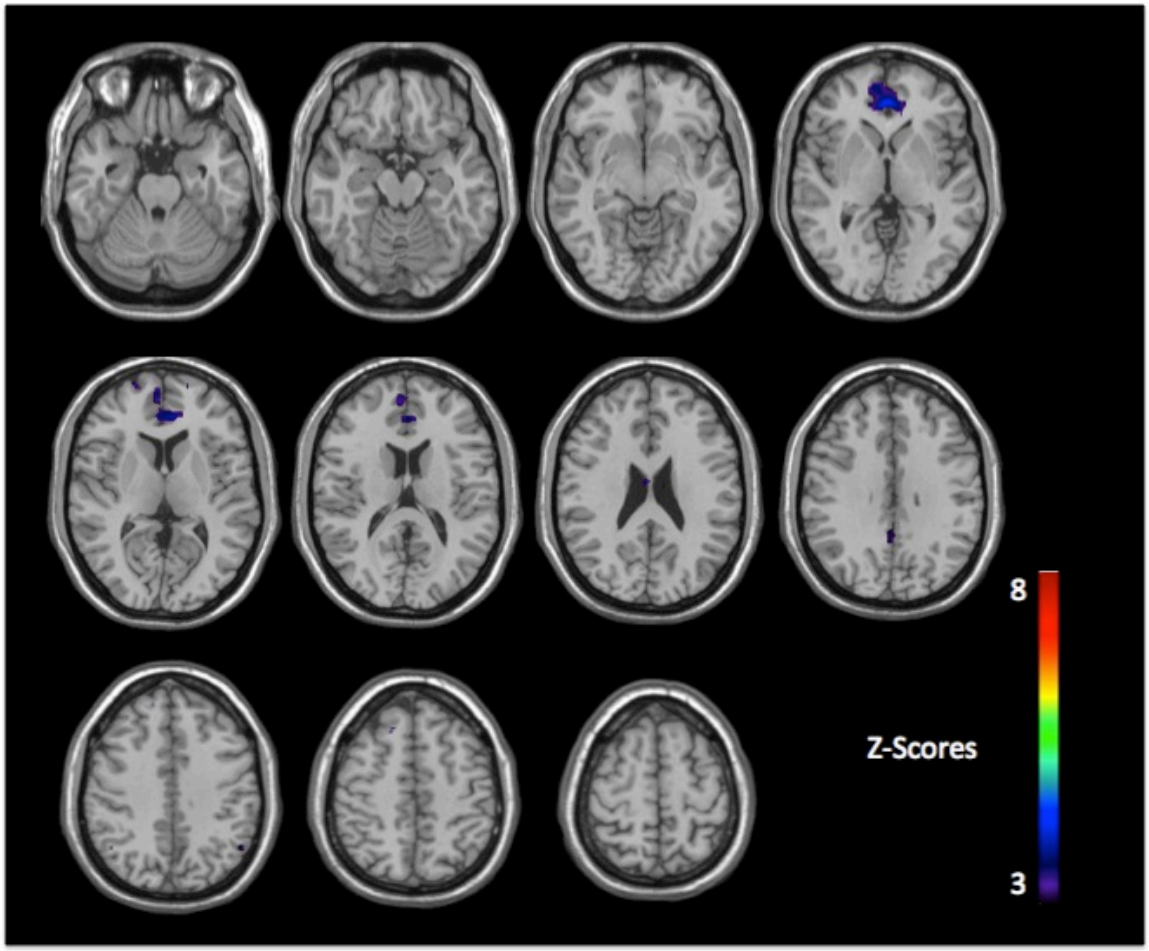
FIGURES

Figure 2. Brain reactivity of chronic smokers to anti-smoking images (relative to neutral)



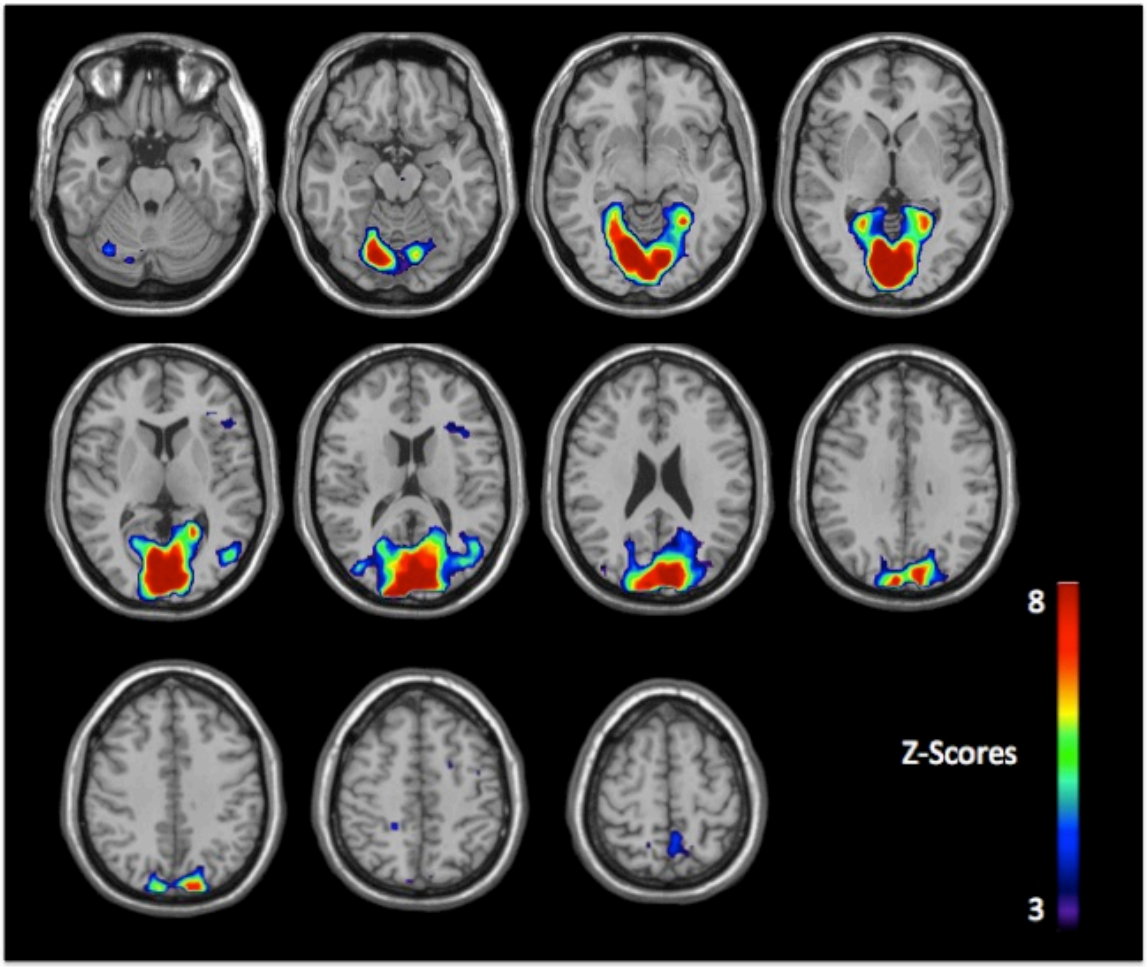
All colored regions were significantly activated. Transition from purple to red illustrates increases in Z-scores.

Figure 2. Brain reactivity of chronic smokers to appetitive smoking-related images (relative to neutral).



All colored regions were significantly activated. Transition from purple to red illustrates increases in Z-scores.

Figure 3. Brain reactivity of chronic smokers to aversive nonsmoking-related images compared to aversive smoking-related images.



All colored regions were significantly activated. Transition from purple to red illustrates increases in Z-scores.

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Adrianna Mendrek contributed to the conceptualization of the project, design of the research protocol, interpretation of results and revision of the article.

Josiane Bourque contributed to the conceptualization of the project, creation of the fMRI task used in this study, recruitment of participants and revision of the article.

Alexandre Dumais contributed to the interpretation of results and revision of the article.

Stéphane Potvin contributed to the conceptualization of the project, design of the research protocol, interpretation of results and revision of the article.

All authors have revised and approved the final version of the article.

Fronto-limbic/sub-cortical connectivity in smokers viewing anti-smoking images: an fMRI study

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ABSTRACT

Despite knowledge of the harmful consequences of smoking on health, tobacco users continue to smoke. Neuroimaging studies have begun to provide insight on the mechanisms underlying this response. Regions involved in executive control and affective processing/persuasion are activated when viewing the negative value of smoking, however these systems can interact in ways that promote or hinder its impact on behavior. Using fMRI, the goal was to examine the functional dynamics between these systems during the processing of images designed to elicit a negative emotional response regarding tobacco smoking, in a group of current smokers. Thirty chronic smokers passively viewed aversive smoking-related, aversive nonsmoking-related and neutral images presented in a block design while being scanned. Functional connectivity analyses showed that the left inferior frontal gyrus is negatively associated to activity in *medial frontal, cingulate, limbic, subcortical and parietal regions* in chronic smokers during the processing of aversive smoking-related material; a pattern significantly greater when drug-related compared to when nondrug-related. Our results suggest that individuals with tobacco dependence present different patterns of functional connectivity depending on whether the aversive stimuli is smoking or nonsmoking-related. Left IFG activity may act to down-regulate activity in regions key to an affective and persuasive response during the processing of anti-smoking material. This mechanism may reduce the extent to which "feeling bad" affects a change in behavior.

Key words: addiction – tobacco – anti-smoking – inferior frontal – emotion – fMRI

1. INTRODUCTION

Approximately 20% of North American adults smoke tobacco (B. King et al., 2011) despite its deleterious effects on physical health. Indeed, smoking tobacco is associated to a three- to nine-fold increased risk, relative to the general population, of developing cancer, pulmonary or cardiac disease (Jha et al., 2013; B. King et al., 2011; Wong, Shields, Leatherdale, Malaison, & Hammond, 2012). Smokers have been shown to be increasingly more aware of the negative consequences of smoking on their health, in part due to the implementation of health warnings and anti-smoking images on cigarette packages (Hammond, 2011). However, one of the most puzzling aspects of drug and tobacco dependence is the persistence of use despite knowledge and/or experience with its undesirable consequences (Jellinek, 1960). In addition to ill health, tobacco consumption is associated to fertility issues, premature aging, social stigma and can impact the health of others (Moyer, 2000). Research can provide a better understanding of why knowledge or experience with the negative value of tobacco use is not sufficient to curb smoking behavior.

A few neuroimaging studies have begun to elucidate on the mechanisms underlying the decreased sensitivity to the negative value of drug consumption. Drug users show diminished behavioral sensitivity to error and punishment, such as a decreased ability compared to controls to learn from negative feedback and persistent risk taking despite potentially negative outcomes (Bechara, 2005; Dom et al., 2006; Hester, Nestor, et al., 2009; Leland & Paulus, 2005; Rossiter et al., 2012), and this behavioral pattern is associated to decreased frontal medial, insula and ACC activity (Bjork, Momenan, Smith,

& Hommer, 2008; Fishbein et al., 2005; Gowin, Harle, et al., 2013; Gowin, Mackey, et al., 2013; Gowin et al., 2014; Wesley et al., 2011). In the context of risky drug-related behavior, we observed a similar brain activation pattern (Dinh-Williams, Mendrek, Bourque, & Potvin, 2014), such that chronic smokers exhibited activity in these medial regions during the processing of nondrug-related aversive images but not during the processing of drug-related aversive images depicting the negative value of smoking. These two sets of negative emotional images were matched for valence and arousal by non-smokers, but elicited decreased medial brain reactivity (e.g., insula, precuneus) in chronic smokers when drug-related. Activity in these regions is important for promoting a negative emotional experience (e.g., MPFC, precuneus, amygdala, insula, ACC) (Hayes & Northoff, 2011) and the MPFC and precuneus are key to self-referential processing (Lieberman, 2010); psychological states that occur when individuals process health messages and that are associated to greater message persuasiveness (Keller, 1996; Stephenson, 2001 ; Wood, 2000; Yzer, Vohs, Luciana, Cuthbert, & MacDonald, 2011). And so, it is possible that lack of activity in these regions (i.e., amygdala, ACC, insula, MPFC, precuneus) during the processing of anti-drug cues may underlie the decreased sensitivity to the negative value of using, characteristic of addiction.

Interestingly, studies examining how drug users process anti-drug information have highlighted the recruitment of regions involved in executive control, such as the inferior frontal gyrus (IFG) and lateral orbitofrontal cortex (LOFC), in addition to medial structures (i.e., amygdala, MPFC, precuneus) during this task (Chua et al., 2011; Dinh-Williams et al., 2014; Falk et al., 2011; Jasinska et al., 2012; Langleben et al., 2009; Ramsay et al., 2013; A. L. Wang et al., 2013). The IFG and LOFC possess a rich set of

connections to cortical and subcortical key to emotional processing and this connectivity is believed to underlie emotion regulation processes (Eippert et al., 2007; T. D. Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). Studies have shown that these regions can up- or down-regulate brain activity in regions associated to an emotional response (Ochsner & Gross, 2005; Ochsner et al., 2004; Ochsner, Silvers, & Buhle, 2012); ultimately, this interaction influences the impact of these emotional events on decision making and behavior (Ochsner & Gross, 2005; Ochsner et al., 2004; Ochsner et al., 2012). Studies have examined this interaction between activity in executive and affective systems while viewing *appetitive* smoking stimuli and have found that a reduced connectivity between the two hinders the ability to resist smoking urges (Janes et al., 2010). Few studies however have investigated functional connectivity in the context of processing *aversive* drug cues. One study has examined how adolescents, with or without prior experience with drugs, process anti-drug cues and found that an increased positive connectivity between executive and affective systems promotes its persuasive impact, hindering the desire to use (Ramsay et al., 2013). The issue however is that this study examined connectivity in non-users and/or non-dependent users. No study to date has examined how these systems interact when *current* drug users, such as chronic smokers, process anti-drug information. It is possible that these systems may interact in a manner that hinders its persuasive impact and impact on smoking behavior. It has been hypothesized that current drug abusers will attempt to minimize their affective reactivity to the negative value of drug use; the executive system in this context may act to down-regulate activity in the affective system (DeSteno, Petty, Rucker, Wegener, & Braverman, 2004; Paulus & Stewart, 2014; Stewart et al., 2014).

Psychophysiological analyses could help better understand the functional dynamics between these systems during the processing of anti-smoking stimuli. Using fMRI, the goal of this study was to investigate in a group of chronic smokers the functional connectivity between frontal structures and regions key to self-processing and emotion generation (e.g., frontomedial cortex, precuneus, amygdala, ACC, insula) during the processing of anti-smoking images; images designed to elicit a negative emotional response regarding tobacco smoking. In order to further characterize this response, this study included an additional aversive condition that will allow us to examine in addiction whether there are differences in connectivity during aversive processing depending on whether the stimuli is drug versus nondrug-related. We hypothesize that lateral prefrontal regions act to down-regulate activity in medial regions key to a negative emotional and motivational response, given the decreased activity in medial regions observed in previous studies. In addition, given that dependence severity and personality traits, such as impulsivity, are thought to moderate an addicts reactivity to drug-related cues and decision making under risk (Brewer, Bowen, Smith, Marlatt, & Potenza, 2010; Leland et al., 2006; Naqvi & Bechara, 2010; Paulus, Lovero, Wittmann, & Leland, 2008; Paulus, Tapert, & Schulteis, 2009; A. Verdejo-Garcia, Clark, & Dunn, 2012), exploratory correlations were performed between brain activity and these important clinical measures.

In all, better understanding of the functional dynamics underlying the processing of anti-smoking stimuli will provide insight on the mechanisms underlying the decreased sensitivity to the negative value of drug consumption, an important clinical feature of tobacco and other substance dependence poorly investigated in research.

2. METHODS

2.1 Participants

Thirty healthy smokers (15 men) were recruited through the research center, affiliated hospital and Internet advertisements. Participants were chronic smokers (between 12 and 33 cigarettes/day; mean: 19.3; SD: 5.7) not currently seeking treatment, aged 18 to 55 years old (mean: 31.8; SD: 9.2), right-handed (except for 1 ambidextrous and 1 left-handed), Caucasian (84%), with no concomitant neurological, axis I or axis II disorder; and no contra-indications for MRI. The average number of years of education was 12.9 (SD= 2.7). None of the participants received psychiatric or neurologic drug treatment. Participants had been smoking cigarette for an average of 15.9 years (SD: 9.6) prior, with their first cigarette at 16.0 (SD = 3.4) years of age, and had tried quitting an average of 2.7 times (SD: 2.7).

Nicotine dependence severity was assessed using the Fagerström Test for Nicotine Dependence (FTND) (Fagerstrom & Schneider, 1989), and cigarette craving with the French Tobacco Craving questionnaire (FTCQ-12) (Berlin et al., 2010) prior to scanning. In addition, our group was required to fill the Readiness to Quit Ladder questionnaire (Abrams DB & PM., 2003). Lastly, the participants completed the Barratt Impulsiveness Scale (BIS-11), a measure of impulsive personality traits (Patton, Stanford, & Barratt, 1995).

In agreement with the *Declaration of Helsinki*, written informed consent was obtained from each participant prior to the testing sessions. The study was approved by the ethics committee of the *Réseau de Neuroimagerie du Québec*.

2.2 fMRI procedure

Thirty to 40 minutes prior to each fMRI scanning session, participants were invited to smoke a cigarette to standardize the period of non-smoking. While in the scanner, participants were instructed to press a button when a picture appeared, in order to monitor their level of attention, and viewed an alternating sequence of aversive (smoking and nonsmoking-related) and neutral images. The aversive smoking-related images consisted of unpleasant and arousing images used in the past and in various countries around the world designed to illustrate the negative value of smoking, such as its association to ill health, death and addiction (e.g., lung cancer, skull smoking, a person trapped in a cigarette). Every picture contained a cigarette and no text was included. The aversive nonsmoking-related and neutral pictures were selected from the International Affective Picture System (IAPS) (Lang et al., 1997). Aversive images were matched in valence and arousal (see Dinh-Williams et al., 2014 for description of stimuli selection) and all images were matched for visual complexity, color and number of faces and body parts.

The task consisted of an alternating sequence of 5 experimental (aversive smoking-related images), 5 aversive IAPS control and 5 neutral IAPS control condition blocks with periods of rest separating the blocks from one another. The rest period consisted of a 15-second blank screen with a fixation cross. Each block lasted 25 seconds and consisted of 5 pictures, presented for 4 seconds each. There was an inter-stimulus interval (blank screen) of an average of 1 second (ranging from 0.5 to 1.5) presented before each picture. Within a block, images were randomly presented. Participants viewed a total of 25 aversive smoking-related, 25 aversive nonsmoking-related as well as 25 neutral pictures.

At the end of the fMRI session, participants were re-presented with the aversive and neutral images, and were asked to rate them for arousal on a scale from 0 (no emotion) to 100 (strongest emotion ever experienced). In addition, participants were asked to rate a series of appetitive smoking-related images from the International Smoking Image Series (ISIS) (D. G. Gilbert & Rabinovich, 1999), used in previous research to elicit a craving response. These craving images were rated on a scale from 0 (images elicit no desire to smoke a cigarette) to 100 (images elicit the strongest desire to smoke).

2.3 fMRI data acquisition

We recorded blood oxygenation level dependent (BOLD) signals using a single-shot, gradient-recalled echo-planar imaging sequence [repetition time (TR)=3000 ms, echo time (TE)=30 ms, flip angle=90º, FOV=224 x 224 mm, slice thickness=3.5, slices=41, matrix size=64 x 64 voxels, voxels size=3.5 x 3.5 x 3.5 mm^3] on a Siemens TRIO MRI system at 3.0 Tesla and a 32-channel, high-resolution, transmit/receive brain volume coil. We then registered the functional volumes to individual high-resolution co-planar anatomical images taken during the same scanning session (three-dimensional, ultrafast gradient echo sequence; repetition time = 2300 ms, echo time = 2.98 ms, flip angle = 9, matrix size = 256 × 256 voxels, number of slices = 176, voxels size = 1.0 mm × 1.0 mm × 1.0 mm).

2.4 fMRI data analysis

We analyzed fMRI data using a statistical parametric mapping software (SPM5: Wellcome Department of Cognitive Neurology, London, UK) according to the methods

outlined by Friston (K. Friston, Holmes, AP, Worsley, KJ, Poline, JB, Frith, CD, and & Frackowiak, 1995). The functional images were realigned to the mean volume of the run to correct for artifacts due to minor head movements, high-pass filtered, spatially normalized into the standardized ICBM152 brain template, and spatially smoothed with a three-dimensional isotropic Gaussian kernel (8 mm FWHM) to improve signal-to-noise ratio.

2.4.1. fMRI main task effects

We used a standard peak-detection approach and the general linear model implemented in SPM5 for our statistical analyses in order to identify the dynamic cerebral changes associated with the processing of aversive stimuli, using a block design. First, we undertook a first-level analysis for each participant to investigate individual brain activation maps associated with our contrasts of interest (aversive smoking-related versus neutral material; aversive nonsmoking-related versus neutral material), and an auto-regressive AR(1) model was used to account for serial correlations. A second-level random-effects model was then implemented to investigate the pattern of activations during the aversive contrasts in our group, using a one-sample *t*-test corrected for multiple comparisons using a Monte Carlo simulation computed with AFNIs 3dClustSim (Ward, 2000). Assuming a per voxel probability threshold of $p=0.001$, after 10000 simulations, a cluster size of 23 contiguous resampled voxels was indicated to correct for multiple comparisons at $p<0.05$.

2.4.2. Psychophysiological interactions analysis

To evaluate the relationship between executive and affective systems activation during aversive processing (smoking and nonsmoking-related), we used the psychophysiological interaction (PPI) method, a multiple regression technique that allows the investigation of functional coupling between regions in relation to the experimental paradigm (K. J. Friston et al., 1997). The seeds were selected in accordance to two criteria: belonging to the set of frontal regions highlighted in previous research on emotion regulation and showing significant activation in aversive smoking (minus neutral) and aversive nonsmoking (minus neutral) contrasts. Two regions met these criteria: the left IFG and lateral OFC. We conducted four PPI analyses to examine connectivity patterns of the left IFG and left LOFC (seed regions) as a function of exposure to aversive smoking-related (versus neutral) and aversive nonsmoking-related (versus neutral) material. Following, we examined differences in strength of connectivity between the left IFG and ROIs for the contrast of aversive smoking compared to nonsmoking-related stimuli. For all PPI analyses, we extracted the first eigenvariate time series using a 10-mm radial centered on the maximally activated voxel within these left frontal ROIs for each participant using the Volume of Interest tool in SPM. The PPI regressor was calculated as the element by element product of the ROI time series and a vector coding for the effect of the tasks (aversive smoking vs. neutral; aversive nonsmoking vs. neutral; aversive smoking vs. aversive nonsmoking). This interaction term was then entered as a regressor of interest in a first level model together with the ROI time series and the vector coding for the task effect. Model contrasts were generated for each subject and subsequently entered into group level analyses (one sample t-test) to test for the effects of positive and negative PPIs for our contrasts of interest. A region of interest (ROI) approach using the “small

volume correction" option of SPM set at a threshold of $p<0.05$ false discovery rate (FDR) corrected for multiple comparisons was used to examine connectivity between frontal regions and regions key to self-processing and aversive response: mPFC, precuneus, amygdala, ACC and insula. The small volume was chosen using a sphere located in the center of the corresponding region according to the *Automated Anatomical Labeling* atlas (Tzourio-Mazoyer et al., 2002).

2.4.3. fMRI correlation analyses

Pearson correlation analyses were performed in SPSS using the peak activations derived from the main fMRI contrast (aversive smoking-related>neutral). The eigenvalues corresponding to each significantly activated region in the one sample t-test were extracted for each participant, and then correlated with tobacco-related (e.g., dependence, cigarettes/day), task-related (e.g., subjective ratings of negative arousal, craving) and clinical (e.g., impulsivity) self-report measures. Similarly, The eigenvalues corresponding to each significantly activated region in the PPI analyses of the main experimental task (aversive smoking>neutral; aversive smoking>aversive nonsmoking) were extracted for each participant, and then correlated with self-report measures.

2.5 Behavioral data analyses

We conducted descriptive analyses to examine demographic and clinical data as well as stimuli ratings of aversion and craving with the *Statistical Package for the Social Sciences*. We performed Pearson's correlation analyses between tobacco-related, task-related and clinical self-report measures.

3. RESULTS

3.1 Self-report

In general, participants were moderately dependent on nicotine; the mean score on the FTND was 4.3 (SD: 2.6), 3.6 (SD: 1.0) on the FTCQ-12, and a median of 4 (X=5.2, SD: 1.3) on the Readiness to Quit Ladder (I sometimes think about quitting smoking, but I have no plans to quit). They presented a mean score of 63.7 (SD: 10.8) on the BIS-11 (ranging from 30 to 120). Participants rated on average the intensity of their negative affect when exposed to aversive smoking-related images at 60.4% (SD: 21.95%), 68.9% for aversive nonsmoking-related (SD: 19.3%) and 10% (SD: 11.86%) for neutral images. Aversive smoking related images were rated as significantly less aversive than aversive nonsmoking-related images ($p<0.001$) and more aversive than neutral images ($p<0.001$). They rated the intensity of their craving when looking at appetitive smoking images at 44.0% (SD: 29.4%) following the fMRI task.

In regards to ratings of anti-smoking stimuli, the greater the motivation to quit, the more participants rated the images as negatively arousing ($r=0.54$, $p=0.01$). In addition, increased scores of impulsivity (total score: $r=0.616$, $p<0.001$) and its second-order factors of attentional ($r=0.480$;$p=0.01$), motor ($r=0.407$;$p=0.032$) and non-planning ($r=0.626$;$p<0.001$) were positively associated with greater reports of craving while viewing appetitive smoking images. Measures of tobacco dependence (FTCQ-12; Fagerstrom) were not significantly correlated with measures of impulsivity or craving following the fMRI task.

3.2 fMRI

3.2.1.Whole brain one-sample t-test.

The one-sample t-test for the contrast of aversive smoking-related images minus neutral material yielded significantly greater activations in regions of the occipital, temporal and parietal lobes, amygdala, lateral orbitofrontal cortex, inferior frontal gyrus (triangular part) and medial prefrontal cortex. The one-sample t-test for the contrast of aversive nonsmoking-related images (IAPS) minus neutral material yielded significantly greater activations in frontal-occipital-temporal-parietal and sub-cortical regions (see Dinh-Williams et al., 2014 for full description of results). Aversive nonsmoking-related images revealed greater activation in parietal regions, the parahippocampus, inferior frontal gyrus and insula compared to aversive smoking.

3.2.2. Psycho-physiological interaction.

During aversive smoking-related image encoding, we found that the left LOFC presented significant negative connectivity with the left mPFC; no positive connectivity was found with any ROI. There were no significant positive connectivity between the left IFG and any ROI. The mPFC, right ACC, left and right insula and left and right precuneus, but not the amygdala, presented a significant negative connectivity with the left IFG during this task (see Table 3, Figure 1). As for the aversive nonsmoking-related condition, we did not observe any significant positive nor negative connectivity between the frontal seed regions and any ROI (see Figure 2). The mPFC, ACC, insula and precuneus, but not the

amygdala, presented a greater negative connectivity with the left IFG during the aversive smoking-related compared to aversive nonsmoking-related task (see Table 3).

3.2.3. fMRI *correlations.*

There was a significant positive correlation between global impulsivity scores of participants on the BIS-11 (r= 0.4; p=0.035) and attention (r= 0.378; p=0.048) with activity in the left IFG. Similarly, we observed a significant correlation between increased severity of tobacco craving (FTCQ-12) and increased left IFG activity (r=0.381; p=0.046). A hierarchical multiple regression analysis showed that both variables remained significantly associated with IFG activity ($p<0.05$). No other significant correlations between clinical and tobacco-related measures with brain activation were observed.

Connectivity between the left IFG and right insula showed positive trend level correlations with second-order factors of impulsivity (i.e., motor) (r=0.368; p=0.05) when processing aversive smoking-related images compared to neutral. In addition, the earlier participant had started smoking, the greater the strength of negative connectivity between left IFG and ACC (r=-0.462; p=0.012), MPFC (r=-0.477; p=0.009), right (r=-0.498; p=0.006) and left precuneus (r=-0.379; p=0.43) during the aversive smoking vs. aversive nonsmoking-related contrast.

4. DISCUSSION

The goal of this study was to examine the functional interaction between frontal regions involved in the processing of anti-smoking material and structures involved in its

aversive and persuasive impact in a group of chronic smokers (not attempting to quit), as well as differences in patterns of connectivity when the aversive stimuli is drug and nondrug-related. The self-report measures and fMRI analyses corroborates findings from previous research, such that exposure to anti-smoking stimuli triggers a negative emotional response (Hammond, 2011; Peters E, 2007; Timmers, 2007) compared to neutral stimuli and independent activity in the amygdala and frontal cortices (e.g. mPFC, IFG, LOFC) (Chua et al., 2011; Falk et al., 2011; Jasinska et al., 2012; Langleben et al., 2009)). In addition, a novel finding in this study is the negative functional coupling observed between lateral prefrontal and *medial frontal, cingulate, limbic, subcortical and parietal regions* in chronic smokers that is specific to the processing of aversive drug-related material; this pattern of connectivity was not found for the processing of nondrug-related aversive stimuli.

Negative connectivity was observed during the processing of anti-smoking images between the left IFG and structures that are key to the experience of an aversive response, such as the ACC and insula. While PPI analyses do not provide any information about directionality, it is possible that this negative connectivity depicts the inhibitory role of the IFG over activity in these two affective regions. Indeed, despite images being matched in valence and arousal by non-smokers, aversive smoking-related stimuli were rated as less aversive and were associated to an absence of activity in regions key to an aversive response (e.g. insula) compared to when aversive stimuli is nondrug-related, brain activation pattern associated to behavioral insensitivity to risk (Paulus et al., 2008; Hester et al., 2009; Crowley et al., 2010; Verdejo-Garcia et al., 2012b; Gowin et al., 2013b; Gowin et al., 2014; Paulus and Stewart, 2014; Stewart et al., 2014;). In addition,

the negative connectivity between executive and affective regions was significantly greater during the processing of aversive stimuli when smoking-related vs. nonsmoking-related; no such functional negative coupling was observed in chronic smokers while processing aversive nondrug-related stimuli. And so, the left IFG activity is negatively associated to activity in regions key to an affective and persuasive response only during the processing of anti-smoking material, but not when nonsmoking-related. This suggests that chronic smokers may be biased to reduce their negative emotional response and associated medial brain reactivity to aversive images when smoking-related, but not when nonsmoking-related. It is possible that the negative interaction between the left IFG activity and regions key to the generation of an emotional response/persuasion (e.g. ACC, insula) is a mechanism associated to dependence that hinders the impact of antidrug stimuli on drug users. On the other hand, a positive interaction between these executive and affective systems may promote the persuasive impact of anti-drug information (Ramsay et al., 2013).

A negative connectivity was also observed between left lateral prefrontal regions (e.g., LOFC, IFG) and the mPFC and precuneus, regions predictive of message persuasiveness. Falk et al. (2011) and Wang et al. (2013) found that greater activity in the mPFC (as well as precuneus) during exposure to anti-smoking information predicted greater declines in smoking at one-month follow-up. Increased activity in these regions during the processing of health campaigns has been hypothesized to reflect the degree of self-relevant processing (Falk, Berkman, et al., 2010; Falk et al., 2011; Falk, Rameson, et al., 2010). In this study however, we observed a negative connectivity between the left IFG and mPFC region; a pattern of brain activity associated to a reduction in self-awareness

and self-referential processing (Brewer et al., 2010; Farb et al., 2007; Ulrich, Keller, Hoenig, Waller, & Gron, 2014). The negative interaction observed in this study then may suggest that increases in lateral prefrontal activity hinder activity in the mPFC, and may act to limit the degree to which anti-smoking material is processed as self-relevant and persuasive.

We observed correlations between addiction-related measures and the pattern of brain activity that helps strengthen the interpretation of our results. In this study, smokers who were less motivated to quit rated anti-smoking images as significantly less negative and arousing, while greater trait impulsivity was associated to stronger craving reports following the anti-smoking fMRI task. This suggests that current drug status, as well as impulsivity, may hinder the degree to which exposure to the negative consequences of smoking triggers an aversive response and decreases the desire to smoke. Indeed, an important characteristic of both drug dependence and impulsivity is a decreased sensitivity to negative consequences, such that the latter does not significantly influence decision-making and behavior (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; DeYoung, 2010; Hester et al., 2013). Past research has highlighted that reduced medial brain reactivity (e.g., mPFC, insula) may underlie this clinical feature (Potts, George, Martin, & Barratt, 2006; Stewart, Parnass, May, Davenport, & Paulus, 2013). In this study, we observed a similar pattern, such that impulsivity and tobacco dependence severity were significantly associated with increased left IFG activity during the processing of aversive smoking-related stimuli. In addition, the negative relationship between left IFG and medial activity during this task is strengthened with greater measure of trait impulsivity (i.e. IFG-insula) and earlier onset of smoking behavior (i.e.

IFG-ACC, IFG-MPFC, IFG-precuneus). And so, the more impulsive and tobacco dependent a smoker is, the more the IFG is engaged and the greater its negative association with activity in regions involved in the aversive and persuasive impact of stimuli (e.g., mPFC, insula).

In all, our results suggest that individuals with tobacco dependence may present responses to negative consequences via lateral prefrontal activity that may reduce the extent to which "feeling bad" affects a change in behavior (Paulus & Stewart, 2014).

This interpretation of our results, while interesting, is hypothetical and more research is needed. Future work will benefit by addressing the limitations of this study. For instance, future research should measure level of attention/processing (e.g. recall measures, thought listing procedure), emotional responding (e.g., physiologically, self-report), self-relevant processing (e.g., self-report, personalized health messages) and persuasion during the task to assess whether increased negative connectivity between the left IFG and limbic/sub-cortical regions is associated to reductions in these psychological states. Future research should also investigate the relationship between executive/affective system interaction and measures of smoking behavior, such as craving (e.g., before, during, after the task) and behavior change (e.g. the level of cotinine at follow-up). The addition of a control group in future studies is also necessary in order to verify whether these interactions are specific to an addictive population or simply a pattern observed in both populations. In addition, this is one of the first studies with the aim of investigating how executive and affective systems interact in users during the processing of anti-drug information; future studies should include additional anti-drug stimuli (e.g., social consequences, health consequences, explicit vs. implicit anti-drug stimuli, real-life cases

vs. generic statements) and investigate differences in users responses.

Ultimately, our results contribute to our understanding of how affective and executive systems will interact in drug users depending on whether the aversive stimuli is drug-related or now. These results have implications for understanding the mechanisms underlying the decreased behavioral sensitivity to negative consequences, characteristic of addiction.

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Conflict of Interest

Over the last 3 years, SP has received funding, not related to the current work, from Eli Lilly, Pfizer and Servier Institutes. The authors declare no conflict of interest.

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TABLES

Table I. PPI analysis of regions coactivated with frontal structures during viewing of aversive smoking-related images (relative to neutral IAPS images). R = Right; L = Left; BA = Brodmann area; p-value is FDR corrected at $p<0.05$.

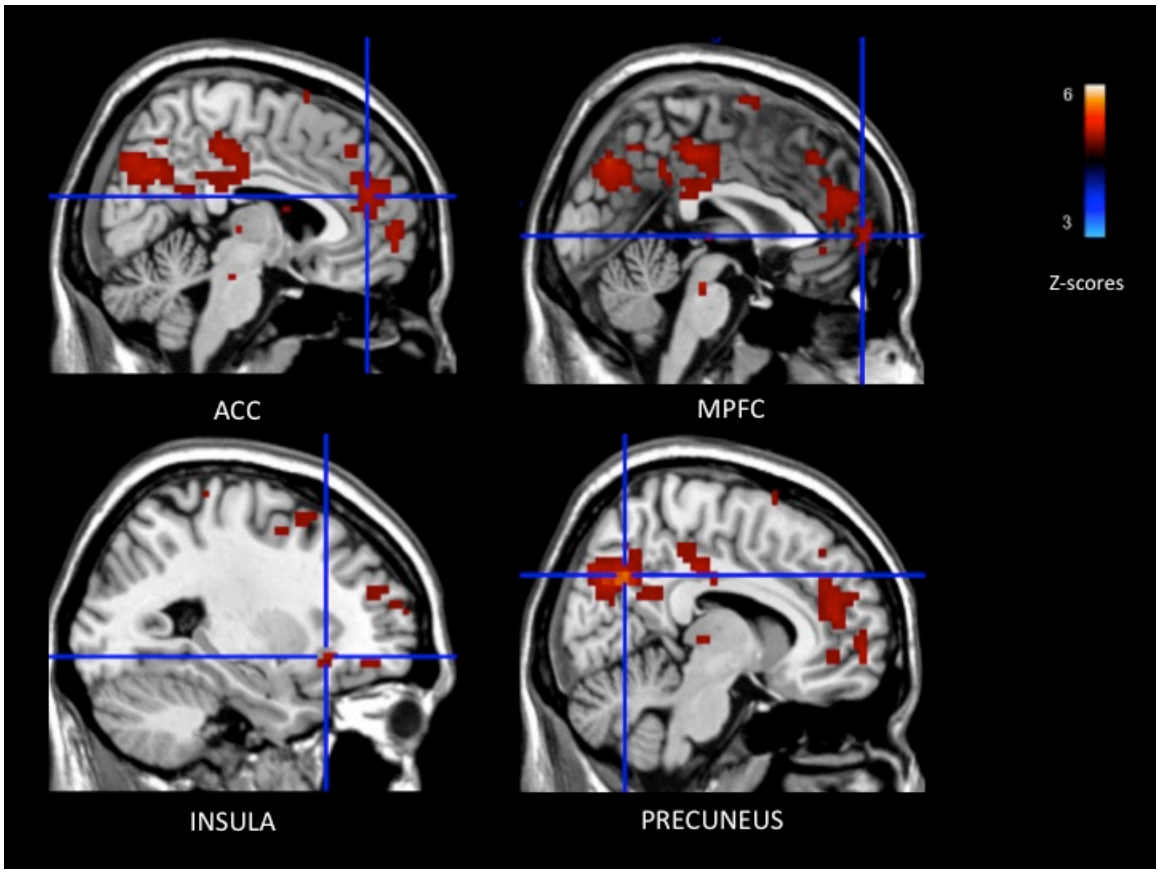
Brain region	R/L	BA	MNI coordinates			Z-scores	Voxels
			x	y	z		
LOFC – negative connectivity							
Medial prefrontal cortex	L	6	-4	32	63	3.58	15
LIFG – negative connectivity							
Medial prefrontal cortex		10	0	60	4	3.56	103
ACC	R	9	4	46	21	4.45	146
Insula	R	13	35	14	-10	3.29	14
Insula	L		-28	24	-7	3.68	20
Precuneus	R	7	7	-63	35	4.6	153
Precuneus	L	7	-7	-70	42	4.55	118

Table II. PPI analysis of regions coactivated with frontal structures during viewing of aversive smoking-related compared to aversive non-smoking-related images (negative IAPS). R = Right; L = Left; BA = Brodmann area; p-value is FDR corrected at $p<0.05$.

Brain region	R/L	BA	MNI coordinates			Z-scores	Voxels
			x	y	z		
LIFG – negative connectivity							
Medial prefrontal cortex	R	10	10	56	4	3.68	58
Medial prefrontal cortex	L	9	-10	38	-32	4.10	126
Insula	L		-28	24	-7	3.99	22
ACC		32	0	21	28	5.29	68
Precuneus	R	7	7	-63	32	4.88	168
Precuneus	L	31	-14	-60	35	4.37	140

FIGURES

Figure 1. Negative connectivity between the left IFG and ROI activations while viewing negative smoking-related images (relative to neutral images).



All colored regions were significantly activated. Transition from purple to red illustrates increases in Z-scores

4 Conclusion

The aim of this study was to elucidate the neurobiological mechanisms that may promote hyposensitivity in chronic smokers (who are not attempting to quit) towards the negative value of smoking. The results thus far suggest there is a bias in the neurobiological response of chronic smokers to aversive material when it is related to their drug consumption. In addition, the contrast between aversive and appetitive smoking-related conditions highlights another neurobiological mechanism that may promote a greater disposition towards smoking, despite knowledge of its detrimental effects on health.

4.1 Aversive processing in Tobacco Use Disorder

4.1.1 Aversive smoking-related stimuli

In this study, we found that aversive smoking-related stimuli (compared to neutral material) yielded significant activations in regions of the visual association cortex and extended visual system (e.g., right fusiform gyrus, right and left inferior occipital gyrus, right middle occipital gyrus, right superior occipital, right supramarginal gyrus, right inferior parietal gyrus, left middle temporal gyrus), as well as the limbic system (e.g., amygdala), medial and lateral prefrontal cortex (e.g., orbitofrontal cortex, inferior frontal gyrus-triangular part). This pattern of activity suggests that smokers experience a negative emotional response when processing reminders of the negative value of their drug consumption.

The amygdala acts as a "relevance detector", such that it quickly assesses the emotional significance of an event or cue and will activate to a greater extent when processing biologically relevant and arousing stimuli (Sander, Grafman, & Zalla, 2003).

In return, it promotes further increases in activity in the visual association cortex and extended visual system that are involved in the degree of perceptual processing and attention being allocated to the stimuli (Tamietto & de Gelder, 2010). This creates a loop by which increased attentional resources are being allocated to the processing of the relevant and arousing stimuli, strengthening its salience and further reinforcing the activation of networks sub-serving emotional processing (Robinson & Berridge, 2008). Activation of this system during the processing of aversive smoking-related material compared to neutral suggests that this event promotes an emotional response. More specifically however, we argue that these stimuli trigger a negative emotional response. Indeed, aversive stimuli (not related to tobacco) have been consistently shown to evoke larger responses than neutral stimuli in these brain regions (Bradley et al., 2003; Lane et al., 1997; Lang et al., 1998; Reiman et al., 1997; Sergerie, Chochol, & Armony, 2008). In addition, images were rated as significantly more negative and arousing than neutral stimuli, and we found considerable neural overlap across the processing of aversive smoking-related and aversive nonsmoking-related images; a set of normative emotional stimuli designed to elicit feelings of unpleasantness (Lang et al., 1997). Furthermore, although the amygdala generally is sensitive to detecting and triggering responses to positively and negatively arousing stimuli (Anderson et al., 2003), it exhibits a bias toward detecting cues signaling potential threats. It is more consistently activated when attending to negative than positive stimuli (Costafreda et al., 2008; Hayes & Northoff, 2011; Kensiger, 2006; O'Doherty et al., 2001). Together, these findings suggest that when nontreatment-seeking chronic smokers are exposed to the negative value of smoking, this material is processed as unpleasant and engages structures responsible for setting the

neural preconditions for negative emotions to arise (Barrett et al., 2007; Lane et al., 1997; Taylor et al., 2000).

We also found increased activity in lateral prefrontal regions, such as the lateral OFC and left IFG, during the processing of anti-smoking stimuli by smokers. Activation of these structures during the processing of emotional stimuli may reflect emotion regulation processes. Humans are capable of implicitly or explicitly altering the nature, magnitude, and duration of their emotional responses (Ochsner et al., 2012). Neuroimaging studies have shown that these prefrontal regions can modulate activity in posterior and sub-cortical systems that generate emotional responses, and consequently, can act to up- or down-regulate one's emotional response to affective stimuli (Goldin, McRae, Ramel, & Gross, 2008; Li & Sinha, 2008; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner & Gross, 2005; Ochsner et al., 2004; Ochsner et al., 2012; Phan et al., 2005; Wager et al., 2008). Left IFG combined with lateral OFC activity however typically reflects the down-regulation of negative affect and the inhibition of a dominant response (Ochsner et al., 2004; Seymour et al., 2007). It is possible that increased activation of these lateral prefrontal regions during this task helps decrease their aversive response to negative depictions of smoking. In order to specify its effects on affective reactivity during this task, functional connectivity analyses were performed between lateral prefrontal and affective regions (see section 4.2.).

In all, our results suggest that chronic smokers may experience an arousing and unpleasant emotional response when attending to the negative value of their consumption. This response can potentially be up or down-regulated by activity in lateral prefrontal regions, which will modulate smokers reactivity to anti-smoking material.

4.1.2 Aversive smoking- vs. nonsmoking-related processing

In order to further characterize the affective processing of aversive smoking cues, we compared the latter to the processing of aversive nonsmoking-related cues that were rated as similarly arousing and negative by a group of 50 non-smokers. Our results suggest a bias in chronic smokers depending on whether the stimulus is smoking or nonsmoking related. Structures activated during the aversive smoking condition were similarly observed during the processing of aversive nonsmoking-related images (e.g, MPFC, IFG, amygdala). These findings are expected given that the aversive smoking and nonsmoking-related images were carefully matched in arousal and valence using the ratings of a group of 50 non-smokers. Both were designed to trigger a negative emotional response. Yet, the pattern of aversive processing observed for aversive nonsmoking-related stimuli was more extensive than for anti-smoking material. There was significantly greater activity in the insula, parahippocampal gyrus, precuneus and inferior frontal gyrus (triangular part and operculum) during the processing of aversive nonsmoking-related stimuli than smoking-related.

These regions are core to aversive processing (Hayes & Northoff, 2011). The insula is thought to represent a viscerotopic map of ascending viscerosensory inputs from the body (Ochsner et al., 2012; Zaki, Davis, & Ochsner, 2012) and has been implicated in the experience of negative affect (Chua et al., 2009; Craig, 2009; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Goldin et al., 2008; Palminteri et al., 2012; Wager & Barrett, 2004). The insula and neighbouring inferior frontal gyrus *opercular part* (IFG) are critical for the integration of physiological and visceral information into conscious emotional and motivational states (Naqvi & Bechara, 2009, 2010), and driving specific

associated actions (i.e., goals) (Craig, 2002). Similarly, the parahippocampal gyrus is involved in promoting a physiological state of arousal associated with an emotional response (Colibazzi et al., 2010). Increases in insular and parahippocampal activity is associated with greater psychological distress (Jarcho et al., 2011) and subjective ratings of negative affect and valence (Blood et al., 1999; Chua et al., 2009). Furthermore, these regions have emerged as important driving forces of behavior (Jarcho et al., 2011; Krawitz et al., 2010; Palminteri et al., 2012). For instance, Falk, Berkman, et al. (2010) found that increased activity in the insula during the processing of persuasive messages targeting sunscreen use predicted subsequent behavior change (e.g., increases in use). Activation of these limbic regions may thus be essential for favoring a visceral aversive response when processing negative consequences and promoting its impact on behavior.

Activation of these structures during the aversive nonsmoking-related condition but not during the aversive smoking-related condition (despite being matched in arousal and valence) suggests that aversive stimuli are processed in a partial manner by smokers when related to their smoking behavior. Smokers exhibit a diminished neural response in affective regions, key to the experience of a visceral aversive response, when exposed to smoking-related aversive stimuli. This process may limit the extent to which these negative events will impact behavior. This pattern of reactivity is consistent with the somatic-marker hypothesis in addiction that posits that the inability for negative consequences to affect the behavior of drug users is attributed to a dysfunctional emotional processing mechanism. Somatic aversive state do not signal the importance of consequences and thus, do not assist in selecting an advantageous response (Verdejo-Garcia & Bechara, 2009). Previous studies on negative consequences in addiction have

also suggested that decreased activity in these affective regions (e.g., insula, parahippocampus) may underlie this clinical feature. And so, dysfunctional emotional processing in these structures while viewing the negative consequences of smoking may be a mechanism underlying its inability to modify the drug seeking behavior of chronic smokers.

4.1.3 Aversive smoking-related processing and clinical measures

In this study, smokers who were less motivated to quit rated aversive smoking-related images as significantly less negative and arousing, while greater trait impulsivity was associated with stronger craving reports following the anti-smoking fMRI task. This is consistent with research demonstrating their role in promoting the maintenance of smoking behavior. Impulsivity is associated with an increased risk of smoking (Ryan, Mackillop, & Carpenter, 2013), craving response to smoking cues (Doran, McChargue, & Spring, 2008; Doran, Spring, & McChargue, 2007) and poorer ability to quit (Covey, Manubay, Jiang, Nortick, & Palumbo, 2008). Similarly, lower motivation to quit and greater tobacco dependence are associated with a decreased sensitivity to the negative consequences of their behavior (e.g., punishment sensitivity) (White et al., 2011) and decreased ratings of the effectiveness of anti-smoking campaigns (Davis et al., 2011; Hammond, 2011). These findings highlight the role these clinical features may play in promoting an increased risk of addictive behavior and a decreased sensitivity towards negative consequences. In this study, our results suggest that current drug status, as well as impulsivity, may hinder the degree to which exposure to the negative consequences of smoking triggers an aversive response and decreases the desire to smoke.

Of interest, both trait impulsivity and tobacco dependence were positively

associated with left IFG activity. In other words, the more impulsive and/or dependent smokers were, the greater the lateral prefrontal activity while viewing aversive smoking-related stimuli. Past research has highlighted that these clinical features modulate users' activity to appetitive drug cues (Jasinska et al., 2014). This is the first study to highlight that the BOLD response in the inferior frontal gyrus during the processing of aversive smoking-related cues is more pronounced for impulsive and dependent smokers. This association however is consistent with previous fMRI studies on risk-taking and punishment in addiction. Similarly to the processing of aversive smoking-related cues that depict the negative consequences of smoking, these paradigms examine the neurobiological response of addicts to risky situations that may results in significantly negative consequences and/or their reactivity to negative feedback about their behavior (e.g., monetary loss). A number of these studies have reported greater lateral prefrontal activity in impulsive and addicted participants during these tasks. Internet addiction is associated with increases in IFG activity during loss (Dong, Hu, Lin, & Lu, 2013). Binge drinking, heroin use and gambling issues are marked by increased activity in the IFG during risky decision-making, where there are potentially negative consequences to their behavior (Gowin, Mackey, et al., 2013). Similarly, in the context of tobacco, Galvan et al. (2013) found that smokers exhibited greater frontal lobe functioning (e.g., IFG and dorsolateral prefrontal cortex) during risk taking than controls and severity of smoking behavior was associated with increases in frontal activity during risk. In addition, young adults that later transitioned to problematic substance use exhibited heightened frontal activation to punishing outcomes (bilateral IFG).

The IFG is part of the cognitive control network and a key locus in inhibitory

control over behavior and affect, as well task switching (Aron, Robbins, & Poldrack, 2004; Ghahremani, Monterosso, Jentsch, Bilder, & Poldrack, 2010; Mitchell, 2011), suggesting a possible role for engagement of prefrontal inhibitory processes in these tasks, as well as the need to recruit greater IFG activity with increases in impulsivity and addiction severity. Indeed, in the context of negative events, it has been proposed that an increased recruitment of the IFG in SUD or impulsive participants reflects a greater need to override or ignore aversive feedback (punishment) (Paulus & Stewart, 2014; Paulus et al., 2009; Stewart et al., 2013). It is possible then that increased lateral prefrontal activity acts to down-regulate one's reactivity to aversive smoking-related cues; and this mechanism is reinforced with increases in impulsivity and addictive severity, making them more prone to being insensitive to the negative consequences of their behavior. This is consistent with the clinical features of substance dependence and impulsivity that are both marked by a decreased sensitivity to negative consequences, whereby they do not significantly influence decision-making and behavior (Baker et al., 2004; DeYoung, 2010; Hester et al., 2013).

Typically however, studies report that impulsivity and dependence are negatively associated with activity in lateral prefrontal regions. Subjects with chronic exposure to cocaine (Li, Milivojevic, Kemp, Hong, & Sinha, 2006; Li & Sinha, 2008; Tomasi et al., 2007), methamphetamine (Baicy & London, 2007), nicotine (Neuhaus et al., 2006), alcohol (Noel, Bechara, Dan, Hanak, & Verbanck, 2007; Noel, Van der Linden, et al., 2007), cannabis (Tapert et al., 2007) and opiates (Verdejo-Garcia, Perales, & Perez-Garcia, 2007; Verdejo-Garcia & Perez-Garcia, 2007; Verdejo-Garcia, Perez-Garcia, Sanchez-Barrera, Rodriguez-Fernandez, & Gomez-Rio, 2007) exhibit decreased activity

in prefrontal circuitry (e.g., left IFG, lateral OFC, CC) compared to controls during emotion regulation and inhibitory control tasks (Goldstein & Volkow, 2011). These results however measure the reactivity of impulsive and/or drug users during self-control tasks, typically in the context of appetitive processing. For instance, drug abusers compared to never-users or ex-users show consistent deficits in delayed discounting tasks. They have difficulty in exerting self-control capacities over selecting an immediate reward and delaying responses for later greater rewards (de Wit, 2009; Petry, 2001). This poor ability for self-control mediated by frontal and ACC activity is believed to underlie the inability of addicts to control their craving response (Bell, Garavan, & Foxe, 2014; Hester & Garavan, 2004 ; Vollm et al., 2010).

In all, this highlights that drug addiction is marked by different neurobiological patterns in various fMRI tasks and together, reflect the different mechanisms underlying the maintenance of drug seeking behavior. Increased frontal activity in the context of negative events may be associated with the inability of negative consequences to impact drug behavior, while decreased activity in the context of self-control events may promote the inability to resist drug urges.

4.2 Functional connectivity during aversive processing

Using psychophysiological analysis, we examined the functional interaction between (a) frontal structures, key to emotional regulation and executive control, that were significantly activated in smokers while viewing aversive smoking-related stimuli, and (b) corticolimbic and related brain structures, key to promoting a negative emotional response and that have been highlighted as potentially dysfunctional in addiction during

aversive processing (i.e., MPFC, precuneus, amygdala, ACC and insula). This method of analyses allowed us to examine how the patterns of activity in the brain are connected to each other during a specific task. A positive connectivity suggests that activity in one region throughout the experiment resembles activity in another specific region, and suggests that they are working together during a specific experimental task. On the other hand, a negative connectivity suggests that activity in one region throughout the experiment produces a correlated opposite effect on another specific region, and suggests that they are working in an opposite manner during this specific task. While not proof of, this pattern suggest that activity in a region is suppressing activity in another (McGrath et al., 2013). And so, functional connectivity analyses will help us understand whether lateral prefrontal structures activated in this task promote or hinder activation of the affective system. This would help us understand how connectivity may influence the reduced aversive response to aversive stimuli, observed in this study, when smoking-related vs. when nonsmoking-related.

4.2.1 Functional connectivity during aversive processing and clinical measures

As mentioned in section 4.1.2, aversive images (smoking and nonsmoking) were matched in valence and arousal by non-smokers. However, smokers found these same aversive smoking-related images less negative and less arousing than aversive images not related to smoking. This study found that decreased brain reactivity in the affective system while viewing these aversive smoking-related images might underlie this behavioral pattern. Functional connectivity analyses further suggest that increased activity in the lateral prefrontal cortex may act to promote this decreased activity in affective regions (during the processing of aversive smoking-related images).

Negative connectivity was observed during the processing of aversive smoking-related images between the left IFG and the affective system, including the ACC, insula, MPFC and precuneus. In addition, lateral OFC activity was negatively associated with activity in the MPFC. This indicates that one system's activity hinders activity in the other during the processing of aversive smoking cues by smokers. While PPI analyses do not provide any information about directionality, it is most likely that this negative connectivity depicts the inhibitory role of the IFG over activity in these affective regions. The IFG and lateral OFC were significantly activated while viewing aversive smoking-related stimuli, but not the ACC, insula and precuneus. Given that these affective regions were not significantly activated, it is unlikely that their reactivity influenced activity in lateral prefrontal areas. In addition, this pattern of negative connectivity is predominantly believed to reflect the inhibitory role of lateral prefrontal regions over medial/sub-cortical structures (Li & Sinha, 2008; Ochsner et al., 2002; Ochsner & Gross, 2005; Ochsner et al., 2004; Ochsner et al., 2012; Phan et al., 2005; Wager et al., 2008). And so, these findings suggest that this negative connectivity depicts the inhibitory role of the executive system over activity in these affective regions.

Interestingly, this pattern of negative connectivity was significantly greater during the processing of aversive stimuli when smoking-related vs. nonsmoking-related. In fact, no such functional negative coupling was observed in chronic smokers while processing aversive nondrug-related stimuli. In other words, the executive and affective systems do not influence each other's activity during the processing of aversive nonsmoking-related cues; however, they do interact when smoking-related. It is possible that lateral prefrontal activity during the processing of aversive nonsmoking-related cues does not attempt to

inhibit affective reactivity, and may account for the greater medial/sub-cortical activity and increased negative emotional response observed in smokers during this task (compared to when smoking-related).

These results demonstrate that there is a bias in aversive processing in tobacco dependence. Lateral prefrontal activity is negatively associated with activity in regions key to an affective response only during the processing of aversive smoking-related material, but not when unrelated to smoking. Chronic smokers may be biased to exert executive control over their affective reactivity to aversive images when smoking-related, but not when nonsmoking-related. In turn, this decreased affective reactivity may act to limit the motivational impact of negative consequences on decision-making and behavior, and ultimately, promote the maintenance of tobacco use. Indeed, this pattern of negative connectivity is strengthened with greater tobacco dependence. The negative relationship between left IFG and medial activity during aversive smoking-related processing is strengthened with greater measure of trait impulsivity (i.e. IFG-insula) and earlier onset of smoking behavior (i.e. IFG-ACC, IFG-MPFC, IFG-precuneus). And so, the more impulsive and tobacco dependent a smoker is, the more the IFG is engaged and the greater its negative association with activity in regions involved in the aversive and persuasive impact of stimuli (e.g., mPFC, insula). These clinical measures predict greater difficulties in quitting (Covey et al., 2008; Dom et al., 2006; Ryan et al., 2013; A. Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2007). Their association with this negative connectivity pattern helps reinforce the notion that this pattern of reactivity to aversive smoking-cues may promote the maintenance of tobacco dependence.

In all, our results suggest that individuals with tobacco dependence may present

responses to negative consequences via lateral prefrontal activity that may reduce the extent to which "feeling bad" affects a change in behavior (Paulus & Stewart, 2014).

4.3 Aversive vs. appetitive smoking-related processing

Because addiction is characterized by an increased sensitivity to appetitive drug-cues and decreased sensitivity to aversive drug-cues, we were interested in examining whether there was a neurobiological response that can explain this behavioral disposition.

Both aversive and appetitive smoking-related images triggered significant activations in the medial prefrontal cortex (MPFC), however the latter, as well as the posterior cingulate/precuneus were significantly more activated during the processing of appetitive smoking cues (see Table 4, Figure 2). MPFC, posterior cingulate and precuneus activity during the processing of appetitive drug cues is believed to play a role in assessing the value of stimuli (Bush, Luu, & Posner, 2000) and its self-relevance (Northoff et al., 2006), promoting a motivational state and drug-seeking behavior (Botvinick, 2007; Cavanna & Trimble, 2006; de Greck M & Bruer U, 2008; Lubman, Yucel, & Pantelis, 2004; Marsh, 2007; Northoff & Hayes, 2011; Rogers et al., 2004). Similarly, in the context of aversive drug cues, activity in these medial structures has been shown to promote smoking cessation and is believed to reflect the degree to which these cues are processed as relevant to the self (Berkman et al., 2011; Falk et al., 2011).

Investigations of the neural basis of the self (i.e. values, knowledge, beliefs, self-concept) have yielded a remarkably consistent body of evidence suggesting that these cortical midline structures are implicated in self-referential thought and self-reflection (Northoff et al., 2006). Lieberman (2010) identified the MPFC (94% of studies) and the

precuneus/posterior cingulate gyrus (63% of studies) as the most commonly reported regions in self-related processing research. This self-processing mechanism has been implicated as an important factor in promoting motivation and goal-oriented behavior (Walter et al., 2005). In the context of appetitive smoking-related cues, increased activity in the mPFC and PCC/precuneus during exposure has been shown to promote smoking behavior. Increased activity is associated with increased severity of tobacco dependence (McClernon, Kozink, & Rose, 2008), greater difficulties in quitting (Janes et al., 2009) and stronger craving responses (McClernon et al., 2005; McClernon et al., 2009; Tang et al., 2012). On the other hand, increases during the processing of aversive smoking cues have been shown to hinder smoking behavior. For instance, increased activity while viewing anti-smoking campaigns is associated with greater message persuasiveness, memory for its content and can predict quitting success (Falk et al., 2011; Langleben et al., 2009; Wang et al., 2013). And so, activation of these cortical midline structures is important for promoting the impact of stimuli, whether appetitive or aversive, on behavior.

It is possible then that: (a) while both smoking and anti-smoking cues trigger MPFC activity (b) greater medial/sub-cortical activity (e.g., MPFC, precuneus/PCC) while processing appetitive compared to aversive smoking-related cues will promote a stronger driving response towards smoking cues despite being exposed to the negative value of smoking. This is consistent with studies showing that hyporesponsiveness of the MPFC during the processing of negative consequences (e.g., wrong answer, monetary loss) in the context of a previously rewarding response has been observed in addiction and hyporesponsiveness or damage of this region is associated with riskier/poorer

decision making (Bechara, 2005; de Ruiter et al., 2012). This medial/sub-cortical pattern for appetitive compared to aversive smoking cues may be a mechanism underlying the inability for negative consequences to sufficiently influence urges to smoke.

4.4 Limitations and recommendations for future research

The interpretation of our results, while interesting, is hypothetical and more research is needed to verify the ideas put forth. Future work will need to address the limitations of this study.

One limitation of the present study is the lack of comparison groups. In the context of aversive processing, our results suggest that chronic smoking is characterized by biased processing of aversive stimuli depending on whether it is smoking or non-smoking related. The inclusion of a control group however is necessary to validate such a claim. The inclusion of a group of non-smokers would have helped verify whether the decreased affective response observed for the aversive smoking-related condition is in fact a characteristic of tobacco dependence, rather than a pattern observed in both populations. If a similar neurobiological pattern is observed, it is possible that this reactivity is a result of the stimuli utilized rather than a mechanism underlying the decreased sensitivity of smokers to negative depictions of smoking. One of the goals of this study however was to examine differences in the processing of smoking cues depending on whether they are appetitive or aversive. And so, in this case, the inclusion of a group of non-smokers would not have benefited this line of research, since they experience an aversive, rather than appetitive response to these cues.

Furthermore, this study would have benefited by comparing how different groups of smokers respond to aversive smoking-related cues. For instance, in this study, smokers had smoked 30-45 minutes prior to the experimental task. The neural activation observed in this study could have been influenced by the recency of smoking. Nicotine alters cerebral blood flow, vascular resistance and BOLD signal (Hall, 1972; Kumari et al., 2003; Skinhoj, Olesen, & Paulson, 1973; Stein et al., 1998). Indeed, studies have shown that satiated and abstinent smokers demonstrate different patterns of brain activity to drug cues (McClernon et al., 2005; McClernon et al., 2009). Increases in the need to smoke (abstinence vs. satiety) may modulate reactivity to anti-smoking cues. Similarly, features of tobacco dependence, such as motivation to quit and dependence severity, have been shown to modulate drug users reactivity to drug cues (Smolka et al., 2006), as well as ratings of anti-drug stimuli (Kothe & Mullan, 2011). With a larger sample of subjects, it would have been advantageous to analyze distinct subgroups (e.g., abstinent vs. non-abstinent; motivated vs. not motivated; high vs. low dependence severity) brain responses during appetitive and aversive processing, smoking or non-smoking-related. It would help us verify whether the patterns of brain activation observed in this study are markers of tobacco dependence and increase with greater severity. However, because our sample was of 30 participants, the scope of the comparison between subgroups (using the median; 15 vs. 15) would have been somewhat limited. We therefore opted for regression analyses between clinical measures associated with tobacco dependence and brain activity observed during our contrasts of interest. Future research would benefit by addressing this issue.

Another possible issue in this study is our final selection of aversive smoking-related images. Our aversive conditions (smoking-related and non-smoking-related) were carefully matched in valence and arousal using the ratings of a group of 50 non-smokers in a preliminary study. The chronic smokers in this study however reported the aversive non-smoking-related images as slightly more aversive (68% vs. 60%) and thus, may account for the dampened aversive brain reactivity observed for the anti-smoking condition. Still, these ratings may also be a result of the diminished sensitivity of chronic smokers to the aversive value of smoking. In addition, the negative images utilized for this study were selected for moderate arousal as to result in an interpretable pattern of brain activity. Our findings are thus limited to the processing of moderately arousing depictions of the negative value of smoking; it is possible that more severe health campaigns, such as the one's currently used in the United States, elicit stronger reactivity in chronic smokers. In this case, it is possible that comparing aversive images matched by smokers in arousal and valence will not demonstrate the same biases in aversive processing. Future research should examine the reactivity of chronic smokers to aversive smoking-related images and aversive control images, rated as similarly negative by smokers.

In addition, this study was interested in examining whether affective mechanisms may reduce the ability of negative consequences to impact the behavior of drug users. This premise is based on the somatic marker hypothesis applied to research in addiction and findings suggesting that decreased aversive processing may promote a decreased sensitivity to negative consequences. However, there are a number of other components involved in this response. For instance, cognitive features, such as argument strength,

attention, framing (positive, negative), credibility, have been shown to be important features promoting the impact of anti-drug information on the behavior of drug users (Wang et al., 2013). More fMRI paradigms can be utilized to further understand the mechanisms involved in this clinical feature of addiction. For instance, future research will benefit by including a control condition that exposes users to negative drug and nondrug-related consequences. A study could examine the differences in how smokers react to the negative consequences of not using sunscreen vs. smoking; this will help determine whether dependence is characterized by a general hyposensitivity to the negative consequences of their behavior or only when drug-related.

Another limitation in this study is the lack of outcome measures. We posit that decreased activity in these medial/sub-cortical structures may undermine the impact of negative consequences on smoking behavior. Examining whether brain data can predict smoking outcome would help reinforce this claim. For instance, Falk et al. (2011) and found that greater activity in the mPFC (as well as precuneus) during exposure to anti-smoking information predicted greater declines in smoking at one-month follow-up using behavioral measures such as urinary cotinine levels or expired carbon monoxide levels (CO). These measures present the advantage of being a biological index of recent smoking, and has been used to predict the ability to remain abstinent (Falk et al., 2011) and changes in smoking behavior (McClernon et al., 2009; Wang et al., 2013). Self-reports of smoking behavior are prone to cognitive biases (Hammersley, 1994; Pierce, 2009) and are not necessarily reflective of actual smoking behavior (Klesges, Debon, & Ray, 1995). Future studies should investigate whether patterns of aversive processing can predict the ability to quit or decreases in smoking at follow-up.

Lastly, the fMRI stimuli could also have been presented in event-related rather than block design. The major trade-off between these two forms of stimuli presentation is of efficiency and power. Event-related design allows us to accurately estimate the shape of the hemodynamic response to a variety of individual stimuli and the variability that your average detectable hemodynamic response has. This is beneficial if you are interested in the timecourse or hemodynamic response function, shape during your experiment. In this study however, we were interested in uncovering with greater certainty all the structures involved in the processing of aversive smoking cues. Block design provides us with more statistical power and thus, the experiment is more likely to detect real activation patterns.

4.5 Conclusion and potential implications

The ability to react appropriately to aversive events is crucial for adaptive behaviour; however, an addict continues to use despite experience with the harmful effects of drug use. The results of this study help further our understanding of this clinical feature and the potential neurobiological mechanisms that underlie it.

Chronic smokers demonstrated reduced activation of affective brain regions while viewing aversive depictions of smoking. This blunted neurobiological activation pattern may limit the extent to which negative drug-related consequences trigger a visceral emotional response and as a result, hinder their ability to motivate healthy decision making and behavior. In addition, exposure to the negative consequences of smoking is not as motivating as the urge to consume. This study was able to demonstrate that greater activation of structures involved in self-relevant processing (e.g., mPFC, precuneus/PCC)

while viewing appetitive cues, compared to aversive depictions of smoking, and may promote this behavioral disposition. In all, there is a bias in how appetitive and aversive smoking cues are processed by chronic smokers that may hinder the ability for negative consequences to modify smoking behavior.

This may have important theoretical but also practical implications for public health. These neurobiological mechanisms may reduce the effectiveness of cessation tools, such as anti-smoking campaigns that attempt to motivate smoking cessation via presentation of the aversive value of smoking. Treatment and interventions for other addictive disorders may benefit from this line of research as this decreased sensitivity to negative consequences is an important clinical feature, common amongst all substance use disorders. Anti-drug efforts may benefit by uncovering how to promote decreased activation of medial/sub-cortical structures (e.g., mPFC, PCC, precuneus) in response to appetitive drug cues, and increased activity in the aversive as well as the self-relevancy systems (e.g., insula, parahippocampus, ACC, mPFC, precuneus) while viewing the negative consequences of consumption. Promoting these processes may be fundamental for improving treatment efforts and efficient health campaigns. Future intervention studies are required to further clarify the mechanisms underlying this clinical feature.

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