EFFECTS OF EXERCISE ON CRAVINGS AND PREFRONTAL BRAIN RESPONSES TO SMOKING CUES IN OVERNIGHT ABSTINENT AND SATED SMOKERS

by

DEREK CHRISTOPHER MONROE

(Under the Direction of Rod K. Dishman)

ABSTRACT

Nearly one-fifth of Americans report smoking cigarettes. Habitual cigarette smokers depend on smoking to improve affect and cope with daily emotional stressors, yet smoking is the leading cause of preventable death in the United States. Tobacco withdrawal syndrome is marked by negative affect, increased mood disturbance (e.g., fatigue, irritability, confusion, anger), and heightened sensitivity to smoking-related cues, making cessation difficult. Exercise during abstinence tempers withdrawal symptoms, and physically active smokers have higher rates of successful cessation. The mechanisms underlying the effects of exercise on withdrawal symptoms, cravings, and cue response are poorly understood, but they are plausibly related to processes in the dorsolateral prefrontal cortex (DLPFC). This dissertation was designed to elucidate the relationship between mood, affective response, and DLPFC response to emotional scenes and smoking cues after exercise among smokers.

The purpose of the first study was to evaluate mood, affective response, and DLPFC response to emotional scenes and smoking cues before and after smoking a cigarette and a bout of cycling exercise. The results indicate that, compared to seated rest, 20 minutes of cycling at a preferred intensity after smoking improved subjective energy, reduced anger, and suppressed DLPFC response to emotionally arousing scenes. This finding may be clinically important for

individuals who desire to quit and might use exercise as a way to manage mood and emotional responsiveness.

The purpose of the second study was to evaluate the effect of vigorous exercise on mood, cravings, and DLPFC response to affective scenes and smoking cues, and their relationships, after overnight abstinence. Results from the second study indicate that cravings, DLPFC sensitivity to unpleasant scenes, and total mood disturbance were increased by overnight abstinence, and 20 minutes of vigorous intensity cycling, increased subjective energy and attenuated cravings. In addition, 70% of the reduction in desire for a cigarette was explained by increased feelings of energy, and 30% of the reduction in desire for a cigarette was explained by right DLPFC response to smoking cues.

The findings of this dissertation are consistent with evidence that a single bout of exercise reduces cravings in smokers. The results extend previous findings by demonstrating that mood disturbance and cravings are closely related during short-term smoking withdrawal and that increased energy and cue-induced avoidance motivations in the DLPFC contribute to reduced cravings after exercise. Furthermore, exercise after a single cigarette protects against mood disturbance and sensitivity to emotional elicitors that plausibly contribute to continued smoking behavior.

INDEX WORDS: affective response, cue response, mood, near infrared spectroscopy, nicotine withdrawal

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DEDICATION

This document, and the work it necessitated, is dedicated to my family: To my parents for their longstanding and unwavering support of my educational pursuits, my siblings who, through their own successes, motivate and inspire me more than they will ever know, and Dianna, for her continued love and patience that got me through this process and carries us on to new adventures.

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"I admire addicts. In a world where everybody is waiting for some blind, random disaster or some sudden disease, the addict has the comfort of knowing what will most likely wait for him down the road. He's taken some control over his ultimate fate, and his addiction keeps the cause of his death from being a total surprise." - Chuck Palahniuk, *Choke*

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Approximately 18% of adults in the United States report regularly smoking cigarettes (Agaku et al., 2014). Smoking is the leading cause of preventable death in the US resulting in approximately 443,000 deaths annually (Adhikari et al., 2009; King et al., 2011), and habitual smoking doubles the risk of all-cause mortality (Prescott et al., 2002; Jacobs et al., 1999). Numerous prospective studies indicate that health outcomes are improved for cigarette smokers who quit (Anstey, Von Sanden, Salim, & O'Kearney, 2007; Critchley & Capewell, 2003; Lightwood, Fleischmann & Glantz, 2001; Kawachi et al., 1997) yet less than 5% of those attempting cessation without aid maintain abstinence 6-12 months later (Hughes, Keely, & Naud, 2004).

Nicotine is primarily responsible for the addictive properties of tobacco cigarettes by promoting chemical dependence, improving mood, and enhancing the incentive salience of cues associated with smoking (Berridge, Robinson & Aldridge, 2009, George & O'Malley, 2004; Green & Rodgman, 1996; Lloyd & Williams, 2000; Mansvelder, Keath & McGehee, 2002; Markou & Paterson, 2009). Tobacco withdrawal syndrome is marked by negative affect, anhedonia, cravings, and hypersensitivity to drug cues and emotional stressors (Gilbert et al., 2007; Robinson et al., 2011). Pharmacological cessation therapies (e.g. opioid agonists, nicotinic cholinergic partial agonists) elicit response similar to nicotine intake to curb cravings yet they have a negligible effect on negative affect and reductions in smoking cue sensitivity appear to depend upon nicotine availability (Ferguson & Shiffman, 2009; Franklin, 2011; Hughes et al.,

2014; Hutchison, 1999). Accumulating evidence suggests that exercise may be a useful adjuvant to traditional cessation therapies (Hughes et al., 2014; Taylor, Ussher & Faulkner, 2007). The adoption of a physically active lifestyle prior to cessation is associated with greater likelihood of successful future quit attempts (Derby et al., 1994) and may mitigate the maladaptive psychological and physiological effects of smoking (Faulkner, Cairney, & Veldhuizen, 2011). Exercise is also used by many to improve affect and cope with stress (Salmon, 2001), yet smokers tend to be less physically active than age-matched non-smokers (Pate et al., 1996). At present, little is known about the effects of an acute bout of exercise after a cigarette, but understanding the etiology of these effects may help educate physical activity recommendations for those intending to quit. In non-smokers, low-to-moderate intensity exercise improves affect (Anderson and Brice, 2011, Reed and Ones, 2006, Woo et al., 2010) and reduces sensitivity to emotional cues (Crabbe, Smith and Dishman, 2007; Smith, 2013; Smith and O'Connor, 2003; Smith, O'Connor, Crabbe and Dishman, 2002). In abstaining smokers, exercise can reduce psychophysiological indices of sensitivity to cigarette cues (Van Rensbug et al., 2009a; Van Rensbug et al., 2009b) and attenuate negative affect (Bock et al., 1999; Taylor, Katomeri & Ussher, 2006) and cravings (Haasova et al., 2013; Scerbo, Faulkner, Taylor & Thomas, 2009).

Abstinence elicits neural activity in response to smoking cues in regions of the prefrontal cortex that are responsible for affective shifts triggered from cue appraisal (Davidson & Irwin, 1999; Etkin, Egner & Kalisch, 2011) and essential in predicting, regulating, and sustaining affect in the absence of elicitors (Davidson, 2004; Dias, Robbins & Roberts, 1996; Morgan, Romanski & LeDoux, 1993; Urry et al., 2006). The dorsolateral prefrontal cortex (DLPFC) integrates affective and gain-loss information during complex decision making and plays a putative role

regulating sensitivity to cigarette cues during abstinence (Krawzyck, 2002; Nestor et al., 2011; Wilson, 2004). It is plausible that changes in affective response and cravings elicited by exercise are measureable by altered activity in the DLPFC (Van Rensburg et al. 2009).

Functional near infrared spectroscopy is a non-invasive technique that uses chromophores as endogenous tracers to quantify relative regional cortical oxygenation (Ferrari, Mottola & Quaresima, 2004; Villringer & Chance, 1997; Villringer & Dirnagl, 1995) and has been demonstrated capable of identifying DLPFC response patterns to visual stimuli in diverse populations and experimental environments. Measurement is less sensitive to movement than magnetic resonance (Hoshi, 2011) making it an ideal technique for measuring frontal cortex activity in response to a bout of stationary exercise. A single bout of moderate intensity exercise increases relative concentrations of oxygenated hemoglobin (HbO_2) and total hemoglobin (tHb), but has smaller, nearly negligible effects on relative concentrations of deoxygenated hemoglobin (HHb) in the prefrontal cortex. Collectively, under the assumptions of neurovascular coupling, these findings are taken to represent increased regional neuronal metabolic activity (Rupp & Perrey, 2008; Rooks et al., 2010; Timinkul, 2008).

No study reported to date has compared the acute effects of a bout exercise on DLPFC sensitivity to standardized emotional (i.e. International Affective Pictures System) and smoking cues (i.e. International Smoking Image Series) in smokers. Abstinence elicits hypofrontality that may contribute to withdrawal experience (Dackis & O'Brien, 2005), and blood flow to the frontal and limbic regions is immediately elevated after smoking two cigarettes (Nakamura et al., 2000). Therefore, it is warranted to assess DLPFC hemodynamic response to cues pre- and post-exercise during sated and abstaining states. A preliminary experiment assessed mood and DLPFC response to emotionally arousing scenes and smoking cues before and after smoking a

cigarette and 20 minutes of i) cycling exercise at a preferred intensity and ii) seated rest. It was hypothesized that, compared to seated rest, exercise would reduce DLPFC response to unpleasant images and that the effect would be related to a subsequent reduction in sensitivity to smoking cues. It was also hypothesized that smoking would increase feelings of energy and reduce negative mood states (i.e. anger, depression, fatigue, tension) and that these changes would be maintained through the exercise condition but not seated rest. A follow-up study sought to compare the effects of vigorous-intensity exercise and seated rest on DLPFC response to emotional smoking cues after overnight abstinence. It was hypothesized that, compared to seated rest, exercise would reduce cue-induced cravings and DLPFC response to smoking cues and the effects would be related to changes in DLPFC response to unpleasant and pleasant cues.

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CHAPTER 2

REVIEW OF LITERATURE

The Diagnostic and Statistical Manual for Mental Disorders, 5th edition (DSM-V) lists 3 criteria for Tobacco Use Disorder: 1) Larger quantities of tobacco over a longer period than intended are consumed, 2) Tolerance for nicotine (i.e. need for increasingly larger doses of nicotine in order to obtain desired effect), 3) Withdrawal symptoms upon cessation of use. Abstinence (i.e. participant-initiated cessation of smoking/cigarette use) or deprivation (i.e. experimenter-initiated cessation of smoking/cigarette use) results in an amalgam of symptoms that fluctuate over time from the last cigarette and are collectively referred to as withdrawal (Hughes, 2007). The DSM-V classifies tobacco withdrawal as the manifestation of four or more of the following symptoms within 24 hours of cessation (or reduction in amount used): irritability/frustration/anger, anxiety, difficulty concentrating, increased appetite, restlessness, depressed mood, insomnia. Withdrawal symptom severity is strongly related to nicotine dependence, and the majority of cessation aids target unpleasant symptoms in order to reduce cravings.

Nicotine, the primary psychoactive ingredient in cigarettes, is a neuromodulator primarily responsible for transient mood improvements after a single cigarette due to widespread stimulation of neuronal nicotinic cholinergic receptors (Pons et al., 2008), increased activity in dopaminergic mesolimbic pathway (Barrett et al., 2004), and decreased enzymatic breakdown of neurotransmitters in the limbic-frontal regions (Fowler et al., 1996). The result is increased activity in the cortico-basal ganglia-thalamic 'reward' network and a lower threshold for midbrain response to rewarding stimuli (Kenny & Markou, 2006). Bierut et al. (2008) identified

an amino acid variant in a nicotinic receptor gene cluster (CHRNA5) that may contribute to the development of habitual smoking among certain populations. Others have reported that heritability accounts for a substantial portion (50-85%) of the individual variation in vulnerability to cigarette smoking behavior with the remaining risk accounted for by individual and shared environmental factors (Batra et al., 2003).

Though the conditions and pathologies that beget habitual cigarette smoking vary between individuals, cigarettes quickly become an easily obtainable source of immediate reward (Hughes, 2001). Cigarette smokers depend on smoking to improve affect and cope with daily emotional stressors (Baker, Brandon, and Chassin, 2004; Ikard, Green, and Horn, 1969). However, smoking contributes to higher perceptions of chronic stress (Naquin and Gilbert, 1996; Ng and Jeffery, 2003; Parrott, 1999) which underlie the pathophysiology of several psychiatric disorders (Bizik et al., 2013; Juster, McEwen, Lupien, 2010; McEwen, 2004). Understanding the cognitive processes and biological mechanisms underlying the transition from an initial cigarette to tobacco abuse and habitual smoking behavior will better inform treatment. Findings on the etiology of tobacco abuse can be divided into two broad theories—that of positive reinforcement and negative reinforcement—whether cigarettes represent primary or secondary negative reinforcers (i.e. reversing mood deterioration and reducing negative affect) or positive reinforcers (i.e. improving mood and increasing positive affect) remains unclear.

Theory of Negative Reinforcement

A model of negative reinforcement posits that 1) the drive to smoke increases in proportion to intensity of withdrawal symptoms or perceived stress and 2) the primary purpose of smoking is to avoid, or at least reduce, negative affect. Applying Solomon's (1977) theory of opponent-processes to smoking behavior, Temes (1977) acknowledged that initial smoking

behavior is driven by appetitive motivations, but suggested that an interruption of affective homeostasis elicits a cascade of counteractive processes. Cycles of immediate positive perturbations in affect, 'a-process', and eventual negative deviations in affect, 'b-process', produce drug dependence. Temes also noted that, in some individuals, the aversive response to a first cigarette may override the positive symptoms and prevent future smoking attempts. Early reports on the physiological, sympathomimetic effects of nicotine were inconsistent with this model.

Nesbitt (1969) was the first to experimentally demonstrate the paradoxical physiological arousing and emotionally calming effects of smoking. Smokers (>7,000 lifetime cigarettes and currently smoking) and non-smokers (< 50 lifetime cigarettes) smoked cigarettes of varying nicotine content. Physiological arousal, operationalized by pulse rate, increased in a nicotine-dose dependent manner and was greater in non-smokers than smokers. After smoking, participants were subjected to electric shocks of varying intensities. Chronic smokers were able to withstand considerably greater shock, as a function of nicotine dose, than chronic non-smokers, and Nesbitt interpreted this increased threshold as evidence of the anxiolytic effects of nicotine. Schachter (1973) coined the term 'Nesbitt's Paradox' and, in the same chapter, laid the foundation for two major critiques of the findings.

First, Schachter recognized that the paradox depends on an assumption that intensity of an emotional state is positively correlated to increased autonomic arousal. This tenet is a lynchpin of a two-factor theory of emotion proposed in an earlier landmark paper by Schachter & Singer (1962), and if this assumption is false, then no paradox exists. Pulse rate data from the original study suggests that smoking induced a 'baseline' level of arousal that was increased by electric shocks in the absence of nicotine; therefore, the authors proposed that emotionality

should follow the same pattern. Likewise, anxiety (i.e. shock endurance threshold) should be blunted by nicotine in the non-smoking group. Schachter dismissed the contradictory results from non-smokers by suggesting that differences between the groups were due to cognitive framing/appraisal. Smokers attributed increased sympathetic arousal to the cigarette, a familiar and 'non-frightening' cue, and therefore were able to remain calm during electric shocks by re-framing increased sympathetic arousal as non-threatening. While this may be a reasonable extension of the findings, it is implausible that smokers sought greater shock intensities simply because of their familiarity with sympathetic activation from years of smoking. These findings led to another question: do mood improvements that follow smoking represent 'absolute' psychological gains or merely reversal of abstinence effects?

If nicotine administration elicits true mood improvements, rather than simply removing unpleasant withdrawal symptoms, then lifetime smokers should generally report less stress than non-smokers. Multiple lines of research indicate a trend to the contrary: smokers are more stressed than their non-smoking peers (Naquin and Gilbert, 1996; Ng and Jeffery, 2003). An important advance came through factor analytic evidence that arousal could be independent from the changes in emotion. Based on self-report data, Russell (1980) developed a Circumplex Model consisting of two orthogonal axes which represented independent factors of affect: pleasure-displeasure along the x-axis and arousal intensity along the y-axis. Multiple lines of evidence led Parrott (1999) to theorize that smoking, "does not confer real benefits in the terms of stress control" and instead, the acute mood improvements merely reflect relief from withdrawal. In a modern body of literature, negative affect elicited by withdrawal is generally considered the prepotent motive for continued smoking behavior (Baker et al., 2004). Through

an extension of the Circumplex Model, two models conceptualize stress experienced by smokers as a state of reduced arousal and increased displeasure.

A "deprivation reversal model" proposes that nicotine acts as a primary reinforcer and that the purpose of smoking is to reduce abstinence-induced stress that results from nicotine deprivation (Parrott, 1994; Schachter, 1978). Findings that smoking cues are capable of eliciting positive affect (Payne et al., 2007) and cravings (McBride et al., 2006) are consistent with this model. Therefore, it may be important for smokers attempting cessation to wean themselves from nicotine. Nicotine replacement therapy allows a smoker to substitute tobacco-derived nicotine for lozenges, chewing cum, or nasal spray and are typically most effective among those unwilling or unable to perform an abrupt cessation (Moore et al., 2009). Although, if the symptoms of withdrawal are strong enough one may never be able to achieve long-term cessation since this method simply substitutes one nicotine source for another.

The 'nicotine resource model' suggests that nicotine is a secondary reinforcer, used to attenuate stress from external cues, and that elevated stress during abstinence results from an inability to cope with the environmental stressors (Warbuton, Revell, Walters, 1988). Evidence suggests that smoking behavior is more readily reinitiated during periods of negative affect and stress (Baker, Brandon, and Chassin, 2004; Ikard, Green, and Horn, 1969).

Opponents to a theory of negative reinforcement point out two important discrepancies. First, while avoiding withdrawal symptoms may be important to understand why smoking behavior is resistant to change, it cannot explain why an individual begins smoking or even why that individual smokes a second cigarette or pack of cigarettes. Second, though the addictive properties of nicotine are well established, the active dose delivered by smoking a cigarette is not potent enough to reverse the severe, unpleasant symptoms that comprise withdrawal syndrome.

Theory of Positive Reinforcement

A more recent theory of positive reinforcement considers that the complex context in which a drug stimulus is perceived is necessary to explain the resulting drug-seeking behavioral response. As Falk et al. (1982) pointed out, if an individual must achieve physical dependence on a drug to experience withdrawal during abstinence, a theory of negative reinforcement doesn't explain why drug use is initiated or sustained long enough to become dependent.

Self-control theorists attempt to describe why a relatively nominal reward obtained immediately after drug use will elicit greater behavioral control than a larger reward (i.e. improved health) obtained after a delay. Underlying this relationship are basic tenets of behavioral economics: habitual smoking behavior progressively leads to the devaluation of non-smoking behaviors and sensitization to the effects of nicotine with repeated administration (Glautier, 2004). Nicotine is a reinforcer in animal models and self-control theory is supported by attenuated drug-seeking behavior with an increasing reinforcement schedule (Donny et al., 1999). Self-control theory was expanded by Muraven & Baumeister (2000) who proposed that individuals have a limited pool of self-control resources which are depleted when succumbing to urges (i.e. smoking during a cessation attempt). Self-control theory emphasizes that the regulation of smoking behavior is driven by behavioral choices and does not consider changes to an internal milieu, but as distance/time from the last cigarette increases, neurotransmitter equilibrium in the limbic-frontal pathway is disturbed (Goldstein & Volkow, 2002)

The presentation of a secondary cue (i.e. visual stimulus) alongside nicotine administration can contribute to the maintenance of the conditioned response (Spealman, & Goldberg, 1981), which suggests that drug-related cues may eventually sustain incentive value. The effect is further explained by Robinson & Berridge (1993) who proposed a theory of

incentive-sensitization, a process by which habitual smoking behavior results from strong associations of smoking-related stimuli to the incentive value of the drug itself. Cues associated with the effects of smoking become conditioned stimuli that activate appetitive processes and stimulate neural pathways to produce 'wanting' (Berridge, Robinson, & Aldridge, 2009; Zubieta et al., 2014).

Chronic smoking induces adaptations in striatal dopaminergic pathways that sensitize it to external stressors so that the incentive value of smoking-cues is greater, causing greater wanting for a cigarette during stress (Erb & Stewart, 1999). Withdrawal potentiates cue-induced dopaminergic transmission between the midbrain and frontal cortex driving drug-seeking behavior which can be measured as an increase in smoking urges and cravings (McClernon et al., 2009; Niaura et al., 1999). Unlike situations involving associative learning in which 'wanting' is directly related to positive hedonic valuation of the stimulus (i.e. pleasure, 'liking'), addiction results in desensitization of 'wanting' which is then decoupled from 'liking' (Berridge & Robinson, 1995). Smokers will not reliably enjoy their thousandth cigarette any more than their tenth cigarette. Therefore, research examining the acute effects of smoking and abstinence should consider not only subjective reports of emotional experience or cravings but also response to smoking related cues.

Cravings, Urges & Cue Response

Cravings are a primary component of a withdrawal syndrome (Shiffman & Jarvik, 1976). Two, single-item, seven-point scales are commonly used to assess desire for a cigarette (DtS) and strength of desire to smoke (SoD). DtS is a Likert-type scale, and though different versions exist, a commonly used version asks respondents to rate their agreement with the statement "I have a desire for a cigarette" (1=strongly disagree, 4=neutral, 7=strongly agree). The scale was

derived from factor analysis of the Questionnaire of Smoking Urges (Tiffany & Drobes, 1991) that found items representing 'desire to smoke' loaded on a factor also representing anticipation of a cigarette and the pleasant, rewarding sensations derived from smoking. Kozlowski & Wilkinson (1987) suggested that the term 'craving' has been diluted by substance abuse researchers whom dissociate it from the magnitude of a desire to administer drugs (e.g. smoke a cigarette), but Tiffany & Drobes concluded that "there is little evidence that smokers distinguished between the terms 'urge' and 'craving' or reserved the term craving to designate a particularly intense desire to smoke" (pp. 1474). Therefore, true to definition or not, colloquial use of the term 'craving' suggests it should be assessed independent of magnitude of desire.

Magnitude is measured separately along a single continuum using the SoD scale prompting respondents to report their "strength of desire to smoke right now" (1=very weak, 7=very strong). The item was introduced by Hajek, Belcher, & Stapleton (1985) in a study of 227 adult smokers who reported the severity of their withdrawal symptoms over a 4 week smoking cessation program. Response to a 'strength of urges to smoke' item did not predict relapse, but the lack of an effect is likely partially due to concomitant use of nicotine replacement therapy (i.e. nicotine chewing gum) (West, Hajek, & Belcher, 1989). The items from this study informed the creation of the Mood and Physical Symptoms Survey (MPSS) (West & Hajek, 2004). The SoD scale was first used in tandem with the DtS scale in a study which demonstrated that administration of glucose may be useful in curbing cravings (West et al., 1999). Whether acute changes in self-reported cravings represent tonic, background fluctuations during withdrawal or a phasic surge elicited by environmental cues is typically indeterminable in most research designs (Ferguson & Shiffman, 2009).

Subjective and psychophysiological response to smoking cues represents heightened smoking urges (Carter & Tiffany, 1999), and increased reactivity to smoking cues is associated with increased likelihood of a failed cessation attempt among those trying to quit (Niaura, 1989; Strong et al., 2011). In the absence of tangible reward, drug cues can be potent effectors and responses represent an interaction between attentional, affective and appetitive mechanisms reflecting an individual's mood and motivational state (Tiffany, 1990). Evidence from animal behavioral models suggests that cue response is explained by both traditional Pavlovian conditioning (i.e. conditioned place preference; Carr, Fibiger, & Phillips, 1989) and a motivational transfer indicative of instrumental/operant conditioning (i.e. nicotine self-administration; Kenny & Markou, 2006). It is generally accepted that visual stimuli can evoke an emotional response. Cue-evoked responses to discrete, emotionally evocative images represents an interaction between attentional, affective, and appetitive mechanisms (Lang, Bradley & Cuthbert, 1997), and parallel activation of top-down and bottom-up regulatory processes are sensitive to physiological arousal and affective states like those experienced during withdrawal (Cinciripini et al., 2006) and exercise (Crabbe, Smith and Dishman, 2007; Davidson, 2003; Smith, 2013).

Role of the frontal cortex in cravings and cue response. The prefrontal cortex (PFC) is responsible for affective shifts triggered from cue appraisal (Davidson & Irwin, 1999; Etkin, Egner & Kalisch, 2011), but is also essential in predicting, regulating and sustaining affect in the absence of elicitors (Davidson, 2004; Dias, Robbins & Roberts, 1996; Leon & Shadlen, 1999; Morgan, Romanski & LeDoux, 1993; Urry et al., 2006). Strong concordance exists between animal studies and human neuroimaging research that indicate aspects of the prefrontal cortex

are integrated into a network involved in processes that sustain tobacco abuse and are sensitive to smoking cues.

Maintenance of smoking behavior is driven by nicotine dependence and marked by a cycle of compulsive nicotine administration, nicotine withdrawal, and cravings. Global cerebral activity is reduced by nicotine administration (Fallon et al., 2004) and smoking (Yamamoto et al., 2003) and may be due to restricted cerebral blood flow (Kubota et al., 1983) or blunted metabolism (Fallon et al., 2004). There is strong evidence for a role of the cortico-basal ganglia-thalamic pathways in the subjective experience that accompanies nicotine administration, and Goldstein & Volkow (2002) first united different theories to suggest a putative role of the PFC in addiction through a mechanism of impaired response inhibition and salience attribution. In the *intoxication phase*, nicotine stimulates midbrain dopaminergic transmission, thereby activating the cortico-thalamic pathways and increasing dopamine availability in the prefrontal cortex to elicit a positive subjective experience (Kalivas, Churchill, & Klitenick, 1993; Nisell et al., 1994). Dysphoria, anhedonia, and *drug cravings* characteristic of *drug withdrawal* are due to disruption of dopaminerigic and opioidergic function in the midbrain which disrupts function in thalamic and frontal cortical circuits (i.e. anterior cingulated cortex, orbitofrontal cortex) (Koob & LeMoal, 2001). This disrupted milieu is difficult to maintain, and eventually allostasis is achieved by *compulsive drug administration*.

In addition to stimulating midbrain and thalamic circuitry, exposure to cues during abstinence elicits cravings which are correlated with activity in the right dorsomedial PFC and anterior cingulate cortex (McClernon et al., 2009) and increased blood flow in the right dorsolateral PFC, right orbitofrontal cortex, and anterior cingulate cortex (Wang et al., 2007). Among 19 studies imaging drug cue-elicited brain response, the dorsolateral PFC, venteromedial

PFC, and antererior cingulated cortex are the most common regions showing significant response (Wilson, Sayette, & Fiez, 2004). Exercise activates similar circuitry which may play a putative role in the effects of exercise on withdrawal symptoms.

Effect of cessation aids on cravings and cue response. Nicotine replacement therapy remains the most commonly used cessation aid among those unwilling or unable to quit outright (Cahill, Stead & Lancaster, 2008; Hughes, Stead, & Lancaster, 2007 ; Gross & Stitzer, 1989). A randomized control trial of 158 smokers demonstrated that, compared a placebo patch, a high-dose nicotine patch reduced craving but did not confer a prophylactic effect against cue-induced cravings (Waters et al., 2004). Moreover, evidence for the long-term efficacy of nicotine replacement therapy is modest (Etter & Stapleton, 2004) and there is a risk among heavy smokers (i.e. >10 cigarettes per day) to become dependent on the new nicotine delivery system (e.g. gum, patch, lozenge, spray, electronic cigarette). There are currently two commonly prescribed pharmacological cessation treatments for those wishing to maintain long term cessation.

Bupropion is an anti-depressant that is commonly prescribed as a cessation aid, and though the mechanism of action is poorly understood, it is best described as a norepinephrine-dopamine reuptake inhibitor. Eight weeks of treatment with bupropion attenuates cravings and reduces activity in the ventral striatum, anterior cingulated cortex, and medial orbitofrontal cortex in response to smoking cues (Culbertson et al., 2011). Less than 20% of individuals treated with bupropion maintain abstinence after 12 months (Simon et al., 2004), and it may be most effective when used concurrently with nicotine replacement therapy to abate cravings and weight gain (Burke, Ebbert, & Hays, 2008).

Varenicline acts as a partial agonist of acetylcholinergic receptors and has indirect agonist and antagonist actions downstream in mesolimbic dopaminergic pathways. In a double-blind, randomized placebo control trial, varenicline doubled 12 month abstinence rates (23.0%) compared to sustained-release bupropion (14.6%) and placebo control (10.3%) (Jorenby et al., 2006). As a smoking cessation agent, it increases dopaminergic tone in order to attenuate cravings and during relapse reduces dopaminergic tone to block the rewarding effects of nicotine. Three weeks of treatment with varenicline attenuated cravings and reduced activity in the ventral striatum and medial orbitofrontal cortex in response to smoking cues (Culbertson et al., 2011; Franklin et al., 2011). Cognitive behavioral therapy and exercise have been investigated as potential adjuvants to traditional pharmacological therapies.

In a randomized control trial that used pedometers to assess activity levels, greater physical activity predicted abstinence at 6 month follow-up. Among those able to remain abstinent over 6 months, greater activity was associated with increased energy and decreased perceived difficulty to sustain abstinence (Prochaska et al., 2008). Only 15% (~60 of 400 participants) reported pedometer values which highlights a common problem of adherence in physical activity interventions. Though the exact dose of physical activity necessary to improve cessation rates is unclear, it appears to work best when adherence is high, group workouts are completed at least three days each week, and when activity is increased prior to cessation rather than simultaneously (Zschucke, Heinz, & Strohle, 2012). Therefore, it is worthwhile to understand the acute effects of exercise on cue response and withdrawal symptoms in current smokers in sated and abstinent states.

Benefits of Exercise in Smokers

In light of numerous, well-documented negative health outcomes associated with tobacco use, and the modest long-term success of smoking cessation interventions (Hughes et al., 2014; Stead et al., 2012), multiple lines of research have sought to examine the effects of physical activity on smoking behavior, withdrawal symptoms, and relapse prevention during cessation. Twenty randomized controlled trials have been conducted to examine the effects of exercise training on cessation outcomes (Ussher, Taylor, & Faulkner, 2014), yet only one study reported a trend toward a protective effect (i.e. greater abstinence rates) of exercise compared to a sedentary control group after 12-months (Marcus et al, 1999). A majority of the studies were under powered, long term follow-ups were not reported, and data describing exercise dose were unreliable or not measured. In summary, it is difficult for individuals to remove a reinforcing, harmful habit (i.e. smoking) while simultaneously adding a salubrious behavior (i.e. physical activity). Despite weak support for exercise as a cessation aid, accumulating evidence suggests that exercise elicits acute and transient reductions in withdrawal symptoms. Subjective report of urges and cravings for smoking and cigarettes using two single-item scales (DtS and SoD) is currently the standard metric for quantifying the effects of exercise on withdrawal severity. As summarized in a recent review by Roberts et al. (2012), ten trials have compared the effects of exercise to a passive control condition on DtS finding a weighted mean difference of −1.90 after exercise (95% CI, −3.06 to −0.75), and nine trials have compared the effect of exercise to a passive condition on SoD reporting a mean weighted difference of −2.41 after exercise (95 % CI, −3.45 to −1.37). Effects of exercise on DtS and SoD reported in these meta-analyses are supported by a recent quantitative synthesis of individual participant data from approximately 450 participants from 17 (DtS) and 15 (SoD) studies (Haasova et al., 2013).

In total, twenty-seven studies have examined the effects of exercise on withdrawal since the first report in 1983. Twenty-four of the 27 studies comparing exercise to a control condition showed a positive effect on cravings (Taylor, Ussher & Faulkner, 2007, Roberts et al., 2012). The effects of exercise after overnight abstinence appears to be particularly robust when cravings are potentiated by simultaneous exposure to a smoking cue and stressor task (Fong et al., 2014). Evidence suggests that multiple cessation treatments confer the best results (Kottke et al., 1988), and a single bout of moderate intensity exercise may have an additive effect on cravings when used in conjunction with nicotine replacement (i.e. lozenge) (Tritter, Fitzgeorge, & Prapavessis, 2015). Moreover, reduced cravings and delayed ad libitum smoking after moderate-intensity exercise are plausibly related to reductions along a positive/rewarding component of craving rather than a desire for relief from withdrawal symptoms (Kurti & Dallery, 2014).

Cravings are central to describing withdrawal among smokers, but other symptoms may be more greatly impacted by exercise. Anxiety was decreased by light intensity exercise, but returned to baseline values within 5-minutes (Daniel et al., 2004). Ten minutes of moderate intensity exercise attenuated irritability and depression compared to a video-watching and passive control groups (Ussher et al., 2001). Positive affect increased and negative affect decreased after 30 minutes of yoga or 30 minutes of aerobic exercise (Elibero et al., 2011), and improved feelings of energy and fatigue have been reported after 50 minutes of walking (Williams et al., 2011). Only one study reported a mediating effect of mood on cravings (Taylor, Katomeri, & Ussher, 2006).

Taylor et al. (2007) emphasized the need for future studies to include biomarkers of cravings to establish biological plausibility. Scerbo et al. (2009) reported reduced cravings after 15 minutes of walking and running compared to passive control but the effects were not related

to changes in salivary cortisol. Van Rensburg et al. (2009, 2012) were the first to utilize fMRI to identify brain loci responsible for the effect of exercise in abstaining smokers. Compared to a time-matched bout of rest, 10 minutes of moderate intensity cycling reduced DtS, attenuated cue-elicited activation in areas associated with visual attention (2012), and produced cue-elicited hypoactivation in midbrain-frontal regions associated with reward and motivation (2009). These two recent trials are consistent with an extensive body of literature describing a role of the frontal cortex in drug addiction. Data from a recent study which used optical imaging to measure PFC changes during exercise among non-smokers indicate that the exercise-induced changes in these regions may be related to affect (Tempest, Eston, & Parfitt, 2014). Optical imaging, (i.e. near infrared spectroscopy) is ideally suited to measure the effects of exercise on changes in frontal cortex response to visual cues.

Functional Near Infrared Spectroscopy (fNIRS)

Functional near infrared spectroscopy (fNIRS) is a non-invasive technique that uses chromophores as endogenous tracers to quantify relative cortical oxygenation (Ferrari, Mottola & Quaresima, 2004; Villringer & Chance, 1997; Villringer & Dirnagl, 1995). Continuous-wave fNIRS devices are cheaper than devices that resolve the NIR signal spatially or temporally, and have been demonstrated capable of identifying DLPFC response patterns to visual stimuli in diverse populations and experimental environments. Measurement is less sensitive to movement than magnetic resonance making it an ideal technique for measuring frontal cortex activity in a behavioral context (Hoshi, 2011). A single bout of moderate intensity exercise increases relative concentrations of oxygenated hemoglobin (HbO_2) and total hemoglobin (tHb), but has smaller, nearly negligible effects on relative concentrations of deoxygenated hemoglobin (HHb) in the prefrontal cortex. Collectively, under the assumptions of neurovascular coupling, these findings

are taken to represent increased regional neuronal metabolic activity (Rupp & Perrey, 2008; Rooks et al., 2010; Timinkul, 2008).

Despite reduced motion artifact, multiple sources of error can contribute to high frequency and low frequency error during data collection. Algorithms to de-trend the data are available alongside a general linear modeling program and statistical parametric mapping function in software adapted from magnetic resonance for near-infrared devices (NIRS-SPM) (Ye et al., 2009). Global trends resulting from respiration, vasomotion, and other experimental errors can be removed from the hemodynamic signal using wavelet minimum description length (Jang et al., 2009). Specifically, this detrending algorithm, adapted from fMRI for NIRS, prevents over- and under-correction by decomposing each signal into global trends, hemodynamic signals, and uncorrelated noise components.

Event-related designs increase the power to detect changes across varying stimuli of interest, but the amount of time necessary to 'wash-out' the hemodynamic response to arousing cues is as yet unknown. Instead, block designs are used to capture hemodynamic response during a task across a large, heterogenous field such as the frontal cortex. In neuroimaging, the general linear model (identical to multiple regression) allows for a quantitative dependent variable (i.e. oxygenation signal) to be regressed on qualitative variables (i.e. stimuli category) to calculate a beta which represents the mean signal response to each regressor. These regressors are also convolved with the canonical hemodynamic response function (HRF) to model expected response, with time and dispersion derivatives to account for delays previously reported in the prefrontal cortex (Buxton et al., 1998; Friston et al., 1998; Plichta et al., 2007). These parameter estimates (i.e. HRF, time derivative, dispersion derivative) can be combined as orthogonal

components to estimate amplitude of the hemodynamic response for each signal at each optode (Calhoun, 2004).

The largest effects on frontal cortex hemodynamics using continuous-wave NIRS (without trend correction algorithms or GLM) have been elicited by emotional induction during exposure to pleasant and unpleasant images (Herrmann et al., 2003) and highly arousing video clips (Leon-Carrion et al., 2007) in healthy populations. Among individuals with substance use disorders, drug-related cues are some of the most salient stimuli resulting in the biggest cognitive deficits (i.e. disinhibition; Li & Sinha, 2009) plausibly mediated by significant regional changes in PFC blood flow and metabolism (Goldstein & Volkow, 2011). Only a few studies have used fNIRS to describe PFC response to drug cues.

In abstaining alcoholics greater reductions in PFC hemodynamic response to alcohol cues were associated with more days of abstinence (Dempsey et al., 2009). Bunce et al. (2012) found that lateral PFC oxygenation in response to cues was greater in current alcoholics compared to recovered alcoholics and non-alcohol abusing controls. DLPFC response was correlated with cravings, and response to food cues was negatively correlated with response to alcohol cues in the right DLPFC. These results are consistent with results from research utilizing functional magnetic resonance, but the authors are unable to apply their findings to currently accepted conceptual frameworks describing addiction and cue response. One of the benefits of NIRS technology is its potential for use in research designs in which functional magnetic resonance would be impractical or impossible. One study assessed DLPFC oxygenation in young adults (with and without attention deficit/hyperactivity disorder; ADHD) as they smoked a cigarette (Gehricke et al., 2013).

Due to reduced PFC oxygenation after smoking in those with ADHD compared to healthy controls, the authors suggest that smoking may be a form of self-medication in this population. As far as we know, NIRS has not been used to measure the effects of exercise on PFC response to emotional scenes or drug cues.

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CHAPTER 3

EFFECTS OF EXERCISE ON AFFECTIVE AND PREFRONTAL BRAIN RESPONSES TO EMOTIONAL SCENES IN SMOKERS AFTER SMOKING A CIGARETTE

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Abstract

The primary factors driving dependence-forming smoking behavior are acute improvements in mood and affective response after smoking a cigarette and unpleasant side effects during abstinence. Exercise during abstinence tempers cravings, improves mood, and reduces sensitivity to smoking cues, an effect that may be related to processes in the dorsolateral prefrontal cortex (DLPFC). It is as yet unknown whether exercise alters DLPFC responses to smoking cues and emotionally evocative scenes in a sated state. Functional near-infrared spectroscopy (fNIRS) was used to measure changes in DLPFC deoxygenated hemoglobin (HHb) in fifteen cigarette smokers (7 heavy smokers, 8 light smokers) who viewed pictures containing emotionally evocative cues and smoking-related cues 1) prior to smoking a cigarette and 2) after conditions of seated rest or 20 minutes of exercise at a preferred intensity. Heavy smokers felt more fatigued at baseline ($p<.05$) and less energetic during resting recovery ($p<.05$) compared to light smokers. Compared to seated rest, cycling enhanced feelings of energy ($p<.001$), reduced anger throughout resting recovery ($p<.01$), and reduced DLPFC response to pleasant ($p=.003$) and unpleasant scenes ($p=.021$) compared to neutral scenes. Cycling for twenty minutes at a self-selected intensity after smoking increased feelings of energy, reduced feelings of anger, and conferred a protective effect against DLPFC response to emotionally evocative scenes.

Keywords: Affective experience, Emotional picture viewing**,** Near-infrared spectroscopy, Preferred exertion

Introduction

Habitual cigarette smokers depend on smoking to improve affect and cope with daily emotional stressors (Baker, Brandon, and Chassin, 2004; Ikard, Green, and Horn, 1969). However, smoking contributes to higher perceptions of chronic stress (Naquin and Gilbert, 1996; Ng and Jeffery, 2003; Parrott, 1999) which underlie the pathophysiology of several psychiatric disorders (Bizik et al., 2013; Juster, McEwen, Lupien, 2010; McEwen, 2004). The neuromodulatory effects of nicotine in the mesolimbic pathways extend to the prefrontal cortex and are primarily responsible for transient mood improvements after smoking a single cigarette (Barrett et al., 2004; Fowler et al., 1996; Pons et al., 2008). Nicotine withdrawal elicits negative affect and cravings (Baker et al., 2004; Zinser et al., 1992), but nicotine dependence alone is not sufficient to explain tobacco dependence. Pharmacological activity of nicotine in the midbrain causes smoking-related cues to take on incentive value as conditioned stimuli which reinforce smoking behavior (for a review see: Chiamulera, 2005). Sensitization to smoking cues during abstinence can reinstate smoking behavior, making cessation particularly difficult (Brandon, 1994; Germain, McCarthy, & Wakefield, 2010; Niaura, 2001; Picciotto, Brunzell, & Cadarone, 2002). Accumulating evidence suggests that exercise may be a useful adjuvant to traditional cessation therapies (Taylor, Ussher & Faulkner, 2007), and, like other cessation aids, exercise may improve withdrawal experience by mimicking the effects of smoking (Taylor et al., 2007). A single bout of exercise can increase energy (Thayer et al., 1993), reduce negative affect (Bock et al., 1999) and reduce tension and stress (Ussher et al., 2001) in abstaining smokers. The efficacy of exercise during cessation is plausibly related to physical activity levels prior to abstinence (Marcus et al., 1997), but the acute effects of exercise among smokers in the maintenance stage have not been described.

Acute improvements in positive affect and reductions in negative affect, which reinforce smoking behavior, can be assessed by subjective and neurophysiological response to discrete, emotionally arousing stimuli (Patrick and Lavoro, 1997). In non-smokers, a single bout of low-to-moderate intensity cycling exercise reduces sensitivity to emotionally arousing images (Crabbe, Smith and Dishman, 2007; Smith, 2013; Smith, O'Connor, Crabbe and Dishman, 2002). Emotional responsiveness involves parallel activation of top-down and bottom-up neural regulatory processes associated with affective states like those experienced during withdrawal and after exercise (Davidson, 2003). Among smokers, nicotine administration can suppress responses to unpleasant and smoking-related cues which accompany withdrawal and maintain smoking behavior (Cinciripini et al., 2006; Engelmann, Gewirtz, Cuthbert, 2011), and exercise confers a protective effect against cue induced cravings which may be related to activity in the dorsolateral prefrontal cortex (DLPFC) (Van Rensburg et al., 2009).

The DLPFC is involved in decision making when integration from multiple sources of information is required (e.g. affect, reward salience) and plays a putative role regulating sensitivity to smoking cues (Krawzyck, 2002; Volkow, Fowler, and Wang, 2003; Wilson, 2004). Moreover, chronic smoking reduces DLPFC volume which may inhibit top-down processing and precipitate greater impulsiveness to rewarding stimuli and sensitivity to unpleasant stimuli (Nestor et al., 2011). The relationship between sensitivity to emotional and smoking cues is as yet unknown, but the acute effects of exercise and smoking are plausibly manifest in the DLPFC.

We used functional near-infrared spectroscopy (fNIRS) to quantify relative changes in DLPFC deoxygenation in response to pleasant, unpleasant, and smoking cues. fNIRS has been used to quantify the acute effects of exercise, smoking, and emotional scenes on changes in frontal cortex hemodynamic status. Acute incremental aerobic exercise reliably increases relative

concentrations of oxygenated and deoxygenated hemoglobin (Rooks et al., 2010; Tempest et al., 2014). The effects of smoking a cigarette are similar to the effects of exercise but more variable (Pucci et al., 2009). The greatest responses to visual cues have been in response to unpleasant images (Hermann et al., 2003) and highly arousing video clips (Leon-Carrion et al., 2007) with a handful of studies showing significant effects of drug cues (e.g. Bunce et al., 2012; Dempsey et al., 2009). As neurovascular coupling continues to be studied, there is debate over the significance of different chromophores (HbO_2 & HHb) measured by NIRS. We analyzed only HHb, because it has been negatively correlated with fMRI-BOLD contrasts in a range of tasks (Cui et al., 2011) and is less sensitive than HbO_2 to changes in extracerebral blood flow measured over the frontal cortex, which is altered after smoking a cigarette (Meekin et al., 2010; Sato et al., 2013). We hypothesized that cycling at a preferred level of exertion would sustain smoking-induced mood improvements and attenuate DLPFC response to unpleasant and smoking cues compared to seated rest. Furthermore, it was hypothesized that changes in mood and affective response would be explained by DLPFC response to emotional scenes and smoking cues.

Materials and Methods

Participants. Fifteen smokers participated in the study. A priori power analysis revealed that 15 participants were needed to detect a moderately sized effect of exercise on DLPFC HHb response to emotional and smoking cues ($\geq$ 0.50 SD or partial η^2 ~.10) at a statistical power >.80, and an alpha level of .05 (Faul et al., 2009). All participants reported smoking $\geq$10 cigarettes per week for at least the last year and $\geq$ 3 hours of moderate physical activity but $\leq$1 hour of vigorous physical activity in the week prior to screening. Participants were identified as heavy smokers (*n*=7) if they reported smoking $\geq$10 cigarettes per day on average during the past year or

as light smokers (n=8) if they reported smoking <10 cigarettes per day during the last year. Classification of smoker status was consistent with related literature (Husten, 2009). Select participant characteristics are shown in Table 3.1. Use of psychoactive medication, contraindications to moderate-intensity exercise (other than smoking), and elevated depressive symptoms (Beck Depression Inventory, BDI; Beck, Ward & Mendelson, 1961) or trait anxiety were cause for exclusion (Spielberger State Trait Anxiety Inventory, STAI; Spielberger, Gorsuch, & Lushene, 1970). The study protocol was approved by the institutional review board and all the participants gave written informed consent prior to screening and laboratory data collection after study procedures, risks, and benefits were explained.

Procedures. Participants completed a series of questionnaires in an online screening survey (*www.qualtrics.com)* to confirm eligibility: a medical questionnaire to confirm contraindications to moderate intensity exercise (including height and weight), Profile of Mood States questionnaire to assess mood states during the past week (McNair et al., 1992), BDI, STAI, smoking questionnaire to assess exposure to cigarettes during the last year, and a 7-day Physical Activity Recall to assess levels of moderate and vigorous (i.e., hard and very hard) physical activity in the week prior to screening (Blair et al., 1985). The 7-day physical activity recall included occupational activities (e.g., moderate: walking at work/to class, cleaning/ sweeping; vigorous: carrying boxes up stairs, constructing/carrying furniture) and leisure time activities (e.g., moderate: walking, washing dishes; vigorous: boxing, resistance training, basketball). There was no difference in physical activity between light and heavy smokers (p>.280).

During the first of two visits to the laboratory, informed consent for participation was obtained. Participants were asked to refrain from alcohol and caffeine consumption and vigorous

exercise for 12 hours preceding each appointment. Participants were also asked to abstain from smoking and nicotine products 2 hours prior to each appointment and to bring a preferred-brand cigarette and a lighter. At the beginning of each visit, participants reported 24-hour cigarette exposure (i.e. “How many cigarettes have you smoked in the past 24 hours?”), performed a baseline carbon monoxide breath analysis using a PiCO+ (Smokerlyzer; Haddonfield, NJ), and completed a Profile of Mood States-Brief Form to assess feelings of tension-anxiety, depression, fatigue, vigor (energy), and confusion (POMS-B; Curran, Andrykowski & Studts, 1995).

Participants were seated on a Lode Cycle Ergometer (Lode BC, Groningen, The Netherlands) and sat motionless while breathing normally for 5 minutes of baseline rest. Participants viewed a picture show (Presentation 16.2; Neurobehavioral Systems, USA) of four, 1-minute blocks of 12 pictures each. Each block consisted of standardized images representing unpleasant (e.g., fearful, threatening, disgusting), neutral (e.g., household objects, rocks, mushrooms) or pleasant (e.g., erotica, sports scenes, puppies) scenes (International Affective Picture System; Lang, Bradley & Cuthbert, 2008) that were presented in a pseudo-randomized order. The last block in each picture show contained smoking-related cues (International Smoking Image System; Gilbert and Rabinovitch, 1999). At the end of each block, participants reported how the images made them feel using an onscreen Self-Assessment Manikin (SAM; Hodes, Cook & Lang, 1985; Lang, 1980). The SAM is a pictographic, 9-point scale that depicts affect along independent continua of valence (i.e., unpleasant to pleasant) and arousal (i.e., arousing to calming). Participants used a keyboard to respond to each SAM scale before they were transported outside in a wheelchair to smoke a cigarette.

After smoking, participants were transported back to the lab, performed a carbon monoxide breath analysis and were seated on the Lode cycle ergometer prior to completion of a

POMS-B. After a three-minute rest period, participants completed 25 minutes of either seated rest or cycling exercise. Cycling exercise began with a 3-minute warm-up and ended with a 2-minute cool down, each at a power output of 25 watts. Twenty minutes of cycling was performed at a preferred intensity: Every five minutes participants were given the option to increase, decrease, or maintain the resistance. Pain, perceived exertion, and fatigue were assessed by Borg 6-20 scales (Borg, 1998), and affective valence and arousal were assessed by SAM. During the seated rest condition, participants were instructed to remain still and breathe normally while seated on the cycle. Order of exercise and rest conditions was randomized across days (*www.randomizer.org*), and participants were not aware of their assigned condition on day 1 until completing the pre-rest or pre-exercise POMS-B. After cycling exercise and seated rest, participants completed a POMS-B prior to viewing a second picture show. There was a 3-minute recovery period during which participants sat resting, motionless, and breathing normally. Participants then completed a final POMS-B.

Dorsolateral prefrontal cortex (DLPFC) deoxygenation was measured continuously (10 Hz) using continuous-wave NIRS (OxyMon MKIII, Artinis Medical Systems, Zetten, The Netherlands) operating at 765nm and 857nm in a four channel configuration. Continuous-wave near-infrared spectroscopy has been described elsewhere (Ferarri, Mottola & Quaresima, 2004); due to an unknown path length, oxygenation is measured as relative change in the concentration of oxygenated and deoxygenated hemoglobin (HbO_2 and HHb respectively). Optodes were placed over areas approximating F_{p1} and F_{p2} of the international 10-20 system for transcranial measurement using bilateral source-detector distances of 35mm and 50mm which resulted in penetrating depths of ~17.5mm and 25mm respectively according to the modified Beer-Lambert law (Delpy et al., 1988).

Preliminary data analysis. Subjectwise relative HHb concentrations, sampled 10 times per second across a test session (excluding the cigarette smoking period), were entered in NIRS-SPM (Ye et al., 2009) run on Matlab (MathWorks, Natick, MA). A block-design matrix was specified by entering onset times and durations for each picture presentation block creating a series of 8 'boxcar' regressors. These regressors were convolved with the canonical hemodynamic response function (HRF) to model expected response, with time and dispersion derivatives to account for differences previously measured in the prefrontal cortex (Buxton et al., 1998; Friston et al., 1998; Plichta et al., 2007). Overall trends resulting from respiration, vasomotion, and other experimental errors were removed from the DLPFC HHb signal using wavelet minimum description length (Jang et al., 2009) The resulting signals were entered into the general linear model to obtain beta weights for each regressor to be used as parameter estimates. No correction for serial correlations was applied. These parameter estimates (i.e. HRF, time derivative, dispersion derivative) were combined as orthogonal components to estimate amplitude of the DLPFC hemodynamic response (Calhoun, 2004) and averaged across recording sites within each hemisphere for input into the primary statistical analysis.

Primary statistical analysis. Statistical analysis was performed using SPSS 21.0 (SPSS Inc, Chicago, IL, USA). DLFPC response to cues at baseline between categories and across conditions were reliable, ICC (2,3) = .749-.795. A change score was computed for HHb by subtracting baseline parameter estimates from post-condition estimates (Post-Baseline=ΔHHb). Preliminary analyses revealed no effect of hemisphere ($p > .23$, $\eta^2 < .10$) and subsequent analyses were collapsed across hemisphere.

To describe subjective and heart rate response to exercise, separate oneway analyses of variance (ANOVAs) with a factor of time repeated (warmup, 5-minute,10-minute, 15-minute,

20-minute, cooldown) were conducted. Multiple repeated measure ANOVAs were conducted to test for changes in mood, DLPFC response, and affective response to cues with condition (cycling, rest), time (baseline, post-cigarette, post-condition, resting recovery), and category (pleasant, unpleasant, smoking, neutral) as repeated factors and smoker status as a between-subjects factor. Significant interactions in cue response were decomposed using simple contrasts. Otherwise, simple effects within each condition and pairwise comparisons were calculated to decompose significant interactions. Bonferroni-correction for multiple comparisons was applied, and Huynh–Feldt (ε) adjusted *p*-values were used. Epsilon is reported where appropriate.

Condition x time repeated measures ANCOVAs also were conducted to determine whether changes in affective response to emotional scenes and smoking cues (i.e. arousal and valence) were explained by DLPFC response to emotional scenes and smoking cues. Reductions in the adjusted F statistic below the critical value (p=.05) and in the size of partial η^2 in the covariate-adjusted, conditional RM-ANCOVA, compared to the unconditional MANOVA model, were interpreted as the covariate accounting for a significant percentage of the change in cravings, i.e., 1 – (conditional η2/ unconditional η2), consistent with standard procedures (Keppel & Wickens, 2004).

Results

Psychological and physiological response to exercise. Perceived exertion (mean ± S.E.; 5min=8.7±0.47, 20min=11.2±0.67), F(1,14)=15.760, η^2=.530, *p*=.001, ratings of pain (mean ± S.E.; 5min=7.9±0.43, 20min=10.5±0.80), F(1,14)=11.145, η^2=.462, *p*<.001, and ratings of fatigue (mean ± S.E.; 5min=8.4±0.45, 20min=10.8±0.61), F(1,14)=14.705, η^2=.512, *p*=.002, increased during exercise. Power output, F(1,14)=8.933, η^2=.390, *p*=.010, increased linearly (mean±S.E.; Start, 5-min, 10-min, 15-min; 40.0, 46.0±2.50, 52.33±4.52, 58.0±6.03). Heart rate

increased during exercise compared to seated rest, $F(1,11)=51.590$, $\eta^2=.791$, $p<.001$ (Fig. 3.1) Response to exercise was not different between light and heavy smokers.

Mood response to post-cigarette exercise and seated rest. Smoking a cigarette increased breath carbon monoxide (mean ± S.E.; Pre=8.7±1.9 ppm, Post=13.4±2.3 ppm), $F(1,14)=34.917$, $\eta^2=.729$, $p<.001$. There were condition x time effects on anger, $F(3,39)=5.390$, $\eta^2=.293$, $p=.003$, $\varepsilon=1.00$ and energy, $F(3,39)=5.739$, $\eta^2=.306$, $p=.003$, $\varepsilon=.983$. Feelings of energy were enhanced ($p<.001$) and anger reduced ($p<.01$) by exercise compared to seated rest. Reduced anger was sustained through resting recovery in the exercise condition (Fig. 3.2). There were time x smoking status effects on fatigue, $F(3,39)=6.411$, $\eta^2=.330$, $p=.004$, $\varepsilon=.726$ and energy, $F(3,39)=3.056$, $\eta^2=.190$, $p=.04$, $\varepsilon=1.00$. Light smokers felt less fatigued at baseline ($p<.05$) and had greater feelings of energy during resting recovery ($p<.05$) than heavy smokers (Fig. 3.3).

Response to IAPS and ISIS images. There was a condition x smoking status effect on arousal ratings of smoking cues, $F(1,10)=11.316$, $\eta^2=.531$, $p=.007$. Smoking cues were rated as more arousing to heavy smokers during seated rest ($p<.01$). Pleasant, $F(1,14)=37.373$, $\eta^2=.727$, $p<.001$, and unpleasant scenes, $F(1,14)=41.560$, $\eta^2=.748$, $p<.001$, were rated as more arousing than neutral scenes independent of smoking status. Pleasant scenes were rated as more pleasant, $F(1,14)=55.563$, $\eta^2=.799$, $p<.001$., and unpleasant scenes more unpleasant, $F(1,14)=70.797$, $\eta^2=.835$, $p<.001$., than neutral scenes. Affective ratings of emotional scenes were not different between exercise or rest conditions ($p>.056$).

There was a condition x category interaction on DLPFC deoxygenation change (ΔHHb), $F(3,39)=6.728$, $\eta^2=.341$, $p=.001$, $\varepsilon=.1.000$. Compared to seated rest, exercise increased ΔHHb to pleasant scenes, $F(1,13)=6.571$, $\eta^2=.336$, $p=.024$, and unpleasant scenes, $F(1,13)=11.389$, $\eta^2=.467$, $p=.005$, relative to neutral scenes (Fig. 3.4). Seated rest reduced ΔHHb response to

pleasant scenes (p=.003) and unpleasant scenes (p=.002) relative to neutral scenes. There were no differences between DLPFC response to neutral and emotional scenes during the exercise condition (p>.341). Changes in anger, energy, and fatigue were not explained by changes in response to emotional scenes or smoking cues (all p values $\leq$ .05 for all adjusted models).

Discussion

Our primary novel finding is that exercise reversed elevated DLPFC response, indicative of increased blood flow and neuronal activity, to emotionally evocative scenes elicited by smoking. Relative to neutral scenes, the effects of smoking and seated rest on DLPFC HHb in response to pleasant scenes (Cohen's dz=0.93 [95% CI:0.64-1.22]) and unpleasant scenes (Cohen's dz=1.00 [95% CI:0.70-1.30]) were large compared to previously reported changes elicited by emotional scenes in non-smokers (Hermann et al., 2003; Cohen's dz=0.08-0.19). This may be partially explained by the effects of smoking on biological substrates underlying hemodynamic response. Cholinergic receptors, widespread throughout the brain, are upregulated in chronic smokers and enhance the acute effects of nicotine (Perry et al., 1999). Ascending cholinergic pathways terminating in the prefrontal cortex modulate cortical hemodynamic response (Sato, Sato, & Uchida, 2001) and selective attention (Witte et al., 1997). Therefore, it is plausible that cholinergically mediated increases in cortical blood flow after smoking were accompanied by attention toward emotional scenes 30 minutes later. Preferred-intensity exercise blunted this effect, although the mechanism underlying that effect remains unclear. Moderate-intensity cycling exercise, similar to that used here, increased attentional bias to pleasant compared with unpleasant faces in a report on non-smokers (Tian & Smith, 2011).

A lack of an effect of exercise or smoking on affective ratings of emotional scenes, while consistent with reports from our lab (Crabbe, Smith & Dishman, 2007; Smith & O'Connor,

2003; Smith et al., 2002) suggests that DLPFC response does not represent changes in affective appraisal. Instead, increased DLPFC activity elicited by pleasant and unpleasant scenes plausibly represents activation of appetitive and avoidance processes similar to effects measured after nicotine administration (Muñoz et al., 2010). Our results support converging lines of evidence from affective neuroscience that the dorsolateral prefrontal cortex is involved in emotional regulation.

Furthermore, the results here extend previous smoking cessation research by demonstrating that the benefits of exercise among smokers are not limited to cessation. Though exercise in a sated state did not have an acute effect on affective or DLPFC response to smoking cues compared to neutral cues, cycling at a preferred intensity produced a transient increase in subjective energy, and suppressed feelings of anger that developed after smoking during seated rest. The invigorating effects of exercise have been reported among non-smokers (Loy et al., 2013) and abstaining smokers (Thayer et al., 1993) but never after a cigarette. Our findings extend a theoretical framework that the benefits of low-to-moderate intensity exercise closely mimic the effects of smoking (Parrot, 1998; Taylor et al., 2006) and that the effects may be related to emotional processing in the DLPFC (Froeliger et al., 2013). It is not surprising that exercise and smoking had negligible acute effects on subjective tension (i.e. anxiety) or depression since individuals with high trait anxiety and depression were screened out. Future studies recruiting individuals with elevated symptoms more representative of the general smoking population may be able to detect significant acute effects. Understanding these effects among those in the maintenance stage is intrinsically important for promoting behaviors, such as exercise, that can dampen the maladaptive effects of smoking or improve survival rates in future cessation attempts.

In an effort to maintain a natural smoking experience, we did not assess smoking topography (e.g. inhalation volume or duration, puff duration or number) or otherwise standardize nicotine intake. Conditioned smoking cues (i.e. preferred brand cigarette) are as important to smoking experience as pharmacological activity of nicotine, and we believe our findings generalize to a broader population of smokers than studies that use standardized cigarettes or nicotine patches. Future studies should seek to measure the time-course of change in cue sensitivity after smoking and exercise in order to determine whether changes represent early-onset withdrawal symptoms or waning effects of a single cigarette. Previous reports of exercise in smokers insufficiently describe the dose of exercise. Using subjective responses (i.e. perceived exertion, fatigue, pain) and heart rate response to cycling we are able to confirm that, when given a choice, smokers will prefer to cycle at a light-to-moderate intensity for 20 minutes after a cigarette. Evaluation of expired gases using indirect calorimetry could improve dose assessment, but restricted ventilation may impact the metabolic demand of exercise in smokers.

Compared to seated rest, the reduction in anger from post-cigarette to post-cycling cue exposure was large (Cohen's *dz*=0.90 [95% CI:0.62-1.19]). Considering that cigarettes are commonly used to cope with emotional stress, this effect could represent a meaningful reduction in risk of relapse for smokers intending to quit. Changes in anger were not explained by DLPFC response to emotional scenes, therefore elevated anger could also be interpreted as symptom of experimental demand. Research should aim to identify a dose of exercise that maximizes mood improvements that persist during exposure to emotional stressors which elicit cravings.

In summary, a single bout of cycling exercise at a preferred intensity confers a protective effect against anger and heightened sensitivity to pleasant and unpleasant cues which manifest shortly after smoking a cigarette. The benefits of exercise were independent of whether

participants were heavy or light smokers, suggesting that there may be a crucial period in the development of nicotine addiction during which exercise could prevent the initial reinforcement of smoking behavior. The relationship between affective response to emotional scenes and smoking cues after exercise encourages study of smokers while they attempt abstinence.

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Table 3.1 Participant Characteristics (Mean±S.D.)

Characteristic	Heavy Smokers (*n*=7)	Light Smokers (*n*=8)	*P*-value (two-tailed)
Age (years)	25.4±5.1	22.3±1.8	.157
BMI	25.7±7.4	24.6±2.8	.733
Annual smoking (cigarettes/week)	85.0±27.5	13.9±6.2	**<.001**
Tension at Screening (POMS)	10.4±3.2	7.0 ±1.8	**.033**
Depression at Screening (POMS)	8.7±2.3	7.9±3.0	.554
Anger at Screening (POMS)	9.1±2.5	7.9±2.3	.333
Vigor (Energy) at Screening (POMS)	13.1±3.8	14.5±3.7	.500
Fatigue at Screening (POMS)	12.9±3.9	7.6±3.8	**.023**
Baseline Depression (BDI-II)	11.3±8.1	6.5±5.2	.210
Baseline Anxiety (STAI-Y1)	50.9±3.6	53.0±3.0	.238

BMI is Quetelet body mass index; MVPA is Moderate-to-vigorous physical activity in previous week; POMS is Profile of Mood States, BDI-II is Beck Depression Inventory-II; STAI-YI is State-Trait Anxiety Inventory Form Y1.

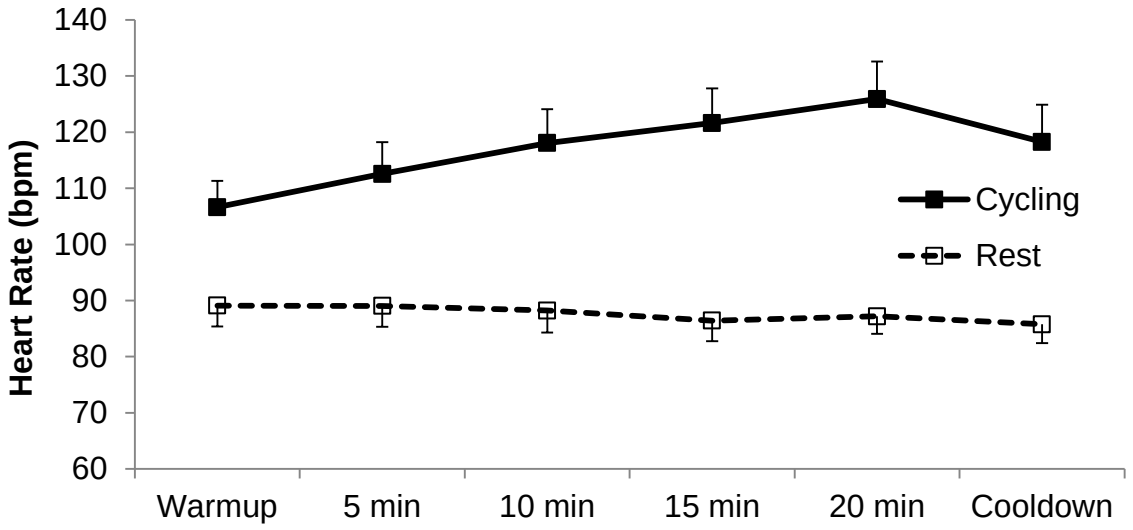

Fig. 3.1 (mean± S.E.) Heart rate response during exercise and rest. Cycling increased heart rate compared to seated rest condition.

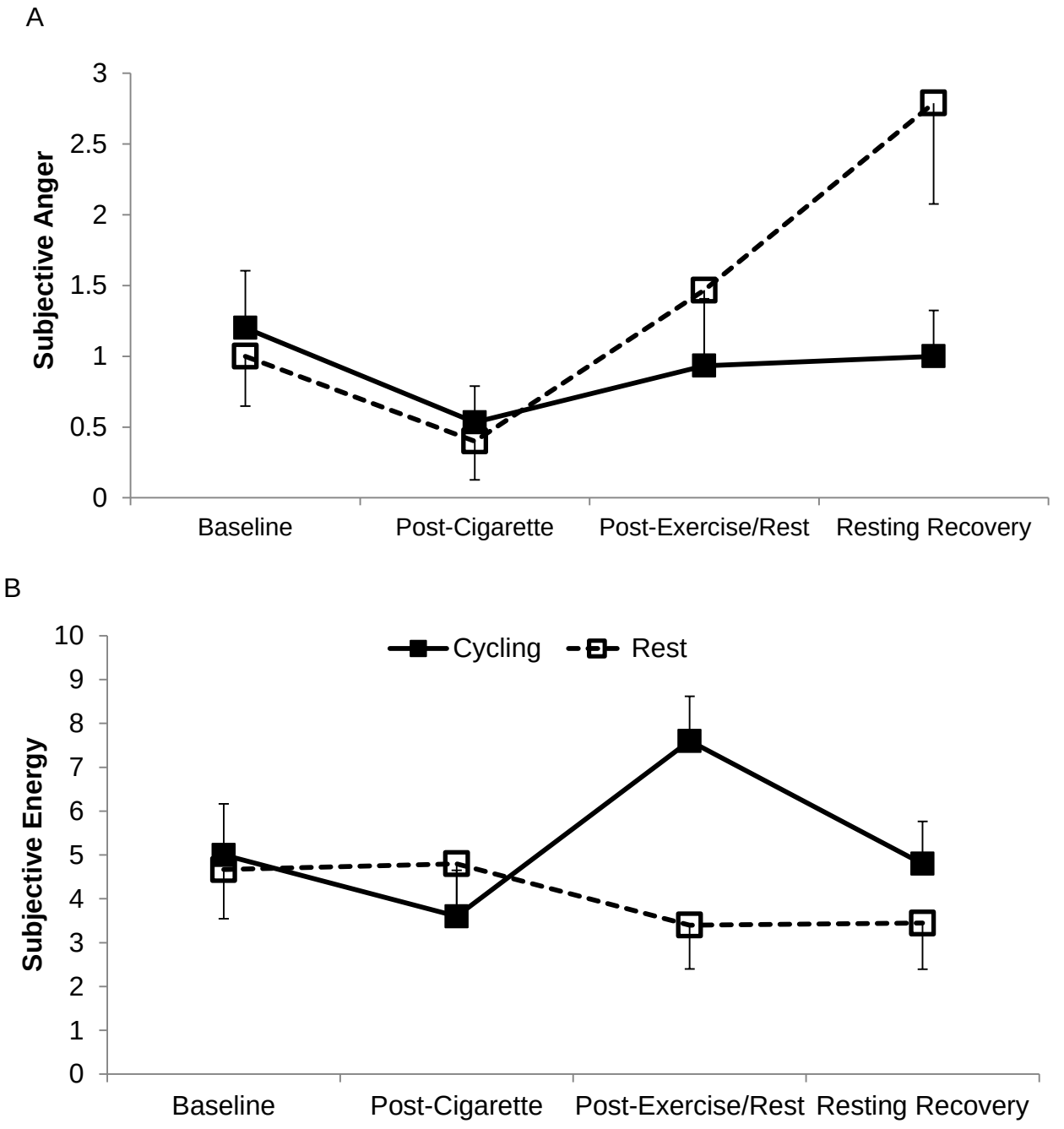

Fig. 3.2 (mean± S.E.) Scores on A) vigor (energy) and B) anger scales of the Profile of Mood States-Brief (POMS-B) during exercise and seated rest test sessions. Subjective energy was increased immediately after exercise compared to seated rest. Anger was decreased by smoking and increased immediately after seated rest and during resting recovery.

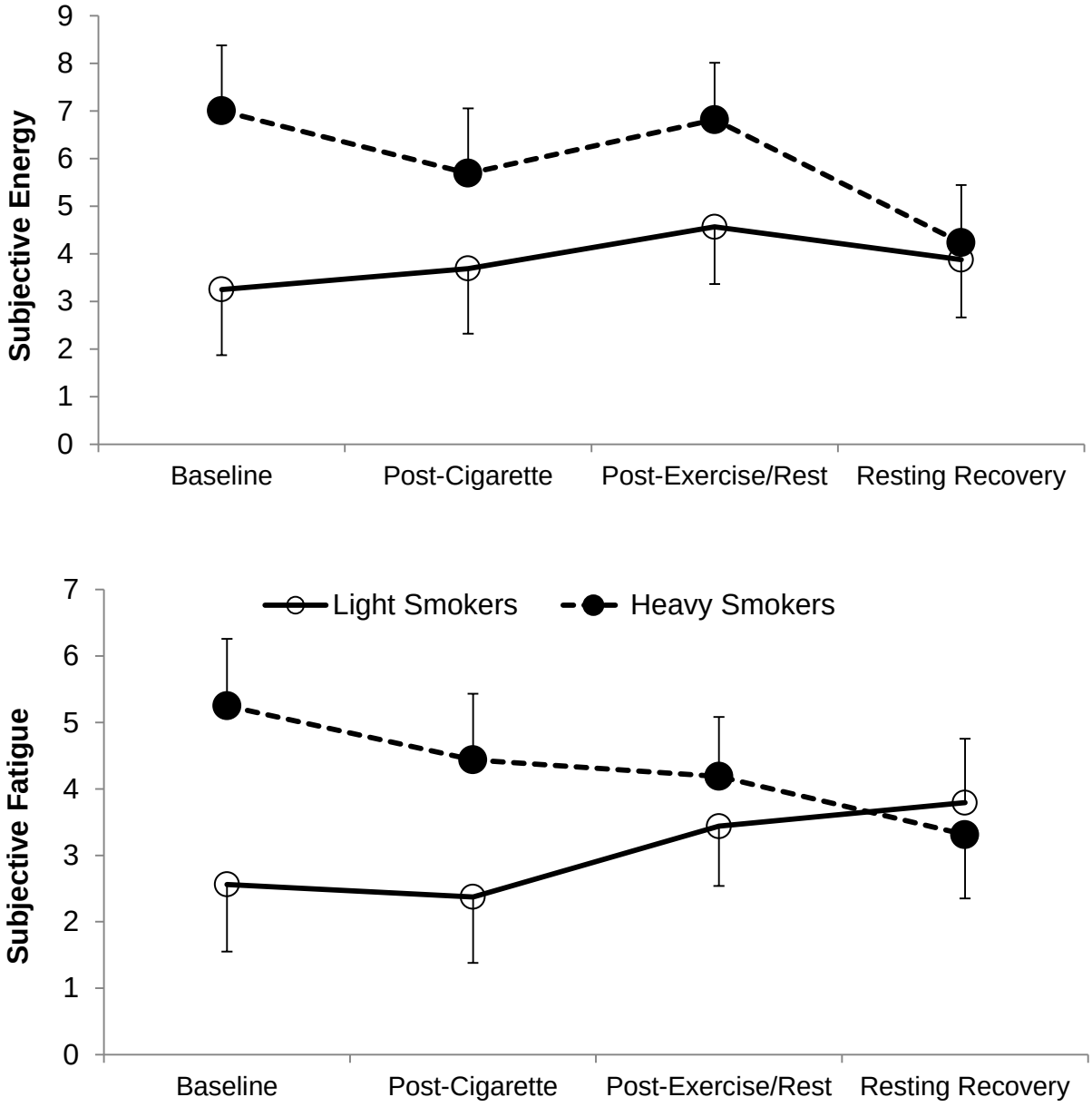

Fig. 3.3 (mean± S.E.) Scores on A) vigor (energy) and B) fatigue scales of the Profile of Mood States-Brief (POMS-B) averaged across sessions in heavy smokers and light smokers. Fatigue was greater and energy less at baseline in heavy smokers (>1/2 pack-per-day on average in the past year) compared to light smokers(<1/2 pack-per-day).

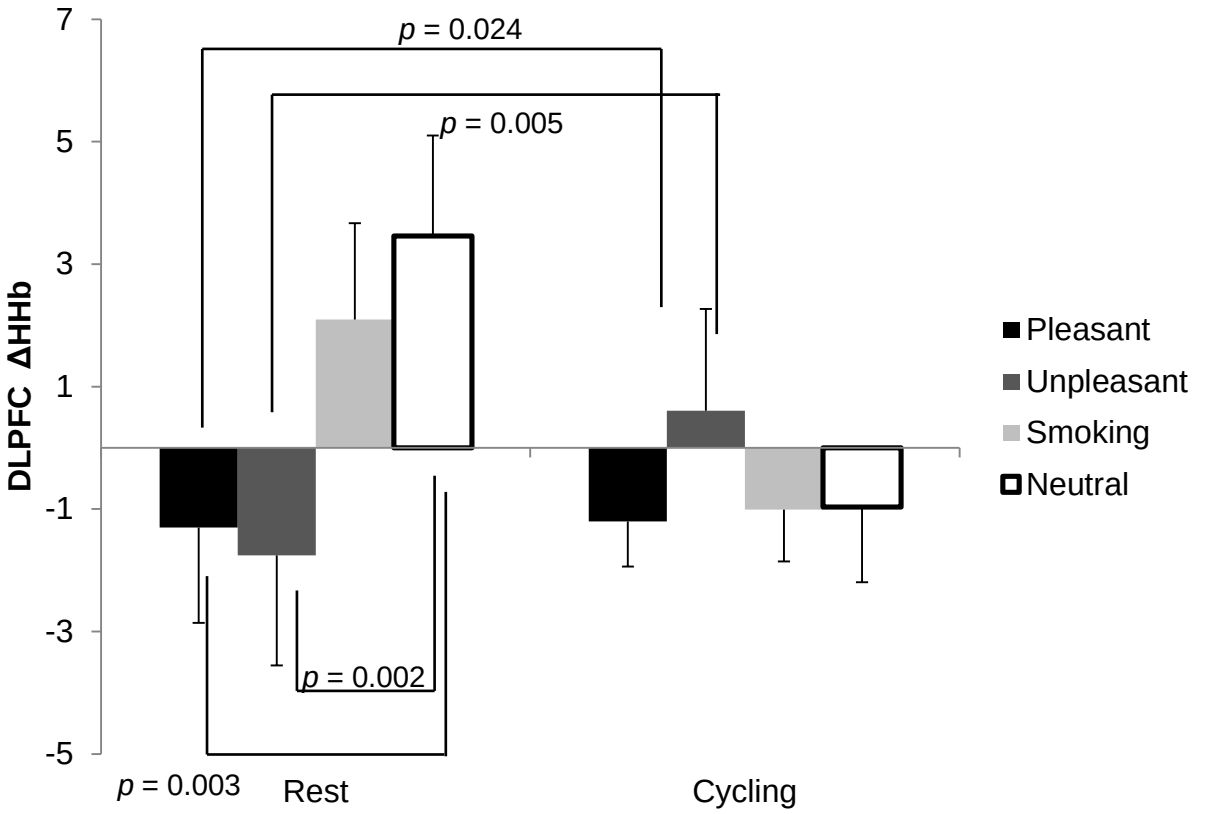

Fig. 3.4 (mean± S.E.) A) Dorsolateral prefrontal cortex (DLPFC) change in deoxygenation (ΔHHb) during seated rest and cycling exercise conditions. Relative to neutral scenes, exercise increased HHb response to pleasant (p=.024) and unpleasant (p=.005) scenes compared to seated rest. Seated rest reduced HHb response to pleasant (p=.003) and unpleasant (p=.002) scenes compared to neutral scenes during seated rest.

CHAPTER 4

EFFECTS OF EXERCISE ON CRAVINGS AND PREFRONTAL BRAIN RESPONSES TO SMOKING CUES IN OVERNIGHT ABSTINENT SMOKERS

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Abstract

Smoking withdrawal is marked by negative affect, feelings of fatigue, and heightened sensitivity to smoking-related cues, making cessation difficult. The dorsolateral prefrontal cortex (DLPFC) integrates affective and incentive salience essential to motivated behavior and is a plausible site of neural effects of exercise on cue-induced cravings during withdrawal. The purpose of this study was to determine the effects of exercise on subjective and DLPFC response to emotional scenes and smoking cues during withdrawal induced by overnight abstinence. Functional near-infrared spectroscopy (fNIRS) was used to measure changes in DLPFC deoxygenated hemoglobin (HHb) in ten cigarette smokers who viewed pictures containing emotional scenes (i.e. pleasant and unpleasant images) and smoking cues 1) during screening in a sated state, 2) at baseline during abstinence, and 3) after seated rest or vigorous-intensity cycling exercise during abstinence. Mood was assessed throughout each visit. Abstinence increased cravings ($p<.01$), reduced bilateral DLPFC HHb response to unpleasant ($p=.05$) scenes, and increased total mood disturbance ($p<.05$) at baseline compared to satiety. Twenty minutes of vigorous intensity exercise increased subjective energy ($p<.01$) and fatigue ($p<.05$) and reduced cravings ($p<.05$) and right-lateralized DLPFC ΔHHb response to smoking cues ($p<.05$). Seventy-two percent of the reduction in craving was explained by increased feelings of energy after exercise, and thirty percent was explained by increased right DLPFC response to smoking cues. We report that cycling exercise attenuated cravings, increased feelings of energy, and increased right DLPFC response to smoking cues in overnight abstinent smokers.

Key words: Cue-induced cravings, Near-infrared spectroscopy, Vigorous intensity cycling

Introduction

Smoking is the leading cause of preventable death in the US (Adhikari et al., 2009; King et al., 2011), and it is projected to account for 10% of deaths worldwide by the year 2020 (World Health Organization, 2010). Numerous studies indicate that health outcomes are improved for cigarette smokers who quit (Anstey, Von Sanden, Salim, & O'Kearney, 2007; Critchley & Capewell, 2003; Lightwood, Fleischmann & Glantz, 2001; Kawachi et al., 1997), yet a quantitative synthesis of 15 studies indicates that less than 5% of those attempting cessation without aid maintain abstinence 6-12 months later (Hughes, Keely, & Naud, 2004). Cessation is difficult because withdrawal enhances sensitivity to emotional stressors, potentiates cravings in response to smoking-related cues, and elicits negative affect which collectively reinforce smoking behavior (Brandon, 1994; Germain, McCarthy, & Wakefield, 2010; Niaura, 2001; Picciotto, Brunzell, & Cadarone, 2002). Pharmacological cessation therapies (e.g. opioid agonists, nicotinic cholinergic partial agonists) have negligible effects on negative affect, but may reduce smoking cue sensitivity during abstinence, although the effect appears to depend upon nicotine availability (Ferguson & Shiffman, 2009; Franklin, 2011; Hughes et al., 2014). Accumulating evidence suggests that exercise elicits acute and transient reductions in withdrawal symptoms (Taylor, Ussher & Faulkner, 2007, Roberts et al., 2012), particularly negative affect and cravings (Bock et al., 1999; Taylor et al., 2006), and may be a useful adjuvant to traditional cessation therapies. Whether post-exercise cravings are related to changes in mood and affect is unclear.

Two different theoretical models explain the development of tobacco abuse through the attribution of withdrawal symptoms to either avoidance or approach processes. The theory of negative reinforcement posits that tobacco dependence develops from a desire to avoid or

ameliorate negative affect that occurs during withdrawal. Multiple lines of research demonstrate that cigarette cravings during withdrawal are related to mood disturbance (i.e. increased fatigue, anxiety, and depression and reduced energy) and negative affect (Baker et al., 2004). Exercise has favorable effects on affect, energy and fatigue, and anxiety in non-smoking populations (Loy et al., 2013; Petruzello et al., 1991; Reed and Ones, 2006). Taylor, Katomeri, and Ussher (2006) were the first to demonstrate that a reduction in self-reported cravings after 20 minutes of walking is mediated by reduced subjective tension-anxiety, yet the effects of exercise appear to be dose-dependent. Nicotine replacement therapy reduces cravings and attentional bias for unpleasant stimuli during overnight abstinence (Gilbert et al., 2007), but the effect of exercise on response to emotionally evocative scenes during withdrawal is as yet unknown. Emotional responsiveness involves parallel activation of top-down and bottom-up neural regulatory processes associated with affective states (Davidson, 2003) like those experienced during withdrawal and (Cinciripini et al., 2006) and after exercise (Crabbe, Smith and Dishman, 2007; Smith, 2013).

The other, more recent theory, recognizes that chronic drug use results in sensitization to pharmacological drug effects and proposes that drug-related cues take on incentive value to become conditioned stimuli. Smoking cues activate appetitive processes and stimulate neural pathways that are chronically activated by smoking (Glautier, 2004; Robinson & Berridge, 1993; Zubieta et al., 2014), while withdrawal potentiates cue-induced craving (e.g. Niaura et al., 1999) and cortico-limbic activation (e.g. McClernon et al., 2009). The prefrontal cortex is essential for emotional regulation and behavioral inhibition in response to salient incentives, processes which are commonly impaired among drug addicts, such as smokers (Goldstein and Volkow, 2011). Converging lines of evidence from affective neuroscience research suggest that lateralized,

hemispheric prefrontal cortex activity represents distinct states of affective arousal (Davidson & Irwin, 1999). Left-hemispheric frontal activity is associated with appetitive motivation and approach behavior, whereas cue-elicited left-lateralized frontal activation is positively correlated with cravings during abstinence (McClernon et al., 2005). Right-hemispheric activity is associated with withdrawal motivation and avoidance behavior, and nicotine administration increases right-lateralized frontal cortex response to smoking cues after overnight abstinence (Gilbert et al., 2007). The dorsolateral prefrontal cortex (DLPFC) is associated with integration of goal-directed information and affective processing, and it plays a putative role regulating sensitivity to smoking cues (Volkow, Fowler, and Wang, 2002; Wilson, 2005). Preliminary evidence suggests that a single session of exercise mitigates DLPFC response to smoking cues (Van Rensburg et al., 2009), but whether reduced sensitivity to smoking cues after exercise is mediated by changes in mood or affective response has not been tested to our knowledge.

Here, we used functional near-infrared spectroscopy (fNIRS) to quantify relative changes in DLPFC deoxygenation in response to pleasant, unpleasant, and smoking cues before and after exercise and seated rest after 15 hours of abstinence. fNIRS has been used to quantify the acute effects of exercise , drug cues, and emotionally evocative stimuli on changes in frontal cortex hemodynamic status. Acute incremental aerobic exercise reliably increases relative concentrations of oxygenated and deoxygenation hemoglobin (Rooks et al., 2010; Tempest et al., 2014). The greatest responses to visual cues have been in response to unpleasant images (Hermann et al., 2003) and highly arousing video clips (Leon-Carrion et al., 2007) with a handful of studies showing significant effects of alcohol cues among alcoholics (e.g. Bunce et al., 2012; Dempsey et al., 2009 We analyzed HHb as an estimate of neurovascular coupling, because it has been negatively correlated with fMRI-BOLD contrasts in a range of tasks (Cui et al., 2011), and

it is less sensitive than HbO_2 to changes in extracerebral blood flow measured over the frontal cortex. We hypothesized that cravings would be reduced after cycling exercise compared to seated rest and that the reduction would be explained, in part, by improved mood, attenuated affective response to emotional scenes, and right-lateralized DLPFC response to smoking cues.

Materials and Methods

Participants. Ten, right-handed smokers participated in the study (3 females, 7 males). An a priori power analysis revealed that 10 participants were needed to detect a large effect of exercise on cue-induced cravings (partial-η^2 ~.14) at a statistical power >.80, and $\alpha < .05$ (Faul et al., 2009). All participants reported smoking $\geq$10 cigarettes per day for at least the last year and $\geq$ 3 hours of moderate physical activity but $\leq$1 hour of vigorous physical activity in the week prior to screening. Use of psychoactive medication, contraindications to exercise (other than smoking), and elevated depressive symptoms or trait anxiety were cause for exclusion. Select participant characteristics are shown in Table 4.1. The study protocol was approved by the institutional review board and all the participants gave written informed consent prior to screening and laboratory data collection after study procedures, risks, and benefits were explained.

Procedures. Participants were asked to refrain from alcohol and caffeine consumption and vigorous exercise for 12 hours preceding each appointment. During the first of three visits to the laboratory, informed consent for participation was obtained and participants completed as series of questionnaires to confirm eligibility. Potential participants completed a Profile of Mood States-Brief Form (POMS-B) to assess feelings of tension-anxiety, depression, fatigue, vigor (energy), and confusion using the response set, “How have you been feeling during the past week, including today” (Curran, Andrykowski & Studts, 1995), a Withdrawal Symptoms Checklist to asses withdrawal symptom magnitude during their last period of abstinence lasting

15 hours or longer (Hughes and Hatsukami, 1986), a Beck Depression Inventory to assess depressive symptoms in the two weeks prior to screening (Beck, Ward & Mendelson, 1961), and a 7-day Physical Activity Recall to assess levels of moderate and vigorous (i.e., hard and very hard) physical activity in the week prior to screening (Blair et al., 1985). This measure of physical activity included occupational activities (e.g. moderate: walking at work/to class, cleaning/sweeping; vigorous: carrying boxes up stairs, constructing/carrying furniture) and leisure time activities (e.g. moderate: walking, washing dishes; vigorous: boxing, resistance training, basketball). Once eligibility was confirmed, participants performed a baseline carbon monoxide breath analysis using a PiCO+ (Smokerlyzer; Haddonfield, NJ) and were familiarized with the protocol and scales used to assess subjective response.

Participants were seated on a Lode Cycle Ergometer (Lode BC, Groningen, The Netherlands) and sat motionless while breathing normally for 5 minutes of baseline rest. Resting blood pressure was assessed using the ausculatory method. Participants viewed a picture show (Presentation 16.2; Neurobehavioral Systems, USA) of four, 1-minute blocks of 12 pictures each. Each block consisted of standardized images representing unpleasant (e.g., fearful, threatening, disgusting), neutral(e.g., household objects, rocks, mushrooms) or pleasant (e.g., erotica, sports scenes, puppies) scenes (International Affective Picture System; Lang, Bradley & Cuthbert, 2008) that were presented in a pseudo-randomized order. At the end of each block participants reported how the images made them feel using an onscreen Self-Assessment Manikin (SAM; Hodes, Cook & Lang, 1985; Lang, 1980). The SAM is a pictographic, 9-point scale that depicts affect along independent continua of valence (i.e., unpleasant to pleasant) and arousal (i.e., arousing to calming). Participants used the keyboard to respond to each SAM scale before they were transported 15 yards outside the laboratory in a wheelchair to smoke a cigarette. The last

block in each picture show contained smoking-related images (International Smoking Image System; Gilbert and Rabinovitch, 1999). After a block of smoking images participants reported cravings using consecutive onscreen single-item scales. First, cravings were assessed by two single-item measures. Participants reported a 'desire to smoke' (DtS) by responding to the statement "I have desire for a cigarette right now" along a 7-point, Likert-like scale (1= strongly disagree, 4=neither agree nor disagree, 7=strongly agree) (Tiffany & Drobes, 1991). Next, participants reported 'strength of desire to smoke' (SoD) along a 7-point scale (1=very weak; 7=very strong) (West, Hajek, & Belcher, 1989). These two items demonstrate validity and reliability, are sensitive to exercise (e.g. Ussher et al., 2001), and are preferred to longer assessments that can obscure true craving measurement (Kozlowski et al., 1996). The participant completed a POMS-B (using the response set, "How are you feeling RIGHT NOW") and was instructed on the procedure for the ramp protocol used for the peak power cycling test.

Participants completed a warm-up on the cycle ergometer for 5 minutes (25 watts). Resistance was increased at a rate of 1 watt every 3 seconds until volitional exhaustion or until the participant was unable to maintain a minimum speed of 60 rpm. Pain, perceived exertion, and ratings of fatigue during exercise were assessed by Borg 6-20 scales (Borg, 1998). Affective valence and arousal in response to picture viewing were assessed by SAM. Participants performed at least 2 minutes of cool down before completing a POMS-B and craving scales (DtS and SoD). Participants were reminded of restrictions for their final two appointments and a return to resting blood pressure was confirmed before leaving the lab.

Participants were asked to abstain from smoking (for 15 hours) and refrain from alcohol and caffeine (for 12 hours) prior to each of their next two appointments. At the beginning of each visit, participants performed a baseline carbon monoxide breath analysis using a PiCO+

(Smokerlyzer; Haddonfield, NJ) to confirm overnight abstinence (CO <10 ppm). Participants reported cravings using DtS and SoD scales, were seated on the Lode cycle ergometer and had their resting blood pressure measured. Participants viewed a slide show, reported affective response using SAM or cravings using DtS and SoD scales, and completed a POMS-B.

Participants completed conditions of 25 minutes of either seated rest or cycling exercise. Cycling exercise began with a 3-minute warm-up and ended with a 2- minute cool down, each at a power output of 25 Watts. Twenty minutes of cycling was performed an intensity corresponding to 60% of peak power achieved during screening. Pain, RPE, and fatigue were assessed after five minutes and fifteen minutes of cycling. Blood pressure was measured after ten minutes of cycling. During the seated rest condition, participants were instructed to sit motionless and breathing normally while seated on the cycle. Order of exercise and rest conditions was randomized across days (*www.randomizer.org*), and participants were not aware of their assigned condition on day 1 until completing the pre-rest or pre-exercise POMS-B. After cycling exercise and seated rest, participants completed a POMS-B prior to viewing a second picture show. There was a 3-minute recovery period during which participants sat resting, motionless, and breathing normally. Participants then completed a final POMS-B.

Heart rate was measured (.2 Hz) during the ramp exercise protocol at screening and exercise and seated rest conditions during abstinence using a Polar 810i heart rate monitor (Polar Electro, Inc., Woodbury, NY). Dorsolateral prefrontal cortex (DLPFC) deoxygenation was measured continuously (10 Hz) using continuous-wave NIRS (OxyMon MKIII, Artinis Medical Systems, Zetten, The Netherlands) operating at 765nm and 857nm in a 4 channel configuration. Continuous-wave near infrared spectroscopy has been described elsewhere (Ferarri, Mottola & Quaresima, 2004); due to an unknown path length, oxygenation is measured as relative change in

the concentration of oxygenated and deoxygenated hemoglobin (HbO_2 and HHb respectively). Optodes were placed over areas approximating F_{p1} and F_{p2} of the international 10-20 system for transcranial measurement using bilateral source-detector distances of 35mm and 50mm which resulted in penetrating depths of ~17.5mm and 25mm respectively according to the modified Beer-Lambert law (Delpy et al., 1988).

Preliminary data analysis. To determine the effects of abstinence on mood, total mood disturbance (TMD) was calculated by summing the raw subscale scores and negatively weighting the vigor subscale. No correction factor was applied, so negative scores were possible.

Heart rate, sampled every 5 seconds and recorded in beats-per-minute, was transferred to Polar Precision Performance Software and exported to Microsoft Excel. 5-minute averages were computed over exercise and seated rest conditions. Individual heart rate reserve was calculated by subtracting the minimum heart rate recorded during seated rest from the maximum achieved during the ramp protocol at screening ($HRR=Max_{ramp}-Min_{rest}$). Percent of heart rate reserve was calculated for each 5-minute period of exercise.

Subject-wise relative HHb concentrations, sampled 10 times per second across a test session (excluding the cigarette smoking period), were entered in NIRS-SPM (Ye et al., 2009) run on Matlab (MathWorks, Natick, MA). A block-design matrix was specified by entering onset times and durations for each picture presentation block creating a series of 8 'boxcar' regressors. These regressors were convolved with the canonical hemodynamic response function (HRF) to model expected response, with time and dispersion derivatives to account for differences previously measured in the prefrontal cortex (Buxton et al., 1998; Friston et al., 1998; Plichta et al., 2007). Overall trends resulting from respiration, vasomotion, and other experimental errors were removed from the DLPFC HHb signal using wavelet minimum description length (Jang et

al., 2009). The resulting signal was entered into the general linear model to obtain beta weights for each regressor to be used as parameter estimates. No correction for serial correlations was applied. These parameter estimates (i.e. HRF, time derivative, dispersion derivative) were combined as orthogonal components to estimate amplitude of the DLPFC hemodynamic response (Calhoun, 2004) and averaged across recording sites within each hemisphere for input into the primary statistical analysis.

Primary statistical analysis. Statistical analysis was performed using SPSS 21.0 (SPSS Inc, Chicago, IL, USA). DLFPC response to cues at baseline between categories were reliable, ICC (2, 3) =.740-.912. A change score was computed for HHb during cycling and rest conditions by subtracting baseline parameter estimates from post-condition estimates (Post-Baseline=ΔHHb).

To test for an effect of overnight abstinence on mood, cravings, and subjective and DLPFC HHB response to emotional and smoking cues, repeated measure analyses of variance (ANOVAs) were computed with condition (screening, cycling, rest) and category (pleasant, unpleasant, smoking, neutral) and hemisphere (left, right) as repeated measures. Planned Helmert contrasts were used to compare abstinent days to screening and simple contrasts were used to compare pleasant, unpleasant and smoking images to neutral images.

To test for an effect of exercise during abstinence on mood, cravings, and affective response to scenes, a series of repeated measure ANOVAs with repeated factors of condition (cycling, rest), time (baseline, post-slideshow, post-condition, resting recovery), and cue category (pleasant, unpleasant, smoking, neutral) were computed. Follow-up repeated measures ANOVAs within each condition and planned simple contrasts were computed to decompose significant interactions. To test for an effect of exercise on DLPFC ΔHHb response to cues,

repeated measures ANOVAs were computed with condition (cycling, rest), category (pleasant, unpleasant, smoking, neutral), and hemisphere (right, left) as repeated measures. Simple effects within each condition and pairwise comparisons were calculated to decompose significant interactions. Bonferroni-correction for multiple comparisons was applied, and Huynh–Feldt adjusted *p*-values were used with epsilon (ε) reported, where appropriate. Effect sizes are reported as partial η^2.

Condition x time repeated measures ANCOVAs also were conducted to determine whether changes in cravings were explained by time-varying mood or DLPFC response to emotional scenes and smoking cues. Reductions in the adjusted F statistic below the critical value (p=.05) and in the size of partial η^2 in the covariate-adjusted, conditional RM-ANCOVA, compared to the unconditional MANOVA model, were interpreted as the covariate accounting for a significant percentage of the change in cravings, i.e., 1 – (conditional η2/ unconditional η2), consistent with standard procedures (Keppel & Wickens, 2004).

Results

Effect of abstinence on mood, cravings, and DLPFC response. Breath carbon monoxide (ppm) was lower after 15 hours of overnight abstinence compared screening, $F(1,9)=10.226$, $\eta^2=.812$, $p=.01$ (mean ± S.D., 7.6 ± 2.7 vs. 15.9 ± 8.5). Abstinence increased ratings of desire to smoke (DtS), $F(1,9)=88.200$, $\eta^2=.907$, $p<.001$, and strength of desire to smoke (SoD), $F(1,9)=16.308$, $\eta^2=.644$, $p=.003$, compared to satiety at screening, and differences between conditions were abolished by exposure to smoking cues during the 1st slideshow (Fig. 4.1a, Fig. 4.1b). Overnight abstinence increased TMD, $F(1,9)=7.273$, $\eta^2=.447$, $p=.025$, compared to a sated condition during screening.

There was a condition x cue category interaction for baseline DLPFC HHb response to slideshow images, $F(6,54)=2.566$, $\eta^2=.222$, $p=.037$, $\varepsilon=.871$. Abstinence reduced baseline DLPFC HHb response to unpleasant scenes, $F(1,9)=4.986$, $\eta^2=.357$, $p=.05$, relative to neutral scenes. Pleasant, $F(1,9)=7.014$, $\eta^2=.438$, $p=.03$ and unpleasant scenes, $F(1,9)=12.090$, $\eta^2=.573$, $p=.007$, were rated as more arousing than neutral scenes. Pleasant scenes were rated as more pleasant, $F(1,9)=10.199$, $\eta^2=.531$, $p=.01$, and unpleasant scenes more unpleasant, $F(1,9)=13.629$, $\eta^2=.602$, $p=.005$, than neutral scenes. Affective ratings of emotional scenes were not different between sated and abstinent conditions ($p>.109$). Thirty percent of increased desire to smoke during abstinence was explained by increased TMD, adjusted $F(2,17)=3.09$, $\eta^2=.266$, $p=.072$.

Subjective and heart rate response to cycling exercise. Cycling for 20 minutes at 60% of the peak power achieved during screening (mean ± S.E.; 204.1 Watts ± 13.69 Watts) increased pain in the lower extremities (mean ± S.E.; 5min=12.2±0.64, 15min=14.3±0.54), $F(1,9)=23.485$, $\eta^2=.723$, $p=.001$, perceived exertion (mean ± S.D.; 5min=13.0±0.54, 15min=14.6±0.56), $F(1,9)=27.429$, $\eta^2=.753$, $p=.001$, and fatigue (mean ± S.D.; 5min=13.1±0.38, 15min=14.4±0.52), $F(1,9)=6.882$, $\eta^2=.433$, $p=.028$. There was a quadratic effect of exercise on increased heart rate, $F(1,9)=78.695$, $\eta^2=.897$, $p=<.001$,(warmup, 5 minutes, 10 minutes, 15 minutes, 20 minutes; % HRR, mean±S.D.; 27.5±5.6, 60.5±9.8, 76.1±8.8, 80.3±9.6, 82.0±10.3).

Effect of exercise on mood, cravings, and response to IAPS and ISIS images. There was a condition x time effect on desire to smoke (DtS), $F(3,27)=4.218$, $\eta^2=.319$, $p=.016$, $\varepsilon=.947$, and strength of desire to smoke (SoD), $F(3,27)=7968$, $\eta^2=.470$, $p=.001$, $\varepsilon=1.000$. Compared to baseline, DtS was reduced after cycling ($p=.05$) (Fig. 4.2a); SoD was reduced after cycling ($p=.015$) and post-cycling smoking cue exposure ($p=.040$) and increased after post-seated rest cue exposure ($p=.05$). There was a condition x time effect on energy, $F(3,27)=10.409$, $\eta^2=.536$,

p=.003, ε=.522, and fatigue, F(3,27)=4.499, η^2=.333, p=.037, ε=.538. Compared to baseline, energy (*p*=.028) and fatigue (*p*=.028) were increased after cycling, and energy was decreased after seated rest (*p*=.025) (Fig.4.2b).

There was a condition x cue category x hemisphere interaction on DLPFC ΔHHb response, F(3,27)=5.641, η^2=.385, p=.004, ε=1.000. In the seated rest condition, right DLPFC ΔHHb response to pleasant cues was reduced compared to the left hemisphere, (*p*=.046), and left DLPFC ΔHHb response to smoking cues was reduced compared to the right hemisphere, (*p*=.030). Cycling exercise decreased right-lateralized DLPFC ΔHHb response to smoking cues, (*p*=.025), compared to seated rest (Fig. 4.3). Affective response to emotional scenes did not differ from baseline or between conditions (*p*<.356)

Thirty-one percent and 72% of reduced DtS in the exercise condition, compared to seated rest, was explained by decreased right-lateralized DLPFC ΔHHb response to smoking cues, adjusted F(3,26)=2.45, η^2=.220, p=.09, and increased feelings of energy, adjusted F(3,26)=.84, η^2=.088, p=.487, respectively.

Discussion

The aim of the study was to determine whether effects of vigorous intensity exercise on mood and cue-elicited responses in dorsolateral pre-frontal cortex (DLPFC) response would explain cravings in smokers who were abstinent overnight. We report that 20 minutes of cycling at a vigorous intensity after ≥15 hours of abstinence reduced desire for a cigarette, and this effect was explained by increased feelings of energy and increased right DLPFC response to smoking cues. Smoking cues are capable of reinforcing smoking behavior during abstinence, and right-lateralized DLPFC activity plausibly represents increased negative affective appraisal (i.e.

avoidance motivations) that manifested as a reduction in cue-induced cravings observed after exercise.

Differential asymmetrical changes in DLPFC response patterns were observed during seated rest and exercise. During seated rest, greater left-lateralized DLPFC response to smoking cues and right-lateralized DLPFC response to pleasant scenes accompanied elevated cue-induced cravings and plausibly represent elevated anhedonia (a common withdrawal symptom) and approach motivations toward smoking cues. Habitual smoking induces chronic neuroadaptation in the dopaminergic and opioidergic pathways between the midbrain and frontal cortex (Xue & Domino, 2003), therefore it is plausible that smoking cues took on incentive value and activated appetitive processes (i.e. "wanting"; Robinson & Berridge, 1993) in a distributed reward network encompassing the mesolimbic dopaminergic system and associated projections to the frontal cortex (Zubieta et al., 2014, David et al., 2005).

Compared to rest, exercise increased right-lateralized DLPFC response to smoking cues which explained 31% of a reduction in cravings. The effect on DLPFC response (Cohen's *dz*=0.84 [95% CI:0.42-1.27]) was moderately large, but considerably smaller than the effect of exercise on DLPFC cue response measured elsewhere using fMRI (Van Rensburg, et al., 2009; Cohen's *d*=3.86) The acute effects of exercise on midbrain dopaminergic transmission are unclear (Wang et al., 2000), but cholinergic receptors, widespread throughout the brain, are upregulated in chronic smokers and enhance the acute effects of nicotine (Perry et al., 1999). Ascending cholinergic pathways terminating in the prefrontal cortex are stimulated during exercise (Woolf & Butcher, 2011) and modulate cortical hemodynamic response (Sato, Sato, & Uchida, 2001) and selective attention (Witte et al., 1997). It is plausible that cholinergically mediated increases in cortical blood flow during exercise increased attention toward smoking

cues thereby eliciting greater right DLPFC response (i.e. withdrawal/avoidance motivations) and reduced cravings. Our findings support evidence that increased craving is related to cue-elicited frontal asymmetry during withdrawal (Knott et al., 2008), and extends preliminary evidence for a neurobiological mechanism underlying the benefits of exercise during withdrawal (Van Rensburg et al., 2009).

Conversely, data collected at baseline during abstinence and screening are consistent with a theory that smoking behavior is maintained through negative reinforcement (Eissenberg, 2004). Compared to screening in a sated state, abstinence elicited greater mood disturbance, greater cravings, and greater DLPFC response to unpleasant cues. Increased bilateral DLPFC response to arousing, unpleasant scenes may be indicative of attentional bias previously demonstrated in during abstinence (Englemann, Gewirtz & Cuthbert, 2011) and consistent with a role of DLFC in affective attention (Ochsner et al., 2009) though fifteen hours of abstinence was not sufficient to alter affective response (i.e. valence and arousal) to emotional scenes. Habitual cigarette smokers depend on smoking to improve affect and cope with daily emotional stressors (Baker, Brandon, and Chassin, 2004; Ikard, Green, and Horn, 1969), and mood disturbance and exposure to unpleasant stimuli are potent elicitors of cravings during withdrawal (Cinciripini et al., 2006, Tiffany & Drobes, 1990).

Twenty minutes of vigorous intensity cycling increased feelings of energy and fatigue, and the increase in energy persisted through post-exercise cue exposure. Previous reports of exercise in smokers insufficiently described or controlled the dose of exercise (i.e. Bock et al., 1999, Daley et al., 2004, Everson, Daley & Ussher, 2006), but we are able to confirm that 20 minutes of cycling at 60% of peak power was a vigorous intensity through subjective responses (i.e. perceived exertion, fatigue, pain) and heart rate response to cycling. As far as we know this

is the first report of cravings and mood after a public-health dose (i.e. ≥ 20 minutes at moderate-to-vigorous intensity) of exercise, which is recommended for other salutary effects of exercise (Physical Activity Guidelines Advisory Committee, 2008).

The results reported here extend previous research that used exercise as method for attenuating withdrawal symptoms in overnight abstinent smokers (Taylor, Ussher, & Faulkner, 2007). The lack of an effect of exercise on affective response to standardized images is consistent with other reports from our lab (Crabbe, Smith & Dishman, 2007; Smith & O'Connor, 2003; Smith et al., 2002). Compared to seated rest, exercise resulted in large reductions in desire to smoke (Cohen's *dz*=0.79 [95% CI:0.37-1.22]) and strength of desire to smoke (Cohen's *dz*=1.60 [95% CI:1.08-2.12]) . These acute effects are comparable to the effect of month of bupropion treatment on cue induced cravings after participants were primed to resist cravings (Culbertson et al., 2011; Cohen's *dz*=1.57[95% CI:1.23-1.91]) and greater than the acute effect of nicotine gum on cue induced cravings (Shiffman et al., 2003; Cohen's *dz*=0.087[95% CI:0.07-0.10]. Acute craving reductions were transient, only lasting for 10 minutes after exercise ended, which suggests that repeated, short bouts of exercise might be performed throughout the day to maximize temporal proximity to cues that may trigger cravings and relapse. A light-intensity bout of cycling or walking might be more easily performed, and lighter doses of exercise have been demonstrated to blunt cravings through a reduction in anxiety (Taylor et al., 2006) and by attenuating the positive valuation of smoking cues (Kurti & Dallery, 2014).

In summary, withdrawal experience during seated rest was marked by increased approach motivations (i.e. greater left-lateralized DLPFC activity) in response to smoking cues and withdrawal motivations (i.e. greater right-lateralized DLPFC activity) in response to pleasant cues. Twenty minutes of vigorous intensity cycling exercise elicited a reduction in cravings that

were partially explained by increased feelings of energy and right-lateralized DLPFC response to smoking cues. These initial findings encourage future research that elaborates whether improved mood and lateralized prefrontal cortex cue response after exercise might explain attenuated withdrawal symptoms. This is the first study, to our knowledge, to demonstrate that reduced cravings after vigorous intensity exercise are sustained during exposure to smoking cues. Future trials should manipulate exercise mode and intensity, include alternate control conditions (i.e. nicotine replacement, smoking a cigarette), and involve longitudinal designs among smokers attempting to achieve cessation.

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Table 4.1 Participant Characteristics

Characteristic	**Participants (*n*=10)**
Age (years)	22.9±2.2
BMI (kg/m^2)	22.1±3.8
Withdrawal Symptom Checklist *(Range: 0-36)*	13.5±3.2
Annual smoking (cigarettes/week)	88±22.2
Total Mood Disturbance at Screening (POMS-B) *(mean±SD*: *38.2±25.0)*	9.8±11.6
Baseline Depression (BDI-II) *(mean±SD*: *22.1±11.2)*[1]	9.1±5.7

BMI is Quetelet body mass index; Values are given as mean ± S.D. and normative values are given in italics where appropriate.

[1]Buckley, Parker & Heggie (2001)

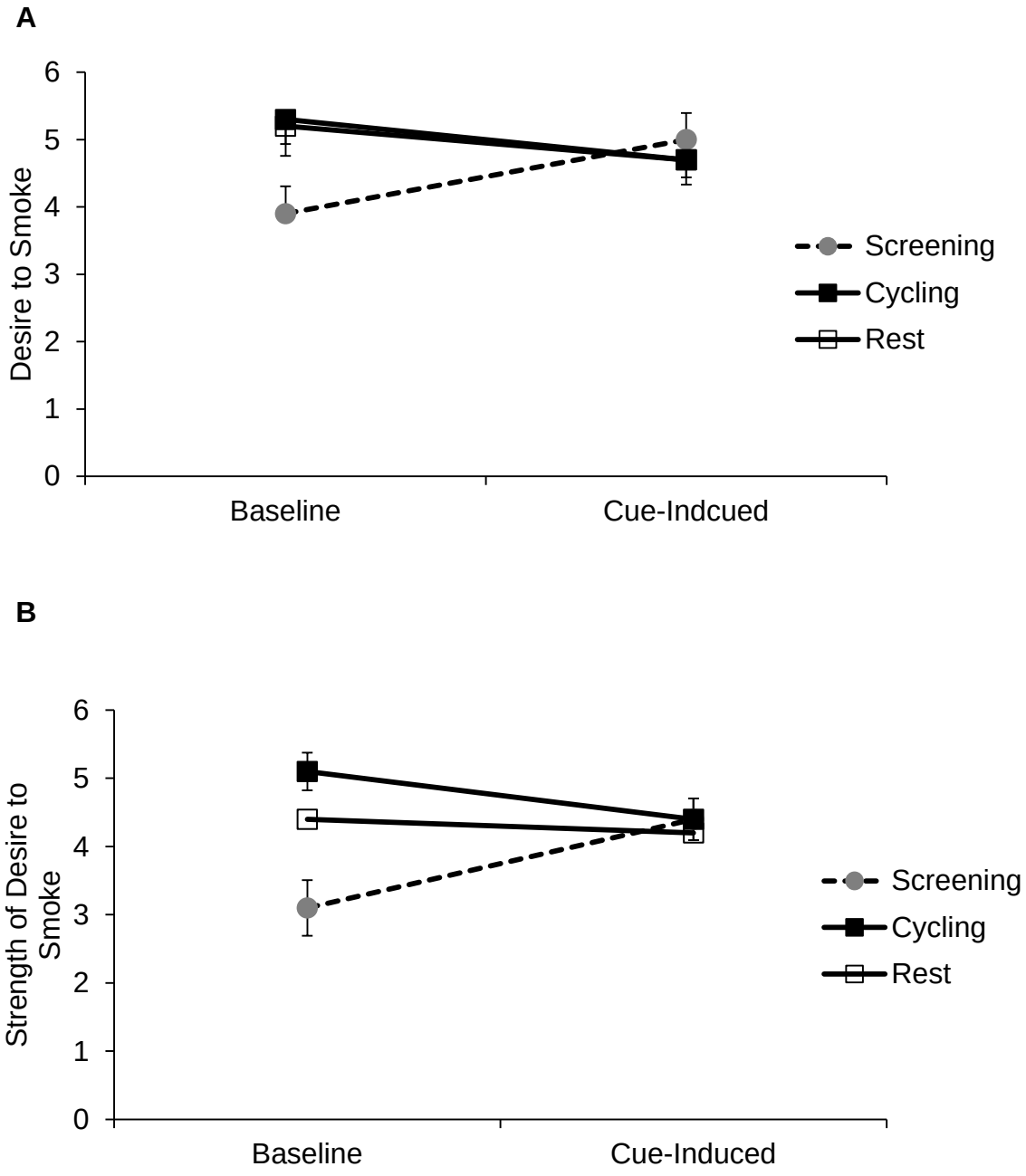

Fig. 4.1 (mean± S.E.) Scores on A) desire to smoke and B) strength of desire to smoke craving scales at baseline and after the 1st slideshow across conditions. Cravings were greater during abstinence (i.e. exercise and seated rest conditions) than during satiety (i.e. screening), but ratings were normalized after the 1st slideshow.

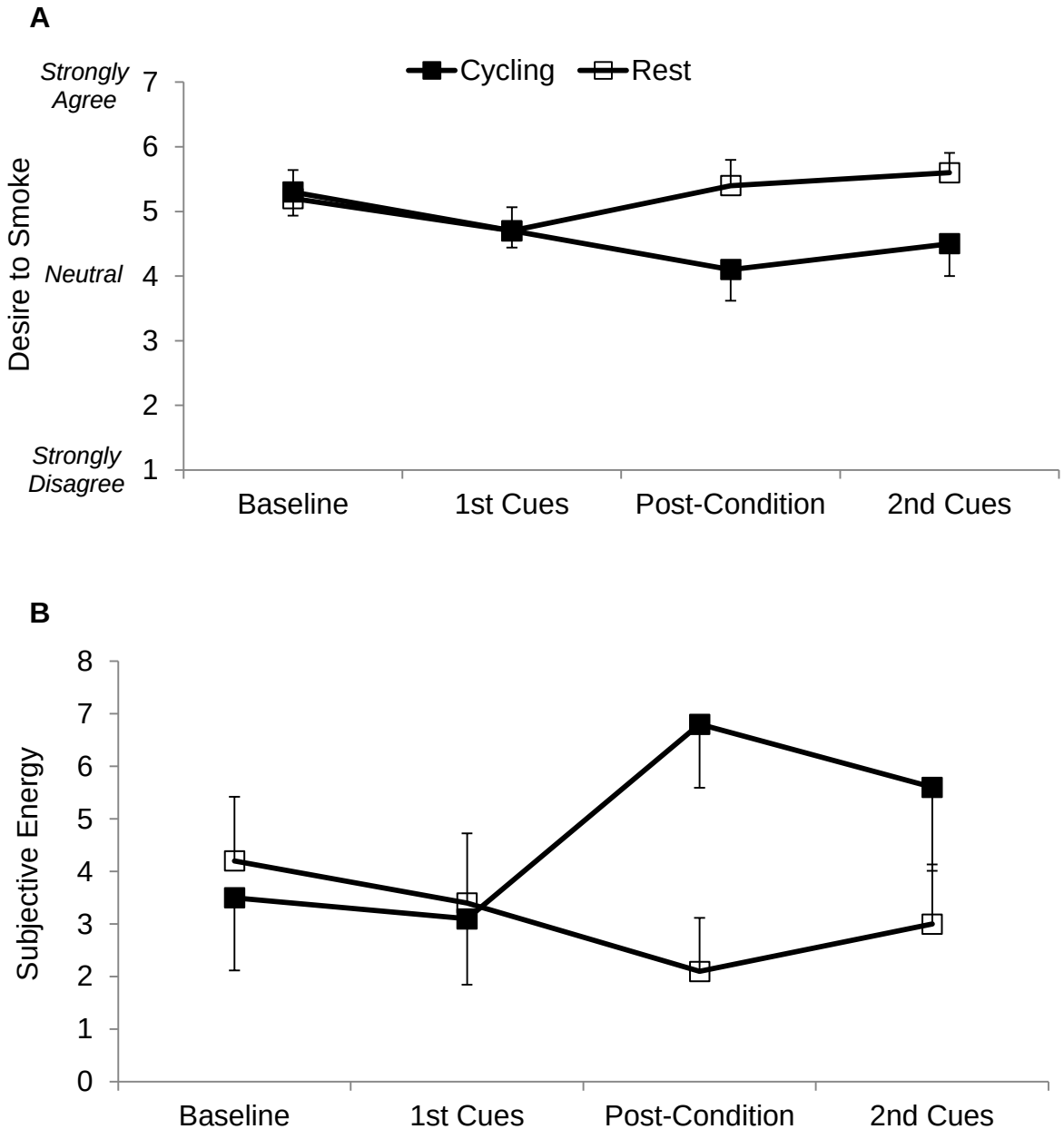

Fig. 4.2 (mean± S.E.) Scores on A) desire to smoke scale and B) vigor (energy) of the Profile of Mood States-Brief (POMS-B) during exercise and seated rest test sessions. Desire to smoke was reduced after cycling compared to seated rest. Subjective energy was increased immediately after exercise compared to seated rest.

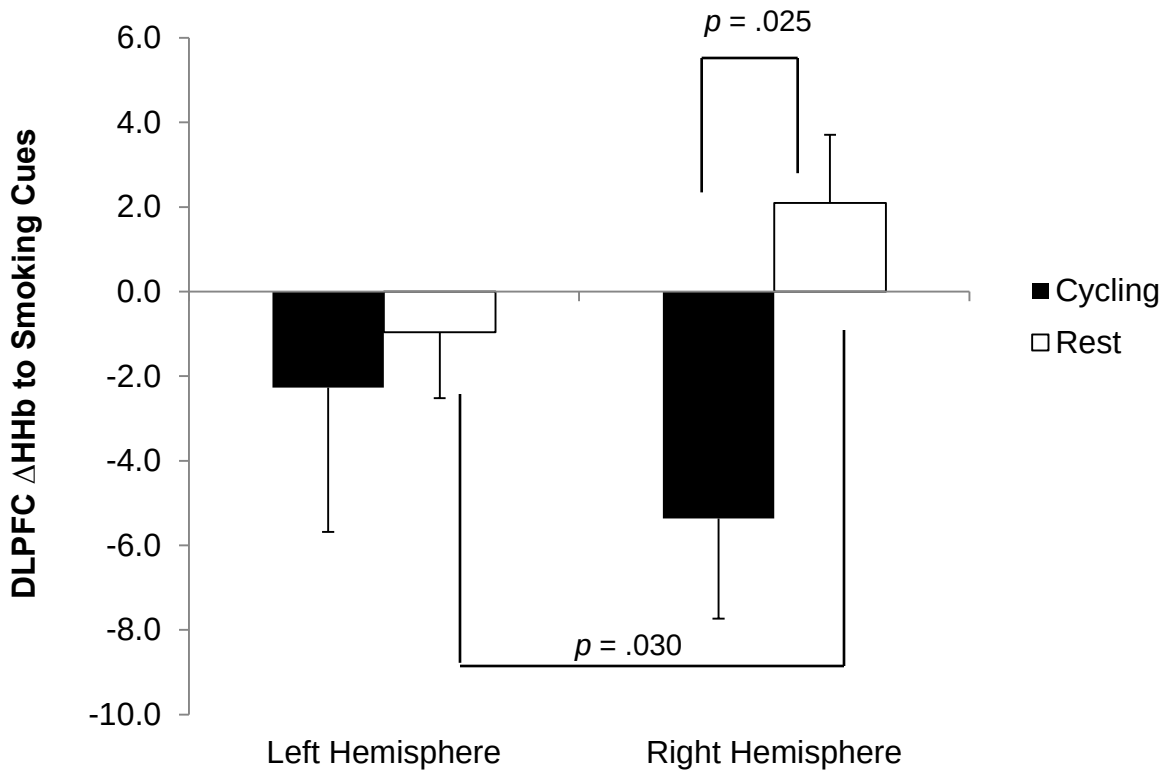

Fig. 4.3 (mean± S.E.) Dorsolateral prefrontal cortex (DLPFC) change in deoxygenation (ΔHHb) during seated rest and cycling exercise conditions. Exercise decreased right hemisphere HHb response to smoking cues (p=.025). During rest, there was a greater reduction in left DLPFC response to smoking cues than in the right DLPFC (p=.030)

CHAPTER 5

SUMMARY

As a primary risk-factor for cardiovascular and cancer mortality, cigarette smoking is a leading cause of preventable death and a burden on public health worldwide. Smoking cessation interventions have modest long-term success due in part to undesirable side-effects from pharmacotherapies and poor adherence. Exercise is a putative adjuvant to smoking therapies as a method to reduce primary and secondary symptoms and attenuate cravings. Despite a handful of studies that promote the benefits of exercise among smokers, the evidence for physical activity interventions to improve cessation and reduce risk of relapse is weak in part due to a poor understanding of the acute effects of exercise. This dissertation sought to elucidate the relationship between acute improvements in mood and reduced cravings elicited by exercise and examine a role of the dorsolateral prefrontal cortex (DLPFC) in regulating sensitivity to emotional scenes and cigarette cues.

The aims of the first study were to determine whether i) smoking a cigarette improved mood and altered affective responding to emotional scenes, ii) changes elicited by a cigarette were sustained by cycling exercise, iii) response to emotional scenes and smoking cues could be measured by dorsolateral prefrontal cortex (DLPFC) deoxygenation, iv) changes in mood and affective response to emotional scenes predicted DLFPC response to smoking cues.

The results suggest that, regardless of smoking status, cycling at a self-selected intensity after smoking improves subjective energy and confers a protective effect against heightened anger and elevated DLPFC response to emotionally arousing scenes that occurred during seated rest. This may be clinically important for individuals who desire to quit. Smokers who are physically

active prior to quitting are more likely to maintain abstinence, and our findings suggest that a single bout of exercise in this population may also be immediately beneficial by reducing mood states may drive some to their next cigarette.

The aims of the second study were to determine whether i) mood disturbance elicited by 15 hours of abstinence explained increased cravings, ii) twenty minutes of vigorous intensity cycling exercise in an abstained state was capable of improving mood and affective response while reducing cravings, iii) changes in cravings were explained by changes in mood or DLPFC response to smoking cues. Results from the second study indicate that cravings, DLPFC sensitivity to unpleasant scenes, and total mood disturbance were increased during abstinence. Vigorous intensity cycling exercise resulted in a transient reduction in cravings compared to seated rest, and the effect was explained by increased feelings of energy and right DLPFC response to smoking cues. This is the first study to quantify the contribution of mood disturbance to cravings between a sated state and short-term abstinence, and our data suggest this relationship is important in understanding the benefits of exercise during withdrawal.

Collectively, these results suggest that DLPFC sensitivity to emotional scenes is altered within 30 minutes of smoking a cigarette and after overnight abstinence, that exercise acutely blunts DLPFC sensitivity to salient cues, and that fNIRS is useful for detecting these effects. The prefrontal cortex is a heterogeneous cortical region highly incorporated into diverse neural networks and behavioral processes. The involvement of the prefrontal cortex in addiction and motivational states has commonly been associated with dopaminergic pathways from the midbrain, and traditional pharmacological cessation aids (i.e. atypical antidepressants) were prescribed to smokers in order to achieve allostasis in these pathways. It is also possible that these effects are due to disrupted cholinergic signaling. Cholinergic receptors are diffuse

throughout the brain, and those localized in pathways to the frontal cortex are important for reward and arousal. In smokers, chronic nicotine administration increases receptor density which leads to tolerance and contributes to withdrawal. Cholinergic receptors modulate cortical blood flow during exercise, therefore it is plausible that the effects of exercise on DLPFC sensitivity are due to cholinergic-mediated increases in blood flow. Future investigations seeking to understand the mechanisms by which exercise is beneficial for smokers should use strong inference models to examine these pathways and assess other regions of the prefrontal cortex. Likewise, researchers using fNIRS to assess cognitive performance and response to sensory stimuli should carefully consider optode placement. Previous multi-channel trials have been able to produce 'heat maps' by maximizing optode density over the frontal cortex. We have demonstrated effects using 4 channels in a linear configuration. Future use of multi-channel devices might seek to compare specific, hypothesis-driven regions to other, non-adjacent integrated regions (i.e. occipital cortex) or regions where minimal hemodynamic change is expected (i.e. motor cortex).

Considering the acute, transient effects exercise, smokers wishing to quit may be best served by repeated, short bouts of exercise to protect against negative mood states, sensitivity to emotional stressors, and cravings that all increase the risk of relapse. Future interventions might target smokers with low levels of occupational physical activity to determine whether brief bouts of activity interspersed throughout the workday, and eventually replacing 'smoke breaks', are beneficial in improving cessation outcomes. Adolescents, more than other groups, are at a high-risk of developing smoking habits and tobacco use disorder. Therefore, prospective cohorts or controlled trials could be used to determine whether physical activity offers a protective effect against the initial reinforcement of smoking behavior.

The effects of exercise seen here after smoking a cigarette or during overnight abstinence extend prior evidence that has suggested palliative benefits of exercise in smokers who plan to quit or who experience withdrawal symptoms during attempts at cessation. The results also have theoretical implications for understanding the neural and cognitive substrates of cravings in cigarette smokers that warrant further investigation. Our findings bolster evidence that exercise might be effectively used to augment other cessation therapies in order to manage mood and reduce the urge to smoke.