SELF-FOCUSED VERSUS OTHER-FOCUSED COGNITIVE STRATEGIES FOR COPING WITH SMOKING CUE EXPOSURE: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY

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The ability to cope effectively during high-risk situations (e.g., exposure to drug-related stimuli during acute withdrawal) is essential for forestalling relapse during attempts to quit problematic substance use. Attempting to exert executive cognitive control over affective reactions is a frequently employed strategy for managing temptation and sustaining cessation. Such attempts are not failsafe, however, with many individuals succumbing to temptation despite reporting the use of cognitive coping strategies. The reasons for such failure, as well as for the observation that the efficacy of coping varies significantly both within and between individuals, remain largely unknown. The goal of the present study was to address this important knowledge gap by investigating the mechanisms underlying cognitive coping in cigarette smokers, with two specific aims. The first aim was to examine the neural correlates of the use of two different forms of cognitive coping during drug cue exposure, with the prediction that the use of a non-self-referential strategy would be associated with relatively greater activation of the DLPFC than a strategy that entails the use of self-referential information. In contrast, it was hypothesized that a strategy that involves the generation and maintenance of self-relevant information would be associated with comparatively greater activation of portions of the anterior medial prefrontal cortex than a strategy in which the focus is on non-self-referential information. The second aim

of the study was to examine whether non-self-referential and self-referential coping strategies are differentially moderated by individual differences in working memory capacity, with the hypothesis that working memory ability would more strongly predict the magnitude of cue-elicited activation of the DLPFC during the use of a non-self-referential coping strategy than during the use of a self-referential coping strategy. Findings suggest non-self-referential and self-referential coping indeed are associated with different patterns of neural activation during cue exposure, although the specific relationships that were observed proved to be more complex than initially hypothesized. In contrast to expectations, however, working memory capacity did not differentially moderate the activation of the DLPFC and measures of cue-reactivity. Potential implications and extensions of these findings are discussed.

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1.0 INTRODUCTION

Cigarette smoking remains one of the leading preventable causes of death and disease in the world (World Health Organization, 2008). This fact is not lost on smokers, millions of whom attempt to quit each year. Unfortunately, however, the vast majority of these attempts end in relapse (Brandon, Vidrine, & Litvin, 2007; Piasecki, 2006). Recent estimates suggest that more than 95% of individuals who attempt to quit smoking without seeking treatment relapse within one year (Hughes, Keely, & Naud, 2004). Relapse rates remain high even for those who receive intense pharmacological and/or psychosocial interventions during a cessation attempt, with an estimated 70% or more of such individuals returning to smoking within one year (Piasecki, 2006). Clearly, developing an understanding of the variables that contribute to relapse, as well as how relapse may be prevented, is a research priority.

It has become increasingly clear that relapse to smoking is a dynamic process that is influenced by a variety of factors (Piasecki, 2006; Piasecki, Fiore, McCarthy, & Baker, 2002; Shiffman, 2005). The cognitive-behavioral model advanced by Marlatt and colleagues (1985) has been particularly influential for understanding the complex nature of relapse. According to this framework, a variety of interpersonal and intrapersonal conditions can serve as precipitants to a relapse crisis (a situation in which one is tempted to use drugs). The probability that such high-risk situations will lead to drug use and eventual relapse is determined by the responses enacted during the episode. Specifically, the degree to which effective coping is implemented is

thought to be the most critical determinant of outcomes during high-risk situations. Within the domain of smoking cessation, coping may be defined as the utilization of overt (behavioral) and/or covert (cognitive) activities for the purpose of preventing smoking (Marlatt & Gordon, 1985; Wills & Shiffman, 1985).

While counterevidence exists for certain aspects of the cognitive-behavioral model (e.g., Shiffman, Hickcox et al., 1996; Shiffman, Hickcox, Paty, Gnys, Kassel et al., 1997), the idea that effective coping is critical for preventing relapse to smoking has received considerable support (Abrams et al., 1987; Baer, Karmack, Lichtenstein, & Ransom, 1989; Bliss, Garvey, Heinold, & Hitchcock, 1989; Bliss, Garvey, & Ward, 1999; Curry & Marlatt, 1985; Evans & Lane, 1981; Glasgow, Klesges, Mizes, & Pechacek, 1985; Hall, Rugg, Tunstall, & Jones, 1984; Shiffman, 1982, 1984; Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996; Stevens & Hollis, 1989; van Osch, Lechner, Reubsaet, Wigger, & de Vries, 2007). The University of Pittsburgh Smoking Relapse Study conducted by Shiffman and colleagues has provided particularly informative data regarding coping during attempted smoking cessation (for a descriptive summary of the study, see Shiffman, 2005). In this observational study, 300 smokers were asked to carry palmtop computers upon which they recorded various aspects of their experience for up to four weeks after initiating a quit attempt. Most relevant to the current research, participants provided data regarding their thoughts, feelings, and behavior during relapse crises after such episodes had concluded. In one paper derived from this dataset, Shiffman and colleagues (1996) examined features that distinguished relapse crises in which participants successfully refrained from smoking (referred to as temptations) from those in which participants smoked (referred to as lapses). In support of the idea that coping substantially reduces the likelihood of relapse, they

found that smokers who reported that they had attempted coping during a relapse crisis were 12 times more likely to have refrained from smoking than were those who did not report coping.

Results from the study indicated that cognitively-oriented coping strategies (e.g., thinking about the health and financial consequences of smoking) were often employed and frequently effective, with participants reporting using such techniques in 94% of episodes in which they had successfully resisted the temptation to smoke (Shiffman et al., 1996). Moreover, cognitive coping appeared to be superior to behavioral coping (e.g., consuming food and/or drink), with only the former category predicting the outcome of relapse crises. Other findings from studies conducted by Shiffman (1982, 1985, 1986) suggest that cognitively-oriented coping is more flexible and less susceptible to situational factors (e.g., affective state) than behavioral coping. Thus, among the various strategies that may be used to cope with temptation, cognitive techniques may have a uniquely important role in preventing relapse to smoking. Indeed, there is evidence that cognitive coping is preferred over behavioral coping by those who have successfully quit smoking (Shiffman, 1985).

Cognitive coping does not appear, however, to be a panacea. Shiffman and colleagues (1996) found that participants reported engaging in cognitive coping in 69% of the relapse crises in which they succumbed to temptation and smoked. Little is known about why cognitive coping seemingly fails in such a surprisingly large number of high-risk situations. Similarly, important questions remain about why certain individuals are more effective at utilizing cognitive coping strategies than are others. For instance, Shiffman and coworkers (1997) found that smokers who relapsed following a quit attempt reported a very similar pattern of coping activity as did those who successfully maintained abstinence, suggesting that at least some variability in outcomes is

driven by differences in the efficiency of coping. To date, research has provided exiguous insight into when and for whom coping will succeed.

The overarching objective of the current research was to shed light on the nature of intra- and inter-individual variance in cognitive coping efficacy. The present study was guided by a conceptual framework drawn from the affective and cognitive neurosciences, in which cognitive coping is viewed as a form of executive control mediated by regions of the prefrontal cortex. In the sections that follow, I briefly review research indicating that exposure to smoking-related stimuli, or smoking cues, elicits in cigarette smokers responses that increase the likelihood of relapse. I then outline a neurocognitive model of emotion regulation and its relation to cognitive coping during smoking cue exposure. Next, I discuss constraints associated with the regulatory resources supporting cognitive coping and the implications that such limitations have for understanding why coping often fails in the presence of drug-related stimuli. Finally, I present a functional magnetic resonance imaging (fMRI) study designed to characterize the relationship between brain responses and measures from a multidimensional assessment of cue reactivity in motivationally-conflicted individuals attempting to engage in cognitive coping during exposure to smoking cues.

1.1 SMOKING CUE EXPOSURE AND RELAPSE

Several prominent models of addiction hold that drug-related stimuli play an important role in the development and maintenance of addictive behavior (for a review of such models, see Drummond, 2000; Niaura et al., 1988; Rohsenow, Niaura, Childress, Abrams, & et al., 1990). Consistent with this view, there is strong naturalistic evidence that cigarette smokers are

vulnerable to relapse in the presence of smoking cues (Marlatt & Gordon, 1985; Shiffman, 1982; Shiffman et al., 1996). In order to better understand the relationship between drug cues and relapse, researchers have sought to elucidate the nature of cue-elicited responses in the laboratory under controlled conditions. The cue reactivity paradigm, which entails exposing substance users to drug cues in order to elicit and measure concomitant changes in one or more response systems (e.g., self-reported urge, cognitive task performance), has been among the most prominent methods used in the study of drug addiction for the past several decades (Drummond, 2000).

Cue reactivity research has demonstrated that cigarette smokers exhibit robust affective, cognitive, and physiological responses when presented with smoking cues (Carter & Tiffany, 1999; Wilson, Sayette, & Fiez, 2004). Importantly, many of these reactions have been linked to relapse. For instance, studies have established a relationship between changes in heart rate during smoking cue exposure and the outcomes of cessation attempts (Abrams, Monti, Carey, Pinto, & Jacobus, 1988; Erickson, Tiffany, Martin, & Baker, 1983; Niaura, Abrams, Demuth, Pinto, & Monti, 1989; Payne, Smith, Adams, & Diefenbach, 2006). Based upon the observation that subsequent poor outcomes were associated with a sharp cue-elicited deceleration in heart rate, Niaura and colleagues (1989) speculated that those who ultimately were less successful at quitting smoking (i.e., those who would go on to relapse) paid more attention to smoking cues than did those who would go on to successfully quit, while the latter may have allocated attentional resources to "internal cognitive processes" (e.g., coping with the temptation to smoke). In accord with this general idea, Waters and colleagues (2003) found that the magnitude of attentional bias that smokers exhibited for smoking-related stimuli predicted the likelihood that they would relapse early during a quit attempt.

There is less laboratory-based evidence directly linking cue-elicited changes in affect to relapse in smokers. Nonetheless, it has been argued that drug cues contribute to relapse in large part because they elicit an affective state that serves to promote drug use (Baker, Morse, & Sherman, 1986; Sayette, 2004). More specifically, under many conditions, drug cues reliably evoke in addicted individuals a strong urge or craving to use drugs (Carter & Tiffany, 1999). Observational data suggest that the state of craving plays a role in relapse to smoking (Allen, Bade, Hatsukami, & Center, 2008; Bagot, Heishman, & Moolchan, 2007; Killen & Fortmann, 1997; Shiffman, Engberg et al., 1997). Moreover, recent data suggest that coping reduces the probability of relapse to smoking in high-risk situations by reducing craving (O'Connell, Hosein, Schwartz, & Leibowitz, 2007). Indeed, O'Connell and colleagues (2007) observed a "dose-response" relationship between coping and craving, such that endorsing the use of a greater number of coping strategies was associated with a larger reduction in self-reported urge to smoke during temptation episodes.

Resisting the temptation to smoke during cue exposure thus appears to be related to both the ability to shift attention away from smoking-related stimuli and the ability to attenuate cue-induced craving. In fact, it is likely that these capabilities are interrelated (Franken, 2003; A. J. Waters et al., 2004). Accordingly, contemporary theoretical models of emotion regulation, which point towards a role for fundamental attentional and mnemonic processes in the modulation of emotional states (Gross, 1998b; Ochsner & Gross, 2007), provide a useful framework for generating hypotheses regarding the mechanisms that might play an important role in coping with cue-elicited responses.

1.2 EMOTION REGULATION VIA EXECUTIVE CONTROL

The model of emotion generation and regulation advanced by Gross (1998a, 1998b) is a particularly applicable starting point for thinking about the process of coping with responses to drug cues. This conceptualization, which incorporates several prominent theories of emotion, holds that the experience of emotion begins with an evaluation of external or internal emotion cues. The evaluation of these cues triggers a coordinated set of behavioral, experiential, and physiological emotional response tendencies. Importantly, these emotional response tendencies, and the actual responses to which they subsequently give rise, are subject to modification. Thus, individuals are able to exert a great deal of control over the manner in which they respond to evocative stimuli. Applying this framework to the domain of smoking cue reactivity, the nature and intensity of the responses evoked by smoking cues may be viewed as alterable by intervening coping processes.

Affective neuroscience research has begun to identify the neurocognitive mechanisms that support cognitively-oriented emotion regulation. This work suggests that the cognitive modulation of affect relies upon systems that support other "cold" forms of executive control, including those involved in selective attention and the maintenance and manipulation of information in working memory (Davidson & Irwin, 1999; Hariri, Bookheimer, & Mazziotta, 2000; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Ochsner & Gross, 2007). According to such perspectives, executive control over emotion is viewed as a phenomenon emergent from interactions between regions of the prefrontal cortex that implement domain-general control processes and other cortical and subcortical regions that are involved in domain-specific affective processes (e.g., appraisal of the affective significance of a stimulus). In particular, certain forms of cognitively-oriented emotion regulation appear to rely in part upon the processes

supported by the dorsolateral prefrontal cortex (DLPFC), a subregion of the prefrontal cortex that has been strongly linked to executive control (Anderson & Tranel, 2002; Fuster, 1997).

1.2.1 Key properties of DLPFC functioning.

Converging evidence suggests that the DLPFC is a region important for the active maintenance of internally represented context information and the biasing of processing in other regions in accordance with these representations (e.g., Courtney, 2004; J. Duncan, 2001; Funahashi, 2001; Kane & Engle, 2002; E. K. Miller & Cohen, 2001; W. Schneider & Chein, 2003). Context information is broadly defined to include diverse types of representations including specific stimulus features, information about task demands or rules, plans for action, or goals and the means to achieve them. Thus, under ordinary circumstances, the DLPFC exerts a modulatory effect on the activity of other regions and serves to guide processing along task-relevant or goal-relevant processing pathways. Supporting this idea, findings from neurophysiological and neuroimaging research suggest that activation in the DLPFC serves to modulate the processing in regions to which it is connected and, importantly, the nature of this influence exhibits dynamic changes as a function of task demands (Funahashi, 2001). Moreover, the control-related processes mediated by the DLPFC appear to be particularly important in the face of interference, such as when it is necessary to prevent attentional focus from being captured by mental or environmental distracters (Kane & Engle, 2002).

Several characteristics of the DLPFC make the region uniquely suited for regulating information processing via active maintenance. Most importantly, extensive neurophysiological studies conducted with nonhuman primates demonstrate that the DLPFC is capable of supporting the representation of task- or goal-relevant information over time. For instance, studies have

shown that DLPFC neurons are able to maintain representations associated with specific stimulus features (e.g., stimulus identity or spatial location; Fuster, 1997). Moreover, DLPFC neurons also encode more complex information, such as the abstract rules governing behavior in a given context (Asaad, Rainer, & Miller, 1998; Ferrera, Cohen, & Lee, 1999), the outcomes associated with response options (Hikosaka & Watanabe, 2000; Leon & Shadlen, 1999; Wallis & Miller, 2003), and complex conjunctions of such information (Asaad et al., 1998; Barone & Joseph, 1989). Functional neuroimaging studies have confirmed that the DLPFC exhibits similar functional properties in humans (Kane & Engle, 2002; Krawczyk, 2002; Pochon et al., 2001; Wager & Smith, 2003).

Many cortical regions exhibit sustained activation over a delay. For instance, neurons in both inferior temporal (E. K. Miller, Li, & Desimone, 1993) and posterior parietal cortices (Constantinidis & Steinmetz, 1996) remain active over brief intervals. However, activation in each of these regions is disrupted by the presentation of intervening stimuli during the delay (the activation in such regions thus reflects the most recent sensory input). In contrast, studies in both nonhuman primates (E. K. Miller, Erickson, & Desimone, 1996) and humans (Sakai, Rowe, & Passingham, 2002) have demonstrated that the DLPFC exhibits distracter-resistant maintenance of task-relevant information. Thus, the DLPFC is well-suited for supporting executive control functions, which depend upon the ability to robustly maintain representations in the face of competing or distracting information.

Additionally, research suggests that the DLPFC is capable of dynamically updating representations in response to changing demands, a property necessary for the effective implementation of flexible cognitive control. Although much remains unknown about how such updating is achieved, recent theoretical work has put forth the idea that the mesocortical

dopamine system may play an important role in the process. Specifically, Cohen and colleagues (Braver & Cohen, 2000; Cohen, Braver, & Brown, 2002; Montague, Hyman, & Cohen, 2004) have suggested that the phasic response of dopaminergic projections from the ventral tegmentum area to the prefrontal cortex alters the responsivity of the DLPFC to afferent signals. In the absence of this phasic response, DLPFC neurons exhibit only transient activation in response to input from other regions. However, when such input is coupled with a phasic dopaminergic response, the DLPFC exhibits sustained firing and the active maintenance of representations.

Thus, the mesocortical dopamine system is thought to 'gate' access to the DLPFC. This perspective has strong links to the notion of a phasic prediction error signal in reinforcement learning theory (Schultz & Dickinson, 2000; Sutton & Barto, 1990), affording the additional benefit of providing a plausible explanation for self-organization within the DLPFC (Braver & Cohen, 2000). That is, the phasic response of DA neurons will, through experience, become associated with those stimuli that are the most salient and behaviorally-relevant (e.g., stimuli predicting the availability of food). As a natural consequence, the PFC will be most sensitive to updating in the presence of the stimulus events most relevant for guiding behavior.

Finally, anatomical studies indicate that the DLPFC is well-suited for integrating information from and modulating the activity of a diverse set of brain regions. The DLPFC is reciprocally connected with regions of parietal, occipital, temporal, premotor, orbitofrontal, and anterior cingulate cortices (Barbas, 2000; Groenewegen & Uylings, 2000; E. K. Miller & Cohen, 2001; Petrides & Pandya, 2002). This rich pattern of connectivity places the DLPFC in position to affect the processing of regions supporting numerous cognitive and affective functions (e.g., auditory, visuospatial, and somatosensory processing, attentional allocation, motor planning, memory retrieval, reward-related processing).

1.2.2 Intentional conflict and cue-elicited activation of the DLPFC.

Based upon a review of the neuroimaging cue reactivity literature, my colleagues and I recently have proposed that the functions supported by the DLPFC may play an important role in the regulation of cue-elicited affective responses (Wilson, Sayette et al., 2004; Wilson, Sayette, & Fiez, 2007). Cue-elicited activation of the DLPFC is commonly observed in active users who presumably anticipate an opportunity to use drugs shortly following experimental participation (McBride, Barrett, Kelly, Aw, & Dagher, 2006; Wilson, Sayette, Delgado, & Fiez, 2005; Wilson, Sayette et al., 2004). In contrast, cue exposure typically does not increase activation of the DLPFC in active users who anticipate an opportunity to use drugs directly following (i.e., a matter of seconds after) the presentation of drug cues (Wilson et al., 2005). Neither does the DLPFC seem to respond to drug cues in addicts who are attempting to quit drug use and who probably do not anticipate having an opportunity to consume drugs shortly following cue exposure (Wilson, Sayette et al., 2004).

We have suggested that this pattern may shed light on the nature of cue-elicited activation of the DLPFC and speculated that the region may respond to drug cues when there is a need to engage in controlled processing (e.g., when drug use intentions and perceived drug use opportunity conflict). This notion is broadly consistent with Tiffany's cognitive model of drug use behavior and craving (Tiffany, 1990). According to Tiffany (1990), consistent practice of drug-seeking and drug-taking behaviors (e.g., a smoker repeatedly lighting his cigarette in the same manner and under similar conditions) causes components of these actions to take on the properties of an automatic process (i.e., they become rapid, relatively effortless, stimulus bound, and difficult to inhibit). The model holds that non-automatic processing resources are recruited when automatized drug use behavior is prompted (e.g., by exposure to drug cues) but impeded in

some manner; specifically, when environmental conditions prevent the completion of drug-use actions or an individual is explicitly trying to prevent drug use. These non-automatic processing resources are purportedly mobilized for the purpose of facilitating (for those seeking to avoid abstinence) or preventing (for those attempting to maintain abstinence) the completion of the activated drug use action plan. They also may, however, reflect a shift of cognitive processing resources onto drug related-information (Sayette, Martin, Hull, Wertz, & Perrott, 2003), and might therefore be associated both with efforts directed at maintaining or avoiding abstinence, as well as enhanced attentional allocation towards drug-related information.

The need to utilize non-automatic resources for resolving such conflict may be particularly acute for the recently abstinent individual attempting to stop problematic substance use. As noted by Lang and colleagues, drug cues can prompt a dynamic competition between motivations to approach and avoid drug use (Breiner, Stritzke, & Lang, 1999; McEvoy, Stritzke, French, Lang, & Ketterman, 2004; Stritzke, Breiner, Curtin, & Lang, 2004). For instance, smokers attempting to quit have been found to demonstrate both strong approach and strong avoidance reactions upon exposure to cigarette cues (Breiner et al., 1999). For such individuals, "the world can be become one big temptation, requiring vigilant effort to resist its allure" (Sayette, 1999, p. 278). Accordingly, the ability to exert executive control when conflicting (approach vs. avoidance) motivations are evoked by drug cues is a critical component of preventing relapse for those in the early stages of behavior change (Monti, Rohsenow, & Hutchison, 2000; Sayette, 2004). Consistent with this position, research has shown that individuals who relapse to smoking often report failing to use learned coping skills (Brandon, Tiffany, Obremski, & Baker, 1990). Similarly, it has been demonstrated that alcoholics' coping skills are impaired following the induction of craving in the laboratory (Abrams et al., 1991).

To date, the majority of behavioral smoking cue-reactivity studies have included participants with no expressed intention of quitting and, as a result, very little is known about cue-reactivity in those attempting to stop smoking (Wertz & Sayette, 2001). Further, behavioral and neuroimaging methods have not, to my knowledge, been used to examine cue-reactivity in recently quit smokers given an opportunity to smoke following cue exposure. Accordingly, the affective, cognitive, and neurobiological responses to drug cues in the situation associated with the most conflict and the greatest risk of relapse in quitting smokers remain uncharacterized (Brownell, Marlatt, Lichtenstein, & Wilson, 1986; Piasecki, 2006). Based upon the evidence reviewed above, it may be predicted that those who are struggling to quit, but who still have a strong, conflicting motivation to use (which may be exacerbated by drug cues), will need to rely heavily upon DLPFC-mediated resources to successfully overcome temptation and remain abstinent.

1.2.3 Potential sites of modulation.

By what mechanisms might the DLPFC and the processes that it supports influence cue-elicited responses? Preliminary hypotheses can be generated on the basis of recent neuroimaging studies of emotion regulation in non-clinical populations, in which participants are asked to regulate their responses to emotionally evocative stimuli. Such research point towards the modulation of stimulus-related activation of the medial orbitofrontal cortex (OFC) as an important part of cognitively-oriented efforts to alter emotional experience (e.g., Ochsner, Bunge, Gross, & Gabrieli, 2002). The OFC is thought to contribute to goal-directed behavior via the assessment of the motivational significance of stimuli and the selection of behavior to obtain desired outcomes (Kringelbach & Rolls, 2004). It has been suggested that the medial and lateral

portions of the OFC have dissociable reward-related functions (Elliott, Dolan, & Frith, 2000; Kringelbach & Rolls, 2004). Specifically, it has been proposed that the medial OFC supports the representation of stimuli associated with positive outcomes (i.e., rewards). In contrast, the lateral OFC is thought to contribute to the inhibition of previously rewarded responses when established contingencies are altered.

There is some indication that the modulation of medial OFC activation may an important component of modifying cue-reactivity. Cue-elicited activation of the medial OFC has been observed in active users anticipating an opportunity to use drugs shortly after cue exposure (i.e., during the experimental session) (Grant et al., 1996; McBride et al., 2006; Wilson et al., 2005). In contrast, studies in which participants presumably have not anticipated an opportunity to use drugs during the experiment generally have failed to observe significant cue-elicited activation of the medial OFC, irrespective of whether these studies recruited active users or users in treatment (most studies reporting cue-elicited activation of OFC found increases falling within more lateral portions of OFC) (Wilson, Sayette et al., 2004). Cue-elicited activation of the medial OFC may therefore reflect explicit representation of drug use expectancy or the processing of drug cues as predictors of reward. Indeed, it has been proposed that activation of the medial OFC might serve to invigorate responses directed towards obtaining and consuming drugs in the presence of environmental cues signaling drug availability (Goldstein & Volkow, 2002; London, Ernst, Grant, Bonson, & Weinstein, 2000; Volkow & Fowler, 2000). Accordingly, one possibility is that the DLPFC may affect cue-elicited responses in part by (directly or indirectly) influencing the activity of the medial OFC (and thus representations of cue value).

The regulation of cue-elicited responses also may involve the modulation of responses in regions supporting basic sensory processing. In a recent fMRI study, Brody and colleagues

(2007) contrasted responses to smoking-related videos in treatment-seeking cigarette smokers when they were instructed to allow themselves to crave with those elicited when they were instructed to try to resist craving. Relative to when instructed to allow themselves to crave, participants in the study exhibited less activation of several regions within extrastriate visual cortex when directed to refrain from craving. Insofar as reduced visual cortex activation reflects less attentional allocation to smoking-related stimuli, this finding is consistent with the notion that shifting attention away from external drug cues is an important component of regulating cue-elicited craving.

Of note, Brody et al (2007) did not find greater activation of the DLPFC when smokers were instructed to resist craving than when they were told to allow themselves to crave. Importantly, the study enrolled treatment-seeking smokers who presumably were not expecting to smoke during the study. As described above, available evidence suggests that non-automatic cognitive resources, such as those supported by the DLPFC, are utilized when intentions regarding drug use conflict with the extent to which drug use is possible (Tiffany, 1990; Wilson et al., 2005; Wilson, Sayette et al., 2004). Thus, the design of the study may not have been optimal for detecting coping-related responses in the DLPFC, which are predicted to occur in treatment-seeking smokers who are faced with an opportunity to smoke.

1.3 COMPETITION FOR LIMITED CAPACITY RESOURCES

The study of the nature and implications of limits in information processing has been a focus of psychological research for several decades (e.g., Baddeley & Hitch, 1974; Broadbent, 1957; Cowan, 2001; Just & Carpenter, 1992; Kahneman, 1973; Kane & Engle, 2002; G. A. Miller,

1956; W. Schneider & Shiffrin, 1977). Such work has made clear that there are important constraints associated with the executive functions supported by the DLPFC: it is possible to attend to and actively maintain only a circumscribed amount of information at any given time. If, as hypothesized, the DLPFC supports processes that are important for coping with cue-elicited craving, it follows that such coping may be impaired if these resources are also demanded by the very cue-elicited responses that are the object of modulation.

Indeed, this argument was advanced 30 years ago by Sjöberg and Johnson (1978) as an explanation for "volitional breakdowns" in those trying to quit smoking:

> It is suggested here that strong mood states brought about by stressors are the cause for a decrease in quality of information processing.…In order to carry through action in an orderly manner according to plans – and in the face of strong, often conflicting wishes – it is necessary to allocate some of the available mental energy to regulating the order of processing wishes. Hence, some energy which otherwise would have been available for the cognitive systems is lost….The effect is selective which means that the withdrawal of energy first affects more sophisticated cognitive mechanisms leaving the more primitive ones. This may leave the door open for a corrupt, twisted, and shortsighted reasoning which generates excuses for changing the initial decision. (p. 151)

In support of this proposition, there is strong evidence that cue-elicited responses place demands upon limited-capacity cognitive resources (Sayette, 1999). For instance, secondary response time paradigms have shown that individuals take longer to respond to an auditory probe during smoking cue exposure than during exposure to neutral cues (Cepeda-Benito & Tiffany, 1996; Juliano & Brandon, 1998; Sayette & Hufford, 1994). More recent findings have demonstrated

that exposure to smoking cues also disrupts the maintenance of information in memory (Heishman et al., 2006; Madden & Zwaan, 2001; Wilson, Sayette, Fiez, & Brough, 2007).

Recently, there has been increasing interest in developing a comprehensive, biologically plausible account of the mechanisms underlying cue-elicited disruptions of cognitive processing (e.g., Franken, 2003; Jentsch & Taylor, 1999; Kalivas & Volkow, 2005; Montague et al., 2004). Many of these theories have focused on the effects of cue-elicited activation of the mesocortical dopamine system on the functioning of the prefrontal cortex. As previously noted, the mesocortical dopamine system is thought to "gate" the access of representations to the prefrontal cortex (Braver & Cohen, 2000; Cohen et al., 2002; Montague et al., 2004). Specifically, on the basis of neurophysiological and computational research, it has been proposed that the DLPFC exhibits sustained firing and active maintenance of information only when afferent signals are coupled with a phasic release of dopamine. In the absence of this phasic response, DLPFC neurons exhibit only transient activation in response to input from other brain regions. Extensive animal research indicates that chronic drug administration results in sensitization of the phasic dopamine response elicited by drug cues (Redish, 2004; Robinson & Berridge, 1993, 2001). Thus, phasic dopamine transmission concomitant with cue exposure may serve to update representations in the DLPFC and initiate the active maintenance of drug-related information in working memory (Brody et al., 2002; Hester & Garavan, 2005).

The contents of working memory appear to guide selective attention such that greater attention is paid to stimuli that share features with actively maintained representations (Awh, Vogel, & Oh, 2006; Downing, 2000; Soto, Heinke, Humphreys, & Blanco, 2005). Consequently, holding drug-related information in working memory may make it particularly difficult to direct attention away from drug-related stimuli (Hester & Garavan, 2005). Thus, in

addition to eliciting craving, exposure to drug-related stimuli may result in a "hijacking" of the neurocognitive resources that are essential for engaging in coping, making it more difficult to resist the temptation to use drugs. As described above, this difficulty may be greatest for those who have conflicting motivations regarding drug use, particularly when drug cues are encountered in the context drug availability. For the smoker who has intentions to quit, but who also still experiences strong desires to smoke, smoking cues coupled with an opportunity to smoke may present a potent combination capable of drawing heavily upon the resources vital for successful coping.

1.4 INDIVIDUAL DIFFERENCES IN CAPACITY LIMITATIONS

The degree to which sufficient executive control resources are available to support cognitively-mediated coping during drug cue exposure is likely to vary across individuals. In a series of studies, Egnle and colleagues have shown that individual differences in working memory ability are associated with variability in the performance of a variety of cognitive tasks (Kane & Engle, 2002). Individuals with relatively low working memory capacity exhibit greater vulnerability to interference than individuals with comparatively high working memory capacity in dichotic listening (Kane & Engle, 2002), antisaccade (Kane, Bleckley, Conway, & Engle, 2001), and Stroop (Kane & Engle, 2003) tasks. Notably, these group differences in interference susceptibility become more evident as task difficulty increases, such as when representations must be maintained in the presence of stimuli that elicit prepotent responses inappropriate for a given context. Further, variability in working memory capacity appears to be related to the functioning of the DLPFC (Kane & Engle, 2002; Mecklinger, Weber, Gunter, & Engle, 2003).

Individual differences in the executive control functions supported by the DLPFC may play an important role in determining the degree to which the cognitive modulation of cue-reactivity is successful. As noted, cue-reactivity may place the greatest demands upon limited capacity resources when control is the most needed; i.e., when stimuli elicit responses that are in competition with intentions regarding drug consumption. Thus, it may be predicted that, under such circumstances, individuals with high working memory capacity will be more successful in implementing executive control than individuals with low working memory capacity.

1.5 COMPENSATING FOR CAPACITY LIMITATIONS

As reviewed above, it appears that cue-elicited activation of the DLPFC may be associated both with efforts directed at avoiding abstinence, as well as enhanced attentional allocation towards drug-related information. Accordingly, the efficacy of cognitively-oriented coping might depend in part upon the extent of the demands placed upon DLPFC and the regulatory processes it is thought to support. According to the classic interpretation of dual-task effects (Kahneman, 1973), performance on tasks that share a common limited resource are impaired when they are performed in combination, as opposed to in isolation. This perspective leads to the novel prediction that cognitive regulatory strategies that rely upon processes supported by regions other than the DLPFC may be a means of compensating for capacity limitations associated with the executive functions mediated by this region.

Recent data provide support for the idea that different coping strategies are neuroanatomically dissociable, with some techniques apparently relying upon the DLPFC to a greater extent than do others. Specifically, a recent study by Ochsner and colleagues (2004)

found that a non-self-referential emotion regulation strategy was associated with activation of the DLPFC bilaterally, while a self-focused strategy recruited an anterior region of the medial prefrontal cortex. The latter finding is consistent with emerging research implicating the medial prefrontal cortex in self-referential processing, such as judging the self-relevance of information and evaluating one's own emotional state (Gusnard, Akbudak, Shulman, & Raichle, 2001; Northoff et al., 2006). Both strategies were successful in modulating self-reported affect and were coupled with corresponding changes in activation of the amygdala, suggesting that both approaches were effective.

Interestingly, certain strategies for coping with craving are dependent in large part upon altering or reinterpreting the significance of drug cues and cue-elicited responses without self-referential processing. For instance, one method for dealing with temptation is to use mental imagery to "transform" feelings of craving into tangible objects that may then be manipulated or reduced in some way (e.g., "kicking away" feelings of urge) (Marlatt & Gordon, 1985). Other methods are more reliant upon generating and maintaining self-relevant information, such as visualizing one's self-image as a non-drug user (Shiffman & Wills, 1985).

The different mechanisms supporting these strategies may have important implications for how successful they are at modulating urge. Extensive research indicates that information actively related to the self is better remembered than information that is processed in other ways (e.g., relating the information to others or processing the information semantically; see Symons & Johnson, 1997). Moreover, to be remembered information that is related to the self appears to be more robust to distracters (such as those that interrupt active rehearsal of information) than information that is not self-referenced (Symons & Johnson, 1997). It is thought these mnemonic advantages are produced by associating novel information with the highly elaborated and well-

organized properties that comprise self-referential information already stored in memory. Thus, in addition to reducing demands upon the DLPFC (as discussed above), coping strategies that involve the use of self-referential information may be less resource demanding than those requiring the generation and maintenance of information that is not self-referenced because the former are encoded more effectively and retrieved more efficiently than the latter. Taken together, it may be predicted that self-referential strategies, which are hypothesized to rely upon the anterior medial prefrontal cortex more so than the DLPFC, may be particularly advantageous for individuals with low working memory capacity.

1.6 SUMMARY AND AIMS OF THE CURRENT STUDY

It is well documented that cognitively-oriented coping is a commonly used and often effective method for forestalling relapse to smoking during high risk situations. For reasons that are poorly understood, however, many individuals who are attempting to quit smoking succumb to temptation despite implementing cognitive coping. The overarching objective of the present research was to address this important knowledge gap by examining the neurocognitive mechanisms underlying cognitive coping using fMRI. The vast majority of prior studies examining coping in quitting smokers have been non-experimental in design (e.g., O'Connell et al., 2007). While such investigations have documented the importance of coping for preventing relapse, they have not characterized the actual mechanisms through which coping operates. In order to overcome this limitation, the current study examined quitting smokers as they utilized specific cognitive coping techniques under controlled laboratory conditions.

The methodology employed in the current investigation was unique relative to prior studies in two ways. First, the sample recruited for the present study was larger than all prior brain imaging studies examining cue exposure in substance using populations (n = 56) (Bonson et al., 2002; Bragulat et al., 2008; Braus et al., 2001; Brody et al., 2004; Brody et al., 2002; Brody et al., 2007; Childress et al., 2008; Childress et al., 1999; Daglish et al., 2001; David et al., 2007; David et al., 2005; Due, Huettel, Hall, & Rubin, 2002; E. Duncan et al., 2007; Filbey et al., 2008; Franklin et al., 2007; Garavan et al., 2000; George et al., 2001; Gilman & Hommer, in press; Grant et al., 1996; Grusser et al., 2004; Heinz et al., 2004; Heinz et al., 2007; Hermann et al., 2006; Kareken et al., 2004; Kilts, Gross, Ely, & Drexler, 2004; Kilts et al., 2001; Kosten et al., 2006; Langleben et al., 2008; Lee, Lim, Wiederhold, & Graham, 2005; Lim et al., 2005; Lingford-Hughes et al., 2006; Maas et al., 1998; McBride et al., 2006; McClernon, Hiott, Huettel, & Rose, 2005; McClernon, Hiott et al., 2007; McClernon, Hutchison, Rose, & Kozink, 2007; McClernon, Kozink, & Rose, 2008; Modell & Mountz, 1995; Myrick et al., 2004; Okuyemi et al., 2006; Olbrich et al., 2006; Park et al., 2007; F. Schneider et al., 2001; Sell et al., 1999; Smolka et al., 2006; Tapert, Brown, Baratta, & Brown, 2004; Tapert et al., 2003; G. J. Wang et al., 1999; Z. Wang et al., 2007; Wexler et al., 2001; Wilson et al., 2005; Wrase et al., 2002; Wrase et al., 2007; Xiao et al., 2006; Yang et al., in press; Yasuno et al., 2007). These investigations included an average of 14 substance using participants (range of 1-42 participants), with only eight studies enrolling 20 or more users (Brody et al., 2002; Brody et al., 2007; Childress et al., 2008; Filbey et al., 2008; Franklin et al., 2007; McClernon et al., 2008; Olbrich et al., 2006; Wilson et al., 2005). As reviewed by Wilson and colleagues (2004), this burgeoning literature has yielded inconsistent findings, probably due in part to the limited power associated with such modest sample sizes. Thus, in addition to offering sufficient power to

address the specific aims described below, the current study provided a distinctively well-powered examination of the neural correlates of cue exposure.

The second noteworthy aspect of the current study concerned the motivational state of participants at the time of cue exposure. In most prior smoking cue-reactivity research, the individuals under study were recruited because they did not intend to quit at the time of their participation (e.g., Sayette, Martin, Wertz, Shiffman, & Perrott, 2001). Other studies have recruited quitting smokers, but enrolled only those individuals who were prescreened to have both a high level of motivation to quit and a strong belief that they would be successful in doing so (e.g., A. J. Waters et al., 2004). To date, very little is known about cue-reactivity in smokers who have conflicting motivations for and against smoking. This is an important oversight, as research indicates that many smokers fall within this unstudied category (Piasecki, 2006; World Health Organization, 2008). In order to shed light on this important issue, the current study presented smoking cues *and* an option of choosing to smoke to individuals with an expressed interest in quitting, circumstances designed to induce conflict between the intention to abstain and the urge to smoke.

One important methodological challenge that arises when attempting to use neuroimaging to study cue-reactivity is that of eliciting potent responses to drug cues under relatively constrained circumstances. Behavioral cue exposure research has demonstrated that heavy smokers respond quite strongly to a cue exposure procedure in which they hold and view a lit cigarette, particularly when they have not smoked for a period of time (Sayette et al., 2001). In contrast, behavioral research suggests that smokers do not respond as strongly to an unlit cigarette (A. J. Waters et al., 2004). Safety concerns preclude presenting smokers with a lit cigarette in fMRI research. Moreover, unlike typical behavioral studies in which participants are

presented with cues while sitting comfortably in a quiet room, participants in an fMRI study must undergo cue exposure in noisy conditions while lying still within the confines of the fMRI scanner.

Nevertheless, there is evidence that cue exposure methods that include the presentation of an unlit cigarette effectively elicit craving in the neuroimaging environment (Brody et al., 2004; Brody et al., 2002; Franklin et al., 2007; Wilson et al., 2005). It was therefore predicted that the cue exposure protocol employed in the current research, which was adapted from that used by Wilson and colleagues (2005), coupled with the provision of an opportunity to smoke, would effectively simulate the high risk situations that smokers encounter in the natural environment. Additionally, the current study employed a multidimensional assessment of cue-reactivity that incorporated self-report, psychophysiological, and neurobiological measures. This comprehensive approach permitted the strengths associated with a given response modality to complement the limitations of another (e.g., physiological responses are less subject to response biases than self-report).

Using this methodological approach, the current study sought to address the following specific aims:

Aim 1: To investigate the neurobiological correlates of non-self-referential and self-referential strategies for coping with smoking cue exposure. Functional brain imaging was used to evaluate the hypothesis that different cognitive strategies for coping with cue-elicited affect are associated with the activation of distinct regions of the prefrontal cortex. Specifically, it was predicted that the use of a non-self-referential strategy during cigarette cue exposure would be associated with relatively greater activation of the DLPFC than a strategy that entailed the use of self-referential information. In contrast, it was hypothesized that a strategy that

involved the generation and maintenance of self-relevant information would be associated with comparatively greater activation of portions of the anterior medial prefrontal cortex than a strategy in which the focus is on non-self-referential information.

Aim 2: To examine whether non-self-referential and self-referential coping strategies are differentially moderated by individual differences in working memory capacity. It was predicted that individual differences in working memory capacity would significantly moderate the magnitude of cue-elicited activation of the DLPFC during the use of a non-self-referential coping strategy. In contrast, it was hypothesized that working memory capacity would have less of a modulatory effect on activation of the DLPFC during the use of a self-referential coping strategy, in large part because such strategies were expected to rely less upon the processes supported by this region, as described above. Thus, it was predicted that activation of the DLPFC would be explained by the interaction of coping strategy and working memory capacity above and beyond the degree to which activation of the region was accounted for by the independent effects of these factors. Similarly, it was hypothesized that coping-related outcomes (e.g., self-reported craving) would be more strongly modulated by working memory ability for a non-self-referential strategy than for a self-referential strategy.

2.0 METHOD

2.1 PARTICIPANTS

Adult cigarette smokers between the ages of 18 and 45 were recruited for this study. Based upon power analyses (see section 2.6.9), a sample size of 60 was targeted. Because research suggests that there are gender differences in the neurobiological responses elicited by drug cue exposure (Kilts et al., 2004), only male smokers were recruited for the study. Participants were recruited through advertisements in the community and local newspapers. These advertisements solicited telephone calls from healthy adult male cigarette smokers who were planning on quitting smoking, willing to enroll in a smoking cessation treatment program, and interested in participating in a paid experiment.

Respondents participated in a telephone screening interview to determine eligibility based upon the following criteria. In order to be eligible, participants had to report smoking an average of 15 to 40 cigarettes per day continuously for at least the two preceding years. Exclusionary criteria included a medical condition that ethically contraindicated nicotine administration, illiteracy, or dependence on any drug other than nicotine or caffeine. Participants additionally had to pass an MRI safety screening. Because many brain functions are known to be lateralized, only strongly right-handed subjects were included in the study. Written informed consent was

obtained from all participants and all procedures were approved by the Institutional Review Board of the University of Pittsburgh. Individuals were paid for their participation in the study.

2.2 QUESTIONNAIRES

To measure individual differences that may influence cue-reactivity, participants completed questionnaires assessing the following: basic demographic information; history of smoking practices; level of nicotine dependence; confidence in ability to abstain from smoking; trait impulsivity, self-control, and affect; level of self-consciousness; and tendency to respond in a socially desirable manner. In addition, participants completed questionnaires measuring current affective state and level of mental fatigue after abstaining from smoking for 12 hours in order to assess the general effects of nicotine withdrawal on these variables. All questionnaires are described in detail below.

2.2.1 Demographics and smoking history.

Basic demographic data on age, ethnicity, and income was obtained with standard forms (Sayette et al., 2001). Smoking history, smoking patterns, motives for smoking, type of cigarettes smoked, and number of past quit attempts were assessed with a previously developed questionnaire (Shiffman, Paty, Kassel, Gnys, & Zettler-Segal, 1994).

2.2.2 Nicotine dependence.

The Nicotine Dependence Syndrome Scale (NDSS) is a scale assessing level of nicotine dependence (Shiffman, Waters, & Hickcox, 2004). The NDSS consists of 30 statements related to smoking habits (e.g., "I smoke consistently and regularly throughout the day."), with participants rating each item according to how well it describes them using a 6-point scale anchored by 1 ("Not at all true") and 6 ("Extremely true"). The scale yields a summary measure of dependence (NDSS-Total; 14 items) and five factor-analytically derived subscales (each having eight items): *Drive* (craving, withdrawal-avoidance, and subjective compulsion to smoke), *Priority* (preference for smoking over other reinforcers), *Tolerance* (reduced sensitivity to the effects of smoking), *Continuity* (regularity of smoking rate), and *Stereotypy* (fixed pattern of smoking). The subscales of the NDSS have demonstrated adequate internal consistency (Cronbach's coefficient $\alpha = .55–.76$), as has the summary score ($\alpha = .84$) (Shiffman et al., 2004). Scores on the NDSS also have been found to correlate with other measures of dependence, predict cessation-related outcomes, and discriminate dependent from regular, but non-dependent, smokers (Shiffman & Sayette, 2005; Shiffman et al., 2004). The NDSS was scored using the regression-based algorithms described by Shiffman and colleagues (2004), with higher scores indicating a higher level of dependence.

2.2.3 Abstinence self-efficacy.

The Relapse Situation Efficacy Questionnaire (RSEQ) is a 43-item questionnaire that assesses smokers' confidence that they can resist smoking under various circumstances (Gwaltney et al., 2001). The RSEQ yields a global measure of abstinence self-efficacy and seven factor-

analytically derived context-specific subscales: *Negative Affect* (eight items) *Positive Affect* (six items), *Social-Food Situations* (eight items), *Idle Time* (six items), *Restrictive Situations* (seven items), *Low Arousal* (six items) and *Craving* (two items). For each item of the RSEQ, participants are asked to rate their confidence in their ability to resist smoking in a particular situation (e.g., "How confident are you that you can resist the temptation to smoke when your craving is high?") using a 4-point scale anchored by 1 ("Not at all confident") and 4 ("Extremely confident"). The context-specific factors of the RSEQ have displayed adequate internal consistency (α = .77–.91), as has the global abstinence self-efficacy index (α = .96), and it has been shown that RSEQ scores predict subsequent cessation outcomes (Gwaltney et al., 2001). Subscale scores were derived by averaging the items forming each factor and the global abstinence self-efficacy score was calculated by averaging the factor scores. Thus, the possible score on both the subscales and global index ranged from 1 to 4, with higher scores indicating greater confidence.

2.2.4 Impulsivity.

Barratt's Impulsivity Scale Version 11 (BIS-11), is a widely used and well-validated measure of impulsivity (Patton, Stanford, & Barratt, 1995). The BIS-11 consists of 30 self-descriptive items (e.g., "I plan tasks carefully") rated on a 4-point scale ranging from "Rarely/Never" to "Almost Always/Always." Four items are reverse scored. The instrument yields an overall impulsiveness score and three subscale scores: M*otor Impulsiveness* (restlessness and acting without thinking; 11 items), *Attentional Impulsiveness* (difficulty concentrating; eight items), and *Non-Planning Impulsiveness* (present orientation; 11 items). Subscale scores were calculated by summing the items forming each factor and the total score was obtained by summing all 30 items. The

possible total score on the BIS-11 ranged from 30 to 120, while possible scores ranged from 8 to 32 for the *Attentional Impulsiveness* subscale and from 11 to 44 for the *Motor Impulsiveness* and *Non-Planning Impulsiveness* subscales. Higher scores on each reflect greater impulsivity.

2.2.5 Trait self-control.

The Trait Self-Control Scale (TSCS) is a recently developed tool for measuring stable individual differences in self-control (Tangney, Baumeister, & Boone, 2004). The TSCS consists of 36 self-descriptive items (e.g., "I have a hard time breaking bad habits") rated on 5-point scale anchored by 1 ("Not at all like me") and 5 ("Very much like me"). Twelve items are reverse scored. The TSCS has demonstrated high internal consistency (α = .89) and scores on the measure have been found to correlate with a variety of behaviors thought to require self-control (Tangney et al., 2004). A total score indexing trait self-control was obtained by summing all 36 responses (the possible score ranged from 36 to 180). Higher scores on the TSCS indicate higher trait self-control.

2.2.6 Self-consciousness.

The revised version of the Self-Consciousness Scale (R-SCS) measures individual differences in self-consciousness (Scheier & Carver, 1985). The questionnaire contains 22 self-descriptive items (e.g., "I often daydream about myself") rated on a 4-point scale anchored by 0 ("Not at all like me") and 3 ("A lot like me"). Two items are reverse scored. The R-SCS consists of three subscales: *Private Self-Consciousness* (tendency to direct attention toward one's inner experience; nine items), *Public Self-Consciousness* (tendency to direct attention towards aspects

of the self that are observable by others; seven items), and *Social Anxiety* (apprehension in social situations; 6 items). The instrument has demonstrated adequate internal consistency (α = .75 for *Private Self-Consciousness*, .84 for *Public Self-Consciousness*, and .79 for *Social Anxiety*) (Scheier & Carver, 1985). Subscale scores were calculated by summing the items forming each factor. Accordingly, possible score ranged from 0 to 27 for the *Private Self-Consciousness* subscale, from 0 to 21 for the *Public Self-Consciousness*, and from 0 to 18 for the *Social Anxiety* subscale. In each case, higher scores reflect a higher level of the construct being assayed.

2.2.7 Reporting biases.

The Balanced Inventory of Desirable Responding Version 6 (BIDR-6) assesses participants' tendency to respond to self-reports in a socially desirable manner (Paulhus, 1991). The BIDR-6 contains 40 self-descriptive items (e.g., "I never regret my decisions") which are rated using a 7-point scale anchored by 1 ("Not True") and 7 ("Very True"). Twenty items are reverse scored. The scale includes two 20-item subscales indexing distinct dimensions of social desirability: *Impression Management* (deliberate adjustment in self-reporting in an attempt to create a positive impression) and *Self Deceptive Positivity* (tendency to give self-reports that are honest but positively biased). Each subscale has displayed adequate internal consistency, with alphas ranging from .68 to .80 for the *Impression Management* subscale and from .75 to .86 for the *Self-Deceptive Positivity* subscale (Paulhus, 1991). For scoring purposes, each item was dichotomized (responses of 6 or 7 were scored 1 and responses of 1 to 5 were scored 0). Subsequently, subscale scores were obtained by summing the items comprising each factor, with the possible score for each ranging from 0 to 20 and higher scores indicating a greater response bias.

2.2.8 Trait and state affect.

The Positive and Negative Affect Schedule (PANAS) was designed to provide a brief assessment of positive and negative affect (Watson, Clark, & Tellegen, 1988). The measure consists of 10 adjectives describing positive affective states (e.g., excited) and 10 adjectives describing negative affective states (e.g., irritable), with each rated along a 5-point scale from 1 ("Very slightly or not at all") to 5 ("Extremely"). The scale may be used to assess affect over various time frames by varying the instructions. For the present study, participants completed the PANAS during the initial screening/consent session with the following instructions in order to assess trait positive and negative affectivity (referred to as PANAS-Trait): "Indicate to what extent you feel this way in general." In order to measure the effects of nicotine deprivation on affective state, participants also completed the PANAS with the following instructions at the onset of the experimental session (referred to as PANAS-State): "Indicate to what extent you feel this way **at the present moment**." Both versions of the PANAS used in the present study have demonstrated good internal consistency (for PANAS-Trait, α = .88 for the positive affect subscale and .87 for the negative affect subscale; for PANAS-State, α = .89 for the positive affect subscale and .85 for the negative affect subscale) (Watson et al., 1988). For both the PANAS-Trait and PANAS-State, subscale scores were obtained by summing the items comprising the factor. The possible score for each subscale thus ranged from 10 to 50, with higher scores indicating greater affect over the timeframe captured by the instructions.

2.2.9 Mental fatigue.

The State Ego Depletion Scale (SEDS) measures level of mental energy/fatigue (Ciarocco, Twenge, Muraven, & Tice, 2007). The SEDS consists 25 self-descriptive items (e.g., "I feel mentally exhausted") each rated on a 7-point scale anchored by 1 ("Not true") and 7 ("Very true"). Eighteen items are reverse scored. Initial studies indicate that the scale has good internal consistency ($\alpha = .90$) and that scores on the measure correlate with daily self-control demands, general well-being, and laboratory manipulations of self-control resources (Ciarocco et al., 2007). A total score indexing level of mental fatigue was obtained by summing all 25 responses (possible score ranges from 25 to 175). Higher scores on the SEDS indicate less mental fatigue.

2.3 BEHAVIORAL ASSESSMENT OF WORKING MEMORY ABILITY

Behavioral measures were utilized to index the working memory ability of all participants. Following the suggestion of Waters and Caplan (2003), a composite measure of working memory ability based upon the performance on the two tasks described below was derived for each participant, which yields estimates of working memory functioning that are more reliable than those based upon a single task.

2.3.1 Operation-word span task.

Participants completed a computerized version of the operation–word-span task (OSPAN), a widely-used measure of working memory capacity (Turner & Engle, 1989). Performance on the

OSPAN correlates with other measures of working memory span and predicts performance on a large number of higher order cognitive tasks (Conway, Cowan, Bunting, Therriault, & Minkoff, 2002; Engle, Tuholski, Laughlin, & Conway, 1999). The OSPAN requires participants to solve a series of math operations while trying to remember a set of unrelated words. For instance, participants may receive the following item on a given trial: Is (9/3) – 1 = 1? (Aunt). For each item, the participant is required to respond indicating whether or not the math operation is correct and subsequently read the presented word aloud. Following a series of items, participants are asked to recall the words from that set in the correct order. Difficulty is varied by altering the length of the operation-word strings. In order to ensure that low OSPAN scores do not simply reflect low effort, participants who do not achieve at least 85% accuracy on math items are excluded. (No participants failed to meet this math accuracy criterion in the current study.)

After three practice trials, each containing two operation-word strings, participants completed 12 experimental trials consisting of a set of between two and six operation-word strings (three trials of each set size). Trials were presented in a fixed randomized order. As suggested by Conway and colleagues (Conway et al., 2005), a partial-credit, unit weighted scoring procedure was used to calculate the total OSPAN score for each participant. Specifically, each item was scored as the proportion of words correctly recalled (i.e., the correct word in the correct serial position), with the scores for the 12 experimental trials averaged and multiplied by 100 to derive the total score (possible range of 0 to 100).

2.3.2 Backward digit span task.

Participants also completed the Backward Digit Span (BDS) subtest of the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III) in order to obtain a convergent measure of working

memory capacity (Wechsler, 1997b). The BDS is a commonly used and well-validated measure, particularly in the domain of neuropsychological assessment (Lezak, 2004). The BDS consists of eight items of two trials each. For each trial, a sequence of digits is read aloud by the examiner at a rate of one digit per second. Subsequently, the participant repeats the entire sequence in reverse order. The pair of trials within an item contains the same number of digits, beginning with two digits for the trials comprising the first item. The number of digits is incremented by one for each subsequent pair of trials, with the final pair of trials in the eighth item each containing nine digits. Each trial was scored as correct if all digits were recalled in the correct order (i.e., backward), with the number of correct trials summed to derive the total score (possible range of 0 to 16). Consistent with standard administration procedures, the task was discontinued if participants failed both trials within a given item. Like the OSPAN task, the BDS entails active maintenance in the face of additional processing demands, which is thought to be critical for engaging executive attentional processes and validly measuring working memory capacity (Conway et al., 2005).

2.3.3 Additional behavioral working memory tasks.

Participants completed three additional behavioral working memory tasks: the Forward Digit Span (FDS) substest of the WAIS-III (Wechsler, 1997b); and the Forward Spatial Span (FSS) and Backward Spatial Span (BSS) subtests of the Weschler Memory Scale–Third Edition (Wechsler, 1997a). In the FDS, participants are read a sequence of digits and must repeat the entire sequence in the order in which it was presented. The FSS and BSS tasks use a structure that is very similar to the FDS and BDS, respectively, except that the stimuli are presented visually instead of orally. Specifically, the experimenter taps out a sequence on an array of

blocks and the participant must subsequently repeat the sequence in the same (FSS) or reverse (BSS) order. These tasks were a part of a broader assessment of memory functioning in smokers and were not a focus of the present study. On the basis of research demonstrating important differences between tasks that require the maintenance of information with (OSPAN, BDS) and without (FDS, FSS) an additional processing component (Conway et al., 2005), as well as between verbal and visuospatial memory processes (e.g., Nagel, Ohannessian, & Cummins, 2007; Smith, Jonides, & Koeppe, 1996), data from the FDS, FSS, and BSS were not included in the composite working memory measure and are not presented herein.

2.4 TASKS PERFORMED DURING FMRI SCAN

2.4.1 Verbal n-back working memory task.

Participants performed several blocks of a verbal n-back working memory task while fMRI data were acquired. In this task, participants are presented with a series of individually displayed letters and must decide whether each presented item is the same as the item presented n-trials previously. A total of 12 letters were presented in 36 second blocks (500 ms stimulus duration, 2500 ms interstimulus interval). Participants performed two versions of the n-back that varied in working memory load in the current study (see Figure 1). In the version with low memory load (0-back), participants were instructed to press a button with their right index finger if a specific target (the letter "X") appeared. In the version with a comparatively high memory load (3-back), participants were instructed to press a button with their right index finger if the currently presented letter matched the letter presented three items previously. For the 3-back, participants

were encouraged to rehearse the three most recently presented letters while continuously updating their list as each new letter appeared.

For both the 0-back and 3-back, participants were instructed to push a button with their right middle finger for all non-target items. For both versions, the probability of an item being a target, new distracter, or repeat distracter was 33%, 47%, and 20%, respectively. In addition to the 0-back and 3-back tasks, participants were given 36 second resting periods (Rest) during which they were asked to relax and view a centrally presented fixation cross. Participants performed a single run of 288 seconds in duration consisting of the following sequence of events: 0-back, 3-back, Rest, 0-back, 3-back, Rest, 0-back, 3-back. E-prime and Integrated Functional Imaging System Stimulus (IFIS) software (Psychological Software Tools, Pittsburgh, Pennsylvania) were used to control computerized stimulus presentation and the collection of responses and response latencies.

The n-back robustly recruits the DLPFC (Ravizza, Delgado, Chein, Becker, & Fiez, 2004), thus permitting functioning of the region to be characterized with a small number of blocks that require only a few minutes to administer. This task served as a "localizer" to generate a DLPFC region of interest (ROI) to apply to data from the primary task, as described below.

2.4.2 Combined smoking cue exposure and coping task.

Participants also completed an fMRI-based cue exposure/coping procedure adapted from prior research (Wilson et al., 2005; see Figure 2) Each run of the task began with a 48 second resting baseline epoch during which participants were asked to relax and remain still with their eyes open. After this initial baseline period, an object was placed in the left hand of the participant

and prerecorded instructions identifying the object were delivered over an intercom system. Participants were instructed to passively view the object, which they held for a period of 74 seconds. In order to allow participants to see what they were holding, a live video feed from a camera focused on their left hand was projected onto a visual display positioned inside the magnet's bore (viewed through a mirror placed above the participants' eyes).

Participants completed three runs of the cue exposure task, during which they held a small notepad, a roll of electrical tape, and a cigarette (one of their preferred brand) in the first, second, and third runs, respectively. The notepad and roll of tape were neutral objects designed to elicit relatively small changes in affect. The first run served as a practice run that allowed participants to acclimate to the task and was excluded from analyses. Because there is strong evidence that exposure to a smoking cues affects responses to subsequently presented items (e.g., Hutchison, Niaura, & Swift, 1999; Sayette et al., 2000; Wilson, Sayette, Fiez et al., 2007), the order in which objects were presented was fixed in the aforementioned sequence.

Immediately prior to the cigarette exposure run, participants were informed that they would be holding a cigarette and were instructed to begin implementing the coping strategy that they had previously been trained to use (described below) as soon as the cigarette was placed in their hand and to do so for the entire time that they held the cigarette. They also were told that they would be given an opportunity to smoke immediately following the cue exposure task. Upon presentation of the cigarette, a prerecorded message was delivered via intercom informing participants that they would be removed from the scanner in 40 seconds and would be able to smoke immediately if they chose to do so.

2.5 PROCEDURE

Participants completed two sessions during the study, which are described in detail below. First, those deemed eligible based upon a telephone screening were scheduled for an in-person session during which additional screening was performed and questionnaires, behavioral working memory assessments, and coping strategy training were administered. Second, those remaining eligible and interested in participating were scheduled for an fMRI-based experimental session during which they performed the n-back working memory and cue exposure/coping tasks.

2.5.1 Initial screening/training session.

Following the telephone screening, eligible participants completed an individual screening/training session scheduled to begin between 11:00 AM and 4:00 PM. During this session, participants were first asked to provide an exhaled carbon monoxide (CO) sample. Measurement of breath CO levels requires the participant to hold their breath for 15 seconds, and then exhale into a hand-held monitor (BreathCo, Vitalograph, Lenexa, Kansas). The CO reading was used to verify smoking status (exhaled CO level > 10 parts per million) and to provide a baseline for comparison on the experimental session day. Participants then were asked to complete a behavioral working memory assessment consisting of the FDS, BDS, FSS, BSS, and OSPAN tasks. Subsequently, participants completed the following questionnaires: demographic information form, NDSS, RSEQ, BIS-11, TSCS, R-SCS, and PANAS-Trait.

Next, participants underwent a behavioral coping strategy training procedure. The training protocol integrated aspects of established coping skills interventions (Monti & Rohsenow, 1999) with procedures that have been successfully implemented in basic behavioral

and neuroscientific affect regulation research (Ochsner et al., 2004). Specifically, participants were assigned to one of two cognitive coping strategy conditions. Half of the participants (those assigned to the Self-Focused condition) were trained to generate and maintain thoughts about the positive effects that quitting smoking would have on them personally. The other half (those assigned to the Other-Focused condition) were trained to generate and maintain thoughts about the positive effects that quitting smoking would have on a particular individual with whom they were close.

These strategies were chosen for several reasons. First, ecological research indicates that similar techniques are spontaneously employed by quitting smokers (e.g., O'Connell et al., 1998). Second, similar strategies are taught in formal urge-specific coping skills interventions (Monti & Rohsenow, 1999). Finally, these strategies differ regarding the degree to which self-relevant information is employed to cope with cue-elicited emotional responses, allowing for the testing of hypotheses concerning the role that this dimension plays in determining which brain regions are recruited during cognitive coping.

During training, participants received explicit instruction and guidance regarding the performance of the strategy that they were to implement in the experimental session. First, participants read a brief description of the relevant strategy. Participants subsequently were asked to attempt to implement this strategy while being presented with smoking-related pictures previously shown to elicit robust cue-reactivity (Mucha, Geier, & Pauli, 1999; Mucha, Pauli, & Angrilli, 1998). Participants completed three practice trials. Following the completion of each practice trial, participants were asked to record what they had been thinking about during the presentation of the smoking-related picture. This material was reviewed by an experimenter who assessed their performance and helped shape their use of the appropriate strategy as necessary.

The experimenter also instructed participants not to use other strategies when performing the practice trials. Results of this procedure indicated that participants were successful in generating material appropriate for the strategy to which they had been assigned (see Appendix A).

After completing the training session, participants were instructed to abstain from smoking for a minimum of 12 hours prior to the experimental session. Participants also were instructed to refrain from consuming drugs or alcohol for the 24 hours preceding the experiment and were instructed to bring a pack of their cigarettes to the experimental session. In order to model the early phases of cessation, the experiment was scheduled to begin 12 hours after participants had initiated an authentic quit attempt. Finally, participants were asked to telephone a randomly assigned (one of two) smoking cessation program located in Allegheny County to enroll. These programs offer free smoking cessation classes led by experienced facilitators who use established guidelines for smoking cessation treatment. Finally, participants were permitted to leave the laboratory.

2.5.2 fMRI-based experimental session.

Individually conducted experimental sessions were scheduled to begin between 11:00 AM and 2:00 PM on a subsequent day. To check compliance with deprivation instructions, participants first reported the last time they smoked a cigarette and then provided an exhaled CO sample. Participants had to have a CO level that was equal to or lesser than that obtained during the screening session. Participants who did not meet the CO requirements were withdrawn from the experiment. Participants next presented their pack of cigarettes and lighter to the experimenter. In order to assess the effects of nicotine deprivation on mood and mental state, participants subsequently completed the PANAS-State and SEDS. Participants also verbally rate their urge

to smoke on a scale from 0 ("Absolutely no urge to smoke at all") to 100 ("Strongest urge to smoke I've ever experienced) (Urge-Baseline) and their affect on a scale from 0 ("I feel very bad right now") and 10 ("I feel very good right now") (Affect-Baseline).

Immediately before scanning, participants were given the following instructions:

> People often wonder whether or not they're going to be able to smoke during the study. So you know what to expect, the answer is YES, you *will* be able to smoke during the study if you want. At some point today you will be removed from the scanner for a brief break when you'll be able to choose to smoke if you wish. As noted in the consent form that you signed, because you are trying to quit smoking, this might affect the final outcome of your quit attempt and your treatment, particularly if you choose to smoke.

These instructions were delivered by an experimenter standing in front of a sign designating the room as a "smoking area for research purposes only." This room was located in close proximity to that housing the fMRI scanner, thus enhancing the likelihood that participants would anticipate having the opportunity to smoke almost immediately after cigarette cue exposure. In addition, participants were asked to review the coping information that they had recorded during the initial screening/training session. They were informed that they would be asked to implement the strategy later during the experiment, at which point they should focus upon the same information.

Participants were then placed in a conventional 3-Tesla head-only Siemens Allegra scanner equipped with a standard transmit/receive head coil. Subsequently, a 40 slice oblique-axial structural series (3.125 x 3.125 x 3.0 mm voxels) was acquired parallel to the anterior commissure-posterior commissure plane using a standard T2-weighted pulse sequence. Participants then completed the n-back and cue exposure tasks while fMRI data were collected.

For each of these tasks, functional images were collected in the same plan as the structural series with coverage limited to the 38 center slices using a one-shot echo-planar imaging (EPI) pulse sequence [TR = 2000 ms, TE = 25 ms, FOV = 20 cm, flip angle = 79°]. Heart rate was recorded during the acquisition of fMRI data using pulse oximetry from the right middle finger (Invivo 4500 Pulse Oximeter, Invivo Research Inc, Orlando, FL).

Additional urge and affect ratings were collected immediately following the second (Urge-Tape, Affect-Tape) and third (Urge-Cigarette, Affect-Cigarette) runs of the cue exposure task after fMRI data acquisition concluded. These ratings were made while participants were still holding the roll of tape and cigarette. Participants were then removed from the scanner and subsequently were presented with an opportunity to smoke. The decision made by each participant was recorded by the experimenter.

After making their decision, all participants were given a brief break. Participants who chose to smoke were escorted outside where they were permitted to smoke one of their cigarettes at their own pace. Subsequently, all participants completed the following questionnaires: smoking history form, BIDR-6, and a post-task questionnaire assessing the participant's experience during the experiment. Next, participants were given an opportunity to participate in additional research examining the relationship between certain brain proteins and neural responses to cigarette cues. This research, which involves the collection and analysis of DNA samples, will not be described herein. Finally, participants were debriefed, paid, and permitted to leave the laboratory.

2.6 DATA ANALYSIS STRATEGY AND HYPOTHESES

2.6.1 Preprocessing of fMRI data.

Analysis of fMRI data was conducted using the Neuroimaging Software package (NIS 3.5), developed at the University of Pittsburgh and Princeton University, as implemented in the Functional Imaging Software Widgets graphical computing environment (Fissell et al., 2003), and the Analysis of Functional NeuroImages software package (AFNI 2.6; Cox, 1996). Prior to statistical analysis, a series of preprocessing steps were employed to correct for artifacts and individual differences in anatomy. Each participant's data were corrected for motion using Automated Image Registration (AIR 3.08; Woods, Cherry, & Mazziotta, 1992) and adjusted for drift within and between runs. Data for which motion exceeded 3 mm or 3° were excluded from subsequent analysis. Structural images from each participant were co-registered to a common reference anatomy. Subsequently, functional images were globally mean-normalized and smoothed using a three-dimensional Gaussian filter (4-mm full width at half maximum) to account for anatomical differences between participants. Group-based statistical images were transformed into standard stereotaxic space (Talairach & Tournoux, 1988) using AFNI.

Additional preprocessing steps were conducted for fMRI data from the smoking cue exposure task. Specifically, for each participant, fMRI signal was averaged over the final 48 seconds of the cue exposure epoch separately for the tape and cigarette/coping conditions; signal collected during the initial 26 seconds of cue exposure was removed to allow for stabilization of responses associated with the instructions identifying the object and, for the cigarette, informing participants that they would have an opportunity to smoke soon. Data also were averaged over the 48 second baseline epochs and a measure of percent change from the preceding baseline

period was calculated for both the tape and cigarette cues. This percent change measure, which was calculated for both functionally-defined ROIs and on a voxel-wise basis, was the blood oxygen level-dependent (BOLD) response of interest for all subsequent analyses of fMRI data.

2.6.2 Multidimensional assessment of cue exposure/coping effects.

Before addressing the aims of the present research, it was important to first evaluate the effectiveness of the combined cue exposure and coping protocol employed in the study. The effects of this manipulation were tested using a multidimensional assessment that included self-reported urge and affect and heart rate responses (heart rate was averaged over the last 48 seconds of the cue exposure epoch for both the tape and cigarette/coping conditions). Based upon a review of the behavioral cue-reactivity literature, it was predicted that these response modalities would be differentially sensitive to the cue exposure/coping manipulation and would therefore only loosely covary (Carter & Tiffany, 1999). This review indicated that self-reported urge, which is perhaps the most widely used index of cue-reactivity, is the response domain most sensitive to drug cues. Accordingly, the effects of the cue exposure/coping manipulation on self-reported urge were of primary interest.

It is important to note, however, that self reports of urge may not correspond perfectly with the actual subjective experience of the rater (Sayette et al., 2000). Furthermore, cue-elicited urge ratings vary significantly as a function of the context in which cues are presented, including whether or not participants anticipate actually using the drugs to which they are being exposed (Wertz & Sayette, 2001). It was not entirely clear how expectancy and other factors (e.g., demand characteristics associated with presenting smoking cues to those beginning a quit attempt) would influence self-reported urge ratings in the current study. Additionally, the effects

of coping itself on urge was difficult to predict, particularly in light of recent data suggesting that coping is effective because it reduces craving (O'Connell et al., 2007). It was therefore important to examine the effects of the manipulation used in the current study on other indices of cue-reactivity, as noted above.

For each of the aforementioned response domains, a mixed model Analysis of Variance (ANOVA) with Coping Strategy (Self-Focused, Other-Focused) as a between-participants factor and Cue (Urge-Tape, Urge-Cigarette) as a within-participants factor was conducted. It was predicted that this analysis would yield a main effect of Cue for each response modality (i.e., self-reported urge, self-reported affect, and heart rate). Specifically, it was hypothesized that, relative to the tape condition, the cigarette/coping condition would be associated with an increase in urge, negative affect, and heart rate. It also was tentatively predicted that there would be a significant Coping Strategy by Cue interaction for each response domain, with cue-elicited increases in urge, negative affect, and heart rate being smaller for the Self-Focused group than for the Other-Focused group. As described above, it was expected that the efficacy of the Other-Focused strategy would be more strongly moderated by working memory capacity than the effectiveness of the Self-Focused strategy. Thus, insofar as there was a similar distribution of working memory ability across strategy groups, it was predicted that the Self-Focused condition would be slightly more effective than the Other-Focused condition, although this effect was expected to be rather small.

The neurobiological responses associated with cue exposure were used an additional index of the effectiveness of the manipulation. Specifically, it was predicted that the cigarette cue would be associated with significant activation of the anterior cingulate cortex. The anterior cingulate is the brain region most commonly linked to cue-reactivity (Brody et al., 2004; Brody

et al., 2002; Brody et al., 2007; Childress et al., 1999; Daglish et al., 2001; David et al., 2005; E. Duncan et al., 2007; Filbey et al., 2008; Garavan et al., 2000; Grusser et al., 2004; Heinz et al., 2004; Heinz et al., 2007; Kilts et al., 2004; Kilts et al., 2001; Langleben et al., 2008; Lee et al., 2005; Lim et al., 2005; Maas et al., 1998; McBride et al., 2006; McClernon et al., 2005; McClernon, Hiott et al., 2007; McClernon, Hutchison et al., 2007; McClernon et al., 2008; Myrick et al., 2004; Okuyemi et al., 2006; Sell et al., 1999; Smolka et al., 2006; Tapert et al., 2004; Tapert et al., 2003; Z. Wang et al., 2007; Wexler et al., 2001; Wilson et al., 2005; Wrase et al., 2002; Xiao et al., 2006). Further, unlike other regions of the brain (most notably, the DLPFC and OFC), the anterior cingulate does not appear to be robustly affected by treatment status, drug use intentions, or how much time must pass before drug use may occur (Wilson et al., 2005; Wilson, Sayette et al., 2004). Based upon such findings, it was expected that both the Self-Focused group and the Other-Focused group would exhibit significant cue-elicited activation of the anterior cingulate.

2.6.3 Neural responses to combined cue exposure and coping task.

The first aim of the current study was to investigate the neurobiological correlates of the use of different coping strategies during exposure to smoking cues. It was hypothesized that the use of a non-self-referential strategy to reduce affective responses elicited by cigarette cue exposure would be associated with relatively greater activation of the DLPFC than a strategy involving the use of self-referential information. In order to provide a focused test of this hypothesis, initial analyses employed an ROI-based approach. Functionally-defined ROIs localized to the DLPFC were first identified using fMRI data collected during the performance of the verbal n-back task. Specifically, a repeated-measure ANOVA was conducted with Memory Load (0-back, 3-back)

as a within-participants factor. The voxel-wise significance threshold was set at $p < .0001$ for this contrast (uncorrected for multiple comparisons), with a spatial extent threshold of 10 contiguous voxels.

To examine the effects of coping strategy on neural responses to smoking cue exposure, DLPFC ROIs identified in this contrast were applied to data from the cue exposure task. Subsequently, a mixed model ANOVA with Coping Strategy (Self-Focused, Other-Focused) as a between-participants factor and Cue (tape, cigarette/coping) as a within-participants factor was conducted. It was predicted that this analysis would yield a main effect of Cue and a Coping Strategy by Cue interaction. Specifically, it was expected that cigarette/coping condition would be associated with greater activation of the DLPFC than the tape condition for both the Self-Focused group and the Other-Focused group, but it was hypothesized that cigarette-related activation of the DLPFC would be greater for the Other-Focused group than for the Self-Focused group.

While the use of ROI-based techniques is consistent with the a priori focus of the current research, it was expected that the manipulations employed in the current study would affect regions other than the DLPFC. Specifically, it was hypothesized that the implementation of a self-referential coping strategy would be associated with greater activation of the anterior medial prefrontal cortex than the use of a non-self-referential strategy. In order to test this hypothesis, a voxel-wise mixed-model ANOVA with Coping Strategy (Self-Focused, Other-Focused) and Cue (tape, cigarette/coping) as a within-participants factor was performed. For all voxel-wise analyses, the per-voxel threshold was set at $p < .005$, with only clusters of eight or more contiguous voxels considered significant. Based upon Monte Carlo simulations conducted using

the AFNI AlphaSim utility (Cox, 1996), this combined threshold results in a corrected mapwise threshold of $p < .05$.

Consistent with the ROI-based approach outlined above, it was predicted that this analysis would yield a main effect of Cue in the DLPFC, with both groups exhibiting greater activation of this region during the cigarette/coping condition than during the tape condition. It was also predicted that both the DLFPC and anterior medial prefrontal cortex would exhibit significant interaction effects. Specifically, as above, it was hypothesized that the DLPFC would demonstrate greater cigarette-elicited increases in activation for the Other-Focused group than the Self-Focused group. In contrast, it was predicted that cigarette-related activation of the anterior medial prefrontal cortex would be greater for the Self-Focused group than the Other-Focused group.

2.6.4 Examining effects of working memory capacity.

The second objective of the current study was to determine whether the Self-Focused and Other-Focused coping strategies were differentially moderated by individual differences in working memory capacity. It was hypothesized that individual differences in working memory capacity would strongly moderate the magnitude of cue-elicited activation of the DLPFC during the use of a non-self-referential coping strategy. In contrast, it was hypothesized that working memory capacity would have less of a modulatory effect on activation of the DLPFC during the use of a self-referential coping strategy, in large part because such strategies are predicted to rely less upon the processes supported by this region.

Regression analyses were conducted to test the hypothesis that the addition of information regarding the interaction between coping strategy and working memory capacity would improve prediction of cue-elicited activation of the DLPFC beyond that afforded by coping strategy and working memory capacity considered independently. Specifically, hierarchical multiple linear regression was used to compare the following models:

$$\text{Model 1:} \quad Y = \beta 0 + \beta 1\, X + \beta 2\, Z + \varepsilon$$

$$\text{Model 2:} \quad Y = \beta 0 + \beta 1\, X + \beta 2\, Z + \beta 3\, XZ + \varepsilon$$

where Y are the measurements (percent change activation of the DLPFC during cigarette cue exposure), X is the coping strategy (dummy code 1's and 0's), and Z is the participants' working memory capacity (composite score calculated by averaging OSPAN and BDS scores). The composite working memory measure was centered in order to reduce multicollinearity and multiplied by the dummy coded coping strategy in order to create the interaction term (Aiken & West, 1991). It was predicted that the addition of the interaction term would significantly improve the fit of the model.

It was hypothesized that a similar relationship between coping strategy and working memory ability would be observed for other indices of cue-reactivity. In order to evaluate this prediction, additional hierarchical multiple regressions were conducted with the same model structure as described above. The outcome variables for these analyses were self-reported urge (Urge-Cigarette), self-reported affect (Affect-Cigarette), and heart rate (averaged over the last 48 seconds of cigarette cue exposure). In each case, it was predicted that the model fit would significantly improve upon the inclusion of the term capturing the interaction between coping strategy and working memory capacity.

2.6.5 Preliminary investigation of responses that predict smoking.

Although not the focus of the present research, the current study provided an opportunity to investigate the relationship between cue-reactivity and clinically-relevant outcomes, albeit in a preliminary manner. As previously described, participants in the proposed study were given an opportunity to smoke shortly following cue exposure, thus permitting an assessment of whether there were systematic differences in cue-elicited responses between those who chose to smoke and those who did not. Accordingly, exploratory analyses were conducted to investigate the relationship between subjective, cardiovascular, and neural indices of cue-reactivity and the decision to smoke.

2.6.6 Estimation of statistical power.

Statistical power is difficult to assess in fMRI, as it is not necessarily uniform across the brain or across studies. Simulation based power predictions indicate that, for a liberal threshold of p = 05, 12 participants are required to achieve 80% power at the single voxel level for typical activations (Desmond & Glover, 2002). Similarly, Friston and colleagues (1999) have proposed that a sample size of 12 generally is sufficient to detect activations of 0.25% (fMRI) at a specificity of 95%. To provide more precise estimates, a power analysis was conducted using prior data to approximate effect sizes for the present research.

Of primary interest in the current study are group differences in activation of the DLPFC by cigarette versus neutral cues. Accordingly, a similar between-groups contrast (i.e., the contrast of cue-elicited DLPFC activation in non-quitting smokers who expected to smoke immediately versus those who anticipated a significant delay before having the opportunity to

smoke) in a prior cue exposure study using the same basic procedures (Wilson et al., 2005) was used to estimate the size of main effects for the current research. This contrast yielded a robust effect size ($d > 1.5$); however, to be conservative, an effect size of $d = 1.2$ was used as an estimate for the magnitude of main effects. Based upon this estimate, it was determined that a sample size of 60 would provide a power of approximately 0.81 to detect effects of cue and coping strategy with alpha set to $p < .005$. Admittedly, power to detect interaction effects may be smaller. Nevertheless, as noted above, the sample recruited for this study was larger than all prior published cue reactivity imaging studies and should be able to provide valuable data for this emerging field.

3.0 RESULTS

3.1 SAMPLE DESCRIPTION

A total of 105 participants who responded to recruitment advertisements were deemed eligible based upon a telephone screening and completed the initial screening/training session. Of these, a total of 24 were scheduled for the experimental session but failed to show for their appointment. An additional 21 participants were excluded prior to completing the experimental session: 10 failed to meet CO criteria, 4 asked to be removed from the scanner due to claustrophobia, 4 did not fit into the scanner, and 3 indicated that they had metal during a final MRI screening conducted just prior to being placed in the scanner (these participants denied having metal in their body in a prior screening). Data from three of the remaining 60 participants who completed the experimental session were excluded due to excessive movement. Thus, usable experimental data was collected from a total of 57 participants (n = 28 for Self-Focused condition, n = 29 for Other-Focused condition).

Independent samples t-tests were performed in order to evaluate the similarity of groups with respect to basic psychosocial characteristics and performance on behavioral working memory tasks (see Table 1). As shown, age, number of cigarettes smoked per day, number of quit attempts, level of nicotine dependence, confidence in ability to abstain from smoking, trait impulsivity, trait self control, trait affect, level of self-consciousness, tendency to give honest but

positively biased self-reports, and behavioral working memory performance were similar across coping strategy conditions (*ps* > .1). There was a marginally significant difference between groups in the tendency towards deliberate socially desirable responding, with Self-Focused participants scoring higher on the BIDR-6 Impression Management subscale than Other-Focused participants.

3.2 BEHAVIORAL N-BACK DATA

Response accuracy and reaction time data were collected during performance of the n-back working memory task. A 2 (Coping Strategy) x 2 (Memory Load) ANOVA with accuracy as the dependent measure yielded a significant effect of Memory Load, $F(1, 55) = 5.07$, $p = .03$, effect size $d = .61$. Consistent with prior research (e.g., Meegan, Purc-Stephenson, Honsberger, & Topan, 2004), participants performed better in the 0-back condition ($M = 85.1\%$ accuracy, $SD = 25.9$) than in the 3-back condition ($M = 78.7\%$ accuracy, $SD = 20.6$). The remaining effects failed to reach significance, suggesting that, as expected, coping strategy did not influence performance on the n-back task: Main effect of Coping Strategy, $F(1, 55) = 1.34$, $p > .2$; Coping Strategy by Memory Load interaction, $F(1, 55) = .03$, $p = .8$.

A 2 (Coping Strategy) x 2 (Memory Load) ANOVA with reaction time as the dependent measure revealed a significant effect of Memory Load, $F(1, 55) = 52.88$, $p < .001$, $d = 1.96$. As in prior research (e.g., Meegan et al., 2004), participants responded more quickly in the 0-back condition ($M = 802.38$ ms, $SD = 221.72$) than in the 3-back condition ($M = 994.07$ ms, $SD = 215.41$). Unexpectedly, a significant effect of Coping Strategy also was observed, $F(1, 55) = 8.49$, $p < .01$, $d = .79$. Participants in the Other-Focused strategy group responded more quickly

(*M* = 828.96 ms, *SD* = 185.87) than did participants in the Self-Focused strategy group (*M* = 969.96 ms, *SD* = 179.47). The Coping Strategy by Memory Load interaction was not significant, $F(1, 55) = 1.71$, $p > .1$.

3.3 EFFECTS OF NICOTINE DEPRIVATION

Independent samples t-tests conducted on self-reported affect and urge data suggested that the coping strategy groups responded similarly to nicotine deprivation (see Table 2). Specifically, the groups did not differ with respect to affective state [PANAS-State positive subscale: $t(55) = .26$, $p > .7$; PANAS-State negative subscale: $t(55) = .47$, $p > .4$; Affect-Baseline: $t(55) = .23$, $p > .8$], mental fatigue [SEDS: $t(55) = 1.35$, $p > .1$], or self-reported urge [Urge-Baseline: $t(55) = .58$, $p > .5$].

3.4 EVALUATING THE CUE EXPOSURE/COPING MANIPULATION

A multidimensional assessment approach that incorporated self-report and psychophysiological measures was used to comprehensively evaluate the effects of the cue exposure/coping protocol used in the present study, as described above. Results provided mixed support for the effectiveness of the manipulation. Data from the assessment of self-reported urge and affect during the cue exposure/coping manipulation are presented in Table 3. Contrary to predictions, a 2 (Coping Strategy) x 2 (Cue) mixed-model ANOVA with self-reported urge as the dependent measure failed to yield significant effects: Main effect of Coping Strategy, $F(1, 55) = .69$, $p > .4$;

Main effect of Cue, $F(2, 55) = .19$, $p > .8$; Coping Strategy by Cue interaction, $F(1, 55) < .01$, $p > .9$. Similarly, an ANOVA conducted with self-reported affect as the dependent measure did not produce any significant results: Main effect of Coping Strategy, $F(1, 55) = .73$, $p > .3$; Main effect of Cue, $F(1, 55) = .03$, $p > .8$; Coping Strategy by Cue interaction, $F(1, 55) = .11$, $p > .7$.

As noted above, prior research suggests that cue-elicited changes in self-reported urge are larger than changes in other response modalities (Carter & Tiffany, 1999). Unlike prior research, however, participants in the current study were asked to engage in coping during cue exposure. It is possible that this coping was successful to some extent, thereby limiting the degree to which cue exposure was associated with increases in urge. Alternatively, participants may have been reluctant to acknowledge and/or report high levels of urge. Providing some support for the latter possibility, urge assessed during exposure to the cigarette (Urge-Cigarette) was negatively correlated with scores on the BIDR-6, a measure of socially desirable responding [$r(57) = -.37$, $p < .01$].

In contrast to self-report, cue exposure was associated with detectable effects for the nonverbal response domains that were assessed, highlighting the utility of the multidimensional approach used in the current study. Due to technical error, heart rate data were not collected for six participants (five participants in the Self-Focused group and one participant in the Other-Focused group). Analyses were conducted on the remaining 49 participants. A 2 (Coping Strategy) x 2 (Cue) ANOVA yielded a significant effect for Cue, $F(1, 49) = 7.84$, $p < .01$, $d = .80$. As expected, heart rate was greater during exposure to the cigarette cue ($M = 61.2$ beats per minute, $SD = 8.6$) than during exposure to the roll of tape ($M = 60.2$ beats per minute, $SD = 8.1$). The remaining effects failed to reach significance: Main effect of Coping Strategy, $F(1, 49) = .32$, $p > .5$; Coping Strategy by Cue interaction, $F(1, 49) < .01$, $p > .9$. These data provide

support for the idea that participants responded differently to the cigarette exposure/coping manipulation than they did to the neutral cue presentation, although this reactivity may reflect several influences (e.g., increased arousal, smoking urge, active coping).

Also as predicted, cue exposure also was associated with significant activation of a large region of the anterior cingulate cortex independent of coping strategy condition (see Table 5 and Figure 5). Taken together with the significant effect observed for heart rate, this finding suggests that the cue exposure/coping manipulation was effective in eliciting predictable changes in psychophysiological and neurobiological responding.

3.5 NEURAL CORRELATES OF CUE EXPOSURE AND COPING

3.5.1 ROI-based analysis.

The first aim of the current study was to investigate the neurobiological correlates of the use of different coping strategies during exposure to smoking cues, with the hypothesis that that the use of a non-self-referential strategy would be associated with relatively greater activation of the DLPFC than a strategy involving the use of self-referential information. In order to provide a focused test of this hypothesis, functionally-defined ROIs localized to the DLPFC were first identified using fMRI data collected during the performance of a verbal n-back task. Brain regions exhibiting a main effect of memory load are presented in Table 4. As expected, this analysis yielded ROIs bilaterally in the DLPFC. As described above, these regions were applied to fMRI data from the cue exposure task, with separate 2 (Cue) x 2 (Coping Strategy) mixed model ANOVAs conducted for data extracted from the left and right DLPFC ROIs. For the left

hemisphere, this analysis yielded a significant main effect of Cue [$F(1, 55) = 8.93$, $p = .004$, $d = .81$] and a significant Coping Strategy by Cue interaction [$F(1, 55) = 4.15$, $p = .047$, $d = .55$]. The main effect of Coping Strategy was not significant, $F(1, 55) = .01$, $p > .9$. Regarding the main effect of Cue, activation of the left DLPFC was greater during the cigarette cue/coping condition ($M = .08$ percent change, $SD = .18$) than the tape condition ($M = -.02$ percent change, $SD = .20$), in accord with predictions. Contrary to hypotheses, however, the Self-Focused group exhibited a larger cigarette/coping related increase in activation of the left DLPFC than did the Other-Focused group, as shown in Figure 3. In order to further probe the nature of this interaction, the effects of cue (tape vs. cigarette/coping) were examined separately for each coping strategy group. Results indicated that the cigarette/coping condition was associated with significantly greater activation than the tape condition for the Self-Focused group [$t(55) = 3.09$, $p < .01$, $d = .83$], but not the Other-Focused group [$t(55) = .81$, $p > .4$].

A very similar pattern of effects was observed in the right DLPFC. Specifically, a main effect of Cue [$F(1, 55) = 11.77$, $p < .001$, $d = .92$] and a marginally significant Coping Strategy by Cue interaction [$F(1, 55) = 2.92$, $p = .09$, $d = .46$] were obtained. As in the left hemisphere, activation was greater during the cigarette/coping ($M = .07$ percent change, $SD = .15$) than during the tape condition ($M = -.04$ percent change, $SD = .20$), with the Self-Focused group exhibiting a larger increase than the Other-Focused group (see Figure 3). Likewise, that the cigarette/coping condition was associated with significantly greater activation than the tape condition for the Self-Focused group [$t(55) = 3.31$, $p < .01$, $d = .89$], but not the Other-Focused group [$t(55) = 1.36$, $p > .1$].

3.5.2 Voxel-wise analysis.

Results from a 2 (Cue) x 2 (Coping Strategy) voxel-wise mixed-model ANOVA conducted on data from the cue exposure/coping task are summarized in Table 5. As shown, several brain regions exhibited a main effect of Cue, including the insula, basal ganglia, thalamus, brainstem, cerebellum, and multiple sites in the frontal, occipital, temporal, and parietal cortices. In each of these areas, activation was greater during the cigarette/coping condition than during the tape condition. Of particular relevance, significantly greater BOLD signal during the cigarette/coping condition relative to the tape condition was detected bilaterally in the DLPFC, with observed patterns mirroring those obtained in the ROI-based analysis described above (see Figure 4). Additionally, a region of the anterior cingulate cortex demonstrated greater activation during the cigarette/coping manipulation than during the tape condition, as previously mentioned. Notably, the right DLPFC and anterior cingulate regions identified in the voxel-wise analysis overlap with those exhibiting a significant effect of memory load in the n-back working memory task (see Figure 5). A significant Cue by Coping Strategy condition interaction was observed in the cuneus (see Table 4). As depicted in Figure 6, the Self-Focused group exhibited greater activation during the cigarette cue than during the tape cue, while the reverse was true for the Other-Focused group.

3.6 EFFECTS OF WORKING MEMORY CAPACITY

Table 6 presents results from hierarchical multiple regression analyses conducted to examine the hypothesis that coping strategy and working memory ability would interact to predict cue-

reactivity. As shown, coping strategy and working memory ability collectively accounted for a marginally significant amount of variance in activation of the left DLPFC (R^2 = 8.1%), $F(2, 54) = 2.38$, $p = .10$. Contrary to predictions, however, the addition of the interaction between working memory ability and coping strategy did not significantly improve the fit of the model, $F(1, 53) = 1.10$, $p = .30$. Coping strategy and working memory ability failed to account for a significant amount of variance in activation of the right DLPFC, $F(2, 54) = 1.03$, $p > .3$, and adding the interaction term did not improve the fit of the model, $F(1, 53) = 0.59$, $p > .4$.

Similar effects were observed for analyses conducted with self-reported urge, self-reported affect, and heart rate as outcome variables. In each case, coping strategy and working memory capacity failed to account for significant variance [$F(2, 54) = .88$, $p > .4$ for self-reported urge; $F(2, 54) = .41$, $p > .6$ for self-reported affect; $F(2, 48) = .46$, $p > .6$ for heart rate], and the interaction did not significantly improve prediction [$F(1, 53) = .60$, $p > .4$ for self-reported urge; $F(1, 53) = .02$, $p > .8$ for self-reported affect; $F(1, 47) = .61$, $p > .4$ for heart rate]. Thus, little support was found for the hypothesis that working memory ability would differentially moderate the effectiveness of the Self-Focused and Other-Focused coping strategies.

3.7 VARIABLES ASSOCIATED WITH SMOKING CHOICE.

As noted above, a total of 8 participants in the Other-Focused group and 5 participants in the Self-Focused group chose not to smoke during the experiment (hereafter referred to as the *Chose-Abstain* group), while the remaining 44 participants smoked when given the opportunity to do so (hereafter referred to as *Chose-Smoke* group). Given the limited sample size of the

former, and because the relationship between coping strategy and choice was not significant [$\chi^2(1, N = 57) = .77, p > .5$], data were collapsed across groups and three additional sets of analyses were conducted in an attempt to identify variables related to the decision to smoke. First, independent samples t-tests were conducted to compare the characteristics of Chose-Smoke and Chose-Abstain participants. As shown in Table 7, participants in the Chose-Abstain group were significantly less nicotine dependent and more confident in their ability to refrain from smoking generally and specifically under conditions of low arousal than were participants in the Chose-Smoke group. Chose-Abstain participants also reported less urge following nicotine deprivation than did Chose-Smoke participants. Additional marginally significant findings suggested that those in the Chose-Abstain group smoked fewer cigarettes per day, had greater confidence in their ability to refrain from smoking in restrictive situations, and were more socially anxious than those in the Chose-Smoke group.

A second set of analyses were conducted to examine whether the Chose-Smoke and Chose-Abstain groups differed in subjective and cardiovascular responses to smoking cue exposure. A mixed-model ANOVA with Group (Chose-Smoke, Chose-Abstain) as a between-participants factor and Cue (Urge-Tape, Urge-Cigarette) as a within-participants factor was conducted with self-reported urge as the dependent measure. This analysis yielded a main effect of Group, $F(1, 55) = 26.34, p < .001, d = 1.38$. Self-reported urge collapsed across cues was significantly lower for the Chose-Abstain group ($M = 34.0$, $SD = 19.69$) than for the Chose-Smoke group ($M = 73.05$, $SD = 19.70$). The main effect of Cue [$F(1, 55) < .01, p > .9$] and the Group by Cue interaction [$F(1, 55) = .03, p > .8$] were not significant. An ANOVA conducted with self-reported affect as the dependent measure did not produce significant results: Main

effect of Group, $F(1, 55) = .22$, $p > .6$; Main effect of Cue, $F(1, 55) = .01$, $p > .9$; Group by Cue interaction, $F(1, 55) = .01$, $p > .9$.

A main effect of Cue [$F(1, 49) = 6.75$, $p = .01$, $d = .74$] was obtained from a 2 (Group) x 2 (Cue: cigarette/coping vs. tape) mixed model ANOVA conducted with heart rate as the dependent measure (heart rate data were collected for 13 Chose-Abstain and 38 Chose-Smoke participants). As above, heart rate was greater during exposure to the cigarette cue ($M = 61.2$ beats per minute, $SD = 8.6$) than during exposure to the roll of tape ($M = 60.2$ beats per minute, $SD = 8.1$). The remaining effects failed to reach significance: Main effect of Group, $F(1, 49) = .65$, $p > .4$; Group by Cue interaction, $F(1, 49) = .08$, $p > .7$.

Finally, a 2 (Group) x 2 (Cue) voxel-wise ANOVA was conducted to determine whether there were any differences between groups in the neural responses associated with cue exposure. As regions exhibiting a main effect of cue have been described previously, this analysis focused solely on identifying regions exhibiting a main effect of Group or a Group by Cue interactions. No regions exhibiting such effects were observed, suggesting that the neural activity during the smoking cue exposure/coping task was similar between groups.

3.8 RESULTS FROM ADDITIONAL EXPLORATORY ANALYSES

3.8.1 Functional connectivity analysis.

One challenge relevant to the hypotheses being tested in the current study concerns the potentially complex neural activation patterns that may underlie the process of coping, particularly given the limited data that is available regarding how attempts to reduce conflict

associated with competing representations influence activation of the DLPFC at a level detectable by functional neuroimaging methods. One approach for beginning to address this issue is to consider DLPFC activation in relation to the activation of other brain regions. Indeed, it has been argued that investigating interregional interactions is critical for understanding the neurobiological processes underlying cognition (McIntosh, 2000).

Accordingly, voxel-wise hierarchical multiple regression analyses were conducted in order to evaluate the hypothesis that the functional connectivity of the DLPFC during cigarette cue exposure would be modulated by coping strategy (as used herein, functional connectivity refers to the degree to which the activation of spatially distinct brain regions correlate; Friston, Frith, Liddle, & Frackowiak, 1993). An approach similar to that utilized for assessing the modulatory effects of working memory ability (see above) was implemented. Specifically, the following models were compared on a voxel-by-voxel basis:

$$\text{Model 1:} \quad Y = \beta 0 + \beta 1\, X + \beta 2\, Z + \varepsilon$$

$$\text{Model 2:} \quad Y = \beta 0 + \beta 1\, X + \beta 2\, Z + \beta 3\, XZ + \varepsilon$$

where Y are the measurements (percent change activation of the voxel during cigarette cue exposure), X is the coping strategy (dummy code 1's and 0's), and Z is the mean-centered percent change activation of the DLPFC region identified in the voxel-wise analysis of data from the cue exposure/coping task. As in prior analyses, it was predicted that the addition of the interaction term would significantly improve the fit of the model.

Table 8 lists the regions in which the addition of the interaction term significantly improved the model fit at a per-voxel statistical threshold of $p < .005$ and spatial extent threshold of eight contiguous voxels (corrected mapwise threshold of $p < .05$). Figures 7 through 12 present the results of the analysis for the right DLPFC, while Figures 13 through 15 present

results for the left DLPFC. These graphs plot the relationship between DLPFC activation and activation of the identified brain region (both during the cigarette/coping manipulation) separately for the Other-Focused and Self-Focused groups. As a visual aid to interpreting the nature of the interaction, the predicted value for each identified region is plotted at high (mean + 1 SD) and low (mean – 1 SD) values of DLPFC activation (Aiken & West, 1991). These figures thus illustrate how the relationship between activation of the DLFPC and other areas varied as a function of coping strategy. For each identified region, one-sample t-tests were conducted separately for the Other-Focused and Self-Focused groups to determine which simple slopes were significantly different from 0 (results presented in Figures 7 through 15).

Six regions were identified in which the interaction between coping strategy and cigarette/coping-related activation of the right DLPFC significantly improved the fit of the model. Greater right DLPFC activation was associated with greater activation of a region of the dorsomedial prefrontal/rostral anterior cingulate for both groups, although the relationship was stronger for the Self-Focused group than the Other-Focused group (Figure 7). Greater activation of the right DLPFC was associated with greater activation of the ventromedial prefrontal/ventral anterior cingulate (Figure 8) and an adjacent portion of the left ventromedial prefrontal cortex (Figure 9) for the Other-Focused group, but not the Self-Focused group. Greater activation of the right DLPFC was associated with greater activation of the left middle temporal gyrus for the Self-Focused group, but not the Other-Focused group (Figure 10). Finally, greater activation of the right DLPFC was associated with lesser activation of the right (Figure 11) and left (Figure 12) cuneus for the Other-Focused group, but not the Self-Focused group.

Three regions were identified in which the interaction between coping strategy and cigarette/coping-elicited activation of the left DLPFC significantly improved model fit. Greater

activation of the left DLPFC was associated with greater activation of two regions of the right inferior frontal gyrus for the Other-Focused group, but not the Self-Focused group (Figures 13 and 14). Greater activation of the left DLPFC was associated with greater activation of the middle temporal gyrus for the Self-Focused group, but not the Other-Focused group (Figure 15).

3.8.2 Linguistic analysis of participant-generated coping material.

As indicated above, participants recorded the material that they generated during the initial training session, and subsequently were asked to review and focus upon the same information during the experimental session. An initial review of this information suggested that were unanticipated and potentially important differences in this data between groups (see Appendix A for a complete list of the material generated by each group). Specifically, many of the participants in the Other-Focused group made reference to the emotional impact that quitting smoking would have on the person they had selected (e.g., how proud or happy the individual would be). In contrast, many of the participants in the Self-Focused group generated relatively concrete statements about the personal benefits of quitting smoking (e.g., to the elimination of smoke-related odors and staining of the teeth and skin).

In order to systematically and quantitatively evaluate the significance of these apparent differences, the text produced by participants was analyzed using the Linguistic Inquiry and Word Count (LIWC) program (Pennebaker, Francis, & Booth, 2001). The material generated by each participant was converted to a computerized text file and spell-checked prior to being submitted to the LIWC program. Subsequently, the software coded each text file for the proportion of self-references and emotional words that it contained. Independent t-tests were used to evaluate whether the coping strategy groups differed along these dimensions. Consistent

with the initial qualitative assessment, marginally significant results indicated that the text generated by Other-Focused participants contained a higher proportion of emotional words than the Self-Focused group, $t(55) = 1.95$, $p = .06$, $d = .52$ (Figure 16). Interestingly, results also suggested that the Other-Focused group also made more self-references [$t(55) = 1.83$, $p = .07$, $d = .49$] than the Self-Focused group. Potential implications of these findings are noted below.

3.8.3 Assessing the motivational state of participants.

A fundamental objective of the current study was to examine cue-reactivity in smokers in the early hours of a cessation attempt, a critical period during which it was predicted that they would be prone to experiencing a high degree of conflict between the motivation to remain abstinent and the pull to resume smoking. Toward this end, an attempt was made to recruit individuals who were planning on quitting smoking and willing to enroll in a smoking cessation treatment program. They then were asked to initiate an authentic quit attempt 12 hours before completing the experimental session.

Despite these steps, the majority of participants chose to smoke when given the opportunity to do so during the experiment. This raises important questions regarding their smoking intentions at the time of cue exposure. Where participants truly struggling to cope with cue-elicited urge and resist the temptation to smoke, or had they already decided to terminate their quit attempt by the time cues were presented, leaving them free to indulge their craving in anticipation of smoking? Indeed, it recently has been demonstrated that smokers' intention to quit can change significantly over relatively short periods of time (Hughes, Keely, Fagerstrom, & Callas, 2005).

In order to assess participants' motivational state during cue exposure, they were asked to rate the degree to which they had attempted to reduce their urge to smoke while holding the cigarette on a scale from 1 ("Not at all") to 5 ("Very much") at the conclusion of the experimental session. They also were asked to rate their current interest in quitting smoking on a scale from 1 ("Not at all interested") to 10 ("Extremely interested"), also at the end of the experiment. Results indicated that, on average, participants did try to regulate their craving during the experiment (M = 3.5, SD = 1.2) and remained interested in quitting after its completion (M = 8.6, SD = 1.2), with the Self-Focused and Other-Focused coping strategy groups responding similarly on these measures [attempt to reduce craving: $t(55) = 1.4$, $p > .1$; interest in quitting: $t(55) = 1.2$, $p > .2$]. While these indices are clearly subject to biases in self-report and, in the case of the question concerning reducing urge, biases in memory, they are at least consistent with the idea that participants were in the intended motivational state during the experiment. Moreover, while most participants in the current study did choose to smoke, the fact that a sizeable minority did not is notable, as prior research indicates that it is typical for all non-treatment-seeking individuals with comparable smoking habits to smoke when given an opportunity to do so following cue exposure (M. Sayette, personal communication).

4.0 DISCUSSION

The overarching aim of this study was to investigate the neurobiological correlates of attempts to modulate cue-elicited affect as a function of the cognitive coping strategy that was employed. It was hypothesized that strategies differing in degree of self-reference would be associated with the activation of distinct regions of the prefrontal cortex. A second aim of the study was to investigate whether non-self-referential and self-referential coping strategies are differentially moderated by individual differences in working memory capacity, with the prediction that the former would be more strongly influenced by memory ability than would the latter.

Before discussing the outcome of these aims and the results of the study, it is useful to discuss the methodological context in which the present findings were obtained. Unlike most prior smoking cue exposure research, participants in the current study indicated that they were interested in quitting. Moreover, individuals in the current study were trained to use cognitively oriented coping techniques and were asked to engage in these strategies while being exposed to a cigarette cue, which further distinguishes the current methods from those used in previous investigations. The cue exposure/coping manipulation was specifically designed to induce conflict between intentions to abstain and desires to quit, thereby modeling the difficult scenario faced by individuals who suddenly encounter an opportunity to smoke early during a cessation attempt.

Because of the unique nature of this manipulation and the likelihood that it would lead to a complex pattern of responses, it was important to use a multidimensional assessment of cue-reactivity. Specifically, the effects of cue exposure were evaluated across self-report, psychophysiological, and neurobiological response systems, with this approach yielding mixed results. Among the modalities that were assessed, the effect of cue exposure on self-reported urge was of primary interest. Research indicates that self-reported urge is the most sensitive index of cue-reactivity (Carter & Tiffany, 1999). Specifically, urge ratings during exposure to drug cues typically are much higher than during the presentation of neutral stimuli. Recent findings suggest that the modified cue exposure methods that must be utilized in neuroimaging research (such as the use of an unlit cigarette) elicit significant increases in self-reported urge, as noted above (Brody et al., 2004; Brody et al., 2002; Franklin et al., 2007; Wilson et al., 2005). Accordingly, it was expected that self-reported urge would be an adequately sensitive index of the effects of the cue exposure/coping manipulation used in the current study.

It is therefore noteworthy that the procedure used in the current study was not associated with increases in urge ratings. Significant cue-reactivity was observed, however, in the nonverbal response modalities that were assessed. Specifically, the cigarette/coping condition was associated with greater heart rate and activation of the anterior cingulate than the tape condition. These findings are encouraging, as research has demonstrated that drug cue exposure is reliably associated with increases in heart rate (Carter & Tiffany, 1999) and activation of the anterior cingulate cortex (Brody et al., 2004; Brody et al., 2002; Brody et al., 2007; Childress et al., 1999; Daglish et al., 2001; David et al., 2005; E. Duncan et al., 2007; Filbey et al., 2008; Garavan et al., 2000; Grusser et al., 2004; Heinz et al., 2004; Heinz et al., 2007; Kilts et al., 2004; Kilts et al., 2001; Langleben et al., 2008; Lee et al., 2005; Lim et al., 2005; Maas et al.,

1998; McBride et al., 2006; McClernon et al., 2005; McClernon, Hiott et al., 2007; McClernon, Hutchison et al., 2007; McClernon et al., 2008; Myrick et al., 2004; Okuyemi et al., 2006; Sell et al., 1999; Smolka et al., 2006; Tapert et al., 2004; Tapert et al., 2003; Z. Wang et al., 2007; Wexler et al., 2001; Wilson et al., 2005; Wrase et al., 2002; Xiao et al., 2006).

The cue exposure/coping manipulation had dissociable effects on verbal and nonverbal indices of cue-reactivity. It is possible that this reflects the influence of factors such as response bias on self-report, whereas physiological and neurobiological measures may have been less sensitivite to these effects. It has been noted that self reports of urge do not correspond perfectly with the actual subjective experience of the rater (Sayette et al., 2000). Rather, myriad factors can influence the degree of correspondence between self-report and subjective state (e.g., individual differences in socially desirable responding). Furthermore, cue-elicited urge ratings vary significantly as a function of the context in which cues are presented, including whether or not participants anticipate actually using the drugs to which they are being exposed (Wertz & Sayette, 2001). In the current study, participants were explicitly recruited because they had an interest in quitting smoking and were asked to engage in coping during cue exposure. Accordingly participants may have been reluctant to acknowledge and/or report high levels of urge during the presentation of the cigarette cue. Providing some support for this idea, urge assessed during exposure to the cigarette was negatively correlated with scores on a measure of the tendency to respond in a socially desirable manner.

An alternative explanation for the lack of a significant effect on self-reported urge concerns aforementioned differences between the cue exposure protocol employed in the current study and the procedures typically used in prior research. Specifically, participants were asked to engage in coping while being exposed to the cigarette cue in the present study, whereas

participants in prior studies generally were not asked to engage in any form of self-regulation. It is possible that this coping was effective to some degree, constraining the extent to which cue exposure was associated with increases in urge ratings. If this explanation is correct, it would suggest that coping has different effects on self-report and nonverbal measures of cue-reactivity. In accord with this general idea, craving response measures often are uncorrelated or only weakly correlated (Tiffany, 1990), perhaps due in part to weak craving manipulations (Sayette et al., 2003).

Early work on the behavioral treatment of fear and avoidance suggests that discordance between verbal/subjective and behavioral responses is more likely early in treatment and under conditions of high demand (e.g., when motivation is high) (Hodgson & Rachman, 1974). In the present research, participants were taught to utilize coping in order to enhance their motivation and ability to remain abstinent, but they received only a minimal amount of training. The observed dissociation may therefore represent initial evidence of the influence of coping on cue reactivity that was detected in the self-reported urge measure, while nonverbal measures continued to reflect increases in arousal associated with cigarette cue exposure. It would be interesting to examine the effects of more extensive coping training across self-report and nonverbal responses to cue exposure.

In summary, the cue exposure/coping manipulation used in this study was associated with an atypical pattern of self-reported urge ratings, perhaps due in part to response biases and/or the effects of coping. More effects similar to those found in prior research were observed for heart rate and anterior cingulate activation, providing some support for the effectiveness of the procedure. In the remainder of this section, results are reviewed in light of the central aims and hypotheses of the study. In line with the key hypotheses of the study, particular emphasis is

placed upon effects localized to the DLPFC and medial cortical structures. Limitations and potential extensions of this work also are discussed.

4.1 CUE EXPOSURE/COPING AND ACTIVATION OF THE DLPFC

Based upon a review of the neuroimaging cue reactivity literature, my colleagues and I recently have proposed that the functions supported by the DLPFC may play an important role in the regulation of cue-elicited affective responses under certain conditions, such as when drug use intentions and perceived drug use opportunity conflict (Wilson, Sayette et al., 2004; Wilson, Sayette, & Fiez, 2007). In the current study, participants had an expressed interest in quitting but, unlike past work (e.g., A. J. Waters et al., 2004), were not required to exceed specific thresholds with respect to their motivation to quit and abstinence self-efficacy. This approach was taken in an effort to recruit individuals who would be representative of the smoker who would like to quit smoking, but who struggles against strong desires to continue smoking. Additional manipulations were employed to enhance motivational conflict during cue exposure. Specifically, participants were asked to engage in coping while being exposed to a cigarette cue, which presumably would enhance their drive and ability to resist the temptation to smoke. They also were informed, however, that they would be given a chance to smoke immediately following cue exposure. The overarching objective of this procedure was to model the relapse-prone situation in which a recently abstinent smoker is tempted by an opportunity to smoke.

On the basis of the above, it was predicted that such circumstances would be associated with significant activation of the DLPFC for both the non-self-referential (Other-Focused) and self-referential (Self-Focused) coping strategies. It was also hypothesized, however, that a non-

self-referential strategy would be associated with relatively greater activation of the DLPFC than a strategy that entailed the use of self-referential information. Results provided only limited support for these propositions. Specifically, the Self-Focused strategy was associated with significant activation of the DLPFC during cigarette cue exposure. In contrast, while activation of the DLPFC was in the expected direction for the Other-Focused coping condition, cigarette-related increases failed to reach significance for this group.

Prior research suggests that the simple maintenance of information does not reliably recruit the DLPFC unless the amount of information exceeds capacity limitations. For instance, maintaining six, but not three, English letters over a delay period is associated with significant activation of the DLPFC (Rypma & D'Esposito, 1999). Activation of the DLPFC is further increased by requiring that maintained information be manipulated in some way. For example, the DLPFC is significantly more active over a delay period in which 5 randomly sequenced letters or words are reordered alphabetically than when the items are maintained in the presented order (Barde & Thompson-Schill, 2002; D'Esposito, Postle, Ballard, & Lease, 1999). One potential explanation for the current results is that it was more effortful for participants in the Self-Focused condition to recall and maintain the concrete information they generated regarding the personal benefits of quitting smoking than it was for those in the Other-Focused condition to focus upon the benefits that quitting would have on someone close to them.

It is also possible, however, that the combined cue exposure/coping manipulation was *more* demanding for the Other-Focused group than the Self-Focused group, in accord with predictions. The degree to which task demands drive increases in activation of the DLPFC is not unbounded. Instead, research indicates that task-related activation of the DLPFC is constrained such that increasing load beyond some threshold results in decreases, rather than further

increases, in the response of this region (Adcock, Constable, Gore, & Goldman-Rakic, 2000; Bunge, Klingberg, Jacobsen, & Gabrieli, 2000; Callicott et al., 1999; Goldberg et al., 1998; Klingberg, 2000). At present, it is not clear whether this pattern reflects physiological limitations (Callicott et al., 1999; E. K. Miller & Cohen, 2001), motivational factors (Jaeggi et al., 2003) or some combination of these and other variables. Nonetheless, these findings point towards an alternative explanation for the group differences in DLPFC activation observed in the current study. Specifically, the Other-Focused group may have failed to demonstrate significant cue effects in the DLPFC because task demands had already reached or exceeded the upper limit of available resources. For example, participants in the Other-Focused condition may have started to actively think about their self-generated coping material upon being exposed to it at the beginning of the experimental session, whereas those in the Self-Focused group did not engage in such cognitive activity (or did so to a lesser extent).

Recent research has provided some support for the notion that substance users exhibit reductions in the ability to recruit the DLPFC to meet increasing task demands under certain circumstances. Xu et al (2005) examined neural activation in cigarette smokers during the performance of a verbal n-back task using fMRI. Participants completed n-back blocks with varying memory load (1-back, 2-back, and 3-back) in two experimental sessions on separate days. Prior to one session, participants abstained from smoking for 14 hours; participants smoked a cigarette prior to the other session (session order was counterbalanced across participants). Comparison of task-related brain activation yielded a significant interaction between test session (satiety, abstinence) and task load (1-back, 2-back, and 3-back) in the DLPFC. Specifically, task-related DLPFC activation in the satiety condition was relatively low during performance of the 1-back task, but was greater at the more difficult task levels. In

contrast, task-related DLPFC activation in the abstinence condition was relatively high at the 1-back level and did not increase further at the more difficult task levels.

My colleagues and I have observed similar effects of cue exposure on task-related DLPFC activation. In a study in which smokers performed a verbal n-back task during which they were presented with smoking-related and neutral stimuli, we found that increases in the difficulty of the task were associated with concomitant increases in activation of the DLPFC when the task was performed in the presence of non-drug cues, but already elevated levels of activation were not further increased as the task became more difficult when the task was performed in the presence of smoking-related cues (Wilson, Brough, Fiez, & Sayette, 2004). If for some reason the Other-Focused coping was less effective than the Self-Focused coping even *before* the presentation of smoking cues (with the former already drawing heavily upon the DLPFC prior to cue exposure), those using the former may have been limited in the degree to which they could recruit processes mediated by the DLPFC during exposure to the cigarette.

Still another possibility is that the observed pattern of DLPFC activation stems from differences between groups in susceptibility to interference. As noted above, there is strong evidence that drug cue exposure is associated with enhanced attentional allocation towards drug-related information under many conditions (Robbins & Ehrman, 2004; Sayette, 1999). The cigarette cue may therefore have served as a distracter vis-à-vis the performance of coping. Recent studies have shown that the presentation of distracters during the performance of working memory tasks is associated with an attenuation of maintenance-related DLPFC activation (Dolcos, Diaz-Granados, Wang, & McCarthy, 2008; Yoon, Curtis, & D'Esposito, 2006). On the basis of such findings, it has been proposed that "sensory gating" (reducing interference from task-irrelevant sensory information) may be one function of the DLPFC activation commonly

observed during the delay period of working memory tasks (Postle, 2005). According to this view, the lack of cue-related DLPFC activation exhibited by the Other-Focused group may reflect increased attention towards the cigarette cue, which might have disrupted their ability to sustain coping. In contrast, the significant cue-elicited activation of the DLPFC demonstrated by the Self-Focused group may indicate that this group was less distracted by the smoking cue and more capable of maintaining coping information in active memory.

Additional research is needed to determine whether the lack of DLPFC activation associated with the use of Other-Focused coping reflects greater or lesser effort relative to the utilization of Self-Focused coping, or perhaps whether differences in interference susceptibility underlie the observed effects. Ideally, such work would involve parametric manipulations of the degree of coping difficulty and the salience of the drug cue, which may be difficult to achieve in practice. There may be ways, however, of inducing broadly dissociable levels of difficulty and/or distractibility. For instance, research has demonstrated that smokers are more responsive to drug cues when deprived than when non-deprived (e.g., Sayette et al., 2001). Therefore, it may be predicted that smokers would have a harder time coping as deprivation increases. Examining the relationship between DLPFC activation and deprivation state might therefore be informative regarding the extent to which the region is influenced by coping difficulty.

4.2 GROUP DIFFERENCES IN FUNCTIONAL CONNECTIVITY

4.2.1 Differential coupling of the right DLPFC and medial cortical regions.

Based upon recent findings from the emotion regulation literature, it was hypothesized that the Self-Focused strategy condition would be associated with comparatively greater activation of portions of the anterior medial prefrontal cortex during cigarette cue exposure than the Other-Focused strategy condition (Ochsner et al., 2004). Traditional analyses failed to provide support for this hypothesis. Results from a multivariate analysis assessing functional connectivity during cigarette cue exposure indicated, however, that activation of the right DLPFC was coupled with activation of medial cortical structures for both the Self-Focused group and the Other-Focused group. The precise regions of the medial frontal cortex with which the DLPFC was correlated differed between groups. Specifically, activation of the right DLPFC was positively correlated with the activation of a region of the dorsomedial prefrontal/rostral anterior cingulate for both groups, although the relationship was stronger for the Self-Focused group than the Other-Focused group (see Figure 7). In contrast, right DLPFC activation was positively correlated with activation of the ventromedial prefrontal/ventral anterior cingulate for the Other-Focused group, but not the Self-Focused group (see Figure 8).

These findings must be considered preliminary given the exploratory manner in which they were obtained. Moreover, it is important to note that the functional connectivity analyses used herein are correlational in nature, which precludes specification of the direction of observed relationships. Nonetheless, the observed pattern is intriguing, as research suggests that the medial cortical wall is comprised of functionally distinct subregions along a dorsal/ventral axis (Bush, Luu, & Posner, 2000; Northoff et al., 2006; Phillips, Drevets, Rauch, & Lane, 2003;

Schmitz & Johnson, 2006). Particularly relevant to the current study, Phillips and colleagues (2003) have argued that a ventral system consisting of ventral regions of the anterior cingulate and prefrontal cortex, as well as the amygdala, insula, and ventral striatum, is important for the identification and representation of the emotional significance of environmental stimuli and the corresponding generation of emotional states. In contrast, they suggested that a dorsal system including dorsal portions of the anterior cingulate and prefrontal cortex contributes to the effortful regulation of emotion.

Altogether, the current findings indicate that the Self-Focused coping strategy was associated with significant cue-elicited activation of the DLPFC that covaried with the activation of the dorsomedial prefrontal/rostral anterior cingulate cortex. According to contemporary models, the anterior cingulate supports cognitive control via the detection of conflict or errors in information processing and the relay of this information to the DLPFC which, in turn, implements adjustments in control on the basis of this input (Botvinick et al., 2004; Brown & Braver, 2005; Kerns et al., 2004; MacDonald et al., 2000). Although the so-called cognitive division of the anterior cingulate is typically considered to be caudal to the site identified in the present study, these patterns are broadly consistent with the idea that executive control resources were utilized during cigarette cue exposure by the Self-Focused group.

Results paint a slightly different picture for the Other-Focused condition. For this group, the cue exposure/coping manipulation was not associated with significant activation of the DLPFC (although means were in the expected direction). Functional connectivity analysis revealed, however, that cigarette-related activation of the DLPFC was positively correlated with the dorsomedial prefrontal/rostral anterior cingulate for the Other-Focused group, providing some evidence that this coping strategy also was associated with the employment of executive

control resources. Only the Other-Focused condition was associated with significant functional connectivity of the DLPFC and ventromedial prefrontal/ventral anterior cingulate. That DLPFC activation was coupled with both dorsomedial and ventral portions of the anterior cingulate for the Other-Focused condition is interesting, as research suggests that these structures have a mutually inhibitory functional relationship. That is, tasks that are associated with increased activation of dorsal regions of the anterior cingulate also typically are associated with decreased activation of the ventral anterior cingulate, and vice versa (Bush et al., 2000; Drevets & Raichle, 1998). It has been proposed that these dynamic interactions occur in part because affective processing might interfere with ongoing cognitive operations (e.g., in the form of distracting emotional thoughts or responses to affectively-salient stimuli) and the suppression of such processing is an important part of task performance (Gilbert & Fiez, 2004). One potential explanation for the results obtained in the current study is that executive control resources were devoted both to "cognitive" operations associated with coping and "emotional" processing related to the salience of the cue and the urge to smoke. Presumably, such coincident processing may serve to undermine the effects of coping.

In contrast, the possibility that the functional connectivity of the DLPFC with both the dorsal and ventral anterior cingulate was beneficial for coping cannot be ruled out. Such an effect may indeed explain, at least in part, why cigarette/coping-related activation of the right DLPFC was negatively associated with activation of the cuneus only for the Other-Focused group. As previously discussed, a recent study by Brody and colleagues (2007) found that smokers exhibited less activation of visual processing regions including the cuneus when directed to refrain from craving during cue exposure. Ventromedial prefrontal and anterior cingulate cortices each are strongly connected to regions associated with basic

emotional/motivational processing (Bush et al., 2000; Ongur & Price, 2000) and the simultaneous activation of these areas and the DLPFC by the Other-Focused group may have been in the service of regulating cue-elicited affective responses. For example, they may have focused on the emotional effects of quitting smoking on someone close to them, with the ventral anterior cingulate activation reflecting representation of this emotional material (e.g., Mom will be proud of me) rather than the salience of the smoking cue. The Other-Focused group may therefore have brought both "cognitive" and "emotional" information to bear during coping, allowing them to successfully shift visual attention away from the cigarette cue. In contrast, the Self-Focused group may have relied primarily on more concrete information for coping (e.g., my teeth will not be stained), which perhaps was less effective at facilitating the disengagement of attention from the cigarette.

The current data do not permit a strong stance to be taken regarding which of the aforesaid possibilities, if any, are responsible for the present findings. This study is limited in particular by an inability to examine dynamic relationships between neural activation and subjective experience. As discussed further in the concluding section of this document, additional research employing methods that assay both cue- and coping-related responses as they unfold over time would be quite informative, and may help disentangle precisely how the brain regions implicated in the current study interact.

4.2.2 Potential laterality effects in functional connectivity of the DLPFC.

As noted above, medial cortical structures, which exhibited functional connectivity with the right DLPFC, were of primary interest in the current study. Differential effects of cue exposure/coping on the left versus right DLPFC were not anticipated in the current study and

were not explicitly modeled in analyses. Observed laterality effects therefore must be interpreted cautiously. Nevertheless, the current results are intriguing, as recent studies using repetitive transcranial magnetic points have identified differences between the involvement of the left and right DLPFC in various processes and behavior, including drug craving (Camprodon, Martinez-Raga, Alonso-Alonso, Shih, & Pascual-Leone, 2007) and risk-taking (Knoch, Brugger, & Regard, 2005; Knoch et al., 2006). This literature is in its infancy and more work is needed to clarify precisely how the functioning of left and right DLFPC differ. The present findings suggest that investigating the nature and implications of such laterality effects in the domain of coping would be informative. For instance, it is noteworthy that activation of the left DLPFC was associated with greater activation of the right inferior frontal gyrus for the Other-Focused group, but not the Self-Focused group, as this region has been implicated in various forms of response inhibition (Aron, Robbins, & Poldrack, 2004). Additional research is needed to determine the extent to which this relationship was functionally relevant for coping with cue-elicited responses.

4.3 (LACK OF) WORKING MEMORY EFFECTS

The second aim of the current study was to examine whether non-self-referential (Other-Focused) and self-referential (Self-Focused) coping strategies are differentially moderated by individual differences in working memory capacity. Because working memory capacity has been linked to the functioning of the DLPFC, and because Other-Focused coping was expected to rely heavily upon the DLPFC, it was predicted that individual differences in working memory capacity would significantly moderate the magnitude of cue-elicited activation of the DLPFC

and other indices of cue-reactivity during the performance of this strategy. In contrast, because the Self-Focused coping was predicted to draw more heavily upon the processes supported by medial cortical structures, it was hypothesized that working memory capacity would have less of a modulatory effect on activation of the DLPFC and cue-reactivity during the use of this technique.

Results failed to support these predictions, perhaps due to the different conditions under which the working memory assessment and the cue exposure/coping manipulation occurred. The behavioral assessment of working memory was conducted during the initial screening session when participants were minimally deprived from nicotine. In contrast, they were asked to engage in coping during cue exposure after abstaining from smoking for at least 12 hours. As noted above, nicotine deprivation has been found to disrupt the working memory performance and memory load-related activation of smokers (Mendrek et al., 2006; Xu et al., 2005). The failure to observe expected relationships between working memory capacity and cue-reactivity may therefore stem, at least in part, from unanticipated effects of deprivation on working memory functioning. It should be noted, however, that the study was designed specifically to examine the relationship between stable (i.e., not situational) working memory abilities and cue reactivity, and the failure to observe such effects may also reflect a different pattern of associations than was expected (e.g., working memory capacity may have affected both coping and cue-reactivity in a similar manner, rather than in the interactive fashion that was predicted). Future research exploring these possibilities would be useful.

4.4 VARIABLES RELATED TO THE DECISION TO SMOKE

A secondary aim of the present investigation was to preliminarily investigate the relationship between cue-reactivity and clinically-relevant outcomes. Participants in the study were given an opportunity to smoke shortly following cue exposure, allowing for an examination of whether there were systematic differences in cue-elicited responses between those who chose to smoke and those who did not. Results from these analyses revealed that those who refrained from smoking during the study were less nicotine dependent than were those who chose to smoke. This is consistent with research demonstrating that nicotine dependence is negatively associated with intentions to quit smoking and success upon attempting cessation (Agrawal, Sartor, Pergadia, Huizink, & Lynskey, 2008; Hellman, Cummings, Haughey, Zielezny, & O'Shea, 1991) and positively correlated with cue-elicited craving (Donny, Griffin, Shiffman, & Sayette, 2008).

Results otherwise provide little evidence for differences between those who smoked and those who did not with respect to cue-elicited psychophysiological and neurobiological responses. This may reflect another example of conditions under which there is discontinuity across measures of cue-reactivity (see above). More likely, the failure to observe significant effects was due to limited power to detect effects given the small number of individuals who did not smoke during the study, as recent investigations have observed relationships between level of nicotine dependence and neural responses to smoking-related cues in smokers (McClernon et al., 2008; Smolka et al., 2006). Such findings suggest that differences in neural activation patterns should have been found in the current study between those who smoked and those who did not, as the former were more nicotine dependent than the latter. Accordingly, additional research with larger samples comparing those who smoke versus those who do not is indicated.

4.5 LIMITATIONS OF THE CURRENT STUDY

While potential weaknesses of the current research have been noted throughout, two important limitations of the study bear repeating. First, and most significant, the failure to observe significant influence of cue exposure on self-reported urge was unexpected and stands in contrast to a large behavioral literature documenting such effects. Potential explanations for this result were offered, with an emphasis on unique aspects of the methods of the current research relative to prior studies (i.e., that participants in this study were asked to engage in coping during cue exposure). Nevertheless, these interpretations await direct empirical scrutiny. Second, although the objective of the study was to examine the effects of coping and cue exposure on smokers in the early stages of a quit attempt, most participants chose to smoke when given the opportunity. This raises important questions regarding their motivational state during the experiment. Thus, while some evidence indicated that participants did indeed attempt to reduce the urge to smoke during cue exposure, the possibility that participants were not in the motivational state of interest cannot be ruled out. That most participants smoked also may have limited the ability to fully evaluate hypotheses regarding coping, as coping did not appear to be particularly effective at a behavioral level.

4.6 SUMMARY AND FUTURE DIRECTIONS

There is strong evidence that successful coping is critical for preventing relapse during high risk situations in those trying to quit smoking. For reasons that remain largely unknown, however, many individuals succumb to temptation under such circumstances despite reporting the use of

coping. The overarching goal of this study was to address this important knowledge gap. More specifically, the first aim of the study was to examine the neural correlates of the use of two different forms of cognitive coping during drug cue exposure, with the prediction that the use of a non-self-referential strategy would be associated with relatively greater activation of the DLPFC than a strategy that entailed the use of self-referential information. In contrast, it was hypothesized that a strategy that involved the generation and maintenance of self-relevant information would be associated with comparatively greater activation of portions of the anterior medial prefrontal cortex than a strategy in which the focus is on non-self-referential information. The second aim of the study was to examine whether non-self-referential and self-referential coping strategies are differentially moderated by individual differences in working memory capacity, with the hypothesis that individual differences in working memory capacity would more strongly moderate the magnitude of cue-elicited activation of the DLPFC during the use of a non-self-referential coping strategy than during the use of a self-referential coping strategy.

Notwithstanding the limitations noted above, results from the current study represent an important first step towards achieving these objectives. Findings suggest that the two coping strategies evaluated in the present study indeed were associated with different patterns of neural activation during cue exposure, although results proved to be more complex than initially hypothesized. Specifically, the Self-Focused coping condition appeared to be associated with the significant engagement of executive control functions. The Other-Focused coping condition did not appear, at first glance, to rely heavily upon such processes. Results from functional connectivity analyses suggested, however, that there was a similar relationship between regions of the brain supporting executive control for the Other-Focused and Self-Focused groups, although the association was weaker for the former. In contrast to expectations, working

memory capacity did not differentially moderate the activation of the DLPFC and measures of cue reactivity as a function of coping strategy, perhaps due to the different conditions under which the working memory assessment and cue exposure occurred. Additional research is needed to elucidate the functional implications of the current findings. In particular, it would be useful to examine the extent to which the apparent lack of executive control utilization during the use of Other-Focused coping reflects overburdened resources, interference effects, or some other factor(s).

In addition to pointing towards areas for additional research regarding the neurocognitive substrates of coping, the current study has important methodological implications. An overarching goal of the study was to examine cue-reactivity in smokers under conditions that have not previously been investigated in detail. Specifically, an attempt was made to create in participants a high degree of conflict between the intention to abstain and the urge to smoke by asking them to quit smoking and subsequently presenting them with smoking cues and an opportunity to smoke. This manipulation presented significant methodological challenges with respect to inducing such a state, as well as how best to assess the outcomes with which the manipulation was associated. Results from the study provide preliminary support for the idea that this unique motivational state can be produced under controlled laboratory conditions. As the results from such research stand to greatly inform our understanding of addiction and relapse, additional work using this approach is indicated. Findings from the current study also underscore the importance of using a multidimensional approach to examining cue-reactivity, particularly under the circumstances outlined above. Finally, this study highlights the potential utility of incorporating analyses for assessing connectivity in the study of the neural correlates of cue reactivity and coping.

Findings from the current study provide support for the idea that efforts to regulate cue-elicited responses rely in part upon neural systems that subserve domain-general executive control processes. A critical next step is determining precisely how regions such as the DLPFC and the operations that they support exert control over responses evoked by drug cues. Toward this end, additional research in which the relationship between neurocognitive processing and the efficacy of self-regulation may be assessed with greater precision would be particularly useful. For example, recent research has demonstrated the feasibility of methods permitting the continuous assessment of self-reported emotional experience (Hutcherson et al., 2005). The application of such techniques to the study of coping and cue-reactivity would help illuminate relationships between moment-to-moment changes in neural activation and self-reported urge. Similarly, research on the neurocognitive correlates of coping during cue-reactivity may benefit from the inclusion of eye tracking technology, as research has indicated that the assessment of eye gaze can be greatly informative for understanding the process of emotion regulation (van Reekum et al., 2007) and cue-elicited craving (Rosse et al., 1997). The use of methodologies such as dynamic experience sampling and eye tracking, coupled with analytic techniques that permit inferences regarding causation (e.g., Granger causality analysis), would stand to greatly advance our knowledge of the process of coping. Finally, additional studies focusing on how coping-related information is generated and recalled, as well as those incorporating more intensive coping training procedures, would be useful.

APPENDIX A

COPING STRATEGY MATERIAL GENERATED BY PARTICIPANTS

Information generated by Self-Focused participants:

I thought how nice it would be to not have to smell smoky anymore and how I'd never have to duck a function because I needed a cigarette
Longer life, no more burnt clothes, no shortness of breath, no clothes that smell like smoke, save a lot of money.
Not getting lung cancer.
No more phlegm. Better long term health.
I was thinking if I didn't smoke I would save a lot of money. I would also have a healthier body.
I was thinking about it being easier for me to exercise without getting out of breath and not getting sick as much.
Smell better. No stains on hand from cigs (yellow). No more burned fingers, clothes, anything. No lung cancer. Better breath. Improved stamina.
I was thinking of being able to be more efficient when doing physical activities - like running and swimming, what I could do with the extra money I would have from not spending it on smoking, I would be less moody.
I won't get lung cancer and other respiratory diseases. I will able to live a long and healthy life if I quit. I will not cough or feel winded if I quit.
My health. Save money. Smelling like an ashtray.
I was thinking about my health and saving money. Thinking about the effect smoking has on my teeth and skin. Thinking about how more active I would be if I didn't smoke.
I was thinking about how I will be in better shape, that I will save 10 or more dollars a day, that my teeth will look better and that I will overall just feel better.

Information generated by Self-Focused participants (continued):

Health benefits. Not smelling like cigarettes. Lung cancer. No more coughing. Being able to run again.
Teeth will be whiter. Breathe better. More energy. More money. Won't smell like cigarettes. No lung cancer.
I won't have yellow teeth, lung cancer, smoker's breath, more money in pocket. My fingers will turn to normal shade.
I'll be able to breathe better. No nicotine stains on fingers, or cigarette smells on clothes. Have more energy and be more active.
I will reduce risk of lung cancer. I will save some money. I will overall be more health conscious. I won't get tar all over my fingers. I won't stink! Oral care will improve!
I won't get sick all the time and I'll be able to run again. No yellow fingernails and no smell. Be around for my kids.
Save money. Be much healthier. Fresher breath. Clothes won't smell of smoke. Cleaner lungs.
Live longer. No holes in clothes. Save money. Feel better.
Be able to breathe clearly. Lower risk of lung cancer.
Extend my life span. Teeth won't be as stained. Save money. My house wouldn't smell like tobacco smoke. I could get more work done at work.
Won't have to buy new clothes every week. Windshield won't need to be cleaned. Won't have to work so much.
I was thinking that quitting smoking would greatly benefit my health. I would be able to maintain my breath while walking or running a lot better. I also was thinking about how nasty cigarettes really are as far as smell of my breath and clothes.
Save money. No cancer. Can still be cool. No smoky hands.
Dying. Lung cancer. Save money. Teeth.
Longer breath. Good teeth. Healthier lungs. Save money.

Information generated by Other-Focused participants:

I was imaging my Mom with a smile of approval. Since she has cancer - she would be most appreciative if I quit being that smoking is a major carcinogen
I was able to picture my friend [friend's name], positive affect of quitting smoking on her - my friend glad I quit
I was thinking about my mother and how pleased she would be to find me not smoking. Mom would be so happy for me.
I was thinking about how much [son's name] wants me to quit smoking. He is aware that it is not good for you, and he doesn't want me to have health problems related to smoking.
It would save [sister's name] a lot more money because I am always borrowing from her. She hates the smell. She can wake up to a smoke free house and don't have to worry about secondhand smoke.
I thought that [trainer's name] would be extremely pleased if I quit. Not only for the obvious health reasons, but also that I gave him my word that I would quit smoking and that I would take my training much more seriously.
[Sister's name] would love for me to live a long life by smoking - she tells me to stop. I love her for staying on me. She worries about me.
Positive effects quitting smoking would have on my daughter.
What quitting would mean to my daughter. She is in first grade came home and told me I was going to die if I didn't stop smoking.
How happy my Aunt would be if I quit smoking because she is against smoking and cancer runs in my family.
My girlfriend would be very pleased if I stopped smoking because she feels it is a very negative habit. My girlfriend would no longer look at me with a look of disgust.
Positive effects quitting smoking would have on my wife.
How [stepson's name] would love for me to not smoke cause he knows that it is not good for me. He knows for me quitting would be better cause I'll be around longer with him in the long run.
My Mom would not have to worry about me having lung and overall health issues and she could see my music career go further.
That my Mom won't have to worry and she won't have to see me light a cigarette. That she will be proud.
My Grandma would not have to worry about my health issues I have when I smoke.
[Roommate's name] won't have to lend me money to buy cigarettes.
Was thinking of the positive effects quitting will have on my son.

Information generated by Other-Focused participants (continued):

That [son's name] wouldn't pick up the habit because he knows that smoking is bad and that everything I do he wants to do and smoking is the one thing that I don't want him getting from me and thinking that it's cool.
If I quit, [friend's name] might quit too. She would be happy for me.
My Mom will be proud of me. She won't have to worry about me getting lung cancer. She won't have to worry about house smelling like smoke.
Reduces [girlfriend's name] chance of starting. Healthier for her (on birth control).
My Aunt would be happy that I quit and she would not have to give any more lectures on quitting smoking. She wouldn't have to breathe in my secondhand smoke.
I would help my girlfriend quit. She won't have to worry about my health. She'll be happy I'm saving money.
Mom won't need to help with cigarette money.
Positive effects on my Mom if I quit.
My daughter won't breathe in my secondhand smoke. I'll be alive to see her get married. She won't watch me get sick. She won't think it's ok to smoke by watching me smoke.
My son doesn't need to see his father lighting a cigarette and smoking. My son doesn't need to breathe secondhand smoke. He will be more joyful and will not look at me strangely when I smoke.
[Friend's name] would know that I care about her. It would give her meaning.
Mom will be happier.
That [son's name] wouldn't pick up the habit because he knows that smoking is bad and that everything I do he wants to do and smoking is the one thing that I don't want him getting from me and thinking that it's cool.
If I quit, [friend's name] might quit too. She would be happy for me.
My Mom will be proud of me. She won't have to worry about me getting lung cancer. She won't have to worry about house smelling like smoke.
Reduces [girlfriend's name] chance of starting. Healthier for her (on birth control).
My Aunt would be happy that I quit and she would not have to give any more lectures on quitting smoking. She wouldn't have to breathe in my secondhand smoke.
I would help my girlfriend quit. She won't have to worry about my health. She'll be happy I'm saving money.

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Table 1. Sample characteristics (means with standard deviation).

Variable	Full sample (n = 57)	Self-Focused group (n = 28)	Other-Focused group (n = 29)	*P*
Age in years	33.61 (8.52)	32.43 (8.67)	34.76 (8.36)	> .3
Cigarettes per day	20.18 (6.02)	20.21 (6.84)	20.14 (5.23)	> .9
Number of quit attempts	3.59 (5.62)	3.08 (4.69)	4.04 (6.39)	> .5
NDSS: Total	0.13 (0.85)	0.08 (0.81)	0.17 (0.9)	> .7
NDSS: Drive	0.07 (0.96)	-0.14 (1.06)	0.28 (0.83)	> .1
NDSS: Priority	-0.22 (1.07)	-0.32 (1.16)	-0.13 (1)	> .4
NDSS: Tolerance	-0.31 (0.96)	-0.16 (0.89)	-0.44 (1.02)	> .2
NDSS: Continuity	-0.18 (1.03)	-0.37 (1.06)	-0.01 (0.99)	> .1
NDSS: Stereotypy	0.39 (1.02)	0.46 (1.11)	0.33 (0.94)	> .6
RSEQ: Global ASE	2.2 (0.41)	2.25 (0.44)	2.16 (0.39)	> .4
RSEQ: Negative Affect	1.6 (0.69)	1.6 (0.74)	1.6 (0.65)	> .9
RSEQ: Positive Affect	2.81 (0.55)	2.86 (0.58)	2.76 (0.53)	> .5
RSEQ: Social-Food Situations	1.79 (0.67)	1.91 (0.79)	1.68 (0.52)	> .1
RSEQ: Idle Time	2.15 (0.57)	2.24 (0.69)	2.08 (0.43)	> .2
RSEQ: Restrictive Situations	2.74 (0.62)	2.75 (0.61)	2.74 (0.64)	> .9
RSEQ : Low Arousal	2.42 (0.57)	2.36 (0.6)	2.48 (0.55)	> .4
RSEQ : Craving	1.9 (0.64)	2.02 (0.71)	1.79 (0.54)	> .1
BIS-11: Motor Impulsiveness	21.47 (5.03)	21.36 (6.4)	21.59 (3.33)	> .8
BIS-11: Attentional Impulsiveness	18.32 (3.74)	18.39 (4.04)	18.24 (3.5)	> .9
BIS-11: Non-Planning Impulsiveness	28.88 (6.01)	28.86 (6.07)	28.9 (6.07)	> .8

(*table continues*)

Table 1 (continued)

	Full sample (n = 57)	Self-Focused group (n = 28)	Other-Focused group (n = 29)	*p*
TSCS	99.11 (18.41)	99.43 (18.5)	98.79 (18.64)	> .8
R-SCS: Private Self-Consciousness	16.89 (5)	16.86 (5.68)	16.93 (4.35)	> .9
R-SCS: Public Self-Consciousness	14.18 (4.07)	14.64 (4.42)	13.72 (3.72)	> .4
R-SCS: Social Anxiety	8.47 (4.81)	7.71 (4.74)	9.21 (4.85)	> .2
BIDR-6: Impression Management	4.79 (3.12)	5.57 (3.33)	4.03 (2.74)	= 0.06
BIDR-6: Self-Deceptive Positivity	5.56 (3.87)	6.04 (3.94)	5.1 (3.81)	> .3
PANAS-Trait: Positive Affect	33.56 (7.38)	33.07 (7.23)	34.03 (7.61)	> .6
PANAS-Trait: Negative Affect	18.77 (7.51)	18.25 (7.47)	19.28 (7.66)	> .6
OSPAN	52.51 (17.05)	52.09 (19.33)	52.92 (14.87)	> .8
BDS	6.19 (2.2)	5.75 (2.27)	6.62 (2.08)	> .1
Composite Working Memory	29.35 (8.99)	28.92 (10.23)	29.77 (7.78)	> .7

Abbreviations: BDS, Backwards Digit Span; BIDR-6, Balanced Inventory of Desirable Responding Version 6; BIS-11; Barrat's Impulsivity Scale Version 11; NDSS, Nicotine Dependence Syndrome Scale; OSPAN, operation word-span task; PANAS, Positive and Negative Affect Schedule; RSEQ, Relapse Self-Efficacy Questionnaire; R-SCS, Revised Self-Consciousness Scale; SEDS, State Ego Depletion Scale; TSCS, Trait Self Control Scale.

[a] Indicates a marginally significant difference between groups ($p < .1$).

Table 2. Effects of nicotine deprivation on subjective state (means with standard deviation)

	Full sample (n = 57)	Self-Focused group (n = 28)	Other-Focused group (n = 29)
PANAS-State: Positive Affect	28.79 (9.12)	28.46 (9.44)	29.1 (8.95)
PANAS-State: Negative Affect	16.4 (5.9)	15.82 (6.57)	16.97 (5.23)
SEDS	77.44 (31.81)	71.68 (28.96)	83 (33.92)
Affect-Baseline	7.09 (1.75)	7.14 (1.86)	7.03 (1.66)
Urge-Baseline	62.51 (25.66)	64.54 (22.58)	60.55 (28.59)

Table 3. Effects of cue-exposure/coping on urge and affect (means with standard deviation)

	Full sample (n = 57)	Self-Focused group (n = 28)	Other-Focused group (n = 29)
Urge-Tape	64.30 (28.8)	61.11 (30.18)	67.38 (27.58)
Urge-Cigarette	63.98 (31.68)	60.64 (33.1)	67.21 (30.48)
Affect-Tape	6.96 (2.28)	6.75 (2.69)	7.17 (1.81)
Affect-Cigarette	7.00 (2.33)	6.71 (2.72)	7.28 (1.89)

Table 4. Regions exhibiting a significant effect of n-back working memory load.

Region of activation	BA	Size (# voxels)	Talairach Coordinates x	y	z	Average F ratio
Superior / middle frontal g (R)	6	10	24	7	52	21.21
Middle frontal g (L)	8	40	-33	5	47	22.23
*Middle frontal g / DLPFC (L)	9/46	21	-46	19	28	22.31
*Middle frontal g / DLPFC (R)	9	51	37	30	26	23.42
Middle / superior / medial frontal g (B)	10	254	-33	52	3	24.99
Anterior cingulate g (B)	32	111	-2	17	39	26.30
Anterior cingulate g / medial frontal g (B)	32/10	47	1	36	-9	22.79
Postcentral g / inferior parietal lobe (L)	40	56	-37	-33	54	21.19
Inferior parietal lobe (L)	40/39	23	-45	-61	40	20.31
Inferior parietal lobe / supramarginal g (R)	40	80	44	-48	38	21.39
Precuneus (B)	7	96	0	-67	43	26.30
Precuneus (R)	19	17	32	-73	41	19.77
Superior occipital g (R)	19/39	11	39	-74	26	20.07
Middle occipital g (L)	19/18	19	-24	-87	19	20.80
Uncus / superior temporal g (R)	28/38	19	31	4	-28	20.14
Cerebellum / lingual g / cuneus (B)	17/18	524	35	-64	-21	23.83
Cerebellum (L)		21	-36	-70	-17	21.77

Stereotaxic coordinates are given for local maxima of activation cluster in Talairach and Tournoux (1988) atlas space. Abbreviations: B, bilateral; BA, Brodmann's area; DLPFC, dorsolateral prefrontal cortex; L, left hemisphere; g, gyrus; R, right hemisphere.

* Indicates a priori region of interest.

Table 5. Regions exhibiting significant effects in voxel-wise analysis of cue exposure data.

Region of activation	BA	Size (# voxels)	Talairach Coordinates x	y	z	Average F ratio	*p*
Main Effect of Cue							
Medial frontal / cingulate g (B)	6/24/32	164	-6	2	50	14.67	**
Middle frontal g / DLPFC (L)	10/46	34	-38	38	25	14.75	**
Medial frontal g (R)	10	11	10	50	21	14.00	**
Middle frontal g / DLPFC (R)	9/46	11	35	29	20	12.98	**
Anterior cingulate g (B)	32/24	10	-6	38	2	9.36	*
Precentral g (R)	6	11	5	-29	59	9.42	*
Precentral g (R)	6	11	31	-3	36	12.74	**
Postcentral g (R)	3	12	34	-22	38	12.92	**
Posterior cingulate g (R)	23	31	6	-27	24	14.62	***
Inferior parietal lobe (R)	40	8	52	-38	22	13.48	**
Superior temporal g (R)	22	11	51	-48	11	13.06	**
Middle temporal g (L)	37	8	-47	-54	-2	13.84	**
Middle temporal g (L)	21	10	-57	-16	-12	9.70	*
Middle temporal g (L)	21	15	-40	1	-22	13.95	**
Parahippocampal g (R)	36	14	30	-35	-7	12.68	**
Parahippocampal g (R)	35	27	16	-23	-14	15.56	**
Precuneus (R)	7	10	20	-46	55	9.11	*
Precuneus (R)	7	11	21	-59	48	9.06	*
Precuneus (L)	7	22	-9	-52	47	13.44	**
Cuneus (R)	18	8	14	-75	21	12.69	**
Middle occipital g (R)	37	9	45	-65	5	14.69	***
Lingual g (R)	19	11	20	-49	-3	14.84	***
Insula (L)	13	26	-45	1	0	13.84	**
Caudate nucleus (L)		13	-12	-7	19	14.70	***
Putamen / caudate nucleus (L)		8	-20	21	4	13.13	**
Globus pallidus (R)		10	14	-4	4	14.46	***
Putamen (L)		9	-24	8	-1	12.87	**
Putamen / globus pallidus (L)		11	-26	-8	-2	14.92	**

(*table continues*)

Table 5 (continued)

Region of activation	BA	Size (# voxels)	Talairach Coordinates x	y	z	Average F ratio	P
Putamen (R)		17	22	7	-6	13.91	**
Thalamus (B)		51	11	-12	13	14.86	***
Brainstem		9	-1	-29	-8	14.05	**
Cerebellum (L)		57	-7	-53	-5	13.47	**
Cerebellum (R)		37	30	-60	-21	15.65	***
Cerebellum (R)		113	13	-80	-22	14.25	**
Cerebellum (L)		80	-36	-69	-23	14.56	**
Group by cue interaction							
Cuneus (B)	18	8	-2	-87	16	10.87	*

Stereotaxic coordinates are given for local maxima of activation cluster in Talairach and Tournoux (1988) atlas space. Abbreviations: B, bilateral; BA, Brodmann's area; DLPFC, dorsolateral prefrontal cortex; L, left hemisphere; g, gyrus; R, right hemisphere.

* $p < .005$, ** $p < .001$, *** $p < .0005$

Table 6. Coping strategy and working memory regressed on cue-reactivity variables.

	ΔR^2	$F_{(change)}$	*P*
Left DLPFC			
Step 1: Coping strategy and working memory	.08	2.38	> .1
Step 2: Coping strategy x working memory	.02	1.10	> .3
Right DLPFC			
Step 1: Coping strategy and working memory	.04	1.03	> .3
Step 2: Coping strategy x working memory	.01	.59	> .4
Self-reported urge			
Step 1: Coping strategy and working memory	.03	.88	> .4
Step 2: Coping strategy x working memory	.01	.60	> .4
Self-reported affect			
Step 1: Coping strategy and working memory	.02	.41	> .6
Step 2: Coping strategy x working memory	.00	.02	> .8
Heart rate			
Step 1: Coping strategy and working memory	.02	.46	> .6
Step 2: Coping strategy x working memory	.01	.61	> .4

Table 7. Characteristics of those who chose to smoke versus those who did not.

	Chose-Abstain (n = 13)	Chose-Smoke (n = 44)	*p*
Age in years	32.62 (8.28)	33.91 (8.66)	> .6
Cigarettes per day	17.38 (3.25)	21 (6.42)	= .06[a]
Number of quit attempts	3.23 (3.72)	3.71 (6.18)	> .5
NDSS: Total	-0.31 (0.99)	0.26 (0.76)	< .05*
NDSS: Drive	-0.28 (0.93)	0.18 (0.96)	> .1
NDSS: Priority	-0.55 (0.8)	-0.13 (1.13)	> .2
NDSS: Tolerance	-0.87 (1.3)	-0.14 (0.78)	< .05*
NDSS: Continuity	-0.27 (1.09)	-0.16 (1.02)	> .7
NDSS: Stereotypy	0.53 (0.8)	0.35 (1.08)	> .5
RSEQ: Global ASE	2.42 (0.43)	2.14 (0.39)	< .05*
RSEQ: Negative Affect	1.85 (0.67)	1.52 (0.68)	> .1
RSEQ: Positive Affect	3.01 (0.62)	2.75 (0.52)	> .1
RSEQ: Social-Food Situations	2.01 (0.65)	1.72 (0.67)	> .1
RSEQ: Idle Time	2.34 (0.67)	2.1 (0.54)	> .1
RSEQ: Restrictive Situations	3.03 (0.58)	2.66 (0.61)	= .06[a]
RSEQ : Low Arousal	2.69 (0.48)	2.34 (0.58)	< .05*
RSEQ : Craving	2.04 (0.48)	1.86 (0.68)	> .3
BIS-11: Motor Impulsiveness	20.69 (3.09)	21.7 (5.48)	> .5
BIS-11: Attentional Impulsiveness	19.23 (3.39)	18.05 (3.83)	> .3
BIS-11: Non-Planning Impulsiveness	30.31 (5.57)	28.45 (6.13)	> .3

(*table continues*)

Table 7 (continued)

	Chose-Abstain (n = 13)	Chose-Smoke (n = 44)	*p*
TSCS	100 (19.09)	98.84 (18.42)	> .8
R-SCS: Private Self-Consciousness	17.69 (4.53)	16.66 (5.16)	> .5
R-SCS: Public Self-Consciousness	13.08 (4.09)	14.5 (4.05)	> .2
R-SCS: Social Anxiety	10.54 (3.84)	7.86 (4.94)	= .08[a]
BIDR-6: Impression Management	4.15 (2.23)	4.98 (3.33)	> .4
BIDR-6: Self-Deceptive Positivity	5.54 (3.28)	5.57 (4.06)	> .9
PANAS-Trait: Positive Affect	33.92 (6.09)	33.45 (7.77)	> .8
PANAS-Trait: Negative Affect	16.31 (6.68)	19.5 (7.66)	> .1
PANAS-State: Positive Affect	30.54 (7.22)	28.27 (9.62)	> .4
PANAS-State: Negative Affect	14.92 (4.29)	16.84 (6.27)	> .3
SEDS	69.46 (32.94)	79.80 (31.47)	> .3
Affect-Baseline	7.38 (1.56)	7.00 (1.80)	> .4
Urge-Baseline	35.31 (24.25)	70.55 (20.09)	< .001*
OSPAN	51.61 (12.35)	52.77 (18.32)	> .8
BDS	7 (2.16)	5.95 (2.18)	> .1
Composite Working Memory	29.31 (6.28)	29.36 (9.71)	> .9

Abbreviations: BDS, Backwards Digit Span; BIDR-6, Balanced Inventory of Desirable Responding Version 6; BIS-11; Barrat's Impulsivity Scale Version 11; NDSS, Nicotine Dependence Syndrome Scale; OSPAN, operation word-span task; PANAS, Positive and Negative Affect Schedule; RSEQ, Relapse Self-Efficacy Questionnaire; R-SCS, Revised Self-Consciousness Scale; SEDS, State Ego Depletion Scale; TSCS, Trait Self Control Scale.

*significant [a] marginally significant

Table 8. Results from voxel-wise hierarchical multiple regression analyses.

Region of activation	BA	Size (# voxels)	Talairach Coordinates x	y	z	Average F ratio
Right DLPFC as predictor						
Medial frontal g / Anterior cingulate (B)	9/32	10	-5	40	19	10.05
Medial frontal g / Anterior cingulate (R)	10/32	46	13	34	-12	10.14
Medial frontal g (L)	11	11	-18	22	-11	10.67
Middle temporal g (L)	22	16	-61	-31	1	11.51
Cuneus (R)	18	8	20	-98	3	9.82
Cuneus (L)	18	11	-16	-99	0	10.87
Left DLPFC as predictor						
Inferior frontal g (R)	45	9	48	25	6	10.81
Inferior frontal g (R)	45	13	44	34	2	10.08
Middle temporal g (R)	21	9	49	4	-25	11.80

Stereotaxic coordinates are given for local maxima of activation cluster in Talairach and Tournoux (1988) atlas space. Abbreviations: B, bilateral; BA, Brodmann's area; DLPFC, dorsolateral prefrontal cortex; L, left hemisphere; g, gyrus; R, right hemisphere.

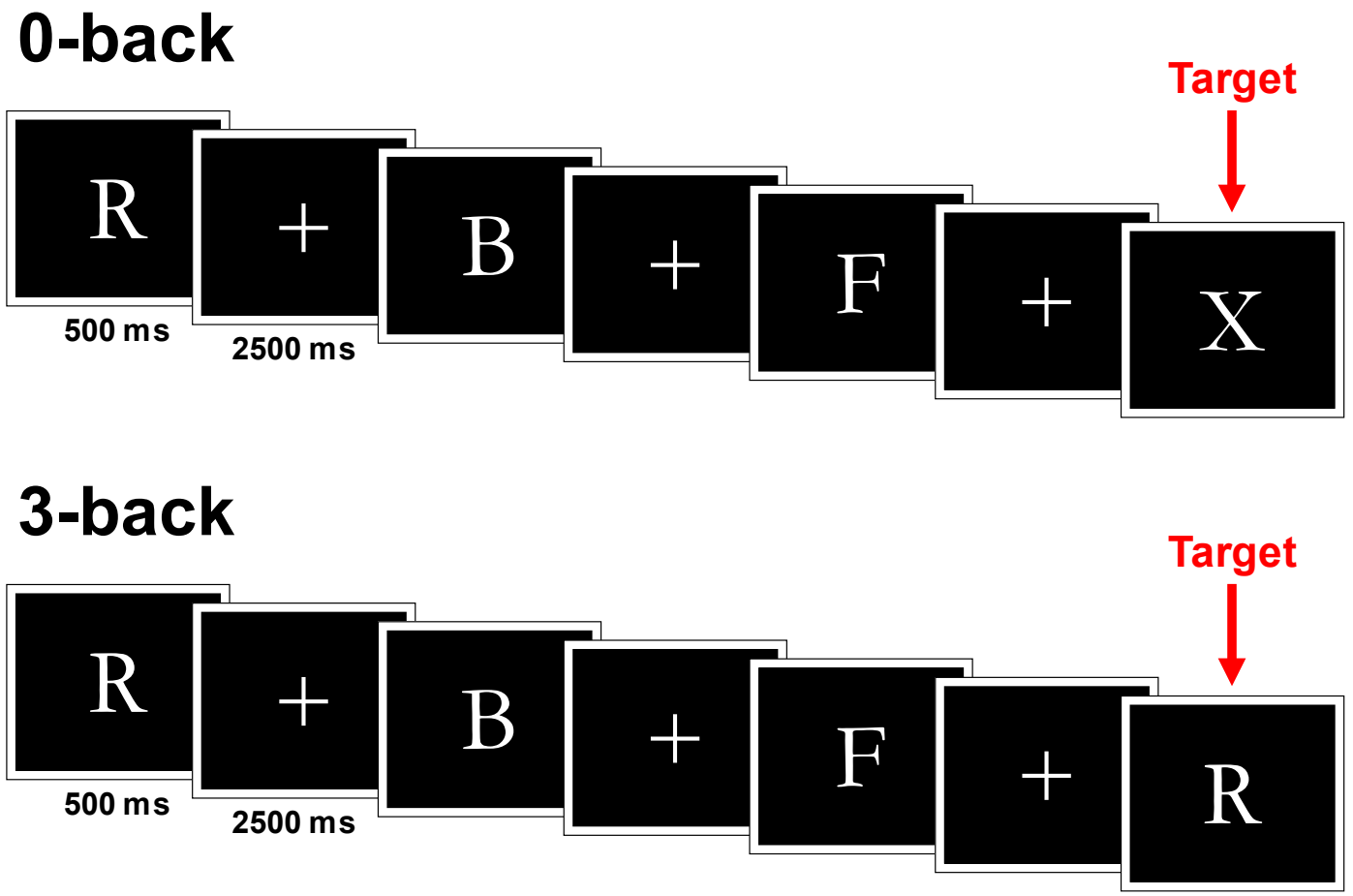

Figure 1. Schematic of the conditions of the n-back verbal working memory task.

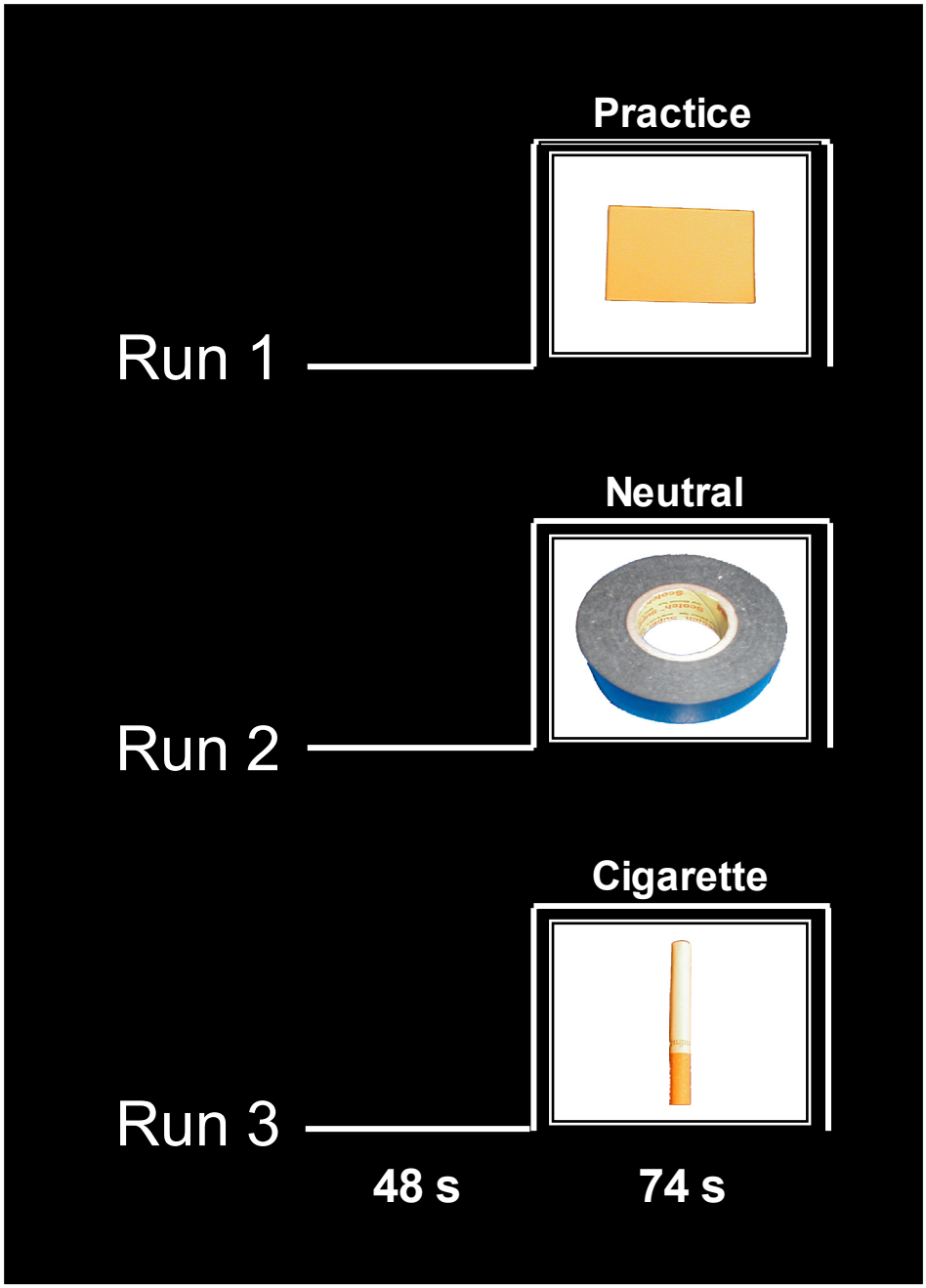

Figure 2. Schematic of the smoking cue exposure task.

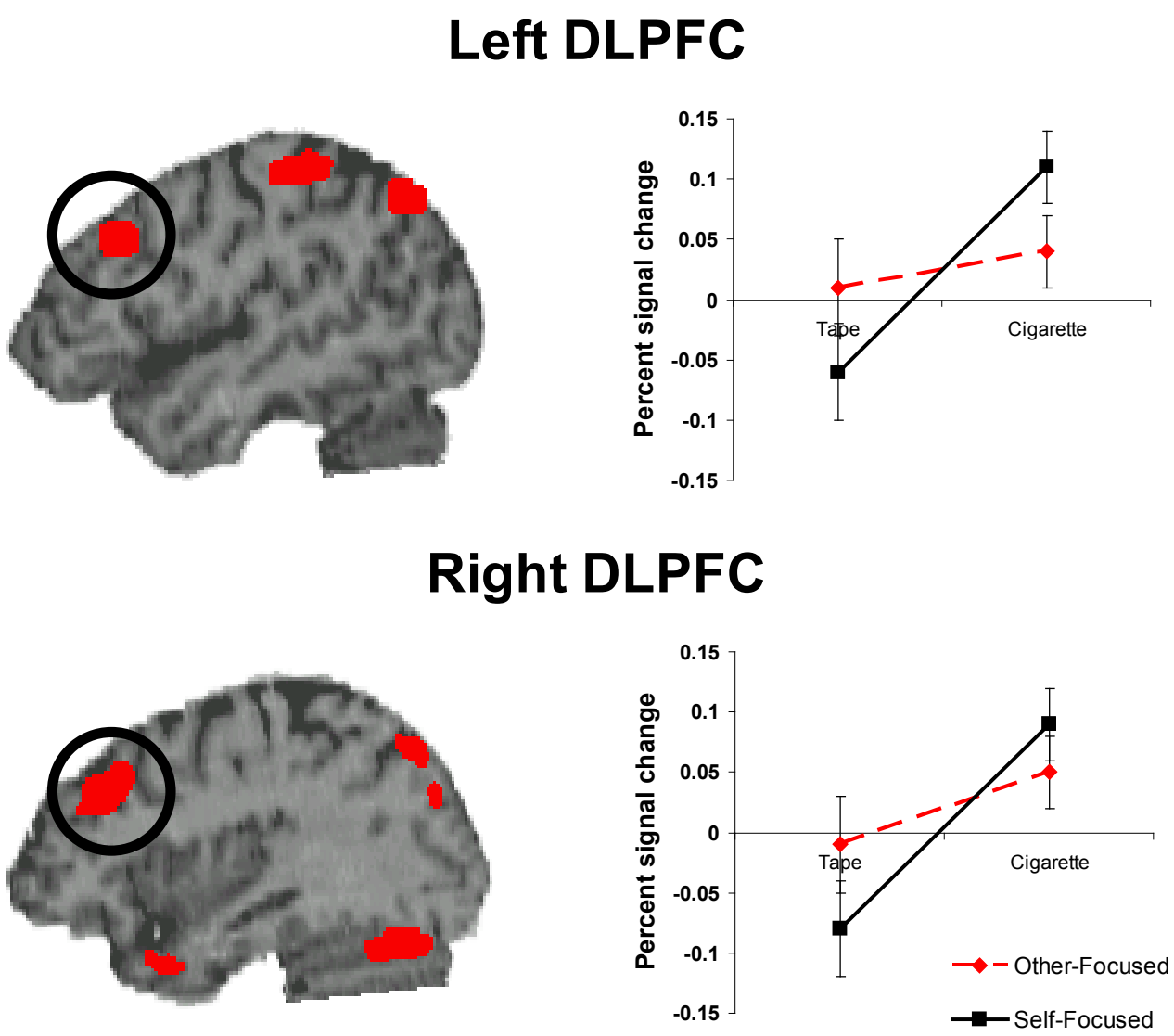

Figure 3. Load-sensitive regions of the DLPFC applied to smoking cue exposure data.

Cue-elicited activation of the left (x = -46, y = 19, z = 28) and right (x = 37, y = 30, z = 26) dorsolateral prefrontal cortex that exhibited a significant effect of memory load. Graphs plot percent signal change for each group.

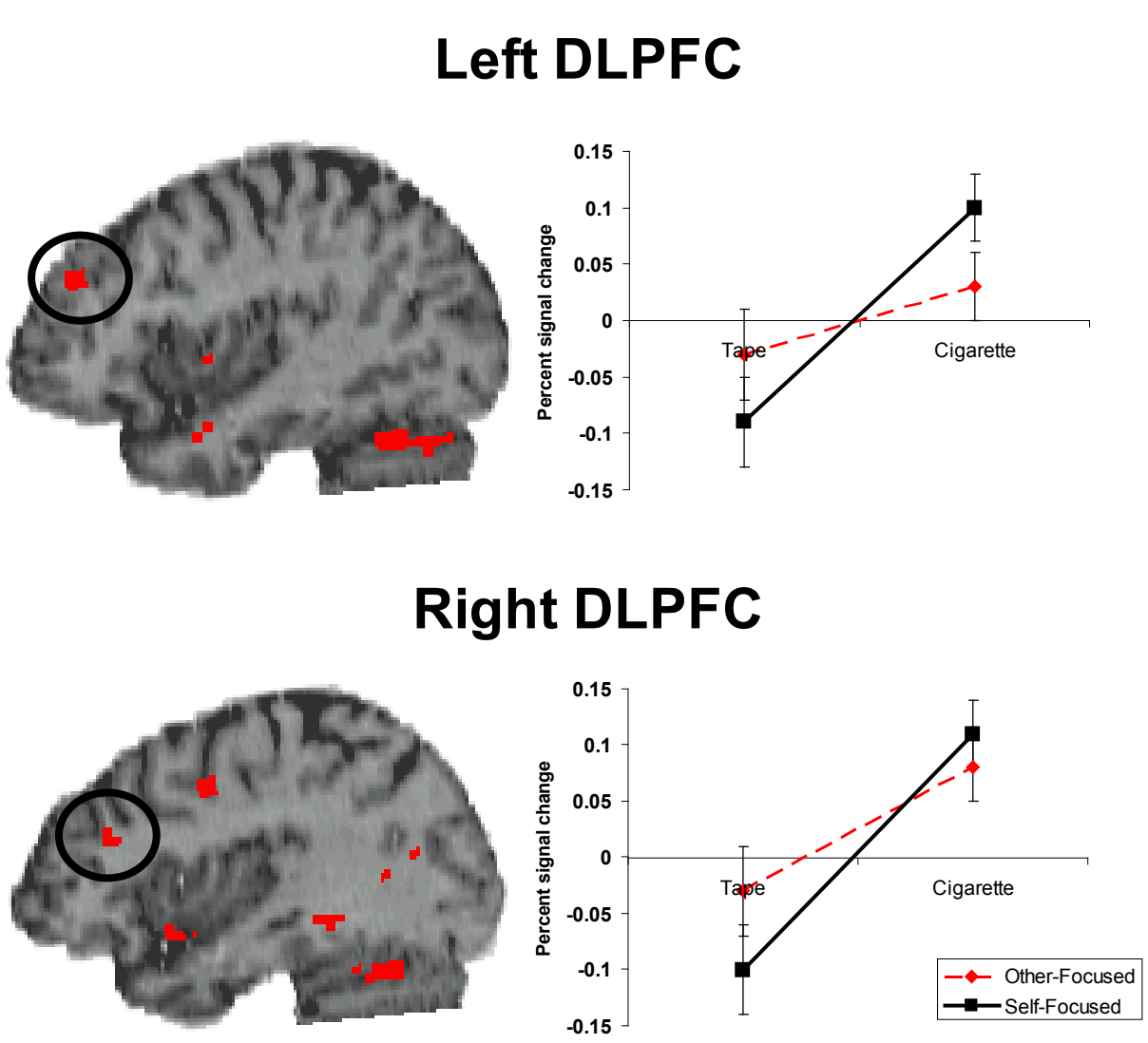

Figure 4. DLPFC regions exhibiting cue-reactivity in voxel-wise analysis.

Cue-elicited activation of the left (x = -38, y = 38, z = 25) and right (x = 35, y = 29, z = 20) dorsolateral prefrontal cortex regions identified via voxel-wise analysis. Graphs plot percent signal change for each group.

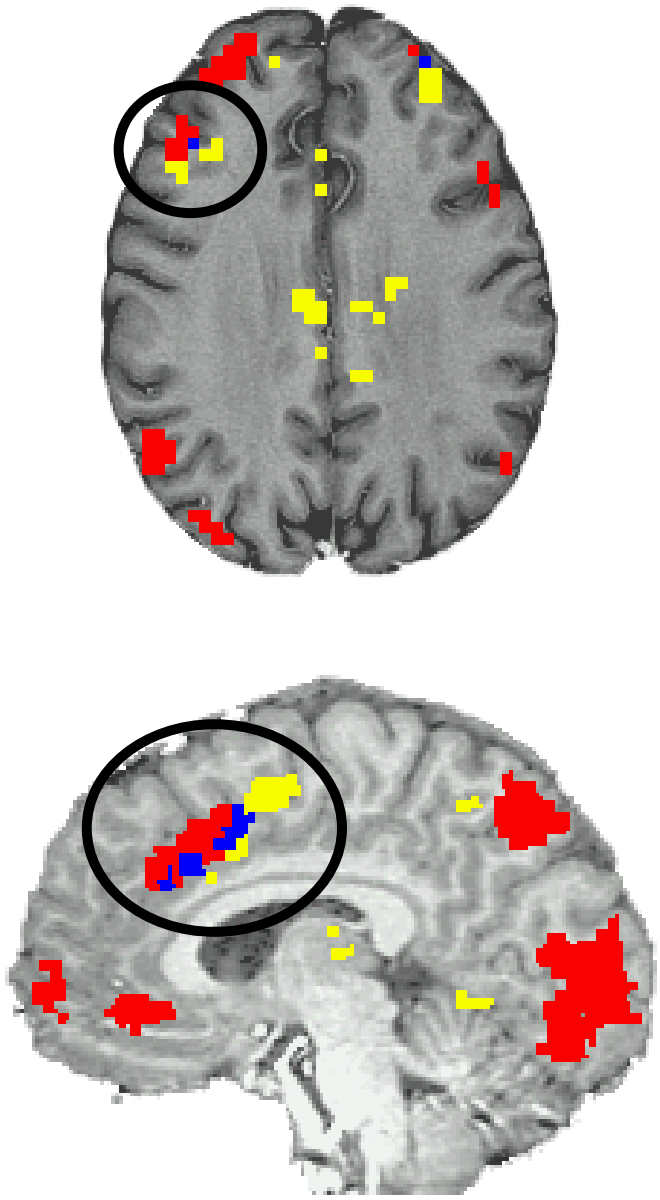

Figure 5. Overlapping n-back and cue exposure activation.

Partially overlapping portions of the right dorsolateral prefrontal and dorsal anterior cingulate cortex exhibited significant activation during the n-back and cue exposure tasks. Voxels exhibiting activation only in the n-back and cue-exposure tasks are depicted in red and yellow, respectively, while overlap voxels are depicted in blue.

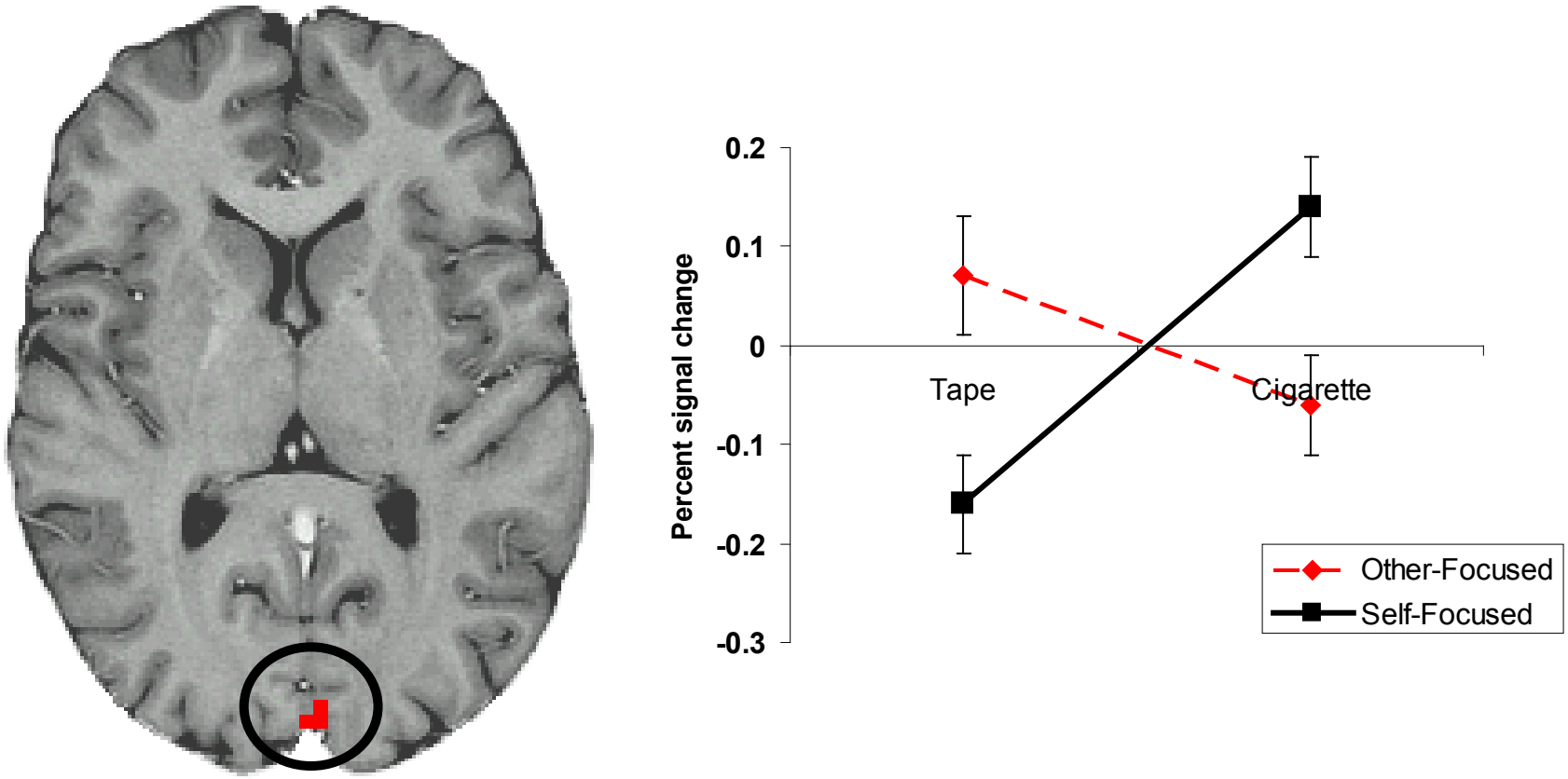

Figure 6. Coping strategy by cue interaction in the cuneus (x = -2, y = -87, z = 16).

Graph plots percent signal change for each group.

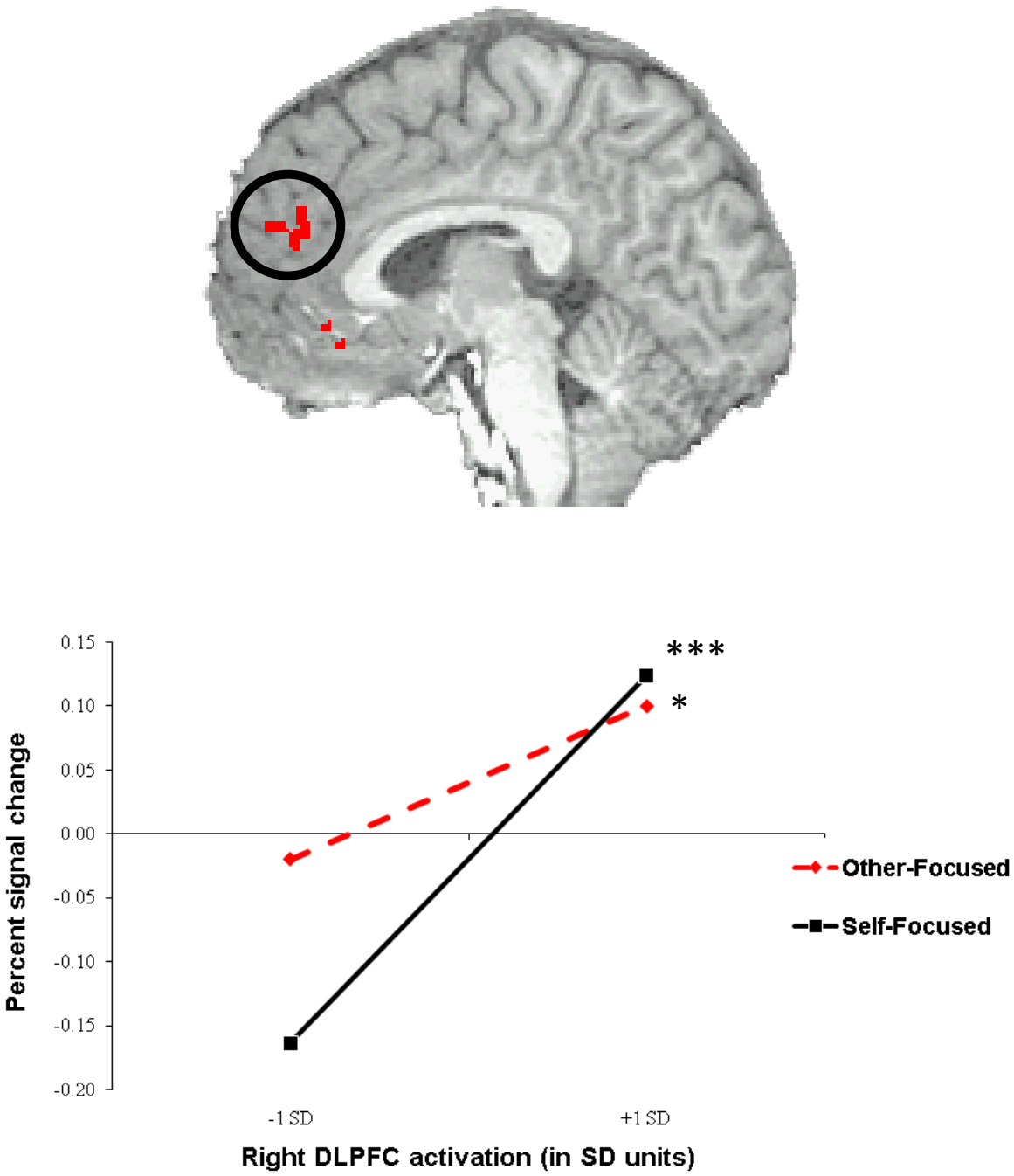

Figure 7. Modulatory effect of coping strategy on relationship between right DLPFC (x = 35, y = 29, z = 20) and mPFC/rACC (x = -5, y = 40, z = 19) activation.

Significance of simple slopes: * $p < .05$ *** $p < .001$

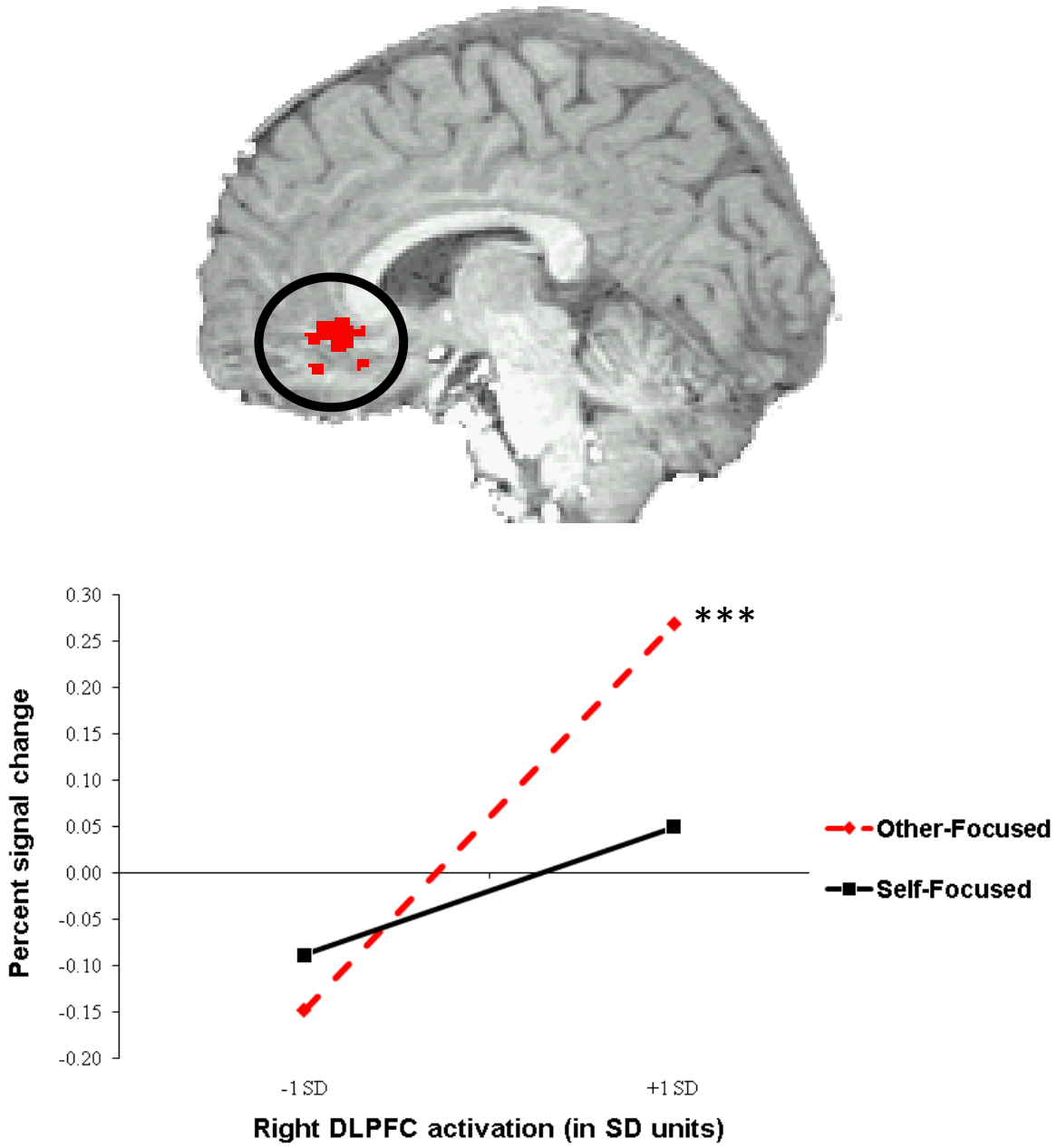

Figure 8. Modulatory effect of coping strategy on relationship between right DLPFC (x = 35, y = 29, z = 20) and mPFC/vACC (x = 13, y = 34, z = -12) activation.

Significance of simple slopes: *** $p < .001$

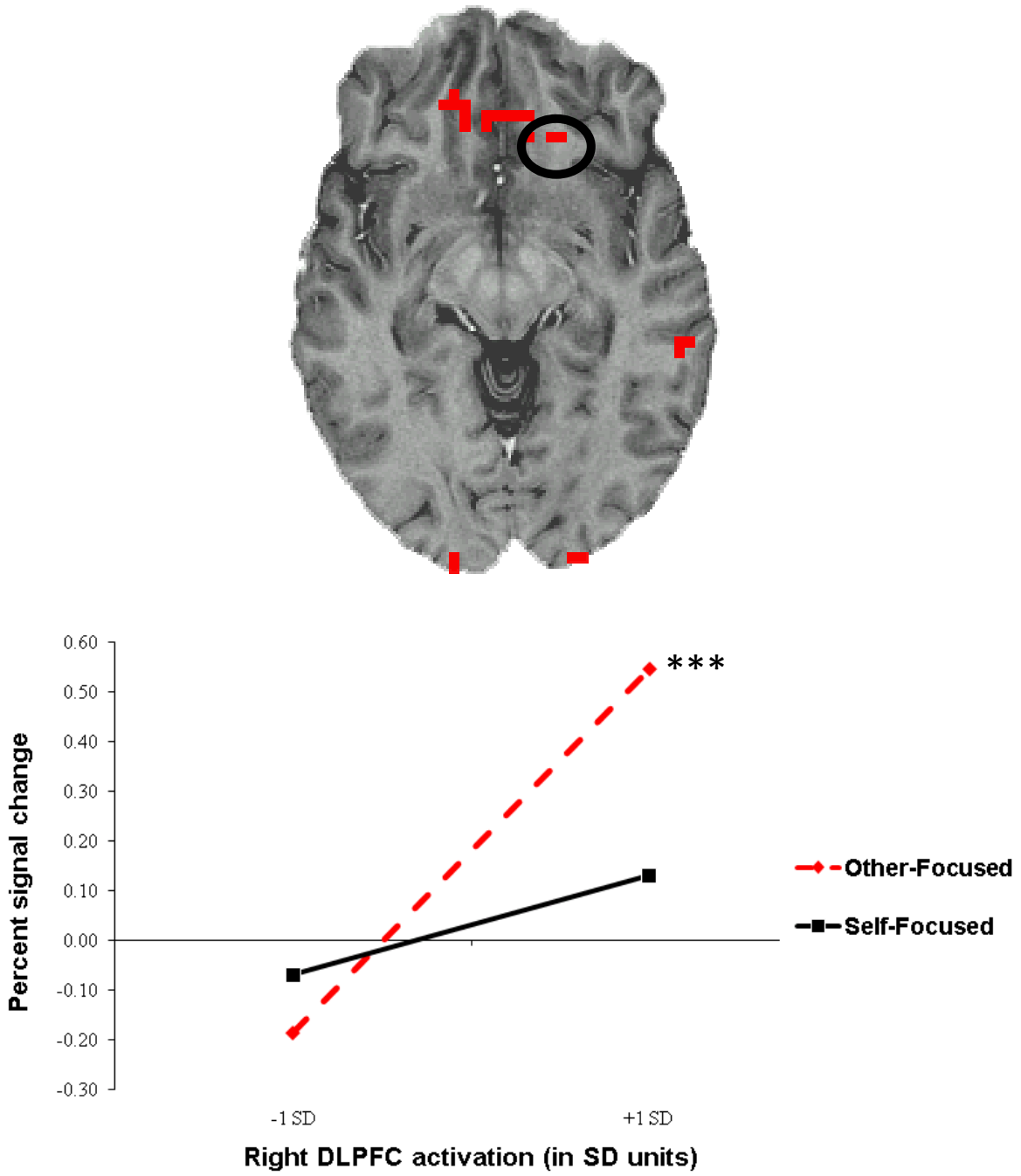

Figure 9. Modulatory effect of coping strategy on relationship between right DLPFC (x = 35, y = 29, z = 20) and vmPFC (x = -18, y = 22, z = -11) activation.

Significance of simple slopes: *** $p < .001$

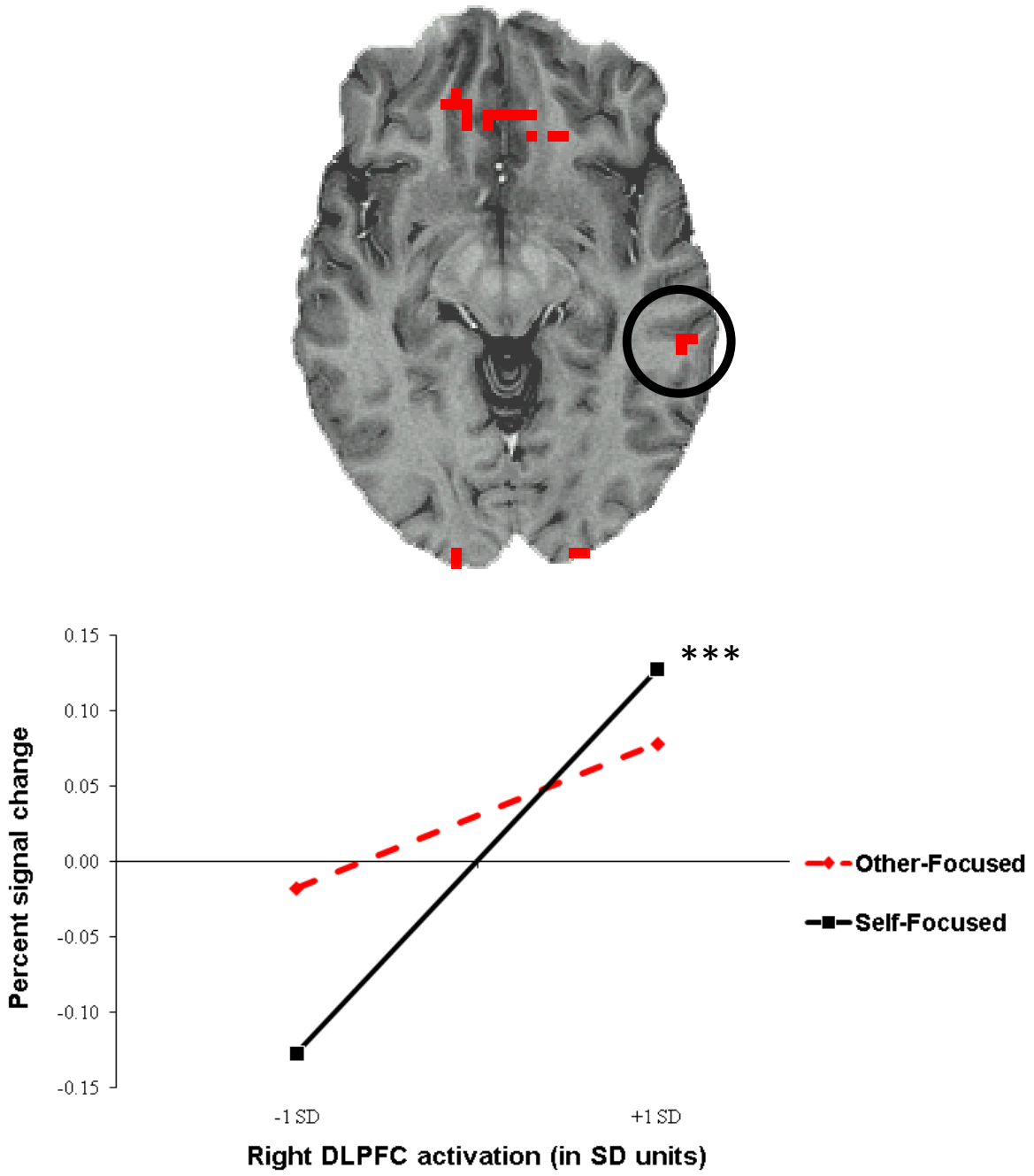

Figure 10. Modulatory effect of coping strategy on relationship between right DLPFC (x = 35, y = 29, z = 20) and middle temporal gyrus (x = -61, y = -31, z = 1) activation.

Significance of simple slopes: *** $p < .001$

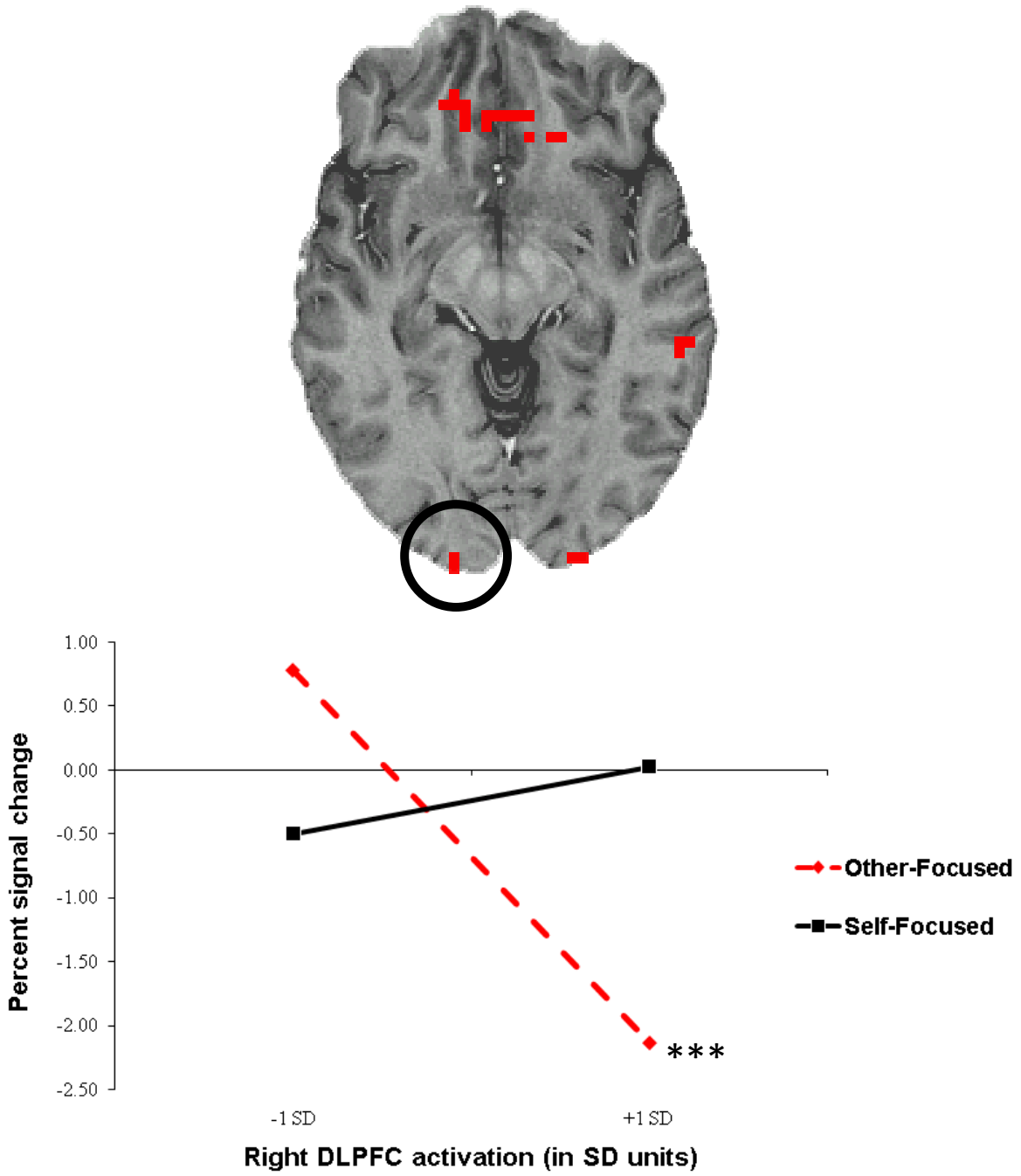

Figure 11. Modulatory effect of coping strategy on relationship between right DLPFC (x = 35, y = 29, z = 20) and right cuneus (x = 20, y = -98, z = 3) activation.

Significance of simple slopes: *** $p < .001$

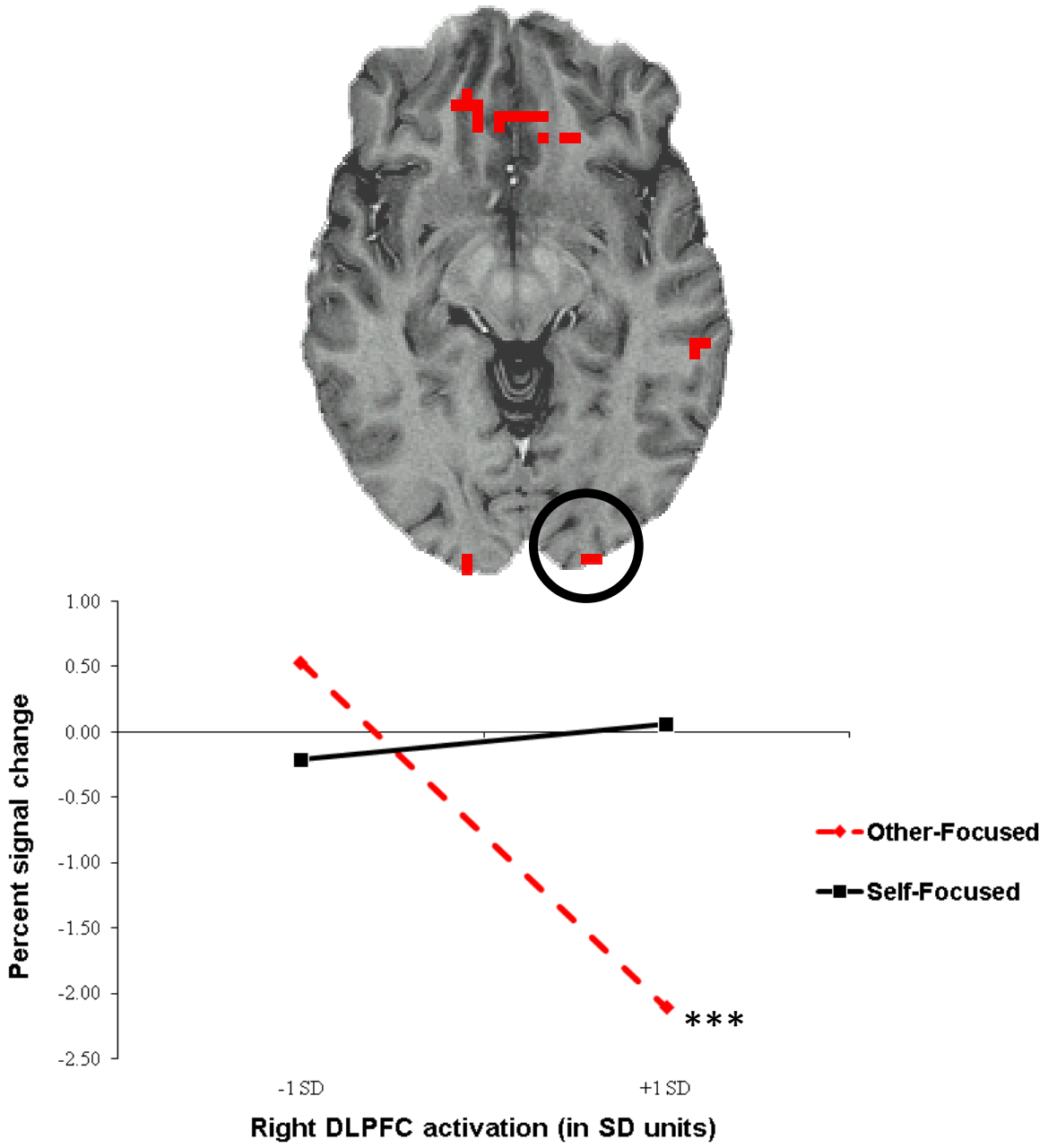

Figure 12. Modulatory effect of coping strategy on relationship between right DLPFC (x = 35, y = 29, z = 20) and left cuneus (x = -16, y = -99, z = 0) activation.

Significance of simple slopes: *** $p < .001$

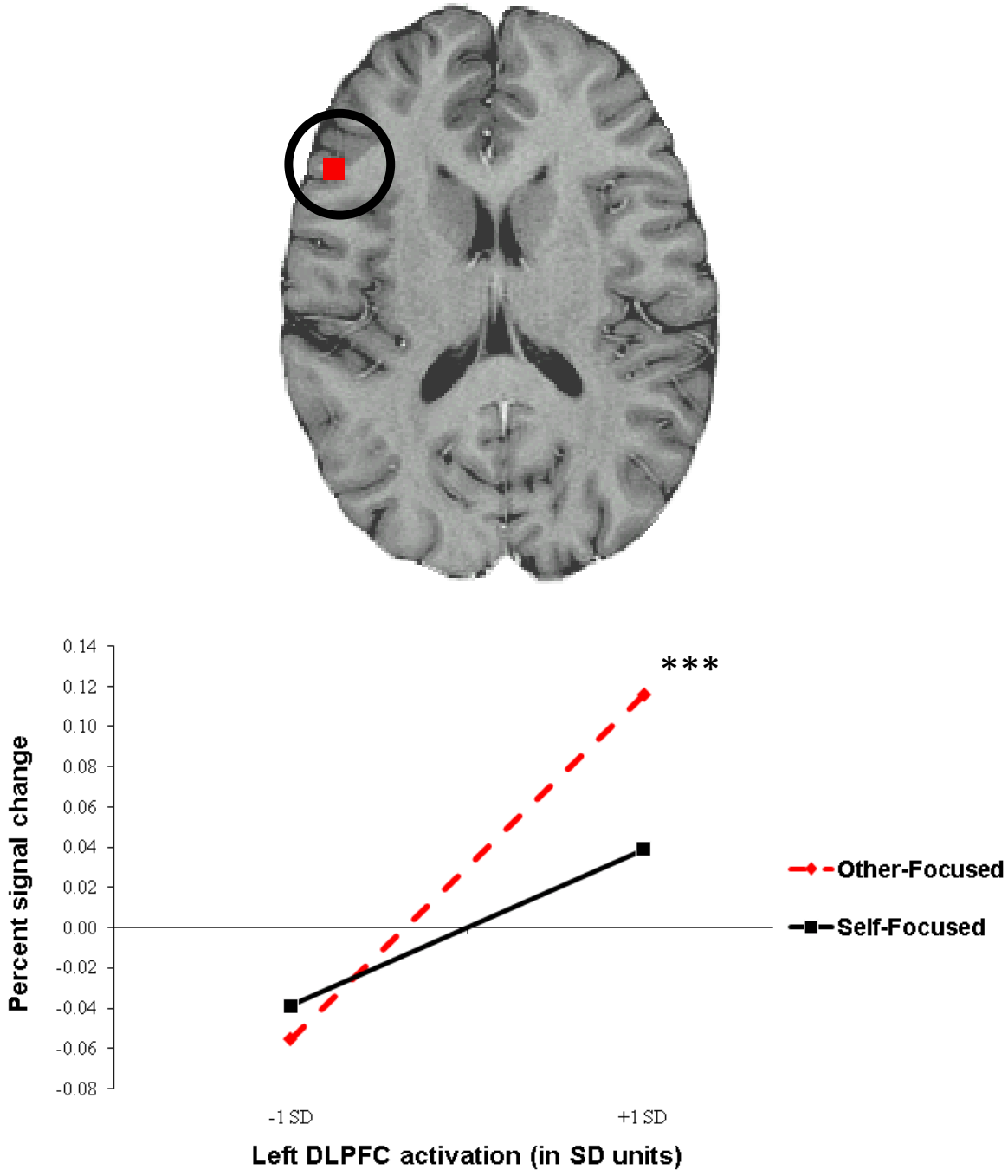

Figure 13. Modulatory effect of coping strategy on relationship between left DLPFC (x = -38, y = 38, z = 25) and left inferior frontal gyrus (x = 48, y = 25, z = 6) activation.

Significance of simple slopes: *** $p < .001$

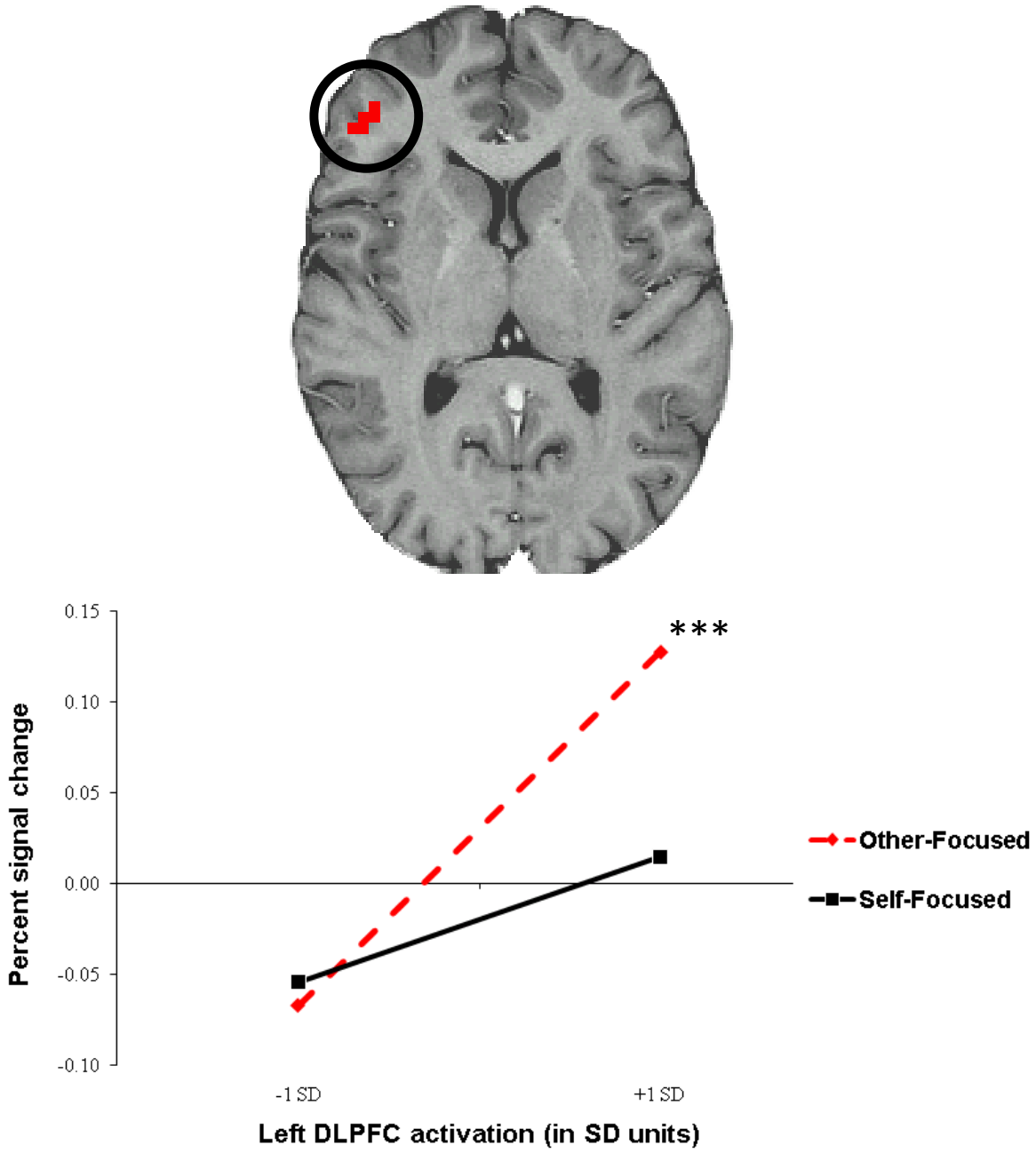

Figure 14. Modulatory effect of coping strategy on relationship between left DLPFC (x = -38, y = 38, z = 25) and left inferior frontal gyrus (x = 44, y = 34, z = 2) activation.

Significance of simple slopes: *** $p < .001$

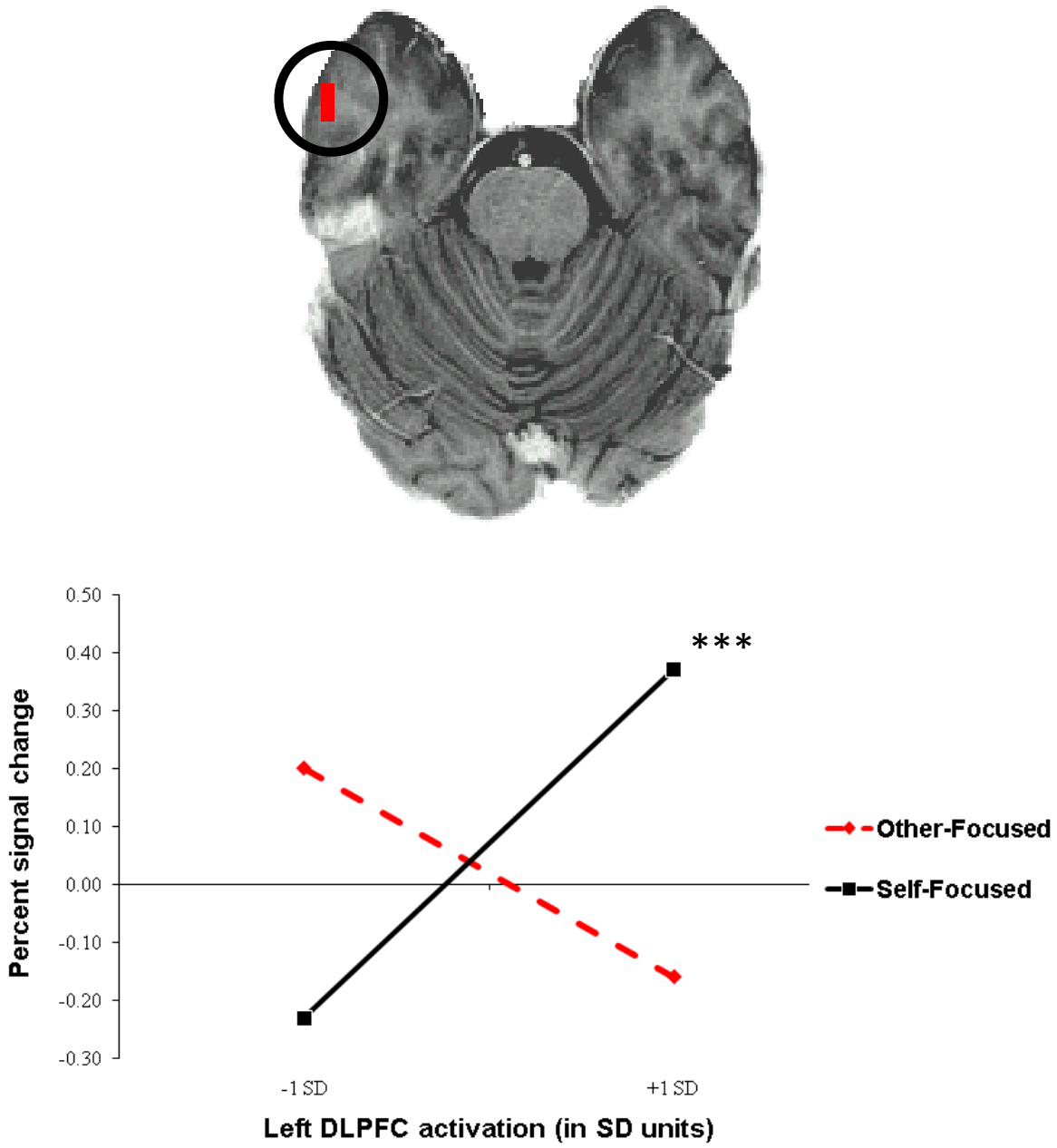

Figure 15. Modulatory effect of coping strategy on relationship between left DLPFC (x = -38, y = 38, z = 25) and right middle temporal gyrus (x = 49, y = 4, z = -25) activation.

Significance of simple slopes: *** $p < .001$

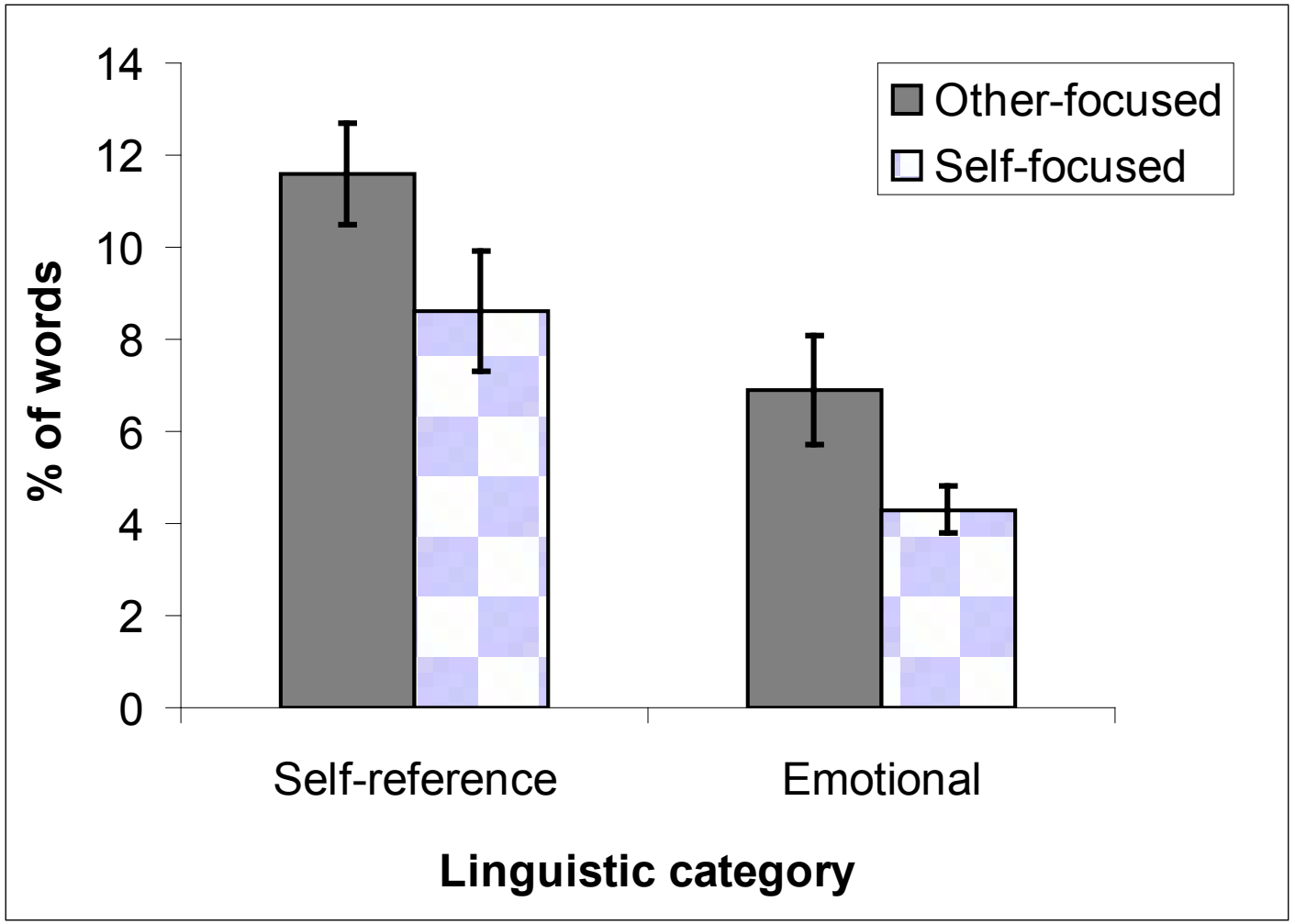

Figure 16. Proportion of words generated by linguistic category and group.