PUTTING CRAVING INTO CONTEXT: EFFECTS OF PERCEIVED SMOKING OPPORTUNITY ON THE NEURAL RESPONSE TO CIGARETTE CUE EXPOSURE

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BS, University of Pittsburgh at Johnstown, 1999

Submitted to the Graduate Faculty of

Arts and Sciences in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2004

UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

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Recent years have seen the emergence of research applying functional neuroimaging to the study of cue-elicited drug craving. This research has begun to identify a distributed system of brain activity during drug craving. Functional magnetic resonance imaging (fMRI) was used to examine the effects of smoking expectancy on the neural response to neutral (e.g., roll of tape) and smoking-related (holding a cigarette) stimuli in male cigarette smokers deprived of nicotine for 8 hours. As predicted, several brain regions exhibited differential activation during cigarette versus neutral cue exposure. Moreover, instructions about smoking opportunity affected cue-elicited activation in several regions. These results highlight the importance of perceived drug availability in the neurobiological response to drug cues.

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1.0 INTRODUCTION

Drug abuse and addiction are major societal problems, with economic costs that exceed $100 billion in the US alone (Holland & Mushinski, 1999). Two broad classes of research have been used extensively in the study of drug addiction: basic research aimed at identifying the neural and pharmacological mechanisms underlying drug addiction in animals, and research aimed at investigating the cognitive and affective processes associated with addiction in humans. More recently, researchers have employed convergent cognitive and neuroscientific techniques in order to provide for a more comprehensive understanding of addiction. In particular, the neurobiological substrata of the distorted motivational and decision-making processes pathognomonic of addiction have been of great interest to researchers interested in advancing a multidimensional account of human drug addiction.

1.1 Functional Neuroimaging

Functional neuroimaging techniques, such as single photon emission tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI), provide powerful tools for the *in vivo* examination of neural functioning (Stern & Silbersweig, 2001). Rapid technological advances in functional neuroimaging techniques and the resultant enhancement in ability to localize the neural circuitry subserving cognitive processes such as perception, attention, emotion, memory, language, and motor function, have greatly advanced our understanding of normal brain

functioning. Importantly, clinical researchers are increasingly using these techniques to examine brain dysfunction in a variety of disorders, such as addiction (Kaufman, 2001).

Functional neuroimaging offers the critical advantage of providing a means for investigating the loci of anomalous function associated with symptomatology. One prominent method for investigating the craving associated with addiction is to expose drug-addicted individuals to drug-associated stimuli and assess concomitant changes across multiple response systems (self-report, cognitive performance and physiological measures). Exposure to drug cues reliably produces a variety of subjective and cognitive sequelae in substance dependent individuals (Carter & Tiffany, 1999). In particular, cue exposure elicits heightened self-reported substance use desire, one index of the drug acquisitive motivational state henceforth referred to as *craving* (Baker, Morse, & Sherman, 1986; Sayette et al., 2000). Only recently have researchers begun to apply functional neuroimaging techniques to the study of drug cue reactivity.

1.2 Searching for the Neural Basis of Craving: Current Limitations

Worden and Schneider (1995) outline three major stages in the neural mapping of cognitive processing: (1) determining the number, location, and stability (i.e., reproducibility within and between subjects) of regions activated by a particular process; (2) replicating and investigating topological characteristics of regional activation; (3) determining stimulus- and task-based differential activation within replicated regions. Neuroimaging studies of cue-elicited craving have thus far operated at the first and, to a lesser extent, second stages of this framework, seeking primarily to localize and replicate regions demonstrating preferential activation by drug-associated stimuli and to determine

whether such regions are stable across addicted populations (e.g., individuals addicted to cocaine vs. heroin). Within the past decade, a rapidly growing body of functional neuroimaging studies has adopted the traditional cue-reactivity procedure as a means for elucidating the neural bases of craving. Thus far, a distributed network of brain regions has been linked to cue-elicited craving, with the amygdala, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and dorsolateral prefrontal cortex (DLPFC) being the most commonly reported loci of activation in 23 neuroimaging studies of cue-reactivity (Wilson, Sayette, & Fiez, 2004; see Figure 1).

Although the above regions have been most frequently associated with human drug craving, they unfortunately have been inconsistently activated across studies. Indeed, the multifaceted nature of craving has posed significant challenges to precise localization and characterization of its constituent neural substrates. For example, significant cue-elicited activation of OFC – a region assuming a prominent role in contemporary neurobiological models of craving (Goldstein & Volkow, 2002; Jentsch & Taylor, 1999; London, Ernst, Grant, Bonson, & Weinstein, 2000) – has been reported by only 8 of 22 studies (Bonson et al., 2002; Brody et al., 2002; Grant et al., 1996; Kilts, Gross, Ely, & Drexler, 2004; Myrick et al., 2004; Tapert et al., 2003; Wang et al., 1999; Wrase et al., 2002; OFC activity not assessed by Maas et al., 1998). Results are similarly discrepant for the amygdala (8 of 22 studies) (Bonson et al., 2002; Childress et al., 1999; Due, Huettel, Hall, & Rubin, 2002; Grant et al., 1996; Kilts, 2001; Kilts et al., 2004; Schneider et al., 2001; Tapert et al., 2003; not assessed by Modell & Mountz, 1995), DLPFC (9 of 23) (Bonson et al., 2002; Due et al., 2002; Garavan et al., 2000; George et al., 2001; Grant et al., 1996; Grüsser et al., in press; Maas et al., 1998; Tapert, Brown,

Baratta, & Brown, 2004; Wrase et al., 2002), and ACC (13 of 23) (Brody et al., 2002; Childress et al., 1999; Daglish et al., 2001; Garavan et al., 2000; Grüsser et al., in press; Kilts, 2001; Kilts et al., 2004; Myrick et al., 2004; Tapert et al., 2004; Tapert et al., 2003; Wexler et al., 2001; Wrase et al., 2002). To date, conflicting results have been largely ignored or vaguely attributed to inter-study methodological variance (Bonson et al., 2002; George et al., 2001; Hommer, 1999; Schneider et al., 2001). No framework has yet been offered to account for the contradictory pattern of results observed across studies.

1.3 Contextual Modulation of Cue-Elicited Craving

1.3.1 Behavioral Evidence.

Recent data contradict the prevailing view that cue-elicited craving is an entirely stimulus-bound response. Instead, craving may be modulated by the context associated with cue presentation (Baker et al., 1986). One contextual factor that significantly influences the response to drug cues is whether or not participants anticipate actually using the drugs to which they are being exposed (i.e., perceived drug use opportunity; Wertz & Sayette, 2001b). When instructed that drugs are available for consumption during an experiment, drug users report substantially higher craving when presented with drug cues than when instructed that drugs are not available for an extended period of time or until after the experiment has concluded (Carter & Tiffany, 2001; Droungas, Ehrman, Childress, & O'Brien, 1995; Juliano & Brandon, 1998). Affective (Carter & Tiffany, 2001; Sayette et al., 2003) and cognitive processes (Juliano & Brandon, 1998; Wertz & Sayette, 2001a) are also differentially influenced by drug cue presentation as a function of whether or not drug use is expected. Similarly, physiological responses thought to reflect arousal, such as skin conductance (Carter &

Tiffany, 2001), heart rate (Lazev, Herzog, & Brandon, 1999), and asymmetrical frontal electrocortical activity (Zinser, Fiore, Davidson, & Baker, 1999), are heightened in contexts predictive of impending drug use. Many of these effects transfer to arbitrary stimuli (e.g., colored cards) that come to be associated with the opportunity, or lack thereof, to consume (Dols, Willems, van den Hout, & Bittoun, 2000; Field & Duka, 2002; Lazev et al., 1999).

1.3.2 Treatment-Seeking Status: A Proxy for Perceived Drug Use Opportunity. To date, neuroimaging studies of craving have not explicitly manipulated perceived drug-use opportunity, making it difficult to assess the degree to which regions observed in previous studies may respond to perception of drug availability as opposed to other factors affecting craving. However, it has been suggested that treatment status affects perceived drug use opportunity (Wertz & Sayette, 2001b). Specifically, those seeking treatment are likely to resist consuming drugs (thus drug use opportunity is absent). In contrast, actively using addicts are likely to perceive the opportunity to consume immediately after, if not during, the experiment. Individuals enrolled in drug treatment programs do appear to exhibit responses consistent with low expectations of drug availability, while those not in treatment exhibit responses consistent with high expectations of drug availability (Wertz & Sayette, 2001b). It also is possible that treatment status may affect neurobiological responses to drug cues.

If treatment-seeking status does affect neural activity elicited by drug cues, such effects would be most readily apparent in neural regions capable of integrating motivational/affective (e.g., current desires) and cognitive (e.g., knowledge of the probability and means of acquiring desired outcomes) information. Prefrontal cortex

(PFC), an area thought to be largely responsible for supporting such flexibility (Groenewegen & Uylings, 2000; Krawczyk, 2002), has not been well investigated in the context of human drug craving. However, an emerging literature suggests that the neural basis for adaptive processing of incentive stimuli is mediated by specific regions of PFC (Balleine & Dickinson, 1998; Krawczyk, 2002; Wallis, Dias, Robbins, & Roberts, 2001). The two PFC regions that have received the most attention vis-à-vis craving are OFC (London et al., 2000; Volkow & Fowler, 2000) and DLPFC (Anton, 1999; Bonson et al., 2002; Grant et al., 1996). 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 (Rolls, 2000). OFC has extensive connections with the striatum as well as limbic regions (e.g., amygdala) and, as a result, is well situated to integrate the activity of several limbic and subcortical areas associated with motivational behavior and reward processing (Groenewegen & Uylings, 2000).

DLPFC also contributes to regulatory processing under conditions requiring the integration of cognitive and motivationally-relevant information (Watanabe, Hikosaka, Sakagami, & Shirakawa, 2002), possibly by integrating information provided by OFC and other regions with which it is connected (Groenewegen & Uylings, 2000). DLPFC plays a central role in reward-processing and decision-making, particularly when information must be maintained over a delay or when multiple sources of information must be used to guide behavior (Krawczyk, 2002).

Taken together, converging evidence suggests that treatment-seeking status may influence the neurobiological responses to drug cues, particularly in specific subregions of PFC. Interestingly, of 23 neuroimaging studies of cue-elicited craving, 12 exclusively

recruited individuals actively using drugs (Bonson et al., 2002; Brody et al., 2004; Brody et al., 2002; Due et al., 2002; Garavan et al., 2000; George et al., 2001; Grant et al., 1996; Maas et al., 1998; Myrick et al., 2004; Tapert et al., 2004; Tapert et al., 2003; Wang et al., 1999); in contrast, 10 studies exclusively recruited individuals seeking or receiving treatment for drug addiction (Braus et al., 2001; Childress et al., 1999; Daglish et al., 2001; Grüsser et al., in press; Kilts, 2001; Modell & Mountz, 1995; Schneider et al., 2001; Sell et al., 1999; Wexler et al., 2001; Wrase et al., 2002)[1]. Thus, variability across these studies may reflect, in part, an unappreciated effect of drug use expectations on cue-elicited neural activity (Meyer, 2000; Volkow et al., 2003).

Table 1 presents DLPFC and OFC activation in studies categorized according to whether or not participants were seeking drug treatment at the time of study participation[2]. Studies were included if they exposed participants to drug-related cues. Cue exposure could be accomplished through a variety of methods (e.g., holding a cigarette, viewing a video of cocaine use). As shown, activation of DLPFC and OFC has been found in the majority of studies in which participants were active drug users. In contrast, studies employing treatment-seeking participants have, with few exceptions, failed to find significant activation of DLPFC and OFC. Interestingly, the incidence of significant activation of other regions commonly associated with craving (e.g., amygdala, ACC) is approximately equally distributed across studies employing actively using and treatment-seeking drug users, suggesting that the effect of treatment status are most robust in these subdivisions of PFC.

[1] The sample recruited by Kilts et al. (2004) was heterogeneous with respect to treatment-seeking status, consisting of both cocaine-dependent women undergoing outpatient treatment and those not receiving treatment.

[2] Brody et al. (2004) did not examine cue main effects (e.g., drug cue versus netural cue) in DLPFC and OFC and was therefore excluded from Table 1.

Increased cue-elicited activation of DLPFC and OFC among active users may reflect explicit representation of this expectancy (by OFC) and the generation and maintenance of behavioral goals aimed at obtaining drug reward (by DLPFC) (Anton, 1999; Bonson et al., 2002; Goldstein & Volkow, 2002). OFC neurons are more active during delay periods when rewards are expected than when no such reward is expected (Hikosaka & Watanabe, 2000). Similarly, DLPFC neurons encode reward expectancy during a delay (Hikosaka & Watanabe, 2000; Wallis & Miller, 2003; Watanabe et al., 2002). Moreover, delay activity of DLPFC neurons has been shown to predict subsequent behavioral responses in rewarded tasks (Wallis & Miller, 2003). Lesions of both OFC (Rolls, 2000) and of rat prelimbic cortex (Balleine & Dickinson, 1998), the functional homologue of the non-human primate and human DLPFC, impair the acquisition and modification of behavior guided by contingencies between responses and outcomes, suggesting that these regions are critical for the control of goal-directed behavior.

1.3.3 Remaining Questions. Studies examining neurobiological responses to drug cues thus far have yielded a complex and contradictory pattern of findings. It is clear that variables relating to participant characteristics, such as treatment status, are critical factors that may reconcile otherwise discrepant findings. It has been proposed that constraints on the perceived drug use opportunity held by participants may underlie such effects. Nonetheless, this factor has not been explicitly manipulated in extant studies and, as such, the degree to which perceived opportunity and other factors related to treatment-seeking status account for these data awaits direct investigation.

Moreover, there are several possible mechanisms by which drug use expectancy may influence neurobiological responses to drug cue presentation in addition to those raised above (i.e., goal-directed processing under conditions in which drug use is expected). For example, those seeking treatment may be motivated to maintain abstinence and may therefore attempt to inhibit cue-elicited craving, perhaps via the use of techniques acquired during treatment (Wertz & Sayette, 2001b). It is quite possible that such efforts to inhibit would produce a different pattern of neural activation compared to the eager anticipation of future drug use. Further, it is likely that perceived drug use opportunity produces different effects in different contexts. For instance, the pattern of neural activity elicited by drug cues in drug-addicted individuals entering drug treatment may significantly differ from that produced in actively using addicts that are explicitly told that they cannot consume for a long period of time. In the former case, individuals do not intend to consume drugs because they are trying to quit (i.e., they are *abstinence-seeking*), while in the latter instance, individuals desire to seek and consume drugs, but are prevented from doing so by situational constraints (i.e., they are *abstinence-avoidant*) (Tiffany, 1990).

1.4 Specific Aims of the Proposed Research

The objective of the proposed research was to address this important gap in our knowledge. Specifically, fMRI was employed to investigate contextual modulation of functional activation in the neural circuitry implicated in human drug craving. The specific aims of the proposed study were as follows:

Aim 1: To identify brain regions that process drug cues independent of perceived drug use opportunity.

Hypothesis 1: Responses in anterior cingulate and amygdala elicited by drug-related stimuli are not dependent upon perceived drug use opportunity. The present study sought to further characterize the neural response to drug cues in humans. It was predicted that drug cue exposure would significantly increase activity in anterior cingulate and amygdala relative to presentation of neutral objects. Further, it was proposed that cue-elicited responses in these regions would not be modulated by perceived drug-use opportunity.

Aim 2: To demonstrate that perceived drug use opportunity modulates the neural response to drug-associated stimuli.

Hypothesis 2: Contextual modulation of the neural response to presented drug cues will be localized to ventral/orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC). It was proposed that perception of drug availability modulates the evaluation of drug-associated stimuli. Specifically, it was suggested that these effects are localized to OFC and DLPFC. Based upon a review of the literature, it was predicted that subjects who anticipate proximal drug use would exhibit significantly greater activation in these PFC subregions.

2.0 METHOD

2.1 Participants

Twenty-two right-handed, male, native English speaking cigarette smokers participated in the experiment (mean age = 24.4 years, SD = 4.9). All participants reported smoking between 20-40 cigarettes per day for at least 24 continuous months (mean cigarettes/day = 21.6, SD = 2.7). Participants were recruited through advertisements in local newspapers. Exclusionary criteria included dependence on any drug other than nicotine or caffeine, illiteracy, or medical conditions that ethically contraindicated nicotine administration. Written informed consent was obtained from all participants. Participants were paid for participation, and all procedures were approved by the Institutional Review Board of the University of Pittsburgh. Data from two participants were excluded from all analyses because of excessive head motion during scanning; subsequent analyses are reported on the remaining 20 participants.

Participants were invited to participate in a 2 hour study. They were randomly assigned to one of two experimental conditions: 1) half of the participants were told that they would be able to smoke during a break at the midpoint of the experimental session (Instructed-Yes; n = 10), 2) the other half were instructed that they could not smoke during the experimental session and would have to wait approximately two hours before smoking (Instructed-No; n = 10). Age, number of cigarettes smoked per day, number of quit attempts, and years of education were similar across instructed smoking expectancy conditions (ps > 0.05, see Table 1).

2.2 Cue Exposure Procedure

Participants completed two cue exposure runs, during which they were asked to hold and look at stimuli that were designed to elicit either (a) minimal changes in craving

(i.e., neutral objects) or (b) stimuli designed to elicit robust increases in craving (one of their own cigarettes). Each cue exposure run began with a 48 second resting baseline epoch during which no objects were held. After the initial rest period, the first cue of the run was placed in the left hand of the participant and instructions identifying the object were delivered over an intercom system. After a period of 74 seconds, the object was removed. A second resting baseline epoch lasting 74 seconds followed removal of the object. Subsequently, the second cue of the run and identifying instructions were presented and the object was held for a period of 74 seconds. During the first cue exposure run, participants were presented with a small yellow notepad (neutral object) and a white plastic golf ball (neutral object). This run served to allow participants to acclimate to the task. During the second run, participants were presented with a roll of black electrical tape (neutral object) and one of their cigarettes (craving-eliciting object).

2.3 Urge rating assessment

Participants verbally rated their urge to smoke on a scale from 0 (labeled "absolutely no urge to smoke at all") to 100 (labeled "strongest urge to smoke I've ever experienced). Urge ratings were provided immediately before the start of each of the two cue exposure runs. Participants also rated their urge at the completion of each run. Thus, a total of 4 urge ratings were obtained from each participant (Urge #1 – Urge #4). Ideally, each of these ratings would have been obtained during stimulus exposure (i.e., while participants were holding each object); however, it was decided to assess urge preceding each run (Urge #1 and Urge #3) rather than during exposure to the first object of the run in order to avoid eliciting unwanted neural activity and because of practical

constraints (e.g. difficulty communicating with participants over scanner noise). Urge ratings obtained at the completion of each run (Urge #2 and #4) occurred after fMRI data acquisition had terminated and while participants were still holding the second object of the run.

2.4 Procedure

Participants who responded to the advertisements completed a preliminary screening interview over the phone. Eligible participants visited the lab for three sessions: a more thorough screening assessment (Session 1), a session in which abstinence instructions were provided (Session 2), and the experimental session (Session 3). Session 2 and Session 3 were conducted eight hours apart on the same day. During Session 1, participants provided an expired air carbon monoxide (CO) sample (CO #1), which was used to verify smoking status. Session 2 occurred eight hours prior to the experimental session, during which subjects returned to the laboratory to smoke one of their cigarettes. After smoking the cigarette, a second CO sample was obtained (CO #2) to provide a baseline for comparison to levels obtained at the start of the experimental session. Subsequently, all participants were instructed not to drink alcohol or use tobacco products or other drugs for 8 hours prior to arriving at the laboratory to participate in the experiment. Participants then presented their pack of cigarettes and lighter to the experimenter and were permitted to leave the laboratory. Experimental sessions were scheduled to begin between 4 pm and 6 pm. To check compliance with deprivation instructions, participants reported the last time they smoked a cigarette and a third CO

sample was obtained (CO #3). For the third CO assessment, samples exceeding half of the CO #2 and/or 16 parts per million resulted in exclusion from the study.

Immediately before scanning began, participants were given instructions regarding whether they would be permitted to smoke during the experimental session. As all participants were informed that the experimental session would last for 2 hours, Instructed-No participants therefore expected a significant delay before having the opportunity to smoke (see also Juliano & Brandon, 1998). For Instructed-Yes participants, smoking expectancy instructions were delivered in a room located in close proximity to that housing the MRI scanner by an experimenter standing in front of a sign designating the room as a "smoking area for research purposes" (actual smoking took place outside, see below). This was done to enhance the likelihood that these participants would anticipate the opportunity to smoke almost immediately after cigarette cue exposure (i.e., that they would be able to smoke after a short trip down the hall). At this point, participants completed the first of two cue presentation runs. Participants then completed a guessing task involving monetary gains or losses (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000) for approximately 45 minutes (data from this task are not presented herein).

Subsequently, participants completed the second cue presentation run. While holding the cigarette during the second run, Instructed-Yes were told that in 40 seconds, they would be removed from the scanner and would be permitted to immediately smoke the cigarette they were holding. Instructed-No participants were told that they would be removed from the scanner in 40 seconds, but would not be able to smoke the cigarette they were holding. Following self-reported craving assessment, all participants were

removed from the scanner for a brief break (about 5 minutes) and those participants told that they would be permitted to smoke were escorted outside where they were permitted to smoke a cigarette at their own pace. Afterwards, participants were returned to the scanner to complete approximately 45 additional minutes of the guessing task (data not presented) and were then debriefed.

2.5 FMRI Data Acquisition and Processing

Participants were scanned using a conventional 1.5 T GE Signa whole-body magnet and standard radio frequency coil. A structural series of 36 contiguous oblique-axial slices (3.75 x 3.75 x 3.8 mm voxels) parallel to the AC-PC line was collected using a standard T1-weighted pulse sequence. Functional images were acquired in the same plane as the structural series with coverage limited to the 20 center slices using a T2*-weighted one-shot spiral pulse sequence (TE=35 ms, TR=1500 ms, FOV=24 cm, flip angle = 70°). FMRI data analysis 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). Following reconstruction, single-subject data was corrected for motion using Automated Image Registration (AIR 3.08; Woods, Cherry, & Mazziotta, 1992) and adjusted for drift between runs. After stripping to remove skull, structural images from each participant were co-registered to a common reference anatomy (Woods, Mazziotta, & Cherry, 1993). In order to form a composite data set for group-level statistical analyses, functional images were transformed into the same space, globally mean-normalized to minimize differences in image intensity between

participants, and smoothed using a three-dimensional Gaussian filter (6-mm FWHM) to account for between-subject anatomical differences. Group-based statistical images were visualized and transformed into standard stereotaxic space (Talairach & Tournoux, 1988) using the Analysis of Functional NeuroImages software package (AFNI 2.6; Cox, 1996).

2.6 FMRI Data Analysis

The set of co-registered functional data was used in all voxel-based statistical analyses, although individual subject data were inspected in order to confirm consistency of results across subjects. FMRI signal averaged over the final 48 seconds of cue exposure for each object was the blood oxygen level-dependent (BOLD) response of interest. The initial 26 seconds of each object exposure epoch was removed to allow for stabilization of responses corresponding to instruction delivery. The first cue exposure run served to allow participants to acclimate to holding object while in the MRI scanner and was not included in analyses.

To isolate regions of interest, a voxel-wise mixed-model ANOVA was performed with instruction set (Instructed-Yes, Instructed-No) as a between-subjects variable and cue (neutral, cigarette) as a repeated measures variable. One objective of this analysis was the localization of regions that exhibited preferential activation by the cigarette cue (main effect of cue). For cue main effects, the voxel-wise significance threshold was set at $p < .005$ (uncorrected). Main effect regions of activation comprised of fewer than five contiguous voxels were not considered significant in order to reduce the risk of false positives (Forman et al., 1995).

In addition to examining cue main effects, the primary analytic objective was the identification of regions that demonstrated differential activation during cue exposure as a function of perceived drug use opportunity (instruction set by cue interaction). Given the exploratory nature of this study and the findings from a prior review pointing to DLPFC and OFC as regions most influenced by perceived drug use opportunity (Wilson et al., 2004), a liberal voxel-wise alpha of $p < .01$ (uncorrected) and spatial extent threshold of three or more contiguous voxels was chosen for detecting an interaction between instruction set and cue. There were no specific a priori hypotheses regarding interaction effects occurring outside of DLPFC and OFC and, because the chosen threshold does not provide adequate protection against type I errors across the whole brain, activations falling beyond these regions are reported for completeness but are not a focus of discussion.

3.0 RESULTS

4.1 Self-reported Urge

A 2 (instruction set) X 4 (time) repeated measures analysis of variance (ANOVA), with the four urge ratings as a repeated measures variable, revealed a main effect of time, $F(3, 54) = 24.9$, $p < .001$. Trend analysis revealed significant linear [$F(1, 18) = 46.5$, $p < .001$] and cubic [$F(1, 18) = 9.7$, $p = 0.006$]. As shown in Figure 3, urge ratings rose over time, with inflection points at Urge #2 and Urge #3. The instruction set by time interaction was not significant. However, based upon the observed effect size

(Cohen's $f < 0.05$) and size of the present sample, power to detect this interaction at $\alpha = 0.05$ was quite low (< 0.10).

4.2 Imaging data

Main Effect of Cue. Regions exhibiting a main effect of cue are summarized in Table 3 and depicted in Figure 4. Significantly greater BOLD signal during cigarette relative to neutral cue exposure was detected in the left superior (BA 19) and middle (BA 18) occipital gyrus, right posterior cingulate gyrus (BA 23), left inferior parietal cortex (BA 39) a large cluster in the anterior cingulate extending to medial frontal gyrus (BA 32/8), bilateral superior/middle temporal cortex (BA 21), right cuneus (BA 18), and right fusiform gyrus. Significantly greater activation during neutral relative to cigarette cue presentation was observed in bilateral middle and posterior cingulate gyrus (BA 24/31), left precuneus (BA 7), bilateral thalamus, bilateral lentiform nucleus (primarily globus pallidus), right middle occipital gyrus (BA 19), a large region encompassing the left lingual gyrus and adjacent cuneus (BA 17/18/19), and left insula (BA 13).

Instruction Set by Cue Interaction. A significant instruction set by cue interaction was observed in multiple foci (see Table 4 and Figure 5a), including bilateral dorsolateral prefrontal cortex (DLPFC; middle/inferior frontal gyri, BA 9/46), two right-lateralized regions in rostrolateral prefrontal cortex (RLPFC; middle frontal gyrus, BA 10), ventromedial prefrontal cortex (VMPFC; medial frontal gyrus, BA 10), left ventrolateral prefrontal cortex (VLPFC; inferior frontal gyrus, BA 47), left cuneus (BA 19), right precentral gyrus (BA 6), right superior (BA 22) and left middle temporal gyrus (BA 21), left inferior/middle occipital gyrus (BA 19/18), and left parahippocampal gyrus. In order

to determine the nature of the interaction for these regions, the effects of cue were examined separately for each instructional group (see Figure 5b). In DLPFC, VLPFC, superior temporal gyrus, occipital gyrus, and parahippocampal gyrus, significantly less activation was found for Instructed-Yes participants during cigarette relative to neutral cue exposure, whereas BOLD signal did not significantly differ between stimulus conditions for Instructed-No participants. In VMPFC, precentral gyrus, and middle temporal gyrus, signal was significantly greater during cigarette relative to neutral cue exposure for Instructed-Yes participants, while there was no difference between cue types for Instructed-No participants. Activation of the cuneus was enhanced by cigarette cue presentation for Instructed-No participants, while cigarette and neutral conditions did not differ for Instructed-Yes participants. Finally, cigarette-related activation of the RLPFC[3] was significantly lower than that elicited during neutral cue exposure for Instructed-Yes participants, while the opposite pattern (cigarette greater than neutral) was observed for Instructed-No participants.

4.0 DISCUSSION

The present study examined neural activity elicited by cigarette cue exposure in male cigarette smokers. Several brain regions exhibited differential activation during cigarette relative to neutral stimulus presentation independent of whether or not participants expected to smoke during the study. This distributed activation included

[3] This double dissociation was significant for the more superior of the two RLPFC regions (z = 14 at local maximum). The more ventral RLPFC region (z = -2 at local maximum) exhibited a trend towards significantly less activation for Instructed-Yes participants during cigarette relative to neural cue exposure [$t(9) = 2.23$, $p = 0.053$].

regions associated with a diverse set of cognitive functions (DeLong, Crutcher, & Georgopoulos, 1985; Maddock, Garrett, & Buonocore, 2001; Mersulam, 1998), including brain areas implicated in the processing of visual (extrastriate cortex) and auditory (superior and middle temporal cortex) information, visuospatial integration (inferior parietal cortex), episodic and autobiographical memory retrieval (posterior cingulate gyrus), and control of movement (lentiform nucleus). Activity in these areas likely reflects, in part, aspects of the cue exposure procedure employed in this study. Specifically, the neutral and drug-related stimulus configurations utilized in this study consisted of visual (e.g., sight of cue), tactile (holding and manipulating cue), and auditory (object identification and instructed smoking expectancy) stimulation.

Although complex, results generally suggest that visuospatial and auditory processing resources were recruited to a greater extent by the cigarette cue than the neutral cue, as reflected by activation patterns in visual (lingual gyrus, cuneus), posterior parietal, and auditory (temporal) cortices (Mersulam, 1998). The larger spatial extent of visual cortex recruited by neutral objects may reflect shifting gaze over a more extensive visual field (i.e., lack of sustained attention to neutral cues) or active inhibition of regions with receptive fields distal from attended to location of the cigarette during its presentation (Kastner, De Weerd, Desimone, & Ungerleider, 1998; Slotnick, Schwarzbach, & Yantis, 2003). In constrast, we observed comparatively greater activation of regions associated with memory-related processing (parahippocampal gyrus, posterior cingulate; Duzel et al., 2003; Maddock et al., 2001) and control of movement (globus pallidus; DeLong et al., 1985) during neutral than cigarette cue exposure. This could reflect more unconstrained mental processing involving retrieval (e.g.,

daydreaming; Binder et al., 1999) during neutral cue presentation, while the cigarette cue was perhaps subject to vigilant processing associated with less episodic recall and more stable physical handling (e.g., holding the cigarette steadfast while staring at it). Alternatively, the neutral objects may have engaged greater memory resources and elicited more extensive physical manipulation than the cigarette cue because they were more novel to smokers than was the cigarette.

Regardless of instructions, there was significantly greater activation of the rostral "affective division" of anterior cingulate cortex (Bush, Luu, & Posner, 2000; Vogt, Finch, & Olson, 1992) during cigarette than neutral cue exposure. The anterior cingulate is the most frequently reported region of activation in studies of human drug craving and has been associated with exposure to cigarette (Brody et al., 2002), alcohol (Grüsser et al., in press; Myrick et al., 2004; Tapert et al., 2004; Tapert et al., 2003; Wrase et al., 2002), cocaine (Childress et al., 1999; Garavan et al., 2000; Kilts et al., 2004; Kilts et al., 2001; Wexler et al., 2001), and heroin (Daglish et al., 2001) cues. As mentioned above, these studies did not directly manipulate perceived drug use opportunity. Thus, the anterior cingulate appears to contribute to aspects of craving that do not depend upon drug use expectancy, such as assessment of the motivational value associated with drug cues based upon experience (Bush et al., 2000; See, 2002).[4] The affective and motivational salience of drug cues as represented by anterior cingulate may reflect value

[4] A recent study by Brody and colleagues (2004) found that cigarette smokers treated with buproprion exhibited less cue-elicited activation of the ACC than did untreated smokers. However, the majority (approximately 70%) of treated participants did not achieve abstinence (i.e., they had "diminished usage") and were not required to abstain before participation. Thus, the extent to which this group anticipated the opportunity to smoke after the study is unclear, making it difficult to ascertain the impact of drug use expectancy versus other treatment-related factors (e.g., direct pharmacologic actions of buproprion) on ACC activation in this study. This study stands in contrast to others classified as treatment studies in a review by Wilson et al. (2004), in which there was typically a minimal period of abstinence required before experimental sessions.

that is dependent upon an extensive drug use history and therefore this region may be less susceptible than are other brain areas to transient fluctuations as a function of perceived opportunity to consume.

Of primary interest, the present study sought to examine the effects of perceived drug use opportunity on neural activity elicited by drug-related stimuli. Several cortical areas exhibited cue-related activation that was modulated by perceived opportunity to smoke. These included regions associated with unimodal and multimodal sensory processing (Mersulam, 1998), with the pattern of results suggesting that anticipating an opportunity to smoke resulted in relatively less attention to auditory and visual aspects of the craving stimulus complex than when such anticipation was not present.

Based upon a review of the literature (Wilson et al., 2004), it was predicted that cue-elicited responses in OFC and DLPFC would be modulated by drug availability. These regions have been reported almost exclusively by studies recruiting active drug users (i.e., those not seeking treatment), suggesting that they may be more responsive to drug cues when future drug use is anticipated (Wilson et al., 2004). Consistent with hypotheses, it was found that regions within OFC and DLPFC were sensitive to smoking expectancy. However, rather than simply observing greater cue-elicited activation of OFC in participants expecting to smoke, it was observed that functional subdivisions within OFC were differentially influenced by drug availability. Specifically, cigarette cue exposure was associated with significantly greater activation of VMPFC, a region closely related to the medial sector of OFC (Krawczyk, 2002), only when smoking was anticipated. In contrast, we observed significantly less cigarette-related activation of VLPFC (i.e., lateral OFC) amongst participants that were expecting to smoke, while the

neutral and cigarette cue did not differ for participants that were not expecting to smoke. We also observed significantly less activation of DLPFC during cigarette than neutral cue exposure in participants expecting to smoke during the study, while neutral- and cigarette-related activity was similar in participants not expecting to smoke. Thus, as previously noted (Wilson et al., 2004), the precise manner in which responses in OFC and DLPFC are affected by drug use expectancy are complex and dependent upon several factors, with patterns based upon coarse distinctions between treatment-seeking and actively using drug-addicted participants differing in important ways from those obtained via an explicit manipulation of drug use expectancy in active smokers.

One factor that exerts significant influence over the effects of perceived drug use opportunity on cue-reactivity is the magnitude of delay anticipated until drug may be consumed. For instance, cue-elicited responses of individuals expecting to smoke almost immediately differ significantly from those of participants expecting to wait only several seconds more before smoking (Sayette et al., 2003). A second factor that may critically affect the impact of drug availability on cue-elicited responses is motivation regarding future drug use. As mentioned, responses elicited by drug cues in drug-addicted individuals entering treatment may significantly differ from those produced in addicts with no intention of discontinuing drug use who are explicitly told that they can or cannot consume for a long period of time (Wertz & Sayette, 2001b). In the former case, individuals do not intend to consume drugs because they are trying to quit (i.e., they are *abstinence-seeking*), while in the latter circumstance individuals desire to seek and administer drugs (i.e., they are *abstinence-avoidant*), but their ability to do so is determined by situational constraints (Tiffany, 1990).

In the present study, abstinence-avoidant smokers anticipating either a relatively short (40 seconds) or long (over 1 hour) delay were presented with one of their cigarettes. This paradigm resulted in significant cue-elicited increases in medial OFC and decreases in lateral OFC only amongst participants expecting to smoke soon. It has been suggested that medial and lateral OFC have dissociable reward-related functions, with medial OFC subserving the representation and monitoring of reward values and lateral OFC recruited when established contingencies are altered and previously rewarded responses must be inhibited (Elliott, Dolan, & Frith, 2000). The majority of previous studies reporting significant within- or between-group activation of OFC by drug cues found significant cue-evoked increases falling within the lateral portion of OFC in actively using participants that presumably anticipated having to wait an extended period of time (i.e., until leaving the experimental setting) before having the opportunity to consume drugs (Bonson et al., 2002; Brody et al., 2002; Myrick et al., 2004). In contrast, Grant and colleagues (1996) found significant cue-evoked activation of medial OFC in active cocaine abusers who were told that they would be allowed to self-administer the cocaine presented to them following completion of experimental procedures. With the exception of one study (Wrase et al., 2002), medial and lateral OFC activation have not been reported by studies recruiting participants enrolled in drug treatment.

Taken together, these data suggest that medial OFC may contribute to explicit representation of drug use expectancy and processing of drug cues as predictors of reward (with a decrease in the need for lateral OFC mediated inhibitory control) when drug use is desired and expected to occur in a relatively short period of time (i.e., in abstinence-avoidant users expecting a short delay). In contrast, lateral OFC may be

selectively recruited for the suppression of cue-elicited responses in abstinence-avoidant users anticipating a protracted delay preceding drug availability. Finally, these subregions of OFC may not respond to drug cues in individuals motivated to avoid consumption (abstinence-seeking) and who therefore do not expect to use for an indefinite period of time.

DLPFC, like OFC, responded differentially to the smoking-related and neutral cue only in smokers expecting an opportunity to smoke almost immediately, exhibiting less activation to the cigarette than the neutral stimulus. As mentioned, the majority of studies recruiting active drug users have reported activation of DLPFC to be significantly increased by drug cues. None of these studies informed participants that they would be able to use drugs without delay. Studies employing treatment-seeking addicts – those presumably motivated to avoid future drug use and, thus, not anticipating the opportunity to consume – have generally failed to find significant cue effects in DLPFC. Thus, it appears that processes mediated by DLPFC are recruited particularly in abstinence-avoidant addicts that anticipate a delay between cue exposure and drug use. In contrast, DLPFC resources appear not to be called upon (or are actively suppressed) in two distinct conditions: when abstinence-avoidant users anticipate almost no delay between cue presentation and drug consumption (as in the present study) or when those undergoing cue exposure are abstinence-seeking. DLPFC plays a central role in reward-processing and decision-making, particularly when information must be maintained over a delay to guide behavior (Krawczyk, 2002). One interesting possibility is that DLPFC mediated generation and maintenance of plans to obtain and consume drugs is augmented when drug use is desired but prevented by obstacles, while such planning (and thus, activation

of DLPFC) is not needed when drug use is not desired or when desire is high but no obstructions to consumption are faced.

Results from this study yielded a third PFC region exhibiting activation that was modulated by smoking expectancy. A double dissociation was found in RLPFC; specifically, activation of RLPFC elicited by cigarette cue exposure was significantly greater than that elicited by neutral stimuli for participants not expecting to smoke during the study (i.e., Instructed-No group), while neutral cues elicited greater activation than did the cigarette for those expecting to smoke (Instructed-Yes group). It has been suggested that rostrolateral PFC is selectively involved in the evaluation of self-generated information (e.g., information that must be inferred; Christoff & Gabrieli, 2000; Christoff, Ream, Geddes, & Gabrieli, 2003). This suggests that Instructed-No participants preferentially engaged in processing of internally-generated information during drug cue exposure, whereas this epoch was not associated with such processing (or even a suppression of such activity) for Instructed-Yes participants. For participants not expecting to smoke soon, this internally-generated information may have been related to future drug seeking (e.g., generating or evaluating plans to smoke after the study). Such processing may have been unnecessary for those holding a cigarette that they expected to smoke almost immediately, consistent with the observation of cue-elicited decreases in DLPFC activation.

The primary aim of this study was to examine the effects of smoking expectancy on the neural response to a cigarette cue. It was previously reported that treatment status, a proxy for drug use opportunity, appears to significantly influence responses to drug-related stimuli in the prefrontal cortex (Wilson et al., 2004). The present study, which

found a significant expectancy effects in OFC and DLPFC, provides additional evidence that drug use expectancy can affect the way in which drug-related stimuli are processed in these regions.

While promising, these initial findings should be interpreted cautiously because of several limitations of this study. Interaction effects were obtained at a fairly liberal statistical threshold by conventional neuroimaging standards. Thus, while confidence in these results is strengthened by the identification of a priori regions of interest, these data must be considered preliminary and in need of replication. In addition, while OFC and DLPFC were successfully identified as regions modulated by smoking expectancy, the observed pattern of effects were fairly complex. I have attempted to account for both points of convergence and points of discrepancy between the current data set and data from a prior review (Wilson et al., 2004) through a consideration of factors (e.g., delay, motivation regarding future drug use) that may significantly affect how perceived opportunity influences cue-reactivity. Nevertheless, these interpretations await direct empirical investigation. Finally, because the current study recruited only male smokers, it is unclear whether similar effects would be observed in female smokers. For instance, research demonstrates that male and female smokers differ in their response to smoking-related stimuli and nicotine administration (Perkins et al., 2001).

Despite these limitations, these findings highlight the importance of perceived drug use opportunity as an area of investigation for addiction researchers using functional neuroimaging to study cue reactivity. Further, these data generate intriguing and testable hypotheses regarding the role of subregions of PFC in drug craving and addiction. Contemporary neurobiological models of addiction and craving emphasize decreased

inhibitory control as a consequence of adulterations to PFC function produced by chronic drug use (Goldstein & Volkow, 2002; Jentsch & Taylor, 1999; London et al., 2000). The present results raise the possibility that, in addition to such inhibitory deficits (i.e., resulting in being "overcome" by urge), the state of addiction also can be associated with the active recruitment of different cognitive processes mediated by regions of PFC in the support of drug acquisition and consumption. On the one hand, medial OFC may contribute to explicit representation of drug use expectancy and processing of drug cues as predictors of reward, with a decrease in the need for lateral OFC mediated inhibitory control, when presented concomitant with proximally anticipated consumption. On the other hand, activation of PFC regions supporting complex cognition and planning (rostrolateral and dorsolateral PFC) may ensue in the face of drug cue exposure when use is delayed or otherwise prevented by obstacles.

More generally, chronic drug use may sharpen the efficiency with which the addicted system recruits resources in the services of drug seeking and acquisition. Indeed, it has been found that smokers lacking proximal drug use expectancy generated more positive, but not negative, aspects of smoking during craving, perhaps because drug-use promoting information is selectively retrieved from or actively maintained in memory (Sayette & Hufford, 1997). Moreover, attentional biases to smoking related stimuli are enhanced (Wertz & Sayette, 2001a) and latency to attempt to access drug cues is decreased (Carter & Tiffany, 2001) as perceived drug use opportunity increases. This suggests that the salience and motivational significance of drug cues is augmented as drug use is approached. Taken together, evidence suggests that the route by which drug cue exposure influences neural and behavioral response systems is complex and context-

dependent. Further research and theory attempting to explicate the role of PFC and other regions in craving and drug use will be enhanced by considering the various ways in which chronic drug use may render the brain more efficient at utilizing available resources to promote further drug intake across contexts.

APPENDIX A:

Object Presentation Instructions

Neutral 1 (both groups):

"Now you will be holding a notepad."

Neutral 2 (both groups):

"Now you will be holding a plastic golf ball"

Neutral 3 (both groups):

"Now you will be holding a roll of tape."

Cigarette (Instructed-Yes):

"Now you will be asked to hold one of your cigarettes. In 40 seconds, you will be removed from the scanner and will be allowed to smoke the cigarette you are holding. Although it took a few minutes to be placed in the scanner, it will only take a few seconds to be removed from the scanner and walk down the hall to a room where you can smoke."

Cigarette (Instructed-No):

"Now you will be asked to hold one of your cigarettes. In 40 seconds, you will be removed from the scanner but you WILL NOT be allowed to smoke the cigarette you are holding. You will have to wait until the end of the study to smoke. Although it took a few minutes to be placed in the scanner, it will only take a few seconds to be removed from the scanner.

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Tables

Table 1. Activation of DLPFC and OFC During Drug-Cue Exposure.

Study	Imaging Modality	Addictive Substance	Drug cue	DLPFC	OFC
Drug users currently not seeking treatment					
Bonson et al. (2002)	PET	Cocaine	Video, Script, Paraph	X	X
Brody et al. (2002)	PET	Cigarette	Video, Tactile		X
Due et al. (2002)	fMRI	Cigarette	Pictures	X	
Garavan et al. (2000)	fMRI	Cocaine	Video	X	
George et al. (2001)	fMRI	Alcohol	Pictures, Gust	X	
Grant et al. (1996)	PET	Cocaine	Video, Paraph	X	X
Maas et al. (1998)	fMRI	Cocaine	Video	X	NA
Myrick et al. (2004)	fMRI	Alcohol	Pictures, Gust		X
Tapert et al. (2003)	fMRI	Alcohol	Pictures		X
Tapert et al. (2004)	fMRI	Alcohol	Words	X	
Wang et al. (1999)	PET	Cocaine	Script, Tactile		X
Drug users currently seeking treatment					
Braus et al. (2001)	PET	Alcohol	Video		
Childress et al. (1999)	PET	Cocaine	Video		
Daglish et al. (2001)	PET	Opiate	Script		
Grüsser et al. (in press)	fMRI	Alcohol	Pictures	X	
Kilts et al. (2001)	PET	Cocaine	Script		
Modell et al. (1995)	SPECT	Alcohol	Gust, Olfactory		
Schneider et al. (2001)	fMRI	Alcohol	Olfactory		
Sell et al. (1999)	PET	Opiate	Video, Drug		
Wexler et al. (2001)	fMRI	Cocaine	Video		
Wrase et al. (2002)	fMRI	Alcohol	Pictures	X	X

X = significant within- or between-group activation, NA = not assessed. Abbreviations: OFC, orbitofrontal cortex; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; SPECT, Single photon emission computed tomography; Drug, drug administration; Gust, gustatory stimulation with drug-related taste; Olfactory, olfactory stimulation with drug-related scents; Paraph, visual presentation of drug paraphernalia; Pictures, visual presentation of drug-related pictures; Tactile, tactile stimulation with drug cues; Script, drug-related craving induction script/interview; Video, audiovisual presentation of drug-related scenes; Words, visual presentation of drug-related words.

Table 2. Participant Demographic Characteristics and Self-Reported Urge.

	Instructed-Yes	Instructed-No
Age	24.1 (4.3)	25.3 (5.9)
Cigarettes/day	21.3 (2.2)	22.0 (3.4)
Years smoking	7.8 (1.9)	8.1 (4.8)
Quit attempts	3.4 (4.9)	1.0 (1.2)
Education	13.4 (1.7)	13.1 (1.3)
Urge #1	59.5 (20.6)	61.5 (23.9)
Urge #2	60.5 (24.1)	62.2 (22.8)
Urge #3	70.5 (25.1)	72.0 (27.1)
Urge #4	76.5 (20.1)	72.3 (27.1)

Table 3. Regions Exhibiting a Main Effect of Cue.

Anatomical Region	Broadmann's Area	Talairach coordinates x	y	z	Average F ratio
Cigarette > Neutral					
L Superior occipital g	19	-41	-77	29	14.06
R Posterior cingulate g	23	4	-43	29	16.36
L Inferior parietal lobule	39	-54	-68	24	12.59
L Ant cing / Superior frontal g	32	-4	43	8	15.02
L Middle occipital g	18	-26	-96	5	16.85
L Superior / middle temporal g	21	-50	-23	-1	23.81
R Cuneus	18	23	-100	-1	12.91
R Superior / middle temporal g	21	56	-28	-3	20.99
R Fusiform g		23	-96	-12	11.24
Neutral > Cigarette					
L Cingulate g	24	-14	-14	39	11.33
R Cingulate g	24	20	-17	38	13.03
L Cingulate g	31	-19	-34	39	11.4
L Precuneus	7	-14	-74	35	11.77
L Thalamus		-7	-34	12	13.07
R Lentiform nucleus		21	-9	7	20.09
L Lentiform nucleus		-19	-13	5	15.54
R Middle occipital g	19	31	-65	6	11.6
L Lingual g / cuneus	17/18/19	-20	-78	5	15.46
L Insula	13	-40	-7	-2	12.9
R Thalamus		4	-10	0	13.05

Brodmann's areas (BA) and stereotaxic coordinates are given for local maxima of activation cluster in Talairach and Tournoux (1988) atlas space. Abbrebiation: g, gyrus.

Table 4. Regions Exhibiting a Significant Instruction Set by Cue Interaction.

Anatomical Region	Brodmann's Area	Y	N	Talairach coordinates x	y	Z	Average F ratio
R Middle frontal g (DLPFC)	9	⇩	ns	30	35	37	12.05
L Cuneus	19	ns	⇧	-8	-96	31	16.27
L Inferior frontal g (DLPFC)	9	⇩	ns	-48	6	25	12.6
R Middle frontal g (DLPFC)	46	⇩	ns	46	18	21	9.31
R Precentral g	6	⇧	ns	70	4	16	10.64
R Superior frontal g (RLPFC)	10	ns	⇧	35	59	14	10.39
L Middle temporal g	21	⇧	ns	-67	-7	-1	12.41
R Middle frontal g (RLPFC)	10	⇩	⇧	37	52	-2	9.88
L Inferior frontal g (VLPFC)	47	⇩	ns	-47	27	-5	9.88
R Superior temporal g	22	⇩	ns	48	7	-6	10.32
L Inferior/middle occipital g	19/18	⇩	ns	-36	-68	-6	11.44
L Superior frontal g (VMPFC)	10	⇧	ns	-8	57	-7	9.22
L Parahippocampal g		⇩	ns	-23	-16	-10	10.31

Brodmann's areas (BA) and stereotaxic coordinates are given for local maxima of activation cluster in Talairach and Tournoux (1988) atlas space. Abbreviations: DLPFC, dorsolateral prefrontal cortex; g, gyrus; N, Instructed-No group; ns, not significant; RLPFC, rostrolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; Y, Instructed-Yes group.

⇧ = significantly greater activation during cigarette relative to neutral cue exposure, ⇩ = significantly greater activation during neutral relative to cigarette cue exposure.

Figure Legends

Figure 1. Lateral (left), mid-saggital (middle) and coronal (right) sections of the brain illustrating neural regions that have been implicated in cue-elicited craving. Abbreviations: DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; AMG, amygdala. (Images modified from Sylvius: Fundamentals of Human Neural Structure, S. Mark Williams, Sinauer Associates, Inc. Sunderland MA).

Figure 2. Schematic diagram of the cue exposure task. During each cue exposure run, subjects completed the following sequence: an initial 48 second resting baseline epoch during which no objects were held, presentation of first object for a period of 74 seconds, a second 74 second resting baseline epoch, second object presented for 74 seconds. Neutral object 1 (notepad) and neutral object 2 (plastic golf ball) were presented during run 1. Neutral object 3 (roll of electrical tape) and cigarette were presented during run 2.

Figure 3. Mean urge to smoke ratings.

Figure 4. Regions exhibiting a significant main effect of cue. Regions in which activity associated with cigarette cue exposure was greater than neutral cue exposure are depicted in red; the reverse (neutral greater than cigarette) are depicted in blue. Images are right-left reversed.

Figure 5. A: Regions exhibiting a significant instruction set by cue interaction. Abbreviations: DLPFC, dorsolateral prefrontal cortex; Inf, inferior; L, left; Parahipp, parahippocampal gyrus; R, right; RLPFC, rostrolateral prefrontal cortex; Sup, superior; Temp, temporal gyrus; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial

prefrontal cortex. Images are right-left reversed. **B:** Graphs plot percent signal change during cigarette cue exposure relative to neutral cue exposure.

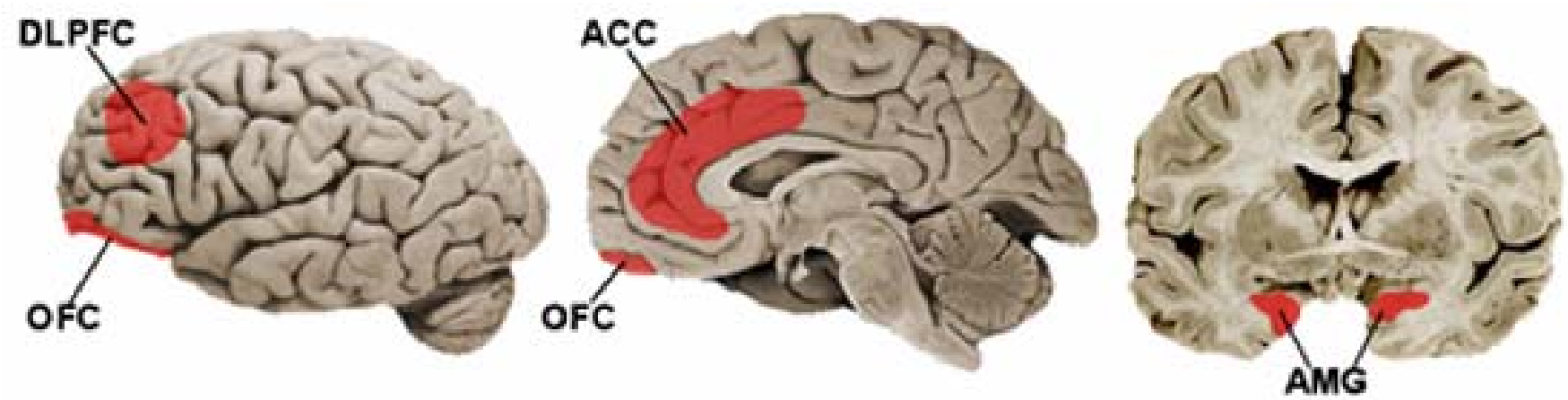

Figure 1

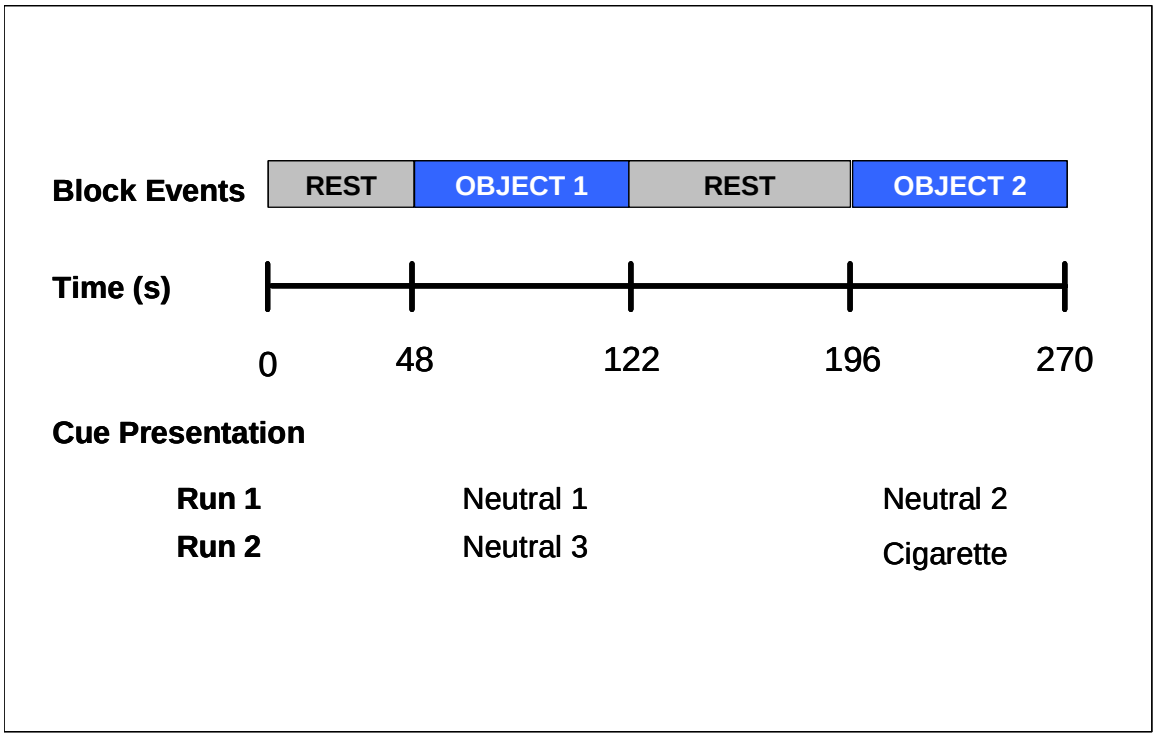
Block Events
REST
OBJECT 1
REST
OBJECT 2
Time (s)
0
48
122
196
270
Cue Presentation
Run 1
Neutral 1
Neutral 2
Run 2
Neutral 3
Cigarette

Figure 2

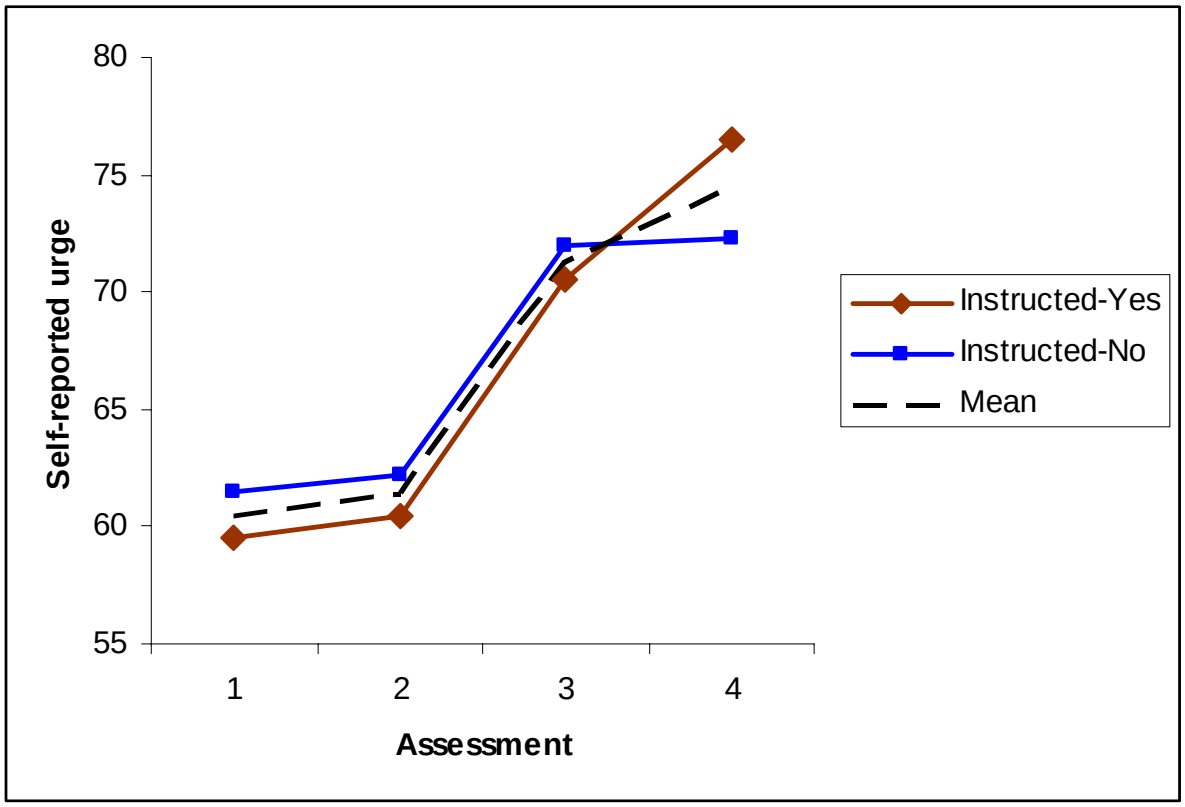
80
75
70
65
60
55
Self-reported urge
1
2
3
4
Assessment
Instructed-Yes
Instructed-No
Mean

Figure 3

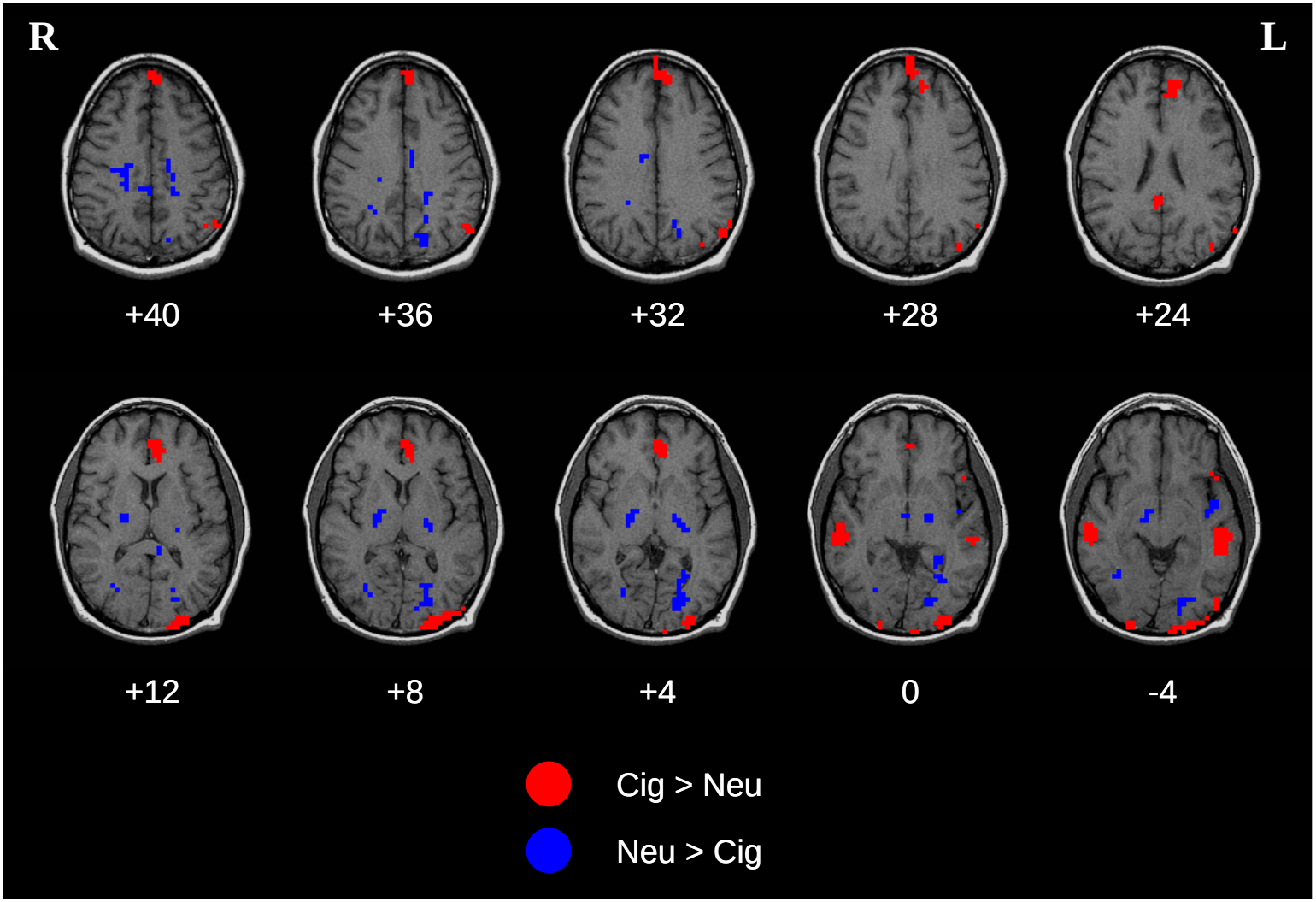

Figure 4

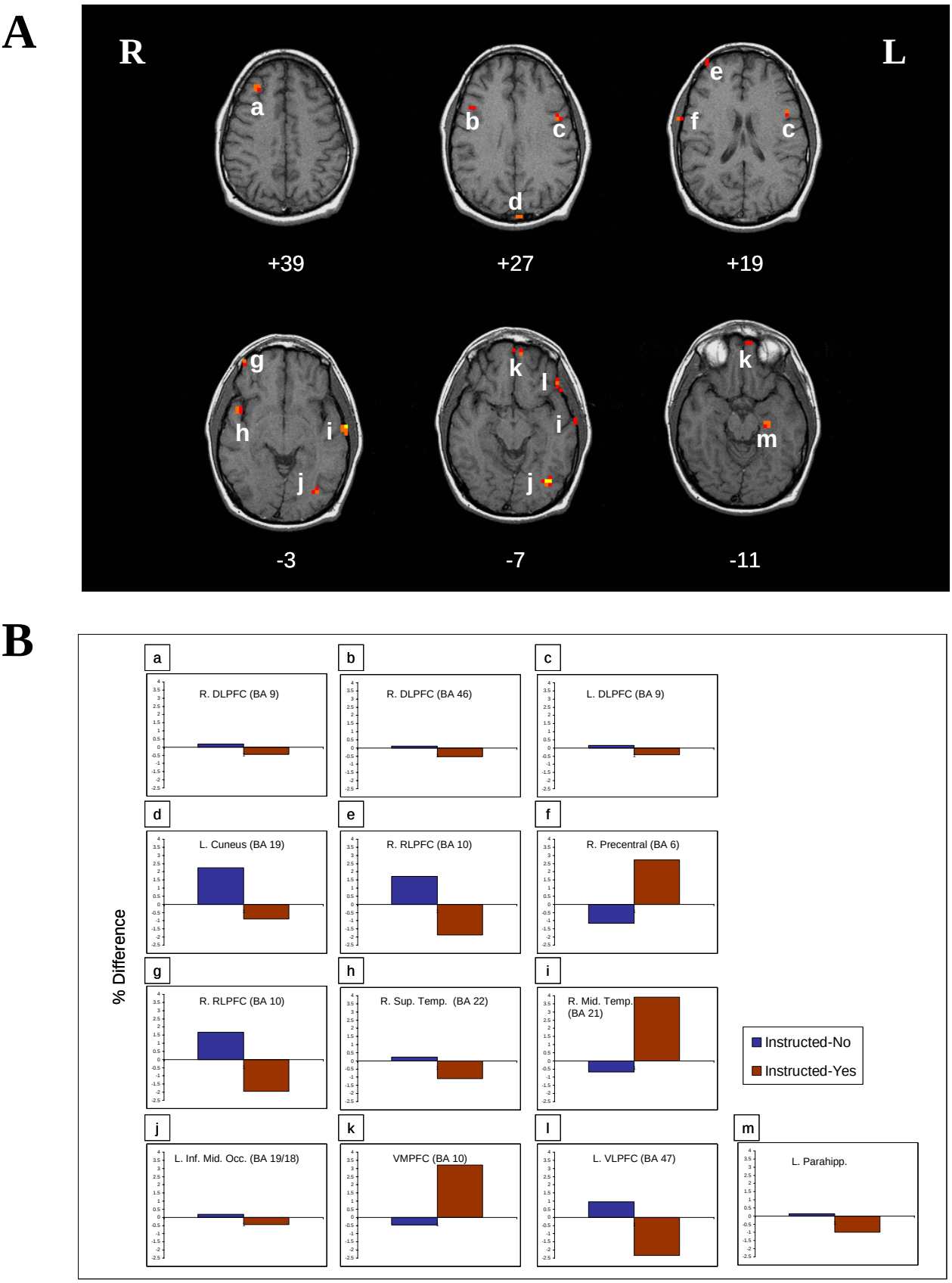
A
R
L
a
b
c
d
e
f
c
+39
+27
+19
g
h
i
j
k
l
i
j
k
m
-3
-7
-11
B
a
R. DLPFC (BA 9)
b
R. DLPFC (BA 46)
c
L. DLPFC (BA 9)
d
L. Cuneus (BA 19)
e
R. RLPFC (BA 10)
f
R. Precentral (BA 6)
g
R. RLPFC (BA 10)
h
R. Sup. Temp. (BA 22)
i
R. Mid. Temp. (BA 21)
j
L. Inf. Mid. Occ. (BA 19/18)
k
VMPFC (BA 10)
l
L. VLPFC (BA 47)
m
L. Parahipp.
% Difference
Instructed-No
Instructed-Yes

Figure 5