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The fMRI BOLD response to unisensory and multisensory smoking cues in nicotine-dependent adults

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Abstract

Given that the vast majority of functional magnetic resonance imaging (fMRI) studies of drug cue reactivity use unisensory visual cues, but that multisensory cues may elicit greater craving-related brain responses, the current study sought to compare the fMRI BOLD response to unisensory visual and multisensory, visual plus odor, smoking cues in 17 nicotine-dependent adult cigarette smokers. Brain activation to smoking-related, compared to neutral, pictures was assessed under cigarette smoke and odorless odor conditions. While smoking pictures elicited a pattern of activation consistent with the addiction literature, the multisensory (odor + picture) smoking cues elicited significantly greater and more widespread activation in mainly frontal and temporal regions. BOLD signal elicited by the multi-sensory, but not unisensory cues, was significantly related to participants' level of control over craving as well. Results demonstrated that the co-presentation of cigarette smoke odor with smoking-related visual cues, compared to the visual cues alone, elicited greater levels of craving-related brain activation in key regions implicated in reward. These preliminary findings support future research aimed at a better understanding of multisensory integration of drug cues and craving.

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Contributors

B.M.C., K.J.H., and F.J.M. conceived and developed the study. B. M.C., K.J.H., H.R.C., and T.L collected and analyzed the study data. B.M.C. wrote the first draft of the manuscript. All authors contributed to the manuscript composition and illustrations, and approved its final form.

Conflict of interest

All authors declare that they have no conflicts of interest.

Keywords

Odors; Smoking; Tobacco dependence; Craving; Cue-reactivity; Neuroimaging

1. Introduction

The rate of current adult smokers in the US is estimated at 42.1 million, approximately 18.1% of adults (Centers for Disease Control and Prevention, 2014). Although nearly 70% of adult smokers report the desire to quit, only 50% make a quit attempt and the vast majority of those (> 90%) relapse back to smoking (Hughes et al., 2004; Piasecki, 2006; Centers for Disease Control and Prevention, 2014). While drug relapse has been associated with a variety of individual, social, and environmental factors (Garvey et al., 1992; Sinha, 2001; Walton et al., 2003), previous research has demonstrated an association between craving and relapse during a smoking quit attempt (Killen and Fortmann, 1997; Shiffman et al., 1997; Herd et al., 2009). As a result, craving has been extensively studied in both the laboratory and naturalistic setting however the precise role of craving remains a focus of debate (Wray et al., 2013).

Cue reactivity is a well-established laboratory paradigm of drug craving (Rohsenow et al., 1994; Drobos and Tiffany, 1997) that generally demonstrates greater effects elicited by drug-related, than neutral cues (Carter and Tiffany, 1999). While the cues employed in studies of drug dependence are typically drug-related visual stimuli (e.g. still pictures or video), a range of stimuli, delivered through various sensory systems, has also been shown to elicit conditioned reactions (Carter and Tiffany, 1999; Erblich and Bovbjerg, 2004; Erblich et al., 2009; Filbey et al., 2009; Yalachkov et al., 2013).

Specifically targeting the olfactory system by using isolated odors, as opposed to odors which may be a component of multi-sensory “in-vivo” cues (e.g. holding/smelling/viewing a cigarette), has revealed the effectiveness of odors as independent cues in eliciting craving (Grusser et al., 2000; McRobbie et al., 2008; Cortese et al., 2015), as well as physiological responses such as increased heart rate and skin conductance (Stormark et al., 1995; Cortese et al., 2015). Studying odor cue reactivity within the functional neuroimaging environment presents its own challenges including the use of an MRI-compatible olfactometer, a sophisticated piece of equipment that delivers precisely timed quantities of odorants. Given this technological requirement, the use of odors as an isolated cue in fMRI drug cue-reactivity studies are rare, with just a handful published in the field of alcohol dependence. However despite the limited available data, findings for odor-elicited drug cue-reactivity (i.e. increased BOLD signal in nucleus accumbens and medial-prefrontal and orbitofrontal cortices; Kareken et al., 2004; Bragulat et al., 2008) are consistent with the extensive drug cue-reactivity literature that demonstrates the involvement of paralimbic and prefrontal cortical areas underlying drug craving and reward (Grüsser et al., 2004; Myrick. et al., 2004; McClernon et al., 2009; Hartwell et al., 2011; Kuhn and Gallinat, 2011; Vollstädt-Klein et al., 2011; Schacht et al., 2013).

In a recent review of the fMRI drug cue-reactivity literature, Jasinska et al., (2014) reported that multisensory drug cues (e.g., haptic) appear to elicit greater brain responses than those

elicited by unisensory drug cues (e.g. visual or script-driven). Significant correlations between brain activity and clinical measures are also more often demonstrated by multisensory than unisensory drug cues (Yalachkov et al., 2012). Together, these findings suggest that multisensory drug cues are more effective than visual alone or other unisensory cues for eliciting drug craving and related physiological reactions. This impression, however, is based upon results from cross-sectional studies, rather than head-to-head analyses. This may be due, in part, to the fact that very few studies employ the appropriate cues and design necessary to answer this basic question. A recent study by Lukas et al. (2013) did present alcohol-related visual and odor cues, both separately and in combination. However, their primary research focus was to assess the effects of naltrexone on the attenuation of alcohol cue-reactivity to detoxified alcohol-dependent adults and did not address the effects of multisensory-versus unisensory-cued brain activation.

Given that real world drug cues are multisensory (e.g. the sight and smell of someone smoking in close proximity) but can also be experienced as unisensory cues (e.g. watching someone smoking in a movie), the present study was designed to examine cue-reactivity in response to visual smoking cues in the presence and absence of a cigarette odor. We hypothesized greater drug cue reactivity to the combination of visual and odor drug cues than to the visual drug cues presented alone.

2. Methods

2.1. Participants

Twenty-two, adult smokers (male=14, female=8), between the age of 18 and 57, were recruited through local advertisement. Potential participants were invited to the laboratory if they met the following criteria: (1) smoked at least 10 cigarettes per day but used no other tobacco products; (2) were non-treatment-seeking or not in active smoking cessation treatment; (3) had no current/lifetime substance dependence or past 30-day abuse of drugs other than caffeine and nicotine; (4) were daily coffee drinkers who reported commonly smoking cigarettes while drinking their morning coffee (i.e., associate coffee and cigarettes), (5) had no current/past history of significant psychiatric illness or treatment; and (6) had no major medical problems including problems with sense of smell. Once IRB-approved informed consent procedures were conducted, the above study eligibility was confirmed with the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., (1998)), urine drug (Wan Han Pu Man Inc., Irwindale, CA) and breath alcohol (Intoximeters, Inc., St. Louis, MO) screens, a detailed tobacco history, a breath carbon monoxide (CO) level 10 ppm (Bedfont Scientific Ltd., Kent, England) and the Fagerstrom Test for Nicotine Dependence (FTND; Fagerstrom, 1978; Heatherton et al., 1991) to assess nicotine dependence, as well as a medical examination and the University of Pennsylvania Smell Identification Test (UPSIT; Doty et al., 1984), a self-administered, 40-item, scratch-and-sniff test used to confirm normosmia, a normal sense of smell. Those that met all study criteria were scheduled for an fMRI exam and instructed to remain abstinent from cigarettes for 12 h before that scheduled time.

2.2. Materials

2.2.1. Olfactometer and odor cues—The six-chamber, MRI-compatible olfactometer (Emerging Tech Trans, LLC, Hershey, PA) allowed precisely timed delivery of odor cues through Teflon™ tubing aimed directly at the nose of each participant. All odor cues were delivered through humidified, room temperature air that flowed at a constant rate of 8 L/min throughout the entire scan. In addition, a fan provided continuous airflow through the bore of the magnet to ensure odor evacuation between each odor cue delivery. The odor cues were previously identified as smoking-related or neutral and formulated to be similar in perceived odor intensity according to methods described previously (Hartwell et al., 2012; Cortese et al., 2015). The four odor cues included a cigarette smoke odor (CIG-O), a smoking-related odor (coffee, COF-O), an odor unrelated to smoking (lavender, LAV-O), and propylene glycol (PG-O), an odorless oil that served as a control “odor” as well as the base ingredient of all other odor cues. Odorants were provided by ScentAir™ (Charlotte, NC).

2.2.2. Craving measures—Subjective reports for baseline craving were assessed prior to the scanning session on 11-point analog scales measuring three aspects of craving. Analog scale #1 measured craving amount and asked, “Right now, I would rate the amount of my craving to smoke as.” (0=very little, 10=a great deal). Analog scale #2 measured craving intensity and asked, “Right now, the intensity of my craving to smoke is.” (0=none, 10=irresistible). And analog scale #3 measured craving control and asked “Right now, if I smoked a cigarette, how much control would I have over additional cravings to smoke?” (0=no control, 10=complete control).

2.3. Procedures

2.3.1. fMRI task—On the day of testing, CO-level-assessed 12-h smoking abstinence was first determined. Participants who did not meet criteria ($CO < 10$ ppm; Jorenby et al., 2006; Piper et al., 2009), were rescheduled. Those confirmed abstinent then provided baseline ratings for their amount of craving, intensity of craving, and control over craving. Next, participants were comfortably positioned in the scanner and asked to verify proper alignment of the odor delivery system by confirming the sensation of air-flow to their nose. A high-resolution anatomical image for subsequent registration was first acquired. Next, participants were given the smoking cue-reactivity fMRI task which consisted of two 540-s runs. Each run consisted of 18 pseudo-randomly interspersed 24-s blocks of either cigarette smoking-related images (CIG-I), non-smoking, neutral, images (NEU-I), or a fixation cross (FIX-I) rest condition, each followed by a 6-s washout period during which the hemodynamic response could return to baseline. The visual cues were provided by Dr. Elliot Stein (Geier et al., 2000) and Dr. Karen Hartwell (Hartwell et al., 2011). The CIG-I and NEU-I picture blocks were composed of five high-resolution advertisement or digital photographs, all matched for intensity, color, and complexity, and individually displayed for approximately 4.8 s. This visual drug cue-reactivity task was developed, validated, and repeatedly published over the past decade (e.g. Myrick et al., 2004; Hartwell et al., 2011; Schacht et al., 2011). In addition to the visual stimuli, one of four odors – freshly lit cigarette (CIG-O), coffee (COF-O), lavender (LAV-O), or propylene glycol (PG-O), the odorless control – was delivered over the first 12 s of each 30-s block (24-s picture and 6-s washout

period). Timing of the odor deliveries was previously piloted for perceptual habituation effects, while providing adequate time (18 s) for odors to dissipate the bore of the magnet between odor presentations. Presentation of each visual block (i.e. CIG-I, NEU-I and FIX-I) was paired with each odor a total of 3 times across the 2 runs (see Fig. 1).

2.3.2. Image acquisition—Functional images were acquired on a 3T Siemens (Erlangen, Germany) TIM Trio scanner, using a gradient echo-planar imaging (EPI) sequence. Image acquisition parameters for each run were: repetition/echo time=2200/35 ms; flip angle=90°; field of view=192 mm; matrix=64 × 64; voxel size=3.0 mm³; and 36 contiguous, transverse slices, that yielded 246 volumes during the 9-m scan.

2.3.3. Image preprocessing and analysis—Data were preprocessed and analyzed with FMRI Expert Analysis Tool (FEAT) Version 5.98, part of FMRIB's Software Library (FSL; Oxford Centre for Functional MRI of the Brain, Oxford, England; Smith et al., 2004). All images underwent removal of non-brain with the Brain Extraction Tool (BET), motion correction with Motion Correction FMRIB Linear Image Registration Tool (MCFLIRT), a high-pass filter (period=90 s), resampling to 2-mm isotropic voxels, smoothing with an 8-mm full-width-at-half-maximum kernel, spatial whitening with a global auto-regressive filter, and regression of the motion parameters. Finally, the preprocessed images were registered with a 12 df affine transformation, first to the participant's high-resolution anatomical image and subsequently to the Montreal Neurological Institute (MNI) 152-subject-average template.

Whole brain analyses for each run were performed separately to examine the main effect of the visual cues under each odor condition – comparing the entire 24-s block of smoking-related (CIG-I) versus neutral (NEU-I) picture cues under the odorless condition (PG-O), to the entire 24-s block of smoking-related (CIG-I) versus neutral (NEU-I) picture cues under the cigarette odor condition (CIG-O). Upper-level analyses first combined runs (fixed effects), then assessed for main effect of cue type (mixed effects: FLAME 1). Clusters were determined by $Z > 2.3$ with a corrected (cluster) significance threshold of $p < 0.05$ (Worsley, 2001). Previous data acquired in our laboratory revealed that while cigarette odors demonstrated significant effects in subjective and objective measures of cue-reactivity in nicotine-dependent adults, lavender and coffee odors were ineffective in this respect (Cortese et al., 2015). Given those findings, CIG-O was the focus of this preliminary investigation and therefore imaging data gathered during the other odor conditions (LAV-O and COF-O) were not assessed.

Using FEATquery, post-hoc, region of interest (ROI) analyses were performed by extracting parameter estimates within 6-mm-radius spheres centered at the following points in MNI space: left ventral striatum (−12, 15, −6), right ventral striatum (12, 15, −6), left dorsal striatum (−12, 15, 6), right dorsal striatum (12, 15, 6), left OFC (−28, 48, −6), right OFC (28, 48, −6), medial prefrontal cortex (0, 54, −4), and anterior cingulate cortex (0, 44, 6). These points were based on coordinates reported previously (Schacht et al., 2011) as well as coordinates of significant activation in the present study [i.e. ALC-I > NEU-I (PG) contrast; see Table 1]. Pearson's correlations were performed in SPSS (version 22.0) to determine

the relationship between craving and the BOLD response to unisensory and multisensory smoking cues.

3. Results

3.1. Participants

Five of the 22 study participants had more than 2 mm of translational or 2° of rotational movement during the scan and were excluded from the analyses. Therefore, the final group consisted of 17 adult smokers that were predominantly male (male=13, female=4), white (white=16, African American=1), and an average age of 29.6 ($SD=9.4$) years. The group smoked an average of 18 cigarettes/day ($SD=7.1$, range=10–35) for an average of 12.2 years ($SD=6.5$, range=2–26). The mean FTND score was 4.94 ($SD=1.8$, range=2–8). All participants tested in the normosmia range (i.e. had a normal sense of smell) for age and sex on the UPSIT ($M=36.8$, $SD=1.3$, range=35–40).

3.2. Unisensory versus multisensory smoking cue-reactivity

In part to replicate the well documented finding of drug cue-elicited BOLD activation in brain regions associated with reward, the main effect of smoking-related visual cues was assessed by comparing CIG-I to NEU-I under the odorless condition (PG-O). This analysis revealed that visual smoking cues (CIG-I) elicited greater activation than neutral cues (NEU-I) in left medial prefrontal cortex and orbitofrontal cortex, as well as left paracingulate gyrus (see Table 1 and Fig. 2). The CIG-I minus NEU-I contrast was also assessed under the CIG-O condition. This comparison demonstrated widespread activation in frontal, temporal, and parietal cortices that included anterior cingulate gyrus and orbitofrontal cortex, bilateral superior temporal gyrus, bilateral precuneus, as well as paralimbic structures including insular cortex and posterior cingulate (see Table 2 and Fig. 2). Comparison of the unisensory and multisensory response revealed that the co-delivery of smoking odor and visual cues compared to only smoking visual cues elicited significantly greater brain activation in mainly frontal (left inferior and superior frontal gyri, bilateral precentral gyri) and temporal regions (bilateral middle and superior temporal gyri, planum temporale, and Heschl's gyrus), as well as the precuneus (see Table 3 and Fig. 2).

3.3. Relationship between craving and unisensory and multisensory smoking cues

Given the 12-h abstinent requirement, baseline subjective craving ratings were relatively high (*amount*: $M=7.6$, $SD=2.6$, range=3–10; *intensity*: $M=6.5$, $SD=2.7$, range=1–10; and *control*: $M=6.5$, $SD=3.1$, range=0–10). Pearson's correlations were utilized to assess the relationship between craving and regional BOLD activation elicited by CIG-I minus NEU-I under the PG-O condition (uni-sensory visual cue) or CIG-I minus NEU-I under the CIG-O condition (multi-sensory odor plus visual cue). Table 4 displays the significant inverse relationship found between self-reported “control over craving” and regional activation in response to the multisensory, but not the unisensory, cues.

4. Discussion

This fMRI study was designed to assess brain reactivity to visual smoking cues in the presence and absence of a cigarette odor cue in 12-h abstinent adult smokers. Our results demonstrated a significant difference between unisensory and multisensory cigarette cue-elicited brain activation. While cigarette-related pictures presented as a unisensory cue demonstrated an activation pattern (e.g. medial prefrontal cortex, cingulate gyrus) consistent with the extensive drug cue-reactivity literature (Grüsser et al., 2004; Myrick. et al., 2004; McClernon et al., 2009; Hartwell et al., 2011; Vollstädt-Klein et al., 2011; Schacht et al., 2013), the multisensory cigarette odor and visual cues elicited significantly more brain activation. This effect was demonstrated in frontal (left inferior and superior frontal gyri, bilateral precentral gyri) and temporal regions (bilateral middle and superior temporal gyri, planum temporale, and Heschl's gyrus), as well as precuneus. Moreover, the multisensory picture plus odor cues not only elicited more activity in the same regions activated by the unisensory visual cues (i.e. precuneus and some areas within frontal and temporal cortices), but elicited significant new activation in regions, including precentral gyrus, that were not activated by the unisensory visual smoking cues. This extended pattern of activation in precentral gyrus, an area involved in motor planning and execution, has previously been shown to be more pronounced when smoking paraphernalia (i.e. cigarettes, ashtrays, cigarette boxes) were held and manipulated versus visualized in still pictures (Yalachkov et al., 2013). As in the report of Yalachkov et al. (2013), our data suggest that sensory modality is an important factor with respect to whether motor areas of the brain are activated by cigarette cues; so that similar to handling a cigarette, the combination of visual and odor cue was necessary to initiate the brain activity associated with planning and carrying-out of drug-taking motor responses.

Our results also suggest that the combination of sensory cues, compared to just visual cues, was best at evoking brain cue-reactivity related to drug craving. Specifically, self-reported "control over craving", acquired just before the MRI scan in our 12-h abstinent smokers, was significantly, inversely, related to multi-sensory (odor plus visual), but not visual only (unisensory), cue-elicited BOLD activity in both ventral and dorsal striatum, as well as other brain regions that demonstrated significant cue-elicited activation including medial prefrontal and anterior cingulate cortices. The stronger relationship between craving and the multisensory cigarette cue as opposed to the visual cue presented alone could be explained by data suggesting that drug availability is one of several important factors with respect to drug craving i.e. drug-dependent individuals may not crave as strongly, even in the presence of drug-related cues, when drugs are not available. We suggest that the cigarette odor cue provides a more authentic representation of cigarette availability, than do still pictures of cigarettes, cigarette packaging, or pictures of someone smoking. And thus, the addition of cigarette odor was necessary to represent drug availability and elicit a BOLD response in striatum and pre-frontal brain regions that was significantly related to control of craving in our smokers. Interestingly, Cyders et al. (2014) used a unisensory, alcohol, odor cue in their investigation of social drinkers and found that greater impulsivity, and negative urgency in particular, mediated the relationship between alcohol-odor elicited prefrontal activation and craving. While they did not report on alcohol odor-elicited activation of motor cortex, and

we did not assess impulsivity, future investigations could determine if the odor-elicited activation of primary motor cortex demonstrated in the present study directly relates to emotion-based impulsive action and subsequent drug use.

Our original data are consistent with the findings from a recent meta-analysis (Yalachkov et al., 2012) and, in turn, the suggestion in Jasinska and colleagues' review of the literature (Jasinska et al., 2014), that multisensory, haptic, drug cues may elicit greater subjective craving and associated brain activation than unisensory (i.e. visual) drug cues. In contrast to the previously studied haptic (handled) cue, the multisensory cue utilized in the present study (visual plus odor) may be more relevant to what smokers encounter during a smoking quit attempt. For example, a smoker who is attempting to quit would likely avoid handling a cigarette, knowing the temptation to smoke that behavior would elicit. Seeing and smelling someone else smoking, on the other hand, may be more difficult to avoid, as being in the vicinity of a smoker can happen by chance. The present results also extend the small but growing literature demonstrating that drug odors effectively elicit craving-related brain responses. While previous alcohol odor cue-reactivity studies (Kareken et al., 2004, 2010) mainly focused on brain regions traditionally associated with reward including the striatum and prefrontal cortex, our multisensory drug cue elicited significant activation in areas of the superior temporal and inferior parietal cortices, multi-modal brain regions thought to integrate sensory information (Gottfried and Dolan, 2003). Given the emerging data suggesting that primary and secondary sensory cortices may have an underappreciated role in reward and drug craving (McClernon et al., 2009; Yalachkov et al., 2010; Hanlon et al., 2014), cortical association regions that underlie sensory integration may also be important targets for future investigations aimed at a better understanding of addiction.

Several limitations exist within this preliminary study. The main limitation relates to the small sample size. Due to motion artifact, nearly 25% of our smokers had unusable functional data. It is possible that the 12-h abstinence requirement contributed to our participants' inability to remain still in the scanner. Future studies may employ "practice sessions" in a mock scanner under similar abstinent conditions to help reduce unwanted movement and/or oversample to appropriately power these types of studies. Our limited sample size ($n = 17$) precluded the complex analysis required to assess all odor cues used in the study (PG-O, CIG-O, LAV-O, and COF-O). However, the decision to target the cigarette odor in the present analysis was justified, in part, by previous data acquired in our laboratory. We recently reported that cigarette odor, but not other odors including lavender and coffee, were effective elicitors of drug craving and associated physiological responses in nicotine-dependent individuals (Cortese et al., 2015). In the future, a full analysis including that of a neutral odor cue (e.g. LAV-O) would be required to determine if a specific drug-related odor was necessary for the augmented visual drug cue-reactivity demonstrated in the present study. Another limitation relates to the unbalanced design (i.e., timing difference) of picture and odor deliveries within our smoking cue presentation. While the current study was an initial attempt to add odors to a well-validated visual drug cue paradigm (e.g., Myrick et al., 2004; Hartwell et al., 2011; Schacht et al., 2011), true interactive effects of visual and odor cues were not possible to determine with our approach. Future investigations may choose alternate methodology such as an event-related design similar to those used in

the studies of Gottfried and Dolan (2003) and Seubert et al. (2010) that would provide the opportunity to assess individual, additive and/or exponential effects of visual and olfactory cues. And finally, one other limitation relates to our exclusion of participants with poor olfactory function. Given that dose and duration (i.e. pack-years) of cigarette smoking is negatively related to olfactory function (Frye et al., 1990), we may have truncated the sample by eliminating the smokers who smoked the most/longest, and in turn excluded those with significant smoking-cued responses.

While the vast majority of drug cue-reactivity studies employ visual cues in their drug craving paradigms, we and other investigators (Kareken et al., 2004, 2010; Bragulat et al., 2008; Lukas et al., 2013; Cortese et al., 2015; Cyders et al., 2014) have begun to demonstrate odors as salient drug cues and that the olfactory system may play a significant role in drug craving and reward. Targeting the olfactory system with the use of odor cues has the potential to contribute more authenticity to studies of drug cue-reactivity. Additionally these methods could help to identify individual smokers who would have a difficult time controlling craving and the automated motor responses (i.e., manipulating a cigarette between fingers, puffing) when in the presence of someone smoking. Ultimately this line of investigation may help to develop specific strategies to address during a smoking quit attempt with the goal of enhancing treatment outcomes.

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Fig. 1.

The olfactory fMRI presentation paired each odor with each visual cue type 3 times. The entire study was divided into two 8-min scanning sessions to reduce fatigue and odor habituation.

Fig. 2. Odor-potentiated BOLD response to visual smoking cues. Smoking versus neutral visual cues (CIG-I > NEU-I) under the odorless condition (PG-O), the cigarette odor condition (CIG-O), and for CIG-O > PG-O.

Table 1

Activation results for the odorless (PG-O) condition: Smoking versus neutral visual cue.

Contrast	Cluster	$z_{\max}$	p	Voxel	MNI (x,y,z)	Anatomy
<i>Smoke > Neutral</i>						
(PG-O)	1	4.56	0.0027	2771	-10, 54, -4	L Frontal Medial Cortex
		4.29			-28, 48, -6	L Orbital Frontal Cortex
		4.06			-16, 44, 6	L Paracingulate Gyrus
		3.96			-16, 22, 32	L Cerebral White Matter
		3.91			-12, 44, 20	L Paracingulate Gyrus
		3.73			-12, 36, 24	
<i>Neutral (PG-O) > Smoke</i> No clusters survived thresholding						

All analyses completed using cluster thresholding ($z > 2.3$ and corrected cluster threshold of $p < .05$) at individual and group levels unless otherwise specified. Voxel is the number of activated voxel within each cluster. $z_{\max}$ is the local maximum z value. MNI (x, y, z) are the MNI coordinates for the local maximum. Anatomy is the Harvard-Oxford Cortical and Subcortical Structural Atlases for the local maximum (or closest label to maximum).

Table 2

Activation results for the cigarette odor (CIG-O) condition: Smoking versus neutral visual cue.

Contrast	Cluster	$z_{\max}$	p	Voxel	MNI (x,y,z)	Anatomy
<i>Smoke > Neutral</i>						
(CIG-O)	1	4.08	0.038	1306	-12, -56, 8	L Precuneous
		3.92			16, -56, 14	R Precuneous
		3.57			2, -46, 12	Postcingulate Gyrus
		3.24			10, -64, 26	R Precuneous
		3.06			-4, -64, 24	L Precuneous
	2	2.90			2, -66, 24	R Precuneous
		4.63	1.26e-05	4543	68, -18, -2	R Superior Temporal Gyrus
		4.61			70, -38, 4	R Middle Temporal Gyrus
		4.38			66, -36, 6	R Superior Temporal Gyrus
		4.20			60, -22, 2	R Superior Temporal Gyrus
3		4.13			52, -58, 14	R Angular Gyrus
		4.12			64, -50, 14	
		5.08	4.77e-07	6224	-42, -28, 0	L Cerebral White Matter
		4.59			-62, -34, 0	L Superior Temporal Gyrus
		4.49			-50, -26, 10	L Heschl's Gyrus
	4	4.28			-44, 4, -4	L Insular Cortex
		4.13			-26, 16, -16	L Orbital Frontal Cortex
		4.04			-38, -16, 0	L Insular Cortex
		4.56	1.06e-08	8330	-6, -36, 44	Postcingulate Gyrus
		4.45			-8, 2, 74	L Superior Frontal Gyrus
<i>Neutral > Smoke</i>		4.44			-16, -22, 78	L Precentral Gyrus
		4.26			-2, 64, -12	Frontal Pole
		4.26			2, -22, 44	Postcingulate Gyrus
		4.02			-2, 22, 32	Anterior Cingulate Gyrus
<i>(CIG-O)</i> No clusters survived thresholding						

All analyses completed using cluster thresholding ($z > 2.3$ and corrected cluster threshold of $p < .05$) at individual and group levels unless otherwise specified. Voxel is the number of activated voxel within each cluster. z_{max} is the local maximum z value. MNI (x, y, z) are the MNI coordinates for the local maximum. Anatomy is the Harvard-Oxford Cortical and Subcortical Structural Atlases for the local maximum (or closest label to maximum).

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Table 3

Activation results for CIG-O minus PG-O: Smoking versus neutral visual cue.

Contrast	Cluster	$z_{\max}$	p	Voxel	MNI (x,y,z)	Anatomy
<i>Smoke>Neutral</i> (CIG-O>PG-O)	1	4.96	0.0003	6770	70, -38, 4	R Middle Temporal Gyrus
		4.81			66, -18, -2	R Superior Temporal Gyrus
		4.46			52, -26, 2	
		4.45			68, -28, 0	
		4.40			66, -26, 12	
	2	4.27			70, -26, 16	
		5.29	5.78e-06	10,873	-44, -30, 8	L Planum Temporale
		5.03			-54, -26, 10	
		4.50			-50, -32, -4	L Middle Temporal Gyrus
		4.43			-62, -32, 0	L Superior Temporal Gyrus
		4.28			-42, -16, 2	L Heschl's Gyrus
		4.12			-50, 20, -6	L Inferior Frontal Gyrus
		5.04	1.43e-06	12,411	30, 130, 70	R Post-Central Gyrus
		4.87			-8, 2, 74	L Superior Frontal Gyrus
		4.67			20, -14, 72	R Precentral Gyrus
	3	4.66			24, -12, 72	
		4.59			-16, -26, 76	L Precentral Gyrus
		4.53			0, -44, 42	Precuneous

All analyses completed using cluster thresholding ($z > 2.3$ and corrected cluster threshold of) at individual and group levels unless otherwise specified. Voxel is the number of activated voxel within each cluster. $z_{\max}$ is the local maximum z value. MNI (x, y, z) are the MNI coordinates for the local maximum. Anatomy is the Harvard-Oxford Cortical and Subcortical Structural Atlases for the local maximum (or closest label to maximum).

Table 4

Pearson correlations between unisensory- and multisensory-elicited regional BOLD activation and baseline craving ratings.

	Brain region	Crave (amount)	Crave (intensity)	Crave (control)
CIG-I > NEU-I (PG-O) (unisensory cue)	Left ventral striatum	−0.047	0.023	−0.118
	Right ventral striatum	0.278	0.281	−0.116
	Left dorsal striatum	−0.081	−0.224	0.371
	Right dorsal striatum	−0.036	−0.271	0.240
	Left orbitofrontal cortex	−0.347	−0.255	0.173
	Right orbitofrontal cortex	−0.024	−0.098	−0.203
	Medial prefrontal cortex	−0.352	−0.151	−0.228
	Anterior cingulate gyrus	−0.303	0.015	−0.282
CIG-I > NEU-I (CIG-O) (multisensory cue)	Left ventral striatum	−0.034	0.100	−0.508*
	Right ventral striatum	−0.192	0.015	−0.671**
	Left dorsal striatum	0.001	0.120	−0.493*
	Right dorsal striatum	0.004	0.142	−0.650**
	Left orbitofrontal cortex	−0.157	0.135	−0.458
	Right orbitofrontal cortex	−0.042	0.084	−0.478
	Medial prefrontal cortex	−0.212	−0.044	−0.555*
	Anterior cingulate gyrus	−0.074	0.075	−0.682**

* $p < 0.05$.

** $p < 0.01$.