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Clarifying the neural basis for incentive salience of tobacco cues in smokers

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ABSTRACT

In functional magnetic resonance imaging (fMRI) studies, smoking cues have been found to elicit increases in brain activity in regions associated with processing rewarding and emotional stimuli. However, most smoking cue studies to date have reported effects relative to neutral control stimuli with no incentive properties, making it unclear whether the observed activation pertains to value in general or the value of cigarettes in particular. The current fMRI study sought to clarify the neural activity reflecting tobacco-specific incentive value versus domain-general incentive value by examining smoking cues, neutral cues, and a third set of cues, monetary cues, which served as an active control condition. Participants were 42 male daily smokers. Compared to neutral cues, significantly greater activation was found in the left ventral striatum in response to tobacco and money cues. Monetary cues also elicited significantly increased activation in the right inferior frontal gyrus and cuneus compared to the other two cue types. Overall, the results suggest that the salience of monetary cues was the highest and, as a result, might have reduced the incentive salience of tobacco cues.

1. Introduction

Cigarette smoking is responsible for the death of approximately 440,000 U.S. citizens each year and 6,000,000 deaths worldwide (National Institute on Drug Abuse, 2009; World Health Organization, 2011). In addition to its impact on health, tobacco use is responsible for hundreds of billions of dollars of economic burden worldwide every year (World Health Organization, 2011). Among current U.S. adult smokers, approximately two-thirds report that they want to quit smoking, although the majority are unsuccessful (American Society of Addiction Medicine, 2010; Centers for Disease Control and Prevention, 2011).

One of the major theories of nicotine dependence is that it is a disorder of learning and memory (Franklin et al., 2007; Olausson et al., 2003). From this perspective, environmental cues play an important role and partially elicit substance use behavior through associative (classical) conditioning. Specifically, neutral environmental stimuli (e.g. people, places, things) that precede drug use become associated with the actual drug use and acquire motivational properties. In the context of smokers, drug-related cues (e.g. a cigarette, another smoker, a cup of coffee) become associated with the act of smoking and, over time, the smoking related cues begin to trigger conditioned responses, including subjective craving and psychophysiological arousal (Conklin et al., 2010, 2013; Thewissen et al., 2007). Furthermore, these associated cues putatively become highly salient over time, triggering compulsive drug seeking and taking even if the expectation of pleasure is diminished (Berridge et al., 2009; Robinson and Berridge, 1993).

Considerable empirical research supports this perspective. Animal and human research has shown that these previously neutral stimuli elicit a number of conditioned drug responses, including physiological indices (Winkler et al., 2011), attentional indices (Robinson and Berridge, 1993), and actual drug seeking and taking behavior (Le Foll and Goldberg, 2006). Following extinction of nicotine-seeking behavior, rats have been shown to reinstate their nicotine-seeking behavior upon presentation of the conditioned stimulus (LeSage et al., 2004). In human cue reactivity studies, nicotine dependent individuals exhibit increases in affect, heart rate, skin conductivity, and subjective craving following the presentation of smoking-related stimuli (e.g. images of cigarettes) (Carter and Tiffany, 1999; Payne et al., 2007; Tiffany et al., 2000;

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MacKillop et al., 2012). Parallel findings have been found for alcohol and other psychoactive drugs (MacKillop and Lisman, 2005; MacKillop et al., 2010; Robbins et al., 1999).

Functional magnetic resonance imaging (fMRI) studies have extended smoking cue reactivity research to understand neural responses, finding that smoking-related cues elicit greater blood-oxygenation-level-dependent (BOLD) activation in regions associated with the processing of reward and emotional stimuli (Due et al., 2002; David et al., 2005; McClernon et al., 2005; Franklin et al., 2007, Versace et al., 2011). These studies typically employ a passive-viewing task, in which participants are instructed to observe photographs or videos of smoking cues and neutral cues. In addition, some of the studies incorporate holding a cigarette and holding a neutral object.

A number of neural profiles have been found to be consistently associated with the presentation of tobacco cues in smokers and hold potential to provide further insight into reward processing and contributors to relapse. Kühn and Gallinat (2011) reviewed 13 studies of daily smokers exposed to smoking-related versus control cues, and found that the ventral striatum, amygdala, anterior cingulate cortex (ACC), and the temporo-parietal junction are consistently activated more by smoking cues versus control cues. Although it was not demonstrated to be consistently active in this meta-analysis, the anterior insula is also thought be important in the experience of appetitive craving and has been associated with the maintenance of tobacco use through cue reactivity and the experience of craving (Engelmann et al., 2012; Versace et al., 2011, Naqvi et al., 2007).

The ventral striatum, amygdala, and ACC all potentially play a unique role in the reactivity of drug addicted individuals to associated substance cues. The ventral striatum is associated with motivational behavior including reward reactivity (Parkinson et al., 1999; Chase et al., 2011). The amygdala is associated with emotional and reward processing (Phillips et al., 2003), and greater activation in this region has been associated with intensity of tobacco cue-induced craving (Smolka et al., 2006). Activity in the ACC is also associated with increases in craving (Goldstein and Volkow, 2002; Jentsch and Taylor, 1999), and it is thought to play a role in the exertion of inhibitory control over behavior and in conflict processing and monitoring (Lubman et al., 2004). Brain imaging studies have demonstrated that both nicotine abstinence and the expectations that smoking will take place can modulate the response of the ACC to smoking cues (McBride et al., 2006; McClernon et al., 2005; Wilson et al., 2005). Furthermore, recent research has found the BOLD response to smoking cues in the ACC and amygdala to predict smoking lapse in nicotine dependent individuals seeking to quit smoking (Janes et al., 2010).

Importantly, most cue reactivity fMRI studies to date have used neutral visual control conditions (e.g. office supplies, non-smoking faces), but have not used an active incentive value control. An exception to this is a study by Versace et al. (2011), who examined neural activity elicited by smoking-related cues, pleasant (e.g. erotic and romantic), unpleasant (e.g. mutilation and sad), and neutral cues. They found only the insula to have a greater BOLD response to cigarette cues relative to all other categories, while in all other clusters, erotic stimuli elicited greater magnitude of BOLD responses. Nonetheless, this is the only study to date that has sought to contextualize tobacco-related neural activity within the larger category of reinforcers and punishments.

The goal of the current study was to extend research on tobacco-specific reactivity by examining it in relation to both conventional control cues and also with a novel set of monetary cues. Money is a powerful nonspecific reinforcer and, as such, can serve as excellent control for brain activity associated with incentive value in general. In addition, as sex differences are present for erotic pictures (Lang et al., 1998; Hamann et al., 2004; Sabatinelli et al., 2004), money is considered advantageous because of no known gender differences. Given the motivational significance of cigarette and money cues, we hypothesized that both would elicit greater BOLD activation than neutral cues in the ventral striatum, amygdala, and ACC. In addition, we hypothesized that smoking cues would elicit significantly greater activation than money cues in the ACC and amygdala, based on the known associations of these regions with craving, inhibitory control, and emotional processing. Finally, given the novelty of this cue reactivity paradigm, exploratory analyses were utilized to examine additional activation differences between the cigarette cues, monetary cues, and neutral cues.

2. Method

2.1. Participants

Daily smokers were recruited via flyers, print, and internet advertising. Inclusion criteria for participation in the study were as follows: 1) male; 2) right handed; 3) 18–55 years old; 4) self-reported smoking of >5 cigarettes a day; 5) baseline expired carbon monoxide (CO) >5 parts per million (ppm); 6) at least a 10th grade education; and 7) computer use >4 days a week to ensure adequate familiarity with computerized assessments. Females were not included because gender differences in cue reactivity have been reported in prior research (Field and Duka, 2004; McClernon et al., 2008; Niaura et al., 1998) and the study was not powered to systematically examine sex differences. Exclusionary criteria were as follows: 1) any head injury more severe than a mild traumatic brain injury (TBI) or >2 mild TBIs; 2) MRI contraindications (e.g. metal implant, claustrophobia); 3) received mental health services within the last six months or prescribed psychotropic medications; 4) actively seeking treatment to reduce tobacco use or having undergone treatment for nicotine dependence in the past 90-days; 5) weekly illicit drug use, other than marijuana; and 6) living with someone who has participated in the study. Forty-four participants were enrolled, with two participants excluded for invalid data (i.e. noncompliant smoking during the session; non-responding during in-scanner assessments, suggesting sleeping). No participants were excluded for excessive in-scanner movement (>3.5 mm) along the *x*-, *y*-, or *z*-axes, leaving a final sample of 42 (76.2% white, 21.4% African American, 2.4% Asian; median income $=<\$30{,}000$, IQR $=<\$15{,}000$–$\$44{,}999$; age $M=26.6$, S.D.$=7.1$; cigarettes per day $M=15.9$ S.D.$=7.5$; Fagerström Test for Nicotine Dependence [FTND] $M=3.1$, S.D.$=1.9$; fMRI session expired CO $M=18.9$, S.D.$=11.3$; past three months marijuana use, median = monthly or less).

2.2. Measures

Subjective motivation for cigarettes and money was assessed immediately before and after the cue reactivity paradigm by asking participants how much they desired each commodity (i.e. money and cigarettes) via a 9-point Likert scale. Level of nicotine dependence was assessed using the FTND (Heatherton et al., 1991). Expired CO was assessed during the screening session and at the start of fMRI session, using a PiCO+ Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK). Demographic information was also collected (e.g. ethnicity, income, and age).

2.3. fMRI protocol

Imaging data were collected at the University of Georgia Bio-Imaging Research Center with a General Electric 16-channel fixed-site Signa HDx 3.0 Tesla MRI scanner. Structural imaging used a high-resolution T1 scan (voxel size 1 mm^3, field of view $=25.6^2$ mm, matrix $=256^2$, slice thickness $=1$ mm). Functional imaging used echo planar imaging (EPI) of T2* scans using a single-shot gradient echo pulse sequence (TR $=2000$ ms, TE $=25$ ms, field of view $=22.5^2$ cm, matrix $=64^2$, voxel size $=3.52\times3.52\times3.5$ mm^3, with 40 contiguous 3.5 mm slices collected axially). Three dummy TRs preceded the functional scans to permit the scanner to reach steady-state equilibrium.

2.4. fMRI stimuli

High-resolution image stimuli sets were developed in three categories: tobacco-related (i.e. images of cigarettes), money-related (i.e. images of US dollar bills), and neutral (i.e. images of visually-matched office supplies). Sample stimuli and a schematic of the paradigm are shown in Fig. 1. The individual pictures were identified via Internet searches and were selected in matched triplets (one tobacco image, one money image, one neutral image) to have analogous layout and complexity, to minimize difference in shapes perceived, in an extra effort to isolate differences in incentive value. There were 32 images of each category chosen and no images were shown twice. Stimuli were programmed using E-Prime 2.0 software (Psychology Software Tools, Sharpsburg, PA, USA) and presented via MR-compatible stimulus-presentation goggles (Resonance

a

b

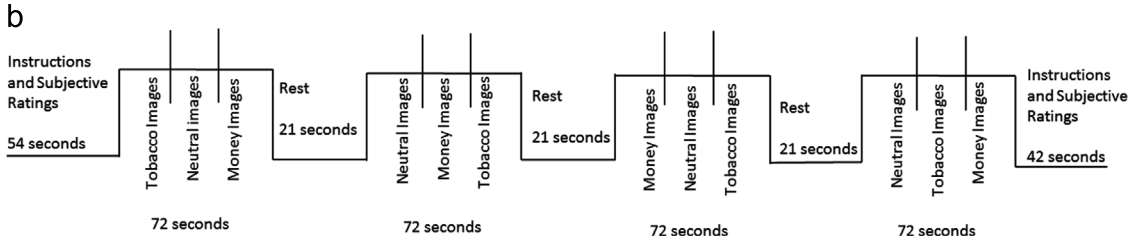

Fig. 1. Sample matched stimuli used within the cue reactivity paradigm (Panel a) and schematic of the cue-reactivity paradigm (Panel b). For Panel A, the images are three of the matched triplets used in the paradigm. In total, participants are shown 32 unique images of each cue type. For Panel B, eight images of varying complexity are presented for each category per block (3 s each).

Technology Inc., Los Angeles, USA). Individual cue images were displayed on a black background for 3 s each, delivered in blocks of eight images for each image type (24 s per block) interspersed with rest blocks of equal length. The full cue reactivity paradigm was comprised of 12 active blocks (four blocks of each cue type) and three rest blocks, totaling 360 s. The order of cue and rest blocks was counterbalanced (Fig. 1B), and every block of stimuli had variable complexity of images embedded within it.

2.5. Procedure

Following a positive phone-screen interview, prospective participants attended a one-hour in-person screening session. Eligibility for the MRI scan was assessed using an MRI safety and contraindication screening questionnaire. Participants who met the eligibility criteria were invited to participate in the fMRI session and those scheduled were explicitly told to not use drugs or alcohol within 24 h of their appointment time.

At the imaging session, participants were told to smoke at the start of the session (if they had not already) to standardize nicotine exposure and withdrawal effects. The protocol prior to the fMRI scan lasted approximately two and a half hours and was comprised of an expired CO assessment, questionnaires, and scan orientation. Throughout this period, participants were not permitted to smoke to create a mild deprivation state, a procedure consistent with other studies utilizing an acute tobacco deprivation to increase the likelihood of interest in tobacco cues (McClernon et al., 2007; Acker and MacKillop, 2013). This was followed by the fMRI scan that lasted one hour. Participants were compensated $15 for the in-person screening, $40 for the fMRI session, and up to $10 for another task at the fMRI session (unrelated to cue reactivity and not reported here). All procedures were approved by the University of Georgia Institutional Review Board.

2.6. Data analysis

Functional imaging data processing and analysis were conducted using Analysis of Functional NeuroImages software (AFNI; Cox, 1996) with follow-up analyses using SPSS 17.0 (IBM, Armonk, NY). Functional datasets were aligned to the T1

Table 1
Omnibus effects and pairwise contrasts for a priori ROIs by cue type.

Region (side; Brodmann area)	*x*	*y*	*z*	*F*(2,44)	*p*	Tobacco versus money *p*	Tobacco versus neutral *p*	Money versus neutral *p*
Ventral striatum (L)	−6	4	−4	5.48	0.006	0.85	0.006	0.008
Ventral striatum (R)	5	5	−5	1.81	0.17	–	–	–
ACC (L; 32)	−4	41	7	0.20	0.82	–	–	–
ACC (L; 32/24)	−5	30	21	1.07	0.35	–	–	–
Amygdala (L)	−19	−5	−15	1.41	0.25	–	–	–

Note. L=Left; R=Right. ACC=anterior cingulate cortex. All spheres are 4 mm-radius (268 mm^3). *x*, *y*, and *z* coordinates correspond to Talairach space.

anatomical dataset and volume-registered (motion-corrected for head movement). Analysis of motion in the scanner verified that no participants moved excessively (>3.5 mm; $M=0.16$ mm, S.D.=0.10 mm) along the *x*-, *y*-, or *z*-axes. Motion-corrected datasets were normalized into Talairach space (Talairach and Tournoux, 1988), and individual volumes from the run were registered to a base volume proximal to acquisition of the anatomical dataset (Saad et al., 2009). The data were then spatially smoothed using a 3.5 mm full width half-maximum (FWHM) Gaussian filter, excluding non-brain voxels. The raw BOLD signal was scaled to percent signal change from the mean signal intensity. For cue reactivity, 3dDeconvolve (Ward, 2002) was applied using three cue-related regressors (neutral, smoking, and money) and six nuisance regressors to account for motion (*x*, *y*, *z*, roll, pitch, yaw). Each regression also accounted for linear, quadratic, and cubic trends.

Both a priori and data-driven exploratory functional ROI strategies were used. This was because some aspects of this study overlapped with previous studies using tobacco cue reactivity paradigms, but the novel introduction of monetary cues made the possibility of unique regions of activation likely. For a priori ROIs, we generated 4 mm-radius spherical ROIs centered on the Talairach-equivalent coordinates from the Kühn and Gallinat (2011) meta-analysis on regions differentially active to tobacco cues (e.g. left ACC (Brodmann area 32), left ACC (Brodmann area 32/24), left amygdala, and left and right ventral striata; coordinates are provided in Table 1). The left temporo-parietal junction specified in the review by Kühn and Gallinat (2011) was at least partially outside of 10 participants' individual anatomical scan, and therefore was not included.

For exploratory analyses, a disjunction (Boolean "OR" logic) mask was generated for each cue (smoking, neutral, or money) in comparison to activity during rest (Amlung et al., 2012; MacKillop et al., 2012; Sweet et al., 2010; Ballard and Knutson, 2009). To correct for type-1 error rate, the average spatial smoothness in the *x*, *y*, and *z* planes was estimated using the residuals from the multiple regression and then inputted to AlphaSim (Ward, 2000) to obtain the minimum cluster extent needed for a family-wise error rate (FWER) of $\alpha<0.05$. Incorporating these parameters, a voxelwise one-sample *t*-test was computed to identify clusters of significant activity in any of the three choice categories ($p<0.0001$, cluster size$\geq$9 voxels, FWER $\alpha<0.05$). For the initial mask at $p<0.0001$, three ROIs were very large and subsumed multiple discrete regions. In these cases voxelwise *p* values were iteratively decreased to identify functionally discrete regions, which were determined using AFNI proportionate overlap with anatomical regions in Talairach space.

For both a priori and exploratory analyses, mean BOLD signal effects for each commodity were extracted from each ROI and imported into SPSS. These mean BOLD percent signal change values were compared using one-way three-level analyses of variance (ANOVAs). Significant effects were followed-up with pairwise *t*-tests to identify specific patterns. The five a priori analyses were not further corrected for multiple comparisons. However, for exploratory analyses, multiple comparison correction was implemented by applying a Bonferroni correction to the significance threshold for disjunction mask ANOVAs.

3. Results

3.1. Subjective ratings

Subjective motivation for tobacco and money is depicted in Fig. 2. Subjective desire for a cigarette was moderate according to the 9-point craving scale prior to the cue exposure and significantly higher in the post-cue exposure condition, $t(41)=2.13$, $p=0.04$, $d=0.66$. Desire for money was high, did not significantly differ between pre- and post-cue exposure conditions, $t(41)=1.46$, $p=0.15$, $d=0.45$, and was statistically unrelated to desire for cigarettes in both pre- and post-cue exposure conditions (pre–pre: $p=0.90$, $r=0.02$; post–post: $p=0.10$, $r=0.26$). The absence of a cue effect and the absence a relationship between money and cigarette motivation might be related to ceiling effects, as the maximum possible rating was eight, and the mean reported desire for money pre- and post-cue exposure conditions was $M=7.26$, $M=7.12$, with S.D. of 1.23 and 1.77, respectively. Notably, the desire for money was significantly greater than for cigarettes at pre- and post-cue exposure conditions (pre: $t(41)=4.58$, $p<0.001$, $d=1.41$; post: $t(41)=3.11$, $p<0.01$, $d=0.96$).

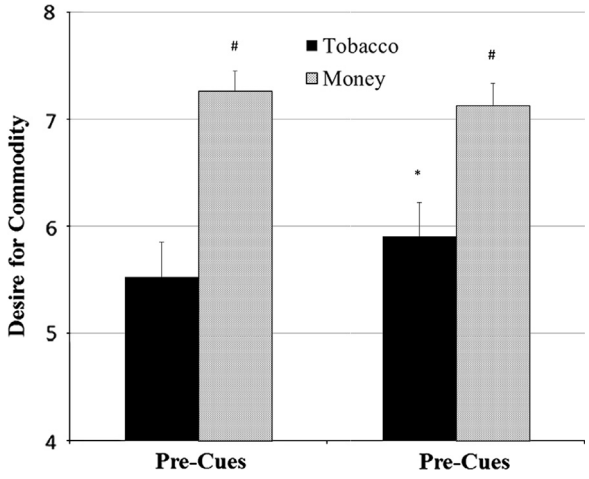

Fig. 2. Subjective ratings of desire for tobacco and money before and after the cue reactivity run. *=significantly different subjective rating for tobacco between pre- and post-cue exposures ($p<0.05$). #=significantly greater subjective rating for money than for tobacco within condition ($p<0.05$). The error bars denote standard error.

3.2. a priori ROI Analyses

Differences in cue-elicited activation in the a priori ROIs are presented in Table 1. Significantly discriminating activation was identified in the left ventral striatum, $F(2,41)=5.48$, $p<0.01$. Specifically, activity associated with tobacco and money cues was greater than neutral cues in the left ventral striatum ($p<0.01$ for both contrasts; see Fig. 3). However, level of BOLD activation did not significantly differ between money and cigarette cues in this region ($p=0.85$). The other a priori ROIs did not significantly differentiate between any cue types as indicated by the non-significant one-way three-level omnibus ANOVAs ($p>0.17$).

3.3. Empirical ROI analyses

Eighteen clusters of significant activity were identified at $p<0.0001$. Three large clusters that subsumed multiple discrete functional regions were further examined. These were: i) bilateral occipital lobe, cuneus, lingual gyrus, parahippocampal gyrus, declive, culmen; ii) right precentral gyrus and postcentral gyrus; and iii) left precentral gyrus, insula, and postcentral gyrus. Using the proposed strategy, these clusters were segregated into seven spatially distinct clusters: left posterior insula, left pre/postcentral gyrus, and left postcentral gyrus at $p<0.00005$; bilateral paracentral lobule at $p<0.00001$; left thalamus/parahippocampal

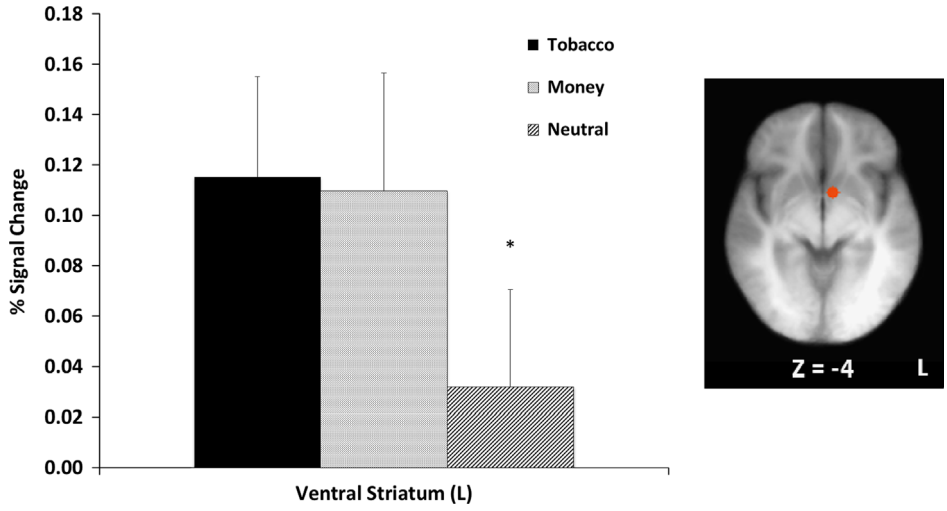

Fig. 3. Significantly discriminating reward cue reactivity in the left ventral striatum. The a priori left ventral striatum is depicted in the adjacent image, which is in radiological conventions (R=L; see Table 1 for coordinates). *=significantly less BOLD signal to neutral cues than tobacco and money cues ($p < 0.05$). The error bars denote standard error.

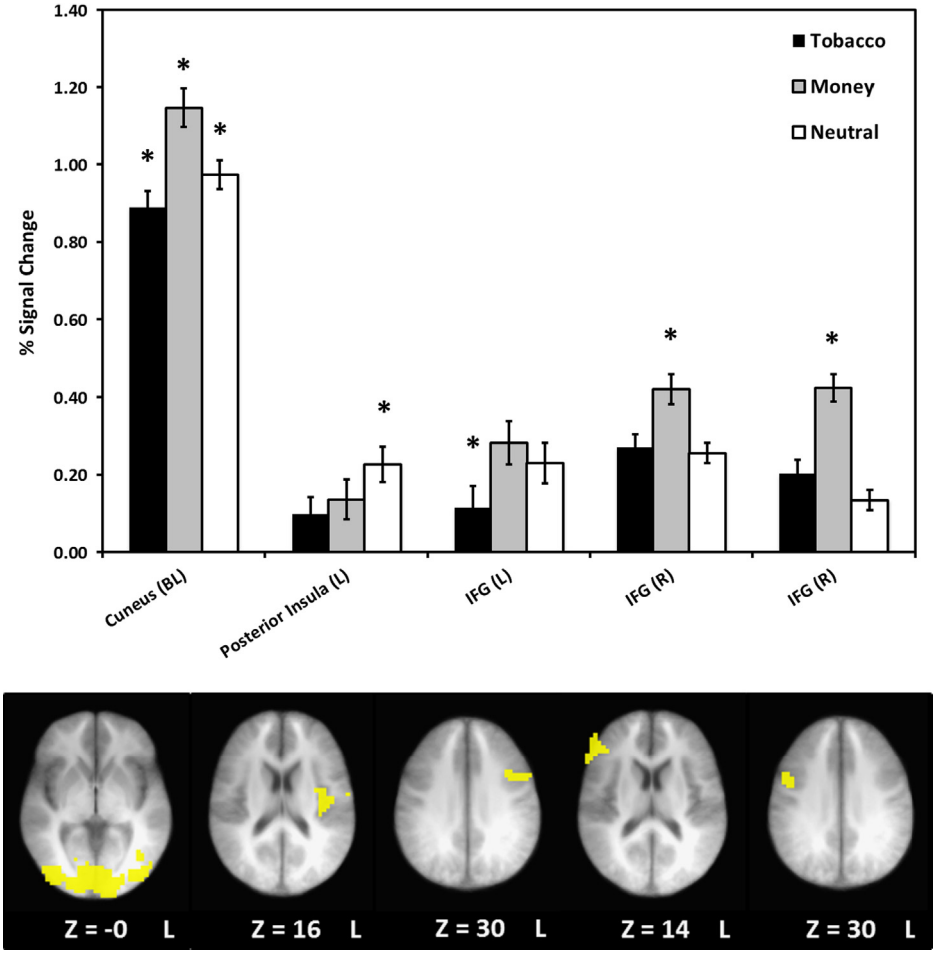

Fig. 4. Empirical ROI analyses significantly discriminating by cue type. Corresponding ROIs are depicted sequentially in axial slices and are presented in radiological convention (R=L; coordinates are depicted in Table 2). *=denotes statistically significant differences in BOLD signal between the specified cue type and the other two cue types ($p < 0.05$).

gyrus at $p < 0.000005$; and bilateral occipital lobe/cuneus and right thalamus/parahippocampal gyrus at $p < 0.0000005$.

In total, 22 clusters were identified as ROIs using this procedure, five of which significantly discriminated between cue type at the Bonferroni corrected p-value ($p < 0.001$); the 17 non-discriminating clusters were not subjected to further analysis but are reported in Supplementary materials. Regions of interest that significantly discriminated between cue type are indicated in Fig. 4

Table 2
Omnibus effects and pairwise contrasts for discriminating empirical regions of interest (ROI) by cue type. Contrasts were only conducted on disjunction mask ROIs that surpassed a Bonferroni-corrected significance threshold of $p < 0.001$.

Extent (mm^3)	Region (side)	*x*	*y*	*z*	*F*(2,41)	*p*	Tobacco versus money *p*	Tobacco versus neutral *p*	Money versus neutral *p*
79,276	Cuneus (BL)	3	−73	0	23.79	7.1×10^{-9}	$2.0 \times 10^{-8}_{m}$	0.02_{n}	0.0002_{m}
4845	Posterior insula (L)	−43	−12	16	7.41	0.001	0.24	0.0003_{n}	0.02_{n}
1544	IFG (L)	−44	8	30	10.39	9.5×10^{-5}	$4.4 \times 10^{-5}_{m}$	0.003_{n}	0.19
3001	IFG (R)	52	30	14	11.31	4.6×10^{-5}	0.0005_{m}	0.73	$5.4 \times 10^{-5}_{m}$
1115	IFG (R)	47	4	30	24.63	4.2×10^{-9}	$2.2 \times 10^{-5}_{m}$	0.10	$4.5 \times 10^{-8}_{m}$

Note: IFG=inferior frontal gyrus; L=Left; R=Right; BL=bilateral; *x*, *y*, and *z* coordinates correspond to Talairach space. m=monetary cues elicited significantly greater activation; n=neutral cues elicited significantly greater activation.

and Table 2, where the results of the pairwise *t*-tests are also presented. Overall, money cues elicited significantly greater activation than both tobacco cues and neutral cues in regions associated with visual and inhibitory processing, including bilateral cuneus and right inferior frontal gyrus (IFG). Money cues elicited significantly greater activation than tobacco cues in the left IFG. Significantly greater response to neutral cues was found compared to tobacco and money cues in left posterior insula.

4. Discussion

The goal of the current study was to clarify the neural activity associated with tobacco-related stimuli by incorporating active control stimuli comprising monetary images. The findings revealed one a priori ROI and five exploratory ROIs that exhibited differential activation to tobacco, money, and neutral cues. Specifically, a priori analyses identified the left ventral striatum as significantly more active to the two reward cues compared to neutral cues. In exploratory analyses, four out of the five discriminating regions were most active in response to monetary cues, suggesting an overall greater salience of monetary cues versus tobacco and neutral cues. Furthermore, tobacco cues demonstrated no significantly greater response in any of the exploratory regions, suggesting that money cues were perceived to be a more salient reward and, in contrast, potentially diminished interest in less desirable rewards. The interpretation of money possessing greater motivational salience than cigarettes is further corroborated by the subjective ratings over the course of the paradigm. Participants in this study reported high motivation for money and comparatively lower motivation for cigarettes. Motivation for money was sustained over time and did not increase, likely due to ceiling effects; in contrast, cigarette craving significantly increased from the start of the paradigm to its conclusion. Overall, the subjective ratings and the exploratory (disjunction mask) analyses (Ballard and Knutson, 2009) suggested that monetary cues possess greater overall motivational significance than tobacco cues in a sample of nicotine dependent smokers.

In terms of the mechanisms in play, the current findings corroborate the notion of the ventral striatum subserving the motivational significance of environmental stimuli (David et al., 2005; Cardinal et al., 2002). Furthermore, the fact that the ventral striatum did not differentiate the type of reward suggests that it is not stimulus specific (e.g. drug only). This finding is consistent with previous literature identifying the ventral striatum as critical for the motivational impact of all classically conditioned stimuli (Cardinal et al., 2002). In the exploratory (disjunction mask) analyses, monetary cues elicited the greatest activation in the cuneus region of the visual cortex, which is further suggestive of generally greatest salience for monetary cues. In addition, left posterior insula activation was found to be greater for neutral cues as compared to smoking and monetary cues. While the anterior insula is the primary region associated with interoceptive processing (Craig, 2002; Critchley, 2005) and the experience of craving for tobacco (and other drugs of abuse) in response to associated cues (Engelmann et al., 2012; Versace et al., 2011), the posterior insula is implicated in processing aversion (Samanez-Larkin et al., 2008). Thus, it appears left posterior insula activation may have reflected diminished aversion to the reward cues. Notably, this study's finding of less activation to both classes of reward cues in the posterior insula is consistent with previous research that identified reduced activation in the posterior insula to drug imagery as compared to neutral imagery (Kilts et al., 2001).

A second profile of considerable interest was significantly different bilateral activation in the IFG, which was selectively more active in response to money cues relative to both tobacco and neutral cues. The right IFG has been implicated in tasks of behavioral inhibition, such as Go/NoGo (Aron et al., 2014), as well as in some studies of tobacco (and general drug) cue reactivity (Chase et al., 2011; Due et al., 2002). Reactivity to tobacco cues in the left IFG has been positively associated with abstinence-induced (24-h of abstinence) increases in craving (McClernon et al., 2005). In a recent study, right IFG was recruited in response to important cues, regardless of whether response inhibition was subsequently executed (Hampshire et al., 2010). Based on this, it appears that the IFG plays an important role in attentional allocation to motivationally relevant environmental stimuli and, in this study, monetary cues were the most salient to the participants.

Contrary to our predictions, we did not identify brain regions that were recruited specifically in response to smoking stimuli. Indeed, in no instance did tobacco cues elicit significantly more activation than money cues. One possibility for this finding is that the competing salience of a highly valued alternative reinforcer (i.e. money) may have reduced the salience of tobacco cues. Importantly, the majority of the smokers in the present sample were of relatively low income; thus, the incentive salience of money for these individuals would be expected to be very high. This is also supported by the high subjective desire for money both in absolute terms (~90% of scale maximum) and in comparison to cigarettes. Therefore, diminished reward reactivity to smoking cues may have been due to comparatively lower desirability than the monetary stimuli. This may also explain why these findings differ from typical paradigms where tobacco cues are exclusively contrasted with neutral cues (Engelmann et al., 2012; Kühn and Gallinat, 2011).

The current study should be evaluated in the context of its strengths and weaknesses. Positive aspects of the study were its sample size, the use of both traditional and active control stimuli, and close matching of stimuli in category triplets. However, the sample was moderate in terms of nicotine dependence and all participants were male, which may limit generalizability to more severely-dependent smokers and females. With regard to this latter point, given previous evidence of gender differences in tobacco cue reactivity (Field and Duka, 2004; McClernon et al., 2008; Niaura et al., 1998), the generalizability of these findings to females is particularly unclear and future studies systematically investigating differences in brain activity between males and females are warranted. In addition, the participants were only

mildly deprived of nicotine and it might be that the incentive salience of tobacco cues was most clearly observed under conditions of more substantial deprivation (Engelmann et al., 2012). A related point is that despite controlling the length of nicotine deprivation in participants, we did not systematically track subjective craving or physiological levels of nicotine immediately prior to the scan. Also noteworthy is that the cue reactivity paradigm did not include rest blocks between conditions, which may have been suboptimal for separating differential patterns of activation. Although this concern is mitigated by the use of 3Ddeconvolve to model the hemodynamic response accurately, the number of volumes obtained by stimulus category, and the counterbalancing of conditions to equalize order effects across conditions and optimize differences; it may be possible for even higher resolution perspectives on differential activation with extended interleaved rest periods. Finally, it is worth noting that the participants were all non-treatment-seeking individuals and it may be that unique neural profiles are evident among smokers who actively want to change their behavior (Chase et al., 2011).

In summary, the current study revealed that both cigarette and monetary cues elicit significantly greater activity in the ventral striatum, but monetary cues also elicited activity in a number of other brain regions that suggested greater salience. The commodity effects observed here provide evidence that the presentation of multiple classes of rewarding stimuli may affect neural responses differently than when rewarding stimuli are presented alone. In other words, clarifying differential reactions to tobacco cues inherently requires other stimuli for comparison, but, equally, active control stimuli have their own properties that will be differentially relevant to participants. Although the study was limited in identification of tobacco-specific regions of interest, these findings suggest that monetary cues may have acutely diminished interest in tobacco cues in nicotine deprived smokers; however, future study of this relationship is warranted to definitively ascertain whether this is the case. Although conjecture, the enduring salience of monetary rewards may explain the success of contingency management in the treatment of substance use disorders, including nicotine dependence (Prendergast et al., 2006). Indeed, given promising recent findings using neuroimaging to predict smoking cessation response (Janes et al., 2010), it is possible that neural reactivity to monetary cues can predict contingency management intervention outcomes. That is, of course, an empirical question. More broadly, the current study reveals the need for further work characterizing and contextualizing the neutral basis for the incentive salience for tobacco and other psychoactive drugs.

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Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2014.06.003.

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