Physiology & Behavior 106 (2012) 317–324

Contents lists available at SciVerse ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Food and drug cues activate similar brain regions: A meta-analysis of functional MRI studies

D.W. Tang [a,b,c], L.K. Fellows [a,b,c], D.M. Small [d], A. Dagher [a,b,c,*]

[a] Department of Psychology, McGill University, Montreal Neurological Institute, 3801 University St, Montreal, Canada QC H3A 2B4
[b] Department of Neurology, McGill University, Montreal Neurological Institute, 3801 University St, Montreal, Canada QC H3A 2B4
[c] Department of Neurosurgery, McGill University, Montreal Neurological Institute, 3801 University St, Montreal, Canada QC H3A 2B4
[d] Psychiatry, Yale University School of Medicine, Psychology, Yale University, The John B Pierce Laboratory, 290 Congress Avenue, New Haven, CT 06519, USA

ARTICLE INFO

Keywords:
Reward
Food
Smoking
Brain imaging
fMRI
PET
Meta-analysis

ABSTRACT

In healthy individuals, food cues can trigger hunger and feeding behavior. Likewise, smoking cues can trigger craving and relapse in smokers. Brain imaging studies report that structures involved in appetitive behaviors and reward, notably the insula, striatum, amygdala and orbital frontal cortex, tend to be activated by both visual food and smoking cues. Here, by carrying out a meta-analysis of human neuro-imaging studies, we investigate the neural network activated by: 1) food versus neutral cues (14 studies, 142 foci) 2) smoking versus neutral cues (15 studies, 176 foci) 3) smoking versus neutral cues when correlated with craving scores (7 studies, 108 foci).

PubMed was used to identify cue-reactivity imaging studies that compared brain response to visual food or smoking cues to neutral cues. Fourteen articles were identified for the food meta-analysis and fifteen articles were identified for the smoking meta-analysis. Six articles were identified for the smoking cue correlated with craving analysis. Meta-analyses were carried out using activation likelihood estimation.

Food cues were associated with increased blood oxygen level dependent (BOLD) response in the left amygdala, bilateral insula, bilateral orbital frontal cortex, and striatum. Smoking cues were associated with increased BOLD signal in the same areas, with the exception of the insula. However, the smoking meta-analysis of brain maps correlating cue-reactivity with subjective craving did identify the insula, suggesting that insula activation is only found when craving levels are high. The brain areas identified here are involved in learning, memory and motivation, and their cue-induced activity is an index of the incentive salience of the cues.

Using meta-analytic techniques to combine a series of studies, we found that food and smoking cues activate comparable brain networks. There is significant overlap in brain regions responding to conditioned cues associated with natural and drug rewards.

1. Introduction

In healthy individuals, food cues trigger hunger and feeding behavior [1]. Likewise, smoking cues trigger craving and relapse in smokers [2]. In both cases the neural response to cues as measured by functional magnetic resonance imaging (fMRI) appears to be a predictor of outcomes: future weight gain for food cues and inability to abstain from cigarettes for smoking cues.

Drug cues have been repeatedly shown to elicit drug-seeking behavior [3,4]. In fact, greater cue reactivity to smoking cues, as measured by fMRI or questionnaire, predicts decreased success at smoking cessation [5,6], and increased smoking persistence [6,7]. There are similar reports in the feeding literature, where cues increase feeding in rats [8], and greater reactivity to food cues in humans predicts future risk of obesity [9,10] and weight gain [11].

Cues are thought to act as Pavlovian conditioned incentives [12,13]. Imaging studies suggest that when people respond to conditioned cues associated with food or smoking, there is a common network of brain regions that is activated, which we refer to as an appetitive network [14], because it assigns value to available rewards and transforms these value signals into actions. Four structures that are commonly identified to be part of this network are the *amygdala and hippocampus* [15–20], *striatum* [16,18,21,22], *OFC* [16,19,23] and *insula* [15,16,18,19,21,22,24–26].

While numerous researchers have suggested that neural responses in the appetitive brain regions to food and smoking cues are similar [14,27,28], three outstanding issues exist. The exact network involved in responding to food and smoking cues during fMRI is not known due to inconsistent methodology in reported studies. Moreover, results are inconsistent because fMRI studies tend to be relatively underpowered [29]. Finally, while not a focus of the current report, there is no

* Corresponding author at: Montreal Neurological Institute, 3801 University St, Montreal, QC, Canada H3A 2B4. Tel.: +1 514 398 1726; fax: +1 514 398 8948.
E-mail addresses: deb.tang@mail.mcgill.ca (D.W. Tang), lesley.fellows@mcgill.ca (L.K. Fellows), dsmall@jbpierce.org (D.M. Small), alain.dagher@mcgill.ca (A. Dagher).

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doi:10.1016/j.physbeh.2012.03.009

published data directly comparing neural response to food and smoking cues in the same individuals.

The purpose of this study was to compare the human neural response to appetizing visual food and smoking cues. We hypothesize that brain responses of people to food cues are qualitatively similar to responses of addicted smokers to smoking cues. A secondary goal of this study was to determine the influence of craving on neural response to smoking cues. We explored this research question by conducting a statistical meta-analysis of brain imaging studies that looked at neural responses to cues that correlated with some measure of craving. There were adequate studies to carry out the craving analysis for smoking cues only.

2. Methods

2.1. General study inclusion criteria

We used PubMed to search for functional neuroimaging studies that utilized a cue reactivity paradigm to study the neural response to drug or food stimuli. The reference lists of these articles were then inspected to identify additional cue-reactivity studies missed by the initial search.

Studies had to use fMRI or positron emission tomography (PET) imaging, publish all activation foci as stereotaxic coordinates, and utilize whole-brain imaging analysis. Studies that published only results from region-of-interest analysis were excluded. Deactivations (neutral stimuli minus food or smoking stimuli) were not included in the current analysis. Additionally, data were taken from healthy adults only (over 18 years of age). Studies published up to December 2010 are included.

In order to compare the neural response to food and smoking, we carried out three meta-analyses: 1) food versus neutral cues 2) smoking versus neutral cues 3) smoking versus neutral cues correlated with craving scores. A food craving or hunger meta-analysis was not carried out because no studies met our inclusion criteria.

2.2. Inclusion criteria for meta-analysis 1: food cues

For the food cue meta-analysis, we used the keywords, "Food, imaging, cues, stimuli, and pictures," to search for relevant articles.

Data were also only included if participants had a healthy normal weight (BMI range: 19 to 25), and were not satiated at the time of scanning. Previous research has shown that participants in a satiated state have a significantly reduced neural response to food cues [30].

Eligible studies used a contrast comparing neural activation during exposure to photos of food and non-food items. Since we were interested in comparing food cue reactivity to smoking cue reactivity, it was important to choose types of foods that had similar incentive value as cigarettes do to smokers, therefore only studies that showed appetizing foods were included (i.e. high calorie, or a combination of high and low calorie food items). Low calorie food items lead to different activation patterns on fMRI [20]. Non-food control stimuli in these studies ranged from pictures of scenery and the environment to household items, such as tools or utensils.

Using the search parameters defined above, we identified a total of 14 of the 159 studies reviewed [15,16,18–23,25,26,31–34]. Table 1 lists the articles that met the criteria for the food meta-analysis.

Table 1
Food meta-analysis articles (Food vs non-food) (14 studies, 142 foci).

Author	Year	n	Food picture cue type	Cue duration	Foci
Beaver*	2006	14	Highly appetizing or bland	1.4 s	13
Cornier	2010	22	Appetizing food	2 s	23
Frank	2010	12	High and low calorie foods	1.5 s	9
Fuhrer	2008	12	Edible	4 s	12
Killgore	2003	13	High and low calorie foods	2.5 s	13
Malik	2006	20	Any	5 s	24
Porubska	2006	12	Appetizing food	2 s	4
Santel	2006	10	High calorie or savory food	3.5 s	3
Schur	2009	10	Fattening and non-fattening	2.4 s	9
Schienle	2009	19	High calorie	Not specified	12
Simmons	2005	9	Any	2 s	6
St-Onge	2005	12	Any	4 s	9
Stoeckel	2008	24	High and low calorie foods	2.5 s	7
Uher	2006	18	Any	5 s	5

* In Beaver 2006, since uncorrected coordinates were listed, only T-values greater than 5.2 were used (i.e. Appetizing-Bland condition).

Table 2
Smoking meta-analysis articles (Smoking versus non-smoking) (13 studies, 153 foci).

Author	Year	n	Cue type	Cue duration	Foci
Brody	2007	42	Videos	45 s	17
Brody[a]	2002	20	Videos and holding object	30 min	7
Dagher	2009	15	Videos	2 min	8
David	2005	14	Pictures	5 s	7
David	2007	8	Pictures	5 s	5
Franklin	2007	21	Videos	Not specified	9
Franklin (DAT-9)	2009	19	Videos and holding object	10 min	8
Franklin (DAT-10)	2009	19	Audio video and holding object	10 min	13
Goudriaan	2010	19	Pictures	5 s	15
Janes	2010	13	Pictures	5 s	23
Lee	2005	8	Videos	Not specified	11
McBride	2006	20	Videos	2 min	31
McClernon 24-h smoking abstinence	2009	18	Pictures	4 s	19

[a] Denotes PET study, all other studies are fMRI.

2.3. Inclusion criteria for meta-analysis 2: smoking cues

For the smoking cue meta-analyses, we used the keywords, "Smoking, imaging, cues, and stimuli" to search for relevant articles. Studies had to use a contrast comparing neural activation during exposure to smoking and non-smoking items.

Data were only included if participants were healthy smokers that were not trying to quit and not taking any cessation drugs. Data from smokers in all smoking states (satiated and abstinent) were included. There is conflicting evidence on the effects of abstinence in smokers. While some research suggests that smokers in a satiated state show greater neural response to smoking cues [35,36], others have shown greater neural response in an abstinent state [37,38]. A meta-analysis of smokers in an abstinent state was not carried out because there are not enough published results to do so — only four studies met our criteria for smokers in an abstinent state (periods of abstinence ranging from 8 to 24 h) [35,37,39,40]. While the effects of smoking abstinence are not clear, smoking cues appear to elicit a comparable response in abstinent and non-abstinent states.

Table 3
Smoking craving meta-analysis articles (Correlation of craving score and smoking versus non-smoking) (7 studies, 108 foci).

Author	Year	n	Cue type	Cue duration	Foci
Brody	2007	42	Video	45 s	11
Brody[a]	2002	20	Video and object in hand	30 min	15
Franklin	2007	21	Audio-video clip with object in hand	Not specified	11
Goudriaan	2010	19	Pictures	5 s	2
McClernon	2009	18	Pictures	4 s	19
Smolka	2006	10	Pictures	6.6 s	21
Yasuno[a]	2007	12	Video	2 min	7

[a] Denotes PET study, all other studies are fMRI.

Table 4
Results from food meta-analysis — brain regions of significant activation in response to food > non-food stimuli.

	Brain area	Volume (mm^3)	x	y	z
L	Lateral OFC	1304	−25	31	−17
L	Anterior insula	328	−35	14	10
R	Anterior insula	752	40	6	−10
L	Anterior insula	432	−38	5	−8
L	Ventral striatum	184	−9	6	−6
L	Middle insula	496	−37	−5	7
R	Middle insula	2736	39	−6	8
L	Amygdala	832	−19	−8	−16
L	Parahippocampal gyrus	936	−21	−34	0
	Precuneus	240	2	−50	35
L	Postcentral gyrus; BA 2	272	−39	−50	59
R	Precuneus	480	29	−57	54
R	Fusiform gyrus	896	38	−71	−14
L	Occipital lobe; BA 19	408	−24	−85	−15
L	Lingual gyrus	1288	−14	−92	−5
R	Lingual gyrus/cuneus	688	12	−93	−6

Eligible studies used a contrast comparing neural activation of exposure to smoking and non-smoking stimuli. Smoking stimuli included pictures or videos of cigarettes and people smoking. Non-smoking stimuli ranged from pictures of scenery to household items such as pencils.

Using the search parameters defined above, we included a total of 13 of the 58 studies reviewed. Table 2 lists the articles that met the criteria for the smoking meta-analysis [35–37,39,41–49].

2.4. Inclusion criteria for meta-analysis 3: smoking correlated with craving condition

The smoking correlated with craving meta-analysis used the same inclusion criteria as the smoking meta-analysis, except studies were required to correlate self-reported levels of craving with activation foci acquired from exposure to smoking versus neutral cues. We used the same keywords as the smoking meta-analysis, which included the keywords, "Smoking, imaging, cues, and stimuli," to search for relevant articles.

Using the search parameters defined above, we included a total of 7 out of the 58 studies reviewed. Table 3 lists the articles that met the criteria for the smoking correlated with craving meta-analysis [37,41,42,45,48,50,51].

We could not perform a parallel study for food craving because our search identified only one published study of food craving and that study did not use pictures of foods [52].

2.5. Activation likelihood estimation

The meta-analyses were carried out using the software package Ginger ALE Brainmap v2.1.1 (http://brainmap.org/index.html), which uses activation likelihood estimation (ALE) as implemented by Turkeltaub et al. [53], and modified by Eickhoff [54]. This technique takes the peak activation coordinates from each study, smoothes them to generate Gaussian spheres, transforms them into a probability distribution map, and compares these maps to a series of randomly generated

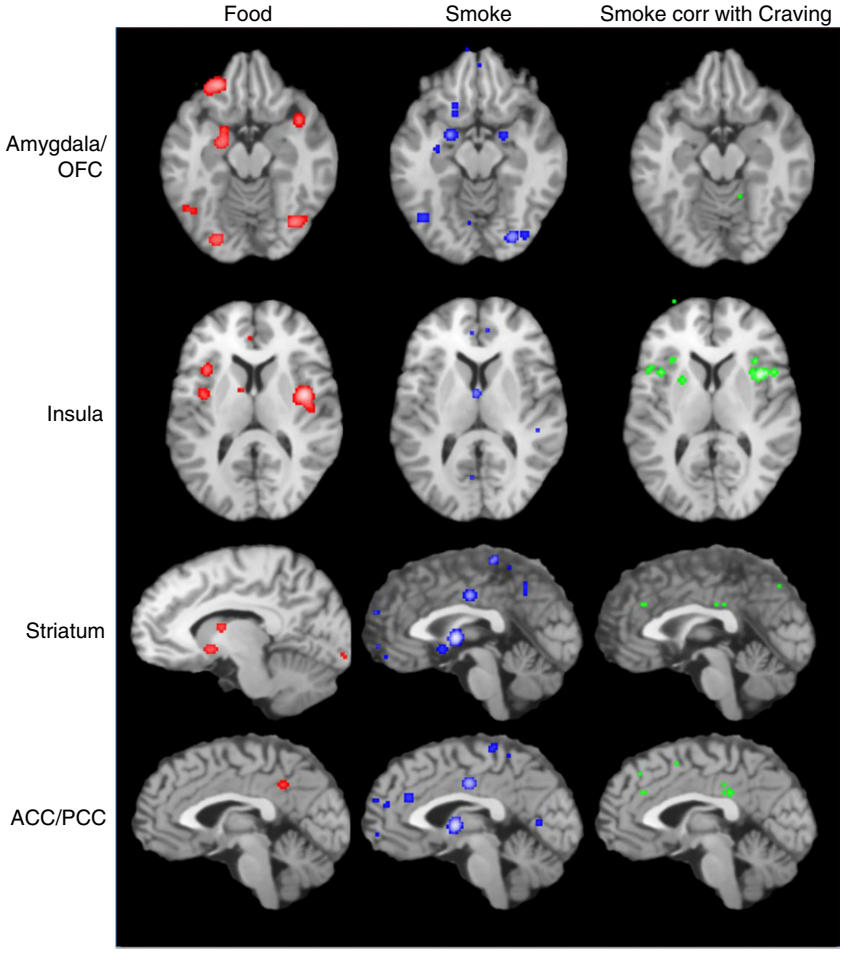

Fig. 1. Images from Food and Smoking Meta-Analyses (Neural response to food cues, smoking cues and smoking cues when correlated with craving is shown in red, blue and green respectively.). Slices taken at Z = −15, −15, −15; Z = 9, 8, 7; X = −8, 1, 1; X = −1, −1, −1; (from left to right; top to bottom).

Table 5
Results from smoking meta-analysis — brain regions of significant activation in response to smoking > non-smoking stimuli.

	Brain area	Volume (mm^3)	x	y	z
L	ACC	352	−5	30	24
L	OFC	240	−16	15	−16
R	Nucleus accumbens	424	5	5	−6
R	Amygdala	320	20	−5	−17
L	Amygdala	752	−20	−4	−17
R	Thalamus	776	0	−5	3
L	PCC	384	−1	−16	35
R	Middle temporal gyrus	224	48	−34	4
R	Area 20; Fusiform gyrus	320	37	−49	−23
L	Fusiform gyrus	688	−41	−68	−18
L	Fusiform gyrus	240	−40	−68	13
R	Fusiform gyrus	400	27	−83	−13

maps to determine significance. ALE identifies brain regions demonstrating statistically significant effects across the entirety of the included studies. Brain maps are thresholded at $p<0.05$, corrected for multiple comparisons.

Significant brain regions of overlap between the smoking and food meta-analyses were identified using a conjunction analysis in Ginger ALE Brainmap, using a $p<0.05$, false discovery rate (FDR) corrected. Significant differences in brain regions between the food and smoking meta-analyses were also identified in a subtraction analysis, using a $p<0.05$, FDR corrected.

Results from the meta-analyses, including overlap between the three meta-analyses, and conjunction analysis were visualized using Mango software (www.ric.uthscsa.edu/mango).

3. Results

In the food cue meta-analysis, we found peak areas of activation in the amygdala, insula, lateral orbital frontal cortex (OFC), ventral striatum, fusiform gyrus and thalamus (Table 4, Fig. 1). Different parts of anterior cingulate cortex (ACC) and medial frontal lobe were activated in 7 of the 14 studies.

For the smoking meta-analysis, we found activation in the amygdala, OFC, ventral striatum, ACC, posterior cingulate cortex (PCC), fusiform gyrus, ventral medial prefrontal cortex (VMPFC), and dorsal medial prefrontal cortex (DMPFC) (Table 5, Fig. 1).

For the smoking correlated with craving meta-analysis we found activation in the insula, lateral prefrontal cortex, parahippocampal gyrus, and precuneus (Table 6, Fig. 1). Note that the smoking correlated with craving meta-analysis may have limited interpretability due to the small sample size.

Since, the amygdala, OFC, striatum and insula are areas of the brain that are commonly identified in studies of cue reactivity and reward that measure neural responses to food-related or drug-related stimuli [14], we also summarize our results specifically for these areas of interest (Table 7).

Fig. 2 shows the peak areas of activation identified in the food and smoking meta-analyses on a single brain map to illustrate the similarities and differences between food and smoking. For the purposes of comparison between food and smoking, smoking and smoking correlated with craving meta-analyses were combined. Interestingly, while the food and smoking conditions yielded similar activations in the amygdala and anterior insula, the OFC and middle insula were different. Specifically, different regions of OFC responded to food versus smoking cues, while mid-insula was only identified in the food meta-analysis.

Table 6
Results from smoking craving meta-analysis — brain regions of significant activation in response to smoking > non-smoking stimuli when correlated with self-report levels of craving.

	Brain area	Volume (mm^3)	x	y	z
L	Middle frontal gyrus	368	−38	10	57
L	Anterior insula		−38	10	7
R	Anterior insula	664	37	9	5
R	Area 40; inferior parietal lobe	352	45	−44	51
R	Area 36; parahippocampal gyrus	744	29	−58	−22

Table 7
Comparison of food and smoking meta-analyses.

Brain region	Food meta-analysis	Smoking meta-analysis	Smoking craving meta-analysis
Amygdala	L	L and R	–
Insula	L (anterior and middle) R (middle)	–	L and R (both anterior)
Orbital frontal cortex	L and R (lateral)	L and R	–
Striatum	Caudate/nucleus accumbens	Nucleus accumbens	–

For the conjunction analysis of food and smoking cue studies, we found significant overlap in the amygdala and the striatum (Fig. 3).

In the subtraction analysis, we found that brain activations in the food meta-analysis were greater than activations in the smoking meta-analysis in the right middle insula, and the left lingual gyrus. No brain regions were identified as significantly greater in the smoking meta-analysis. Fig. 4 shows significant differences ($p<0.05$, FDR corrected) between food and smoking meta-analyses.

4. Discussion

We found considerable overlap in the neural regions consistently involved in responding to food and smoking cues, notably in regions of the brain associated with reward processing, including the striatum, amygdala, OFC, and anterior insula. The conjunction analysis demonstrated overlap in the amygdala and the striatum ($p<0.05$, FDR corrected). Different parts of OFC were activated by food and smoking cues. Moreover, while the anterior insula was activated by food and smoking cues, the mid-insula was only activated by food cues, consistent with its presumed role as ingestive cortex [55].

4.1. Brain regions

4.1.1. Amygdala

The amygdala plays a critical role in emotional learning and in the association of cues with reward [56] by encoding the value of the

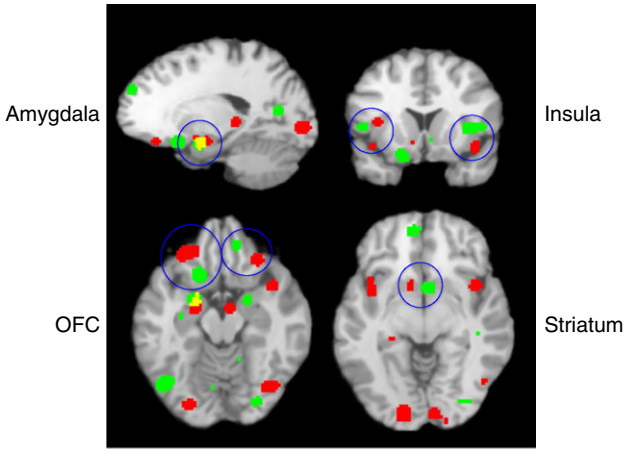

Fig. 2. Similarities between food (red) and smoking (green) meta-analyses in the amygdala, insula, OFC, and striatum. Note that smoking and smoking craving conditions have been combined. Yellow indicates overlap between the two meta-analytic regions. Slices are taken at X = −17, Y = 11; Z = −17, −7 (from left to right; top to bottom).

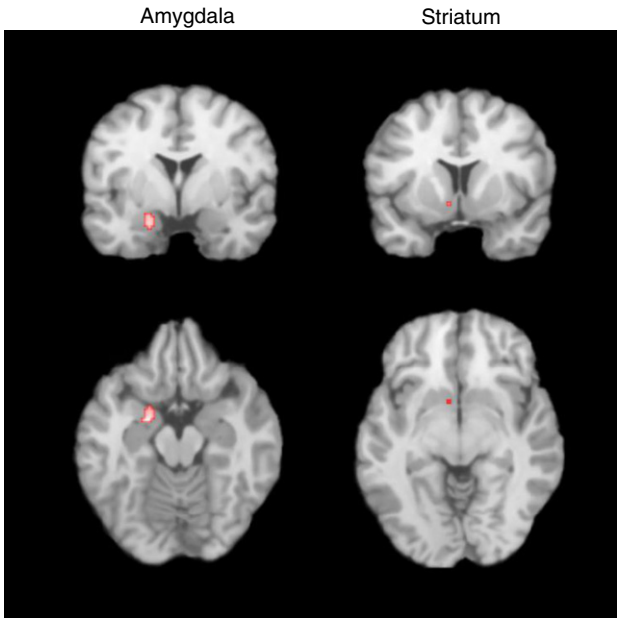

Fig. 3. Conjunction of food and smoking meta-analyses. Significant overlap was found in the left amygdala (left; top slice y = −5, bottom slice z = −17) and striatum (right; top slice y = 6, bottom slice z = −7) ($p<0.05$, FDR corrected).

reward predicted by the conditioned stimuli [57]. Damage to the amygdala impairs an animal's ability to respond appropriately to conditioned cues predictive of reward [58]. Consistent with the animal literature, human imaging research shows that the amygdala responds to a variety of rewarding stimuli, including cues that are associated with food [30] and drugs, such as nicotine [59], cocaine [60], and marijuana [61]. Put together, these findings suggest a role of the amygdala in responding to appetitive cues broadly defined. Various forms of appetitive behavioral responses to conditioned cues have been shown to depend on amygdala connections to lateral hypothalamus, subtantia nigra, OFC [8,62], and striatum [63].

Consistent with this literature we found that studies of smoking and food cues produce consistent and overlapping responses in the amygdala (Fig. 3). Interestingly, amygdala activation was not identified in the smoking correlated with craving meta-analysis.

4.1.2. Orbital frontal cortex (OFC)

The function of the OFC is complementary to that of the amygdala, and research links the amygdala, via interactions with the OFC, to the process of encoding the current incentive value of a stimulus [58,64–66]. Damage to the connection between the amygdala and OFC impairs the ability to assign values to cues and carry out many types of goal-directed behaviors [8]. Much primate and human imaging research suggests a role for the OFC in decision-making that results primarily from its computation of the value of available options and actions [65,67,68].

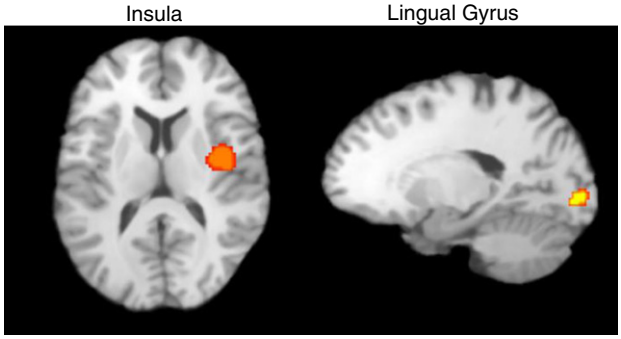

Fig. 4. Results from subtraction of food minus smoking meta-analyses shows that the difference in activation of right middle insula (left; z = 11) and left lingual gyrus (right; x = −17) is significant (FDR corrected, $p<0.05$). No regions were in the smoking minus food were significantly different.

While both the food and smoking meta-analyses identified the OFC, this region was not identified in the conjunction analysis, likely because the peaks for food and smoking did not overlap anatomically. The lateral extent of smoking and food related activation peaks identified here differed somewhat (Fig. 2): smoking cues activated more medial regions between (x = 6 to 16 mm), while food related peaks were more lateral (x = 25 to 28 mm). There appears to be a distinction in the nature of the coding that occurs in medial versus lateral regions, with positive reinforcers consistently activating more medial regions. For example, in an early PET study, Small et al. [69] mapped OFC activation correlated to ratings of declining pleasantness and motivation as subjects ate chocolate to satiety. In this study they found a dichotomy between activity in the lateral and medial OFC, as medial OFC (x = 17 mm) activity increased with increasing reward value, while the lateral OFC (x = 42 mm) showed the opposite response, increasing with decreasing motivation to eat. Note that both OFC peaks in our meta-analysis can be said to belong to relatively medial regions that respond to rewarding stimuli however, and none of the peaks were as lateral as x = 42 mm, the area responding to satiety and reduced motivation in Small et al.'s study. A large meta-analysis of all OFC activations confirmed the lateral/medial dichotomy, with positive reinforcers activating areas ranging from the medial surface of the hemisphere all the way to x = 30 mm [70]. Therefore, both smoking and food cues activate regions within the appetitive portion of the OFC.

As with the amygdala, OFC activation was not identified in the smoking correlated with craving meta-analysis, which might suggest that the OFC has a unique role in responding to smoking cues, but not craving; however the small numbers could have obscured an effect, as extensive literature implicates the OFC in computing the value of stimuli [65]. Nonetheless, only one out of the seven studies in the craving meta-analysis reported bilateral activation of the OFC [41]. There are also many reported inconsistencies on the role of the OFC in drug cue reactivity and craving [66,71]. Dom's review of 20 studies [71] suggested that participants in acute drug withdrawal demonstrated hyperactivity in the OFC, whereas participants who were simply abstinent demonstrated hypoactivity in the OFC. This suggests that OFC activity and craving might be related to the length of the abstinence period. Moreover, craving questionnaires may not be a good indicator of the value of a stimulus, which is perhaps what the OFC computes [70].

4.1.3. Insula

The insula is a heterogeneous region, sensitive to a wide range of sensory and bodily states [72], and of especial significance to food intake as it contains the primary taste cortex [73]. In humans it is thought that the mid-insula represents primary taste cortex, while imaging studies have identified activation of anterior insula extending to the fronto-opercular cortex in response to a wide range of emotional, sensory and cognitive tasks, perhaps reflecting a common role in awareness [72]. The insula has been shown to respond to taste in humans [74], and to food cravings [52], and is theorized to also have a role in visceral interoceptive sensations [75]. More than taste cortex, the insula is often referred to as ingestive cortex, as it responds to most sensory properties of food [76]. The insula is also implicated in the devaluation of food cues when eating to satiety [64,69].

The insula may have a specific role in cigarette craving. In human smokers, acquired damage to the insula reduced craving for cigarettes [77]. Insula damage also disrupts drug craving in animals [78]. Consistent with this, we found that the insula has a specific role in craving for cigarettes, as the insula (specifically the anterior insula) was only identified in our smoking correlated with craving meta-

analysis, and not in the simple smoking meta-analysis. This finding suggests that only high craving situations elicit insular activity during tobacco cue reactivity.

Similar to the smoking correlated with craving results, the anterior insula was identified in the food meta-analysis. While food cravings were not correlated with neural response to food cues in any of the studies included here, it is conceivable that anterior insula activation in the meta-analysis is the result of relatively high levels of food craving in hungry volunteers exposed to food pictures. Although there were no imaging studies explicitly correlating brain activity to hunger level, numerous imaging studies demonstrate that insula response to food cues is greater in the hungry than the sated state [79–81]. While no large-scale studies exist, there is emerging data to suggest that the insula may also have an effect on weight gain susceptibility. For example, two single case reports of patients with insular damage reported significant post-operative weight loss [82,83]. In addition, insula atrophy was found to be associated with compulsive binge eating in patients with fronto-temporal dementia [84].

In the food meta-analysis, we also identified the middle insula. This region was not identified in either of the smoking meta-analyses. Our subtraction analysis even showed that activity in the middle insula was significantly greater than the smoking meta-analysis (Fig. 4; $p<0.05$, FDR corrected). Since food is ingested and nicotine is not, we theorize that activation of the middle insula, through its associations as the primary taste cortex, reflects a sensory representation of food.

4.1.4. Striatum

Food and smoking cues both significantly activated the ventral striatum (Fig. 3). In the food meta-analysis, we found activation in the nucleus accumbens and caudate, whereas in the smoking meta-analysis, we found activation in the nucleus accumbens as well as the thalamus.

Considerable evidence suggests that the approach behavior and reinforcement learning that occur during cue conditioning occur via dopamine release in the ventral striatum. Cues cause burst firing of dopamine neurons after they have become conditioned to predict reward [85] and this is reflected in dopamine release in the ventral striatum [86,87]. Moreover the magnitude of this response appears to correlate with the incentive motivational properties of the cue [87]. While changes in BOLD signal cannot be assigned to one particular neurotransmitter it is worth noting that numerous experiments demonstrate a BOLD signal in the striatum [65] that has identical temporal characteristics to the reward prediction error signal measured from primate dopamine neurons [88].

It may seem surprising that we did not find striatal activation in the smoking correlated with craving condition, however the role of the striatum in high craving conditions, such as prolonged abstinence, is not clear, and there are conflicts in the literature. While two smoking studies reported striatal activation following overnight and 24 hour abstinence [37,39], other studies, including a follow-up study by David, failed to find striatal activation following abstinence [35,36,40]. In fact, David's follow-up study in female smokers found that smokers in the non-abstinent condition had greater striatal activation than in the abstinent condition [35].

4.1.5. Anterior cingulate cortex (ACC)

Both types of cue activated regions of rostral ACC extending down to vmPFC. The ACC has a role in reinforcement-guided decision-making [89,90]. Decision-making requires integration of information that includes previous experiences and expectations, and research shows the ACC facilitates this process. Monkeys with ACC lesions, were impaired when they had to integrate past information to obtain reward. For example, these monkeys did not show deficits in decision-making immediately after making an error, but rather the impairment became evident in obtaining sustained reward on a reinforced guided decision-making task, and when they were required to integrate risk and payoff in a dynamic foraging task [90]. The ACC may also play a role in making optimum action-based decisions [91].

4.1.6. Visual areas

The studies included in our meta-analyses all used visual stimuli. The meta-analytic results included visual areas such as the occipital lobe, precuneus, cuneus, fusiform, parahippocampal gyrus, and lingual gyrus, which likely derive from the salience of appetitive cues. It has been theorized that projections from the amygdala and OFC modulate activity in posterior visual areas [30], such as the primary visual cortices and postcentral gyrus, to increase the salience of relevant cues [15,30].

4.2. Summary

By using meta-analytic techniques to combine a series of studies, we have identified regions consistently activated in food and smoking cue reactivity studies. As expected, the four regions (amygdala, OFC, insula, and striatum) previously hypothesized to form a common appetitive network [14], were all identified as areas of significant activation for neural responding to food and smoking cues. We propose that the response in these regions is a measure of the incentive salience [13] of conditioned cues.

The amygdala, insula, striatum and OFC are interconnected and work together to signal the presence of rewarding cues. For example, despite the importance of the striatum in signaling reward, a recent study showed that the nucleus accumbens depends on the amygdala for cue responding, and inactivation of the amygdala can impair the ability of this network to respond to rewarding cues [63].

One of the factors that link the regions in this reward cue signaling network may be dopamine. Many of the identified regions in the food and smoking meta-analyses receive dopaminergic projections, in particular in the amygdala, insula, OFC and striatum [14]. Dopamine neurons fire in response to rewards, and over time signal the presence of a reward predicting cues [85]. Dopamine is released in response to drug and food cues [92].

4.2.1. Study limitations

Despite the informative nature of our meta-analyses, it is important to note some of the limitations in this study.

First, meta-analytic studies will always be limited by the original study designs. Brain regions such as the amygdala and OFC have blunted responses following repeated presentations of stimuli [93,94], because of habituation. All of the studies included in our meta-analyses used repeated presentations of stimuli.

In addition, the OFC and amygdala are known to be highly susceptible to artifact, signal dropouts, and spatial distortions. It is therefore likely that activation in these brain regions is underreported. This may explain in part the finding of unilateral activation for some structures such as the amygdala. It is important to note that, however, the negative findings in brain imaging meta-analyses must be interpreted with caution. Besides the issue of signal dropout, meta-analyses are based on thresholded statistical maps, so negative findings are not interpretable in a statistical sense. That is, the rate of false negatives is uncontrolled.

Another limitation is result specificity. Since we carried out a meta-analysis of significant brain activation peaks that were published, we can only draw general conclusions about our data. The published peaks represent thresholded statistical maps, and therefore lack much of the information of the original fMRI data from which they were generated.

With regard to the craving meta-analysis, special attention needs to be taken when interpreting null results (e.g. the lack of activation in the OFC). The findings in the craving meta-analysis are less robust

because of they are not only affected by the limitations described above, but they are also dependent on a correlation with self-report craving scores. Previous research suggests that self-report craving is not always a reliable measure due to a number of factors, including the experimental context and differences in response styles of participants [95].

Finally, in our meta-analyses, desire for food and cigarettes were not well controlled for. Participants in the food studies were all food deprived for a certain period of time, but exactly how hungry each individual participant was is hard to quantify. The same problem existed for participants in the smoking studies, who in some studies had just smoked a cigarette, and in other studies had been abstinent for a long period of time. In the food literature, there was not enough data to conduct a meta-analysis to identify brain regions correlated with food craving. In the smoking literature, it is not clear if smoking state, such as abstinence or satiation, has any effect on neural response to smoking cues.

4.2.2. Significance of findings and future work

Despite these limitations, our results provide a general overview of the similarities between food and smoking cue processing, and shed some light on drug craving.

The next step will be to deepen our understanding of the similarities and differences between smoking and eating. We need to determine why smoking cues elicit a neural response when satiated, while food cues result in a blunted response when satiated. It will also be interesting to determine if people can become addicted to certain foods. One way to prove this may be to show that neural response to addicted food cues elicits a response even when participants are satiated. Another important issue to address is quantifying craving or desire for food or cigarettes. Novel paradigms that explicitly measure goal value of drug or food stimuli have recently been used to address this issue [96], but more work in this area is needed. Finally, given the relationship between the insula and craving in smoking, and our finding that the insula is involved in neural response to food cues when participants are hungry, one important area for future research is to explore the emerging relationship between the insula, eating behavior, and weight change.

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