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

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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

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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.