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# Visual cortex activation to drug cues: A meta-analysis of functional neuroimaging papers in addiction and substance abuse literature

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ABSTRACT

*Background:* Although the visual cortex does not typically receive much attention in addiction literature, neuroimaging studies often report significant activity in visual areas when drug users are exposed to drug cues. The purpose of this meta-analysis was to investigate the frequency with which occipital cortex activity is observed during drug cue exposure and to determine its spatial distribution.
*Methods:* A comprehensive literature search was performed of human functional neuroimaging studies of drug cue-reactivity. Fifty-five studies were used to determine the frequency with which clusters of significant visual cortex activity during visual drug cues versus non-drug cues were reported. The spatial distribution of visual cortex activations was determined via activation likelihood estimation (ALE; FDR corrected, $p < 0.01$) in a subset of these studies ($n = 24$).
*Results:* Eighty-six percent of studies that reported fMRI results for drug versus neutral visual cues within a substance-dependent group showed significant drug-elicited activity in the visual cortex. ALE revealed clusters in the left secondary visual cortex (BA 19) and clusters in the primary visual cortex (BA 17) that were consistently activated by drug cues.
*Conclusions:* These data demonstrate that the visual cortex, often overlooked in our discussions of the neural circuitry of addiction, consistently discriminates drug cues from neutral cues in substance dependent populations. While it remains unclear whether drug cue-elicited activation in occipital cortex is related to the rewarding properties of the drug and/or attentional mechanisms, these data support further exploration.



## 1. Introduction

Drug cue-reactivity – the array of psychological, physiological, and behavioral effects elicited by drug-related stimuli – has been utilized for more than two decades in an attempt to understand drug craving and dependence (Rohsenow et al., 1991; Drummond, 2001; Carter and Tiffany, 1999). As of 2014, there were over 100 functional neuroimaging studies that investigated cue-reactivity in a range of drug using populations. These studies have provided substantial knowledge regarding the neural response to drug cues, revealing a common set of brain regions which are now classically considered a part of the network engaged in response to drug cues and craving. These oft-cited brain regions – up-regulated in the presence of visual drug cues – include the medial prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, insula, and the striatum (Kühn and Gallinat, 2011; Schacht et al., 2013). These established regions are similarly reported in non-human primate studies of drug self-administration (Porrino et al., 2004), and rodent studies of drug reinstatement (McFarland et al., 2003; Dayas et al., 2007).

In addition to frontal and striatal brain regions, human neuroimaging studies of drug cue-reactivity often observe activation in another fundamental brain region that is given much less emphasis—the visual cortex. Although significant drug cue-elicited activity in the occipital cortex is commonly demonstrated and has been found in previous meta-analyses of drug cue-reactivity (Chase et al., 2011; Engelmann et al., 2012; Schacht et al., 2013), it is rarely reported as a primary finding and has historically not been given very much consideration in the context of addiction. More recently however, numerous investigations have described significant drug

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cue-elicited activity in visual cortex that directly relates to a host of clinical factors such as cigarette craving during 24-h abstinence but not satiety (McClernon et al., 2009), resisting craving for cigarettes (Brody et al., 2007), as well as measures of self-recognition of problematic cocaine use and desire to change (Prisciandaro et al., 2014). Given these associations, and the fact that visual cortex activity specific to drug cues is compatible with emerging literature regarding the role for primary visual cortex in reward processing (Shuler and Bear, 2006; Yalachkov et al., 2010), we suggest that occipital cortex, including primary visual cortex, activation in response to drug cues deserves much more consideration.

To this end, the primary goal of this proof of concept study was to document and localize the involvement of the visual cortex during functional magnetic resonance imaging (fMRI) studies of drug cue-reactivity. Specifically, the aims were to quantify the frequency with which occipital cortex activity is observed across drug classes and, through activation likelihood estimation (ALE; Turkeltaub et al., 2002; Eickhoff et al., 2012), determine the spatial locations in occipital cortex that are most frequently activated.

## 2. Methods

### 2.1. Inclusion criteria and identification of articles

We conducted a comprehensive PubMed electronic database search of all English language, addiction-related studies published by August, 2013 that assessed the neural response to drug-related cues using fMRI. Keywords for the imaging component were "imaging", "MRI", and "BOLD". For the addiction component we searched "addict*", "drug", "abuse", as well as individual classes/types of drugs including "nicotine", "smok*", "cocaine", "stimulant", "methamphetamine", "alcohol*", "opiate", "heroin", "marijuana" and "cannabis". Lastly, we searched all "cue", "cue-reactivity", and "craving" studies. The goal was to identify (1) f MRI experiments of drug cue-reactivity that (2) presented visual cues to a substance-abusing population, (3) analyzed the data in a whole-brain approach (that included the occipital lobe), and (4) reported the results of drug versus non-drug cues within the substance-using population. Papers were selected after examination of the methods, and chosen if criteria of an fMRI drug cue-reactivity primary investigation were met. The reference sections of those selected were also searched for additional pertinent investigations.

This literature search resulted in 109 manuscripts of which 5 meta-analyses and 13 non-cue-related or inaccessible papers were excluded, leaving 91 original fMRI drug cue-reactivity articles. Of the 91 studies, 76 used visual cues [static images ($n = 61$), video ($n = 11$), viewing a self-holding cue ($n = 3$), and virtual cues (i.e., 2D/3D smoking-related images and environments; $n = 1$)]. Studies using non-visual cues [script guided imagery ($n = 5$), taste cues ($n = 3$), presentation of words ($n = 5$), odors ($n = 1$), and infusion ($n = 1$)] were not included in the subsequent analyses. Fifty-five of these 76 studies used a whole-brain approach.

To determine the frequency with which cue-induced craving studies observed visual cortex activity to drug cues, these 55 articles were thoroughly examined, noting information from all tables and figures, sample size, characteristics of the subject population, cue-exposure paradigm, analytic approach, statistical thresholding, the nature of the control condition/group, the cluster size, and the spatial location of visual cortex activity if it was observed. Of these 55 studies that performed a whole-brain voxel-based analysis of the BOLD response to visual cues of a drug in a substance-using group, 28 reported a detailed table of results describing regional brain activity elicited from a drug-cue versus neutral contrast in the substance-using group (Fig. 1, Table 1, top).

### 2.2. Activation likelihood estimation (ALE)

To determine and localize the regions within the visual cortex (e.g., primary versus secondary visual cortex) that were most consistently activated, an activation likelihood analysis (ALE) was performed on the subset of the 28 studies, namely the ones that detected significant occipital lobe activity to drug versus neutral cues ($n = 24$). The coordinates of the peak activity within the occipital cortex for these 24 studies were entered into an ALE analysis. Only the clusters in the visual cortex were entered into the analysis, as this investigation was not designed as a comprehensive analysis of all brain regions implicated in drug cue-reactivity. ALE was performed with the GingerALE software (Turkeltaub et al., 2002), which uses an updated ALE algorithm for minimizing within-experiment and within-group effects (Eickhoff et al., 2012). Likelihood estimation values were computed for all focal locations from contributing contrasts. The null distribution statistic from the likelihood estimation was calculated with full-width at half maximum values empirically determined by the sample size of each contributing study. Values were then subjected to a false discovery rate (FDR) of $p < .01$ with a minimum extent threshold cluster threshold of 100 $mm^3$.

## 3. Results

### 3.1. Visual cortex activity during cue-induced craving: descriptive analyses

Of the 55 studies that used fMRI and whole-brain analyses to examine drug-related visual cues, 50 (91%) reported significant activity in the occipital lobe (primary and secondary visual cortices) during cue exposure. This drug-cued activity in occipital cortex was observed across multiple drug classes (alcohol, cocaine, marijuana, tobacco; Table 1) and there was no significant difference in frequency between the drug classes. Among the 28 studies that reported detailed results from a whole brain analysis of drug cues versus neutral cues in a substance abusing population, 24 (86%) reported significant drug-cued activity in the occipital cortex (Table 1, bottom, Table 2).

Although not included in the initial analysis, a posthoc assessment of drug cue-reactivity studies that used stimuli other than visual ($n = 15$) revealed that six (40%) observed visual cortex activity to the non-visual drug cues (2 script, 1 odor, 2 word, 1 taste).

### 3.2. Distribution of activity within the occipital lobe: Activation likelihood estimation analyses

Among the 24 studies that reported results from a whole-brain analysis of drug versus neutral cues and observed activity in the occipital cortex, ALE revealed several independent clusters that were consistently activated. These included discrete clusters in both the primary visual (left BA 17) and secondary (left and right BA 18/19) visual cortices (Table 3 and Fig. 2).

## 4. Discussion

Drug cue-reactivity is one of the most common paradigms employed in human substance abuse literature, largely because drug cue-induced craving is one of the most robust factors that lead to continued use and relapse across substances. Our discussions on treatable-targets for addiction typically focus on the frontal and striatal areas that are activated by drug-related cues. The results of the present investigation however highlight the importance of another often overlooked brain region that is consistently activated by drug cues relative to non-drug cues, the primary and secondary visual cortices. Although the role of the visual cortex in addiction is seldom discussed at scientific meetings, the vast majority of drug cue exposure studies (86%) found significant occipital cortex activation in substance users who were exposed to visual drug cues compared to neutral cues. Activation likelihood estimation revealed that this activity is present in distinct areas of BA 17 and BA 19. Furthermore, this activity was observed across multiple drug classes (alcohol, cocaine, marijuana, tobacco). Thus, it appears that addiction can directly affect primary sensory cortex, suggesting that the effects of drug cue-reactivity are more widespread and fundamental than previously appreciated. It is highly likely that addiction influences basic sensory processing via its effects on cognitive processes that are known to modulate activity in BA 17. Here, we discuss some of the more likely cognitive processes underlying the enhancement of activity in BA 17, and the implications for our basic understanding of addiction.

### 4.1. Attention and reward processing in the visual cortex

The primary visual cortex (BA 17) encodes elementary features of visual stimuli such as local contrast, spatial location, spatial frequency, orientation, and ocularity (Hubel, 1982). An extensive body of work has shown that the representation of these basic visual features can be significantly modulated by attention as well as the