The Neural Basis of Drug Stimulus Processing and Craving: An Activation Likelihood Estimation Meta-Analysis

Henry W. Chase, Simon B. Eickhoff, Angela R. Laird, and Lee Hogarth

Background: The capacity of drug cues to elicit drug-seeking behavior is believed to play a fundamental role in drug dependence; yet the neurofunctional basis of human drug cue-reactivity is not fully understood. We performed a meta-analysis to identify brain regions that are consistently activated by presentation of drug cues. Studies involving treatment-seeking and nontreatment-seeking substance users were contrasted to determine whether there were consistent differences in the neural response to drug cues between these populations. Finally, to assess the neural basis of craving, consistency across studies in brain regions that show correlated activation with craving was assessed.

Methods: Appropriate studies, assessing the effect of drug-related cues or manipulations of drug craving in drug-user populations across the whole brain, were obtained via the PubMed database and literature search. Activation likelihood estimation, a method of quantitative meta-analysis that estimates convergence across experiments by modeling the spatial uncertainty of neuroimaging data, was used to identify consistent regions of activation.

Results: Cue-related activation was observed in the ventral striatum (across both subgroups), amygdala (in the treatment-seeking subgroup and overall), and orbitofrontal cortex (in the nontreatment-seeking subgroup and overall) but not insula cortex. Although a different pattern of frontal and temporal lobe activation between the subgroups was observed, these differences were not significant. Finally, right amygdala and left middle frontal gyrus activity were positively associated with craving.

Conclusions: These results substantiate the key neural substrates underlying reactivity to drug cues and drug craving.

Key Words: Addiction, craving, cue, imaging, meta-analysis, reactivity

Stimuli that predict rewards are known to elicit instrumental behavior that leads to the acquisition and consumption of that reward (1–3). Similarly, stimuli that have been paired with drugs of abuse can elicit drug-seeking and taking behavior (4–7). Such reactivity to drug-associated cues is thought to play a fundamental role in maintaining addictive behavior (8). Dopamine seems to play an important role in the influence of drug cues on addictive behavior, given its involvement in both Pavlovian conditioning (9–11) and in encoding the reward value of drugs (12–15) and nonpharmacological reinforcers such as gambling (16,17) and video gaming (18). Furthermore, a brain network that receives dopaminergic innervation—including the striatum, amygdala/hippocampus, and prefrontal cortex (PFC) (19–23)—plays a crucial role in sustaining addictive behavior.

The cue-reactivity paradigm (24–26), in which physiological, behavioral, or subjective responses to drug-related stimuli are examined in drug users, dominates human addiction research. Reactivity to addiction-relevant cues has also been examined in problem gamblers (27) and excessive video gamers (28). A large number of these studies have examined the neural responses to drug cues and craving with functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Two previous descriptive reviews of these imaging studies (29,30) have attempted to consolidate the consequent findings. Wilson *et al.* (30) divided studies on the basis of whether the participants were seeking treatment for their addiction or not. Studies on participants who were not seeking treatment were considerably more likely to show PFC activation to drug related cues than studies of those who were. Given the role of the PFC in high-level decision making (31), the preferential activation of the PFC in nontreatment seekers was interpreted as evidence for the cue eliciting an intention or expectation of taking the drug. A subsequent review of neural drug cue reactivity studies by Naqvi and Bechara (29) focused on the insula and argued that activations associated with drug craving were often located in this region. They also discussed a neurofunctional account of the role of the insula in addiction, in light of lesion (32) and anatomical evidence (33). Their account was consistent with the somatic marker hypothesis (34), in which visceral information plays an important role in influencing emotion and decision making. Garavan (35) later reconsidered extant neuroimaging data, arguing the role of the insula to be complex and susceptible to a variety of moderating factors, including cognitive control, satiety, genetics, and gender differences. Thus, there remains uncertainty about the precise role of the region in drug craving.

Previous reviews (29,30) have treated activations of a given region as a binary variable. However, quantitative approaches for coordinate-based meta-analyses of neuroimaging data have been developed, exploiting the rich information within whole-brain contrasts. One such method is activation likelihood estimation (ALE), which identifies statistically significant convergence across published activation coordinates, via a whole brain activation likelihood map (36–38). There are several advantages of this approach, including the identification of specific coordinates rather than regions; the stipulation of a null distribution, which affords a principled

From the School of Psychology (HWC, LH), University of Nottingham, University Park, Nottingham, United Kingdom; Institute of Neuroscience and Medicine (SBE), Research Centre Jülich; JARA-BRAIN (SBE), Jülich-Aachen Research Alliance, Jülich; Department of Psychiatry and Psychotherapy (SBE), RWTH Aachen University, Aachen, Germany; and the Research Imaging Institute (ARL), University of Texas Health Science Center, San Antonio, Texas.

Authors HWC and SBE contributed equally to this work.

Address correspondence to Henry Chase, B.Sc., M.Sc., M.Phil., Ph.D., Western Psychiatric Institute and Clinic and Department of Psychiatry, University of Pittsburgh School of Medicine, 121 Meyran Avenue, Pittsburgh, PA 15213. E-mail: chaseh@upmc.edu.

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statistical testing procedure; and the reduction of bias from the use of regions of interest or small volume correction.

The current study applied the ALE method to published studies of drug cue reactivity and craving to identify consistently activated regions. In an attempt to reflect the extent of addiction research, we included appropriate cue reactivity studies investigating drugs of abuse or non-substance addictions, which satisfied our methodological criteria. We expected to observe drug cue-related neural activity in brain regions including the ventral striatum, PFC, amygdala/hippocampus and insula. Second, we expected studies with nontreatment seekers to show drug cue-related activity in the PFC (30). Because the amygdala is thought to mediate cue-induced reinstatement of drug seeking (39) and reduced amygdala volume in treatment-seeking alcoholic persons has been shown to predict craving and relapse (40), we anticipated amygdala activation to be greater in treatment-seeking participants.

Several approaches have been taken to assess the relationship between variation in craving, both between and within participants, and brain activation (Table S3 in Supplement 1). We compiled these experiments, despite their different methodologies, for a separate meta-analysis. It was hypothesized that craving-related activity might be more likely to show convergence in the insula, because the subjective experience of craving—regardless of how it is elicited—might depend on interoceptive signals (29). However, other affect-related regions might show involvement in craving, including the amygdala or PFC, as has been shown in previous studies (40,41).

Methods and Materials

Study Selection Criteria

We imposed criteria for selecting studies from the extant drug cue reactivity literature (over 50 fMRI and PET studies) in an attempt to ensure that selected contrasts were suitable for quantitative meta-analysis and that there was some methodological consistency, despite the variety of approaches employed for cue presentation. A study was selected if it included a contrast of drug cue presentation with a control stimulus or baseline (henceforth control) in a group of drug users. A secondary contrast was conducted in which we focused on studies reporting an association between neural activity and craving. A variety of methods were used to address this relationship, which are briefly described in Table S3 in Supplement 1. From this pool of work, studies were selected for the present meta-analysis if they followed the criteria outlined in the following text (studies and further details are listed in Table S1 in Supplement 1) and excluded if they did not (Table S2 in Supplement 1).

Analyses must be computed across the whole brain and not restricted with partial coverage, regions of interest, or small volume correction. The studies must present coordinates in an XYZ format, either in Talairach or Montreal Neurological Institute (MNI) space. Studies reported in Talairach coordinates were transformed into MNI coordinates with the Lancaster transform (38).

Studies included substance-dependent participants as specified by DSM-IV criteria or similar, were heavy drinkers (42), or used drugs regularly (43) thereby fulfilling the criteria for drug abuse (F1x.1) in the ICD-10 (44) or suffered from a non-substance addiction not currently included in DSM-IV (28). No consideration for the age of the participants was made.

Studies employing a factorial design, in which a secondary factor (e.g. a cognitive task manipulation) or group (e.g. user/non-user) was introduced or manipulated on top of the basic drug versus neutral stimulus contrast, were generally excluded. However, if activations from a sub-group or sub-contrast were reported in isolation, such studies were included if they followed the basic drug versus control design. If two scans were performed, between which there might be an abstinence period or treatment, the first scan of the two was included. Studies that incorporated drug delivery during the protocol were excluded, although some studies where participants received pharmacotherapy were included.

A wide selection of cue types was included (images, stories, odors). Where there was a choice, the contrast that used the most similar control stimulus to the drug stimulus was included.

Distinction was made on the basis of whether the majority of participants were treatment-seeking or not. In one case (45), approximately one-half of the sample was made up of treatment- and nontreatment-seeking individuals, respectively, and this study was excluded from this subgroup analysis.

No selection was made on the basis of statistical threshold, because false negatives are more problematic for the procedure than false positive activations. All studies were obtained from peer-reviewed journals.

Activation Likelihood Estimate Algorithm

The meta-analysis was carried out on the studies listed in Table S1 in Supplement 1 with a revised version (38) of the ALE approach (36,37) implemented in MATLAB (MathWorks, Natick, Massachusetts). This algorithm aims to identify areas showing a higher convergence of findings across experiments than would be expected under a spatially random spatial association. The ALE treats the reported foci as centers of three-dimensional Gaussian probability distributions reflecting the spatial uncertainty associated with each reported set of coordinates. The probabilities of all foci reported in a given experiment were then combined for each voxel, resulting in a modeled activation map. The union across these yields voxel-wise ALE scores, which describe the convergence of results across the whole brain. To distinguish "true" convergence between studies from random convergence (i.e., noise), ALE scores were compared with an empirical null-distribution reflecting a random spatial association between experiments. A random-effects inference is thereby invoked, focusing on inference on the aforementioned chance convergence between studies rather than clustering of foci within a particular study. Computationally, deriving this null-hypothesis involved sampling a voxel at random from each of the modeled activation maps and taking the union of these values in the same manner as done for the (spatially contingent) voxels in the true analysis. The p value of a "true" ALE was then given by the proportion of equal or higher values obtained under the null-distribution. The resulting nonparametric p values for each meta-analysis were then thresholded at a cluster level threshold of $p < .05$ and transformed into Z scores for display. Contrast analyses between subgroups of the entire dataset were determined by ALE subtraction analysis, including a correction for differences in sample size between the subgroups (46,47).

Anatomical labeling of the resulting regions was facilitated by the SPM Anatomy toolbox (48,49), which defines coordinates of histologically distinct regions of the human brain via probabilistic cytoarchitectonic maps. Activations were labeled in terms of the most probable histological region(s) it occupied, with a Maximum Probability Map. Details of the cytoarchitecture, inter-subject variability, and location of area borders employed in the present study are referenced in the articles by Caspers *et al.* and others (50–64).

Contrasts

Separate meta-analyses were performed with the ALE approach to test our hypotheses. A meta-analysis on the results reported for

Table 1. Number of Experiments, Participants, and Foci

Contrast	Maps, *n*	Participants, *n*	Foci, *n*
Drug > Control	35	522	401
Not Seeking	21	333	222
Seeking	13	159	161
Positive Craving Correlation	18	248	138

Displays the number of experiments, participants, and foci that constituted each meta-analysis.

drug versus control cue contrasts addressed the neural correlates of drug cue stimulus processing, and meta-analysis of the results reported for positive craving correlations was used to determine neural regions associated with craving. A final analysis involved splitting experiments reporting a "drug versus control" cue contrast into studies of treatment-seeking and nontreatment-seeking participants. Individual analyses were performed for each group separately, and activation of the two groups was contrasted directly (46,47). Details of the experiments, participants, and foci used for each contrast are presented in Table 1.

Results

Drug and Control Cue Effects

Several regions of significantly convergent findings were observed when coordinates from the drug versus control contrast were analyzed (Figure 1, Table 2): the left amygdala; the bilateral inferior occipital gyrus; the right ventral striatum; and medial regions of the orbitofrontal cortex (OFC), the right inferior frontal gyrus (rIFG), the posterior cingulate, and superior frontal gyrus.

Treatment-Seeking Versus Nontreatment-Seeking Participants

Bilateral amygdala/hippocampus activation was associated with the drug versus control contrast in treatment-seeking participants. Nontreatment-seeking participants, by contrast, activated OFC and rIFG but not the medial temporal lobe (MTL). Ventral striatal and occipital activation was observed in both subgroups (Figure 2, Table 3). No significant differences were seen when the subgroups were compared.

Craving Correlations

Three regions of consistent activation were identified when coordinates were pooled from all experiments reporting a positive association of regional brain activity with craving—situated in the right amygdala, right inferior parietal cortex, and left middle frontal cortex (Figure 3, Table 2).

Summary

The ventral striatum, amygdala, and OFC were associated with increased activation in drug versus control contrasts, consistent with our hypotheses. The amygdala was activated in treatment-seeking participants and was associated, with the left middle frontal gyrus and right parietal lobe, with craving. By contrast, the OFC and rIFG were activated consistently by drug cues in nontreatment-seeking participants. Ventral striatum and occipital activity were common to both groups. None of the performed meta-analyses, however, revealed any statistically significant convergence in the insula.

Discussion

In the present study, we identified convergence of published neuroimaging results on the processing of drug- or addiction-related cues and craving in populations of drug users with the ALE meta-analysis technique. Consistent with previous studies of Pavlovian conditioning with drug reinforcement, such cues activated the ventral striatum, OFC, and amygdala. Amygdala activity was more consistently observed in studies involving treatment-seeking participants and was also associated with craving, whereas orbitofrontal activity was observed in studies where participants were not treatment-seeking. Another prefrontal region, the left middle frontal gyrus was associated, along with the right parietal cortex, with craving.

The Role of the Nucleus Accumbens

Preclinical evidence points toward a central role for the nucleus accumbens in drug reinforcement (12,13), and it is likely that this structure (65) is responsible for the activations we observed in the right ventral striatum. Preclinical research in animals suggests that this region plays an important role in Pavlovian conditioning (66), control of instrumental behavior by Pavlovian cues (67–69), and drug-seeking behavior by drug-paired cues (70). However, whether dopamine release in the nucleus accumbens plays a key role in cue-induced drug seeking is uncertain: several groups find dopamine release in the nucleus accumbens is not modified by drug-paired cues (71,72) or observe complex effects (73,74), whereas others see robust responses (75). As an alternative, glutamate neurotransmission (76,77), either from the PFC (78) or midbrain neurons projecting to the accumbens (79), is another potential candidate cause of the ventral striatal response to drug cues.

The Role of the PFC

Several PFC loci were identified in our analyses. We observed the rIFG to be activated by drug cues, both in the full sample and in the nontreatment-seeking subgroup. This activation might relate to attentional deployment while categorizing salient stimuli (80) or inhibitory control over craving (81). The superior frontal gyrus was identified within the main drug > control contrast: this region might also play a role in attentional processes (82) evoked by drug cues. However, neither of these regions of PFC was central to the expectancy hypothesis (30), because of the focus on the OFC and dorsolateral prefrontal cortex (DLPFC) in that review. In this light, the identification of the left middle frontal gyrus (DLPFC) within the

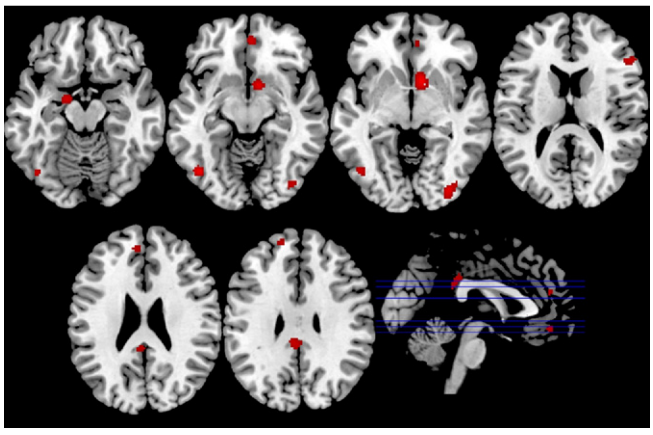

Figure 1. Figure showing activations that accompany the drug versus control contrast. The *Z* coordinates of each slice are displayed in blue. Left amygdala, medial orbitofrontal cortex, right ventral striatum, bilateral occipital cortex, left superior frontal gyrus, posterior cingulate, and right inferior frontal gyrus are shown to be activated. The *Z* coordinates of the displayed slices are (top row, left to right) −15, −10, −5, 15, (bottom row) 25, and 30.

Table 2. Regions of Activation Observed After Different Contrasts Including the Entire Sample

Contrast	Region	Subregions	Voxels	*X*	*Y*	*Z*
Drug vs. Control	Right Ventral Striatum		175	9	10	−5
Drug vs. Control	Left Amygdala	64.7% Left Amygdala (SF); 25.0% Left Amygdala (LB);	103	−19	−5	−18
Drug vs. Control	Orbitofrontal Cortex		60	4	46	−9
Drug vs. Control	Right Inferior Frontal Gyrus	97.7% Right Area 45	44	52	29	16
Drug vs. Control	Left Superior Frontal Gyrus		67	−9	50	26
Drug vs. Control	Posterior Cingulate Cortex		100	−3	−36	31
Drug vs. Control	Right Inferior Occipital Gyrus	24.0% V4 22.2% V3v	127	35	−84	−5
Drug vs. Control	Left Inferior Occipital Gyrus		178	−45	−69	−4
Positive Craving Correlation	Left Middle Frontal Gyrus		56	−37	8	60
Positive Craving Correlation	Right Amygdala	64.0% Right Amygdala (SF)	43	27	0	−13
Positive Craving Correlation	Right Inferior Parietal Lobule	50.0% Right hIP2 46.6% Right IPC (PFm)	43	45	−44	52

Column 3 includes proportions of an activation overlapping with a given region (if the region is included in the SPM Anatomy toolbox). Only regions that account for over 10% of the location of the activation are reported in this column. SF, superficial group; LB, laterobasal group (53,130); PFm, subregion of the inferior parietal cortex (50,51); hIP2, subregion of the intraparietal sulcus (52); IPC, inferior parietal cortex.

craving contrast is intriguing and suggests that craving might be associated with expectancy of drug taking (83,84). Alternatively, activation in this region might reflect an attempt to regulate craving (85).

A medial region of the OFC showed greater activation by drug cues compared with control cues and was consistently activated in the nontreatment-seeking subgroup. There is substantial evidence that this region plays a role in appetitive behavior and decision making (86,87), in particular with regard to expectations of reward (88) predicted by conditioned stimuli (89–94), which can control instrumental action selection (95). With reference to drug-paired cues, Baeg *et al.* (96) observed increased activity in OFC neurons of rhesus monkeys after stimuli paired with cocaine delivery, particularly if delivery was also contingent on a response after stimulus presentation. Together, these data add further support to the view that OFC activation in nontreatment-seeking drug users reflects an expectation or intention to take a drug in the near future (30).

However, we regard our findings with respect to the OFC as somewhat preliminary. The OFC is a difficult region from which to obtain accurate fMRI measurements, unless specific measures are taken to reduce susceptibility artifacts (e.g., [97]). This issue is likely to cause heterogeneity across studies and might well influence the exact location of our OFC locus. Other factors might contribute to the differential pattern of results between the two subgroups, which do not appeal to the expectancy account. Our failure to observe robust OFC activation in treatment seekers might reflect diminished frontal function in these participants (98), perhaps as a result of differences in personality (99,100) or neurotoxic effects of drug intake (101). Alternatively, these participants might be capable of greater inhibitory control over OFC activation caused by self-control mediated by the DLPFC (102). Within-participant experiments—in which expectancy (e.g., [103,104]), self-control, or other factors such as mood are manipulated—might address these issues further. The abstinence or otherwise of the participants is also likely to be a key determinant of the pattern of neural activity (105). It was difficult to dichotomize the groups on this variable, however, because the extent of drug abstinence within the treatment-seeking group was not always clear in the reviewed studies and also seemed to vary within the respective groups.

MTL Structures—Amygdala and Hippocampus

Medial temporal lobe regions including the amygdala and, to a lesser extent, the hippocampus showed consistent drug cue-related activity. The activation of these MTL regions was particularly reliable in studies investigating treatment-seeking participants. The amygdala has been consistently associated with various forms of appetitive Pavlovian processing (106–108) and drug seeking, in particular via its interactions with the nucleus accumbens (109). Basic research suggests that the amygdala seems to play a particularly critical role in cue-induced relapse of drug seeking after an extinction procedure (39). In this light, our finding of amygdala activation in treatment seekers is particularly salient: the normal dosing regimen of these participants will have been changed, and hence exposure to drug cues might be expected to re-activate drug memories**.**

Activity in the right amygdala was also observed in a separate meta-analysis of studies which investigated within- or between-participant associations of neural activity and craving. Behavioral evidence suggests that drug conditioned cues and satiety can have separate influence on craving (110), and the amygdala might be

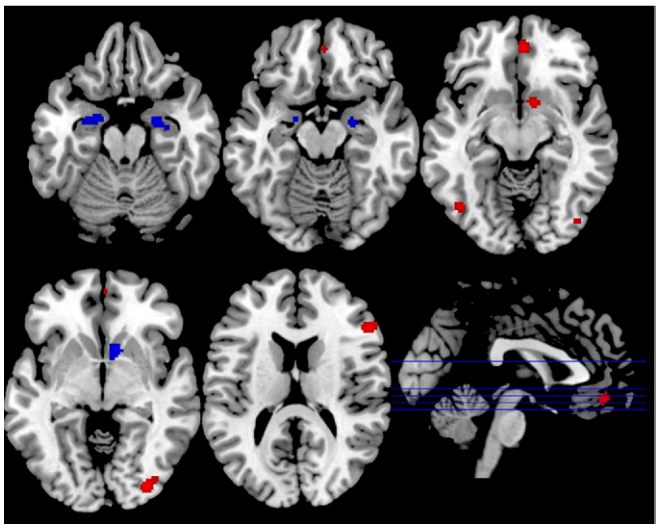

Figure 2. Figure showing the differences between the groups. Treatment seekers activated the bilateral amygdala (blue), whereas nontreatment seekers activated orbitofrontal cortex and right inferior frontal gyrus (red). The *Z* coordinates of the displayed slices are (top row, left to right) −20, −15, −10, (bottom row) −5, and 15.

Table 3. Regions of Activation Observed Using the Drug vs. Control Contrast Within the Two Subgroups

Contrast	Region	Subregions	Voxels	*X*	*Y*	*Z*
Seeking Treatment	Right Hippocampus/Amygdala	39.3% Right Amygdala (LB); 32.9% Right Amygdala (SF); 24.5% Right Hippocampus (CA)	78	25	−8	−19
Seeking Treatment	Left Amygdala	56.3% Left Amygdala (LB); 39.0% Left Amygdala (SF)	60	−22	−5	−19
Seeking Treatment	Right Ventral Striatum		70	9	12	−2
Seeking Treatment	Right Superior Occipital Gyrus		69	28	−66	46
Seeking Treatment	Left Middle Occipital Gyrus	12.9% (V5)	64	−47	−69	3
Not Seeking Treatment	Orbitofrontal Cortex		77	3	48	−10
Not Seeking Treatment	Right Inferior Frontal Gyrus	99.0% Right Area 45	76	53	29	16
Not Seeking Treatment	Right Ventral Striatum		49	10	7	−7
Not Seeking Treatment	Right Inferior Occipital Gyrus	22.2% (V3v)	87	35	−84	−4
Not Seeking Treatment	Left Inferior Occipital Gyrus		45	−43	−68	−9

Column 3 includes proportions of an activation overlapping with a given region (if the region is included in the SPM Anatomy toolbox). Only regions which account for over 10% of the location of the activation are reported in this column. SF, superficial group; LB, laterobasal group (53,130); CA, Cornu ammonis (53).

capable of integrating these pathways (106), to create an output that reflects the intensity of consequent emotional response (111). Furthermore, the structural integrity of the amygdala was found to predict abstinence-induced craving, further supporting a causal role for the region in the experience of craving (40).

It was notable that amygdala activation impinged upon the hippocampus in the treatment seekers, as there is a small but steadily increasing body of literature implicating the latter region in drug seeking. Stimulation of the ventral subiculum can prompt drug seeking in rats (112), whereas the dorsal (but not ventral) subiculum plays a significant role in the reinstatement of cocaine seeking by cocaine itself (113). Separate influences of the amygdala and hippocampus on drug seeking (114) are yet to be established in humans.

The Role of the Insula Cortex

No support was obtained for the hypothesis that the insula would show drug cue or craving related activity. Our selection criterion might in part account for this null finding: several of the studies reviewed by Naqvi and Bechara (29) (and also Wilson *et al.* [30]) employed region-of-interest analyses that were excluded from our analysis. Moreover, although many studies included in our analysis reported insula activation in either the cue or craving contrast, the exact coordinates occupied a wide range of cortex. Its size and heterogeneity might reduce the chance of mapping a reported insula activation onto a particular locus. More attention should be paid to the exact subregion of the insula activated, given the specialization of function between subregions (115). Finally, the putative moderating role of variables such as genetics and gender in determining insula activation (116) might also tend to reduce power to detect an activation in this region.

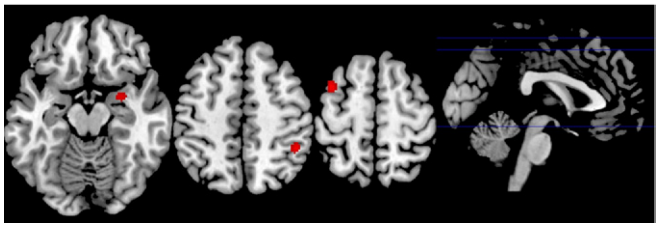

Figure 3. Figure showing right amygdala, left middle frontal, and right parietal activation that accompanies increases in craving (positive craving correlation). The *Z* coordinates of the displayed slices are −15, 50, and 60.

Additional Regions of Significant Convergence

An important advantage of employing ALE meta-analysis to analyze whole brain imaging techniques such as fMRI or PET is that it is harder to dismiss activation in regions that are not hypothesized a priori to play a role in a particular psychological process as false positives. Posterior cingulate activation observed in the drug > control contrast might reflect an evaluation of the value of drugs prompted by drug cues (117). Occipital cortex activation was reliably observed and was likely caused by the preponderance of visual presentation of drug cues in our sample. Poor matching of the visual properties of the drug and control stimuli is a possible explanation, although reward-related modulation of visual cortex seems a more plausible alternative (118,119).

The parietal region identified in the craving contrast might play a role in attention (120), suggesting that activation of this region is consistent with the recruitment of attentional processes by drug stimuli (121–123), particularly during craving (123). The reverse contrast (activations that increase with decreasing craving) leads to a small region of overlap in the postcentral gyrus (Area 3b: MNI coordinates 42, −22, 50), perhaps reflecting an unanticipated sensorimotor effect but probably not reflective of inhibitory control as predicted (124). The relatively small number of studies ($n = 8$) contributing to this contrast should lead this result to be considered tentatively.

Strengths and Limitations

The reliability of conclusions drawn from a meta-analysis is dependent on the number of studies included. The modest number of included studies limited our power to perform more detailed contrasts of different procedures, drug types, or substance user populations. This activity might generalize to other classes of drug or to nonchemical addictions (e.g., 28), but currently insufficient studies exist to examine this proposal systematically. Different drugs might vary on several dimensions, including the kind of processes that control drug seeking (habits: Dickinson *et al.* [125]; or goal directed control: Olmstead *et al.* [126]), and it is plausible that divergent activations between different subclasses of drugs will be observed.

The meta-analysis might yet be susceptible to various biases present in the literature. Indeed, certain trends in the field of addiction research, such as the focus on legal drugs like alcohol and nicotine or the heterogeneity of how the drug user population is defined, are also reflected in the current data. We attempted to minimize such effects by identifying as wide and heterogeneous a pool of studies as possible, reducing the impact of particular re-

search groups, patient groups, or methodological procedures. Spurious false positive data are likely to be poorly localized and therefore be less readily identified by our technique.

The possible presence of false negatives in the original data is also important to consider, and various methodological factors might prevent the replication of certain important effects. One crucial factor is the temporal evolution of the neural representation of the cue reactivity response. How best to design the paradigm for fMRI (e.g., whether to use a block or event-related design) and to model the hemodynamic response function remain open questions. Our meta-analysis integrates across different modeling approaches, reducing a potential bias but also power if one model should be superior. Future ALE meta-analyses might compare different design and modeling strategies. Models that make weaker assumptions about the shape of the hemodynamic response function, including Finite Impulse Response (127), and data-driven methods such as independent components analysis (128) could be of great value for further characterization of the neural response to drug cues. Properties in question will include its temporal dynamics, identification of distinct and stereotyped contributions to the activation and possible deactivations. A final caveat is that the kernel representing the probability density function of the activation location was validated for localization accuracy with fMRI but not PET experiments (38). Although it has been suggested that the accuracy of peak localization in PET (which is important in the context of meta-analytical uncertainty modeling) is comparable to that in fMRI in spite of the larger point-spread function (129), this topic certainly warrants further investigation.

Despite the challenges of integrating the current literature, we argue that our approach provides a principled basis for defining the neural underpinning of drug cue reactivity and that the neural circuit we identify will be a recurring motif in this project. That this circuitry is already a major concern of animal models of drug addiction provides persuasive evidence for the utility of translational research programs of psychiatric disorders.

Summary

With the ALE method of meta-analysis, we identified consistent drug-cue–related activation in the ventral striatum, amygdala, and OFC as well as an association between amygdala and right parietal and left middle frontal activation with drug craving. We observed cue-related amygdala activation in treatment-seeking participants and cue-related orbitofrontal activation in participants not seeking treatment but not vice versa. These findings accord with preclinical studies of cue-related drug seeking and support the proposal that treatment status might influence cue-related brain activation.

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