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NEURAL SUBSTRATES OF CUE-REACTIVITY: ASSOCIATION WITH TREATMENT OUTCOMES AND RELAPSE

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Abstract

Given the strong evidence for neurological alterations at the basis of drug dependence, functional magnetic resonance imaging (fMRI) represents an important tool in the clinical neuroscience of addiction. fMRI cue-reactivity paradigms represent an ideal platform to probe the involvement of neurobiological pathways subserving the reward/motivation system in addiction and potentially offer a translational mechanism by which interventions and behavioral predictions can be tested. Thus, this review summarizes the research that has applied fMRI cue-reactivity paradigms to the study of adult substance use disorder treatment responses. Studies utilizing fMRI cue-reactivity paradigms for the prediction of relapse, and as a means to investigate psychosocial and pharmacological treatment effects on cue-elicited brain activation are presented within four primary categories of substances: alcohol, nicotine, cocaine, and opioids. Lastly, suggestions for how to leverage fMRI technology to advance addiction science and treatment development are provided.

Keywords

addiction; cue-reactivity; fMRI; medication development; substance use disorder; treatment

Introduction

The clinical neuroscience of substance use disorders (SUDs) is predicated on knowledge gained from animal models of addiction, which suggest that dysfunction of the brain systems underling motivated, goal-directed behavior, as well as networks responsible for the inhibitory control of such behaviors, are fundamental components of the neurological alterations subserving the development of SUDs (Kalivas and Volkow, 2005). These models

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suggest that motivated, goal-directed behavior is represented in the brain by an interconnected network of areas, such as the ventral tegmental area (VTA), ventral striatum (VS), ventromedial prefrontal cortex (vmPFC), amygdala, lateral hypothalamus, and hippocampus, that rely primarily on dopamine, GABA, opioid, and glutamate signaling (Kalivas and Volkow, 2005; Kauer and Malenka, 2007; Nestler, 2005). This network is thought to be responsible for the acute rewarding effects of drugs of abuse (Berridge and Kringelbach, 2008; Le Merrer et al., 2009), the goal-directed behavior and exertion of effort in attaining these drugs (Salamone and Correa, 2012), and, after repeated drug use, the development of incentive salience to stimuli associated with these substances (Berridge and Kringelbach, 2008; Berridge and Robinson, 1998). Chronic drug use is known to alter various neurotransmitter systems and synaptic structure within these networks, leading to impairments in motivational drive and sensitized conditioned responses to drug-related cues (Kalivas and Volkow, 2005), including cue-induced craving for the substance (Berridge and Robinson, 1998; Kauer and Malenka, 2007; Wise, 1988). Furthermore, dysfunction of higher cortical areas responsible for the regulation of motivational drives, including the lateral orbitofrontal cortex (OFC), inferior frontal gyrus (IFG), dorsolateral prefrontal cortex (dlPFC), and dorsal ACC (dACC) (Bechara, 2005; Koob and Volkow, 2010), may aid in the progression to compulsive substance use in later stages of addiction potentially by synergizing deficiencies in the function of the reward/motivation system (Kalivas, 2009; Lubman et al., 2004).

Given the strong evidence for neurological alterations at the basis of drug dependence (e.g., Goldstein and Volkow, 2011; Parvaz et al., 2011; Volkow et al., 2012), functional magnetic resonance imaging (fMRI) represents an important tool in translating these preclinical insights to brain function in humans affected by addictive disorders. While there has been a focus on developing fMRI-based biomarkers for psychiatric disorders in general (Fu and Costafreda, 2013), the field of addictions has yet to identify reliable biomarkers, fMRI-based or otherwise. Importantly, diagnostic and prognostic biomarkers are only as useful as their ability to add value to existing clinical and behavioral systems. With that in mind, one promising notion is that understanding addiction neurobiology at the level of individual brain function will allow the development of more efficacious psychosocial and pharmacological interventions. In particular, it has been argued that neuropsychological and pharmacological therapies for addiction must target affected brain circuits, particularly the reward/motivation network (Konova et al., 2013). Thus, fMRI represents a promising avenue to not only enable identification of these dysfunctional neurological mechanisms underlying addiction, but also to potentially serve as an objective and quantifiable measure for evaluating changes associated with treatment beyond what can be gathered from self-report or behavior alone (Menossi et al., 2013).

Cue-reactivity is one of the longest-studied phenotypes in substance use research, and several recent meta-analyses (Chase et al., 2011; Engelmann et al., 2012; Schacht et al., 2013a) and reviews (Jasinska et al., 2014; Yalachkov et al., 2012) summarize the neuroimaging literature on this phenotype, including a variety of individual difference variables that affect it. Because addiction neurobiology, and cue-reactivity in particular, has a strong learning and memory component (Kalivas and Volkow, 2005; Robinson and Berridge, 1993), the presentation of drug cues appears to reliably produce activation of

neural circuits involved in learning and memory, as well as brain regions associated with the aforementioned reward/motivation network, such as the VS, amygdala, PFC, cingulate, precuneus, and the insula (Camara et al., 2009; Engelmann et al., 2012; Schacht et al., 2013a). In theory, greater cue-induced craving in the laboratory should predict greater risk for relapse when similar cues are faced in the natural environment and, in turn, a therapy's ability to blunt cue-induced craving in the laboratory should be a proxy marker of that treatment's real world efficacy (Drummond, 2000; Marlatt, 1990; Monti et al., 2000). These ideas are consistent with the notion of craving as a translational phenotype in addiction, which is exemplified by the recent addition of craving as a symptom in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (Hasin et al., 2013). However, there is limited experimental support for either hypothesis, which is potentially driven by the conceptual limitations of measuring self-reported craving (Drummond et al., 2000; Perkins, 2009). Thus, fMRI based cue-reactivity paradigms are well positioned to advance our understanding of the involvement of neurobiological pathways subserving the reward/motivation system in addiction and offer a translational platform by which interventions and behavioral predictions can be tested.

This review focuses on research that has applied fMRI cue-reactivity paradigms to the study of adult SUD treatment responses. Based on the conceptual framework that has evolved over the last two decades, pharmacological and psychosocial treatments are hypothesized to influence brain activation within the reward/motivation and inhibitory networks (via bottom-up and/or top-down control over these regions), which in turn, is thought to predict treatment success and relapse propensity. As such, research utilizing fMRI cue-reactivity paradigms for the prediction of relapse is reviewed, and psychosocial and pharmacological treatment effects on cue-elicited brain activation are presented within four primary categories of substances: alcohol, nicotine, cocaine, and opioids. Lastly, future directions for how to leverage fMRI technology to advance addiction science and treatment development are proposed.

Prediction of Relapse from Cue-Elicited Activation

To date, eleven studies have examined prospective associations between brain activation and relapse among individuals dependent on alcohol, nicotine, and cocaine; nine of which employed drug cue reactivity paradigms (see Table 1). However, several issues cloud interpretation of these findings and hinder efforts to synthesize this literature. First, quantifications of relapse have varied widely across studies. In general, breath tests for exhaled carbon monoxide and urine drug screens conducted with varying frequency have been used to define nicotine and cocaine relapse, while alcohol relapse is frequently captured only by patient self-report; however, a recent study in non-treatment seeking alcohol drinkers suggests self-report data is highly consistent with biomarkers of alcohol intake (Simons et al., 2015). Second, most studies have implicitly endorsed an abstinence-based treatment model, defining relapse as any subsequent substance use; re-initiation of heavy use has not been well studied. Third, many studies have compared baseline neuroimaging data between dichotomized groups of patients who either relapsed to any use or remained abstinent; fewer have used regression-based models to predict the magnitude of

subsequent substance use. Nonetheless, data suggest several promising associations between cue-elicited brain activation and relapse that warrant careful consideration.

Alcohol

Grüsser and colleagues (2004) were the first to report an association between cue-elicited activation and relapse. Among a sample of detoxified, abstinent, alcohol dependent inpatients, the authors found that greater visual alcohol cue-elicited activation of the dorsomedial prefrontal cortex (dmPFC) predicted patients' total drinking following discharge. Interestingly, adding patients' subjective craving at the time of the scan to this predictive model only marginally increased the explained variance in drinking. Further, the patients who relapsed relative to the patients who maintained abstinence demonstrated greater cue-elicited activation of the right anterior cingulate cortex (ACC), dorsal striatum (DS), and thalamus.

A follow-up study from the same authors replicated the positive association between relapse and alcohol cue-elicited dmPFC activation using the same definition of relapse in a larger sample of detoxified, abstinent, alcohol-dependent inpatients (Beck et al., 2012). However, the relapsing patients, relative to the abstainers, also demonstrated *less* cue-elicited activation of two reward-related areas: right VTA and bilateral VS. This unexpected result may have derived from the authors' use of the "biological parametric mapping" technique to account for marked atrophy of a wide variety of cortical midline structures, including dmPFC, ACC, OFC, VS, amygdala, and VTA, among the relapsing patients. However, despite other findings that relapsers display structural abnormalities relative to abstainers (Cardenas et al., 2011; Durazzo et al., 2011), few other studies have considered the influence of structural atrophy on prediction of relapse from functional data.

The association between cue-elicited activation and relapse has also been examined among patients with alcohol use disorders (AUDs) who have already begun treatment. Greater visual alcohol cue-elicited activation of the left dlPFC midway through a six-week outpatient randomized clinical trial of gabapentin (described further below) predicted a greater proportion of heavy drinking days in the subsequent three weeks, irrespective of medication group (Schacht et al., 2013b). This region was lateral to the dmPFC region identified in the aforementioned studies (Beck et al., 2012; Grüsser et al., 2004). Notably, the authors defined relapse continuously, rather than categorically, and speculated that the different regional association might suggest that different brain areas are associated with relapse propensity depending on whether cue-elicited activation is measured before, during, or after treatment.

Seo and colleagues (2013) examined the relationship between brain activation in response to tailored auditory alcohol cue, stress, and neutral imagery scripts during treatment and relapse to drinking. During the fifth week of a six-week residential inpatient treatment program, imagery scripts were administered during fMRI scanning to abstinent, alcohol-dependent inpatients, who were then followed for 90 days after discharge. Although activation elicited by the alcohol cue scripts did not predict relapse during the follow-up period, greater bilateral VS, vmPFC, and precuneus activation during the neutral scripts, which were associated with stress-induced alcohol craving during the experiment, strongly

predicted time to first drink and time to first heavy drinking day. Hyperactivity in these regions during the neutral scripts increased the risk of relapse to heavy drinking by six (VS) to 14 (precuneus) times, indicating the importance of stress, independent of alcohol cue-reactivity, to relapse propensity.

Two recent reports from the Central Institute of Mental Health in Mannheim, Germany (Bach et al., 2015; Jorde et al., 2014) have investigated the moderating roles of the mu opioid receptor (OPRM1) and atrial natriuretic peptide transcription factor (GATA4) genetic polymorphisms on relapse propensity as predicted by neural markers of cue-reactivity. Both studies employed a visual alcohol cues task in a sample of recently abstinent alcohol dependent inpatients. In the Bach et al., (2015) study, greater cue-elicited DS activation was associated with shorter time to relapse, however no effect of OPRM1 genotype was observed. The Jorde et al. (2014) study reported an interaction between the GATA4 genotype and cue-elicited amygdala activation on relapse propensity, such that greater bilateral amygdala activation was associated with lower risk of relapse in AA homozygotes, yet no such association for G-allele carriers was found.

Lastly, a recent study by Reinhard and colleagues (2015) tested the predictive utility of multiple data aggregation techniques for region of interest (ROI) analyses using visual cue-reactivity data acquired from a recently abstinent alcohol dependent sample. After the initial cue-reactivity data was acquired, the participants of this study were assessed on their alcohol use biweekly for 80 days. Greater cue-elicited activation of the VS, OFC, and the ACC predicted shorter time to relapse at the whole-brain exploratory level of analyses ($p < .005$ uncorrected for multiple comparisons, cluster size ≥10 voxels). However, only cue-elicited VS ROI activation was found to significantly predict relapse when various aggregation techniques were utilized.

Nicotine

Cue-elicited activation of reward- and cognitive-control-related regions may also predict smoking cessation outcomes among nicotine-dependent individuals. The earliest study of this phenomenon reported a relationship between attenuated smoking cue-elicited VS and thalamic activation prior to quitting and better abstinence rates one month after quitting, in a sample of treatment-seeking smokers (described below; McClernon et al., 2007). Subsequently, Janes and colleagues (2010) administered a visual smoking cue-reactivity task to abstinent, nicotine-dependent women before they began an outpatient smoking cessation trial, during which they received weekly cognitive behavioral therapy (CBT) and nicotine replacement therapy (NRT). Relapsers, compared to those who remained abstinent during the trial, displayed greater smoking cue-elicited activation in a variety of reward- and control-related regions, including bilateral insula, dlPFC, posterior cingulate cortex (PCC), parahippocampal gyrus, putamen, thalamus, and cerebellum.

Using a different kind of “cue”, Chua and colleagues (2011) reported that, among 87 treatment-seeking smokers, greater dmPFC and precuneus response to visual and audio smoking-cessation messages tailored to subjects’ individual needs and interests pre-quit was associated with better odds of quitting over a 10-week trial, even after controlling for other outcome related factors such as pre-quit smoking severity and use of NRT.

Most recently, Versace and colleagues (2014) used a cluster analysis technique to identify two groups of smokers that differed in pre-quit levels of BOLD smoking cue-reactivity in regions such as the precuneus, DS, vmPFC, and dlPFC: a “low reward sensitivity” group (n=24) which exhibited greater smoking cue, relative to pleasant stimuli responses, and a “high reward sensitivity” group (n=31) which exhibited greater responses to pleasant stimuli, relative to smoking cues. The low reward sensitivity group was found to be more likely to relapse during the trial as compared to the high reward sensitivity group, further supporting cue-reactivity of reward- and control-related regions as potentially useful predictors of relapse.

Cocaine

Consistent with the conclusions of Seo and colleagues’ (2013) alcohol study, stress-elicited brain activation has also been reported to predict cocaine relapse. The same authors also tested stress imagery scripts among abstinent, cocaine-dependent inpatients, and found that increased vmPFC activation during stress, relative to neutral, imagery was associated with a shorter time to first cocaine use and a greater likelihood of cocaine use during follow-up (Sinha and Li, 2007). Further, greater stress-elicited activation of the posterior insula predicted a greater likelihood of subsequent cocaine use, and greater activation of the PCC predicted larger amounts of self-reported cocaine use per subsequent occasion of use.

Cocaine cue-elicited activation was not directly tested in the Sinha and colleagues (2007) study, however, cue-elicited activation has been reported to prospectively predict cocaine relapse in two other studies. Kosten and colleagues (2006) were the first to report such an association. Abstinent, cocaine-dependent inpatients were exposed to video cocaine cues during fMRI scanning while enrolled in a two-week inpatient treatment program, and then entered a 10-week outpatient randomized, placebo-controlled trial of the selective serotonin reuptake inhibitor sertraline. All patients received weekly CBT during the outpatient period, and submitted to urine toxicology screening three times per week. Those who relapsed to any cocaine use during the outpatient period, relative to those who remained abstinent, demonstrated greater cocaine cue-elicited activation of the PCC and right precentral gyrus.

Cocaine cue-elicited activation has also been associated with relapse to cocaine use over a much briefer interval (described further below; Prisciandaro et al., 2013a). Abstinent cocaine-dependent patients were administered a visual cocaine cue-reactivity task before they began a one-week randomized, placebo-controlled trial of *D*-cycloserine and cue-exposure therapy. Controlling for treatment effects, those who relapsed to cocaine use, relative to those who maintained abstinence, displayed greater cue-elicited activation of bilateral primary visual cortex, right insula, and right DS.

Opioids

To date, no neuroimaging studies of opioid relapse propensity have been conducted. In fact, very few studies have investigated neural factors associated with opioid dependence treatment outcomes in general. As with other drugs of abuse, opioid-related visual cues elicit significant BOLD activation among opioid dependent individuals, which in turn could potentially serve as a marker of relapse propensity. For example, in a study of 14 male

opioid dependent patients on stable methadone maintenance therapy, heroin-related visual cues, relative to neutral cues, elicited greater activation in a wide variety of areas, including the dlPFC, ACC, PCC/precuneus, mesocorticolimbic regions (e.g., bilateral medial thalamus, pons, caudate), and visuospatial-attention regions (e.g., fusiform, middle occipital gyrus, right superior parietal lobule, and left inferior occipital gyrus) (Wang et al., 2011b). Furthermore, recent results suggest this cue salience endures even following opioid administration in opioid-maintained individuals. Specifically, greater heroin cue-related activation of an *a priori* region of interest (ROI), the OFC, and reduced craving were observed following administration of heroin, as compared to placebo, among 27 heroin dependent patients maintained on heroin in a within-subject, crossover design (Walter et al., 2014). The relationship between drug cue-reactivity and relapse and treatment-related outcomes in opioid addiction, however, remains unknown and represents an important gap in the clinical neuroscience literature.

Summary of Relapse Prediction

Despite differences in methodologies, cue-elicited activation of the dorsal PFC was positively associated with relapse propensity in five of the 14 studies reported above. Interestingly, while several psychosocial intervention studies have also reported treatment-related reductions in cue-elicited dorsal PFC activation (see below), relatively few pharmacological intervention studies have identified this area as a key region of treatment-induced change, possibly highlighting a difference in neurobiological pathways by which pharmacologic interventions may be operating (e.g., via bottom-up processes; Konova et al., 2013). Cue-elicited activation of the thalamus was also positively associated with relapse in three of four smoking studies, yet only one of four alcohol studies, suggesting discrepancies in the predictive validity of regional activation across substances of abuse. At this point, one critical limitation of this literature is the lack of a specific region that reliably predicts relapse. Some have argued that neuroimaging research suffers from a bias in which scientists often report the one region that is significant while ignoring other regions, leading to little consistency across studies and a high probability of Type I error (Radua and Mataix-Cols, 2012). While it is too early to make this assertion for the relapse prediction literature, it would be reassuring to see a common region (e.g., dorsal PFC) continue to emerge in the majority of studies.

The relapse literature as a whole, however, is encouraging and advances neuroimaging cue-reactivity tasks as a potentially valuable tool for translating neuroscience into clinically meaningful behavioral predictions. An important next step will be to determine whether this relatively expensive and complex method outperforms less costly and easily accessible behavioral markers (e.g., past substance use, severity at baseline) in its ability to predict both treatment response and subsequent relapse. Notably, recent data suggest that behavioral and personality assessments outperform neuroimaging in terms of predicting future substance use (Whelan et al., 2014). However, cue-reactivity studies that incorporate a pharmacological challenge, thereby perturbing a specific biological mechanism related to relapse, may have a greater probability of accurately predicting future use (i.e., relapse) in the context of treatment studies.

Pharmacological Treatment Effects on Neural Substrates of Cue Reactivity

Significant resources have been devoted to evaluating whether pharmacological treatments for adult SUDs affect brain activation elicited by cue-reactivity paradigms. Table 2 presents a detailed list of these studies separated by substance of abuse. The majority of these pharmacologic agents have demonstrated efficacy to some degree in behavioral and clinical trials; however their mechanisms of action remain largely unknown.

Alcohol

Of the potential medications for AUDs studied using fMRI tasks, naltrexone, a competitive opioid receptor antagonist, has received the most attention. An earlier study by Myrick et al. (2008) tested the effect of naltrexone, ondansetron, their combination, or matched placebo on alcohol cue-reactivity in the scanner. All three active drug conditions revealed reductions in region-specific activation as compared to placebo, with the naltrexone alone condition exhibiting attenuation of primarily fronto-straital activation in response to alcohol cues. Visual and olfactory alcohol cue-reactivity was also attenuated by extended-release naltrexone treatment (Lukas et al., 2013), yet the affected regions implicated by this study (e.g., angular gyrus, superior frontal gyrus [SFG], cingulate gyrus) exhibited very little overlap with the results from the Myrick et al. (2008) study. Another more recent investigation of naltrexone led by one of the current authors (Schacht et al., 2013c) also failed to replicate the results of the Myrick (2008) study; however, Schacht and colleagues (2013c) observed a moderating role of the genetic polymorphisms of the OPRM1 gene and the dopamine transporter gene (DAT1/SLC6A3) on the effects of naltrexone on neural processing of alcohol cues. These findings, suggest that pharmacogenetic effects observed at the clinical and behavioral levels (Ray et al., 2012) may also be detected using cue-reactivity fMRI paradigms and further highlight the complexity of naltrexone's effect on neural processing of alcohol cues.

A recent study by Mann et al. (2014) extended the results of these previous studies by utilizing an alcohol fMRI cue-reactivity paradigm to predict the treatment efficacy of naltrexone and acamprosate for reducing relapse rates. Specifically, recently abstinent alcohol dependent patients were scanned on the cue-reactivity task at baseline, randomized to naltrexone or acamprosate treatment, and assessed biweekly for alcohol use during the 84-day treatment period. The authors observed an effect for the naltrexone group, such that patients with high baseline cue-elicited VS activation had better outcomes on naltrexone as compared to those with low cue-elicited VS activation. No associations between baseline level of VS cue-reactivity and time to relapse were observed in the acamprosate group. The null finding for acamprosate is consistent with a previous null report of acamprosate on neural markers of alcohol cue-reactivity in psychiatric inpatients with alcohol dependence (Langosch et al., 2012). These two studies suggest that acamprosate, an approved medication for AUD with potential glutamatergic inhibitory action (Littleton and Zieglgänsberger, 2003), may be affecting alcohol use through mechanisms independent of cue-reactivity.

A number of experimental drugs have also been tested for modulatory effects on neural markers of cue-reactivity. For example, aripiprazole, an atypical dopamine D2 partial

agonist, was associated with the attenuation of striatal response to alcohol cues in alcohol dependent patients (Myrick et al., 2010), yet when combined with escitalopram in patients with comorbid major depressive disorder and alcohol dependence, adjunctive aripiprazole was associated with increased activation of the ACC (Han et al., 2013). Further, treatment with amisulpride, an atypical dopamine D(2/3) antagonist, was associated with decreased visual alcohol cue-elicited activation of the right thalamus (Hermann et al., 2006).

Preclinical studies have suggested that the *N*-methyl-*D*-aspartate (NMDA) receptor partial agonist *D*-cycloserine (DCS) may facilitate extinction of conditioned responses through enhancement of glutamate-dependent synaptic plasticity (Myers and Carlezon, 2012). This effect has shown particular promise in the treatment of fear conditioning in anxiety disorders. However, clinical trials of DCS in addiction have been at best negative, with some suggestion that DCS may actually potentiate cue-elicited craving (Olive et al., 2012). Nonetheless, DCS was recently tested in a sample of alcohol dependent patients who were pre-selected for the presence of alcohol cue-elicited VS activation at baseline (Kiefer et al., 2015). In this study, all patients underwent an alcohol cue-reactivity paradigm at baseline then again 3-weeks after the start of a cue-exposure treatment (CET). Patients who received DCS prior to CET training sessions exhibited decreased alcohol cue-elicited activation of the VS and DS post-treatment, as compared to those who received placebo; however, no differences in relapse rates were observed between the medication groups during the 90-day follow-up period.

A preliminary study of varenicline, an α4β2 nicotinic acetylcholine receptor (nAChR) partial agonist with potential effects on striatal dopaminergic functioning (Feduccia et al., 2014), among non-treatment-seeking alcoholics demonstrated reduced cue-elicited activation of bilateral OFC, but did not affect cue-elicited activation of the VS or medial PFC (Schacht et al., 2014). In contrast, no support for the efficacy of varenicline (either alone or in combination with naltrexone) with regards to its effects on neural processing of alcohol taste cues was found in our own preliminary work testing varenicline, naltrexone, and their combination in a sample of non-treatment seeking heavy-drinking smokers (Courtney et al., 2013). These null results were observed despite evidence for the efficacy of varenicline (alone and in combination with naltrexone) for attenuation of neural cue-reactivity to cigarette cues relative to placebo (Ray et al., 2014b).

The combination treatment of two GABAergic medications with potential clinical efficacy for alcohol withdrawal, gabapentin and flumazenil (Leggio et al., 2008; Myrick et al., 2009), was associated with increased dorsal ACC alcohol cue-elicited activation among subjects with higher pre-treatment alcohol withdrawal, and dorsal ACC activation was associated with greater resistance to craving. The authors suggest that these findings indicate differences in task-related deactivation, which was associated with greater control over alcohol-related thoughts (Schacht et al., 2013b).

Nicotine

Given the popularity of NRT for the treatment of nicotine dependence, it is not surprising that multiple smoking cue-reactivity studies have included the administration of NRTs. The first such study reported reduced smoking cue-elicited amygdala activation following a

combination of NRT and reduced-nicotine-content cigarettes (also described below; McClernon et al., 2007); and a second study observed widespread increases and hippocampal decreases in BOLD response to smoking cues following long-term NRT (tapered down over time) and abstinence (Janes et al., 2009); however, the independent effects of NRT on fMRI markers of cue-reactivity in these studies are unclear. Acute NRT administration following overnight abstinence was associated with greater smoking cue-elicited striatal and amygdalar activation in a sample of non-treatment seeking smokers (Xu et al., 2014); yet, discrepancies in treatment seeking status and duration of abstinence complicate the integration of these NRT results with those previously described.

Bupropion and varenicline have also been investigated within neuroimaging cue-reactivity protocols due to their demonstrated clinical efficacy on smoking cessation (e.g., Garrison and Dugan, 2009; McCarthy et al., 2008). Bupropion, an antagonist at a subset of nicotinic acetylcholine receptors and weak dopamine and norepinephrine reuptake inhibitor, was associated with reductions of smoking cue-elicited VS and medial OFC activity in treatment-seeking smokers (among other regions; Culbertson et al., 2011). Varenicline treatment was also associated with reductions of cue-elicited activation in the VS and medial OFC in non-treatment seeking smokers (Franklin et al., 2011) and reductions in VS activation in non-treatment seeking heavy-drinking smokers (Ray et al., 2014b). Interestingly, the combination of varenicline and naltrexone treatment in heavy-drinking smokers demonstrated additional regional reductions (i.e., SFG, ACC) in smoking-cue reactivity that were not observed in groups treated with varenicline or naltrexone monotherapies (Ray et al., 2014b), suggesting that the combination of varenicline and naltrexone may be effective for attenuating additional brain mechanisms of smoking cue-reactivity in this subsample of smokers (Ray et al., 2014a, b). Furthermore, these three aforementioned studies reported reductions in self-reported craving associated with the medication effects in their samples, highlighting potential neural mechanisms of action for these clinically effective smoking cessation agents.

Cocaine

Likely driven by the lack of FDA-approved medications for stimulant use disorders, a diverse set of pharmacological agents have been investigated using functional cue-reactivity paradigms in cocaine dependent populations. Little consilience is observed across these studies however, including only slight overlap of regional changes and differences in the direction of medication-induced effects. For example, baclofen, a GABA-B receptor agonist thought to reduce mesolimbic dopamine release, was observed to reduce BOLD activation in response to subliminal cocaine cues in a number of frontal, striatal, and midbrain regions in patients with cocaine dependence (Young et al., 2014). In contrast, guanfacine, an α2 receptor agonist, was associated with greater cocaine imagery activation in a number of areas including prefrontal and limbic regions (Fox et al., 2012), and modafinil, an analeptic drug that is thought to interact with dopamine transporters resulting in stimulatory effects (Zolkowska et al., 2009), was associated with increases in activation of the ACC and VTA in response to cocaine-cues (Goudriaan et al., 2013). Both the latter two studies reported medication-related reductions in self-reported craving (Fox et al., 2012; Goudriaan et al., 2013), whereas there is little support for the effect of baclofen on reducing cocaine craving

(e.g., Kahn et al., 2009; Shoptaw et al., 2003), highlighting potential disparate mechanisms of action of these medications; however, much more research is needed in this area before strong conclusions can be made.

Opioids

Most fMRI studies of opioid dependence are conducted on samples of patients maintained on substitution therapies, namely methadone or buprenorphine. The independent effect of these pharmacologic agents on drug-cue reactivity remains largely unstudied. This greatly limits inferences that can be drawn regarding how these medications may alter neural processing subserving any medication-related treatment outcomes, and as a result, the studies reported below are not included in Table 2.

In effort to investigate the effect of methadone on heroin cue-reactivity, heroin dependent patients (n = 25) were administered an fMRI visual heroin-related cue reactivity task twice (3-4 weeks apart), once approximately 90 minutes before scheduled methadone dosing (pre-dose), and once 90 minutes after the dosing (post-dose). Results revealed reductions in heroin-related cue reactivity in the insula, amygdala, and hippocampus at the post-dose (versus pre-dose) scan (Langleben et al., 2008). Similar results were obtained when contrasting cue-reactivity immediately after receiving buprenorphine (5-45 min following dose) versus cue-reactivity at approximate buprenorphine peak levels (60-105 min following dose) in a separate within-subject, cross-over study of heroin dependent patients (n = 12). Specifically, reductions in heroin-related cue activation were observed in regions including the left VTA, thalamus, middle temporal gyrus, right amygdala, hippocampus, precentral gyrus, and postcentral gyrus immediately following the dose as compared to activation at peak levels (Mei et al., 2010). However, activation of certain regions may be stable across pharmacologic manipulations (e.g., OFC and ventral ACC; Langleben et al., 2008), suggesting that learned drug-cue responsivity may persist in relevant regions despite long-term substitution therapy.

Summary of Pharmacologic Interventions

The summary and interpretation of results across pharmacologic intervention studies is, at best, tentative due to the wide range of molecular targets and methodological differences across studies. For example, variations in dosing, timing of scans, ROIs investigated, and sample demographics significantly add to the complexity of integrating across study findings. Furthermore, many of the studies to date involved small samples sizes and were likely underpowered. Even still, the lack of consilience across pharmacological studies is surprising and suggests that the utility of fMRI cue-reactivity studies of pharmacologic treatments should be given greater consideration. The effects of bupropion and varenicline on VS and OFC smoking cue-elicited activation show the most consistency across studies, yet only three studies have tested these medications using fMRI smoking cue-reactivity paradigms so far and it remains unknown if these effects will persist with repeated testing.

What can be concluded with certainty, however, is that functional cue-reactivity paradigms are capable of detecting alterations in BOLD signal induced by pharmacologic interventions. Despite this, the selection of fMRI paradigms should be in alignment with the purported

mechanisms affected by the medication, as not all pharmacological interventions will target cue-reactivity pathways to the same degree. The field is now challenged to effectively capitalize on this observation by establishing consistent methodological practices within medications to enhance the reliability and interpretability of medication-related BOLD results. The use of perfusion sequences such as arterial spin labeling (ASL) could prove fruitful in this endeavor as alterations in cue-elicited BOLD signal may be confounded by medication-induced changes in baseline cerebral blood flow (CBF). Quantification of medication-related CBF alterations is particularly important for investigations of chronic medication administration, and would add confidence to the interpretation of medication-induced BOLD changes as reflecting underlying pharmacological alterations in brain processing (Wang et al., 2011a). Lastly, cue-reactivity protocols that enable associations between pharmacologic results and clinically meaningful behavioral outcomes, such as relapse propensity, are much better positioned to identify the neurobiological pathways by which these medications operate to change substance use behavior.

Psychosocial Treatment Effects on Neural Substrates of Cue Reactivity

As compared to pharmacological treatments, fMRI cue-reactivity paradigms have been less frequently applied to the study of psychosocial interventions for SUDs. However, as outlined in Table 3, at least eight studies have examined psychosocial treatment effects on cue reactivity, either alone or in combination with pharmacological intervention. Most of these studies have focused on small samples of alcohol- and nicotine-dependent individuals, and have evaluated the effects of relatively brief treatments. Despite the increased statistical power they offer, pre-/post-treatment designs have not been widely used, nor have placebo treatments (e.g., waitlist controls or supportive psychotherapy) been employed as a statistical control. Perhaps due to these issues, there is little consistency in results to date.

Alcohol

The first published study of treatment effects on alcohol cue-elicited activation demonstrated some of the methodological issues inherent to this line of research. Among treatment-seeking alcohol dependent patients, Schneider and colleagues (2001) tested the effects of three weeks of CBT combined with the tricyclic antidepressant doxepin on olfactory alcohol cue-elicited activation. Before treatment, patients demonstrated cue-elicited activation of the right amygdala and left cerebellum that was not present in a group of matched controls. After treatment, activation of these regions was not present in either group. However, the difference between time points was not statistically tested; further, it was not possible to disentangle the effects of CBT and doxepin, nor those of time, as no placebo was used to control either the psychosocial or pharmacological intervention.

The Schneider study essentially tested the effects of treatment-as-usual (TAU) on cue-elicited activation, but recent studies have made more theoretically driven attempts to modulate this phenomenon. Vollstädt-Klein and colleagues (2011) examined the effects of cue-exposure therapy (CET) in abstinent, AUD patients engaged in an inpatient treatment program. Patients were randomly assigned to TAU or to CET, consisting of both real exposure to alcoholic beverages and imaginal exposure to situations involving cues judged

likely to precipitate relapse. Relative to baseline, patients who received CET, compared to those who received TAU, demonstrated reduced visual cue-elicited activation in the left insula, VS, DS, and bilateral ventral ACC, inferior parietal lobule (IPL), and dorsal PFC. These results are consistent with the Kiefer et al. (2015) study which demonstrated CET-related cue-reactivity reductions the bilateral insula, VS, DS, thalamus, hippocampus, IFG, MFG, and ACC. Although CET has not historically demonstrated strong effects on actual substance use (Conklin and Tiffany, 2002), this study suggested that it may ameliorate some of the neural substrates of conditioned cue-reactivity.

Motivation to change has also been investigated as a potential modulator of the neural substrates of cue-reactivity. Feldstein Ewing and colleagues (2011) conducted motivational interviewing (MI) therapy sessions with treatment-seeking alcohol dependent patients, and made audio recordings of patients' responses to open-ended questioning intended to elicit ambivalence about their current drinking and intentions to change their behavior. Subsequently, these recordings were divided into instances of "change talk", or statements supporting behavioral change, and "counterchange talk", or statements supporting the status quo. Each patient's statements were transcribed and presented by sight and sound in the scanner immediately before alcohol-related or neutral taste cues (the taste cue paradigm reported by Filbey et al., 2008). Relative to counterchange talk, cue-elicited activation during change talk was reduced throughout the brain, with local maxima in dorsal PFC and left IPL. There were no areas in which change talk engendered greater cue-elicited activation than counterchange talk, suggesting a widespread, nonspecific effect.

Lastly, cognitive bias modification (CBM) training was tested for neural cue-reactivity effects within a sample of abstinent alcohol dependent individuals (Wiers et al., 2015). In this study, participants underwent a visual alcohol cue-reactivity scan before and after 6 sessions of CBM training or a sham intervention. Cognitive bias modification training was found to reduce alcohol cue-elicited activation of the amygdala relative to baseline activation and to the sham intervention in an ROI analysis. Further, the post-intervention decrease in right amygdala activation was found to correlate with a decrease in self-reported craving in the CBM group, but not in the sham group, advancing the amygdala as a potentially important region linking cue-reactivity and subjective craving.

Nicotine

CET has also garnered attention in the smoking literature, and one study has investigated the effects of this approach on the neural substrates of smoking cue-reactivity. McClernon and colleagues (2007) explored the effects of an extinction-based smoking cessation program, in which treatment-seeking, nicotine-dependent smokers switched to reduced nicotine cigarettes for two to four weeks while wearing a transdermal nicotine patch, before ultimately attempting to quit. Because the patch maintained a steady blood level of nicotine, patients did not experience nicotine withdrawal when they switched to the reduced nicotine cigarettes, but their nicotine intake was no longer contingent on smoking behavior or cues. Relative to baseline, visual nicotine cue-elicited activation was reduced bilaterally in the amygdala after treatment, although this activation rebounded somewhat after the quit

attempt; other ROIs (ACC, PFC, hippocampus, striatum, thalamus, and insula) did not display treatment-related reductions in activation.

The effects of at least two novel psychosocial interventions on smoking cue-reactivity have also been investigated. One study explored the acute effects of cardiovascular exercise on smoking cue-elicited activation (Janse Van Rensburg et al., 2012). In a randomized crossover design, abstinent, non-treatment-seeking smokers engaged in 10 minutes of moderate-intensity stationary cycling and rested passively for the same duration, and were administered a visual smoking cue-reactivity task after each treatment. Cue-elicited activation of primary and secondary visual cortex was present in the resting control group, but was not significant in the exercise group. However, activation differences between treatments were not significant, and concerns about changes in blood oxygenation and brain perfusion after acute exercise limit the interpretability of these findings.

A more promising novel non-pharmacological intervention to attenuate neural cue-reactivity may be real-time neurofeedback. When instructed to resist craving during exposure to nicotine cues, relative to allowing themselves to crave, smokers have been reported to display greater activation of left dorsal ACC, dmPFC, precuneus, and PCC (Brody et al., 2007a). Building upon this finding, Li and colleagues (Li et al., 2013) administered a visual smoking cue-reactivity task to abstinent, non-treatment-seeking smokers, and instructed them to either allow themselves to crave a cigarette or to resist the urge to smoke when they saw smoking-related pictures. ROIs that demonstrated greater cue-elicited activation for either of these conditions were then individually generated; for each subject, the “crave” ROI was centered near the ventral ACC, and the “resist” ROI near the right dmPFC. A thermometer icon was then used to “feed back” the magnitude of cue-elicited activation from each ROI to subjects, who were instructed to try to either decrease (for the “crave” ROI) or increase (for the “resist” ROI) the values displayed on the thermometer. Subjects were not able to control dmPFC, but were able to reduce ventral ACC activation; further, there was a strong positive correlation between cue-elicited ventral ACC activation and subjective craving. Importantly, greater activation of ventral ACC during craving (and volitional reduction of this activation) (Li et al., 2013) and greater activation of dorsal ACC during resistance to craving (Brody et al., 2007a) are consistent with the theory that ACC consists of “affective” (ventral) and “cognitive” (dorsal) subdivisions that are related to different aspects of motivated behavior (Bush et al., 2000). Real-time neurofeedback from this region may thus represent an innovative treatment strategy for substance use disorders.

Cocaine

To extend research on the effects of CET and extinction interventions on alcohol and smoking cue-elicited brain activation, pharmacological potentiation of CET among individuals with cocaine dependence has also been explored. Prisciandaro and colleagues (2013b) tested the effects of two sessions of CET, paired with either DCS or placebo, among treatment-seeking individuals with cocaine dependence. Relative to baseline, CET reduced visual cocaine cue-elicited activation in a variety of reward-related areas, including bilateral VS and OFC, right insula and IFG, and left ventral ACC. However, these effects could represent habituation to the cue paradigm, as the psychosocial treatment was not controlled

with a waitlist or other inactive treatment. Further, as compared to placebo, DCS was associated with *enhanced* cue-elicited activation of occipital areas (angular and middle temporal gyri and lateral occipital cortex), suggesting that DCS administration prior to cue exposure might prevent extinction of cocaine cue-reactivity.

Despite this negative result, a sub-analysis from the aforementioned study (Prisciandaro et al., 2014) revealed another potential psychosocial mechanism for modulation of cue-elicited brain activation: motivation to change. Pre-treatment scans from some of the treatment-seeking patients were compared to scans from a demographically matched sample of cocaine dependent, non-treatment-seeking individuals. Non-treatment-seeking subjects displayed greater cocaine cue-elicited activation of bilateral dlPFC, left OFC and occipital cortex, and right PCC. Consistent with a prior review of functional neuroimaging studies of cue-reactivity, cue-elicited dlPFC and OFC activation were present almost exclusively among non-treatment-seeking subjects (Wilson et al., 2004), suggesting that cue-elicited activation of these areas might be moderated by individuals' perception of the opportunity to use a substance. Interestingly, Prisciandaro and colleagues (2014) also reported effects of motivation to change as a function of scores on the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES; Miller and Tonigan, 1996). Different stages of change were associated with differential cue-elicited activation of a wide variety of largely non-overlapping areas. Lower scores on the Recognition scale were associated with greater activation of occipital and temporal areas; lower scores on the Ambivalence scale were associated with greater activation of left hippocampus and dorsal PFC and right occipital cortex; and lower scores on the Taking Steps scale were associated with greater activation of right OFC and paracingulate gyrus. Thus, treatment seeking and greater motivation to change were broadly associated with reduced cocaine cue-elicited brain activation, and could reflect greater resistance to craving, as described by Brody and colleagues (2007a) .

Summary of Psychosocial Interventions

The literature on psychosocial SUD intervention effects on neuroimaging measures is in its infancy, but to date, there is little consistency in findings. Across studies, the most commonly observed effects have been treatment-induced reductions of cue-elicited activation of the dorsal PFC and amygdala. The somewhat reliable involvement of the dorsal PFC in both psychosocial and relapse prediction studies is promising, and may reflect enhanced frontal regulation of salience attribution during cue processing (Goldstein and Volkow, 2011; Hare et al., 2009). The amygdala has been previously identified as having a critical role in stimulus-reward learning (Baxter and Murray, 2002; Everitt et al., 1999). With its functional connections to the prefrontal cortex (Baxter and Murray, 2002; Stamatakis et al., 2014), the PFC-amygdala circuit may prove to be an important component of psychosocial treatment effects on drug cue-reactivity; however, much more research is needed to conclude this with certainty. Interestingly, only the two studies involving CET interventions reported reduced cue-elicited activation of other reward-related areas, such as the VS and insula, possibly highlighting disparate pathways by which different types of psychosocial interventions may be operating. Taken together, these results hint at potential neurobiological mechanisms by which psychosocial interventions might affect behavior, but significant work in delineating the precise substrates of these mechanisms is still needed.

Future Directions

This manuscript reviewed the utility of fMRI cue-reactivity paradigms on the evaluation of treatment effects and relapse prediction among adults with SUDs. Prediction of treatment response is the ultimate goal of the personalized medicine approach to SUDs, which aims to use patient-level characteristics to inform the selection of treatments from which they are most likely to benefit. Overall, little consilience exists in the literature reviewed. Extant data hints at the involvement of brain areas associated with the regulation of motivated behavior and reward in both relapse and successful treatment (see Table 4 for a summary of the findings), although one would expect greater convergence of findings if this network is the main point of dysfunction in the development of addiction. While neuroimaging studies hold great promise for evaluation of treatment efficacy and relapse prediction, research in this area has been limited by small sample sizes, varying study populations, limited research on other substances of abuse (e.g., marijuana, amphetamine-type stimulants), and disparate methods. Expansion to other these substances and replication of extant findings is critical for future progress.

Standardization of neuroimaging paradigms and methods would greatly facilitate the translation of findings across populations as well as promote much needed replication of findings. The cue-reactivity paradigm, which targets the reward network and has been the focus of this review, represents an opportunity for standardization. To that end, specific aspects of the paradigm, such as cue type (e.g., visual, gustatory, olfactory) and trial duration should be consistently operationalized. Likewise, study population should be carefully considered as it has been argued that treatment-seekers differ meaningfully from non-treatment seekers in laboratory-based experimental paradigms of medications development (Perkins et al., 2010). Interestingly, fMRI studies have also shown that individuals can voluntary suppress, or “resist,” the expression of cue-induced craving in the scanner (Brody et al., 2007b), which suggests that standardizing procedures, including task instructions, and crucial sample characteristic (e.g., treatment-seeking status) may be key to achieving consilience in the literature. This level of rigor will set the stage for fMRI-based studies of addiction to provide clinically useful biomarkers of medication response as well as mechanistic insights into effective pharmacotherapies.

Further, studies that seek to understand the effects of specific treatments on brain function and relapse need to be designed so that causality can be determined. For example, if the theory is that a given treatment influences a given brain network, which in turn influences relapse, it would imply that mediational analyses can be used to examine changes in brain function as the mechanism that explains the effect of the treatment on relapse. In addition, it is important to consider temporal sequence. Ideally, neuroimaging data should be collected during treatment and prior to the behavioral outcomes measures, in order to demonstrate that the effect of the treatment on brain function prospectively predicts treatment outcome. Without such a temporal sequence, it is difficult to know the direction of the effects. For instance, it is possible that a treatment could decrease substance use and this decrease could engender a decrease in neural reactivity to substance cues.

While the cue-reactivity paradigm represents an important candidate for advancing the contribution of functional neuroimaging studies to treatment development and personalized medicine, it is important to recognize that other probes of addiction vulnerability, and as a result treatment targets, should be considered. Preclinical studies have convincingly distinguished between sign and goal trackers with underlying implications for stimulus-reward learning and addiction (Flagel et al., 2011; Flagel et al., 2010), while only the first group may effectively be captured by paradigms focused on the salience of cues. Increasingly, addiction neurobiology has focused on the transition to habitualness of alcohol and drug intake (Everitt and Robbins, 2005) as well negative reinforcement and alleviation of protracted withdrawal (Koob and Le Moal, 2005). Experimental paradigms that can effectively capture these multiple facets of addiction, inside and outside of the scanner, are needed to more fully capture vulnerabilities and treatment targets beyond the scope of cues reactivity.

With these design considerations in mind, future fMRI studies can help inform medication development for substance use disorders by elucidating initial efficacy and potential mechanisms of action of both psychosocial and pharmacological interventions. In turn, this knowledge can be used to design new and more effective treatments or to identify patient groups that may be inclined to respond more favorably to one treatment versus another. In the future, neuroimaging assessments may be used to determine whether a given treatment is having the desired effect early in the treatment process, providing an early signal of success or allowing providers to change treatments if positive effects are not observed. Staging of treatments, similar to standard practices in oncology may also be reached in the context of biologically-based phenotypes offered by neuroimaging studies. In so doing, clinical neuroscience may ultimately fulfill its promise of offering significant advances in treatments for SUDs.

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Table 1

Associations between cue-elicited brain activation and relapse to substance use (as organized by substance).

First author, year	Substance	Cue type	*N*	Follow-up interval	Relapse definition	Results
Grüsser, 2004	Alcohol	VIS	10	90 days	≥ 5/3 drinks (men/women) (self-report)	• Greater dmPFC activation predicted greater subsequent total alcohol intake • Relapsers (n=5) had greater right ACC, DS, and thalamus activation than abstainers
Beck, 2012	Alcohol	VIS	46	90 days	≥ 5/3 drinks (men/women) (self-report)	• Relapsers (n=30) had greater dmPFC activation than abstainers, but less right VTA and bilateral VS activation
Schacht, 2013	Alcohol	VIS	48	24 days	% of days with ≥ 5/4 drinks (men/women) (self-report)	• Greater left dlPFC activation predicted more frequent subsequent heavy drinking
Seo, 2013	Alcohol	AUD	45	90 days	Time to first drink/first heavy drinking day (self-report)	• Active cue-elicited activation did not predict relapse • Greater bilateral VS, vmPFC, and precuneus activation during neutral scripts predicted shorter time to first drink and time to first heavy drinking day
Jorde, 2014	Alcohol	VIS	46	90 days	≥60g/48g per day (men/women) (self-report)	• Greater bilateral amygdala activation (ROI) associated with lower risk of relapse in AA homozygotes of the GATA4 genotype • No association between relapse and amygdala activation in G-allele carriers
Bach, 2015	Alcohol	VIS	46	90 days	≥60g/48g per day (men/women) (self-report)	• Greater DS activation associated with shorter time to relapse
Reinhard, 2015	Alcohol	VIS	49	80 days	≥ 5/4 drinks (men/women) (self-report, compared to biomarkers at group level)	• Greater activation of the VS (ROI) predicted relapse
McClernon, 2007	Nicotine	VIS	16	30 days	Carbon monoxide (CO) level < 9 ppm	• Greater VS and thalamic activation predicted relapse. • No associations between relapse and cue-elicited activation of other ROIs (ACC, PFC, hippocampus, striatum, insula)
Janes, 2010	Nicotine	VIS	21	56 days	≥ 1 cigarette (self-report)	• Relapsers (n=9) had greater bilateral insula, dlPFC, posterior cingulate, parahippocampal gyrus, putamen, thalamus, and cerebellum activation than abstainers
Versace, 2014	Nicotine	VIS	55	180 days	CO level < 10 ppm and cotinine < 15 ng/ml	• Individuals with greater DS (putamen/caudate), precuneus, middle temporal gyrus, precentral gyrus, postcentral gyrus, thalamus, vmPFC, and dlPFC activation more likely to relapse
Kosten, 2006	Cocaine	VIS	17	70 days	Positive UDS (urine collected 3×/week)	• Relapsers (n=9) had greater posterior cingulate and right precentral gyrus activation than abstainers • Greater left precentral and superior temporal gyri and posterior cingulate activation was associated with worse treatment effectiveness
Prisciandaro, 2013	Cocaine	VIS	28	7 days	Positive UDS (one sample)	• Relapsers (n=6) had greater bilateral primary visual cortex, right insula, and right DS activation

Abbreviations: VIS = visual; AUD = auditory; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; DS = dorsal striatum; vmPFC = ventromedial prefrontal cortex; VS = ventral striatum; VTA = ventral tegmental area.

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Table 2

Pharmacological treatment effects on cue-elicited brain activation (as organized by substance).

First author, year	Substance	Cue Type	Dose and duration of medication	Active *N*	Control *N*	Scan timing*	Results
Hermann, 2006	Alcohol	VIS	400 mg amisulpride (one dose)	10	n/a	Pre/post	• Amisulpride reduced activation of right thalamus
Myrick, 2008	Alcohol	VIS/GUS	50 mg naltrexone (NTX) × 7 days	23	24	Post	• NTX reduced activation of right VS, right medial PFC, right supramarginal gyrus, and bilateral OFC compared to placebo
			0.5 mg ondansetron (OND) × 7 days	23	24		• OND reduced activation of right SFG, cingulate gyrus, cerebellar vermis, and primary visual cortex compared to placebo
			50 mg NTX, 0.5 mg OND × 7 days	20	24		• NTX/OND combination reduced activation of right VS, right DS, and right MFG compared to placebo
Myrick, 2010	Alcohol	VIS/GUS	15 mg aripiprazole (APZ) × 14 days	14	16	Post	• APZ reduced activation of right VS compared to placebo • Greater VS activation was related to drinking during time on medication in APZ group but not placebo
Langosch, 2012	Alcohol	VIS	Acamprosate (1332/1998 mg) × 14 days	12	10	Pre/post	• No activation differences between acamprosate and placebo or between pre- and post-treatment scans.
Lukas, 2013	Alcohol	VIS/OLF	380 mg, i.m. extended-release NTX (single dose, delivered 14 days before testing)	15	13	Pre/Post	• NTX reduced pre/post activation of the SFG, supramarginal gyrus, postcentral gyrus, and angular gyrus (odor cues) compared to placebo • NTX reduced pre/post activation of the orbital gyri, cingulate gyrus, IFG, and MFG (visual cues) compared to placebo
Schacht, 2013b	Alcohol	VIS	1200 mg gabapentin (GBP) × 14-21 days + 2 mg flumazenil (FMZ) infusions on each of first 2 days of treatment.	28	20	Post	• GBP/FMZ combination increased dorsal ACC activation among subjects with higher pre-treatment alcohol withdrawal compared to placebo • Dorsal ACC effect was associated with greater resistance to craving • Greater dlPFC activation predicted subsequent heavy drinking across all subjects
Schacht, 2013c	Alcohol	VIS	50 mg NTX × 6 days	35	39	Post	• For OPRM1 A118G G allele carriers, NTX reduced VS activation among DAT1 VNTR 10-repeat (10R) allele carriers compared to 9-repeat (9R) allele carriers • NTX reduced medial PFC activation in 10R carriers compared to 9R carriers
Han, 2013	Alcohol	VIS	15 mg aripiprazole + 20 mg escitalopram × 6 weeks	14	17 (escitalopram only)	Pre/Post	• Adjunctive aripiprazole increased pre/post activation of the left ACC vs. escitalopram only • Left ACC effect negatively associated with craving
Schacht, 2014	Alcohol	VIS/GUS	2 mg varenicline (VAR) × 14 days	18	17	Post	• VAR reduced bilateral OFC activation compared to placebo

First author, year	Substance	Cue Type	Dose and duration of medication	Active *N*	Control *N*	Scan timing*	Results
Mann, 2014	Alcohol	VIS	50 mg NTX or 2 g acamprosate (ACP) .× 84 days	36 (NTX)	28 (ACP)	Pre	• NTX in high VS activation (ROI) individuals (n=19) associated with longer time to relapse than NTX in low VS activation individuals (n=17) • No association between VS cue-reactivity (high n=10, low n=18) and time to relapse in ACP group
Kiefer, 2015	Alcohol	VIS	50 mg *D*-cycloserine (DCS) 1 hr before CET + CET (mean 7.68 sessions)	16	16	Pre/Post	• DCS+CET decreased activation of VS and DS (pre/post effect not tested between groups)
Janes, 2009	Nicotine	VIS	21 mg (or highest tolerated dose) nicotine patch (NRT) × 4 weeks, 14 mg × 14 days, then ≤7 mg × 14 days + 2-18 mg lozenges or gum (as needed)	13 (females)	N/A	Pre/Post	• NRT increased activation of the SFG, precentral gyrus, MFG, IFG, ACC, PCC, superior temporal gyrus, inferior parietal lobe, supramarginal gyrus, and caudate • NRT reduced bilateral activation of the hippocampus
Xu, 2009	Nicotine	VIS	Nicotine patch (NRT), dosage not provided (applied 4 hrs before testing)	19	19	Post (crossover)	• NRT increased activation of the left amygdala and bilateral VS
Culbertson, 2011	Nicotine	VIS	300 mg bupropion (BUP) × 8 weeks	14	16	Pre/post	• BUP reduced pre/post activation of the left medial OFC, left VS, and bilateral ACC compared to placebo • Bilateral medial OFC and left ACC effects positively correlated with pre/post changes in craving
Franklin, 2011	Nicotine	VIS/AUD	2 mg VAR × 3 weeks	11	11	Pre/post	• VAR reduced pre/post activation of the VS and medical OFC, and increased activity in ACC, PCC, lateral OFC, SFG, and dlPFC (ROIs) (comparisons with placebo group not statistically tested)
Ray, 2014	Nicotine	VIS	2 mg varenicline (VAR) × 10-12 days	10	10	Post	• VAR reduced activation of VS ROI compared to placebo • Whole brain: VAR reduced activation of the precentral gyrus, right insular cortex, left thalamus, and right DS (caudate), right IFG, and cerebellum
			25 mg NTX × 10-12 days	10			• NTX reduced activation of VS ROI compared to placebo • Whole brain: NTX reduced activation of the right insular cortex, right DS (putamen and caudate), bilateral precentral gyrus, and right IFG
			2 mg VAR + 25 mg NTX × 10-12 days	10			• VAR+NTX reduced activation of VS, bilateral ACC, and right SFG ROIs compared to placebo • Whole brain: VAR+NTX reduced activation of the bilateral OFC, insular cortex, right ACC, thalamus, DS (caudate), and cerebellum
Goudriaan, 2013	Cocaine	VIS	200 mg Modafinil (single dose)	13	13	Post (crossover)	• MOD increased activation of the right ACC and reduced VTA • MOD effect in ACC associated with reductions in craving

First author, year	Substance	Cue Type	Dose and duration of medication	Active *N*	Control *N*	Scan timing*	Results
							• MOD modulated activation to healthy control levels (no sig group differences; n=16)
Fox, 2013	Cocaine	AUD	<3 mg Guanfacine × 26 days	6	9	Post	• GUA reduced activation of the he left dlPFC, vmPFC, OFC, and premotor cortex, bilateral amygdala, hippocampus, hypothalamus, superior/middle/inferior temporal lobe, cerebellum, and inferior occipital gyrus compared to placebo
Young, 2014	Cocaine	VIS	60 mg Baclofen ×7-9 days	11	12	Post	• BAC reduced activation of the VS, ventral pallidum, amygdala, midbrain, and OFC compared to placebo

Abbreviations: VIS = visual; AUD = auditory; OLF = olfactory; GUS = gustatory; ROI = region of interest; VS = ventral striatum; DS = dorsal striatum; PFC = prefrontal cortex; dlPFC = dorsolateral prefrontal cortex; OFC = orbitofrontal cortex; SFG = superior frontal gyrus; IFG = inferior frontal gyrus; MFG = middle frontal gyrus; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; VTA = ventral tegmental area.

Table 3

Psychosocial treatment effects on cue-elicited brain activation (as organized by substance).

First author, year	Substance	Cue Type	Type and duration of treatment	Active *N*	Control *N*	Scan timing	Results
Schneider, 2001	Alcohol	OLF	Cognitive behavioral therapy (CBT; 15 sessions) + 150 mg doxepin × 21 days	10	n/a	Pre/post	• Right amygdala and left cerebellum activation present at baseline and absent following CBT/doxepin treatment (pre/post effect was not statistically tested)
Feldstein Ewing, 2011	Alcohol	GUS	Motivational interviewing (1 session; change talk [CT] vs. counterchange talk [CCT])	13	n/a	Post	• Relative to CCT, activation during CT was globally reduced, with local maxima in dorsal PFC (left postcentral gyrus, SFG) and left inferior parietal lobule • No areas observed where activation was greater during CT than CCT
Vollstädt-Klein, 2011	Alcohol	VIS	Cue exposure therapy (CET; 9 sessions) × 21 days	15	15	Pre/post	• Relative to baseline and to treatment as usual, CET reduced activation of left insula and bilateral ventral ACC, inferior parietal lobule, dlPFC and dmPFC • ROI analysis found CET-induced reductions in left VS and DS activation
Wiers, 2015	Alcohol	VIS	Cognitive bias modification (CBM) training (6 sessions) × 21 days	15	17	Pre/Post	• CBM reduced activation of the bilateral amygdala (vs baseline) and left amygdala (vs sham) in ROI analysis • Decrease in right amygdala activation correlated with decrease in craving in CBM group only • No treatment effects in VS ROI
McClernon, 2007	Nicotine	VIS	Extinction-based smoking cessation + nicotine replacement therapy (NRT) × 14-28 days	16	n/a	Pre/post	• Combined treatment reduced bilateral amygdala activation relative to baseline, and reduced bilateral thalamic activation in patients who maintained one month abstinence • No treatment effects in other ROIs: ACC, PFC, hippocampus, striatum, insula
Janse Van Rensburg, 2012	Nicotine	VIS	Cardiovascular exercise (1 10-m session)	20	20	Post (crossover)	• Activation of primary and secondary visual cortex present after rest and absent after exercise (activation differences between exercise and rest were not significant)
Li, 2013	Nicotine	VIS	Real-time neurofeedback (1 session)	10	n/a	Pre/post	• When given feedback of cue-elicited activation of dmPFC and ventral ACC, subjects could not control dmPFC, but were able to reduce ventral ACC activation • Ventral ACC activation was positively
Prisciandaro, 2013	Cocaine	VIS	CET (2 sessions) + 50 mg *D*-cycloserine (DCS) × 7 days	10	15	Pre/post	• All patients (all of whom received CET) demonstrated widespread reduced activation relative to baseline • DCS + CET, relative to placebo + CET, blunted reduction of activation of angular/middle temporal gyri, lateral occipital cortex

Abbreviations: VIS = visual; OLF = olfactory; GUS = gustatory; ROI = region of interest; PFC = prefrontal cortex; dlPFC = dorsolateral prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; SFG = superior frontal gyrus; ACC = anterior cingulate cortex; DS = dorsal striatum; VS = ventral striatum.

Table 4

Summary of findings from relapse, pharmacological, and psychosocial intervention cue-reactivity studies.

- Alcohol
  - Greater cue-elicited dorsal prefrontal cortex (PFC) activation most commonly related to increased risk for relapse (3 of 7 studies)
  - Pharmacologic interventions most commonly related to reductions in cue-elicited ventral striatum (VS)* activation (5 of 11 studies)
  - Psychosocial interventions most commonly related to reductions in cue-elicited dorsal PFC and amygdala activation (2 of 4 studies each)
- Nicotine
  - Greater cue-elicited thalamus (3 of 3 studies) and dorsal PFC (2 of 3 studies) activation most commonly related to increased risk for relapse
  - Pharmacologic interventions most commonly related to reductions in cue-elicited VS* and orbitofrontal cortex (OFC) activation (3 of 5 studies each)
- Across alcohol and nicotine studies
  - Greater cue-elicited dorsal PFC activation most commonly related to increased risk for relapse (5 of 10 studies)
  - Pharmacologic interventions most commonly related to reductions in cue-elicited VS* (8 of 16 studies) and OFC (5 of 16 studies) activation
  - Psychosocial interventions most commonly related to reductions in cue-elicited dorsal PFC (2 of 7 studies) and amygdala (3 of 7 studies) activation

Notes: Some of the “most common” findings were actually only present in ≤ 50% of the reviewed studies and, therefore, the results presented in this summary table should not be taken as evidence that there is consilience across cue-reactivity studies. Additionally, there were too few cocaine and opioid studies available to make conclusions within these substances.

*many studies considered in the review which reported VS effects were derived from ROI analyses