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Neural correlates of attentional bias in addiction

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A small but growing neuroimaging literature has begun to examine the neural mechanisms underlying the difficulty that substance-use dependent (SUD) groups have with ignoring salient, drug-related stimuli. Drug-related attentional bias appears to implicate the countermanding forces of cognitive control and reward salience. Basic cognitive neuroscience research suggests that ignoring emotionally evocative stimuli in our environment requires both up-regulation of control networks and down-regulation of processing in emotion and reward regions. Research to date suggests that attentional biases for drug-related stimuli emerge from a failure to sufficiently increase control of attention over salient, but task-irrelevant stimuli. While SUD samples have typically shown increased activity in the cognitive control regions (ie, lateral prefrontal and dorsal anterior cingulate), during attentional bias such increases appear to have been insufficient for the concomitant increases in processing by the emotion/reward regions (ie, amygdala, insula, and striatum). Given the potential contribution of attentional biases to perpetuating drug use and the development of interventions (both pharmaceutical and cognitive-behavioral) to treat biases, understanding the neural basis of successfully reducing bias remains an important, but as yet unanswered, question for our field.

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Key words: Attentional bias, cognitive control, executive function, fMRI, selective attention.
stimuli are presented to either active or abstinent users have demonstrated significant activation in regions such as the amygdala, nucleus accumbens, and hippocampus. These results have been interpreted as an example of the Pavlovian, or conditioned associative learning, whereby repeated pairing of a cue stimulus (eg, spoon used to heat and administer crack cocaine) and the subsequent drug-induced euphoria results ultimately in the cue stimulus alone being able to evoke a similar response from the underlying neural circuit. Presentation of the cue alone does not evoke euphoria; rather activation of the system appears to increase “wanting” and increased compulsion to seek the drug. This type of conditioned associative learning is typically found with other reinforcing stimuli (eg, food, pain), and items conditioned in this way are reinforced as salient to the individual.

Learning the salience of stimuli and, in turn, allowing salience to reflexively direct our attention (particularly visual attention) appears to have a logical and evolutionary advantage. Thus, when navigating a complex multistimulus environment, our attention is captured by those items that we find rewarding (eg, food) or that could harm us (eg, predators). As salience directs attention reflexively, a greater level of cognitive control must be imposed to ignore, or control attention away from, the salient stimulus and instead attend to a less salient stimulus. Top-down cognitive control, the process whereby conscious internal goals take precedence over automatic processes, is critical to a number of psychological processes that may contribute to drug addiction, such as inhibitory control and selective attention.

Exerting cognitive control over salient but task-goal irrelevant stimuli has been demonstrated by cognitive neuroscience research in healthy participants to require activation in the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex, and inferior parietal regions. Egner and Hirsch, using variants of the Stroop visual paradigm often used in attentional bias work, have demonstrated that reducing attentional bias for salient, but task-irrelevant, information involves amplification of processing (and associated cortical activity) of task-relevant information by cognitive control regions such as the dorsolateral prefrontal cortex. When reducing bias to emotionally evocative stimuli, the dorsolateral prefrontal gyrus (DLPFC) and medial prefrontal cortex (both rostral and dorsal ACC) show increased activity that is reciprocal to a reduction of amygdalar activity, suggesting some level of top-down inhibition of emotional processing.

If ignoring emotionally evocative stimuli in our environment requires both up-regulation of control networks and down-regulation of emotional processing, then the neural basis of attentional bias for drug-related stimuli may be the result of a reduction in the efficiency of either regulation mechanism, or indeed, both. Goldstein et al. performed a series of studies in cocaine users in which they consistently demonstrated hypoactivation of the dorsal and ventral region of the ACC during a modified emotional Stroop task. They also found hyperactivation in cocaine users for cocaine words in the subcortical striatal regions (substantia nigra). Further analysis of the hypoactivation observed in the ACC during cocaine cues indicated that it was also present during other task conditions when cocaine-dependent patients were compared to matched controls. This result suggests that the ACC hypoactivity could not be the result of attentional bias for cocaine cues, but rather reflects a more general deviant cognitive process in cocaine users. While the imaging data are consistent with the hypothesis of failing to up-regulate control regions being associated with increased attentional bias for drug-related stimuli, these studies did not find a significant group difference in reaction-time measures of attentional bias. The modified version of the emotional Stroop task (eg, see Figure 1) used to measure attentional bias, which for the purposes of imaging separated the presentation of the drug-related word from the opportunity to respond to it by 2 seconds, was unable to measure the effect of the attentional incongruence during stimulus presentation during the subsequent opportunity to respond. Interestingly, one study that showed a similar pattern of decreased cognitive control activity (left dorsolateral prefrontal cortex) and increased mesocorticolimbic activity (nucleus accumbens and amygdala) during an attentional bias task, also failed to find a significant bias to drug-related stimuli in its sample of cigarette smokers. The reduction in the control network activity was also identified irrespective of stimulus condition, and the effect was more pronounced in abstinent ex-smokers when compared to current smokers or non-smokers.

Subsequent functional magnetic resonance imaging (fMRI) studies in SUD samples have typically failed to replicate these findings of down-regulation of cognitive control regions during attentional bias. Studies examining dependent stimulant- alcohol- nicotine-using participants have found increased activation in the control network, principally the lateral prefrontal and dorsal ACC regions, during attentional bias for drug-related stimuli. Interestingly, almost all of these studies have found one of lateral prefrontal or ACC, rather than both, regions to be up-regulated during within-subject comparisons between drug-related and neutral conditions. A recent study has also demonstrated that neurochemical evidence of
greater dorsal ACC (dACC) dysfunction [via magnetic resonance (MR) spectroscopy] was correlated with higher levels of attentional bias in cigarette smokers. Similar to the majority of these studies, have also been able to show a relationship between individual differences in attentional bias and cognitive control network activity. For example, Hester and Garavan showed that increased bias for cocaine-related stimuli (relative to neutral stimuli) was associated with increased right inferior frontal cortex activity ($r = 0.47$), and Janes et al. (2010) found that dACC activity was correlated with bias for nicotine stimuli ($r = 0.41$). Given the relatively small samples of participants and the distribution of bias scores, the moderate strength of these correlations is encouragingly robust. They do, however, appear consistent with the behavioral research highlighting the predictive value of bias scores within samples of drug-dependent participants, wherein the within-group variability of attentional bias has been sufficient to predict treatment outcomes measures.

In keeping with the increased cognitive control network activity during attentional bias, drug-dependent populations have also demonstrated increased activity in limbic and mesocorticobasal networks. A number of studies have found that the increased attentional bias shown to drug-related stimuli is associated with increased activity in the insula cortex, amygdala, and striatum. For example, Luijten et al. showed that activation in the left insula was associated with attentional bias related craving. Interestingly, Janes et al. (2010) showed that the functional connectivity between the insula and cognitive control regions was reduced in smokers who slipped after an attempt to quit. Nestor et al. found that the nucleus accumbens was more strongly activated in current smokers, as compared to ex-smokers, for smoking pictures in a pictorial Stroop task. Because the difference in nucleus accumbens activation was not significant between smokers and nonsmoking controls, the difference between current smokers and ex-smokers may suggest that smokers who show reduced attentional bias-related brain activation in the nucleus accumbens (i.e., the ex-smokers in the current study) have greater success in quitting smoking over time (at least 12 months in this study).

The pattern of increased attentional bias and greater activity in both cognitive control and limbic networks across these studies has typically been interpreted via a reciprocal mechanism. The increased saliency of drug-related stimuli requires a greater level of control to ignore, hence the greater activity in the control system to counteract the greater activity in the limbic system to the salient stimulus. While control systems are more active, they are not sufficient to reduce the level of bias to control-group levels. That within-SUD group

Figure 1. An example of stimuli from the drug-related emotional Stroop task (adapted from Hester et al.). In the emotional Stroop task, word stimuli are presented in a range of colored fonts, with participants instructed to respond as quickly and accurately as possible with the response button associated with the words’ font color. A single trial presented the word stimulus for 2000 ms awaiting the participant’s response, followed by a blank screen (interstimulus interval (ISI)) for 750 ms. Blocks of trials were presented in a range of categories: drug-related words (see panel A), neutral words (panel B), and incongruent words (panel C). Drug-related words in this example were stimuli that cocaine-dependent participants generated prior to the experiment, which they associated with cocaine. The task attempts to measure attentional bias by requiring participants to control their over-learned but task-irrelevant response (to read the word) and thereby ignore the salient stimulus (drug-related word), in favor of responding to the task-relevant stimulus feature (font color). Neutral words (panel B) are used in the experiment to act as a control comparison, and are matched to the drug-related words for word length and frequency of use, but they differ in terms of emotional salience. Incongruent stimuli (panel C), or classic ‘Stroop’ stimuli, index underlying cognitive control ability by requiring participants to ignore the salient but task-irrelevant feature (the word) in favor of the less salient but task-relevant feature (font color).

Differences in bias level have been found to correlate with either control activity, limbic activity, or the connectivity between them also appears consistent with the hypothesis that successfully controlling bias requires up-regulation of the control system and down-regulation of the limbic response. This hypothesis is not unique to attentional bias; for example,
Table 1. Functional MRI studies of attentional bias for drug-related stimuli in SUD samples

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Measures</th>
<th>Main results—behavioral</th>
<th>Main results—imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ersche et al.</td>
<td>18 stimulant users 10 HC</td>
<td>Stimulant word Stroop task after placebo and single doses of paramipexole and amisulpride</td>
<td>Stimulant users had longer RT than HC to stimulant words relative to neutral words</td>
<td>Drug &gt; Neutral SUD &gt; HC l-vPFC, r-cerebellum Effects of dopamine manipulation differ between high and low compulsivity subgroups</td>
</tr>
<tr>
<td>Goldstein et al.</td>
<td>14 cocaine users 15 HC</td>
<td>Adapted Cocaine word Stroop task</td>
<td>No differences between drug and neutral words</td>
<td>Drug &gt; Neutral rvACC, medOFC</td>
</tr>
<tr>
<td>Goldstein et al.</td>
<td>17 cocaine users 17 HCb</td>
<td>Adapted Cocaine word Stroop task</td>
<td>No differences between groups</td>
<td>Drug and Neutral SUD &lt; HC substantia nigra</td>
</tr>
<tr>
<td>Goldstein et al.</td>
<td>13 cocaine users 14 HC</td>
<td>Adapted Cocaine word Stroop task after placebo and single dose methylphenidate</td>
<td>No differences between groups</td>
<td>Drug &gt; Neutral Placebo: SUD &lt; HC dACC Methylphenidate: -</td>
</tr>
<tr>
<td>Hester and Garavan</td>
<td>16 cocaine users</td>
<td>WM task with neutral and cocaine pictures</td>
<td>Longest RT and decreased accuracy during high WM load and cocaine pictures</td>
<td>During High WM Cocaine &gt; Neutral l-IOG, r-IFG</td>
</tr>
<tr>
<td>Janes et al.</td>
<td>28 woman smokers</td>
<td>Smoking cue reactivity during scanning and Smoking word Stroop task outside scanner</td>
<td>Wide range of SIS on Smoking word Stroop task</td>
<td>Smoking &gt; Neutral Positive correlation with SIS: Bilateral insula, bil-PHG, l-amygdala, l-OG Negative correlation SIS: precuneus</td>
</tr>
<tr>
<td>Janes et al.</td>
<td>19 woman smokers 8 slipped 11 abstinent 8 weeks after testing</td>
<td>Smoking cue reactivity during scanning and Smoking word Stroop task outside scanner</td>
<td>SIS higher in smokers that slipped after quit attempt compared to non-slippers</td>
<td>Smoking &gt; Neutral Positive correlation with SIS: bil-Insula and dACC</td>
</tr>
<tr>
<td>Luijten et al. (2011)</td>
<td>18 smokers 19 non-smoking HC</td>
<td>AB Line Counting task with smoking and neutral pictures</td>
<td>No differences between groups</td>
<td>Smoking &gt; Neutral Smokers &gt; HC r-dACC, r-SPL, l-STG</td>
</tr>
<tr>
<td>Luijten et al.</td>
<td>25 smokers 24 non-smoking HC</td>
<td>AB Line Counting task with smoking and neutral pictures after placebo and haloperidol</td>
<td>No differences between groups</td>
<td>Smoking &gt; Neutral Smokers &gt; HC l-dACC, r-DLPFC, l-SPL after placebo. Group x Medication interaction in l-dACC and r-DLPFC, with post-hoc tests showing no group differences after haloperidol in these regions.</td>
</tr>
</tbody>
</table>
### Table 1. Continued

<table>
<thead>
<tr>
<th>Study</th>
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<th>Measures</th>
<th>Main results—behavioral</th>
<th>Main results—imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marhe et al.</td>
<td>26 cocaine users</td>
<td>Cocaine word Stroop task</td>
<td>RT cocaine words &gt; neutral words</td>
<td>Smoking &gt; Neutral</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No difference for accuracy</td>
<td>No significant group activation, while individual differences in r-dACC activation were positively associated with cocaine use three months after treatment.</td>
</tr>
<tr>
<td>Nestor et al.</td>
<td>13 smokers</td>
<td>Pictorial Stroop paradigm with smoking, evocative, and neutral pictures</td>
<td>No differences between groups</td>
<td>Smoking pictures</td>
</tr>
<tr>
<td></td>
<td>10 ex-smokers</td>
<td></td>
<td></td>
<td>Smokers &gt; ex-smokers NACC</td>
</tr>
<tr>
<td></td>
<td>13 non-smoking HC</td>
<td></td>
<td></td>
<td>Smoking &gt; Neutral</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Smokers: bilateral NACC and l-amygdala</td>
</tr>
<tr>
<td>Vollstädt-Klein et al.</td>
<td>38 alcohol dependent patients</td>
<td>Alcohol and neutral reactivity during scanning and dot-probe task outside the scanner</td>
<td>RT to probes replacing alcohol pictures &lt; neutral pictures</td>
<td>Cue induced activation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive correlations with RT AB effect in bil-IFG, bil-Insula, bil-precentral gyrus, l-(para) hippocampus, l-thalamus, l-lingual gyrus, l-precuneus, l-MTG/STG, r-putamen, bil caudate, l-ACC</td>
</tr>
</tbody>
</table>

HC, healthy controls; SUD, substance use–dependent patients; RT, reaction times; AB, attentional bias; SIS, smoking interference score, defined as the difference in reaction time between smoking and neutral scores (positive SIS scores reflect attentional bias for smoking cues); WM, working memory; bil-, bilateral; r-, right; l-left; vPFC, ventral prefrontal cortex; ACC, anterior cingulate cortex (rv, rostroventral; cd, caudal dorsal; d, dorsal); medOFC, medial orbitofrontal cortex; IOG, inferior occipital gyrus; IFG, inferior frontal gyrus; PHG, parahippocampal gyrus; OG, occipital gyrus; SPL, superior parietal lobe; STG, superior temporal gyrus; DLPFC, dorsolateral prefrontal gyrus; NACC, nucleus accumbens, MTG, middle temporal gyrus.

*Significant at trend level.

1. 15 cocaine users and 11 controls were also included in Goldstein et al. (2009).22
2. 19 smokers were also included in Janes et al. (2010).32
research examining cognitive strategies to reduce craving in cigarette smokers has demonstrated a similar reciprocal relationship.\(^\text{38}\)

Successful control of attention in healthy control studies has suggested that avoiding bias is typically achieved by preparatory up-regulation of control systems to focus on task-related, rather than salient, stimuli.\(^{\text{19,20,39}}\) Rather than having to shift attention away from salient (drug-related) stimuli, the more successful approach has been for prefrontally driven control mechanisms to up-regulate preparatory activity in those regions critical to the nonsalient but task-related stimuli. Research to date has not typically explored the issue of whether SUD groups do not attempt such preparatory control network activity (see Stippekiho et al.\(^{\text{40}}\) for an exception), or whether having attempted it, they fail to engage the necessary level of activity to reduce bias. The clinical intervention research specifically targeting attentional bias appears predicated on the principle that with sufficient training and incentive, such preparatory control can assist in reducing bias. The relative success of such approaches to date,\(^{\text{41}}\) although they are in the relatively early days, appears consistent with the hypothesis that attentional bias arises from the failure, rather than an inability, of SUD patients to engage in preparatory control.

**Conclusion**

The current neuroimaging literature examining attentional bias in SUD samples has demonstrated a pattern of increased bias for drug-related stimuli being associated with both increased activity in cognitive control (prefrontal and anterior cingulate cortices) and emotion processing (amygdala, insula, nucleus accumbens) brain networks. The inconsistencies in the small, but growing, literature include the variation in finding group differences for key nodes of the control network, notably the dorsal ACC. Some of the variation may be due to specific neuroimaging task design parameters, for example, those tasks that limit the behavioral bias shown by participants\(^{\text{22,24}}\) or the extent to which they produce stimulus conflict.\(^{\text{26,31}}\) Many of the tasks used rely on the presented stimulus prompting an overlearned response, which must be overcome via greater cognitive control. The cognitive control demands of a specific task can influence its ability to detect attentional bias toward drug-related stimuli, but not always. For example, the level of attentional bias shown by an individual on the emotional Stroop test does not always correlate with their incongruent Stroop bias.\(^{\text{42}}\) It seems likely that some variability in dACC activity is due to the extent to which such conflict resolution is required. While such effects are consistent with the finding of dACC activity differences between groups across a variety of executive function tasks,\(^{\text{18}}\) it may not necessarily be specific or informative to our understanding of attentional bias.

The current data appear largely consistent with the hypothesis that attentional biases for drug-related stimuli emerge from a failure to sufficiently increase control of attention over salient, but task-irrelevant, stimuli. While SUD samples have consistently shown increased activity in the cognitive control network during attentional bias, such increases appear to have been insufficient for the concomitant increases in processing by the emotion network. Two questions arising from this remain relatively unanswered: The first question is whether this underlying neural mechanism for bias is specific to drug-related stimuli when compared to other emotionally salient stimuli (see Field and Cox\(^{\text{4}}\)). While behavioral studies of drug-related bias and imaging studies of craving suggest that other evocative stimuli will induce the same effect,\(^{\text{10,43}}\) imaging studies of drug-related attentional bias have typically not explored this more general relationship. Second, to date, the literature has not focused on comparing successful and failed attempts to ignore drug-related stimuli, either within a session or between them. While statistical power may be at issue, such analyses would help to identify the neural mechanism associated with successfully reducing bias in the short- and long-terms. Given the recent development of specific interventions targeting attentional bias,\(^{\text{41}}\) analyses of pre-post intervention fMRI data examining the neural mechanisms associated with the successful reduction of bias could be highly influential to treatment intervention development.

**Disclosures**

The authors do not have anything to disclose.

**References**


