Published in final edited form as:

Exp Clin Psychopharmacol. 2014 December ; 22(6): 469–483. doi:10.1037/a0037806.

A Critical Review of the Literature on Attentional Bias in Cocaine Use Disorder and Suggestions for Future Research

Robert F. Leeman, Ph.D.,

Department of Psychiatry, Yale School of Medicine and VA VISN1 MIRECC, VA Connecticut Healthcare System

Cendrine D. Robinson, M.S.,

Department of Medical and Clinical Psychology, Uniformed Services University of the Health Sciences

Andrew J. Waters, Ph.D., and

Department of Medical and Clinical Psychology, Uniformed Services University of the Health Sciences

Mehmet Sofuoglu, M.D., Ph.D.

Yale School of Medicine and VA VISN1 MIRECC, VA Connecticut Healthcare System

Abstract

Cocaine use disorder (CUD) continues to be an important public health problem and novel approaches are needed to improve the effectiveness of treatments for CUD. Recently, there has been increased interest in the role of automatic cognition such as attentional bias (AB) in addictive behaviors and AB has been proposed to be a cognitive marker for addictions. Automatic cognition may be particularly relevant to CUD as there is evidence for particularly robust AB to cocaine cues and strong relationships to craving for cocaine and other illicit drugs. Further, the wide-ranging cognitive deficits (e.g., in response inhibition and working memory) evinced by many cocaine users enhance the potential importance of interventions targeting automatic cognition in this population. In the current paper, we discuss relevant addiction theories, followed by a review of studies that examined AB in CUD. We then consider the neural substrates of attentional bias including human neuroimaging, neurobiological and pharmacological studies. We conclude with a discussion of research gaps and future directions for attentional bias in CUD.

Keywords

attentional bias; cocaine; cognition; neuroimaging; pharmacotherapy

Drug and alcohol use disorders continue to be a worldwide problem. Unfortunately, currently available interventions are only modestly effective (Amato et al., 2013; Magill &

Correspondence concerning this article should be addressed to Robert Leeman, Department of Psychiatry, Yale School of Medicine, Substance Abuse Center, CMHC, 34 Park Street, Room S200, New Haven, CT 06519; Tel: (203) 974-7373; Fax: (203) 974-7606; robert.leeman@yale.edu.

DISCLOSURES

The other authors have no disclosures.

Ray, 2009; Maisel, Blodgett, Wilbourne, Humphreys, & Finney, 2013; Smedslund et al., 2011). Thus, novel approaches that will enhance the effectiveness of currently available treatments are needed. Addictive behaviors, like other behavioral problems, are thought to be based largely on automatic, associative processes that are elicited by substance-associated cues in the environment (Marteau, Hollands, & Fletcher, 2012; Rooke, Hine, & Thorsteinsson, 2008; Stacy & Wiers, 2010). Among automatic processes, attentional bias (AB) to drug cues has been proposed to contribute to motivation to seek drugs (Field & Cox, 2008). When one has AB to drug cues, “those cues are able to grab and hold the attention in preference to other cues in the environment” (Field, Marhe, & Franken, in press). Notably, AB is believed to have two main components: initial orienting (i.e., “grabbing”) and then maintenance of attention (Field & Cox, 2008). In addiction research, AB is related yet distinct from the phenomenon of cue reactivity. The goal of cue reactivity studies is typically to assess the extent to which cue presentation leads to compensatory or appetitive responses that mirror actual drug use itself. In AB research, the focus is specifically on how drug cues are perceived (Field & Cox, 2008).

In addition to being an assessment tool for addictive behaviors, in a limited number of studies to date (Attwood, O'Sullivan, Leonards, Mackintosh, & Munafo, 2008; Field & Eastwood, 2005; Fadardi & Cox, 2009; Field, Duka, Tyler, & Schoenmakers, 2009; Schoenmakers, Wiers, Jones, Bruce, & Jansen, 2007; Schoenmakers, de Bruin, Lux, Goertz, Van Kerkhof, & Wiers, 2010), AB has been targeted in computer-based behavioral interventions in order to reduce attentional bias to cues for licit substances (Macleod, 2012). If proven to be effective, such approaches may be especially relevant for substance use disorder (SUD) treatment, including treatment for illicit drug use, given that in the United States about ten percent of those who were estimated to need treatment for SUD actually receive it (Schulden, Lopez, & Compton, 2012).

The main goal of this paper is to critically review the literature on AB for its potential use as an assessment tool and treatment target for cocaine use disorder (CUD). We focus on CUD, rather than all SUDs, for several reasons. First, some studies have reported that those with CUD, compared to non-users or occasional users, display particularly robust AB for cocaine cues (Copersino et al., 2004; Liu et al., 2011; Smith, Simon Jones, Bullmore, Robbins, & Ersche, 2014). Evidence also suggests that AB for cocaine cues may be stronger than for other drugs of abuse (e.g., marijuana; Carpenter, Schreiber, Church, & McDowell, 2006; Sharma & Money, 2010). Further, relationships between craving and AB have been found to be stronger for cocaine and other illicit drugs than for licit substances (Field, Munafo, & Franken, 2009). These findings all support the potential of AB as a treatment target for CUD. Second, many individuals with CUD, especially early in abstinence and treatment initiation, demonstrate cognitive deficits in different domains including attention, working memory, and response inhibition (Jovanovski, Erb, & Zakzanis, 2005; Woicik et al., 2009). These deficits may limit the benefits of more traditional behavioral treatments like cognitive behavioral therapy (CBT), where the individual is required to learn new information and skills (Aharonovich, Nunes, & Hasin, 2003). Thus, interventions targeting automatic processing may be especially useful for CUD treatment. Third, there is a great need to develop effective treatment approaches for CUD. Unlike tobacco, alcohol or opioid addiction, no effective pharmacological treatments are available for CUD despite intense

research efforts (Potenza, Sofuoglu, Carroll, & Rounsaville, 2011). Regarding behavioral treatments for CUD, effect sizes are modest and outcomes vary widely across individuals (Dutra et al., 2008). Clearly, there is room for novel approaches that may lead to more effective treatments for CUD.

We begin by providing a brief review of current models of addiction and the potential utility of AB as a cognitive marker for CUD (Ersche et al., 2010; Kilts et al., 2013; Marhe, Luijten, van de Wetering, Smits, & Franken, 2013). We then discuss the neurobiological mechanisms underlying AB and conclude with a discussion of potential treatment strategies targeting AB for cocaine addiction and future directions in this research area. This review complements several recent reviews of AB in addiction (Field et al., in press; Hester & Luijten, in press; Luijten, Field, & Franken, in press; Wiers, Gladwin, Hofmann, Salemink, & Ridderinkhof, 2013) and other neuropsychiatric disorders (Beard, Sawyer, & Hofmann, 2012; Browning, Holmes, & Harmer, 2010; Van Bockstaele et al., in press). The present review is unique from prior reviews in the addictions in that it covers all key aspects of AB research for one particular addiction (i.e., to cocaine) as opposed to prior reviews that have focused on AB in addiction in general or have focused on one area of AB research (e.g., neuroimaging, pharmacology studies).

Models of Addiction Relevant to AB

In spite of intense translational research focusing on the neurobiological mechanisms underlying addiction, no biological or cognitive markers have been identified that uniquely define addiction. As a result, addiction continues to be described primarily at the behavioral level and our understanding of the main features of addiction have remained relatively unchanged over the past 50 years (Wise & Koob, 2014). Compulsive drug use remains a key feature of addiction; however, neuroadaptations that lead to compulsive drug use remain a matter of debate (Stacy & Wiers, 2010). For example, aberrant-learning theories of addiction propose a shift from impulsive and novelty-driven to compulsive and habitual patterns of use to characterize the progression of drug use from experimentation to addiction (Everitt et al., 2008; Tiffany, 1990). This impulsivity-to-compulsivity or habit shift has been linked to parallel changes in location of predominant neural activity associated with addictive behaviors, from the cortical to striatal region and within the striatum, from primarily the ventral to the dorsal part (Everitt et al., 2008). Thus, for aberrant-learning models, the main neuroadaptation that defines addiction is aberrant learning mediated by a progressive ventral to dorsal striatal shift.

Alternate negative reinforcement or opponent process theories propose that the negative motivational state or affect that develops as a result of long-term drug use is the main mechanism that leads to motivation for ongoing drug use behavior (Koob, Caine, Parsons, Markou, & Weiss, 1997; Koob & Le Moal, 2008). According to negative reinforcement theory, the primary change that occurs with the onset of addiction is the development of a negative motivational state, along with drug users' efforts to alleviate this state.

In contrast, incentive-sensitization theory emphasizes the attribution of motivational salience to reward associated cues (Robinson & Berridge, 1993). This produces automatic appetitive

processes that invoke a conditioned response of “wanting” a substance. Accordingly, drug cues become so salient that they cause drugs to be wanted independent of any pleasure they yield (Berridge & Kringelbach, 2008). Thus, for incentive-sensitization theory, development of incentive salience or incentive motivational effects of drugs or drug associated stimuli is the main mechanism that leads to ongoing drug use. The underlying neuroadaptations for incentive salience are thought to be mediated by the mesolimbic dopamine pathway (Robinson & Berridge, 1993).

A common feature of these models is to present a unitary account of addictions across drugs of abuse. A recent review questioned this unitary model approach by highlighting the differences between stimulant and opioid addiction regarding neurobiological, behavioral and cognitive measures (Badiani, Belin, Epstein, Calu, & Shaham, 2011). Thus, addiction models, rather than being mutually exclusive, may pertain to certain addictions more closely than others (Stacy & Wiers, 2010). Negative-reinforcement theory may fit opioid use disorder most closely, which is characterized by severe physical and psychological withdrawal (Lobmaier, Gossop, Waal, & Bramness, 2010). Aberrant-learning theory may fit tobacco use disorder well, which is maintained by a relatively weak reinforcer (i.e., nicotine) (Caggiula et al., 2001). Incentive-sensitization theory may be particularly relevant to stimulant (cocaine and methamphetamine) use disorder, which is characterized by intense cravings, strong responsiveness to drug cues and generally mild withdrawal (Sofuoglu, Dudish-Poulsen, Brown, & Hatsukami, 2003). There has also been a suggestion, with some supporting evidence among nicotine dependent individuals, that incentive salience may be more applicable at the earlier stages of development of addiction, while aberrant learning may be more applicable at later stages (Mogg, Field & Bradley, 2005). Further evidence, particularly from longitudinal studies, is needed to assess this contention definitively, both for nicotine dependence and other addictions.

Incentive-sensitization theory also provides a framework to identify cognitive antecedents or cognitive markers (e.g., attentional bias) of addictive behaviors. The “wanting” response that results from development of incentive salience is thought to mediate enhanced attention to drug cues and craving (Field et al., in press; Robinson & Berridge, 1993). According to a related theoretical perspective, an individual with AB to drug cues will be more likely to attend to drug cues—which provokes craving—than an individual with a lower AB (Field & Cox, 2008; Franken, 2003). Franken’s (2003) model also proposed that craving can cause AB, and that craving can cause drug use or relapse.

An alternative to incentive-sensitization as a theoretical framework underlying AB is current concerns theory (Klinger & Cox, 2011). In the context of AB, current concerns theory would predict that any substance related goal (i.e., to seek/use or to avoid substances), not only appetitive drives, could lead to AB. Findings of stronger AB among treatment seekers (Liu et al., 2011; Vadhan et al., 2007) would be predicted by current concerns theory but not by incentive sensitization theory.

While these theoretical models emphasize the neuroadaptations that lead to uncontrollable drug use, this does not mean that addicted individuals have no control over their drug use. For example, contingency management approaches, which provide financial incentives as an

alternative to drug use, can substantially reduce or eliminate drug use for weeks or months across many addictions (Dutra et al., 2008). Thus, the influence of automatic processes such as attentional bias, which increases risk of drug taking/relapse, is balanced by reflective or executive processes, which attempt to inhibit automatic processes or their output (Wiers et al., 2013). Executive function, rather than being unitary, can best be characterized as a collection of related but separable functions (Friedman et al., 2008). Among these functions, response inhibition, working memory, and sustained attention are particularly relevant to addiction (Sofuoglu, DeVito, Waters, & Carroll, 2013). These executive functions have been shown to be impaired in long term cocaine users, compared to occasional users or healthy controls (Jovanovski et al., 2005). While some evidence supports impairment of executive functions as a result of cocaine use, other studies have suggested that these impairments predate the initiation of drug use (Aytaclar, Tarter, Kirisci, & Lu, 1999). Addiction theories generally acknowledge the importance of impaired executive functions in facilitating initiation and maintenance of drug use behavior and the difficulty many individuals have in resisting habitual drug use once established. This conceptualization is referred to as a dual-process theory because of the emphasis on two qualitatively distinct processes: automatic (or “implicit”) and controlled or executive (or “explicit”) (e.g., Kahneman, 2011; Wiers et al., 2013). These processes may also serve as separate treatment targets as discussed in the following sections.

AB as a Cognitive Marker for CUD

AB has been put forth by multiple investigators as a potential cognitive marker for CUD and relapse vulnerability (Ersche et al., 2010; Kilts et al., 2013; Marhe, Luijten, et al., 2013). Accordingly, we will outline evidence in favor of AB to cocaine cues among cocaine users (particularly those meeting criteria for CUD) in this section. We will first explain how AB is measured and then present behavioral evidence for AB in cocaine users along with evidence to support the theoretically proposed relationship to craving in this population. We will continue by presenting evidence relating AB to other cognitive issues among cocaine users and conclude with evidence that AB to cocaine cues may predict treatment outcome.

Measurement of AB

AB is measured most commonly with the use of one of two reaction time tasks: most frequently with a drug version of the Stroop task and in some studies with a visual probe (VP) task involving drug-related words or images (Field et al., in press). Less commonly, studies have utilized eye tracking to measure AB (see Field & Cox, 2008 for more detailed descriptions of each of these methods).

Drug Stroop tasks are a form of emotional Stroop task in which participants are asked to name the color in which neutral and drug-related words are printed with frequent drug users having longer latencies to name the color of drug-related words, which is interpreted as evidence of AB to drug cues (Cox, Fadardi, & Pothos, 2006). Some studies involving cocaine users have utilized Stroop tasks including words for multiple drugs (e.g., Carpenter, Martinez, Vadhan, Barnes-Holmes, & Nunes, 2012; Vadhan et al., 2007), while others involved cocaine words exclusively (Copersino et al., 2004; Liu et al., 2011; Marhe, Luijten, et al., 2013). Cocaine users have exhibited an AB to cocaine cues in drug Stroop tasks in

multiple studies (e.g., Copersino et al., 2004; Hester, Dixon, & Garavan, 2006; Liu et al., 2011).

VP tasks rely upon the tendency for individuals to respond faster to a probe (e.g., a small dot) when it is presented in an attended (versus unattended) region of a visual display (Posner, Snyder, & Davidson, 1980). Individuals tend to respond faster to probes that replace motivationally salient stimuli than to those that replace neutral stimuli (Mogg & Bradley, 1998). This tendency is interpreted as an AB. In the addictions, drug-related word and image cues have been incorporated into VP tasks. A meta-analysis showed that AB measured with VP tasks related significantly to actual substance use (Rooke et al., 2008). VP tasks have been used less frequently than drug Stroop tasks in cocaine studies. A few studies have reported evidence of AB with VP tasks, however these effects have been moderated by subject characteristics or effects of experimental manipulations (Bardeen, Dixon-Gordon, Tull, Lyons, & Gratz, 2014; Montgomery et al., 2010; Tull, McDermott, Gratz, Coffey, & Lejuez, 2011; see Table 1).

In eye tracking studies, eye movements in response to drug cues are measured in comparison with neutral cues in order to gauge selective attention to these cues. We are aware of only one AB study with eye tracking involving cocaine users, which yielded evidence interpreted by the authors as offering support for AB among cocaine cues (Rosse et al., 1997; Rosse, Miller, Hess, Alim, & Deutsch, 1993). Given the existence of only one published study and the reliance on qualitatively different dependent variables in eye tracking compared to reaction time tasks, we did not include the Rosse et al. (1993; 1997) findings in our review of behavioral effects of AB discussed below.

Recently, the reliability with which AB is assessed among substance users has been questioned (Ataya et al., 2012). However, studies included in this analysis all came from one research group and involved social alcohol drinkers and cigarette smokers. Recent studies involving cocaine users have shown that AB can be assessed reliably with the cocaine Stroop task. For instance, Waters, Marhe and Franken (2012) reported an internal (split-half) reliability estimate of 0.68 for the cocaine Stroop task.

Behavioral evidence supporting attentional bias to cocaine-related stimuli

Studies included in the remainder of this section were found by conducting parallel searches in the databases Google Scholar and PubMed. A general search was conducted in Google Scholar using the search terms “cocaine” and “attention.” In PubMed, we searched for “cocaine” and “attention*” in the title and abstract fields. Among the resulting references, we retained papers reporting results of studies that utilized drug Stroop, drug VP or other AB assessments among samples that contained at least some individuals identified as cocaine users. In addition to these database searches, we included all papers meeting these same qualifications that were cited in the following reviews of AB in the addictions: (Field & Cox, 2008; Field et al., in press; Hester & Luijten, in press; Luijten et al., in press; Wiers et al., 2013).

Our search yielded the 23 studies described in Table 1. Most behavioral results included in the table were reported in the published papers from these studies, however some additional

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results were obtained by contacting authors. Overall, evidence supports a robust AB to cocaine cues among cocaine users (particularly those with CUD). Of these 23 studies, 17 reported significant findings supporting AB to cocaine cues among cocaine users. Specifically, multiple studies reported that a drug-related AB was observable among cocaine users but not among healthy controls (Copersino et al., 2004; Ersche et al., 2010; Gardini, Caffarra, & Venneri, 2009; Hester et al., 2006; Liu et al., 2011; Montgomery et al., 2010; Smith et al., 2014). Evidence suggests that AB for cocaine cues may be stronger than for other drug cues. In a treatment sample, cocaine cues were associated with significantly longer reaction times in a drug Stroop task than heroin or marijuana cues were (Carpenter et al., 2006). A small sample of currently abstinent, lifetime crack cocaine users showed an AB to non-word letter strings that had been paired repeatedly with cocaine-related images in a procedure taking place prior to the task but not to non-cocaine-conditioned letter strings. The investigators were not able to produce a similar phenomenon in a sample of marijuana users in a separate study (Sharma & Money, 2010). There is also evidence for differential cocaine-related AB among those at varying levels of drug use severity. Smith et al. (2014) reported evidence suggesting an AB to cocaine words among stimulant dependent but not among recreational cocaine users. There is evidence for stronger AB to drug cues among actively using drug dependent individuals (including cocaine) compared to abstinent individuals in recovery as well (Gardini et al., 2009).

Among the negative studies in Table 1, 4 come from the same research group (Goldstein, Alia-Klein, et al., 2009; Goldstein et al., 2007), which uses a form of drug Stroop designed explicitly for neuroimaging studies. This form of the task includes a 2-second delay between stimulus presentation and response and is not designed to yield significant behavioral results (Goldstein et al., 2009, p. 6002). Methodological details including duration of stimulus presentation can affect drug Stroop results (Cox et al., 2006; Field & Cox, 2008). Further, all 6 negative studies enrolled relatively small samples of between 14 to 34 participants. In addition to the 6 negative studies, one positive study, which reported a significant attentional bias to cocaine cues on a visual probe task reported a lack of attentional bias on a cocaine Stroop task (Montgomery et al., 2010).

Of the 17 studies reporting positive results, 6 reported caveats to their findings. In 4 studies, AB was observable only following an experimental manipulation (e.g., Tull et al., 2011). There is precedent for AB to drug cues to be increased by pertinent experimental manipulations (Cox et al., 2006).

In 5 studies, AB applied only to a subset of participants with a history of cocaine use (e.g., Gardini et al., 2009). In one study, AB to cocaine cues was observable among treatment seeking but not among non-treatment seeking cocaine dependent individuals (Vadhan et al., 2007). Similarly, while Liu et al. (2011) reported stronger cocaine AB in general among cocaine dependent individuals as compared to healthy controls, among the cocaine dependent participants, AB was stronger among treatment seekers. Current concerns theory (Klinger & Cox, 2011) more readily accounts for these findings than incentive-sensitization theory, however findings from several studies support incentive-sensitization as an theoretical framework for substance-related AB, as well (Franken, 2003). At this time, there

is support for both theories and a lack of definitive evidence to conclude that either theory explains the majority of findings in this area (Field & Cox, 2008).

Relationship to craving

Attentional bias to drug cues and craving have been linked theoretically (Franken, 2003), thus one would predict significant relationships between these constructs. A meta-analysis showed a significant though small relationship overall between craving and AB to drug cues, however, this relationship was found to be stronger for illicit drugs such as cocaine than for licit substances (Field, Munafò, & Franken, 2009). Additional studies published after this meta-analysis have also reported significant relationships between AB to drug cues and craving among cocaine users (Goldstein, Alia-Klein, et al., 2009; Marhe, Waters, van de Wetering, & Franken, 2013).

Relationship to other cognitive outcomes

Though a specific cognitive operation associated with addiction, AB to drug cues likely relates to broader cognitive impairments among cocaine users as well, particularly those with CUD. Multiple studies have reported poorer performance among cocaine users on Stroop tasks with non-drug-related stimuli (Carpenter et al., 2006; Copersino et al., 2004; R. Hester et al., 2006; though see Gardini et al., 2009 for null findings) and significant positive correlations have been reported between performance on drug-and non-drug Stroop tasks (Kilts et al., 2013). On non-Stroop tasks, slower reaction times overall (i.e., not only to drug cues) have been reported among cocaine dependent compared to healthy controls (Sokhadze et al., 2008). Further, Liu et al. (2011) found positive correlations between cocaine-related AB and commission errors on a continuous performance task. This finding suggests possible relationships between AB and executive function deficiency/impulsivity among cocaine users, who tend to have difficulty with response inhibition as measured with continuous performance and similar tasks (Pike, Stoops, Fillmore, & Rush, 2013). In another study, AB to cocaine cues was observable only on trials in which working memory load was high (Hester & Garavan, 2009), providing further evidence linking AB with executive function difficulties.

Relationship to clinical outcomes

Multiple studies have related AB to outcomes among cocaine users in treatment. Cocaine dependent patients with stronger AB had worse outpatient clinical trial outcomes (Carpenter et al., 2006; though see Carpenter et al., 2012 for opposing results). Among heroin dependent inpatients who also tended to be cocaine dependent, AB to drug cues measured using hand-held devices was predictive of subsequent temptation to use drugs (Waters et al., 2012). In the same study, AB assessed during these temptation episodes predicted subsequent relapse (Marhe, Luijten, et al., 2013), suggesting that AB to drug cues “may function as an ‘early warning signal’ for imminent relapse” (Field et al., in press, p. 1). In an aforementioned study relevant to treatment outcome, AB to drug cues was found among current, active users of cocaine and/or heroin, but not among currently abstinent individuals in recovery from dependence on these drugs (Gardini et al., 2009). Given the lack of pre-/post comparisons among patients in treatment, these findings cannot be considered

definitive, but nonetheless suggest further that AB typifies active drug use and dependence and that AB can potentially be alleviated in the course of recovery.

Neural Substrates of AB

Human neuroimaging studies

Neuroimaging studies found in the literature search described above are described in this section and in Table 2. We found 9 such studies particular to cocaine. All of these studies utilized fMRI to identify patterns of activity in the brain associated with AB to substance-related cues (see Hester & Luijten [in press] for a review). To date, there is a great deal of heterogeneity in the findings from these studies. In their review of neuroimaging studies pertaining to attentional bias in the addictions, Hester and Luijten (in press) describe an a priori hypothesis that attentional bias to drug cues should relate to hypoactivity in frontal cortical regions tied to cognitive control and hyperactivity in subcortical regions of the brain associated with affective processing. As they point out, Goldstein, Alia-Klein et al. (2009) showed this predicted pattern of frontal hypoactivity (including in the anterior cingulate cortex [ACC]) and in a separate study showed hyperactivity in the subcortical substantia nigra (Goldstein, Tomasi, et al., 2009). However, these patterns of neural activity have not been replicated in subsequent studies. Again, notably, the Goldstein et al. group used an alternate drug Stroop task with a 2-second pause between stimulus presentation and response. This unique feature of their task may relate to the differing findings in their studies compared to others. Across these other studies, findings have tended to show hyperactivity in frontal cortical regions and in some cases hyperactivity in subcortical regions as well (Ersche et al., 2010; Hester & Garavan, 2009; Smith et al., 2014). While Kilts et al. (2013) also found hyperactivity in multiple prefrontal areas, arguably, this study comes the closest to Goldstein et al. in affirming the a priori hypothesis of frontal cortical hypoactivity and subcortical hyperactivity. Kilts et al. reported that cocaine AB was negatively correlated with activity in a neural network believed to be associated with cognitive control and positively correlated with activity in networks associated with attention to stimuli, salience attribution and processing of negative affective properties of stimuli (see Table 2). On the other hand, the notion that hypoactivity in frontal cortical regions underlies AB is not universally held. Smith et al. (2014) reported a pattern of frontal hypoactivity to cocaine words among recreational cocaine users who tended to have weaker attentional bias than stimulant dependent individuals. Accordingly, Smith et al. posited that this pattern of activity may be protective.

Findings from neuroimaging studies have demonstrated that AB to cocaine stimuli is associated with different patterns of neural activity than control stimuli. However, the precise nature of the patterns of neural activity associated with AB to cocaine cues has yet to be identified definitively and replicated. The promise these methods show is indicated, for instance, by the Marhe, Luijten et al. (2013) finding that stronger AB-related activity in the right dorsal ACC predicted cocaine use at follow-up in a treatment sample. The possibility that neural activity to cocaine cues could reliably predict clinical outcome is exciting, but requires extensive additional research to be posited with confidence.

Basic neurobiology and neuropharmacology of AB

The neurobiological mechanisms underlying AB remain to be elucidated. Preclinical studies point to the role of neuromodulators, including DA, acetylcholine (ACh), norepinephrine, and serotonin, in mediating multiple components of reward: hedonia (“liking”), motivation (“wanting”) and learning (Berridge & Kringelbach, 2008). While most research on motivational aspects of drug addiction focused on DA, cumulating evidence supports a concerted role of neuromodulators in this process. The cell bodies of these neuromodulatory neurons are located in the brain stem and through their widespread projection they influence many brain functions (Sara, 2009).

Dopamine

DA neurons originate from the ventral tegmental area (VTA) of the midbrain and target a number of limbic and cortical structures that contribute to motivation to seek and obtain reinforcement from drugs, including the nucleus accumbens (NAc), amygdala, and prefrontal cortex (PFC). The ways in which DA contributes to motivation to seek drugs is an area of active research and ongoing debate (Robinson & Berridge, 2000; Wise, 2013).

Both phasic bursting and tonic pacemaker states of DA neurons may differentially participate in the motivational aspect of drug addiction (Wise, 2013). Phasic bursting of DA neurons signal unexpected rewards including drugs or conditioned drug-related stimuli and have been proposed to mediate a rapid salience attribution to drug associated stimuli. In contrast, the tonic pacemaker state of DA neurons and the resultant change in extracellular concentrations of DA may reflect long-term adaptations to drug use. It has been suggested that whereas phasic activity of DA neurons is related to detection of salient stimuli, the tonic state reflects level of arousal and motivation (Boureau & Dayan, 2011). Thus, both phasic and tonic activity of DA neurons likely contributes to development of incentive-salience resulting in increased motivation for drug use. The contribution of DA in the development of attentional bias for drug associated stimuli is supported by a pharmacological fMRI study (Goldstein et al., 2010). In that study, methylphenidate, which enhances synaptic levels of DA and NE, attenuated AB for cocaine words in a cocaine Stoop task. In another study by (Ersche et al., 2010), AB itself and AB-related brain activity were reduced by DA agonist pramipexole among low compulsive stimulant dependent individuals with the opposing effects of increasing behavioral AB and accompanying brain activity among their high compulsive counterparts (see Table 3).

Acetylcholine

ACh, through both nicotinic and muscarinic type receptors (nAChR and mAChR, respectively), contributes to attentional and reward functions. Cholinergic and DA neurons interact closely at the VTA, NAc, and PFC (Sofuoglu & Mooney, 2009). In the VTA, both nAChR and mAChR stimulate DA neurons. In the NAc, cholinergic interneurons integrate cortical and subcortical information related to reward. In the PFC, increased ACh release accompanies development of psychomotor sensitization to amphetamines, suggesting participation of the prefrontal cholinergic system in neuronal adaptations leading to addiction (2006). Further, in a rat model of reward sensitivity, some rats, called sign-trackers, were especially prone to attribute incentive salience to reward cues, relative to

others, called goal-trackers (Paolone, Angelakos, Meyer, Robinson, & Sarter, 2013). In addition, sign trackers displayed relatively poor attentional control and attenuated ability to increase prefrontal ACh during periods of high attentional demand. These findings suggest the importance of ACh and DA interactions in reduced ability to resist reward cues (Paolone et al., 2013). It will be of great interest to determine the role of ACh in mediating attentional bias to drug cues in humans.

Norepinephrine

Similar to ACh, norepinephrine (NE) is another neuromodulator that is closely linked to DA, both anatomically and functionally. Activation of noradrenergic neurons in the locus coeruleus, via stimulation of DA neurons in the VTA, results in DA release in the NAc.

Studies in rats and monkeys have shown that locus coeruleus neurons respond to the salience and significance of stimuli (Sara, 2009). Locus coeruleus neurons are particularly sensitive to stimuli that require a shift in attention and behavioral adaptation. In the prefrontal cortex, NE is required for optimum working memory and sustained attention functions. The importance of NE in mediating shifts in attention and in promoting optimal behavioral performance suggests that NE plays an important role in salience attribution to drug associated stimuli. To our knowledge, no human studies have been conducted to determine the role of NE in attentional bias.

Serotonin (5-HT)

5-HT neurons, located in the brain stem, project diffusely to the cortex, hippocampus, amygdala, striatum, thalamus, and hypothalamus. Consistent with this widespread distribution, 5-HT participates in many functions including the hedonic, motivational and learning aspects of reward (Kranz, Kasper, & Lanzenberger, 2010). Preclinical studies have demonstrated that 5-HT provides tonic inhibitory control over DA. Consistent with these findings, 5-HT opposes some DA effects: 5-HT induces behavioral inhibition and is associated with satiety and punishment (Boureau & Dayan, 2011). However, for other functions, 5-HT and DA have a synergistic role. At the behavioral level, increased 5-HT levels reduce cue-induced cocaine seeking behavior (Burmeister, Lungren, Kirschner, & Neisewander, 2004).

In a recent human study, escitalopram, a selective 5-HT reuptake inhibitor, compared to placebo, reduced AB to cocaine-related words in a cocaine Stroop task (Liu et al., 2013). However, this treatment effect was not observed following prolonged treatment with escitalopram (see Table 3). To summarize, preclinical and a few human studies support the contribution of neuromodulators, DA, ACh, NE, and 5-HT in mediating AB for cocaine-associated cues.

AB Modification

In attentional bias modification (ABM), individuals are trained to shift their attention away from drug cues and toward neutral cues (Wiers et al., 2013). While there have been no ABM studies for cocaine and other illicit drugs, ABM has had clinically-observable results for other conditions, including prevention and declines in anxiety (Amir, Beard, Burns, &

Bomyea, 2009; Hazen, Vasey, & Schmidt, 2008; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002; See, MacLeod, & Bridle, 2009) and depression (Browning, Holmes, Charles, Cowen, & Harmer, 2012).

Single-session ABM has been associated with decreased attentional bias for alcohol (Field & Eastwood, 2005; Schoenmakers et al., 2007; Field, Duka, Eastwood, Child, Santarcangelo, & Gayton, 2007) and cigarettes (Attwood et al., 2008; Field, Duka et al., 2009), along with some evidence of impact on actual substance use and craving in these studies. Other single-session ABM studies have reported non-significant craving reduction for alcohol (Field et al., 2007; Schoenmakers et al., 2007) and cigarette smoking (Field, Duka et al., 2009).

As a result, multi-session ABM for alcohol was developed and tested by Schoenmakers et al. (2010), who found significant effects in reducing attentional bias with modest clinical gains (i.e., increased time to relapse and faster discharge among inpatients). However, attentional bias was not associated with decreased likelihood of relapse and did not have an effect in decreasing craving. Fadardi and Cox (2009) found within-subject decreases in attentional bias to alcohol cues and alcohol consumption among problem drinkers following a multi-session, multi-faceted intervention aimed at reducing attentional bias. However, given that the intervention included personalized feedback and other elements designed to enhance motivation to change, along with the lack of a control group, it is difficult to ascertain whether attentional retraining specifically led to these changes. Finally, in a study of non-treatment-seeking smokers, Kerst & Waters (in press) reported that ABM reduced attentional bias over time but did not reduce smoking behavior.

ABM is a relatively new research area and many important questions have yet to be addressed (Wiers et al., 2013). These include the optimal number of retraining sessions, the optimal number of trials within each retraining session, relative efficacy of these procedures for prodromal versus substance-dependent people, and the relative value of traditional, laboratory-based sessions versus those conducted over the internet and/or on mobile devices.

Discussion and Future Directions

AB as an assessment tool for CUD

There is sufficient evidence to conclude that strong AB to cocaine cues is common among cocaine users, particularly those with CUD (see Table 1). However, there have been negative studies, thus not all cocaine users have performed on tasks in a manner indicative of AB. An important future research direction will be to learn more about individual difference variables that may be associated with intensity of AB to cocaine cues. Sex differences have been under-addressed in studies of cocaine-related attentional bias. Most studies enrolled few females and only 4 studies included in our review reported results of analyses to test for effects of sex (Bardeen et al., 2014; Kilts et al., 2013; Montgomery et al., 2010; Tull et al., 2011). Sex differences are pertinent given basic research findings suggesting stronger reinforcing effects of cocaine in females (Carroll, Morgan, Lynch, Campbell, & Dess, 2002) and human findings suggesting that degree of cocaine reinforcement may vary based on menstrual cycle phase (Evans, Haney, & Foltin, 2002;

Sofuoglu, Dudish-Poulsen, Nelson, Pentel, & Hatsukami, 1999). Thus, sex differences and comparisons based on menstrual phase are important future directions for research on AB to cocaine cues. Context may be an important issue as well. Some cocaine users may display AB in their everyday, drug-using environments but not within typical laboratory conditions. Studies showing stronger AB to cocaine cues following salient experimental manipulations (i.e., trauma scripts, Bardeen et al., 2014; Tull et al., 2011) and alcohol administration (Montgomery et al., 2010) are suggestive as these manipulations may have approximated the actual drug-using contexts of these individuals, which enhanced their AB to cocaine cues.

A promising pattern of results concerns prediction of clinical outcome of CUD treatment based on intensity of AB (Carpenter et al., 2006). Recent evidence suggests more precisely that AB may be an indicator of temptation to use drugs in the near future (Waters et al., 2012) and relapse risk shortly thereafter (Marhe, Waters, et al., 2013). Given the potential clinical impact of these recent findings, it would be valuable to replicate and extend these results (Field et al., in press). The use of hand-held devices in this study (Marhe, Waters, et al., 2013) is notable, specifically the value of assessing AB during participant identified temptation episodes, which is only possible with the use of portable devices. This line of research could be extended to cocaine users outside of inpatient treatment where the benefits of portable, convenient assessment of AB could be combined with the utility of ecological momentary assessment (Epstein & Preston, 2010) to learn about pertinent information including the participant's current context, including their location, who they are with etc. and relationships between these variables and AB.

In future attentional bias studies among cocaine users, it would be helpful for investigators to characterize their study samples as carefully as possible with regard to certain key variables, which have been found to relate to AB. These include whether participants are treatment seeking or not (Vadhan et al., 2007) and participants' severity of use (Smith et al., 2014), including how frequently they use/and or whether they meet diagnostic criteria for CUD.

Lastly, to date, neuroimaging studies of AB in cocaine have utilized only fMRI and the majority of these studies had small sample sizes. There has been a great deal of heterogeneity of findings as well (Table 2), which may be addressed, in part, with the inclusion of larger samples. Greater consistency in methods across studies, particularly the details of the AB tasks used, may also help to reduce inconsistent results across studies. In addition, all neuroimaging studies should report both imaging and behavioral results so that readers may better understand the findings in the context of the broader literature on AB in the addictions. Further, use of other neuroimaging methods such as PET would provide additional information, for instance on neurotransmitter activity underlying AB, which may inform further testing of pharmacotherapy to ameliorate AB.

AB as a treatment target for CUD

Given the need for novel treatments for CUD, it would be valuable to test attentional bias modification for this indication. Prior studies suggest some efficacy for alcohol and cigarette smoking (Attwood et al., 2008; Field & Eastwood, 2005; Schoenmakers et al., 2010), but these results have been limited. There have been negative results published, particularly with

single-session retrainings, and publication bias is always a possibility. There is reason to believe though that AB may be especially robust for cocaine cues (Table 1), more so than for some other addictions (Carpenter et al., 2006; Sharma & Money, 2010) and with comparatively strong correlations with craving (Field, Munafò, & Franken, 2009). For these reasons, attentional bias modification (ABM) may be particularly impactful among patients with CUD. Use of portable devices with their added convenience and accessibility may be particularly important to the delivery of this intervention, for multiple reasons. In addition to the general need to enhance access to addiction treatment (Schulden et al., 2012), the convenience of portable devices would increase the likelihood that CUD patients receive an adequate “dose” of the intervention. While the optimal number of ABM sessions is not yet known, it is highly likely that multiple sessions are needed (Schoenmakers et al., 2010).

Possible use of ABM in combination with other treatments

Targeting executive functions—ABM may be combined with procedures that enhance executive functions. Cognitive biases are particularly detrimental among substance users with weaker working memory (Sharbanee et al., 2013), suggesting that if working memory could be enhanced, cognitive biases might exert less influence. Cocaine users frequently experience particularly strong cognitive impairments during early abstinence, which may then lead to poor treatment retention and outcome (Woicik et al., 2009). Poorer executive function has also predicted early treatment dropout among cocaine dependent individuals (Verdejo-Garcia et al., 2012). Thus, working memory difficulties and other cognitive impairments have clinical implications. Working memory has been targeted in recent interventions with stimulant dependent patients, with success in terms of reducing impulsive choices (Bickel et al., 2011).

Pharmacotherapies—Medications targeting DA, Ach, NE, and 5-HT may have utility in attenuating AB for cocaine. Given the promising findings with methylphenidate in reducing AB for cocaine (Goldstein et al., 2010), other DA transporter inhibitors (e.g., modafinil) may also be effective in reducing AB for cocaine.

Among cholinergic medications, medication that increases synaptic Ach levels (i.e., cholinesterase inhibitors) or stimulates Ach receptors (e.g., varenicline) may also warrant studies to determine if they reduce AB in cocaine users. In a previous study, we found that galantamine, a cholinesterase inhibitor that also has direct effects on the nAChR, improved sustained attention in abstinent cocaine users (Sofuoglu, Waters, Poling, & Carroll, 2011) and is undergoing testing as treatment for cocaine addiction. Given the promising findings of Liu et al. in attenuating AB for cocaine with escitalopram, further studies using 5-HT transporter inhibitors and other serotonergic medications may also be warranted (Liu et al., 2013).

Conclusions

CUD is an important public health problem and novel approaches are needed to improve the effectiveness of treatments for CUD. Automatic cognition may be particularly relevant to CUD as there is evidence for a robust AB to cocaine cues and strong relationships to craving for cocaine and other illicit drugs. Further, wide-ranging cognitive deficits (e.g., in response

inhibition and working memory) evinced by many cocaine users enhance the potential importance of interventions targeting automatic cognition. Given that AB appears to be particularly relevant to cocaine use and the great need for novel treatments, attentional bias modification (ABM) should be tested for CUD treatment. ABM could be utilized either as a stand-alone treatment or in combination with existing interventions (e.g., pharmacotherapy).

Acknowledgments

This research was supported by National Institutes of Health grants K01 AA 019694, K02-DA021304, the Veterans Administration Mental Illness Research, Education and Clinical Center (MIRECC), the Connecticut Department of Mental Health and Addiction Services and the Connecticut Mental Health Center. Dr. Sofuoglu serves as an expert witness on behalf of Pfizer in lawsuits related to varenicline. The funding sources had no role other than financial support. The contents of the manuscript are solely the responsibility of the authors and do not necessarily represent the official views of any of the funding agencies. The authors would like to thank Dr. Ken Carpenter, Dr. Marc Copersino, Dr. Karen Ersche, Dr. Ingmar Franken, Dr. Rita Goldstein, Dr. Robert Hester, Dr. Shijing Liu, Dr. Reshmi Marhe, Dr. Catharine Montgomery, Dr. Dinkar Sharma and Dr. Estate Sokhadze for generously providing additional results beyond those that were published in their papers and Christine Nogueira for editorial assistance.

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Table 1

Behavioral results from attentional bias (AB) studies involving cocaine (COC) users

Author	Participants	Design	AB Task(s)	Main behavioral findings: (+/- AB in ms [SD])
Bardeen (2014)	Inpatient TS CD, all trauma-exposed with (n = 22, 32% male) or without comorbid BPD (n = 36, 69% male)	Comparisons by BPD status & gender AB tested after trauma or neutral script (within-subject)	VP task: COC & neutral images	COC AB in BPD males (n = 7) after trauma script (+27 ms[22]) but not after neutral script (-7 ms[42]). No COC AB non-BPD males (+8 ms[15]) (d=1.01), BPD females (-6 ms [14]) (d=1.79) or non-BPD females (-14 ms[19]) (d=1.99) after trauma or neutral script *.
Carpenter (2006)	Outpatient TS DD (N = 80, 78% male), including some CD (n = 45, 73% male)	Outcome study	Drug Stroop	COC AB among CD (+23 ms[101]) COC AB associated with ↑positive urines & ↓treatment weeks completed
Carpenter (2012)	Outpatient TS CD (N = 25, 88% male)	Outcome study Contingency Management (CM) protocol	Drug Stroop	COC AB (+20 ms[120]) not significant COC AB associated with ↑treatment outcomes after CM vouchers ended
Copersino (2004)	Non-TS CD with (n = 23, 83% male) & without schizophrenia (n = 20, 90% male) Controls with (n = 19, 89%) & without schizophrenia (n = 20, 70% male)	Comparisons between CD & schizophrenia groups	COC Stroop ¹	COC AB in CD without schizophrenia (+98 ms [74]) but not COC with schizophrenia (-54 ms [104]) (d=1.68), or Controls with (-54 ms[116]) (d=1.56) or without schizophrenia (+16 ms[16]) (d=1.53) ** COC AB associated with ↑craving
Ersche (2010)	Non-TS SD (n = 18, 83% male) Healthy controls (n = 18, 83% male)	Comparison with controls Pharm study fMRI study	Stimulant Stroop	Stimulant AB effect on placebo (+106 ms [117]) in SD, & +48 ms[70] in controls (d=0.60) Stimulant AB associated with ↑compulsivity
Franken (2000)	Inpatient TS CUD (N = 16, 81% male)	Association with craving	COC word VP	COC AB (short SOA = +3 ms[77]; long SOA = +6 ms[51]) not significant COC AB not associated with craving
Gardini (2009)	DD (cocaine [n = 24] & heroin [n = 45], 90% male among DD): active users & those in recovery Healthy controls (n = 25, 56% male)	Comparison of active users (n = 23) with those in recovery & healthy controls (n = 25)	COC Stroop Heroin Stroop	AB (COC & Heroin) (+21 ms[25]) was larger than in Controls (+5 ms[14]) (d=0.79), recovered community-treated (+7 ms[12]) (d=0.71), and recovered replacement (0 ms[18]) (d=0.96) ***
Goldstein (2007)	CUD including active users (TS status not reported) & in remission (N = 14, 64% male)	fMRI study	COC Stroop ²	COC AB (-6 ms) not significant
Goldstein, Alia-Klein (2009)	Non-TS CUD (n = 17, 76% male) Healthy controls (n = 17, 82% male)	Comparisons with controls Monetary reward (within-subject) fMRI study	COC Stroop ²	COC AB not significant in CUD (-5 ms) or Controls (0 ms), & no group difference

Author	Participants	Design	AB Task(s)	Main behavioral findings: (+/- AB in ms [SD])
Goldstein, Tomasi (2009)	Non-TS CUD (n = 15, 80% male) Healthy controls (n = 15, 67% male)	Comparisons with controls fMRI study	COC Stroop ²	COC AB not significant in CUD (-5 ms) or Controls (-1 ms), & no group difference
Goldstein (2010)	Non-TS CUD (n = 13, 92% male) Healthy controls (n = 14, 100% male)	Pharm study fMRI study COC AB task performed only after medication/placebo, no baseline task	COC Stroop ²	COC AB not significant on medication in CUD (2 ms) or Controls (0 ms), or on placebo in CUD (-6 ms) or Controls (0 ms) & no group difference or difference by medication condition
Hester (2006)	Current COC users, TS- & diagnostic status not reported (n = 23, 70% male) Healthy controls (n = 23, 70% male)	Comparisons with controls	COC Stroop: word & picture types	COC AB in COC users (word = +123 ms[174], picture = +159 ms[292]) larger than AB in Controls (word = +38 ms[89], picture = -4 ms[121]) (word $d=0.62$, picture $d=0.73$)
Hester, Garavan (2009)	Current COC users, TS- & diagnostic status not reported (N = 16, 63% male)	WM load within-subject manipulation fMRI study	WM task ³	Significant COC AB with high WM load (+99 ms[195]) but not low WM load (-20 ms[78])
Kilts (2013)	TS (inpatient/outpatient not reported) CD (N = 42, 74% male)	fMRI study	COC Stroop ⁴	COC AB (+73 ms[89]).
Liu (2011)	CD (TS & non) (n = 37, 89% male) Healthy controls (n = 32, 53% male)	Comparisons with controls Association with impulsivity	COC Stroop	COC AB (+20 ms[45]) in CD but not Controls (-6 ms[28]) ($d=0.37$). COC AB stronger among treatment seekers. AB correlated with commission error rate on immediate memory task in CD (not controls)
Liu (2013)	Non-TS CD (N = 23, 91% male)	Pharm study	COC Stroop	COC AB at baseline (+67 ms[32])
Marhe, Luijten (2013)	Inpatient TS CD (N = 26, 85% male)	Outcome study fMRI study	COC Stroop	COC AB (+86 ms[64]) COC AB not predictive of use at 3-months
Montgomery (2010)	Regular COC users, TS & diagnostic status not reported (n = 32, 47% male) Healthy controls (n = 40, 48% male) All regular EtOH users	Comparisons between COC users and controls AB tested after EtOH or placebo (between-subject)	VP & COC Stroop ¹	COC users have COC AB after EtOH (+13 ms[8]) but not placebo (-11 ms[7]) on VP task ($d=0.79$). Controls have no AB on VP task (after EtOH: -6 ms[7] [$d=0.49$], after placebo: -1[6] [$d=0.39$]) ^{****} AB on Stroop not significant among COC users (0 ms[3]) or controls (0 ms[4]), EtOH manipulation did not affect Stroop results Sex entered as covariate in analyses of VP and Stroop but did not affect results
Sharma (2010)	Lifetime crack users, self-reported current abstinent, some TS but unclear how many, diagnostic status not reported (N = 16, 81% male)	Exposed to non-word letter strings paired with COC-related images, then administered version of Stroop	Stroop ⁵ with COC-conditioned & non-conditioned letter strings	AB to conditioned cues (+82 ms[151]); largest on trial following cue (+208 ms); smaller in subsequent trials (+69 ms)

Author	Participants	Design	AB Task(s)	Main behavioral findings: (+/- AB in ms [SD])
Smith (2014)	SD (n = 50, 88% male) & recreational COC users (n = 27, 52% male), some TS but unclear how many Healthy controls (n = 52, 64% male)	Comparisons with recreational users & healthy controls fMRI study	COC Stroop	COC AB (+90 ms[161]) for SD but not recreational COC users (-23 ms[75]) or Controls (+18 ms[98]) (<i>d</i> for SD/recreational comparison=0.90; <i>d</i> for SD/controls comparison=0.54)
Tull (2011)	Inpatient TS CD, all trauma exposed, with (n = 30, 27% male) or without comorbid PTSD (n = 30, 83% male)	Comparisons by PTSD status AB tested after trauma or neutral script (within-subject)	COC image VP task	CD/PTSD had higher COC AB after trauma script (+16 ms[7]) than after neutral (-9 ms[7]), result applied to both sexes; CD/non-PTSD had lower COC AB after trauma script (-3 ms[8]) than after neutral (+22 ms[8]) (<i>d</i> for trauma script=0.45; <i>d</i> for neutral script=0.78) ****
Vadhan (2007)	TS (n = 17) & non-TS CD (n = 20), male only	Comparisons between TS & non-TS	Drug Stroop	COC AB in TS (+49 ms[65]) but not non-TS (-5 ms[68]) (<i>d</i> =.81)
Waters (2012) & Marhe, Waters (2013)	Inpatient TS HD, 88% CD (N = 68, 85% male)	AB tested during temptation & at random times (within-subject) Outcome study	Drug Stroop ⁶	COC AB (+43 ms[163]); ↑ at temptations (+68 ms[152]) than at random times (+36 ms[165]). Early relapsers higher AB than non-relapsers during temptations

Key: AB (attentional bias) = RT on cocaine trials minus RT on neutral trials; *d* = Cohen's *d* effect size estimate for comparison of attentional bias to cocaine cues between groups; BPD = borderline personality disorder, CD = cocaine dependent, CUD = cocaine use disorder (includes those meeting diagnostic criteria for cocaine abuse or dependence), DD = drug dependent, EtOH = alcohol, HD = heroin dependent, PLA = placebo, PTSD = post-traumatic stress disorder, RT = reaction time, SD = stimulant dependent, TS = treatment seeking, VP = visual probe, WM = working memory

Unless otherwise noted, Stroop tasks used word stimuli and were administered via computer.

¹ Stroop not administered via computer.

² Version of Stroop task used included a 2-second period when participants looked at word stimuli before responding, thus task not designed to yield an attentional bias to COC stimuli, also included monetary reward contingencies for accurate responses.

³ WM task included high (random) or low memory load (sequential) number strings presented against COC, blank or neutral backgrounds.

⁴ Word counting version of COC Stroop.

⁵ Stroop task involved non-word letter strings, some that had been conditioned to drug cues via repeated pairings with COC-related imagery before Stroop task and some that had not been conditioned.

⁶ Stroop administered on hand-held devices at random times and during participant-initiated temptation episodes

* Effect sizes for comparison with BPD males after trauma script. No AB to cocaine cues after either trauma or neutral script among other groups. For other groups, results shown for AB to cocaine cues after trauma script.

** Computed assuming 50 words per list. Raw data are as follows: COC AB in CD without schizophrenia (+4.9 sec) but not COC with schizophrenia (-2.7 sec), or Controls with (-2.7 sec) or without schizophrenia (+0.8 sec). Effect sizes for comparison with cocaine users without schizophrenia.

*** Effect sizes for comparison with current drug dependent group

**** Adjusted means (adjusted for score on Alcohol Use Disorders Identification Test [AUDIT; Saunders et al. 1993]), figures in parentheses standard errors rather than standard deviations. Effect sizes for comparison with cocaine users after EtOH

Adjusted means (adjusted for age, income, depression, anxiety, stress), figures in parentheses standard errors rather than standard deviations. Effect size comparisons between cocaine dependent individuals with and without PTSD. Separate effect size comparisons for trauma and neutral scripts.

Table 2

Results of fMRI attentional bias (AB) studies involving cocaine (COC) users

Author	Participants	Design	AB Task(s)	Main fMRI findings
Ersche (2010)	Non-TS SD (n = 18, 83% male) Healthy controls (n = 18, 83% male)	Comparison with controls Drug Condition (within-subjects) Compulsivity (between-subjects)	Stimulant Stroop	SD (vs. Controls) had ↑activation of the left ventral PFC & right cerebellum (cocaine vs. neutral contrast) ↑AB associated with ↑activation of the left ventral PFC & right cerebellum (cocaine vs. neutral contrast).
Goldstein (2007)	CUD including active users (TS status not reported) & in remission (N = 14, 64% male)	Within-subjects comparisons of responses to drug vs control words	COC Stroop ¹	No differences for cocaine vs. neutral contrast ↓Rostro-ventral ACC & medial OFC (cocaine vs. neutral contrast) correlated ↑cocaine errors minus neutral errors (but not AB)
Goldstein, Alia-Klein (2009)	Non-TS CUD (n = 17, 76% male) Healthy controls (n = 17, 82% male)	Comparisons with controls	COC Stroop ¹	Differences for cocaine vs. neutral contrast not reported ↓ACC & medial OFC activity and ↑ left dl/dm PFC & left cerebellum in CUD vs. controls, apparently on both neutral & cocaine trials
Goldstein, Tomasi (2009)	Non-TS CUD (n = 15, 80% male) Healthy controls (n = 15, 67% male)	Comparisons with controls	COC Stroop ¹	↑activation of mesencephalon (where the ventral tegmental area & substantia nigra are located) (cocaine vs. neutral contrast) for CUD but not controls
Goldstein (2010)	Non-TS CUD (n = 13, 92% male) Healthy controls (n = 14, 100% male)	Comparisons with controls Pharm study	COC Stroop ¹	20 mg methylphenidate ↑ (normalized) ACC & medial OFC activation in CUD, particularly on cocaine words
Hester, Garavan (2009)	Current COC users, TS- & diagnostic status not reported (N = 16, 63% male)	WM load within-subject manipulation	WM task ²	During high (not low) WM load, activity in left inferior occipital cluster ↑for cocaine vs. neutral backgrounds During high (not low) WM load, activity in right inferior frontal gyrus ↑for cocaine vs. neutral backgrounds
Kilts (2013)	TS (inpatient/outpatient not reported) CD (N = 42, 74% male)	Network-level correlation analysis	COC Stroop ³	↑activation of dlPFC, dmPFC, ventromedial (vmPFC), posterior cingulate cortex (PCC), right IFC, and right occipitotemporal cortex (cocaine vs. neutral contrast) ↑ AB related to ↑ recruitment of inferior frontal–parietal–ventral insula network & frontal–temporal–cingulate network ↑ AB related to ↓ recruitment of sensory–motor–dorsal insula network Sex entered into regression analyses. Patterns of activity appeared to apply to both sexes with the exception of one significant gender effect not interpreted in text of article.

Author	Participants	Design	AB Task(s)	Main fMRI findings
Marhe, Luijten (2013)	Inpatient TS CD (N = 26, 85% male)	Outcome study	COC Stroop	No differences for cocaine vs. neutral contrast ↑right dorsal ACC contrast (cocaine minus neutral) predicted ↑ COC use at 3-month
Smith (2014)	SD (n = 50, 88% male) & recreational COC users (n = 27, 52% male), some TS but unclear how many Healthy controls (n = 52, 64% male)	Comparisons with recreational users & healthy controls	COC Stroop	Recreational users showed ↓activation in OFC, ACC & posterior cingulate compared to SD & controls for cocaine vs. neutral contrast (SD & controls did not differ)

Key: ACC = anterior cingulate cortex, CD = cocaine dependent, CUD = cocaine use disorder (includes those meeting diagnostic criteria for cocaine abuse or dependence), dl = dorsolateral, dm = dorsomedial, OFC = orbitofrontal cortex, PFC = prefrontal cortex, SD = stimulant dependent, TS = treatment seeking, vm = ventromedial, WM = working memory

Unless otherwise noted Stroop tasks used word stimuli and were administered via computer.

¹Version of Stroop task used included a 2-second period when participants looked at word stimuli before responding, also included monetary reward contingencies for accurate responses.

²WM task included high (random) or low memory load (sequential) number strings presented against COC, blank or neutral backgrounds.

³Word counting version of COC Stroop.

Table 3

Results of attentional bias (AB) studies pertaining to pharmacotherapy involving cocaine (COC) users

Author	Participants	Design	Active pharm tested	Main pharmacology findings
Ersche (2010)	Non-TS SD (n = 18, 83% male) Healthy controls (n = 18, 83% male)	Drug Condition (within-subjects) Compulsivity (between-subjects)	amisulpride (dopamine antagonist) & pramipexole (agonist) & PLA	Effect of Drug Condition on AB in SD was moderated by compulsivity: 0.5 mg pramipexole di-hydrochloride tended to ↓AB in low compulsives & ↑AB in high compulsives 400 mg amisulpride had opposite effects
Goldstein (2010)	Non-TS CUD (n = 13, 92% male) Healthy controls (n = 14, 100% male)	Drug Condition (within-subjects)	methylphenidate	20 mg methylphenidate ↓ errors of commission on COC words Data for effect of Drug Condition on AB not reported
Liu (2013)	Non-TS CD (N = 23, 91% male)	Drug Condition (between-subjects)	escitalopram	↓AB with 10 mg escitalopram (vs. PLA) at 5-hr post-dose but not days 2–5

Key: = cocaine use disorder (includes those meeting diagnostic criteria for cocaine abuse or dependence), DA = dopamine, OFC= orbitofrontal cortex, PFC= prefrontal cortex, PLA = placebo, RT = reaction time, WM = working memory