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Review

What is abnormal about addiction-related attentional biases?

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ABSTRACT

Background: The phenotype of addiction includes prominent attentional biases for drug cues, which play a role in motivating drug-seeking behavior and contribute to relapse. In a separate line of research, arbitrary stimuli have been shown to automatically capture attention when previously associated with reward in non-clinical samples.
Methods and results: Here, I argue that these two attentional biases reflect the same cognitive process. I outline five characteristics that exemplify attentional biases for drug cues: resistant to conflicting goals, robust to extinction, linked to dorsal striatal dopamine and to biases in approach behavior, and can distinguish between individuals with and without a history of drug dependence. I then go on to describe how attentional biases for arbitrary reward-associated stimuli share all of these features, and conclude by arguing that the attentional components of addiction reflect a normal cognitive process that promotes reward-seeking behavior.

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1. The role of attentional bias in addiction

One of the features that characterize addiction is strong attentional biases for drug cues (see Field and Cox, 2008; Rooke et al., 2008; for reviews). When an individual becomes addicted to a substance, stimuli associated with that substance acquire a powerful ability to automatically capture attention that is not evident in individuals without a history of substance abuse (Hogarth et al., 2003, 2005; Lubman et al., 2000; Mogg et al., 2003; Nickolaou et al., 2013a,b; Stormark et al., 1997; see Fig. 1A). Similar attentional biases can also be observed in heavy but non-dependent substance users (Field et al., 2004b; Townshend and Duka, 2001), suggesting that experience with a drug reward creates learning-dependent changes by which associated stimuli become persistently attention-grabbing.

Importantly, there is evidence that addiction-related attentional biases reflect more than just an epiphenomenal curiosity, but rather contribute to the pathology of drug dependence. The magnitude of attentional bias for drug cues has been shown to be predictive of later relapse during the course of treatment (Carpenter et al., 2006; Cox et al., 2002; Marissen et al., 2006; Waters et al., 2003b; Powell et al., 2010), and such attentional biases are thought to mediate the incentive salience of drug cues (Berridge, 2012; Berridge and Robinson, 1998; Robinson and Berridge, 1993). Even after periods of abstinence, attentional biases for drug cues can still be observed (Field and Cox, 2008; Field et al., 2013; Marissen et al., 2006; Stormark et al., 1997), providing a persistent biasing signal that draws the individual to opportunities to experience the drug reward, potentially complicating attempts to maintain abstinence. However, the utility of addiction-related attentional biases as a tool in clinical assessment has not been established (Field et al., 2014), and failures to predict later relapse have also been reported (Field et al., 2013; Waters et al., 2003a).

2. Parallels with normal cognition

In a different line of research using mostly non-clinical samples, attentional biases have been observed for arbitrary stimuli previously associated with non-drug, often monetary, reward (for reviews, see Anderson, 2016a; Awh et al., 2012; Chelazzi et al., 2013). Following a training period in which participants are rewarded each time they locate a searched-for target stimulus, participants complete a test phase in which these previously reward-associated stimuli now appear as task-irrelevant distractors during visual search for a different target. Attention is biased to select such previously reward-associated distractors in this case (Anderson et al., 2011a,b, 2014, 2016c; see Fig. 1B). Similar attentional biases are either not observed or are substantially weaker following otherwise equivalent training in which rewards are not given (Anderson, 2016b; Anderson et al., 2011a,b, 2012, 2014; Failing and Theeuwes, 2014; Wang et al., 2013; Qi et al., 2013); thus, the reward learning imbued associated stimuli with height-

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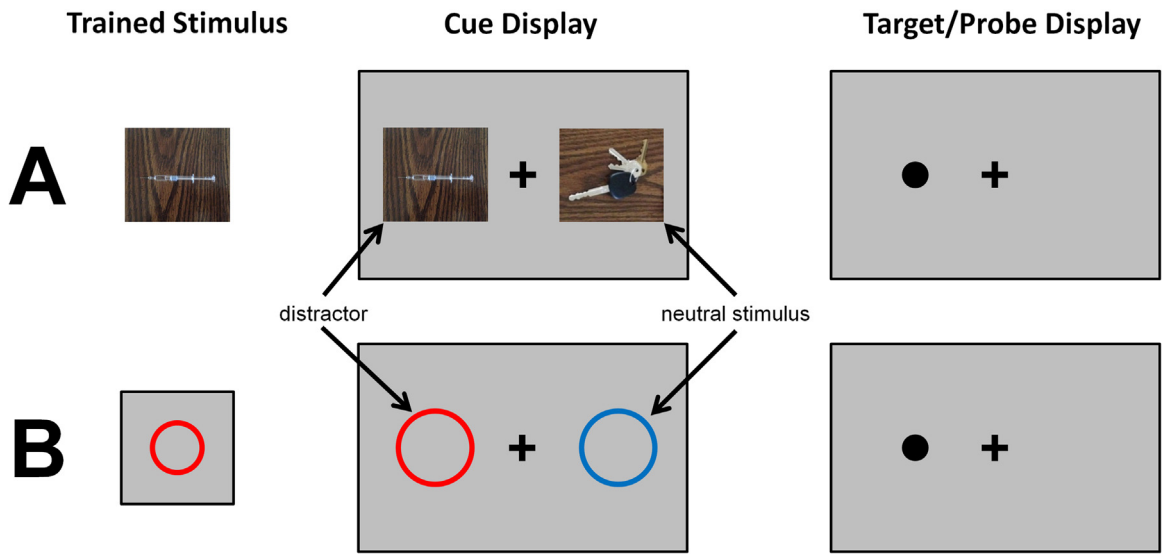

Fig. 1. Sample comparison of attentional biases for drug cues and arbitrary reward cues. For drug cues (A), the "training" involves real-life drug use in situations where the cue is present. For arbitrary reward cues (B), the cue is used to predict a reward outcome (often monetary gains) in the context of a laboratory experiment. When presented alongside a neutral stimulus after training, both cue types (now called distractors because they are explicitly task-irrelevant) facilitate processing of a target or probe appearing at their location after a brief delay (in this example, measured by the speed with which a probe dot is detected). These two forms of learned attentional bias share several important characteristics.

Table 1
Summary of key features that are common to attentional biases towards drug stimuli in addicted populations and attentional biases towards arbitrary reward cues in healthy participants.

Features of Attentional Bias	Arbitrary Reward Cues	Drug Cues
Resistant to conflicting goals	√	√
Endure long after learning	√	√
Overlapping neural mechanisms	√	√
Biases approach behavior	√	√
More prominent in drug- dependent populations	√	√

ened attentional priority. This has been referred to as *value-driven attentional capture* (Anderson, 2013).

Research on the value-driven control of attention has progressed more or less independently of research on addiction-related attentional bias, and there is currently very little cross-talk between the respective literatures. In this review, I will make the case that these two literatures are measuring the same cognitive process, that addiction-related attentional biases are a particular example of value-driven attention, providing a fruitful opportunity for translating findings from one literature to the other. Such a correspondence is not immediately obvious, as addiction-related attentional biases possess several striking characteristics that are not typically observed in normal cognition and can appear distinctly pathological. However, these same features can be observed in healthy individuals in the context of a psychology experiment (see Table 1). In short, following a few hundred trials of an associative learning task, any person can exhibit some of the most salient attentional characteristics of a drug-dependent individual. In the sections that follow, I outline five criteria that capture some of the key characteristics of addiction-related attentional biases, and describe how value-driven attention fulfills each of these criteria.

2.1. Criterion 1: automatic and resistant to conflicting goals

If the goal is to draw an analogy with addiction-related attentional biases, it is not enough to argue that reward history can also bias attention to non-drug stimuli. Addiction-related attentional biases occur when the drug cues are completely irrelevant to the task and in a context in which participants have the goal of attending to a different stimulus (Carpenter et al., 2006; Field and Cox, 2008; Field et al., 2004a,b, 2013; Marhe et al., 2013; Lubman et al., 2000; Marissen et al., 2006; Mogg et al., 2003; Stormark et al., 1997; Townshend and Duka, 2001), and under conditions in which the participant desires abstinence (Carpenter et al., 2006; Cox et al., 2002; Field et al., 2013; Marhe et al., 2013; Marissen et al., 2006; Waters et al., 2003b). This striking failure of current goals to overcome the bias to attend to drug cues attests to the powerful automaticity of this bias and helps to explain why sustaining desired abstinence can be so difficult (Berridge, 2012; Berridge and Robinson, 1998; Carpenter et al., 2006; Marissen et al., 2006; Robinson and Berridge, 1993).

It turns out that arbitrary stimuli, when previously associated with non-drug reward, can similarly capture attention in spite of conflicting goals. Even under conditions in which participants are aware that previously rewarded stimuli are irrelevant to the current task and should be ignored, and even when they are no longer expecting to receive any explicit rewards, these distractors capture attention and impair performance (e.g., Anderson et al., 2011a,b, 2014). Perhaps the most striking example of this can be found in a study in which participants were rewarded for identifying red and green targets during a training phase, and then completed a test phase in which they searched for a shape-defined target. On a subset of trials during the test phase, one of the non-targets was rendered in a previously reward-associated color from training. Color was completely irrelevant to the task and participants were informed of this, and no monetary rewards were available. The previously reward-associated non-targets (distractors) were only distinguishable on the basis of their particular color, apart from which there was nothing attention-grabbing about these stimuli. In spite of these conditions, search performance was impaired by the previously reward-associated distractors (Anderson et al., 2011b) and the distractors were fixated much more frequently than other non-targets (Anderson and Yantis, 2012). Thus, the reward learning had imbued these stimuli with an attention-capturing quality they did not have before, causing them to overpower goal-directed attentional selection.

The failure to ignore previously reward-associated stimuli even when completely irrelevant to the current task is now a well-

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replicated finding (Anderson, 2016b; Anderson et al., 2011a,b, 2012, 2014; Anderson and Yantis, 2012; Della Libera and Chelazzi, 2009; Failing and Theeuwes, 2014; Hickey et al., 2010a; Krebs et al., 2010; Le Pelley et al., 2015; Theeuwes and Belopolsky, 2012; Wang et al., 2013; Qi et al., 2013; see Anderson, 2016a, for a review). Even when participants are motivated by currently available reward to ignore previously reward-associated stimuli, they are unable to do so (Anderson et al., 2013b). An arbitrary stimulus can acquire an attention-capturing quality that resembles that of drug cues when repeatedly paired with a reward in a simple training procedure, similarly overpowering the intensions of the individual to ignore it and focus on something else. The inability to exert control over attentional selection as a result of associative reward learning is not unique to addictions.

2.2. Criterion 2: robust to extinction

One of the most striking features of addiction-related attentional biases is their persistence. Even after periods of sustained abstinence, attentional biases for drug cues can still be observed (Field and Cox, 2008; Marissen et al., 2006; Stormark et al., 1997). The learning processes underlying addiction involve stable changes in the brain that shape attention even well after the learning has occurred. Value-driven attention as measured in a psychology experiment, in contrast, might instead reflect a tendency to perseverate in what has been rewarding in the recent past that is short-lived, without any enduring reshaping of the attention system.

Early demonstrations of the influence of reward learning on attention revealed a perseveration of attentional biases several days after the learning occurred (Anderson et al., 2011b; Della Libera and Chelazzi, 2009). This suggested the possibility of long-term changes in attentional priority, but it is still not on the timescale characteristic of addictions. A pair of follow-up studies demonstrated value-driven attentional biases that were evident over half a year after the reward learning (Anderson and Yantis, 2013), particularly for impulsive individuals (Anderson et al., 2016b). Apparently, a few hundred experimental trials pairing arbitrary stimuli with monetary reward outcome is sufficient to generate the sort of enduring attentional biases that have been observed in previously drug-dependent patients.

2.3. Criterion 3: linked to dopamine signals within the dorsal striatum

Drug-dependence is associated with persistent changes in dopamine release within the striatum (Volkow et al., 2003). Dopamine signaling in the dorsal striatum is thought to be important for the learning and execution of habits, being shaped by reward prediction and prediction-error signals in the ventral striatum (Graybiel, 2008). The release of dopamine in the dorsal striatum has been specifically linked to cue-evoked drug craving (Volkow et al., 2006; Wong et al., 2006) and is thought to play a role in signaling incentive salience (Berridge, 2012; Berridge and Robinson, 1998; Volkow et al., 2002). Neural reactivity to drug cues is reduced with a dopamine antagonist (Luijten et al., 2012). If addiction-related attentional biases reflect a specific case of value-driven attention, then attentional biases for stimuli associated with non-drug reward should also be mediated by dopamine signaling within the dorsal striatum.

Research in non-human primates has identified neurons within the dorsal striatum, in particular within the tail of the caudate, that increase their responding to cues once these cues have acquired value through association with reward (in this case, liquid reward; Yamamoto et al., 2013). Furthermore, these changes in neuronal sensitivity were accompanied by orienting biases during free viewing (Yamamoto et al., 2013), and stimulation of neurons in this region evokes eye movements (Yamamoto et al., 2012). Functional magnetic resonance imaging in humans confirms that neural responses in this area are associated with involuntary attentional capture by reward cues in spite of conflicting search goals (Anderson et al., 2014).

The aforementioned studies are ambiguous with regards to the underlying neurotransmitter signaling, however, reflecting general metabolic demands (Anderson et al., 2014) and electrical activity (Yamamoto et al., 2012, 2013). Identification of the role of dorsal striatal dopamine specifically was provided in a positron emission tomography (PET) study (Anderson et al., 2016c). In that study, the magnitude of attentional bias for color stimuli previously associated with monetary reward was correlated with dopamine release within the right caudate and posterior putamen. The correspondence between these activations and the neural correlates of cue-evoked drug craving as revealed by PET (Wong et al., 2006) are striking. One possible reason for this correspondence, as argued in this paper, is that cue-evoked drug craving is mediated by the automatic value-driven orienting of attention, which reflects a general learning mechanism that is not specific to drug reward.

Other brain areas implicated in addiction-related attentional biases include the anterior cingulate cortex (ACC; Luijten et al., 2011, 2012; Janes et al., 2010a; Marhe et al., 2013; Nestor et al., 2011; Vollstadt-Klein et al., 2012), amygdala (Janes et al., 2010a,b; Nestor et al., 2011; Vollstadt-Klein et al., 2012), nucleus accumbens (NAcc; Nestor et al., 2011), insula (Janes et al., 2010a,b; Luijten et al., 2011; Vollstadt-Klein et al., 2012) and dorsolateral prefrontal cortex (DLPFC; Janes et al., 2010a; Luijten et al., 2012; Vollstadt-Klein et al., 2012). The ACC (Hickey et al., 2010a), amygdala (Ousdal et al., 2014; Peck and Salzman, 2014a,b), insula (Wang et al., 2015), and the ventral tegmental area (Hickey and Peelen, 2015), which contains dopaminergic projections to the NAcc (e.g., Schultz, 2002), have also been implicated in the orienting of attention to arbitrary reward cues. The author is not aware of any studies relating activity within the DLPFC to attentional capture by reward cues, which may reflect particular aspects of the different methodologies that tend to be used across fields (see Section 3. Comparison of Experimental Procedures) or processes particularly engaged by drug-related stimuli.

2.4. Criterion 4: linked to biases in approach behavior

The prior criteria all concern the processing of sensory information without regards to its effect on behavior. As discussed previously, attentional biases for drug cues are thought to mediate drug-seeking behavior via their incentive salience (Berridge, 2012; Berridge and Robinson, 1998; Robinson and Berridge, 1993). Direct support for this can be found in studies relating attentional biases for drug cues to addiction relapse (Carpenter et al., 2006; Cox et al., 2002; Marissen et al., 2006; Waters et al., 2003b; Powell et al., 2010), along with studies demonstrating that addiction-related attentional biases predict drug craving (Field et al., 2004a, 2005, 2013; Franken et al., 2000; see Field et al., 2009, for a meta analysis) and that manipulating attention to drug cues modulates the desire to consume the drug (Field and Eastwood, 2005; Field et al., 2007). In short, addiction-related attentional biases facilitate approach and consummatory behavior. Can a similar relationship between attention and action be observed for attentional biases for arbitrary reward cues learned in a psychology laboratory?

Several recent studies support a link between value-driven attention and decision-making and action selection. Value-driven attentional capture by an irrelevant stimulus impairs the ability to choose between two differently-valued options in a speeded forced-choice task, resulting in less optimal choice performance (Itthipuripat et al., 2015). Attentional processing of reward-

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associated stimuli also predicts related economic risk-taking, with greater attentional bias for a high-value cue associated with larger wagers in a gambling task (San Martin et al., 2016). Task-irrelevant but previously reward-associated stimuli bias hand movements in a reaching task, causing compensatory deviations in reach trajectory when competing for selection with the target (Moher et al., 2015). Perhaps more directly related to addictions, previously reward-associated but currently task-irrelevant stimuli more strongly evoke an associated response in both a flankers task (Anderson et al., 2012) and a Stroop task (Krebs et al., 2010, 2011). Such stimuli have also been shown to escape inhibitory processing in a cued go/no-go task, with their associated response signals more strongly influencing behavior (Anderson et al., 2016a); that is, response inhibition processes that are normally effective at suppressing the associated behavior signaled by a no-go stimulus fail to do so when that stimulus is previously associated with reward. In summary, when an arbitrary reward-associated stimulus captures attention, this attentional orienting is associated with a bias in approach behavior.

Evidence also supports a link between attentional biases for arbitrary reward cues and the incentive salience of the associated reward. The most direct evidence for this can be found in a study in which arbitrary cues were paired with chocolate odor (Pool et al., 2014). Such chocolate-associated cues captured the attention of individuals who reported liking chocolate. However, these same cues ceased to capture attention when the participants were satiated on chocolate, suggesting that such value-driven attentional capture was better explained by whether participants wanted the associated reward at the time that the cue was experienced. In further support of this idea, attentional capture by arbitrary reward cues tends to be correlated with the reward drive component of the behavioral activation system (see Carver and White, 1994) rather than the reward sensitivity component (Hickey et al., 2010b; Qi et al., 2013), suggesting that the motivational rather than the hedonic qualities of reward contribute to the development and expression of attentional bias. Additional research is needed to more firmly establish the relationship between the wanting/motivational and the liking/hedonic aspects of reward as they contribute to value-driven attentional biases.

2.5. Criterion 5: can distinguish between individuals with and without a history of drug-dependence

Addiction-related attentional biases are not evident in individuals without a history of drug dependence (Hester et al., 2006; Lubman et al., 2000; Mogg et al., 2003), and the magnitude of attentional biases for drug cues predicts later relapse (Carpenter et al., 2006; Cox et al., 2002; Marissen et al., 2006; Waters et al., 2003b; Powell et al., 2010). If such addiction-related attentional biases are reflective of a more basic mechanism of value-driven attention, then value-driven attentional biases for non-drug reward cues may similarly differentiate drug-dependent individuals from individuals with no history of drug dependence. One possibility is that the sensitivity of the attention system to irrelevant reward information is altered in addiction, such that drug dependence is broadly associated with difficulty ignoring arbitrary reward cues (i.e., including, but not limited to, cues associated with drug reward).

Evidence from methadone-maintained opioid-dependent patients supports this idea. The magnitude of attentional capture by stimuli previously associated with monetary reward was substantially larger in this patient group compared to matched controls (Anderson et al., 2013a). A follow-up study demonstrated that this addiction-related difference in attentional bias is not limited to individuals who are actively drug-dependent. Individuals with a history of substance dependence who were not actively using drugs, as confirmed via urinalysis, also exhibited elevated value-driven attentional capture compared to individuals with no history of substance dependence, a difference that was mediated by trait impulsiveness (Anderson et al., 2016b). Such findings suggest that value-driven attention, as a basic cognitive mechanism, contributes to actual drug abuse.

3. Comparison of experimental paradigms

The aforementioned parallels must be understood in the context of the different methodologies used in each of the two attentional bias literatures. Methodologies commonly used in the addiction-related attentional bias literature include the visual/dot-probe task (e.g., Field et al., 2004a,b; Lubman et al., 2000; Mogg et al., 2003), free viewing of naturalistic images (e.g., Rosse et al., 1993, 1997; Wong et al., 2006; Volkow et al., 2006) or the completion of a secondary task while viewing naturalistic images (e.g., Luijten et al., 2011, 2012; Nickolaou et al., 2013a), and the addiction-Stroop task in which drug-related words serve as task-irrelevant input (e.g., Carpenter et al., 2006; Cox et al., 2002; Marissen et al., 2006; see Cox et al., 2006, for a meta-analysis). Studies of value-driven attention in non-clinical samples, in contrast, tend to use simple visual stimuli in tasks designed to isolate spatial-attentional competition between the target and a distractor, such as the additional singleton and visual search paradigms (e.g., Anderson et al., 2011a,b, 2014; Chelazzi et al., 2014; Feldmann-Wustefeld et al., 2016; Lee and Shomstein, 2014); however, the visual/dot-probe task (e.g., Failing and Theeuwes, 2014; Muller et al., 2016; Pool et al., 2014; Stankevich and Geng, 2014; Sun et al., in press), naturalistic images (Anderson, 2015; Hickey and Peelen, 2015), free viewing methods (Anderson and Yantis, 2012; Yamamoto et al., 2013), and the Stroop task (Krebs et al., 2010, 2011) have also been employed in the study of value-driven attention. Thus, although these literatures tend to rely on related but different experimental paradigms, core findings have been validated using common methodologies.

Better integration of these different methodologies across fields holds promise in furthering our understanding of both the clinical and non-clinical sides of reward-related attentional bias. The highly controlled tasks used in the non-clinical attentional bias literature may prove useful in better isolating specific components of attentional bias in addiction, such as biased competition as assessed through the additional singleton paradigm, that may be of particular interest to a clinical theory. Exploration of these paradigms as a clinical measure might also prove fruitful in light of concerns pertaining to the reliability (Ataya et al., 2012) and clinical utility (Field et al., 2014) of common measures of addiction-related attentional bias. On the other side of the equation, the tasks commonly used in the clinical literature offer more ecological validity and tap into the effects of lifelong learning in naturalistic contexts, something that is poorly understood in the non-clinical literature. Such an approach could help facilitate novel insights into the broader role of attentional biases in real-world behavior.

Another difference between addiction-related and value-driven attentional bias measures that bears mention, owing to differences in the nature of the underlying associative learning, is that drug cues are not uniquely associated with rewarding or otherwise positive outcomes. Drug cues are also associated with punishing outcomes, all of the negative consequences of drug use, and as such are fundamentally cues of a mixed valence. There are some studies demonstrating phenotypically similar attentional biases using arbitrary stimuli associated with monetary loss (Wang et al., 2013; Wentura et al., 2014) and electric shock (Schmidt et al., 2015a,b; Wang et al., 2013), suggesting that basic mechanisms of punishment learning also shape attention. Much less research has been conducted on punishment-driven attentional bias, which is beyond the scope of this review. However, it is noted that such atten-

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tional biases may also share key features with addiction-related attentional biases, with the latter not being restricted to only reward-related processes. This is clearly an important issue to be addressed in future research, from both the clinical and non-clinical sides.

4. Summary and conclusions

Several of the hallmarks of addiction-related attentional biases can be found in normal, healthy individuals with no history of drug dependence following brief associative learning between arbitrary stimuli and reward outcomes. The attentional phenotype of addiction can be created in a laboratory setting, with its ability to overpower conflicting goals, its robust persistence over extended periods of time, its underlying neural mechanisms, and its ability to influence overt behavior. Such value-driven attentional biases can also differentiate between drug-dependent individuals and individuals with no history of drug dependence, further suggesting a relationship between learned attentional biases and struggles with addiction that extends beyond the effects of drug reward per se.

In spite of these similarities, there is currently very little cross-talk between the clinical and non-clinical attentional bias literatures. This is unfortunate, as it limits scientific progress. Studies of value-driven attention should inform addiction research and vice versa, as there are clear and meaningful parallels between what the two are measuring. For example, detailed mechanistic insights concerning the value-driven control of attention in non-clinical samples can be used to make predictions about the specific components of attention that are influenced by drug use. Similarly, manipulations of attentional biases towards arbitrary reward cues should inform efforts to modulate drug-related attentional biases in patients, which remains a challenge (Field et al., 2014). On the other side of the equation, general theories concerning the control of attention should seek to account for phenomena observed in the addiction literature, as several of these phenomena speak to the fundamental architecture of the attention system more broadly. In this way, greater cross-talk between these areas holds promise in deepening our understanding of both core mechanisms of human attention and the effects of drug use on attention, as well as facilitating translational breakthroughs in the effort to reduce reward-related attentional biases and curb addictive behaviors.

The clinical utility of addiction-related attentional biases as a measure has not been established (Field et al., 2014). Although several studies have demonstrated a link between measured attentional bias to drug cues and subsequent treatment outcome (Carpenter et al., 2006; Cox et al., 2002; Marissen et al., 2006; Waters et al., 2003b; Powell et al., 2010), results from other studies have been inconsistent (e.g., Field et al., 2013; Marhe et al., 2013; Waters et al., 2003a). Addiction-related attentional biases are also not limited to biases in initial orienting, at times encompassing subsequent inhibition of drug-related stimuli (e.g., Field et al., 2013; Peuker and Bizarro, 2014; Stormark et al., 1997). As noted in the previous section, addiction-related attentional biases can be measured in several different ways, each of which may tap particular aspects of attentional processing that could be differently related to patient outcomes. Deconstruction of the different components of value-driven attention could shed light on these complexities and aid in the development of experimental tools that better isolate the components of attention most critical to behavioral outcomes, and greater cross-talk between the clinical and non-clinical attentional bias literatures would help facilitate this effort.

It has been argued throughout this review that addiction-related attentional biases and attentional biases for arbitrary reward cues reflect the same underlying cognitive process. This is not to say that addiction-related attentional biases do not influence or are influenced by factors that distinguish drug addiction from other forms of reward learning, including withdrawal and substance-related brain plasticity (e.g., Volkow et al., 2003). Understanding these unique interactions is likely critical to understanding the pattern of addiction as well as predicting and influencing treatment outcomes. However, the development, expression, and neural representation of drug-related attentional biases themselves have a parallel in normal cognition, and it is likely that core principles of information processing are shared between the two of them.

In conclusion, it is argued that attentional biases for drug cues, as powerful as they are, are neither a unique consequence of the physiological effects of a substance of abuse or the result of a process that is itself pathological. Rather, the brain is wired to afford high priority to reward cues, and drug reward powerfully recruits this basic cognitive architecture. Such attentional biases serve the important purpose of facilitating previously rewarded behaviors, but can become pathological when these behaviors are no longer beneficial. Greater understanding of the basic architecture of value-driven attention should inform our understanding of how addiction-related attentional biases develop and manifest; likewise, findings concerning addiction-related attentional biases provide valuable insights into the basic architecture of attention that theories of the control of attention should strive to incorporate.

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Contributors

Brian A. Anderson is the sole author of this article and is responsible for its contents.

Conflict of interest

None.

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