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Missing motoric manipulations: rethinking the imaging of the ventral striatum and dopamine in human reward

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Abstract

Human neuroimaging studies of natural rewards and drugs of abuse frequently assay the brain's response to stimuli that, through Pavlovian learning, have come to be associated with a drug's rewarding properties. This might be characterized as a 'sensorial' view of the brain's reward system, insofar as the paradigms are designed to elicit responses to a reward's (drug's) sight, aroma, or flavor. A different field of research nevertheless suggests that the mesolimbic dopamine system may also be critically involved in the motor behaviors provoked by such stimuli. This brief review and commentary surveys some of the preclinical data supporting this more "efferent" (motoric) view of the brain's reward system, and discusses what such findings might mean for how human brain imaging studies of natural rewards and drugs of abuse are designed.

Keywords Reward · Addiction · Dopamine · Ventral striatum · Nucleus accumbens · PET · fMRI · Motor

The mammalian brain's reward system is critical in the search for food and survival. Distortion of this circuitry is also believed to play a key role in the development of (and perhaps resistance to) drug addiction (Haber and Knutson 2010; Koob and Volkow 2016). For this reason, a large body of research in both human and animal behavioral neuroscience has targeted brain reward pathways.

The mesolimbic dopamine system is a central aspect of the brain's reward circuitry. A considerable body of research presumes what might be termed a "sensorial" view of dopamine, wherein striatal dopamine transmission is a response to an exogenous stimulus— either a drug as the direct result of its pharmacologic actions, or a stimulus that has become associated with the drug's actions via Pavlovian learning. The capacity of a drug- (or even non-drug reward) associated stimulus— a sight, smell, or taste— to induce dopamine transmission has been interpreted as reflecting drug/reward wanting (the incentive salience model Robinson and Berridge 1993), or as a teaching signal that enables organisms to calculate reward probabilities and predict when a reinforcer will be available (the reward learning model; Schultz et al. 1997). Perhaps more plausibly, a combination of these two phenomena may be operative, as Berridge (2012) notes that most studies of mammalian reward prediction and prediction error are conducted during when animals are in states of deprivation to heighten wanting and assure that they engage the paradigm.

In the context of these two theoretical views (i.e. incentive salience or reward learning and prediction), a large number of human brain imaging studies have examined responses to drug, food, or monetary reward "cues." Using functional magnetic resonance imaging (fMRI), and less often positron emission tomography (PET), such work has demonstrated that drug and natural reward (food) cues do, indeed, provoke ventral striatal activity (Noori et al. 2016). Consistent with the incentive salience model, many clinically oriented studies conceptualize these Pavlovian stimuli as tempting individuals into reward consumption through this striatal activation. In experiments of this sort, little is nevertheless required of subjects but to observe and detect the presence of the reward cues. However, another body of findings suggests that this "sensorial" view may not capture the entire picture of striatal activity.

An alternate (or much more likely, complementary) line of thinking derived from largely animal work indicates that mesolimbic dopamine is critical to the *execution* of motivated behaviors. This preclinical work suggests that it may therefore be important to separate

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responses to reward-related cues from responses related to the effortful behavior to acquire rewards. Indeed, the midbrain's dopaminergic input into the telencephalon targets what are commonly understood to be key elements of the *motor* system: the basal ganglia, of which the ventral striatum is a part. As designed (and perhaps as constrained by the nature of the experimental environment and apparatus), many human brain imaging studies are less well equipped to account for the motoric aspect of reward related behavior.

In this manuscript I will first briefly review the relevant anatomic pathways. I will then review the preclinical data supporting this more "efferent" (motor) view of the brain's mesolimbic dopamine system in reward, focusing in particular on food and alcohol, although the concepts should, in principle, extend to any addictive drug. I will then discuss how these data might be considered when designing human brain imaging experiments to accommodate this more efferent theory of the brain's reward system.

Reward system anatomy

Excellent in-depth reviews of the primate and human reward system are available elsewhere (e.g., Haber and Knutson 2010). For brief context, and in broad overview, midbrain dopamine neurons in the substantia nigra (SN), ventral tegmental area (VTA), and retrorubral area (RRA) project to the striatum (caudate and putamen; Fig. 1).

The ventrolateral tier of the SN projects to the lateral sensorimotor striatum (putamen). The SN's dorsal tier targets the ventral caudate and putamen, while the adjacent VTA sends axons to the nucleus accumbens (Haber et al. 2000). Several regions of frontal cortex also receive dopamine afferents from the dorsolateral SN (dorsolateral/dorsomedial prefrontal) and VTA (medial, ventromedial frontal); RRA regions send afferents to these same cortical areas with a similar topological orientation (Williams and Goldman-Rakic 1998).

In turn, limbic and frontal association cortices project back to the striatum, with ventromedial orbital (particularly important in the representation of a reward's subjective value; see Hare et al. 2009, 2011) and lateral orbitofrontal cortices targeting the ventromedial striatum. The dorsal anterior

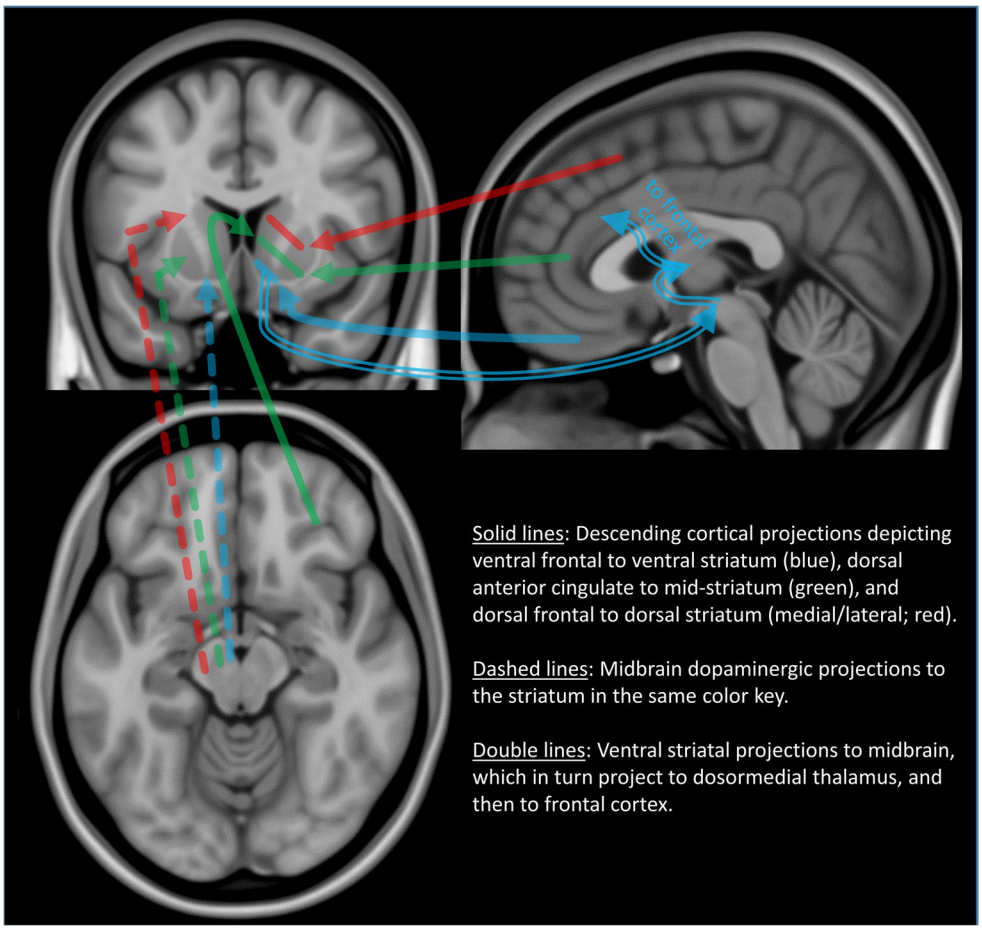

Fig. 1 Schematic of approximate reward pathways between cortex and striatum, as adapted from Haber et al. (2000, 2006), Haber and Knutson (2010), and Sesack and Grace (2010). See the respective publications for more detail

cingulate targets medial caudate and putamen, while dorsolateral prefrontal cortex projects to dorsomedial and dorsolateral (caudate and putamen) striatal areas (Haber et al. 2006). Along with input from other regions not covered here (e.g., amygdala, insula, hippocampus, hypothalamus), this system is thus poised to assimilate information regarding stimulus salience, reward value, and perceived reward probability—all consistent with the abundance of literature showing that drugs and drug-related stimuli evoke dopaminergic transmission in the ventral striatum (Koob and Volkow 2016).

The ventral striatum does not, however, rest afferent to frontal cortex in this isolated geography. First, intrastriatal integration is accomplished via a series of spiraling straitonigro-striatal connections, through which information within limbic, association, and motor striatum can be exchanged (Haber et al. 2000). Second, the ventral striatum sends efferent projections to frontal regions via the ventral pallidum, subthalamic nucleus, dopaminergic midbrain, and dorsomedial thalamus (see Sesack and Grace 2010 for detail on the pathways). Thus, as a whole, the ventral striatum is poised to function in both sensory and motor domains.

Mesolimbic dopamine and reward-related motor behaviors

In the environment, problems often lie not just in the elevated state of desire evoked by food and drug-related stimuli, but in the relentless *behavior* engendered by these provocative cues, such as persistent drug seeking pursued to the exclusion of more constructive actions (i.e., criterion 3 for an alcohol use disorder; American Psychiatric Association 2013). In this vein, pre-clinical studies show that striatal dopamine is linked to more than simply a response to rewards or their related sensory properties. Rather, ventral striatal (i.e., nucleus accumbens) dopamine release also appears to be closely associated with the *goal-directed motor behavior* needed to procure rewards (Salamone et al. 2012).

A compelling preclinical example of this phenomenon comes from Roitman and colleagues (Roitman et al. 2004). In this study using the high-temporal resolution technique of fast-scanning cyclic voltammetry (FSCV) in behaving rodents, ventral striatal dopamine was released in response to food associated cues. However, the authors also showed that ventral striatal dopamine transients peaked at, and were tightly time-locked to, the animal's goal-directed behaviors to obtain the food reward. In a separate study using in vivo microdialysis (a recording technique with less temporal resolution than FSCV), Ostlund et al. (2011) isolated food seeking behaviors from food receipt/consumption, and similarly showed that accumbens dopamine release was related to lever pressing behaviors to obtain reward. Although dopamine did not track lever-pressing (food seeking) rate, or number of lever presses/rewards earned, there was a significant reduction in lever-press related dopamine release after eating to satiety (Ostlund et al. 2011).

Using FSCV with an addictive drug rather than food, Phillips et al. (2003) also showed that dopamine release in nucleus accumbens peaked when animals lever-pressed for cocaine (also see Owesson-White et al. 2009 for a similar result). Compellingly, electrical stimulation of the VTA, which induced dopamine release in nucleus accumbens, led to spontaneous lever pressing for cocaine. Similarly, Adamantidis and colleagues (2011) found that optogenetic stimulation of the VTA reactivated previously extinguished food-seeking behaviors. Further underscoring the dopaminergic origins of such goal directed behaviors, pharmacologic inactivation of burst firing in the VTA slows goal-directed sucrose seeking and attenuates nucleus accumbens dopamine transients during seeking (Cacciapaglia et al. 2011). Conversely, dopamine D2 receptor over-expression in nucleus accumbens enhances food seeking and acquisition behaviors without affecting satiety (Trifilieff et al. 2013).

Thus, the animal literature makes clear that, in addition to responding to cues of reward's presence, ventral striatal dopamine transmission is also tightly linked to reward-seeking behaviors, themselves.

Effortful behavior

Although simple instrumental behaviors (e.g. an isolated lever press) to obtain reward are associated with ventral striatal dopamine release, a body of preclinical literature further suggests that accumbal dopamine is critical to surmount more imposing obstacles that interfere with access to food and rewards (Salamone et al. 2007).

In contrast to the studies that measure dopamine transmission, an alternate technique is to test for effortful behaviors after dopamine *depletion*. Dopamine depletion in animals does not change food liking behaviors or appetite, but it does change how effort is deployed (Salamone et al. 2012). For example, selective dopamine depletion with 6-hydroxydopamine (6-OHDA) lesions in nucleus accumbens does not alter responding for food reward when a low ratio response (low effort) is required, but dopamine depletion does dampen responding at higher (more difficult) response ratios, and shifts choices to a less preferred, yet more easily obtained, food (Cousins and Salamone 1994). Similarly, the effects of dopamine antagonism on effort are particularly evident when work-related requirements increase unexpectedly (Ostlund et al. 2012). St. Onge and Floresco (2009) found that dopamine receptor (D_1, D_2) antagonism in rodents decreased choices for larger, riskier food rewards, while amphetamine (which increases synaptic dopamine) augmented preference for the larger/riskier reward. Dopamine antagonism in

rat nucleus accumbens also has greater effects on efforts to gain access to alcohol than on alcohol consumption itself (Czachowski et al. 2001, 2002). Similar human phenomena have been observed, with dopamine depletion depressing effort to obtain cigarettes (Venugopalan et al. 2011), and amphetamine increasing effort to work for money (Wardle et al. 2011).

In neurophysiological studies, the magnitude of mesolimbic dopamine release predicts the speed with which animals initiate action sequences to obtain sucrose reward (Wassum et al. 2012)— data consistent with dopamine's importance to motivational 'vigor' (Niv et al. 2007). Midbrain dopamine neuron spiking activity also declines with increasing fatigue and decreasing effort (Pasquereau and Turner 2013), while striatal dopamine progressively 'ramps' as animals navigate to move closer to obtaining a sweet reward (Howe et al. 2013). In humans, the magnitude of amphetamine-provoked dopamine release is correlated with a willingness to exert effort for larger rewards (Treadway et al. 2012).

Not all data in this area are consistent. In a study where cues signaled varying effort, Day et al. (2010) did not observe accumbal dopamine release during lever presses for sucrose pellets. Gan, et al. (2010) also did not find accumbal dopamine release during increased effort demand when animals decided between a reference choice and choices between alternatives differing in reward value or effort. At least in this particular behavioral choice paradigm, accumbal dopamine increased when the alternate choice involved unexpectedly low effort.

Collectively, a number of findings nevertheless strongly suggest that mesolimbic dopamine is important to overcoming response costs in the search for rewards (Phillips et al. 2007). In this way, dopamine likely functions not only to facilitate learning the incentive value that reward cues eventually come to possess (Berridge 2012), but also to translate such information into the motivated effort required to "seal the deal" (Westbrook and Braver 2016).

Human brain imaging

As previously noted, a substantial proportion of human brain imaging work in the field of alcohol and addiction has been devoted to the ventral striatal response to reward-associated stimuli. A much smaller literature has been devoted to examining the motoric aspects of reward related behaviors, where some findings resemble those in animals. As one example, the monetary incentive delay task (Knutson et al. 2000) pairs a symbol with the chance to win amounts of money, contingent upon a successfully timed behavior (button press). The brain response often studied (ventral striatal activation) is that to the reward cue, just prior to the motor response. However, at least two studies found that when this motor requirement was omitted, ventral striatal responses to passive (non-instrumental) monetary reward anticipation were either absent or weak (Bjork and Hommer 2007; Bjork et al. 2012, although two studies do not support this idea; Delgado et al. 2008; Lewis et al. 2014). Kroemer et al. (2014) also used fMRI to show that higher than average effort was associated with stronger anticipatory cue responses in the ventral striatum.

Our lab's experiments with PET and the tracer [^{11}C] raclopride to examine dopamine release are also suggestive in this regard. As endogenous dopamine release displaces raclopride, changes in the tracer's measured binding potential are used to infer dopamine release as a function of behavioral state (Dewey et al. 1993). First, our early work showed no significant striatal dopamine release when alcohol was infused intravenously while healthy subjects were at rest (Yoder et al. 2007), although an effect did occur when alcohol was infused unexpectedly, consistent with the anticipated effects of a prediction error (Yoder et al. 2009). Ramchandani et al. (2011) reported significant striatal dopamine release from passive (non-instrumental) intravenous IV alcohol infusion, but only in those who possessed the rare 'G' allele of the *OPRM1* μ–opioid receptor gene. In a larger, more recent study, we did detect right unilateral dopamine release from passive IV infusion in non-treatment seeking alcoholics, but not healthy controls (Yoder et al. 2016). Subjects were, however, aware that the baseline condition involved no infusion of any sort, and that alcohol infusion was imminent in the subsequently planned challenge condition. Stimulus salience and anticipation could thus affect these results.

With regard to alcohol-related cues, we recently reported spatially limited (*unilateral*) alcohol flavor cue-induced ventral striatal dopamine release *without* (*i*) instrumental self-administration behaviors (effort), (*ii*) any expectation of intoxication, and (*iii*) alcohol intoxication (Fig. 2a and Oberlin et al. 2013). However, we showed *bilateral* ventral striatal dopamine release using an operant self-administration (instrumental) paradigm that delivered alcohol flavor cues in the context of expected and received alcohol intoxication (Fig. 2b and Oberlin et al. 2014). This at least suggests that the instrumental behaviors required in this paradigm may be adding to the observed signal.

Other studies reporting significant ventral striatal dopamine release from alcohol (Boileau et al. 2003; Setiawan et al. 2014; Urban et al. 2010) also involved traditional instrumental self-administration behaviors through oral ingestion. Clearly our own data leave other possibilities open, such as the expectation of intoxication. Thus, while far from dispositive, the body of findings implies that goal-directed (self-administration) behaviors may well contribute to human ventral striatal dopamine release.

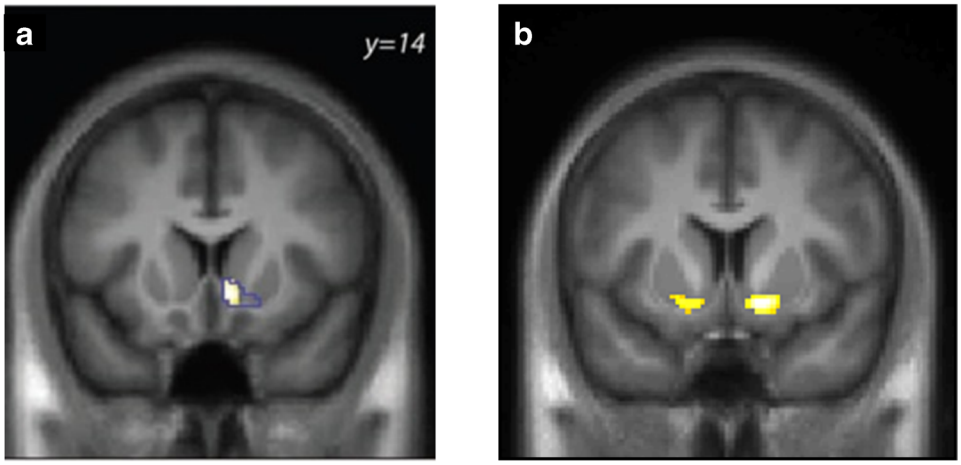

Fig. 2 **a** Unilateral beer flavor-induced ventral striatal dopamine release (compared to control flavor) with no instrumental self-administration behaviors, no expected intoxication, and no alcohol intoxication. **b** Bilateral ventral striatal dopamine release during instrumental self-administration of beer flavor, expected intoxication, and intravenous alcohol (compared to self-administration of a control flavor, no expected intoxication, and saline infusion)

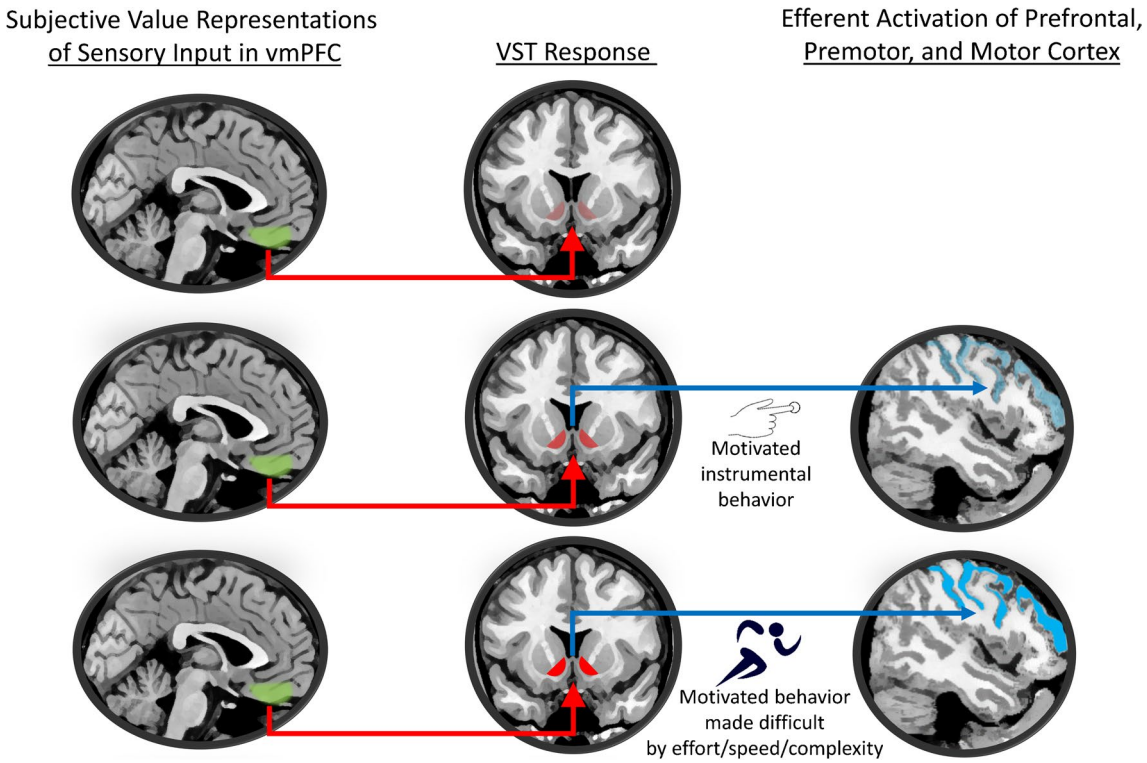

Fig. 3 Hypothetical pathways and effects related to (*top*) passive viewing of reward conditioned stimuli (cues) without opportunity for reward acquisition, (*middle*) reward cues with consequent instrumental behaviors in service of reward acquisition, and (*bottom*) reward cues with instrumental reward acquisition behaviors that require effort expenditure, such as to circumvent obstacles. Subjective value of the reward (here presumed constant across rows) is represented in ventromedial prefrontal cortex (vmPFC; green shading), and made available to the ventral striatum (VST; afferent projections as red arrows; see Fig. 1 for more detail). Greater activation of the VST (represented as progressively brighter shades of red) should be observed with greater instrumental effort, and thus induce greater activation of prefrontal, premotor, and motor cortex (progressively brighter shades of light blue) via VST efferents (dark blue arrows) to frontal regions (see Fig. 1 and Sesack and Grace 2010 for a hypothetical model of efferent projections)

Testable predictions

In accordance with some approaches to studying animals (e.g., Czachowski and Samson 2002; Czachowski et al. 2002), reward paradigms for human brain imaging experiments may need to pay much greater attention to dissociating effects that are due to a reward's Pavlovian associations, and those that might be due to motoric elements involved in either procuring reward or in the behaviors of drug self-administration. In some cases, and as done with animals, this might most cleanly entail separate brain imaging paradigms (imaging data) involving cue exposure and reward seeking/acquisition behaviors so as to minimize any signal overlap between the two. Any act of self-administration would, however, need to be accomplished so as to not measure responses to the drug itself. This latter consideration is not straightforward, as it necessitates avoiding responses related to reward prediction errors (i.e., declines in striatal or midbrain responses related to the unexpected absence of a drug effect; Schultz et al. 1997).

Given the findings reviewed above, and with such a framework in mind, one might then hypothesize a gradient of ventral striatal activity as depicted in Fig. 3. With passive exposure to a cue representative of a valued drug or food reward, some degree of ventral striatal activation (a BOLD contrast difference in fMRI or dopamine release measured in PET) should indeed occur, as previously established. This is the "sensory" stage at which most human studies of drug stimuli operate (i.e., Fig. 3, *top*). However, significantly greater ventral striatal activation should become apparent when subjects act to acquire the reward via some instrumental behavior (Fig. 3, *middle*). With rising effort expenditure to overcome obstacles to reward acquisition (such as a greater need for attention, speed, or endurance; Fig. 3, *bottom*), a parametrically greater degree of ventral striatal activation should ensue. Finally, a concomitant prediction would be a corresponding (and correlated) gradient of increasing activity in frontal cortices (motor, premotor, dorsolateral prefrontal) related to the instrumental behaviors, as well their antecedent planning. As suggested by work in animals, however, ventral striatal activation as measured in these circumstances should not predict reward *consumption*, itself (Czachowski et al. 2001; Czachowski and Samson 2002; Salamone and Correa 2002).

Conclusions and future directions

The human brain's response to drug-associated cues is a frequently employed approach in neuroimaging studies of drug and alcohol use disorders, and in the risk for their development. However, the reactive response to a drug-associated cue in the brain's striatal reward areas may capture only part of the dynamic, and ignore (or depending on the paradigm, blur) striatal aspects of motivated motor behaviors and effort. Separating the effects of reward-related cues from responses related to the effortful behavior to acquire rewards may be important to a broader and more complete understanding of the neurocircuitry changes comprised by addiction and its attendant risk factors for both disease development and treatment relapse.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the studies from the author's lab.

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