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Anticipatory Reward Processing in Addicted Populations: A Focus on the Monetary Incentive Delay Task

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Abstract

Advances in brain imaging techniques have allowed neurobiological research to temporally analyze signals coding for the anticipation of rewards. In addicted populations, both hypo- and hyper-responsiveness of brain regions (e.g., ventral striatum) implicated in drug effects and reward system processing have been reported during anticipation of generalized reward. Here, we discuss the current state of knowledge of reward processing in addictive disorders from a widely used and validated task: the Monetary Incentive Delay Task (MIDT). The current paper constrains review to those studies applying the MIDT in addicted and at-risk adult populations, with a focus on anticipatory processing and striatal regions activated during task performance, as well as the relationship of these regions with individual difference (e.g., impulsivity) and treatment outcome variables. We further review drug influences in challenge studies as a means to examine acute influences on reward processing in abstinent, recreationally using and addicted populations. Here, we discuss that generalized reward processing in addicted and at-risk populations is often characterized by divergent anticipatory signaling in the ventral striatum. Although methodological/task variations may underlie some discrepant findings, anticipatory signaling in the ventral striatum may also be influenced by smoking status, drug metabolites and treatment status in addicted populations. Divergent results across abstinent, recreationally using and addicted populations demonstrate complexities in interpreting findings. Future studies will benefit from focusing on characterizing how impulsivity and other addiction-related features relate to anticipatory striatal signaling over time. Additionally,

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identifying how anticipatory signals recover/adjust following protracted abstinence will be important in understanding recovery processes.

Keywords

Addiction; impulsivity; monetary incentive delay task; reward; striatum; anticipation

Introduction

Reward processing contributes importantly to adaptive decision-making by facilitating the prediction of future events. In particular, neural processes during anticipation occur immediately prior to choice and are thereby optimally ordered in time to influence decision-making(1). Alterations in anticipation-related neural signals could be disadvantageous and compromise abilities to select between different courses of action. Understanding reward processes has significant implications for many psychiatric conditions, particularly addictive disorders, where drug-seeking behavior is attributed to altered reward/reinforcement sensitivities. Thus, neurobiological research has focused not only on understanding sensitivities to drug cues, but also to non-drug rewards, and how alterations in generalized reward processing may represent a vulnerability and/or a maintenance factor in addicted populations. Theories, including Reward Deficiency Syndrome(2), Allostatic Hypothesis(3), Incentive Salience(4), and Temporal-Difference Reinforcement Learning(5), emphasize hypo- or hyper-responsiveness, particularly in the ventral striatum (VS), across reward processing phases and addiction stages. However, neuroimaging research of reward processing has produced seemingly ambiguous and contradictory findings. While differences in findings may relate to methodological/sample characteristics, they also demonstrate emerging theoretical and empirical sophistication in understanding cognitive components of addiction neurobiology. These refinements include consideration of additional constituents underlying cognitive processes in addiction: saliency, valence, magnitude, choice, guessing and motor preparation, all of which may influence reward signals. Conjointly, technological advances provide greater anatomical specificity in neuroimaging; for example, in anatomically dissecting the striatum and identifying complex, dissociable functional roles for its subdivisions(6-9). These efforts together with more rigorous approaches being used in neuroimaging studies (e.g., multiple-comparison corrections, jittered stimuli presentations), contribute to a matured understanding of generalized reward processing.

This review seeks to synthesize reward processing findings in addictions, identify research gaps and future study directions. Anticipatory-reward-processing studies employing a widely used, well-validated task, the Monetary Incentive Delay Task (MIDT), are reviewed in addicted and at-risk adults, with a focus on striatal areas implicated during anticipatory phases. Even limiting discussion to the MIDT, various task versions exist, together with different methodological and modeling approaches applied (Table 1). Although methodological/task variations may underlie some discrepant findings, MIDT studies of generalized reward processing in addicted and at-risk populations have produced divergent findings. We further explore how anticipatory VS signaling may be influenced by smoking status, the presence of drug metabolites and treatment status in addicted populations.

1. MIDT: Advantages, assumptions and unanticipated findings

1.1. Brief history—The MIDT is integrated within theories of human decision-making and on how reward expectations shape behavior. The task, developed for scanning studies by Knutson, Hommer and colleagues, is modeled on an instrumental conditioning task developed by Schultz for use in animal neurophysiological studies(1,10-13). The task effectively explores the premises of multiple theories underlying addictions by parsing aspects of valence, magnitude, as well as motivational from hedonic stages of reward processing, and permitting study of whether distinctions in these domains recruit divergent neuroanatomical and neurochemical substrates. This decomposition of elements empirically integrates computational theories to clarify mechanisms of reinforcement learning. In animal models, probabilistic reward delivery guides associative learning by shifting phasic dopaminergic signaling to cues predicting reward(10,14). Similarly, probabilistic reward delivery on the MIDT increases anticipatory activity in the human VS(11,12), a key projection area of midbrain dopaminergic neurons. Thus, anticipatory processing provides a neural account of subjective cue value; a composite of an individual's current reward potential estimate together with the accrued learning across previous trials. Accordingly, this incentive cue salience can gauge incongruencies between experienced reward and anticipated rewards, enabling a framework to test reward-based learning theories(15-17) and how neural responses may change with experienced or predicted reward.

This framework also applies to learning components in addiction, where heightened anticipatory responding to drug cues may trigger motivational and emotional states related to craving; in contrast, other types of reinforcers may be devalued, thereby maintaining the addiction cycle(3,18). Thus, decoding the distinct neurocircuitry generating this anticipatory affect has implications for understanding approach and avoidance behavior on a second-to-second timescale, with the possibility of an improved index of affect dynamics and resultant behavior in both healthy and addicted populations(1,19).

The MIDT has a low cognitive demand and simple learning component; participants are instructed to respond to a target as quickly as possible, without learning complicated contingencies or making decisions. As such, it bypasses many cognitive variables such as guessing and choice inherent in decision-making tasks (e.g., the Iowa Gambling Task), which may influence reward processing. The MIDT permits examining generalized reward processing using monetary incentives, which are generally valued, scalable, and can be positive and negative in value(20). Moreover, this task has the advantage of assessing individual sensitivity to non-drug related reward processing, potentially compromised in addicted populations. Specifically, the task separates reward phases, through modeling reward anticipation and receipt. While heightened sensitivity to drug-related cues is observed in addicted populations(21), the MIDT allows interrogation of how generalized anticipatory reward processing may be altered in addiction. Nevertheless, even though similar behavioral performance and subjective ratings suggest comparable motivation among healthy and addicted populations, differences specific to monetary valuations on neural measures may still exist(22).

The original task is described in detail elsewhere(1,11,12,23). Briefly, during the first, anticipatory phase of the task, an individual observes a cue signaling the trial type (i.e. win,

loss or neutral), whereafter a target appears on the screen for a variable duration requiring that the subject respond with a button press. In the subsequent outcome phase of the task, an individual receives performance feedback and is updated on cumulative earnings. Importantly, this design disentangles the motivational from hedonic aspects of reward(12) and on a neurobiological level demonstrates spatial distinction in striatal versus medial prefrontal cortex (mPFC) recruitment during anticipatory and outcome processing, respectively(12,13). Therefore, VS and mPFC activation during specific MIDT phases may provide measures of neural sensitivities to reward anticipation and receipt to non-drug rewards.

The VS, encompassing the nucleus accumbens (NAc), is considered a fundamental region linking motivation and action(24) and where addictive drugs exert their rewarding effects (25,26). The finding that anticipatory reward processing during the MIDT activates the VS parallels findings in animal literature(27), providing a unifying account of how brain signals code incentive stimuli. However, a meta-analysis of MIDT studies(1) identified activation foci during gain versus non-gain contrasts in brain areas whose anatomical coordinates more closely correspond with the caudate or dorsal striatum (DS) rather than the NAc. This meta-analysis finding was somewhat unanticipated given that the VS and DS have been ascribed functionally dissociable roles in the reward system(6,28,29). The use of these meta-analysis coordinates as regions of interest (ROIs) in subsequent MIDT studies has led to application of ‘NAc’ and ‘VS’ to areas corresponding more closely with DS regions. Accurate identification of striatal regions is key in clarifying and understanding many study findings, particularly as a locus-of-control shift from VS to DS is posited to underlie the transition from voluntary to habitual drug use(30). Potential mislabeling of striatal areas may contribute to ambiguous findings and possibly obscure functional distinctions; therefore, the current review describes striatal areas based on their anatomical coordinates.

1.2. Dopaminergic signaling and the MIDT—Analogous to electrophysiological studies demonstrating dopamine (DA) neurons encoding differences between the anticipated reward relative to the experienced one, an important assumption underlying MIDT performance is that VS activity reflects endogenous DA signaling(10,31). To date, only 2 human studies have directly examined the relationship between functional and neurochemical activity using Positron Emission Tomography (PET) and fMRI activation during the MIDT in the same participants. While the first study(32), reporting uncorrected results, found a relationship between reward-related [^{11}C]raclopride displacement during PET and VS activity during MIDT performance, a subsequent study did not(33). This latter study, however, reported [^{11}C]raclopride binding potential changes in the posterior caudate, potentially affected by motor components involved with the button press. Nonetheless, the absence of observable [^{11}C]raclopride displacement on a task with intermingled rewarding and non-rewarding conditions may prove difficult for the temporal resolution of PET imaging. More broadly, striatal DA release may not fully encompass functional changes captured during fMRI – indeed, similar functional-neurochemical investigations in other monetary reward/novelty tasks have reported *decreases*, rather than expected increases in DA transmission during unpredictable rewards(34,35). In the case of addicted populations, understanding alterations in DA release may further be complicated by striatal adaptations in dopaminergic receptor affinity, reuptake or availability(36); a better understanding of neurovascular coupling between dopaminergic

alterations and relative cerebral blood volume is necessary for interpreting how the BOLD signal relates to endogenously released DA. An imbalance in tonic-phasic signaling could differentially impair DA system regulation at different addiction stages; while phasic dopaminergic cell firing may convey anticipatory signaling(37,38), tonic signaling modulates these phasic bursts(39). Chronic drug exposure increases tonic activity, resulting in attenuated phasic signaling(39). Altogether, these findings reveal that the relationship between striatal BOLD changes during the MIDT and DA activity remains to be clarified; functional–neurochemical links may be only partially dopamine-dependent, and may represent a more heterogeneous signal reflecting other neurotransmitter systems, or even indicate differences in the excitatory tone of cells as of yet not clearly understood.

1.3. Is neutral 'normal'? Modeling assumptions and interpretations—A pragmatic consideration relates to the MIDT contrasts applied to examine specific constructs. The design permits the investigation of contrasts among multiple dimensions, including between different reward phases (i.e. anticipation versus outcome), valence (i.e. wins versus losses) as well as parametric responses (e.g. $5 vs $1 wins). Most commonly, however, investigations consist of gain versus non-gain contrasts across each of the anticipatory or the outcome phase, in order to isolate specific constructs of interest (i.e. control for visual stimuli, button press etc.). Thus the non-gain (sometimes referred to as 'neutral' or 'no outcome') in which participants win or lose $0 is used as a type of baseline to effectively limit the influence of non-valence related activity. Thus a non-gain contrast presents a more nuanced modeling of the brain data, relative to baseline conditions (e.g., looking at a fixation cross). Even so, this contrast presumes that non-gain-related activity is comparable as a baseline between the 2 experimental groups – an often-untested assumption. Alterations occurring during the non-gain condition (e.g. blunted/heightened signaling) could significantly alter findings of a double-contrast, when examining between-group differences.

Another assumption underlying the MIDT is the absence of behavioral differences on the task: while this can be considered problematic(40), it represents an effective approach for examining neural effects of the task that are not confounded by group differences in performance. Together with faster reaction times to rewarding versus neutral trials, similar success rates are important in establishing comparable motivation across participants. Task calibration during the practice session is meant to preclude behavioral differences and minimize learning effects; however, neural activity during scanning may still partly reflect learning differences in task acquisition, rather than reward processing *per se*. According to reward prediction theory, an individual still learning the task in the scanner may produce less anticipatory activity and greater outcome processing as the neural signals predicting reward delivery have not yet developed. Additionally, the anticipation phase includes not only the anticipation of the potential reward, but also the motivation to work for the reward, thereby further complicating interpretations (41).

2. MIDT findings in addicted populations

The first MIDT studies examining reward processing in addiction were conducted in alcohol-dependent (AD) populations. Two early studies(42,43) report diminished anticipatory VS processing in detoxified, inpatient AD males relative to healthy controls (HC), during both

gain and loss conditions (Table 1). Many significant between-group differences emerge during anticipatory and not outcome phases of reward processing(43), suggesting greater inter-individual differences sensitivities to anticipatory responses(44). However, two other AD studies(45,46) found no anticipatory differences in inpatients undergoing AD treatment; notably, all patients were regular smokers, with a majority meeting current/past dependence for non-alcohol drugs, mostly cocaine (discussed below). In one study(46), a modified MIDT included 'frustration trials' where participants were required to repeat some trials to obtain rewards, thereby examining anticipatory processes involving greater persistence. These frustration trials revealed an increased VS hemodynamic response (across groups) to the first, but not the second response trial(46); specifically, the AD group exhibited greater VS deactivation during frustration trials. Although deactivation could denote greater sensitivity to non-predicted non-rewards(40), it may also indicate an accelerated decline in motivation, since VS activation also reflects the effort to work for a reward (41). Another MIDT study(45), controlling for motor-preparatory effects during anticipation, found that AD groups did not differ from controls in VS recruitment during pre-response reward anticipation; however, post-response anticipatory VS activity in AD subjects did not survive multiple comparison correction, suggesting lowered VS activation in this group.

In nicotine dependence (ND), current smokers exhibit reduced valence-related anticipatory activity in the left VS, anterior cingulate cortex (ACC) and right superior frontal gyrus during MIDT performance(47). Increased developmental and longitudinal studies will clarify whether hypoactive VS anticipatory signaling represents a neurobiological precursor for substance use, with subsequent substance use additionally attenuating this signaling. Indeed, chronic nicotine administration may blunt reward signals in fronto-striatal areas and/or synergistically combine with other drugs or drug metabolites. For example, relative to non-users, chronic cannabis users who also smoke cigarettes exhibit reduced reward anticipation on the MIDT in VS, caudate, putamen and prefrontal cortical areas; however, when controlling for smoking status with a ND control group, chronic cannabis users do not differ in VS recruitment, while altered recruitment in caudate, putamen and prefrontal areas still emerge(48). These findings highlight the benefit of including a smoking control group when examining other addicted populations (that frequently exhibit ND comorbidity).

Nevertheless, another study with matched nicotine use across experimental groups found *increased* right VS anticipatory activation relative to controls using a modified MIDT(49). The conflicting findings across the two cannabis-related studies may be accounted for by analytic differences (the latter contrasted reward activity relative to a fixation cross, rather than a neutral condition). More likely, however, this seemingly divergent result may relate to a distinct difference between participants: inclusion criteria for one study required negative urine toxicologies(48), whereas a positive THC urine screen was requisite in the other(49). The presence of THC or related metabolites, therefore, underscores a potential role for residual intoxication or partial withdrawal when examining signals in chronic drug users with varying stages of abstinence. In occasional users, a positive urine screen may reveal residual intoxication with subacute drug effects, whereas for others it could reflect partial withdrawal, with potentially different influences on neural activities.

Similarly, the potential roles of drugs or drug metabolites and abstinence stages may account for seemingly ambiguous findings reported in cocaine dependence (CD). Increased anticipatory activity in the caudate and right insula was observed in CD in one study(50), while another(51) reported diminished anticipatory processing in the dorsal caudate in CD. The former study investigated a treatment-seeking group with very recent cocaine use (some individuals reporting cocaine use at or very close to the scan date), whereas the latter included patients with 1-2 years of abstinence. Another study(52) using an MIDT variant parsing the anticipation phase into prospect and anticipation phases(53) showed that current and former CD groups differed comparably from a non-addicted group. No significant striatal differences in anticipatory gain or loss processing were observed when contrasting former versus current CD groups(52). Notably, however, the majority of participants in the former CD group included participants with current ND, with roughly ¼ of the sample methadone-maintained, thereby making it difficult to assess incentive processing unmasked by other drug effects (see section 3). In sum, findings across CD studies suggest that clinical differences including treatment-seeking status, length of abstinence, and drugs or drug metabolites (whether in residual intoxication or partial withdrawal) may be important contributors explaining some of the variability in findings in addiction studies.

The expanded addiction category in DSM-5 now includes the first non-substance-based addictive disorder, gambling disorder (GD)(54). MIDT studies in GD investigate the unique situation in which disorder-related cues are in fact monetary; they also interrogate reward-processing mechanisms in a non-substance addiction. One MIDT study of individuals with GD reported diminished frontostriatal activity during both anticipation and outcome of wins and losses, relative to HCs(55). Another study(56) reported diminished ventromedial caudate activation in GD, relative to both an obsessive-compulsive disorder (OCD) and HC group. Importantly, participants in this latter study had GD for less than 5 years, with no other comorbidities. Across both studies, striatal signaling appears less valenced, in that diminished activity is evident across wins and loss relative to comparison groups, a finding reminiscent of those reported in substance-dependent populations(42,43).

2. Anticipatory striatal associations with addiction characteristics

The relationships between anticipatory striatal activity and impulsivity-related constructs appear across addictive disorders and have significant implications for research and treatment efforts. An association between VS activity and impulsivity during anticipatory processing was initially observed in AD(43). This relationship between heightened impulsivity and reduced anticipatory VS signaling has also been noted in adult Children of Alcoholics (COAs) (53) and in GD(55). VS anticipatory activity also relates to substance use; in AD, it correlates inversely with alcohol craving (42). In ND, plasma nicotine concentrations negatively correlate with signal change in the VS and putamen(47). These correlations demonstrate a rather consistent inverse relationship between addiction characteristics of drug intake with neural measures of reward processing. Notably, many of the relationships between addiction characteristics and VS activity occur exclusively in the addicted or at-risk population, suggestive of an important marker of motivational mechanisms underlying addiction vulnerability(57).

An important future direction involves the use of developmental models and monitoring throughout treatment and recovery. For example, in individuals with CD, months of treatment correlates positively with reward anticipation in the left caudate, but two studies demonstrate that abstinence duration in CD correlates negatively with the VS(51,52); as such, striatal reactivity to reward anticipation and outcome may dynamically change with treatment and abstinence progression. Accordingly, discrepant findings, particularly in CD populations, may reflect different addiction stages, with potentially different roles for the DS and VS relating to abstinence and length of treatment(51). These findings may reflect not only the direction but also lability of the VS signal: the VS may be more reactive during active addiction (and acute substance use) and during the onset of abstinence, but may become less reactive during prolonged abstinence(51). Diminished DS response during reward anticipation may also occur during abstinence, yet may over the long term provide a marker of treatment success. These possibilities warrant direct examination.

3. Drug challenges

Drug challenges in MIDT studies in addicted populations may help disentangle state versus trait effects and highlight complexities in interpreting findings and controlling for smoking status across populations. To date, no study has directly examined the effects of acute cocaine administration on the MIDT; however, two studies examining dopaminergic challenges with commonly abused stimulants demonstrate reductions in anticipatory VS signaling in non-addicted populations. While dextroamphetamine administration may blunt anticipatory-related VS activation, it may also extend the duration of the signal, thereby altering endogenous tonic rather than phasic signaling(58). Similar to dextroamphetamine, an oral methylphenidate (MPH) challenge in healthy males produced reduced anticipatory signaling, but increases in recreational D-amphetamine (dAMPH) users(59). In contrast, during placebo administration, recreational dAMPH users show reduced VS responding relative to non-users, suggesting altered striatal function even with recreational dAMPH use. Given the exploratory and cross-sectional nature of these studies, more longitudinal research is necessary to disentangle developmental from potential neurotoxic effects occurring from recreational drug use. Nonetheless, these different findings in placebo versus drug and non-users versus recreational users may account for findings in MIDT populations with positive or unverified toxicology screens. For example, subacute drug effects may stimulate incentive processing, alter the lability of VS signalling and modify VS-impulsivity relationships(49,50).

Nicotine patch administration in a smoking population highlights state- versus trait-related changes in motivational processes. Specifically, in a MIDT separating anticipatory valence from magnitude, attenuated VS activity during anticipatory valence showed a state-specific change in incentive processing in smokers during nicotine exposure(47). Together with increased DS activity during anticipatory magnitude-processing in smokers during the nicotine patch, these results suggest important modulatory effects of this drug in incentive processing in smokers. Future studies should examine anticipatory signaling in non-smokers as well as ‘chipper’ groups following a nicotine patch to further disentangle acute versus chronic effects of the drug on the brain (i.e., given a possibly sensitized response in ND). Notably, alterations in receptor availability between healthy, recreationally-using, and addicted populations may further complicate interpretations. For example, compromised D2 DA receptor occupancy in

ND individuals may leave less room for a further increase in response to monetary reward following a drug challenge(60). Accordingly, a THC challenge produces reduced anticipatory VS responding in ND, but slightly increases activity in HC participants(60). HC responses to THC have produced ambiguous results (see(61)), therefore acute THC and nicotine challenge studies are important to characterize HC responses.

In sum, the implication of these findings in smoking groups is wide-ranging, particularly given the high rates of ND in many psychiatric populations. Considering nicotine's effect on the reward system, these results emphasize the importance of carefully monitoring smoking chronicity and nicotine intake prior to scanning, as well as potentially including a smoker control group when examining other populations.

Conclusions and future directions

The findings from MIDT studies of addicted populations suggest altered anticipatory processing in the VS relative to control populations. While many studies report attenuated VS activity in an addicted/at-risk population, such findings are not consistently ascertained. Discrepancies in MIDT findings may not only be due to task design, but also to acute drug effects, particularly nicotine, as well as addiction phase. Additionally, results suggest that individual differences in fronto-striatal recruitment, particularly the VS, reflect impulsivity and addiction-related characteristics. Taken together, there may exist both trait and state considerations in understanding the neural correlates of reward anticipation in addictions. Task design should streamline contrasts (e.g. limiting the influence of non-valence-related activity through contrasts that control for motor preparation, visual stimuli, etc.) and include loss trials to prevent/limit adaptation to rewards(60). Indeed, systematically evaluating how loss processing may differ in addicted populations remains difficult, as many studies do not report loss trial findings(50-53,60) or even include them(44,48,61,62). The latter trial structure may influence incentive processing as individuals habituate to receiving rewards. Studies reporting loss trial results often describe similar striatal responses to those evidenced during gain>neutral contrasts(42,43,46,49,55-57,63), although some studies report divergent findings(49,58,59). Few directly examine valence effects through gain– loss contrasts; therefore, more information on negative incentive processing is needed in addicted groups. Allostatic models suggest neuroadaptations related to negative reinforcement as central to the addiction cycle particularly during protracted abstinence(3). Finally, anticipatory–outcome phase contrasts could provide an axiomatic approach to the reward-prediction-error hypothesis(64).

Another source of variance largely unexplored on the MIDT is the role of counterfactual thinking in which responses to a given trial are related to previous trial performance. Cognitive biases, particularly in some addicted populations, could produce mixed emotions as an individual may have perceived hitting the target, or have a different response to neutral trials. Although experimental groups mostly do not differ in subjective ratings on different trials, these ratings are collected upon scan completion and do not necessarily reflect responses at each given trial. Nonetheless, how best to do so is complicated as collecting information on a person's expectation and response to each trial would interrupt the flow of the task and alter its essence(65).

With only a few exceptions, most study samples to date are relatively small (<20; Table 1); improvements in amalgamating data across scanners will aid in further substantiating findings. Efforts to combine MIDT data across sites should be promoted to increase sample sizes and promote addiction research. Nonetheless, extant findings highlight the importance of verifying the presence or absence of drugs or drug metabolites through urine screens and careful characterization of smoking status. In this way, the MIDT may help characterize neuroadaptations of anticipatory incentive signaling occurring in acute and extended periods of drug self-administration and abstinence. Divergent results across abstinent, recreational-using and addicted populations demonstrate complexities in interpreting findings. Moreover, characterizing how impulsivity and other addiction-related features relate to anticipatory striatal signaling over time will be important in understanding how anticipatory processes recover/adjust following protracted abstinence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Population	Author (year)	Clinical Group M/F	HC M/F	Urine Screen?	Image Analysis	MC	Phase/ Contrast	Striatal Response	Coordinates	Correlations with Striatal Response	Comments
Alcohol Dependence(AD)	Wrase et al., 2007 (42)	16M	16M	∪	WB ROI	✗ ✓	Gain > Neutral	↓	-16,12,-4	- Alcohol Craving in AD negatively correlates with bilateral VS activation (-8,15,-4 &12,12,-4)	- AD in-patient detoxification treatment - controlled for smoking status
							Loss > Neutral	↓	-16,12,-4		
	Bjork et al., 2008 (46)	12M 11F	12M 11F	∪	WB ROI	✓	Gain > Neutral	—	TC: ±10,10,-4	- HC group VS response correlated positively with self-reported excitement - collapsed across groups, VS signal positively correlates with self-reported impulsivity scores	- AD inpatients; high CD comorbidity + other substances - all smokers - inclusion of frustration trials
							Loss > Neutral	—			
	Beck et al., 2009 (43)	19M	19M	∪	WB ROI	✗ ✓	Gain > Neutral	↓	12,15,-6	- VS activity negatively correlates with self-reported impulsivity on the Barratt Impulsivity Scale, including Cognitive, Nonplanning and Motor subscales	- controlled for smoking status
							Loss > Neutral	↓ **(trend)**			
	Bjork et al., 2012 (45)	15M 14F	12M 11F	∪	WB ROI	✓	Pre-response: Gain Neutral	—	TC: ±8,11,0		- AD inpatients; high CD comorbidity + other substances

Population	Author (year)	Clinical Group M/F	HC M/F	Urine Screen?	Image Analysis	MC	Phase/ Contrast	Striatal Response	Coordinates	Correlations with Striatal Response	Comments
											- all smokers - Two-stage anticipatory cuing: • Pre-response reward anticipation • Post-response reward anticipation ➢ Loss trials not included in MIDT task
							Post-response: Win > Hit	—		- Across groups, uncorrected VS activity during post-response reward anticipation on low rewards positively correlates with self-reported impulsivity on the NEO-IF	- AD group contrast of WIN>HIT trials in the VS did not survive multiple-comparison correction
Children of Alcoholics	Andrews et al., 2011 (53)	10M 20F	7M 12F	∪	WB ROI	✓ ✓	A1 Gain > baseline	↑	Caudate: -21,-36,18		- modified paradigm with 2 anticipatory phases (same as Patel et al., 2013; Balodis et al., 2012): • A1= prospectof gain + motorpreparation • A2 =anticipation ➢ Loss trial results not reported
							A2 Gain > baseline	↓	VS: 9,12,-6	VS activity negatively correlates with self-reported compulsivity and reward/ punish ment sensitivity	
	Yau et al., 2012 (57)	12M 8F	12M 8F	✗	WB ROI	✓ ✓	Gain > Neutral	↓	-10, 13, -8 & 11, 13, -8	- Across the entire sample: positive correlation with drinks per week (trend at loss level) - Within COAs: positive correlation with drinks per week, lifetime alcohol volume, externalizing	- decreased VS activity was driven by the COAs with low-risk drinking

Population	Author (year)	Clinical Group M/F	HC M/F	Urine Screen?	Image Analysis	MC	Phase/ Contrast	Striatal Response	Coordinates	Correlations with Striatal Response	Comments
										risk during both win and loss anticipation	
Cocaine Dependence (CD)	Jia, Worhun-sky et al., 2011 (50)	12M 8F	12M 8F	✗	ROI	✓	Gain > Neutral	↑	Caudate 10,8,3	–	- Treatment-seeking, cocaine use ~5 days ➢ Loss trial results not reported
	Bustame-nte et al., 2013 (51)	17M	18M	∪	ROI	✓	Gain > Neutral	—	10,8,0 & -10,10,-2		- neutral condition requires no response ➢ Loss trial results not reported
							Gain > Neutral	↓	Caudate 12,5,19	- Left caudate correlates positively with months of treatment	
	Patel et al., 2013 (52)	Current: 24M 18F Former: 26M 9F	26M 21F	∪	ROI	✓	A1 Gain > baseline	—	Custom-drawn	- in former CD group, VS activity negatively correlated with abstinence (uncorrected)	- modified paradigm with 2 anticipatory phases (same as Andrews et al., 2010; Balodis et al., 2012): • A1 = prospectof gain + motorpreparation • A2 =anticipation
							A2 Gain > baseline	—			
							A1 Loss > baseline	—			
							A2 Loss > baseline	—			
Stimulant Challenge Studies	Knutson et al., 2004 (58)	–	6M 2F	✗	ROI	✗	Gain > Neutral	↓	TC: ±11,12,-2–	- Striatal activity during both placebo and AMPH conditions correlated positively with self-rated positive arousal	- 0.25mg/kg oral dextroamphetamine (AMPH) - Relative to placebo, AMPH reduced activity to higher magnitude wins, but increased striatal activity to losses
							Loss > Neutral	↑			
	Schouw et al., 2012 (59)	Recreational users: 8M	8M	∪	ROI	✗	Gain > Neutral	↓		–	- used voxels that showed a significant interaction effect to create a mask to determine mean percent BOLD change
							Loss > Neutral	—			

Population	Author (year)	Clinical Group M/F	HC M/F	Urine Screen?	Image Analysis	MC	Phase/ Contrast	Striatal Response	Coordinates	Correlations with Striatal Response	Comments
			8M	∪	ROI	✗	Gain > Neutral	↓			- 35mg oral methylphenidate
		Recreational users: 8M		∪	ROI	✗	Gain > Neutral	—			
Nicotine Dependence(ND)	Rose et al., 2013 (47)	13M 15F	16M 12F	∪	WB ROI	✓ ✓	PRIME-1 Valence	↓	Caudate -13,10, 0 9,12,2 (TC)		Modified MIDT with 2 primes; PRIME-1 representing valence (Gain>Loss) PRIME-2 representing magnitude
		13M 15F	16M 12F	∪	WB ROI	✓ ✓	PRIME-1 Valence	↓	VS -13,10,-8 (TC)		- Smokers with nicotine patch relative to non- smoking HC group (without patch)
							PRIME-2 Gain Magn itude	↑	Caudate -7,6,6 (TC)		
							PRIME-2 Loss Magn itude	↑	Caudate -10,1,1 4 (TC)		
		13M 15F	–				PRIME-1 Valence	↓	Putamen 24,-4,4 (TC)	- VS activity negatively associated with plasma nicotine levels	
	Jansmaet al., 2013 (60)	10M	11M	∪	ROI	✗	Gain > Neutr al	↓	±12,14,-8		- administration of 6mg THC or placebo ➢ Loss trial results not reported
Marijuana Dependence	Van Hell et al., 2010 (48)	13M1F Smokers: 11M3F	11M2F	∪	WB ROI	✓	Gain > Neutral	↓	±14,14,-8(TC)	–	- non-treatment seeking ➢ Loss trial results not included in MIDT task - negative urine screens for THC in almost all participants - decreased VS in both Smokers and cannabis users relative to HCs
	Nestor et al., 2010 (49)	14M	14M	∪ +THC	WB	✓	Gain > Baseline	↑	20,8,-4	VS activity during 'win' correlates positively with # of reported lifetime joints smoked	- MIDT version collapsed across magnitude - all MD participants had positive THC urine toxicology
							Loss > Baseline	—			
	Filbey et al., 2013 (63)	47M 12F	5M 22F	∪ +THC	WB	✓	Gain > Neutral	—	MNI extents on x: 8-16; y=15-6; z=-4--12		- required positive urinalysis for THC metabolites, but excluded for other drugs - HC group showed no sig. difference during either incentive

Population	Author (year)	Clinical Group M/F	HC M/F	Urine Screen?	Image Analysis	MC	Phase/ Contrast	Striatal Response	Coordinates	Correlations with Striatal Response	Comments
											condition (gain or loss)–may be driving effect?
							Loss > Baseline	—			
	Van Hell et al., 2012 (61)		11M	∪	ROI	✗	Gain > Neutral	–	Dorsal caudate -8,4,4 & 12,8,0		- 6mg THC administration or placebo - ROI based on pooled group activation maps: ➢ Loss trial results not included in MIDT task
Gambling	Balodiset al., 2012 (55)	10M 4F	10M 4F	∪	WB ROI	✓ ✓	A1 Gain	↓			- modified paradigm with 2 anticipatory phases (same as Andrews et al., 2010; Patel et al., 2013): • A1 = prospectof gain + motor preparation • A2 =anticipation
							A2 Gain	↓	10,12,-11	VS activity correlates negatively with self-reported motor impulsivity	
							A1 Loss	↓			
							A2 Loss	↓	-10,12,-11	VS activity correlates negatively with self-reported impulsivity and cognitive impulsivity on the Barratt Impulsivity Scale	
	Choi et al., 2012 (56)	15M	15M	✗	WB ROI		Gain > Neutral	↓	0,3,0		- no comorbidities in the GD group (except smoking) – duration of illness < 5 years
							Loss > Neutral	↓	0,3,0		

M= Male; F= Female; ∪ = Urine Screen; ✗ = not done; ✓ = done; WB=Whole Brain Analysis; MC Correction= Correction for Multiple Comparisons; ROI = Region of Interest; ↓ = decreased striatal activity; ↑ = increased striatal activity; VS = Ventral Striatum; HC = Healthy Control; THC =Tetrahydrocannabinol; TC= Talairach Coordinates; MNI=Montreal Neurological Institute Coordinates (x,y,z), unless stated, all coordinates are in MNI.