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Dysregulation of Behavioral Control of Impulsivity

THESIS

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ABSTRACT OF THE THESIS

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by

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The capacity for top-down control is thought to contribute to the maladaptive and impulsive reward seeking seen in a number of neuropsychiatric disorders, including drug addiction. Elucidating the behavioral and neurobiological mechanisms underlying impulsivity is crucial for developing newer, more effective prevention and treatment strategies across a wide range of psychiatric disorders. While the specific mechanisms underlying this dysregulation are unclear, it is believed to involve persistent adaptations in neural systems that mediate and regulate the expression of Pavlovian incentive motivation.

Specific Aims

Reward-predictive cues acquire a powerful influence that promotes exploratory reward-seeking behavior. Other cognitive information such as the timing and probability of an expected reward are used to flexibly regulate this motivational response, improving the efficiency of reward pursuit and retrieval. The capacity for top-down control is thought to contribute to the maladaptive and impulsive reward seeking seen in a number of neuropsychiatric disorders, including drug addiction. Elucidating the behavioral and neurobiological mechanisms underlying impulsivity is crucial for developing newer, more effective prevention and treatment strategies across a wide range of psychiatric disorders. While the specific mechanisms underlying this dysregulation are unclear, it is believed to involve persistent adaptations in neural systems that mediate and regulate the expression of Pavlovian incentive motivation.

Our lab has developed a novel rodent behavioral task based on the Pavlovian-instrumental transfer (PIT) paradigm that selectively assays the motivational and behavioral control processes that regulate cue-triggered reward seeking. Our approach is based on the natural tendency for rats to engage in exploratory instrumental reward-seeking behavior when presented with a cue that signals a low probability of imminent reward (weak cue), but rapidly inhibit such behavior when presented with a cue that signals a high probability of imminent reward (strong cue), when exploratory reward seeking is unnecessary and should be omitted to facilitate reward retrieval. Impulsivity is represented in the maladaptive inability to suppress the urge to seek reward in order to retrieve the reward. We plan to use this approach to investigate the dysregulation of the

functional circuitry mediating impulsivity leveraging the disruptive influence of chronic cocaine exposure.

Based on preliminary findings, our working hypothesis is that repeated cocaine exposure weakens behavioral control, preventing rats from curbing their urge to seek out reward when cues signal that free reward is imminent. The **dorsomedial prefrontal cortex (dmPFC)** is widely implicated in the regulation of motivated behavior and our own preliminary findings demonstrate that it is crucial for adaptively controlling cue-motivated behavior based on reward expectancy. It communicates with the **nucleus accumbens (NAc)**, a central hub of incentive motivation and a key neural substrate mediating impulsivity via dense glutamatergic projections. Its contributions to cocaine-related dysregulation of cue-motivated behavior remain unknown. We will critically test the hypothesis that repeated cocaine use disrupts cue-elicited dmPFC-NAc engagement, resulting in the loss of adaptive control over cue-motivated behavior.

Aim 1: Measure the effects of cocaine exposure on the dmPFC-mediated regulation of cue-motivated behavior. We will use fiber photometry calcium recordings to measure the effects of chronic cocaine treatment on both cue- and response-related dmPFC activity in rats previously exposed to a well-characterized regimen of cocaine or saline exposure. We predict that dmPFC activity will be attenuated in rats with a history of cocaine exposure during the presentation of the strong cue relative to the weak cue, as compared to vehicle-treated rats. This will measure the degree to which impulsivity can be suppressed following long-term drug-induced plasticity.

Aim 2: Probe the influence of the dmPFC → NAc pathway on behavioral control over cue-motivated behavior.

Using a dual viral approach using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), we will determine the degree to which **dmPFC → NAc** activity can adaptively regulate cue-motivated behavior. Inhibiting dmPFC communication may disrupt behavioral control over cue-motivated behavior, increasing impulsivity.

Significance: This project will fill critical gaps in knowledge regarding the impact of chronic cocaine exposure on the regulation of Pavlovian incentive motivation via dmPFC-NAc activity. We plan to examine potential sex differences based on a growing body of clinical and preclinical work indicating that females are more vulnerable to cue-elicited cocaine craving.

Significance

Cues associated with cocaine and other abused drugs can elicit intense cravings and are believed to promote pathological drug use and relapse. Previous research has shown that animals given repeated exposure to drugs develop exaggerated motivational responses to reward-predictive cues, suggesting a profound dysregulation in the brain systems that support such behavior (Marshall & Ostlund 2018, Le Blanc et al. 2013). There are, however, competing theories to account for this excessive and uncontrolled impulse to seek out and consume rewards. In this paper I will briefly outline these accounts and propose experiments to tease apart putative neurobehavioral mechanisms contributing to drug-induced dysregulation of cue-motivated behavior.

Incentive sensitization theory, proposed by Robinson & Berridge (1993), emphasized the important role that the mesolimbic dopamine system plays in motivation and drug addiction. Animals given repeated exposure to psychostimulants like cocaine develop sensitized behavioral and mesolimbic dopamine responses when given subsequent drug challenges, indicating upregulation in this system (Wyvell & Berridge 2001, Halbout et al. 2019, Wassum et al. 2013, Ostlund et al. 2014). It was therefore proposed that drug-induced sensitization in the mesolimbic dopamine system increases motivation via increased dopamine release in the nucleus accumbens, which is strongly implicated in motivation for natural and drug rewards (Aitken et al. 2016).

An alternative view is that excessive forms cue-motivated behavior do not reflect a simple increase in incentive-motivation processing, but instead reflect a loss of adaptive control over this behavior. For instance, premature or inappropriate reward-seeking actions may be impulsive or insensitive to inhibitory control. Dalley & Robbins (2017) and

others (Jentsch & Taylor 1999, Jentsch & Pennington 2014) have emphasized that excessive drug- and reward-seeking response may result from such a loss of inhibitory control. Dysregulated prefrontal cortex (PFC) function has been broadly implicated in impulsivity including its role in drug addiction (Narayan & Laubach 2017).

While there is evidence implicating both mesolimbic and prefrontal circuits in drug-induced dysregulation of motivated behavior, much remains unclear regarding both the specific psychological mechanisms underlying such behavior or their relation to functional changes in these circuits. There remains a need to determine how these circuits contribute to motivation and impulse control in the context of cue-motivated reward seeking and how these processes may be dysregulated following repeated exposure to drugs like cocaine.

Previous research on this topic has used a wide range of behavioral assays of motivation and impulse control, but often fail to selectively parse these psychological processes. As an alternative, I propose using an alternative approach that builds upon the well-established and -controlled Pavlovian-Instrumental Transfer (PIT) paradigm, which can provide dual readouts of both the response-invigorating motivational to some cues and the response-inhibiting influence of other cues based on their distinct relationships with reward. Below is an outline of my proposal.

Innovation

To address and dissociate the conflicting theories underlying impulsivity, we developed a novel rodent model of impulsivity, leveraging the disruptive influence of cocaine on behavioral control over cue-motivated behavior. Built off an existing paradigm that measures the spontaneous influence of Pavlovian cues on motivational behavior (Pavlovian Instrumental Transfer), the probabilistic PIT (pPIT) task uses reward expectancy as a driver of motivational seeking behavior, and the adaptive ability to inhibit such behavior when a reward is certain. This novel approach draws on a rat's natural tendency to seek rewards in the presence of cues that weakly predict rewards, and their ability to rapidly suppress this response when a cue strongly predicts rewards. Our approach allows us to more clearly differentiate between the increased sensitization of cues that drive motivation, and the cortical control over such motivational behaviors, allowing us to pinpoint where dysregulation of these functions may occur.This task also lends the ability to parse the extent of this dysfunction in a drug context, and specifically target its molecular mechanistic underpinnings.

Approach

The nucleus accumbens and incentive sensitization

Robinson and Berridge (1993) developed the incentive sensitization theory of addiction, using a multi-faceted approach to address the neural and psychological factors that define compulsive drug-seeking. Here, they described how the neural changes that proceed drug use are in large part mediated by dopamine release. Drugs and drug-paired

cues heighten this neurochemical response, leading to a sensitization effect, thus increasing drug-craving and -seeking (Wyvell & Berridge 2001).

This theory posits the dopaminergic system as the common neural substrate mediating this excessively motivated state that mediates drug craving and seeking. Increased dopamine release in the mesolimbic system during drug use can be correlated with increasing the incentive "value" or salience of that drug, as the neurotransmitter release induces persistent changes in the brain (Nestler 1997). Well-characterized drugs such as amphetamine and cocaine induce locomotor activation, which increases with repeated administration, and can be seen as a behavioral correlate of sensitization. Other substances, such as opioids, nicotine, and alcohols, are known to manifest similar dopaminergic neurotransmissions.

The Robinson and Berridge paper also highlights the difference between "wanting" and "liking", in the sense that drugs can increase "wanting" of a drug, regardless of whether there is an according pleasurable effect of the drug. Such effects are seen in rodent self-administration studies, where an "addicted" subject will continue to lever-press to self-administer a drug, despite potential aversive consequences such as a foot shock. This sense of craving is resistant to punishment, modeling a heightened motivational drug-seeking state. Similarly, conditioned place tests can be used to observe a preference or aversiveness for the drug-associated context.

While the mesolimbic dopaminergic system encompasses a number of brain regions, we focus here on the nucleus accumbens (NAc), as a key region mediating the motivational influence of drugs. Studies correlate phasic dopamine release in the NAc with drug administration, while lesion and chemogenetic studies show that both NAc dysfunction and

dopamine antagonists reduce drug "wanting" and seeking (Simon et al. 2007, Aitken et al. 2016). The incentive sensitization theory hypothesizes that dopaminergic transmission increases the salience of a drug or a drug-associated cue, which can lead to increased motivation and excessive reward-seeking. While it is unquestionable that drug exposure can increase this type of action-selection and lead to impulsivity, it remains unclear if this effect is due to an increase in motivation, or a loss of control over motivation.

The prefrontal cortex and inhibitory control

Our fight-or-flight response allows us to survive in situations where time to think is extremely limited. These fundamental, knee-jerk behaviors, made in response to internal and external stimuli, are important and extremely adaptive. However, there are many situations that require some premeditation and forethought, integrating current situations and past experiences to select an action that is appropriate in particular circumstances. In these instances, the spontaneous actions ingrained in our subconscious mind, may actually be maladaptive.

Such complex decisions are governed largely by the prefrontal cortex. This higher forebrain area is involved in the regulation of decision making, suppressing impulsive behaviors when appropriate to choose the most appropriate response (Narayan & Laubach 2017). In subjects facing addiction, we see that this becomes significantly impaired. Cues illicit unregulated responses, and affect action selection maladaptively. The need to consider the deterioration of adaptive control over cue-motivated behavior in drug addiction remains a key area for future research.

There are a number of assays available to observe impulsivity and its dysregulation (Dalley et al. Dalley & Robbins 2017). Such tasks often utilize delayed instrumental responses to a reinforcer for a reward, such as in DRL, and punishment for premature responding, such as in the 5-choice serial reaction time task (5CSRTT). Further, the stop-signal task can assay stopping impulsivity–the ability to quickly inhibit a response in the face of a specific cue in order to receive the reward. Successful completion of these tasks rely largely on frontal cortical areas.

While such tasks exist to probe impulsivity in its many forms, these tasks are unable to distinguish the source of the dysfunction–whether there is a heightened motivational response, or a breakdown in the ability to regulate these motivational responses, both of which have been observed in subjects facing drug addiction. There remains a need to utilize existing assays in innovative ways that allows us to delineate these two leading theories underlying impulsivity in a carefully controlled manner.

Modeling adaptive control over cue-motivated behavior using reward expectancy:

Pavlovian Instrumental Transfer taps into the spontaneous motivational influence of Pavlovian cues to seek reward (lever-press). This behavior underlies cue-triggered relapse, wherein an internal or external cue associated with the drug can elicit a “wanting” or “craving” of the drug, even after a long period of abstinence. Normal subjects are able to inhibit this response, especially in the face of adverse consequences. The inability to suppress drug-seeking in the face of such cues, despite consequences, is a well-characterized addiction behavior. Despite the pressing nature of this symptom, the neural substrates underlying this process are not well-characterized.

Our lab has utilized PIT to better understand how drug use can impact the motivational influence of cues. Rats with a history of repeated cocaine exposure show increased cue-motivated reward-seeking on the PIT task (Le Blanc et al. 2013). However, this result may not reflect a simple increase in incentive motivation. During PIT testing, cues that are weakly associated with reward are more effective at triggering lever pressing (i.e., motivation) than cues that strongly predict reward, which instead elicit approach to the site of food delivery. These and other findings suggest that strong reward-predictive cues engage cognitive control processes to actively suppress the motivation to lever-press to allow for the more adaptive food-cup approach response (Ostlund & Marshall 2021). Interestingly, previous studies showing that amphetamines and cocaine sensitize PIT expression have employed strong reward-predictive cues that normally evoke little lever pressing in drug naive control groups (Marshall & Ostlund 2018). This suggests that drug exposure increases cue-motivated behavior by disrupting expectancy-based inhibitory control over incentive motivation rather than by increasing motivation *per se*.

Our novel pPIT task allows us to carefully observe Pavlovian incentive motivation and control of this motivation in the same task, in the same animal. It leverages the power of reward prediction to guide cue-motivated behaviors, tapping into both cue-elicitive motivation to seek-out rewards (i.e., during low-probability cues), and the tendency to suppress that motivation to facilitate reward retrieval (i.e., during high-probability cues). The task hinges on the ability of the animal to use reward expectancy to adaptively guide their behavior, and preliminary studies in the lab demonstrate a deterioration of this response in drug-exposed animals. The dmPFC, which is known to regulate motivation,

specifically based on reward expectancy, is likely a crucial neural substrate that mediates this response, and is the focus of this study.

Chemogenetic approach: In order to specifically target dmPFC to NAc activity, we will use a Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) dual virus approach, bilaterally injecting a Cre-expressing adeno-associated virus (AAV) in the dmPFC (AAV-hSyn-DIO-hM4Di-mCherry) along with a retrograde Cre-dependent AAV in the NAc (AAV-EF1a-mCherry-IRES-Cre) in order to specifically target dmPFC projections to the NAc. We will have 2 groups of rats, which will receive a dmPFC infusion of the Cre-dependent AAV carrying either the inhibitory DREADD hM4Di or a fluorescent reporter lacking an inhibitory DREADD (EYFP). This will allow us to selectively and reversibly inhibit dmPFC projections to the NAc with systemic clozapine N-oxide (CNO) administration (5mg/kg). Recent research in our lab demonstrates that CNO does not elicit nonspecific effects on adaptive control of cue-motivated behavior. This approach also allows for local inhibition of neural circuits without chronic intracerebral guide cannula implants, minimizing trauma to brain tissue in the target structure.

Probabilistic Pavlovian Instrumental Transfer task: Animals will undergo two phases of training, as well as a test. For the first nine days of training, known as the Pavlovian phase, animals learn to associate an auditory cue (CS1) with a weak (30% chance) food pellet reward predictor, and a different auditory cue (CS2) with a strong (100% chance) food pellet predictor. Normal animals show an increase in food port entry in the presence of the strong predictive cue, using reward expectancy to guide their behavior. In a second 9 days,

during the Instrumental phase, animals learn to press a lever on a random interval schedule of reinforcement (in this case, 60 seconds), such that lever-pressing may yield a food pellet reward. After sufficient training, the animal is then retrained in the Pavlovian phase for approximately 5 days, after which the animals will receive a Test. Here, both auditory cues (CS1 and CS2) will be presented alongside the lever, to demonstrate the spontaneous influence of the auditory cues on the motivational action (lever-pressing). Normal animals increasing lever-press in response to the weak cue, while checking the food port more in response to the strong cue. However, chronic drug use may weaken this adaptive behavioral flexibility. In order to test animals in maladaptive state, we subject the animals to a cocaine exposure protocol after the Instrumental phase of pPIT. Only then will they receive retraining and then a test, done during the optimal window of drug-induced locomotor sensitization.

Cocaine exposure protocol: In order to sufficiently expose subjects to chronic drug use prior to the pPIT test, we adapted a protocol that has been established to induce addiction-like behaviors (Hankosy & Gulley 2012). Rats will be divided into 2 groups, with Group A exposed to cocaine (15mg/kg), and Group B exposed to saline for 6 consecutive days via IP injection. 20 minutes post-exposure, subjects will be placed in their operant boxes for 45 minutes in order to causally associate their context with the effects of the drug. The rats will then remain in their home cages for 12 days undisturbed, given the evidence that this is the window of withdrawal that elicits locomotor sensitization. After this, rats will receive 5 days of Pavlovian retraining, followed by a day of instrumental retraining (RI60s), then extinction. Subjects will then receive a test, where the lever is presented,

along with both auditory cues for 10 trials each (Cue 1 x 10, Cue 2 x 10) in a randomized order. Lever-pressing, food port entries, and beam breaks will be recorded.

Measuring cell activity in the dmPFC: Rats will receive unilateral intra-NAc infusions of a retrogradely transported AAV to express GCaMP (AAVretro-syn-FLEX-jGCaMP7f-WPRE), a genetically encoded calcium sensor, in NAc-projecting dmPFC neurons, which will be visualized through a chronically implanted optical fiber in the ipsilateral dmPFC (Martianova et al. 2019). We will record GCaMP and control (isosbestic) fluorescence with fiber photometry during the PIT task at 3-6 weeks post-surgery, during the optimal viral expression window.

Sex as a biological factor: Some reports suggest that female rats show increased impulsive cocaine-seeking as compared to male rats (Moschak & Carelli 2021). According to our preliminary data, sexes do not significantly differ in the regulation of cue-motivated behavior. While the present study is not designed to investigate sex differences in behavior, groups will include equal numbers of males and females, and will have the power to detect large sex differences. If marginal trends are detected, we will consider increasing our power to detect sex differences. Regardless, sex will be included as a factor in all analyses and will be reported in the resulting publication.

Aim 1: Measure the effects of cocaine exposure on the dmPFC-mediated regulation of cue-motivated behavior.

We will use fiber photometry calcium recordings to measure the effects of chronic cocaine exposiure on both cue- and response-related dmPFC activity. Animals will receive an intra-dmPFC virus expressing GCaMP, as well as a cannula for the optic fiber. They will then undergo pPIT, along with a cocaine exposure regimen prior to testing. During the testing phase, we will measure dmPFC Ca2+ release as a correlate of neural activity. *We predict that dmPFC activity will be attenuated in rats with a history of cocaine exposure during the presentation of the strong cue relative to the weak cue*, as compared to vehicle-treated rats. This will measure the degree to which impulsivity can be suppressed following long-term drug-induced plasticity.

Aim 2: Probe the influence of the dmPFC → NAc pathway on behavioral control over cue-motivated behavior.

Using a dual viral approach using DREADDs, we will determine the degree to which dmPFC → NAc activity can adaptively regulate cue-motivated behavior. Inhibiting dmPFC communication may disrupt behavioral control over cue-motivated behavior, increasing impulsivity. Prior to any pPIT training, we will bilaterally infuse an AAV expressing a Cre-dependent inhibitory DREADD, while a Cre-recombinase-expressing retrograde AAV will be bilaterally infused into the NAc. The virus in the dmPFC will only express the inhibitory DREADDs in the presence of Cre-recombinase. The retrograde virus in the NAc will express Cre-recombinase in the soma of the neurons that have terminals in the NAc. Therefore, only the dmPFC neurons with terminals at the NAc will express the inhibitory DREADD, allowing us to systematically inject CNO 30 minutes prior to the testing phase. *We predict that inhibition of dmPFC → NAc projections will impair cognitive control over*

motivation, leading to an increase in reward-seeking behavior regardless of the strong or weak predictive cue due to the inability to inhibit motivational impulses even in the presence of a more adaptive alternate response.

Timeline, alternative outcomes, and future plans:

Given our pilot data demonstrating feasibility and proof-of-concept for the main elements of a proposal, we are confident in our ability to successfully accomplish the aims described above. Aim 1 will be completed over Year 1, in order to run both males and females, transfected with either hM4Di, hM3Dq, or a fluorescent vehicle reporter. Year 2 will see the integration of Aim 2, using fiber photometry to measure cell activity *in vivo* during pPIT.

It is important to note that even if the hypotheses outlined above are not supported, there is rationale to support the alternative outcomes, having the potential to contribute to the ongoing study of motivation, and the behavioral control over motivation.

One potential path forward may be to study dopaminergic signaling in the dmPFC. While Aim 2 looks to measure general cell activity via calcium signaling, there is evidence to narrow down the specific molecular substrate at work as dopamine, due to the dense connectivity between the dmPFC and NAc (Ishikawa et al. 2008), and the corresponding behavioral output that is linked to dopamine release (Ostlund et al. 2014).

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