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OPPOSING EFFECTS OF ACUTE AND CHRONIC D-AMPHETAMINE ON DECISION-MAKING IN RATS

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Abstract—Amphetamine and other drugs of abuse have both short-term and long-lasting effects on brain function, and drug sensitization paradigms often result in chronic impairments in behavioral flexibility. Here we show that acute amphetamine administration temporarily renders rats less sensitive to reward omission, as revealed by a decrease in lose-shift responding during a binary choice task. Intracerebral infusions of amphetamine into the ventral striatum did not affect lose-shift responding but did increase impulsive behavior in which rats chose to check both reward feeders before beginning the next trial. In contrast to acute systemic and intracerebral infusions, sensitization through repeated exposure induced long-lasting increased sensitivity to reward omission. These treatments did not affect choices on trials following reward delivery (i.e. win-stay responding), and sensitization increased spine density in the sensorimotor striatum. The dichotomous effects of amphetamine on short-term and long-term loss sensitivity, and the null effect on win-stay responding, are consistent with a shift of behavioral control to the sensorimotor striatum after drug sensitization. These data provide a new demonstration of such a shift in a novel task unrelated to drug administration, and suggests that the dominance of sensorimotor control persists over many hundreds of trials after sensitization.

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Key words: striatum, dopamine, learning, addiction, decision-making.

INTRODUCTION

Animals learn from reinforcement by a neural mechanism thought to involve dopamine. Dopaminergic neurons in the midbrain code for a reward prediction error (RPE) signal by increasing their firing rate when an unexpectedly good reward is presented, and decrease firing when a smaller than expected reward or the omission of a reward occurs (Schultz et al., 1997; Fiorillo et al., 2003; Roesch et al., 2007). This error signal is the basis for many models describing how humans and animals can use trial-and-error learning to make beneficial decisions in novel environments or tasks (Montague et al., 1996; Frank et al., 2004; Pessiglione et al., 2006).

Dopamine neurons densely innervate the striatum, a structure strongly implicated in reinforcement-based learning (O'Doherty et al., 2006; Frank et al., 2007; Johnson et al., 2007; Ito and Doya, 2009; Kimchi and Laubach, 2009). The rodent striatum is often conceptually divided into ventral, dorsomedial, and dorsolateral sub-regions, which are thought to be homologous to the nucleus accumbens, caudate, and putamen in primates (Balleine and O'Doherty, 2010). It has been suggested that these sub-regions are components of parallel circuits between the cortex, basal ganglia, and thalamus (Alexander et al., 1986; Haber, 2003; Voorn et al., 2004). These circuits appear to have distinct information processing capabilities and can interact to control decision-making. For instance, instrumental conditioning paradigms have suggested that the dorsomedial striatum (DMS) encodes action-association outcomes (Yin et al., 2005) that allow it to form mental models of its environment (Daw et al., 2005). In contrast, the dorsolateral striatum (DLS) appears to encode stimulus–response associations that are built up over repetition without such models (Packard and McGaugh, 1996; Jog et al., 1999; Featherstone and McDonald, 2004) and are insensitive to altered reward contingencies such as devaluation (Yin et al., 2004). These are generally conceptualized as habits that are engaged reflexively (Jog et al., 1999).

We recently discovered that the DLS mediates so-called lose-shift (or lose-switch) responding, wherein animals tend to shift responses to an alternate option following reward omission (Skelin et al., 2014). This is important for two reasons: this strategy may influence behavioral flexibility, particularly after reward contingencies change; and it is a new behavioral barometer of the prevalence of DLS-mediated control of choice. The dorsolateral striatum may thus influence behavioral flexibility in normal and drug-induced states by affecting animals' responses after reward omission by promoting lose-shift

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Abbreviations: AMPH, amphetamine; DLS, dorsolateral striatum; DMS, dorsomedial striatum; MSNs, Medium Spiny Neurons; PBS, Phosphate-Buffered Saline; PFA, paraformaldehyde; RPE, reward prediction error; VS, ventral striatum.

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responding. Acute (on board) amphetamine increases extracellular dopamine, norepinephrine, and other monoamines, particularly in the uptake-transporter rich striatum (Pontieri et al., 1995; Heien et al., 2005). We hypothesized that acute amphetamine (AMPH) would decrease lose-shift responding by attenuating the negative RPE signal associated with a loss. On the other hand, sensitization has been posited to shift the control of behavior to DLS (Everitt and Robbins, 2005, 2013; Lucantonio et al., 2014). This would lead to the dominance of DLS-driven responses in behavioral control. As such, we expect an increase in lose-shift strategy following amphetamine sensitization. This shift of control to sensorimotor systems may correspond with the increase in the dendritic spine density in the DLS, and decreases in DMS and OFC, induced by sensitization (Crombag et al., 2005; Jedynak et al., 2007). Our findings support these hypotheses, and highlight lose-shift responding as a novel measure of the dorsolateral striatum function in models of addiction.

EXPERIMENTAL PROCEDURES

Subjects

Subjects were 32 adult male Long-Evans rats (Charles River Laboratories Inc., Sherbrooke, Quebec) weighing 250–350 g. Animals were pair-housed in a climate-controlled vivarium under a 12:12 light:dark cycle (lights on 7:30 a.m.). Animals were given access to water for one hour on behavioral testing days, but otherwise had *ad libitum* access to food and water. All procedures were approved by the University of Lethbridge Animal Welfare Committee, following the guidelines of the Canadian Council on Animal Care.

Apparatus and choice task

Behavioral testing was performed in aluminum operant chambers (26 × 26 cm) containing two cue lights and a central port flanked by two sucrose delivery feeders (see Skelin et al. (2014) for details). The central port and sucrose feeders contained infrared sensors to detect entry and exit. For behavioral testing, animals were placed in the operant chamber for one hour sessions. Control of the task was automated by an Arduino Mega microcontroller (Digi-key Electronics, Thief River Falls, Minnesota, USA) receiving commands via custom software on a computer. Illumination of the cue lights indicated the beginning of a new trial, signaling the animal to nose-poke in the central port. A tone (6 kHz; 150 ms duration) then prompted the animal to select one of the two sucrose delivery feeders. If the correct feeder was chosen, a reward (60 μL of 10% sucrose solution) was delivered after a 0.5s delay. If the incorrect feeder was chosen no sucrose was delivered. Once a feeder was chosen, or if no feeder was chosen in the 15 s following a nose-poke, the trial ended and the animal had to return to the central port to initiate a new trial.

In the first session of behavior shaping, animals were rewarded upon every feeder entry following a nose-poke in the central port to train them to perform the nose-poke and feeder entry sequence. In the second session, the probability of reward was 50% for each feeder entry following a nose-poke to train them to learn that not all valid responses lead to reinforcement. In all subsequent sessions, reinforcement was controlled by an algorithm that attempted to minimize the number of rewards given to the animal by predicting which feeder it would select. This was done by examining the choices and reinforcements from the previous four trials (Lee et al., 2004). If either feeder was selected at a greater than chance rate (probability > 0.5 with the binomial test, $p < 0.05$), it would be unrewarded for the upcoming trial. The task thus implements a two-player competitive choice task, which is sometimes called 'Matching Pennies'. Over consecutive days of training, two small (4.0 cm), medium (8.5 cm), or long (13.5 cm) parallel barriers were added to the operant chamber to separate the central nose-poke port and the feeders. This introduced a choice cost by forcing animals to navigate around it and also reduced feeder bias from body orientation by promoting posture that was orthogonal to the wall in which the port and feeders were mounted. Rats were trained until they completed two consecutive sessions of at least 150 trials with the long barriers. This criterion was met by training session 13 for all rats in the study. All subsequent training and testing sessions were run with the long barriers.

Drug preparation and injections

For experiments 1 and 2, D-amphetamine hemisulfate (Sigma–Aldrich, Oakville, Ontario, CAN) was dissolved in 0.9% saline at three different concentrations so that animals received approximately the same injection volume across dosages. D-amphetamine solution was delivered by intraperitoneal (IP) injection at one of three dosages (0.5 mg/kg, 1.0 mg/kg, or 1.5 mg/kg) for experiment 1, and an escalating dose (1.0mk/kg, 2.0 mg/kg, and 2.0 mg/kg twice per day) was given in experiment 2. Injection sites were rotated and sides alternated to minimize irritation. For experiment 3, D-amphetamine hemisulfate (0, 20, and 40 μg/μl) was made in the same manner as the previous experiments using Phosphate-Buffered Saline (PBS) rather than saline, and was infused into DLS or ventral striatum (VS).

Experiment 1: acute effects of AMPH on the choice task

After initial shaping, animals were randomly divided into four groups of four to receive acute AMPH in a counterbalanced block design. Injections were administered 15 min prior to testing on the behavioral task over a period of 8 days using the following schedule: saline injection, injection 1, no injection, injection 2, no injection, injection 3, no injection, and injection 4. The initial saline injection was to habituate animals to the procedure and was not used for analysis. Injection days consisted of one of the three amphetamine dosages or vehicle (Saline). The order in which the drug dosages were administered on injection days was counterbalanced across subjects.

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