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Inattention, impulsive action, and subjective response to D-amphetamine

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ABSTRACT

Background: Both impulsivity and sensitivity to the rewarding effects of drugs have long been considered risk factors for drug abuse. There is some preclinical evidence to suggest that the two are related; however, there is little information about how specific behavioral components of impulsivity are related to the acute euphorigenic effects of drugs in humans. The aim of the current study was to examine the degree to which both inattention and impulsive action predicted subjective response to amphetamine.
Methods: Healthy adults ($n = 165$) performed the behavioral tasks and rated their subjective response to amphetamine (0, 5, 10, and 20 mg). Inattention was assessed as attention lapses on a simple reaction time task, and impulsive action was measured by stop RT on the stop task. Subjective response to amphetamine was assessed with the Drug Effects Questionnaire (DEQ) and the Profile of Mood States (POMS).
Results: Hierarchical linear regression analyses showed significant negative associations between attention lapses and subjective response to amphetamine on DEQ measures. By contrast, stop RT was positively associated with responses on both DEQ and POMS measures. Additionally, a dose-response relationship was observed, such that the strength of these associations increased with higher doses of amphetamine.
Conclusions: These findings suggest that inattention is associated with *less* subjective response to amphetamine. By contrast, the heightened sensitivity to stimulant drug reward observed in individuals high in impulsive action suggests that this might be one mechanism contributing to increased risk for stimulant drug abuse in these individuals.

1. Introduction

Both impulsivity and sensitivity to the rewarding effects of drugs have long been considered risk factors for drug abuse. Drug users are more impulsive than non-abusers, and evidence from both non-human and human studies suggests that impulsivity pre-dates the onset of drug-taking, and thus may play a causal role (de Wit, 2009; Perry and Carroll, 2008). Separate research has linked drug reward sensitivity to propensity for abuse, although the direction of the link is not clear. On the one hand, drugs that produce greater euphoria and stimulation are more likely to be abused (Fischman and Foltin, 1991; Jasinski, 1991), and drug users typically report experiencing greater euphoria from drugs than nonusers (Lasagna et al., 1955). On the other hand, Schuckit and colleagues (e.g., Tolentino et al., 2011) have reported that with alcohol, individuals who experience a low level of subjective response are at increased risk for developing alcohol-related problems. The idea here is that these individuals need to take more of the drug to experience the desired effect, and thus are exposed to higher levels (Schuckit, 1994). Evidence has been obtained in support of both hypotheses (King et al., 2011; Morean and Corbin, 2010; Newlin and Thomson, 1990; Quinn and Fromme, 2011). Thus, various lines of evidence indicate that both impulsivity and sensitivity (high or low) to drug effects may play a role in the development of drug use problems.

One question that arises is whether impulsivity is related to sensitivity to drug reward (i.e., whether both are related to a similar underlying process). There is some evidence from studies with rodents that they are related, but relatively little evidence with humans. In rodents, animals high in impulsive action (defined by high levels of anticipatory responses on a 5-choice serial reaction time task) show greater sensitivity to cocaine and nicotine reinforcement than low impulsive animals, as evidenced by higher rates of self-administration (Dalley et al., 2007; Diergaarde et al., 2008). Moreover, these studies show that impulsivity and sensitivity to drug reward are both associated with dopaminergic function, particularly D2 receptor availability. In humans, individuals high on the personality trait of impulsivity report a heightened subjective response to amphetamine (Hutchison et al., 1999; Kelly et al., 2006; Kirkpatrick et al., 2013; Oswald et al., 2007). However, few studies

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have examined subjective drug effects in relation to specific behavioral measures of impulsivity. Impulsivity is thought to encompass several distinct aspects of behavior, including difficulty in response inhibition, difficulty controlling attention, inability to delay gratification, and increased risk taking (de Wit, 2009; Dick et al., 2010), which may relate to substance abuse in different ways (Courtney et al., 2012; Diergaarde et al., 2008; Fernie et al., 2010; Weafer et al., 2011). To date, there is little information about how these specific behavioral subtypes of impulsivity are related to the acute euphorigenic effects of drugs in humans.

The current study focused on the relation between euphoria produced by a prototypic stimulant, D-amphetamine, and two behavioral measures related to impulsivity: inattention and impulsive action. Inattention refers to distractibility or difficulty sustaining attention for long periods of time, and it may be measured by examining variability in reaction times on a simple reaction time task, wherein higher proportions of long reaction times are thought to reflect lapses in attention (de Wit, 2009). Several studies have reported that individuals exhibiting more attention lapses report *less* positive subjective response to amphetamine (Allman et al., 2010; Lake and Meck, 2013; McCloskey et al., 2010). Impulsive action (also known as behavioral inhibition) involves difficulty controlling behavior, and is often measured with the stop signal task (Logan et al., 1997). In this task, participants must respond quickly to go signals but occasionally inhibit responses to a stop signal. Difficulty inhibiting the prepotent response indicates greater impulsive action. Heavy drinkers and stimulant abusers exhibit greater deficits in response inhibition than healthy controls (Fillmore and Rush, 2002; Li et al., 2006; Monterosso et al., 2005; Rubio et al., 2008). How this form of impulsive behavior is related to the acute euphorigenic effects of drugs has yet to be studied.

The aim of the current study was to examine the degree to which both attention lapses and response inhibition predicted subjective response to amphetamine within the same individuals. Based on previous findings, we hypothesized that greater attention lapses would be associated with blunted amphetamine response. Based on studies with laboratory animals, we hypothesized that poorer response inhibition, on the other hand, would be related to greater amphetamine-induced euphoria.

2. Methods

2.1. Design

These data were taken from a larger study examining genetic influence on response to amphetamine (Hart et al., 2012). The study utilized a within-subjects design in which healthy young adults received a placebo and three doses of D-amphetamine (5, 10, and 20 mg) over four experimental sessions. Doses were administered in a randomized and double-blind fashion. Physiological, subjective, and behavioral measures (including inattention and behavioral inhibition tasks), were recorded over 3.5 h following drug administration.

2.2. Participants

Volunteers were recruited from the community through online and printed advertisements. Inclusion criteria included age 18–35, BMI between 19 and 26, at least a high school education, fluency in English, no current or past year DSM-IV diagnosis, no lifetime history of substance dependence, no serious medical conditions, and no night shift work. Females who were not on hormonal contraception were tested only in the follicular phase of their menstrual cycle (White et al., 2002). Because these data were collected as part of a larger genetic study, all participants were Caucasian.

2.3. Measures

2.3.1. Behavioral measures.

2.3.1.1. Simple reaction time task (SRT). The SRT was taken from the Automated Neuropsychological Assessment Metrics (ANAM; Reeves et al., 2006) and was used to measure inattention. Participants executed a key press as quickly as possible to a target presented on the computer screen at variable intervals. Based on a participant's distribution of reaction times (RTs), a deviation from the mode score was calculated as the difference between a participant's mean and modal RT. This value represents the proportion of unusually long RTs, which are inferred to reflect momentary lapses in attention. As such, greater deviation from the mode scores indicate more attention lapses (de Wit, 2009; McCloskey et al., 2010).

2.3.1.2. Stop task. Impulsive action was assessed using the stop task (Logan et al., 1997). In this task, participants are instructed to respond as quickly as possible to 'go' signals presented on the computer screen, and to inhibit responses on trials in which a stop signal (auditory tone) occurs. The duration of the delay between presentation of the stop signal following the go signal is adjusted until the participant is able to successfully inhibit the response on 50% of trials. Participants completed four blocks on this task, and performance data from the last two blocks was used to calculate the measure of impulsive action (i.e., stop reaction time). Stop RT was calculated by subtracting the final mean delay of the stop signal from the mean go RT. A participant's data was considered valid if the percentage of successful inhibition on stop trials fell within the range of 37.5–63% and if target accuracy was at least 80%.

2.3.2. Subjective response measures.

2.3.2.1. Drug effects questionnaire (DEQ). The DEQ consists of three items on a visual analog scale (0–100 mm) that measure subjective drug response. Participants rate the extent to which they 'like drug', 'feel drug', and 'want more'.

2.3.2.2. Profile of Mood States (POMS; McNair et al., 1971). The modified POMS consists of 72 adjectives commonly used to describe momentary mood states and has been factor analyzed into eight scales (Friendliness, Vigor, Anxiety, Fatigue, Elation, Depression, Anger, and Confusion). Participants indicate how they feel at the moment in relation to each adjective on a 5-point scale from 'not at all' (0) to 'extremely' (4). We focused our analyses on the Elation, Vigor, and Friendliness scales, as these represent the typical positive, rewarding effects of amphetamine (e.g., de Wit and Phillips, 2012; Fischman and Foltin, 1991; Jasinski, 1991).

2.4. Procedure

Participants first attended an orientation session in which they provided informed consent and were familiarized with laboratory procedures and study protocol. They were instructed to abstain from drugs, including alcohol, for 24 h prior to each session, and to not consume any food after midnight. They were instructed to maintain their normal caffeine and nicotine intake to avoid withdrawal. The study was approved by the Institutional Review Board of the University of Chicago and was carried out in accordance with the Declaration of Helsinki.

The experimental sessions took place from 9 am to 1 pm, and were separated by at least 48 h. Participants were tested individually. Upon arrival to the lab, they were given a light snack, and compliance with drug abstinence was verified by both self-report and breath and urine screens. Baseline (pre-drug) physiological and subjective measures were obtained. At 9:30 am, drug was administered in opaque capsules. Subjective and physiological measures were assessed at 30, 60, 90, 150, and 180 min after capsule administration. Participants performed a battery of cognitive assessments, including the SRT and stop task, beginning at 90 min after capsule administration. For these analyses, we focus on attention lapses and stop RT assessed during the placebo session, using these as an indicator of 'trait' levels of inattention and impulsive action. Participants left the lab at 1:00 pm, after confirmation that physiological measures had returned to baseline. Once all four experimental sessions were complete, participants were debriefed and compensated for their time.

2.5. Data analysis

An area under the curve (AUC) was calculated following placebo and 5, 10, and 20 mg amphetamine for the six subjective response measures of interest: DEQ Like Drug, Feel Drug, and Want More; POMS Elation, Vigor, and Friendliness. Hierarchical linear regression analyses were then conducted to examine the degree to which attention lapses and stop RT on the placebo session predicted subjective response to amphetamine. Change from placebo AUC was calculated for each subjective measure by subtracting placebo AUC from each active dose of amphetamine AUC, and these served as the dependent variables in the regression models. For all analyses, age, gender, and placebo session order (i.e., session 1, 2, 3, or 4) were entered in Step 1, and the two behavioral measures (attention lapses and stop RT) were entered in Step 2. Additionally, dose effects for the behavioral measures were examined with one-way repeated measures analyses of variance (ANOVAs) with amphetamine dose (placebo, 5, 10, or 20 mg) as the factor, and correlational analyses were performed to investigate the degree to which amphetamine effects on the behavioral measures were associated with amphetamine effects on subjective measures.