Published in final edited form as:

Drug Alcohol Depend. 2013 November 1; 133(1): 127–133. doi:10.1016/j.drugalcdep.2013.05.021.

Inattention, impulsive action, and subjective response to *d*-amphetamine

Jessica Weafer and Harriet de Wit*

Department of Psychiatry and Behavioral Neuroscience, University of Chicago, 5841 S. Maryland Ave., Chicago, IL 60637

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 euphorogenic 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.

Keywords

amphetamine; inattention; impulsive action; subjective effects; humans

© 2013 Elsevier Ireland Ltd. All rights reserved.

*Corresponding author: Harriet de Wit, Department of Psychiatry and Behavioral Neuroscience, MC 3077, University of Chicago, 5841 S. Maryland Ave., Chicago, IL 60637, Phone: 773-702-1537, Fax: 773-834-7698, hdew@uchicago.edu.

Contributors Jessica Weafer conducted the data analysis and wrote the first draft of the manuscript. Both authors contributed to and have approved the final version of the manuscript.

Conflict of Interest Jessica Weafer declares no conflict of interest. Harriet de Wit has received support from Unilever for a project unrelated to this study.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 nonhuman 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 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 euphorogenic 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 euphorogenic 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 hours 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 (RT's), 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 RT's, 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 analogue scale (0 to 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 hours 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 9am to 1pm, and were separated by at least 48 hours. 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.

3. RESULTS

3.1 Sample characteristics

198 participants completed this study. Of these, valid attention lapse data were collected from 192 (four participants were missing data and two outliers with scores greater than four standard deviations above the mean were removed). Valid stop RT data were collected from 170 (five participants were missing data, two were outliers, and 21 did not meet the task accuracy criteria described above). Exclusion of these participants resulted in a final sample size of 165 (89 males and 76 females; mean age = 23.5, SD = 3.4). Current and lifetime substance use for the sample is presented in Table 1.

3.2 Baseline behavioral measures

Mean attention lapse score (i.e., deviation from the mode) for the sample in the placebo condition was 42.9 ms (SD = 28.6; range -27.7 – 150.0). Mean stop RT for the sample in the placebo condition was 192.9 ms (SD = 45.8; range 108.0 – 383.5). Correlational analyses revealed a significant association between attention lapses and stop RT ($r = .24$, $p < .01$), such that individuals with more attention lapses demonstrated longer stop RTs.

3.3 Relation of behavioral measures to subjective amphetamine response

DEQ—Separate hierarchical regression analyses were conducted for the DEQ measures of Like Drug, Feel Drug, and Want More in response to 5, 10, and 20 mg amphetamine (Table 2a). Together, the demographic and placebo session order variables entered at Step 1 did not account for a significant amount of variance in any of the DEQ measures following either the 5 mg or 20 mg doses ($ps > .28$). For the 10 mg dose, gender was a significant predictor of Feel Drug, with women reporting a more pronounced drug effect. Step 2 tested the degree to which the two behavioral components (attention lapses and stop RT) predicted subjective response. Addition of these two components into the model significantly increased the amount of variance explained for all three DEQ scales following the 20 mg dose ($R^2 > .05$; $ps < .02$). Analyses of individual beta weights showed that attention lapses significantly predicted Like Drug, $b = -.29$, $p < .001$; Feel Drug, $b = -.30$, $p < .001$; and Want More, $b = -.20$, $p = .01$. The negative slope indicates a negative association between attention lapses and subjective response. Thus, consistent with previous findings, greater attention lapses were associated with less subjective drug response. Stop RT was also a significant predictor of DEQ Like Drug ($b = .17$, $p = .04$); Feel Drug ($b = .16$, $p = .04$); and Want More ($b = .18$, $p = .03$). In contrast, stop RT was positively related to subjective response, such that longer stop RT's were associated with a heightened subjective drug response. For the 10 mg dose, addition of attention lapses and stop RT significantly increased the variance explained for both Like Drug ($p = .03$) and Feel Drug ($p = .01$). Again, attention lapses were negatively related to subjective response, and stop RT was positively related to subjective response. No significant associations were found between the impulsivity components and subjective response following the 5 mg dose of amphetamine.

POMS—Separate hierarchical regression analyses were conducted for the POMS Elation, Vigor, and Friendliness scales, and the results from these analyses are presented in Table 2b. The demographic and dose order variables entered at Step 1 (i.e., age, gender, and placebo session) did not account for a significant amount of variance in any of these measures following the 10 or 20 mg doses ($ps > .09$). For the 5 mg dose, placebo session order was a significant predictor of ratings of Vigor ($p = .03$), and age was a significant predictor of ratings of Friendliness ($p = .02$). The behavioral measures entered at Step 2 resulted in a

significant increase in variance explained for both Elation and Vigor for the 20 mg dose ($R^2 > .05$; $ps < .02$), and there was a trend toward a significant increase for Friendliness ($R^2 = .04$; $p = .06$). Analysis of individual beta weights showed that stop RT was a significant predictor of for all three scales: Elation, $b = .22$, $p < .01$; Vigor, $b = .23$, $p < .01$; Friendliness, $b = .18$, $p = .03$, with greater impulsive action predicting greater subjective response. By contrast, attention lapses did not significantly predict any of these measures ($ps > .18$). Addition of the two behavioral components into the model did not increase the variance explained for any of the POMS measures for either the 10 or 5 mg doses.

3.4 Amphetamine effects on behavioral measures

Amphetamine improved task performance on both behavioral tasks (one way repeated measures ANOVAs $Fs > 4.9$; $ps < .01$). Change from placebo scores were calculated by subtracting scores in the active dose conditions from scores in the placebo condition, such that positive values indicated improvement of task performance under the drug. Mean attention lapses following each active dose of amphetamine compared to placebo were as follows: 5 mg ($M = 3.6$, $SD = 36.3$), 10 mg ($M = 12.2$, $SD = 33.2$), and 20 mg ($M = 15.6$, $SD = 28.7$). One sample t tests of these change scores showed that amphetamine significantly reduced attention lapses following the 10 and 20 mg doses ($ts > 5.0$, $ps < .001$), but not the 5 mg dose ($p = .18$). Mean stop RT following each active dose compared to placebo was as follows: 5 mg ($M = 10.2$, $SD = 61.7$), 10 mg ($M = 15.2$, $SD = 65.2$), and 20 mg ($M = 15.7$, $SD = 65.3$). One sample t tests showed that all three doses of amphetamine (5, 10, and 20 mg) reduced stop RT compared to placebo ($ts > 2.0$, $ps < .05$).

3.5 Associations between behavioral and subjective response to amphetamine

Correlational analyses tested the degree to which amphetamine effects on behavioral measures were associated with subjective response to the drug, and these are presented in Table 3. The table shows that amphetamine effects on attention lapses were negatively correlated with responses on the DEQ measure of Feel Drug in the 5 mg dose condition ($p < .01$). In the 20 mg dose condition, attention lapses were significantly associated with both Feel Drug and Like Drug ($ps < .01$), and there was a trend for an association with Want More ($p = .051$). The negative correlations indicate that individuals showing the most pronounced improvement in attention lapses reported the smallest amphetamine effect on subjective response. By contrast, amphetamine effects on stop RT were positively correlated with Feel Drug following the 10 mg dose and increased subjective response on each of the POMS scales of Elation, Vigor, and Friendliness following both the 10 mg and 20 mg doses ($ps < .05$), with stronger associations observed at higher drug doses. The positive association indicates that individuals who showed a greater drug-induced improvement in stop RT also reported the greatest increase in subjective mood.

4. DISCUSSION

This study examined associations between two components related to impulsivity (i.e., inattention and impulsive action) and subjective response to amphetamine. As hypothesized, heightened inattention was associated with less subjective response (i.e., lower ratings on DEQ measures of drug liking, feel drug, and want more), and the strength of this negative association increased with higher doses of amphetamine. These findings are consistent with previous studies that have shown a negative association between inattention and amphetamine liking (Allman et al., 2010; Lake and Meck, 2013; McCloskey et al., 2010). We extended these previous studies to also investigate associations between impulsive action and response to amphetamine.

Interestingly, we found that greater levels of impulsive action predicted *greater* drug-induced increase in subjective reward, as measured by both the DEQ measures and the POMS scales of Elation, Vigor, and Friendliness. These findings contrast with the negative association between DEQ measures and attention lapses, but parallel findings from animal studies that show rodents high in impulsive action self-administer greater amounts of cocaine and nicotine (Dalley et al., 2007; Di Ciano et al., 2008), suggesting greater sensitivity to stimulant reward in impulsive animals as well. Further, amphetamine improved performance on both behavioral measures, and effects of amphetamine on behavioral responses were related to subjective responses to the drug: subjects who exhibited greater enhancement of attention after amphetamine reported less subjective response, whereas subjects who exhibited a greater improvement on stop RT reported greater subjective response.

It seems paradoxical that subjective responses to amphetamine would be negatively correlated with attention lapses but positively correlated with long stop RT. The findings of greater impulsive action and greater euphorogenic response to amphetamine fit with a larger existing literature and with neurobiological findings (see below). By contrast, the association between DEQ ratings and attention lapses is in some ways difficult to explain. Although it has now been replicated several times (Lake and Meck, 2013; McCloskey et al., 2010), it is unclear why more attention lapses would be associated with lesser subjective drug effects. One possibility is that inattentive individuals pay less attention to interoceptive drug cues, resulting in decreased awareness of subjective drug effects. However, the current study showed that amphetamine improved attention, and that greater enhancement of attention was associated with less subjective drug response. Thus, enhanced attention following amphetamine does not produce a corresponding increase in subjective response (as would be expected if subjective response was driven by attention to interoceptive cues). Another possibility is that the reduced sensitivity to subjective amphetamine effects is related to general dampened reward sensitivity. Individuals with deficits in attention, including those with ADHD, often show corresponding deficits in reward and motivation systems (e.g., Sonuga-Barke, 2003; Volkow et al., 2009), and this could potentially contribute to a dampened response to the rewarding effects of stimulant drugs. It is important to note that these associations were only observed with the DEQ measures, which involve responding on a visual analogue scale. The POMS scales are derived from ratings of 72 adjectives and therefore require a greater degree of participant involvement to complete. For inattentive individuals, this could result in more variable responding (due to lack of attention to the measure), and thus it is likely that the POMS is a less sensitive measure of drug response for inattentive individuals than the DEQ. Further, the DEQ asks specifically about drug effects, whereas the POMS asks about more general mood states, and this could be another factor contributing to the increased sensitivity of the DEQ to subjective drug response.

The observed relationship between impulsive action and subjective amphetamine response suggests a common underlying neurobiological substrate. Both impulsivity and drug reward are strongly linked to the dopamine system (Del Campo et al., 2011; Di Chiara et al., 2004; Koob and Volkow, 2010; Volkow et al., 2007). Thus, it is possible that impulsive action and heightened subjective response to amphetamine could be linked via common underlying dopaminergic functioning. Preclinical studies indicate that dopamine activity in the ventral striatum, particularly D2 receptor availability, is associated with both drug reward and impulsive action. In rodents, high impulsive action is associated with lower D2 receptor availability and lower dopamine activity in the nucleus accumbens (Dalley et al., 2007; Di Ciano et al., 2008). Similarly, in humans, there is an inverse relation between D2 receptor availability and stop task performance (Ghahremani et al., 2012), and the D2 agonist cabergoline improves performance on this task (Nandam et al., in press). Importantly, an inverse relation has also been observed between D2 receptor binding and

subjective response to the stimulant methylphenidate in healthy non-drug abusing humans (Volkow et al., 1999, 2002), and stimulant abusers have reduced D2 receptor binding (Lee et al., 2009; Volkow et al., 2002). Taken together, these findings suggest that reduced D2 receptor binding is a potential neurobiological factor that might link greater impulsive action and heightened sensitivity to stimulant reward.

The observed correlations between drug effects on behavioral measures and drug effects on subjective response emphasize the importance of differentiating between baseline, or 'trait', levels of inattention and impulsive action, and malleable 'state' levels. That is, although individuals who are inattentive in the drug free state become more attentive in response to amphetamine, they do not show a corresponding increase in subjective response. In fact, the negative association between amphetamine effects on attention and subjective response is strengthened at higher drug doses. Conversely, individuals with high baseline levels of impulsive action show improvement in inhibitory control following amphetamine, yet they report increased subjective drug response at higher doses. As such, it does not appear that state levels of inattention or impulsive action following drug administration are directly related to subjective response. Rather, it is likely that there are common underlying factors related to inattention and impulsive action in the drug-free state that predict sensitivity to drug effects both on these behavioral measures and on subjective response.

These findings have potential implications regarding the roles of impulsivity and subjective drug reward in risk for drug abuse. First, individuals high in inattention and low on subjective response may be at more risk for abuse. Lower level of drug response may lead to higher drug intake to produce the desired effects. Alternately, lower sensitivity to amphetamine reward could be a protective factor, because they experience less enjoyment of drug effects. The fact that high inattention was also accompanied by lower drug liking and less desire for more drug, suggests that these individuals are not at high risk for stimulant drug abuse. By contrast, impulsive action is strongly associated with excessive and problematic drug use (Fillmore and Rush, 2002; Li et al., 2006; Monterosso et al., 2005; Rubio et al., 2008), and so this combination of high impulsive action and greater experiences of drug-induced euphoria may constitute a real risk factor for future drug use. The current findings are the first to demonstrate an increased sensitivity to stimulant drug reward in individuals high in impulsive action, suggesting that this might be one mechanism contributing to such risk for abuse in these individuals.

The present study had several limitations. Amphetamine reward was measured with self-report measures, which have some inherent limitations. Although we used well-validated measures that are known to be sensitive to drug effects, there is always a possibility of response biases and experimenter demand characteristics, and there is no way to ensure that participants responded accurately and honestly (e.g., Rosenberg, 2009; Sayette et al., 2000). However, these risks are reduced by the double-blinding procedures used. Another potential limitation is that the 'trait' measures of behavioral impulsivity were assessed following placebo administration in a randomized dose design. Although we controlled for placebo session order in the regression analyses, it is still possible that task familiarity could affect performance on these tasks. Additionally, it is not possible to rule out expectancy effects of placebo administration on impulsivity task performance. Finally, it is important to note that the current sample was comprised of healthy adults with no history of stimulant dependence. It will be important for future studies to examine these relationships in stimulant users, as associations between impulsivity and inattention and subjective drug response could be even more pronounced in these individuals.

In sum, the current study provides novel findings on the relation between subjective response to amphetamine and two components related to impulsivity (inattention and

impulsive action). Results saw a diverging pattern of association between the two components and drug response, emphasizing the importance of considering multiple facets of impulsivity in relation to subjective drug response. It will be important for future studies to examine the associations between additional components of impulsivity (e.g., impulsive choice, risk taking) and subjective response to stimulant drugs. Further, investigations of impulsivity and other drug-induced reward will help determine if the current findings are specific to stimulants, or if they are also seen in other drugs classes, such as alcohol, THC, or opiates.

Acknowledgments

Role of Funding Source This research was supported by National Institute on Drug Abuse Grants DA002812 (Harriet de Wit), DA021336 and DA027545 (Abraham A. Palmer), and DA033756 (Jessica Weafer). The NIDA had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

References

- Allman AA, Benkelfat C, Durand F, Sibon I, Dagher A, Leyton M, Baker GB, O'Driscoll GA. Effect of D-amphetamine on inhibition and motor planning as a function of baseline performance. *Psychopharmacol (Berl)*. 2010; 211:423–433.
- Courtney KE, Arellano R, Barkley-Levenson E, Galvan A, Poldrack RA, Mackillop J, Jentsch JD, Ray LA. The relationship between measures of impulsivity and alcohol misuse: an integrative structural equation modeling approach. *Alcohol Clin Exp Res*. 2012; 36:923–931. [PubMed: 22091877]
- Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DE, Laane K, Pena Y, Murphy ER, Shah Y, Probst K, Abakumova I, Aigbirhio FI, Richards HK, Hong Y, Baron JC, Everitt BJ, Robbins TW. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science*. 2007; 315:1267–1270. [PubMed: 17332411]
- de Wit H. Impulsivity as a determinant and consequence of drug use: a review of underlying processes. *Addict Biol*. 2009; 14:22–31. [PubMed: 18855805]
- de Wit H, Phillips TJ. Do initial responses to drugs predict future use or abuse? *Neurosci Biobehav Rev*. 2012; 36:1565–1576. [PubMed: 22542906]
- Del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2011; 69:e145–157. [PubMed: 21550021]
- Di Chiara G, Bassareo V, Fenu S, De Luca MA, Spina L, Cadoni C, Acquas E, Carboni E, Valentini V, Lecca D. Dopamine and drug addiction: the nucleus accumbens shell connection. *Neuropharmacology*. 2004; 47(Suppl 1):227–241. [PubMed: 15464140]
- Dick DM, Smith G, Olausson P, Mitchell SH, Leeman RF, O'Malley SS, Sher K. Understanding the construct of impulsivity and its relationship to alcohol use disorders. *Addict Biol*. 2010; 15:217–226. [PubMed: 20148781]
- Diergaarde L, Pattij T, Poortvliet I, Hogenboom F, de Vries W, Schoffelemeier AN, De Vries TJ. Impulsive choice and impulsive action predict vulnerability to distinct stages of nicotine seeking in rats. *Biol Psychiatry*. 2008; 63:301–308. [PubMed: 17884016]
- Femie G, Cole JC, Goudie AJ, Field M. Risk-taking but not response inhibition or delay discounting predict alcohol consumption in social drinkers. *Drug Alcohol Depend*. 2010; 112:54–61. [PubMed: 20580495]
- Fillmore MT, Rush CR. Impaired inhibitory control of behavior in chronic cocaine users. *Drug Alcohol Depend*. 2002; 66:265–273. [PubMed: 12062461]
- Fischman MW, Foltin RW. Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. *Br J Addict*. 1991; 86:1563–1570. [PubMed: 1786488]
- Ghahremani DG, Lee B, Robertson CL, Tabibnia G, Morgan AT, De Shetler N, Brown AK, Monterosso JR, Aron AR, Mandelkern MA, Poldrack RA, London ED. Striatal dopamine D(2)/D(3) receptors mediate response inhibition and related activity in frontostriatal neural circuitry in humans. *J Neurosci*. 2012; 32:7316–7324. [PubMed: 22623677]

- Hart AB, Engelhardt BE, Wardle MC, Sokoloff G, Stephens M, de Wit H, Palmer AA. Genome-wide association study of d-amphetamine response in healthy volunteers identifies putative associations, including cadherin 13 (CDH13). *PLoS One*. 2012; 7:e42646. [PubMed: 22952603]
- Hutchison KE, Wood MD, Swift R. Personality factors moderate subjective and psychophysiological responses to d-amphetamine in humans. *Exp Clin Psychopharmacol*. 1999; 7:493–501. [PubMed: 10609984]
- Jasinski DR. History of abuse liability testing in humans. *Br J Addict*. 1991; 86:1559–1562. [PubMed: 1786487]
- Kelly TH, Robbins G, Martin CA, Fillmore MT, Lane SD, Harrington NG, Rush CR. Individual differences in drug abuse vulnerability: d-amphetamine and sensation-seeking status. *Psychopharmacol (Berl)*. 2006; 189:17–25.
- King AC, de Wit H, McNamara PJ, Cao D. Rewarding, stimulant, and sedative alcohol responses and relationship to future binge drinking. *Arch Gen Psychiatry*. 2011; 68:389–399. [PubMed: 21464363]
- Kirkpatrick MG, Johanson CE, de Wit H. Personality and the acute subjective effects of d-amphetamine in humans. *J Psychopharmacol*. 2013; 23:256–64. [PubMed: 23343596]
- Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010; 35:217–238. [PubMed: 19710631]
- Lake JJ, Meck WH. Differential effects of amphetamine and haloperidol on temporal reproduction: dopaminergic regulation of attention and clock speed. *Neuropsychologia*. 2013; 51:284–292. [PubMed: 22982605]
- Lasagna L, Von Felsinger JM, Beecher HK. Drug-induced mood changes in man. I observations on healthy subjects, chronically ill patients, and postaddicts. *JAMA*. 1955; 157:1006–1020.
- Lee B, London ED, Poldrack RA, Farahi J, Nacca A, Monterosso JR, Mumford JA, Bokarius AV, Dahlbom M, Mukherjee J, Bilder RM, Brody AL, Mandelkern MA. Striatal dopamine d2/d3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. *J Neurosci*. 2009; 29:14734–14740. [PubMed: 19940168]
- Li CS, Milivojevic V, Kemp K, Hong K, Sinha R. Performance monitoring and stop signal inhibition in abstinent patients with cocaine dependence. *Drug Alcohol Depend*. 2006; 85:205–212. [PubMed: 16725282]
- Logan GD, Schachar RJ, Tannock R. Impulsivity and inhibitory control. *Psychol Sci*. 1997; 8:60–64.
- McCloskey M, Palmer AA, de Wit H. Are attention lapses related to d-amphetamine liking? *Psychopharmacol (Berl)*. 2010; 208:201–209.
- McNair, D.; Lorr, M.; Droppleman, L. Profile of Mood States. Educational and Industrial Testing Service; San Diego: 1971.
- Monterosso JR, Aron AR, Cordova X, Xu J, London ED. Deficits in response inhibition associated with chronic methamphetamine abuse. *Drug Alcohol Depend*. 2005; 79:273–277. [PubMed: 15967595]
- Morean ME, Corbin WR. Subjective response to alcohol: a critical review of the literature. *Alcohol Clin Exp Res*. 2010; 34:385–395. [PubMed: 20028359]
- Nandam LS, Hester R, Wagner J, Dean AJ, Messer C, Honeysett A, Nathan PJ, Bellgrove MA. Dopamine D(2) receptor modulation of human response inhibition and error awareness. *J Cogn Neurosci*. 2013; 25:649–656. [PubMed: 23163418]
- Newlin DB, Thomson JB. Alcohol challenge with sons of alcoholics: a critical review and analysis. *Psychol Bull*. 1990; 108:383–402. [PubMed: 2270234]
- Oswald LM, Wong DF, Zhou Y, Kumar A, Brasic J, Alexander M, Ye W, Kuwabara H, Hilton J, Wand GS. Impulsivity and chronic stress are associated with amphetamine-induced striatal dopamine release. *Neuroimage*. 2007; 36:153–166. [PubMed: 17433881]
- Perry JL, Carroll ME. The role of impulsive behavior in drug abuse. *Psychopharmacol (Berl)*. 2008; 200:1–26.
- Quinn PD, Fromme K. Subjective response to alcohol challenge: a quantitative review. *Alcohol Clin Exp Res*. 2011; 35:1759–1770. [PubMed: 21777258]
- Reeves DL, Bleiberg J, Roebuck-Spencer T, Cernich AN, Schwab K, Invins B, Salazar AM, Harvey SC, Brown FH Jr, Warden D. Reference values for performance on the automated

- neuropsychological assessment metrics V3.0 in an active duty military sample. *Mil Med.* 2006; 171:982–994. [PubMed: 17076451]
- Rosenberg H. Clinical and laboratory assessment of the subjective experience of drug craving. *Clin Psychol Rev.* 2009; 29:519–534. [PubMed: 19577831]
- Rubio G, Jimenez M, Rodriguez-Jimenez R, Martinez I, Avila C, Ferre F, Jimenez-Arriero MA, Ponce G, Palomo T. The role of behavioral impulsivity in the development of alcohol dependence: a 4-year follow-up study. *Alcohol Clin Exp Res.* 2008; 32:1681–1687. [PubMed: 18631324]
- Sayette MA, Shiffman S, Tiffany ST, Niaura RS, Martin CS, Shadel WG. The measurement of drug craving. *Addiction.* 2000; 95(Suppl 2):S189–210. [PubMed: 11002914]
- Schuckit MA. Low level of response to alcohol as a predictor of future alcoholism. *Am J Psychiatry.* 1994; 151:184–189. [PubMed: 8296886]
- Sonuga-Barke EJ. The dual pathway model of AD/HD: an elaboration of neuro-developmental characteristics. *Neurosci Beh Rev.* 2003; 27:593–604.
- Tolentino NJ, Wierenga CE, Hall S, Tapert SF, Paulus MP, Liu TT, Smith TL, Schuckit MA. Alcohol effects on cerebral blood flow in subjects with low and high responses to alcohol. *Alcohol Clin Exp Res.* 2011; 35:1034–1040. [PubMed: 21332525]
- Volkow ND, Fowler JS, Wang GJ, Swanson JM, Telang F. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. *Arch Neurol.* 2007; 64:1575–1579. [PubMed: 17998440]
- Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Wong C, Hitzemann R, Pappas NR. Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D(2) receptors. *J Pharmacol Exp Ther.* 1999; 291:409–415. [PubMed: 10490931]
- Volkow ND, Wang GJ, Fowler JS, Thanos PP, Logan J, Gatley SJ, Gifford A, Ding YS, Wong C, Pappas N. Brain DA D2 receptors predict reinforcing effects of stimulants in humans: replication study. *Synapse.* 2002; 46:79–82. [PubMed: 12211085]
- Volkow ND, Wang GJ, Kollins SH, Wigal TL, Newcorn JH, Telang F, Fowler JS, Zhu W, Logan J, Ma Y, Pradhan K, Wong C, Swanson JM. Evaluating dopamine reward pathway in ADHD: clinical implications. *JAMA.* 2009; 302:1084–1091. [PubMed: 19738093]
- Weafer J, Milich R, Fillmore MT. Behavioral components of impulsivity predict alcohol consumption in adults with ADHD and healthy controls. *Drug Alcohol Depend.* 2011; 113:139–146. [PubMed: 20863628]
- White TL, Justice AJ, de Wit H. Differential subjective effects of D-amphetamine by gender, hormone levels and menstrual cycle phase. *Pharmacol Biochem Behav.* 2002; 73:729–741. [PubMed: 12213517]

Table 1

Current and lifetime substance use for sample (n=165)

Current substance use	
Alcohol (drinks/week)	5.9 (5.0)
Cigarettes (per week)	1.2 (2.9)
Caffeine (cups/week)	8.3 (5.8)
Marijuana (times/month)	1.6 (4.2)
Lifetime substance use (% ever used)	
Stimulants	33.3
Sedatives	10.3
Opiates	24.2
Marijuana	79.4
Hallucinogens	38.8
Inhalants	10.3

Table 2a

Hierarchical regression analyses predicting subjective response to amphetamine (DEQ)

DEQ Measure	AUC 5 mg vs placebo			AUC 10 mg vs placebo			AUC 20 mg vs placebo		
	R ²	B (se)	Beta	R ²	B (se)	Beta	R ²	B (se)	Beta
<i>Like Drug</i>									
Step 1	.01			.02			.02		
Age		0.02 (0.05)	0.03		-0.01 (0.08)	-0.01		0.08 (0.09)	0.07
Gender		0.47 (0.35)	0.11		0.92 (0.54)	0.14		0.63 (0.61)	0.08
Placebo Session		-0.03 (0.16)	-0.01		0.19 (0.25)	0.06		-0.30 (0.28)	-0.09
Step 2	.04			.07*			.11**		
Age		0.01 (0.05)	0.01		-0.02 (0.08)	-0.02		0.03 (0.09)	0.03
Gender		0.52 (0.35)	0.12		1.02 (0.53)	0.15		0.78 (0.59)	0.10
Placebo Session		-0.08 (0.16)	-0.04		0.22 (0.25)	0.07		-0.28 (0.27)	-0.08
Attention Lapses		-0.01 (0.01)	-0.11		-0.02 (0.01)	-0.16*		-0.04 (0.01)	-0.29***
Stop RT		-0.01 (0.00)	-0.11		0.01 (0.01)	0.18*		0.01 (0.01)	0.17*
<i>Feel Drug</i>									
Step 1	.02			.06*			.01		
Age		0.01 (0.05)	0.01		-0.01 (0.06)	-0.01		0.04 (0.07)	0.04
Gender		0.65 (0.35)	0.15		1.18 (0.41)	0.22**		0.55 (0.48)	0.09
Placebo Session		0.01 (0.16)	0.01		0.16 (0.19)	0.06		-0.06 (0.22)	-0.02
Step 2	.04			.11**			.10**		
Age		-0.01 (0.05)	-0.01		-0.02 (0.06)	-0.03		0.01 (0.07)	0.01
Gender		0.70 (0.36)	0.16		1.25 (0.40)	0.24**		0.68 (0.46)	0.11
Placebo Session		0.00 (0.16)	0.00		0.19 (0.19)	0.08		-0.05 (0.21)	-0.02
Attention Lapses		-0.01 (0.01)	-0.12		-0.02 (0.01)	-0.17*		-0.03 (0.01)	-0.30***
Stop RT		0.00 (0.00)	0.04		0.01 (0.00)	0.20*		0.01 (0.01)	0.16*
<i>Want More</i>									
Step 1	.02			.03			.02		
Age		0.00 (0.07)	0.00		0.04 (0.09)	0.04		0.21 (0.11)	0.15
Gender		0.75 (0.48)	0.12		0.92 (0.59)	0.12		0.44 (0.71)	0.05

DEQ Measure	AUC 5 mg vs placebo			AUC 10 mg vs placebo			AUC 20 mg vs placebo		
	R ²	B (se)	Beta	R ²	B (se)	Beta	R ²	B (se)	Beta
Placebo Session		−0.27 (0.22)	−0.10		0.38 (0.27)	0.11		−0.08 (0.33)	−0.02
Step 2	.03			.05			.08 [*]		
Age		−0.01 (0.07)	−0.01		0.03 (0.09)	0.03		0.18 (0.11)	0.13
Gender		0.78 (0.49)	0.13		0.99 (0.59)	0.13		0.55 (0.70)	0.06
Placebo Session		−0.30 (0.22)	−0.11		0.41 (0.27)	0.12		−0.02 (0.32)	−0.01
Attention Lapses		−0.01 (0.01)	−0.05		−0.01 (0.01)	−0.11		−0.03 (0.01)	−0.20 [*]
Stop RT		−0.00 (0.01)	−0.04		0.01 (0.01)	0.14		0.02 (0.01)	0.18 ^{**}

Note. DEQ = Drug Effects Questionnaire; AUC = Area under the curve.

* $p < .05$,

** $p < .01$,

*** $p < .001$

Table 2b

Hierarchical regression analyses predicting subjective response to amphetamine (POMS)

DEQ Measure	AUC 5 mg vs placebo			AUC 10 mg vs placebo			AUC 20 mg vs placebo		
	R ²	B (se)	Beta	R ²	B (se)	Beta	R ²	B (se)	Beta
<i>Elation</i>									
Step 1	.03			.01			.04		
Age		2.07 (1.32)	0.12		-0.65 (1.47)	-0.04		2.41 (1.53)	0.12
Gender		7.64 (8.66)	0.07		12.90 (9.55)	0.11		17.34 (10.06)	0.14
Placebo Session		-5.32 (3.95)	-0.11		-0.26 (4.40)	-0.01		-6.63 (4.61)	-0.11
Step 2	.04			.03			.09*		
Age		1.81 (1.33)	0.11		-0.75 (1.49)	-0.04		2.20 (1.52)	0.11
Gender		8.74 (8.68)	0.08		13.54 (9.57)	0.11		17.86 (9.89)	0.14
Placebo Session		-5.53 (4.00)	-0.11		0.38 (4.44)	0.01		-5.11 (4.57)	-0.09
Attention Lapses		-0.24 (0.16)	-0.12		-0.14 (0.17)	-0.07		-0.24 (0.18)	-0.11
Stop RT		0.05 (0.10)	0.05		0.16 (0.11)	0.13		0.31 (0.11)	0.22**
<i>Vigor</i>									
Step 1	.05*			.03			.03		
Age		3.96 (2.07)	0.15		-0.47 (1.92)	-0.02		2.68 (2.23)	0.10
Gender		-7.88 (13.56)	-0.05		8.10 (12.41)	0.05		19.62 (14.65)	0.11
Placebo Session		-13.68 (6.19)	-0.17*		-10.84 (5.71)	-0.15		-10.75 (6.7)	-0.13
Step 2	.07*			.05			.08*		
Age		4.35 (2.08)	0.16*		-0.19 (1.92)	-0.01		2.62 (2.21)	0.09
Gender		-9.33 (13.57)	-0.05		7.30 (12.37)	0.05		19.42 (14.40)	0.11
Placebo Session		-12.18 (6.25)	-0.15		-9.06 (5.74)	-0.13		-8.11 (6.65)	-0.10
Attention Lapses		0.27 (0.24)	0.09		0.12 (0.22)	0.04		-0.15 (0.26)	-0.05
Stop RT		0.15 (0.15)	0.08		0.25 (0.14)	0.15		0.47 (0.16)	0.23**
<i>Friendliness</i>									
Step 1	.05*			.02			.03		
Age		4.72 (1.98)	0.19*		1.60 (1.87)	0.07		3.81 (1.97)	0.15
Gender		-5.83 (12.98)	-0.04		17.83 (12.13)	0.12		8.11 (12.92)	0.05

DEQ Measure	AUC 5 mg vs placebo			AUC 10 mg vs placebo			AUC 20 mg vs placebo		
	R ²	B (se)	Beta	R ²	B (se)	Beta	R ²	B (se)	Beta
Placebo Session		-10.05 (5.93)	-0.13		-5.80 (5.59)	-0.08		-6.96 (5.91)	-0.09
Step 2	.05			.03			.07		
Age		4.59 (2.01)	0.18*		1.58 (1.90)	0.07		3.54 (1.96)	0.14
Gender		-5.34 (13.1)	-0.03		18.09 (12.22)	0.12		8.89 (12.81)	0.06
Placebo Session		-10.28 (6.03)	-0.13		-5.11 (5.67)	-0.07		-5.48 (5.91)	-0.07
Attention Lapses		-0.10 (0.24)	-0.04		-0.07 (0.22)	-0.03		-0.30 (0.23)	-0.11
Stop RT		-0.00 (0.15)	-0.00		0.14 (0.14)	0.09		0.32 (0.14)	0.18*

Note. POMIS = Profile of Mood States; AUC = Area under the curve.

* $p < .05$,

** $p < .01$,

*** $p < .001$

Table 3
Correlations between amphetamine effects (compared to placebo) on subjective and behavioral measures

	5 mg			10 mg			20 mg		
	Attention Lapses	Stop RT	Attention Lapses	Stop RT	Attention Lapses	Stop RT	Attention Lapses	Stop RT	Attention Lapses
DEQ									
Like Drug	-.14	-.12	-.06	.12	-.22**	.10			
Feel Drug	-.21**	-.07	-.04	.19*	-.28**	.05			
Want More	-.08	.01	.01	.05	-.16	.09			
POMS									
Elation	-.06	.07	.02	.17*	.06	.28**			
Vigor	.06	.08	.09	.18*	.13	.26**			
Friendliness	-.06	.01	-.05	.20*	.03	.18*			

Note. DEQ = Drug Effects Questionnaire, POMS = Profile of Mood States.

* $p < .05$,

** $p < .01$.