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Individual differences in timing of peak positive subjective responses to d-amphetamine: Relationship to pharmacokinetics and physiology

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Abstract

Rate of delivery of psychostimulants has been associated with their positive euphoric effects and potential addiction liability. However, information on individual differences in onset of d-amphetamine's effects remains scarce. We examined individual differences in the time to peak subjective and physiological effects and the pharmacokinetics/pharmacodynamics of oral d-amphetamine. We considered two independent studies that used different dosing regimens where subjects completed the drug effects questionnaire at multiple time points post d-amphetamine. Based on the observation of distinct individual differences in time course of drug effects questionnaire "feel", "high", and "like" ratings (DEQ_{H+L+F}) in Study 1, subjects in both studies were categorized as early peak responders (peak within 60 minutes), late peak responders (peak > 60 minutes) or nonresponders; 20–25% of participants were categorized as early peak responders, 50–55% as late peak responders and 20–30% as nonresponders. Physiological (both studies) and plasma d-amphetamine (Study 1) were compared among these groups. Early peak responders exhibited an earlier rise in plasma d-amphetamine levels and more sustained elevation in heart rate compared to late peak responders. The present data illustrate the presence of significant individual differences in the temporal pattern of responses to oral d-amphetamine, which may contribute to heightened abuse potential.

Keywords

d-amphetamine, subjective effects, individual differences, pharmacokinetics, addiction

Introduction

Positive subjective responses to drugs of abuse may be a risk factor for repeated use and addiction (de Wit and Phillips, 2012; Haertzen et al., 1983). As these positive subjective effects (liking, high) have been tied to drugs' abuse potential (Lambert et al., 2006) and the timing of drug delivery to the brain is thought to impact these effects (Volkow et al., 2004), demonstrating differences in the timing of subjective drug liking/high ratings across individuals may offer insights into individual variability in addiction risk.

Significant variability exists in both subjective and physiological effects of oral d-amphetamine (dAMPH) (Brauer et al., 1996; Brown et al., 1978; de Wit et al., 1986; Dommissie et al., 1984). In a controlled human drug discrimination study, only about half of participants successfully discriminated between low oral doses (up to 10 mg) of dAMPH and placebo (Chait et al., 1985, 1989). Chait et al. (1989) found that those who were able to discriminate amphetamine from placebo reported greater "high" and "stimulated" scores on visual analog scales (VAS) than the non-discriminators. Other studies have linked individual differences in responses to amphetamine to personality (Hutchison et al., 1999; Kelly et al., 2006; Kirkpatrick et al., 2013), behavioral (Weafer and de Wit, 2013), and genetic factors (Hart et al., 2012a, 2012b, 2014; Nurnberger et al., 1982; Yarosh et al., 2015). However, none of these studies have

examined the time course of the positive subjective effects associated with acute psychostimulants or the relationship of these temporal patterns to differences in pharmacokinetics or peripheral drug effects.

To date, studies of individual differences in responses to psychostimulants have largely focused on the peak response or accumulated response over time (such as area under the curve), but have not examined individual differences in the time course,

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especially the time to peak effect. However, both preclinical and clinical work suggests that time to peak effect may be critical in determining the subjective and addictive responses to psychostimulants. Drugs with a faster onset of effects, or routes of administration associated with fast onset, have a higher potential for abuse (Fischman, 1989; Oldendorf, 1992). In nonhuman primates, faster administration of cocaine maintains higher rates of self-administration (Balster and Schuster, 1973; Kato et al., 1987), and in humans routes of administration that deliver the drug more rapidly (e.g. intravenous vs. smoked vs. intranasal) increase the likelihood for individuals to become dependent on the drug and experience other adverse consequences (Ferri and Gossop, 1999; Gossop et al., 1992; Hatsukami and Fischman, 1996). In addition, cocaine, methylphenidate, and diazepam produce greater positive subjective effects when they are administered rapidly (Abreu et al., 2001; de Wit et al., 1993; Kollins et al., 1998; Nelson et al., 2006). Thus, variability across individuals in the rate of absorption, or the rate of onset of the central effects, may help to explain some of the variability in the quality and magnitude of the drugs' effects.

Here, we sought to investigate the time course of positive subjective effects, physiological, and pharmacokinetic responses to oral dAMPH in young adults. We used two datasets. In Study 1 we examined subjective responses in 54 participants who were administered 0.43 mg/kg oral dAMPH as part of a positron emission tomography (PET) protocol (Buckholtz et al., 2010; Samanez-Larkin et al., 2013; Treadway et al., 2012). After observing significantly different temporal patterns in this initial study, we sought to replicate and extend these findings in Study 2, using data from an independent large, counter-balanced, double-blind, oral dAMPH (10 and 20 mg) drug challenge study with healthy young adults ($n = 398$) (Hart et al., 2013). Both datasets included subjective drug effect ratings and physiological measures collected at multiple time points after both oral dAMPH and placebo. The first study also included pharmacokinetic measures of plasma levels of amphetamine, allowing us to test for differential rates of drug absorption.

Methods

Subjects

Study 1 was conducted at Vanderbilt University ($n = 54$) and Study 2 at the University of Chicago ($n = 398$). Participants at both sites were healthy individuals 18–35 years old with no known past or present neurological or psychiatric diagnoses, no history of substance use disorders, and no current use of psychoactive medications or other psychoactive substances aside from moderate use of caffeine (less than three caffeinated beverages per day), nicotine (less than 10 cigarettes per day) or alcohol (less than 15 drinks per week). All subjects were native English speakers, and had at least a high-school education. Women were tested during the follicular phase of their cycle. The final samples consisted of 49 individuals from Study 1 (25 male; age: 22.12 ± 3.17) and 387 participants from Study 2 (200 male; age: 23.27 ± 3.64) with DEQ measures at all time points for the dAMPH and placebo sessions. Participants gave written informed consent, as approved by the Vanderbilt University Institutional Review Board or University of Chicago Institutional Review Board, respectively.

Drug administration

Participants in Study 1 received placebo for their first experimental session and a target dose of 0.43 mg/kg oral dAMPH during their second session. The actual administered dose of dAMPH in Study 1 was rounded to the nearest 2.5 mg (mean actual dose = 30.5 mg, range = 20–42.5 mg) based on individual participants' weight to achieve the targeted 0.43 mg/kg dose. Participants in Study 2 received placebo, 10, and 20 mg dAMPH in a blind, randomized design. Because the 0.43 mg/kg dose in Study 1 is equivalent to ~30 mg fixed dose in these participants, we focused on the 20 mg dAMPH and placebo data from Study 2 in our initial replication analysis. We also investigated the 10 mg dAMPH dose from Study 2 as a test of the generalizability of our findings to lower doses of dAMPH.

Procedure

Sessions were separated by at least 48 hours. Participants were tested for recent drug use and pregnancy before each session. They were instructed not to eat for three hours before the sessions to standardize drug absorption. Study 1 was a PET imaging study, and subjects completed the drug effects questionnaire (DEQ; see below) 60, 120, 180, 270, and 345 minutes after ingesting the capsule, and physiological measures were obtained at pre-capsule, 15, 30, 45, 60, 80, 100, 120, 150, and 180 minutes. In Study 2 subjects completed the DEQ before and 30, 60, 90, 150, and 180 minutes after capsule ingestion, and heart rate and blood pressure were measured before and at 30, 60, 90, 150, and 180 minutes. In Study 1 plasma samples were obtained 60, 120, 180, and 270 minutes after capsule ingestion.

Drug effects questionnaire

In Study 1, individuals rated on a 100 mm labeled magnitude scale (Lishner et al., 2008): (a) feel any substance effect(s) ("feel"); (b) feel high ("high"); (c) like the effects ("like"); (d) want more of the substance ("want more") from NOT AT ALL (0 mm) to MOST IMAGINABLE (100 mm). Study 2 assessed the same questions employing a 100 mm visual analog scale with anchors at NOT AT ALL (0 mm) and EXTREMELY (100 mm). These questions constitute the DEQ. The DEQ has good psychometric properties, including tests of the construct validity of its four subscales and convergent validity of its ratings with other measures of subjective drug response (Morean et al., 2013) including the profile of mood states (POMS; Johanson and Uhlenhuth, 1980) and Addiction Research Center Inventory (ARCI; Martin et al., 1971). Furthermore, the DEQ is sensitive to the effect of dAMPH (Brauer et al., 1996; de Wit et al., 1986). DEQ values were recorded as proportions of the 100 mm scale (values range from 0 to 1). In Study 1, we first investigated patterns across all DEQ items as a global measure of subjective effects after dAMPH versus placebo. We created an average DEQ_{All} dAMPH minus placebo score at each time point by calculating the difference in dAMPH versus placebo ratings at each time point across the four DEQ scales ("feel", "like", "high", "want more"), summing these difference scores, and dividing by the number of scales (4). The time course of the DEQ_{All} scores were then investigated. Based on evidence that DEQ "high", "like", and "feel", but not "want", have similar temporal profiles

(see “DEQ subjective effects time courses by peak groups in Study 1” section in “Results”) we subsequently investigated mean DEQ “high”/“like”/“feel” (DEQ_{H+L+F}) scores as our primary response measure.

Within Study 2, two versions of the DEQ were used. The first 161 subjects completed a bipolar DEQ dislike/like scale with anchors at EXTREMELY DISLIKE and EXTREMELY LIKE drug, respectively, whereas the remaining 237 participants completed a unipolar DEQ like scale and a separate dislike scale. The questionnaire was modified because the bipolar scale was susceptible to misinterpretation and because it was accepted that subjects could “like” certain effects while “disliking” others, at the same time. For this analysis, the data from the bipolar DEQ dislike/like scale were transformed to create a value comparable to the 100 mm unipolar scale (a rating 50% toward the EXTREMELY LIKE end of the scale = DEQ like rating of 0.5). There were no differences in the temporal patterns in DEQ ratings when either the unipolar or bipolar DEQ like ratings were used. Thus, for simplicity, we report data from the full dataset in Study 2.

Other measures of subjective drug response collected in Study 2

In addition to the DEQ, the POMS (Johanson and Uhlenhuth, 1980) and ARCI (Martin et al., 1971) were collected at baseline, 30, 60, 90, 150, and 180 minutes post dAMPH and placebo. We focused on POMS elation and ARCI amphetamine ratings here as a test of the generalizability of our DEQ groups to other commonly studied measures of positive subjective response. Data were analyzed as 20 mg dAMPH minus placebo day scores on these measures across the six time points.

Physiological measures

Heart rate and blood pressure (diastolic and systolic) were collected at intervals described above (“Procedure”). For simplicity, mean arterial pressure (MAP) is presented from the blood pressure data, derived from the following equation: $MAP = ((2 \times \text{diastolic BP}) + \text{systolic BP})/3$.

Peripheral amphetamine absorption measure

For Study 1, plasma amphetamine levels were analyzed via a selegiline + metabolites assay conducted by NMS Laboratories. High performance liquid chromatography and tandem mass spectrometry were used to determine concentration of amphetamine with a minimum reporting level of 5 ng/mL.

Data analysis

To determine how to best stratify potential differences in DEQ time course in our participants, we first sorted individuals in Study 1 based on when their DEQ_{All} score peaked after dAMPH administration. Earlier work indicates that on average subjective liking responses to oral dAMPH (20 mg) peak between 60 and 90 minutes after ingestion (Brauer et al., 1996; Rush et al., 2001). In this study we were particularly interested as to whether a group of individuals could be identified with rapid peaks within an hour

of administration. We therefore separated individuals based on their peak DEQ response: less than or equal to 60 min after capsule (early), more than 60 min after the capsule (late), or no response to the drug (nonresponders). Amphetamine nonresponders were defined as individuals whose average DEQ_{All} dAMPH-placebo ratings never exceeded 0.1 units (> 1 standard deviation below mean DEQ_{All} across all subjects).

In Study 1, DEQ, physiological, and plasma amphetamine measures were compared across DEQ peak groups and time post drug using repeated measures ANOVA. In Study 2, DEQ and physiological measures were compared across the DEQ groups. Follow-up post-hoc tests were performed where either significant omnibus effects were observed or at the 60-minute post dAMPH time point specifically as this is where our DEQ values deviated the most across early and late peak responders. Finally, Pearson’s correlation analyses were performed across variables of interest when appropriate and significant results reported with 95% confidence intervals (CI).

Results

Determination of DEQ peak groups

In Study 1, 12 (24.5%) participants displayed their highest DEQ_{All} scores ~60 minutes after oral dAMPH administration and thus were classified as early peak responders. Twenty-six participants were classified as late peak responders (53.1%: see Table 1 for distribution of peak DEQ_{All} times in this group) and 11 were nonresponders (22.4%).

DEQ subjective effects time courses by peak groups in Study 1

As expected, our DEQ_{All} groups in Study 1 differed in their temporal profile (time \times group interaction: $F_{(8,184)} = 7.73, p < 0.001, \eta^2 = 0.24$; Figure 1) with a significant elevation in DEQ_{All} at 60 minutes post dAMPH in early peak responders (0.45 ± 0.12) relative to late peak responders ($0.23 \pm 0.21; t_{36} = 3.43, p = 0.002$). No differences were observed at any other time point between the responder groups and the responder groups did not differ in their max DEQ_{All} ratings ($t_{36} = 0.38, p = 0.71$).

To explore whether each of the four DEQ domains (“like”, “high”, “feel”, “want more”) showed a similar temporal pattern across groups, we investigated each DEQ dAMPH minus placebo measure over time across our three DEQ_{All} peak groups. We observed significant group \times time interactions on all DEQ measures (min $F = 5.16, \max p = 0.001$) except “want more” drug, $F_{(8,184)} = 1.253, p = 0.271$. Thus, the three DEQ scales of “high”, “like”, and “feel” drug best captured the early–late peak distinction in the temporal patterns of subjective responses. Therefore, in all subsequent analyses we classified subjects based on the time course of the average of their “high”, “like” and “feel” ratings (DEQ_{H+L+F}). We note that our proportions of early ($n = 11, 22.4\%$), late ($n = 27, 55.1\%$) and nonresponders ($n = 11, 22.4\%$) using DEQ_{H+L+F} were very similar to those using the complete DEQ_{All} ratings and that only three participants’ categorization changed across our responder groups via this new method (see Table 1 for breakdown of peak times for DEQ_{All} and DEQ_{H+L+F} across groups). However, the temporal differences between groups became more pronounced (group \times time interaction:

Table 1. Distribution of participants falling into each DEQ peak group, listed by time of peak DEQ measure.

Distribution of peak responders' peak DEQ times by DEQ _{All} and DEQ _{H+L+F}						
Time post (min)	DEQ _{All} early peak	DEQ _{All} late peak	DEQ _{H+L+F} early peak	DEQ _{H+L+F} late peak	Early peak % concord.	Late peak % concord.
Study 1 (average dose: 0.43 mg/kg)						
60	12	–	11	–	90.9%	–
120	–	7	–	9	–	66.7%
180	–	8	–	8	–	87.5%
270	–	10	–	10	–	90%
345	–	1	–	0	–	–
Study 2 (20 mg dAMPH data; average dose: 0.30 mg/kg)						
30	11	–	11	–	90.9%	–
60	78	–	82	–	86.6%	–
90	–	97	–	101	–	88.1%
150	–	61	–	56	–	87.5%
180	–	28	–	26	–	88.5%

Numbers of participants falling into each DEQ peak group (either via DEQ_{All} or DEQ_{H+L+F} ratings) are listed in the table beside the time of their peak DEQ_{All} or DEQ_{H+L+F} ratings. Note that early peak responders had to have peak ratings at 60 minutes or earlier while late peak responders had to report peak ratings after 60 minutes. The far right columns report the percent concordance (% concord.) of DEQ_{All} early or late peak responders that fall into the same peak time bin using DEQ_{H+L+F} ratings to determine peak time.

Time post = time post dAMPH administration; % concord. = % concordance between DEQ_{H+L+F} and DEQ_{All} peak times; – = peak time point not applicable for that peak group.

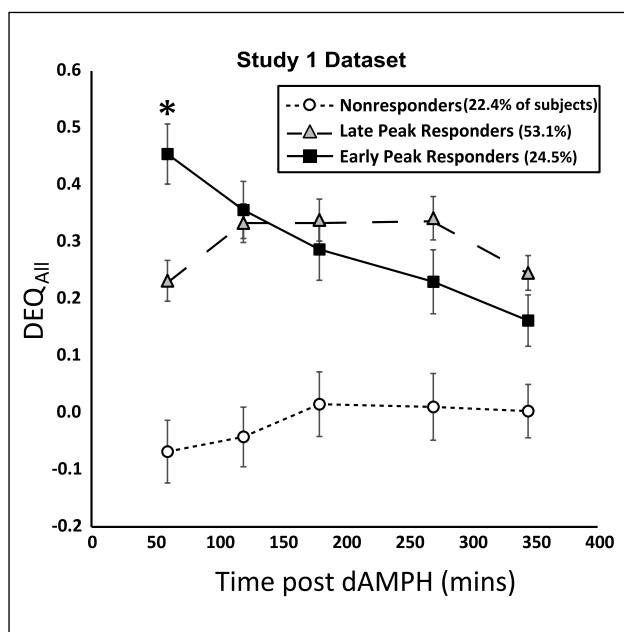


Figure 1. Time course of DEQ_{All} ratings varies by DEQ_{All} peak groups in the Study 1 dataset.

Study 1 DEQ_{All} values (dAMPH minus placebo, averaged across four DEQ scales) plotted by DEQ_{All} peak response time groups result in three distinct time courses of amphetamine's subjective effects. Note that nonresponder data points hover around zero and x-axis lies at -0.2.

*Early and late peak responder groups significantly different, $p < 0.05$.

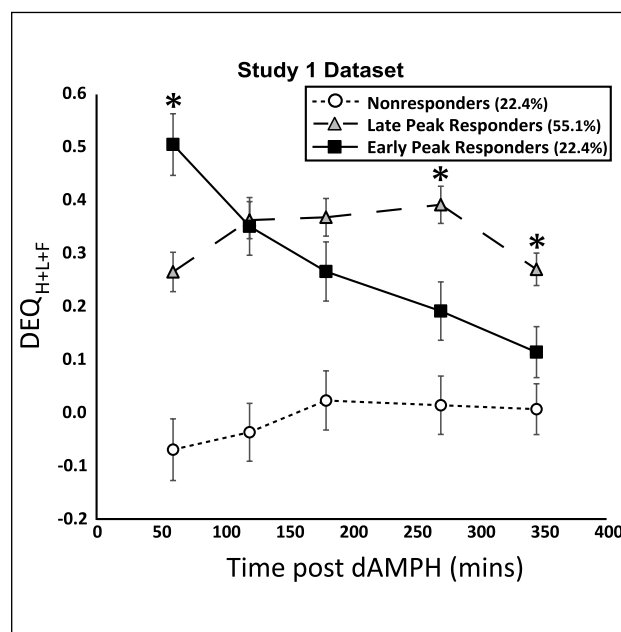


Figure 2. Time course of DEQ_{H+L+F} ratings varies by DEQ_{H+L+F} peak groups in the Study 1 dataset.

Study 1 DEQ_{H+L+F} values (dAMPH minus placebo, averaged across DEQ "high", "like", and "feel" scales) plotted by peak DEQ_{H+L+F} response time groups result in three distinct time courses of amphetamine's subjective effects.

*Early and late peak responder groups significantly different, $p < 0.05$.

$F_{(8,184)} = 10.35, p < 0.001, \eta^2 = 0.29$) with significant differences between early and late peak DEQ_{H+L+F} responders at 60 ($t_{(29,47)} = 4.013, p < 0.001$), 270 ($t_{36} = -2.72, p = 0.01$), and 345 minutes ($t_{36} = -2.43, p = 0.02$; Figure 2). Again, among the responder groups, max DEQ_{H+L+F} ratings did not vary ($t_{36} = 0.19, p = 0.85$).

DEQ subjective effects time courses by DEQ_{H+L+F} peak groups in Study 2

Based on the findings from the Study 1 dataset that DEQ_{H+L+F} ratings exhibit different temporal profiles across individuals and vary significantly across multiple time points, we sought to

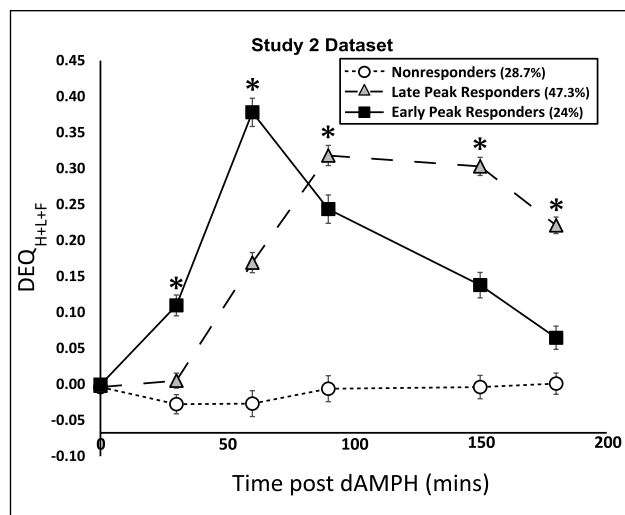


Figure 3. Time course of DEQ_{H+L+F} varies by DEQ_{H+L+F} peak groups in the Study 2 dataset. DEQ_{H+L+F} values at each time point after d-amphetamine plotted by DEQ_{H+L+F} peak response time groups. *Early and late peak responder groups significantly different, $p < 0.01$.

replicate our findings in a larger, independently collected dataset (Study 2). We determined DEQ_{H+L+F} peak groups in this dataset using the 20 mg oral dAMPH dose (-0.3 mg/kg) as this most closely approximated the 0.43 mg/kg dAMPH dose used in Study 1. Using the same criteria as applied to Study 1 above, we found 111 participants were classified as nonresponders (28.7%), 93 as early peak responders (24.0%), and 183 as late peak responders (47.3%) on our DEQ_{H+L+F} measure. We note there was high concordance between DEQ_{H+L+F} and DEQ_{All} groups in this replication dataset (see Table 1), suggesting overall temporal differences in subjective responses across participants is driven by changes in DEQ_{H+L+F} ratings over time. Consistent with the findings from Study 1, a significant Time \times DEQ_{H+L+F} group interaction was found on DEQ_{H+L+F} scores ($F_{(10,1920)} = 77.62, p < 0.001, \eta^2 = 0.23$; Figure 3). An elevation in DEQ_{H+L+F} ratings emerged in early peak responders (0.11 ± 0.18) relative to the late peak responders (0.005 ± 0.14 ; $t_{274} = 5.26, p < 0.001$) already at 30 minutes post dAMPH which remained elevated at 60 minutes ($t_{274} = 7.62, p < 0.001$). By 90 minutes post drug, DEQ_{H+L+F} was significantly elevated in the late peak responders (0.32 ± 0.23) relative to the early peak responders (0.24 ± 0.19 ; $t_{274} = -2.65, p = 0.008$), which remained elevated at 150 ($t_{274} = -6.54, p < 0.001$) and 180 minutes ($t_{274} = -6.71, p < 0.001$). As in Study 1, the max DEQ_{H+L+F} ratings did not differ across our early (0.40 ± 0.18) versus late peak responders (0.41 ± 0.20 ; $t_{274} = -0.61, p = 0.54$).

Secondary analysis of the four DEQ ratings in the Study 2 dataset treated in isolation revealed several notable findings. First, the DEQ “like”, “high”, and “feel” ratings demonstrated very similar temporal profiles (Figure 4), as seen in Study 1. Second, the DEQ_{H+L+F} responder groups differed consistently across time in “like”, “high”, and “feel” measures starting at 30 minutes post dAMPH (except at 90 minutes where they were equivalent in DEQ like). Whereas the early peak DEQ_{H+L+F} responders were already showing subjective effects at 30 minutes post dAMPH, the late peak DEQ_{H+L+F} responder group had not yet shown any evidence of a subjective effect. When looking at

DEQ “want more” ratings, we found early peak DEQ_{H+L+F} responders were also elevated in this measure at the 30- (0.105 ± 0.264) and 60-minute (0.403 ± 0.312) time points compared to late peak DEQ_{H+L+F} responders (0.020 ± 0.223 and 0.193 ± 0.313 ; $t_{274} = 2.65, p = 0.009$ and $t_{274} = 5.27, p < 0.001$, respectively). However, once elevated, early peak responders maintained high “want more” ratings at the later time points of 90, 150, and 180 minutes, as observed in late peak responders (Figure 4).

Early peak responders have faster slope to peak DEQ_{H+L+F} but decline from peak is similar to late peak responders

The DEQ_{H+L+F} time course data (Figures 2 and 3) suggest that early peak responders have a faster rise to peak DEQ_{H+L+F} and a steeper decline in DEQ_{H+L+F} values after peak compared to late peak responders. We sought to investigate this potential difference in responder groups by quantifying the slope to peak DEQ_{H+L+F} and decline from peak DEQ_{H+L+F} for each subject in the Study 2 dataset. We used Excel’s built-in slope function to measure the rise in DEQ_{H+L+F} as a function of time (in minutes) from capsule intake until peak DEQ_{H+L+F} , with higher values representing steeper increases in DEQ_{H+L+F} with time. Although there was a significant relationship between time to peak and slope ($r = -0.22, p < 0.001$), the correlation is relatively modest because slope assesses the magnitude of change over time, which does not impact the time to peak measure. Furthermore, examination of rate of increase in subjective response (slope to peak) provides a closer parallel to the rate hypothesis of drug addiction risk (Fischman, 1989; Gorelick, 1998; Oldendorf, 1992), which emphasizes the slope of pharmacological action and corresponding subjective responses. We found that early responders had significantly higher slope to peak values (0.0057 ± 0.0038) than the late responders (0.0046 ± 0.0028 ; $t_{224} = 2.40, p = 0.017$). Furthermore, in the first 30 minutes after dAMPH administration, the early responders displayed higher DEQ_{H+L+F} slopes (0.00385 ± 0.0063) versus late responders (0.00022 ± 0.0050 ; $t_{224} = 4.45, p < 0.001$), suggesting a faster ramping up of subjective effects in these individuals before the majority (89.7%) reach their peak effects at 60 minutes. No group differences were observed in the rate of decline from peak DEQ_{H+L+F} ratings ($t_{203} = -0.76, p = 0.45$). Because there was variability within each DEQ_{H+L+F} peak group as to when each individual reached their peak, especially in the late responders, we also compared individual participants’ DEQ_{H+L+F} ratings from their own peak to two time points post-peak, but again found no significant time \times group effect for the rate of decline in these ratings in either the Study 1 ($F_{(2,46)} = 1.194, p = 0.31$) or Study 2 ($F_{(2,384)} = 0.707, p = 0.49$) dataset. Thus, the higher DEQ_{H+L+F} ratings observed at later time points in late responders (Figures 2 and 3) results from the heterogeneity in peak time across subjects in that group (see Table 1) rather than a group difference in rate of decline in those subjects relative to early peak responders.

DEQ_{H+L+F} peak groups compared on demographic measures

Study 1’s DEQ_{H+L+F} groups were well matched on age (22.1 ± 3.0 for nonresponders; 22.6 ± 3.6 for late peak responders; 21.1 ± 1.9

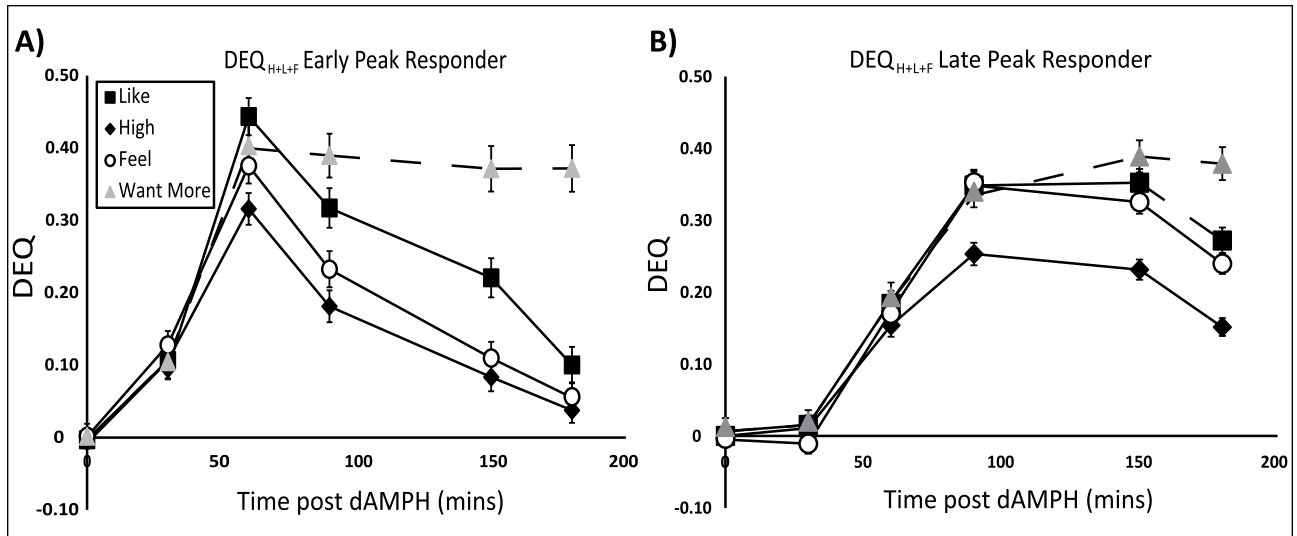


Figure 4. Time course of all DEQ subscales by DEQ_{H+L+F} peak groups in the Study 2 dataset.

A. DEQ_{H+L+F} early peak responders. (Note that DEQ “like”, “feel”, “high”, and “want more” peak at ~60 minutes post dAMPH and that DEQ “like”, “feel”, and “high” decline with time to not be different from each other at 180 minutes (solid lines). DEQ “want more” does not show this temporal pattern, however, remaining elevated at later time points (dashed-line).)

B. DEQ_{H+L+F} late peak responders. (Note that DEQ “feel”, “high”, and “like” peak at 90 minutes and “want more” at 150 minutes. “Want more” remains elevated at 180 minutes while “like”, “high”, and “feel” have begun to decline by this time point.)

Note also that responder groups differ on DEQ “want more” at 30 and 60 minutes ($p < 0.01$) but not at later time points while DEQ “like”, “feel”, and “high” differ across the DEQ_{H+L+F} responder groups at 30, 60, 150, and 180 minutes ($p < 0.002$) with differences in “high” ($p = 0.011$) and “feel” ($p < 0.001$) but not “like” ($p = 0.20$) at 90 minutes.

for early peak responders; $F_{(2,46)} = 0.83, p = 0.44$) but sex distribution differed across these groups ($\chi^2 = 10.55, p = 0.005, df = 2$). A high proportion of females were observed in the nonresponder group (90.9%) and males in the early peak responder group (72.7%) with the late peak responder group showing a 60:40 male:female distribution. For Study 2, DEQ_{H+L+F} groups were also well matched on age (23.1 ± 3.7 for nonresponders; 23.4 ± 3.8 for late peak responders; 23.2 ± 3.1 for early peak responders; $F_{(2,384)} = 0.14, p = 0.87$) and closely matched the age of participants in Study 1. Furthermore, in the larger Study 2 dataset, we observed no differences in sex distribution across the three DEQ_{H+L+F} groups ($\chi^2 = 0.25, p = 0.89, df = 2$) with all being ~50% male. Due to the larger power in Study 2, we believe the sex differences observed across groups in Study 1 is probably a spurious finding. The three DEQ_{H+L+F} groups likely do not differ in their sex distributions. Regardless, covarying for sex in Study 1 did not alter our key time \times DEQ_{H+L+F} group effects on DEQ_{H+L+F} ratings or differences in dAMPH absorption and peripheral stimulation (MAP, pulse) we report below.

Pharmacokinetic differences across DEQ_{H+L+F} groups

A natural question arises as to whether the differential temporal patterns of subjective responses can be attributed to pharmacokinetics. In the Study 1 dataset, we assessed peripheral absorption by measuring plasma amphetamine at 60, 120, 180, and 270 minutes post drug and asked whether differences in dAMPH absorption at these time points related to DEQ_{H+L+F} ratings. While we did not find a statistically significant time \times group interaction on plasma amphetamine ($F_{(6,126)} = 1.34, p = 0.24$) across our three

DEQ_{H+L+F} peak groups, we did find that plasma amphetamine was higher in our early peak responders at 60 minutes (where the groups also differed on DEQ_{H+L+F} ratings) post drug (51.7 ± 23.2) versus the nonresponders (27.0 ± 9.1) and late peak responders ($32.7 \pm 18.4, F_{(2,43)} = 5.35, p = 0.008$, Figure 5). This difference in plasma amphetamine was not present at the later time points and peak levels of plasma amphetamine did not differ across groups ($F_{(2,43)} = 0.50, p = 0.61$). Thus, the early peak responders appear to have faster peripheral absorption of amphetamine than the other groups. This difference in absorption may explain some of the differences in time course of DEQ_{H+L+F} ratings in Study 1 as there is a positive correlation between DEQ_{H+L+F} at 60 minutes and plasma amphetamine at 60 minutes ($r = 0.34, p = 0.022$; $CI: 0.09, 0.54$). However, covarying for plasma amphetamine at 60 minutes does not remove the DEQ_{H+L+F} group \times time effect on DEQ_{H+L+F} ratings ($F_{(8,168)} = 5.31, p < 0.001, \eta^2 = 0.18$). Given the plasma amphetamine results, we additionally analyzed whether weight-adjusted dAMPH dose (in mg/kg) might relate to DEQ_{H+L+F} peak ratings or peak times as this measure was available in both study datasets.

Comparing weight-adjusted dAMPH dose by DEQ_{H+L+F} groups

Differences in administered dAMPH dose relative to an individual’s weight could potentially drive the observed DEQ_{H+L+F} group differences. In Study 1, dosings were rounded to the nearest 2.5 mg, and thus had a small amount of variability relative to the target dose of 0.43 mg/kg. Therefore, we used the recorded number of 2.5 mg dAMPH capsules administered to subjects in Study 1 to calculate the weight-adjusted dose administered to

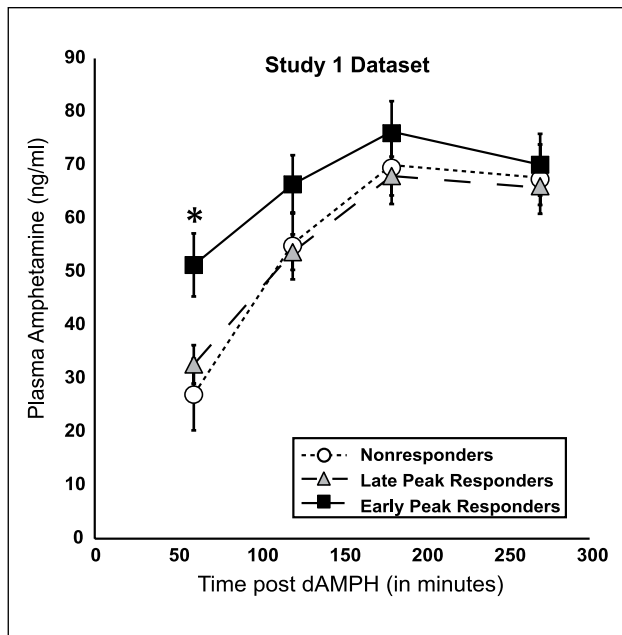


Figure 5. Plasma amphetamine rises early in the early peak DEQ_{H+L+F} responder group.

Relative to the other peak groups, early peak responders from the Study 1 dataset have significant differences in plasma amphetamine present at 60 minutes post drug. There are no plasma amphetamine differences across groups at the other time points tested.

* $F_{(2,43)} = 5.35, p = 0.008$.

each participant (in mg/kg) and compared it across our peak responder groups. Interestingly, dAMPH dose was not correlated with early ($r = 0.007, p = 0.97$) or peak ($r = 0.16, p = 0.26$) plasma amphetamine levels, suggesting that the small variation in dose administered across individuals (range: 0.398–0.449 mg/kg) was not enough to differentially affect plasma levels. Nonetheless, we found that the late peak responders had higher weight-adjusted dAMPH doses than the other groups ($F_{(2,46)} = 5.35, p = 0.008$; Table 2). Co-varying for weight-adjusted dAMPH dose, however, did not alter our group \times time effect on DEQ_{H+L+F} ratings ($F_{(8,180)} = 9.22, p < 0.001, \eta^2 = 0.29$). Furthermore, the smaller dose (0.423 mg/kg) administered to the early compared to the late peak responder group (0.434 mg/kg) would make it even less likely that dAMPH dose is associated with an early peak in its positive subjective effects. In addition, we calculated the weight-adjusted dAMPH dose in the Study 2 dataset for both the 20 mg and 10 mg dAMPH doses. The DEQ_{H+L+F} peak time groups in Study 2 did not differ in this measure at either oral dAMPH dose (max $F = 0.53$, min $p = 0.59$; Table 2). As a final analysis of the relationship between dAMPH dose and subjective effects, we correlated weight-adjusted dAMPH doses (in mg/kg) in both studies (including both 10 and 20 mg doses in Study 2) to DEQ_{H+L+F} maximum ratings and found a significant correlation ($r = 0.315, p < 0.001$; $CI: 0.24, 0.37$), as expected. We then correlated weight-adjusted dAMPH dose to DEQ_{H+L+F} peak time in each study dataset separately (as the range of DEQ collection times varied across the datasets) and found a positive correlation between weight-adjusted dose and DEQ_{H+L+F} peak time in Study 1 ($r = 0.375, p = 0.02$; $CI: 0.01, 0.57$) and Study 2 ($r = 0.192, p < 0.001$; $CI: 0.10, 0.27$)

responders such that those receiving larger effective doses of dAMPH tend to peak in their DEQ_{H+L+F} ratings later in time in both datasets. Thus, higher dAMPH dose is associated with higher subjective response to dAMPH (DEQ_{H+L+F} rating) but not associated with earlier DEQ_{H+L+F} peak times and cannot explain the different time courses we observed in DEQ_{H+L+F} ratings in these data.

Physiological differences across DEQ_{H+L+F} groups

In Study 1, early peak responders exhibited qualitatively higher MAP values at earlier and lower MAP values at later time points compared to late peak responders (Table 3). Specifically, we observed a significant DEQ_{H+L+F} group \times time interaction on MAP ($F_{(18,360)} = 2.00, p = 0.009$). However, post-hoc comparisons of MAP across our groups identified no significant differences (Table 3). No differences were observed between early versus late peak responders when looking at diastolic and systolic blood pressure measures separately. Of note, although there was not a significant difference between peak responder groups on MAP at any time point, plasma amphetamine at 60 minutes was significantly correlated with MAP at this time point ($r = 0.46, p = 0.001$; $CI: 0.14, 0.68$), supporting a relationship between peripheral amphetamine levels and heightened blood pressure (Asghar et al., 2003).

In Study 2, we observed a significant DEQ_{H+L+F} peak group \times time interaction on MAP ($F_{(10,1915)} = 4.68, p < 0.001$). While significant or near-significant differences were observed between nonresponders and the peak responder groups at 60, 90, 150, and 180 minutes (Table 3), early and late peak responders only differed in the final time point measured (180 minutes) where late peak responders had significantly elevated MAP values relative to early peak responders ($t_{273} = 2.45, p = 0.015$; Table 3; Supplementary Figure 1). We observed similarly large DEQ_{H+L+F} peak group \times time interactions when looking at systolic ($F_{(10,1920)} = 3.81, p < 0.001$) and diastolic blood pressure ($F_{(10,1915)} = 3.55, p < 0.001$) separately, with the late peak responders having significant elevations in both measures (systolic: $t_{273} = 2.24, p = 0.015$; diastolic: $t_{273} = 2.08, p = 0.038$) at 180 minutes compared to early peak responders.

Early peak responders also tended to show elevated heart rate after dAMPH relative to the other groups (Table 4). Briefly focusing on Study 1's data, we observed a significant effect of time on pulse post dAMPH ($F_{(8,328)} = 3.85, p < 0.001$), but no significant DEQ_{H+L+F} peak group \times time interaction ($F_{(16,328)} = 0.81, p = 0.68$). However, we note that we are underpowered in Study 1 to observe DEQ_{H+L+F} group differences here ($n = 8$ for early peak responders with pulse data at all time points tested). There was no relationship between plasma amphetamine at 60 minutes and pulse at the same time point ($r = -0.096, p = 0.53$). Investigating heart rate data in the larger Study 2 dataset, we observed a significant effect of time ($F_{(5,1915)} = 17.11, p < 0.001$) and a significant DEQ_{H+L+F} peak group \times time interaction ($F_{(10,1915)} = 2.19, p = 0.016$), but no between group difference on pulse ($F_{(2,383)} = 1.58, p = 0.21$). Specifically, a DEQ_{H+L+F} group difference in pulse is present at 60 minutes post amphetamine ($F_{(2,384)} = 3.11, p = 0.046$), driven by the early peak responder group having higher pulse readings than the nonresponders ($t_{202} = 2.16, p = 0.032$) and late peak responders ($t_{274} = 2.21, p = 0.028$;

Table 2. Comparing weight-adjusted dose of dAMPH (mg/kg) administered across DEQ_{H+L+F} groups from each study dataset.

DEQ _{H+L+F} group differences in weight-adjusted dAMPH dose administered			
Nonresponders (N)	Early peak (EP) responders	Late peak (LP) responders	Significantly different by group <i>F</i> , <i>p</i>
Study 1			
0.425 ± 0.010	0.423 ± 0.014	0.434 ± 0.011	5.35, 0.008
Study 2 (20 mg dose)			
0.302 ± 0.047	0.297 ± 0.047	0.297 ± 0.045	0.53, 0.59
Study 2 (10 mg dose)			
0.151 ± 0.023	0.148 ± 0.023	0.148 ± 0.023	0.53, 0.59

Weight-adjusted dose of dAMPH (mg/kg) ± standard deviation for each DEQ_{H+L+F} group in Study dataset 1 and 2 are reported. dAMPH = d-amphetamine.

Table 3. Mean arterial pressure data compared across DEQ_{H+L+F} groups from each study dataset.

DEQ _{H+L+F} group mean arterial pressure comparisons across time post oral dAMPH				
Time post (min)	Nonresponders (N)	Early peak (EP) responders	Late peak (LP) responders	Post-hoc group differences (# <i>p</i> < 0.05; * <i>p</i> < 0.005)
Study 1 (average dose: 0.43 mg/kg)				
0	81.5 ± 7.4	79.5 ± 7.6	79.5 ± 7.6	<i>ns</i>
15	82.9 ± 7.5	82.3 ± 7.0	81.3 ± 9.0	<i>ns</i>
30	81.8 ± 8.0	83.2 ± 9.9	82.1 ± 8.4	<i>ns</i>
45	88.1 ± 8.6	97.0 ± 13.8	86.7 ± 11.1	<i>ns</i>
60	90.6 ± 10.2	99.3 ± 16.6	92.7 ± 12.9	<i>ns</i>
80	95.9 ± 11.8	97.8 ± 13.5	97.5 ± 13.7	<i>ns</i>
100	96.0 ± 9.1	96.5 ± 14.8	98.4 ± 12.0	<i>ns</i>
120	98.5 ± 8.9	97.5 ± 13.0	100.1 ± 12.0	<i>ns</i>
150	99.3 ± 9.1	96.2 ± 9.8	98.5 ± 11.2	<i>ns</i>
180	99.2 ± 11.6	92.9 ± 6.6	100.2 ± 11.6	<i>ns</i>
Study 2 (20 mg dose; average dose: 0.30 mg/kg)				
0	87.0 ± 8.4	86.7 ± 8.3	87.9 ± 8.4	<i>ns</i>
30	85.9 ± 9.2	88.0 ± 9.4	86.8 ± 9.7	<i>ns</i>
60	92.3 ± 9.6	96.7 ± 9.8	95.4 ± 11.0	EP > N*, LP > N#
90	95.1 ± 10.5	98.4 ± 10.6	98.9 ± 11.1	EP > N#, LP > N*
150	96.7 ± 10.3	97.8 ± 10.3	100.1 ± 10.3	LP > N#
180	96.2 ± 9.5	96.0 ± 9.1	99.0 ± 9.7	LP > N#, LP > EP#

#*p* < 0.05; **p* < 0.005.

Mean arterial pressure ± standard deviation for each time point post oral dAMPH is displayed by DEQ_{H+L+F} group. Significant differences across groups via post-hoc t-tests are noted.

dAMPH = d-amphetamine; time post = time post oral dAMPH; min = minutes; *ns* = not significant.

Table 4, Supplementary Figure 2). The early peak responders' pulse remains elevated from the other groups at the 90-minute time point (vs. late ($t_{274} = 2.03$, $p = 0.044$) and nonresponders ($t_{202} = 2.03$, $p = 0.044$), respectively) but not at the later time points.

Generalizability of DEQ_{H+L+F} groups to dAMPH response: 10 mg dose in Study 2

To determine whether the DEQ_{H+L+F} groups we have identified can apply to distinguish responses to lower doses of dAMPH, in the Study 2 sample we examined whether responder groups classified by their 20 mg DEQ_{H+L+F} ratings predicted DEQ_{H+L+F} ratings to 10 mg dAMPH. This analysis shows how generalizable the groupings we have identified are to doses that are less likely

to produce large subjective effects. Importantly, this analysis also avoids the potential circularity of looking at temporal differences in ratings that themselves contributed to the classification system. Critically, we observed a significant DEQ_{H+L+F} group × time interaction on the 10 mg dAMPH-placebo DEQ_{H+L+F} ratings ($F_{(10,1895)} = 7.187$, $p < 0.001$; Figure 6) and significant between group effects ($F_{(2,379)} = 7.89$, $p < 0.001$). These differences were driven mainly by the early peak responders having significantly higher DEQ_{H+L+F} ratings at 60 minutes than late peak responders ($t_{274} = 2.843$, $p = 0.005$) and nonresponders ($t_{202} = 4.46$, $p < 0.001$). Late responders did not show significant elevations in DEQ_{H+L+F} ratings compared to nonresponders until 90 minutes ($t_{292} = 3.80$, $p < 0.001$). By that time point, there is no difference in DEQ_{H+L+F} ratings between early and late peak responders

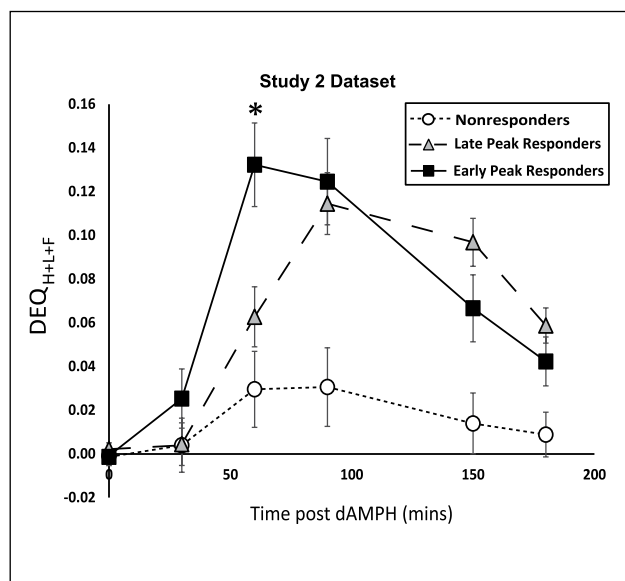
Table 4. Heart rate data compared across DEQ_{H+L+F} groups from each study dataset.

DEQ _{H+L+F} group pulse comparisons across time post oral dAMPH				
Time post (min)	Nonresponders (N)	Early peak (EP) responders	Late peak (LP) responders	Post-hoc group differences (#p < 0.05; *p < 0.005)
Study 1 (average dose: 0.43 mg/kg)				
0	73.4 ± 11.5	63.0 ± 10.1	69.5 ± 11.5	ns
15	68.3 ± 8.1	58.2 ± 8.7	67.9 ± 11.4	ns
30	67.7 ± 5.9	61.3 ± 9.6	67.1 ± 12.6	ns
45	67.3 ± 7.7	62.3 ± 7.4	68.8 ± 13.4	ns
60	69.2 ± 7.6	67.2 ± 13.4	69.1 ± 10.1	ns
80	69.3 ± 7.8	59.3 ± 10.3	71.3 ± 15.2	ns
100	71.0 ± 8.8	59.3 ± 10.1	70.2 ± 15.6	ns
120	72.6 ± 9.4	60.8 ± 8.9	73.3 ± 12.3	ns
150	74.2 ± 9.8	67.5 ± 14.8	73.5 ± 14.7	ns
180	70.6 ± 8.9	66.5 ± 8.7	75.5 ± 18.7	ns
Study 2 (20 mg dose; average dose: 0.30 mg/kg)				
0	67.6 ± 11.8	66.8 ± 10.5	67.1 ± 11.0	ns
30	65.7 ± 10.8	67.6 ± 12.3	65.4 ± 10.0	ns
60	68.0 ± 11.4	71.8 ± 13.0	68.4 ± 11.5	EP > LP#, EP > N#
90	67.6 ± 10.7	71.4 ± 13.0	68.3 ± 11.8	EP > LP#, EP > N#
150	67.5 ± 10.5	70.2 ± 12.4	68.9 ± 12.0	ns
180	68.6 ± 11.5	71.1 ± 11.8	69.4 ± 12.1	ns

#p < 0.05; *p < 0.005.

Data presented as average pulse (beats per minute) ± standard deviation for each time point post oral dAMPH are displayed by DEQ_{H+L+F} group. Significant differences across groups via post-hoc t-tests are noted.

dAMPH = d-amphetamine; time post = time post oral dAMPH; min = minutes; ns = not significant.

**Figure 6.** Early peak DEQ_{H+L+F} responders as defined with 20 mg dAMPH dose show elevated DEQ_{H+L+F} 60 minutes post 10 mg dAMPH.In the Study 2 dataset, 20 mg dAMPH DEQ_{H+L+F} groups differ in the temporal profiles of their DEQ_{H+L+F} ratings after 10 mg dAMPH.

*Early responders significantly different from late responders, p = 0.005.

($t_{274} = 0.15$, $p = 0.88$). Thus, the 60-minute time point still shows differences in DEQ_{H+L+F} ratings between early and late responders even when the dose of dAMPH is low.

Generalizability of DEQ_{H+L+F} groups to other positive subjective measures collected in Study 2

As a final test for the generalizability of our DEQ_{H+L+F} groupings to other measures of positive subjective effects experienced on dAMPH, we analyzed these groups for differences in time course of POMS Elation and ARCI Amphetamine ratings at the 20 mg dAMPH dose relative to the placebo administered in Study 2. We found a significant effect of DEQ_{H+L+F} group and group × time interaction on both POMS Elation (group: $F_{(2,382)} = 10.43$, $p < 0.001$; group × time: $F_{(10,1910)} = 9.92$, $p < 0.001$) and ARCI Amphetamine ratings (group: $F_{(2,384)} = 33.78$, $p < 0.001$; group × time: $F_{(10,1920)} = 13.24$, $p < 0.001$; Supplementary Figure 3). Specifically, DEQ_{H+L+F} early peak responders had higher POMS Elation ratings (4.32 ± 4.75) than late peak responders at 60 minutes (3.08 ± 5.12 , $t_{274} = 1.95$, $p = 0.052$) while late peak responders POMS Elation was higher at 150 (4.66 ± 5.62 vs. 2.88 ± 4.58 , $t_{274} = -2.64$, $p = 0.009$) and 180 minutes post drug (3.55 ± 5.00 vs. 2.05 ± 4.55 , $t_{273} = -2.43$, $p = 0.016$). For ARCI Amphetamine ratings, early peak responders had higher ratings at 30 (1.01 ± 1.89 ; $t_{274} = 2.43$, $p = 0.016$) and 60 minutes (3.18 ± 2.63 ; $t_{274} = 3.24$, $p = 0.001$) compared to late peak responders (0.39 ± 2.08 and 2.07 ± 2.72 , respectively). By contrast, late peak responders ARCI Amphetamine scores were higher at 150 (3.35 ± 2.82 vs. 2.40 ± 2.46 , $t_{274} = -2.76$, $p = 0.006$) and 180 minutes (2.72 ± 2.85 vs. 2.00 ± 2.46 , $t_{274} = -2.11$, $p = 0.036$) post drug. Importantly, max POMS elation ($t_{274} = -1.56$, $p = 0.12$) and ARCI Amphetamine ($t_{274} = -0.90$, $p = 0.37$) ratings did not differ across the two DEQ_{H+L+F} peak responder groups. Thus, the temporal effects we observed on

our DEQ_{H+L+F} ratings extends to other measures of dAMPH's positive subjective response.

Discussion

Across two independent samples, we observed marked individual differences in the time course of positive subjective effects of oral dAMPH administration resulting in three distinct DEQ_{H+L+F} peak groups, that differ in DEQ_{H+L+F} , POMS Elation, and ARCI Amphetamine ratings over time. These groups differ not only in their self-reported positive subjective effect (e.g. pharmacodynamics) profiles but also in features of their pharmacokinetic and physiological response time courses.

Differences in pharmacokinetic time course and positive subjective effects

In Study 1, we found that individuals reporting early peak responses also tended to have a more rapid rise in levels of plasma amphetamine than the other DEQ_{H+L+F} peak groups (Figure 5). Furthermore, correlation analyses demonstrated that DEQ_{H+L+F} at 60 minutes post amphetamine moderately correlated with plasma amphetamine levels at this time point ($r = 0.34$). We presume that the early rise in plasma amphetamine in the early peak responders is associated with early entry of amphetamine into the brain and subsequent release of the neurotransmitter dopamine (DA) via blockade and reversal of DA uptake through the dopamine transporter (DAT) (Jones et al., 1998; Pifl et al., 1995). However, this difference in early plasma amphetamine levels cannot fully account for the differences in DEQ_{H+L+F} across time, as covarying for this plasma difference did not remove the time \times group effect on DEQ_{H+L} ratings (η^2 went from 0.29 to 0.18).

It is worth noting that several variables will affect oral dAMPH absorption and its ultimate delivery to the brain. Administered dAMPH dosage and plasma amphetamine levels offer a narrow window into these complex processes. For example, our data suggest that subtle differences in oral dAMPH dosage due to the narrow range in dosages (0.398–0.449 mg/kg) achieved around the target dose of 0.43 mg/kg do not necessarily translate to differences in plasma levels. Study 1 late responders had a higher dAMPH dose on a mg/kg basis (Table 3) but no difference in plasma levels compared with nonresponders (Figure 5). In fact, dAMPH dose was not correlated with early ($r = 0.007$, $p = 0.97$) or peak ($r = 0.16$, $p = 0.26$) plasma amphetamine levels. Traitwise individual differences in peripheral metabolism and absorption of the drug may swamp small differences in dosing (Custodio et al., 2008; Martinez and Amidon, 2002). Statewise differences in stomach contents from last meal (Fleisher et al., 1999; Williams et al., 1996) (despite instructions to eat a light lunch) as well as speed of drug transit through the gastrointestinal tract (Riley et al., 1992) can also affect peripheral absorption of orally administered drugs.

Once dAMPH has entered the blood stream, it still must reach its target in the brain (DAT) to produce its pharmacologic effect (DA release). A variety of variables could affect these processes including differences in rate of dAMPH entry into the brain via the blood brain barrier, differences in DAT expression, and variation in dAMPH-induced DA release based on DA synthesis capacity, levels of the DA metabolizing enzyme monoamine oxidase (MAO), and vesicular monoamine transporter 2 (VMAT2)

(Sulzer et al., 2005). Clearly, then, peripheral (plasma) levels may not be closely related to central levels of dAMPH and, subsequently DA release and the subjective effects that accompany it (Abi-Dargham et al., 2003; Drevets et al., 2001; Volkow et al., 2004). Strikingly, in our data, nonresponders and late peak responders do not differ in their plasma amphetamine levels across any time point we measured (Figure 5) despite differences in these groups' subjective effects (DEQ), suggesting these individuals may differ in brain dAMPH and DA levels via a yet-to-be identified process. Clearly, more work is needed to explain the degree to which dAMPH pharmacodynamics and pharmacokinetics contribute to the individual differences in subjective effects we observe and what specific peripheral and central mechanisms may be involved.

Differences in subjective versus physiological time courses of amphetamine's effects

We observed a partial dissociation between the time course of subjective and physiological effects of dAMPH. For example, dAMPH increased blood pressure across all subjects tested. Even individuals who did not show positive subjective responses after oral dAMPH (nonresponders) showed increases in MAP after drug intake, though this effect was slower and attenuated compared to the responder groups, especially with the lower dAMPH dose used in Study 2. While we observed a positive relationship between early (60 minutes) plasma amphetamine levels and MAP in Study 1, MAP was not statistically different between the early and late peak responder groups at early time points in either dataset. By contrast, pulse was higher in the early peak responder group at 60 minutes (Study 2), even though it was not associated with plasma amphetamine levels at this time point (Study 1). Thus, while some peripheral stimulation differences are noted (particularly for pulse), neither study dataset suggests that the individual differences in subjective responses are primarily the result of differences in peripheral stimulation.

We also observed a steeper decline in positive subjective effects with time compared to changes in MAP or pulse with time in the early peak responders. Although past studies have noted that cardiovascular effects often last longer than subjective effects (Asghar et al., 2003), this has not previously been considered in terms of individual differences. The differential time courses between positive subjective and physiological effects of oral dAMPH may have important implications for avoiding unintentional health consequences in those using prescribed or illicit amphetamine. Early peak responders, in whom we see a more rapid decline in subjective responses relative to pulse and MAP, could potentially seek to administer more d-AMPH when the positive subjective response to the drug declines, but the elevated heart rate and blood pressure from the initial drug exposure would still be present. A subsequent dose of the drug could then elevate the physiological effects to dangerous levels in these individuals.

Generalizability of subjective effect differences: Beyond a single dose, measure

One limitation of the differences we observed in positive subjective responses to dAMPH in Study 1 is the potential circularity in examining DEQ responses of subjects categorized on the basis of

those same ratings. However, we replicated the observed DEQ_{H+L+F} time course effect differences in Study 2 using the grouping criteria devised in Study 1. The replicability and generalizability of the different subjective effect time courses we observe to dAMPH is supported by the fact that DEQ_{H+L+F} group status based on a 20 mg dAMPH dose predicts subjective responses on both a different, lower dose of dAMPH (10 mg) and on different subjective response measures (ARCI Amphetamine scores and POMS Elation ratings) in the Study 2 dataset. These data, thus, support identification of a group of individuals with heightened early subjective responses to dAMPH that diminish faster with time relative to the rest of the subject population. These early peak responders, based on previous work implicating fast drug delivery with heightened abuse potential, would be expected to be a group at risk for developing drug addiction.

Implications for addiction liability

It has been suggested by researchers studying both humans (Abreu et al., 2001; Gossop et al., 1992; Spencer et al., 2006; Volkow et al., 2007) and animals (Kollins et al., 2001; Samaha and Robinson, 2005) that the speed of delivery to the brain determines the degree of reinforcement associated with psychostimulant drugs and their abuse liability. In fact, some researchers have proposed a “rate hypothesis” linking the speed of drug delivery to its addictive potential (Gorelick, 1998; Oldendorf, 1992). Work in rats has demonstrated that the speed with which cocaine is delivered intravenously determines the rodents’ subsequent motivation to self administer the drug and has long-term impact on DA D2 receptor density in the caudate (Minogianis et al., 2013). Similarly, speed of injection impacts the rate of DAT uptake of cocaine in rats, and its reinforcing effect as measured by self-administration in monkeys (Woolverton and Wang, 2004). In humans, the critical role for the speed of drug delivery in subjective drug “high” was demonstrated by Volkow et al. (2001) who showed that oral methylphenidate induces increases in extracellular DA at a slower timescale and results in little reported euphoric effects compared to i.v. administration (Volkow et al., 1999c, 2001) despite similar levels of total DAT occupancy (Volkow et al., 1999a; see Volkow et al., 2004 for review). Additional work has demonstrated that similar levels of total striatal DAT occupancy by psychostimulants (Volkow et al., 2000) can produce differences in positive subjective effects based on the timing of delivery of these drugs to the brain (Spencer et al., 2006; Volkow et al., 1998). Although this past work has been focused on the effects of different psychostimulant drugs or routes of administration, the present data suggest there may be important individual differences in the speed of acute psychostimulant effects. Specifically, individuals with faster absorption and faster binding of psychostimulants to DAT in the striatum would be predicted to have more rapid positive subjective effects after psychostimulant administration and hence greater addiction vulnerability.

Most of the animal (Bradberry, 2002; Woolverton and Wang, 2004) and human literature (Abreu et al., 2001; Nelson et al., 2006; Volkow et al., 2000) on psychostimulant delivery speed and reinforcement effects has focused on intravenous administrations that cause far faster rise times than the oral administration used here. This raises the question of whether the biological bases of the responses we report here are similar to those observed

with i.v. psychostimulants. Work by Spencer et al. (2006) is thus particularly relevant in that they contrasted different oral methylphenidate formulations on DAT occupancy and feel and liking subjective effects, and demonstrated that the short-acting formulation whose DAT occupancy peaked quickly (~1 hr after drug) produced greater subjective effects (Spencer et al., 2006) than the longer acting formulation. Hence, individual differences in the rate of psychostimulants’ impact on DAT are likely of import for both rapid and slower routes of psychostimulant delivery. Based on Spencer et al.’s (2006) work, and the similar targets of action between methylphenidate and dAMPH, occupancy of DAT and the subsequent rise in extracellular DA in the striatum would be expected to occur more rapidly in early peak responders, tracking their fast peak in dAMPH “high”/“like”/“feel” ratings.

The role of different subjective effects in the development of addictions is complex. While some researchers have suggested a link between initial positive euphoric effects and an increased risk for developing addiction (Haertzen et al., 1983; Lambert et al., 2006) and indeed research supports a link between psychostimulant-induced DA release and subjective drug high/euphoria (Abi-Dargham et al., 2003; Drevets et al., 2001; Volkow et al., 1999c), others have found a stronger association with drug wanting (Leyton et al., 2002). This fits with the incentive salience theory of addiction (Robinson and Berridge, 1993) which argues that sensitization to the incentive properties of a drug (drug wanting) can progress to drug craving and ultimately addiction. Preclinical work suggests that the speed of drug delivery to the brain can induce greater incentive sensitization (Samaha et al., 2002, 2004; Samaha and Berridge, 2005), suggesting a link between fast drug delivery and its eventual ability to become addictive. However, we observed no differences in DEQ “want more” ratings across our early versus late responder groups. One potential reason could be the result of the current study’s focus on initial subjective effects to dAMPH in psychostimulant naïve individuals. It is possible that “want more” ratings could vary across individuals after repeated exposure to psychostimulants as preclinical studies suggest that incentive salience sensitization normally develops after repeated psychostimulant pairings (Lorrain et al., 2000; Mendrek et al., 1998). Thus, we might expect early peak responders, who demonstrate faster dAMPH absorption (which, according to Samaha’s work should promote increased incentive sensitization), would be more likely to develop greater cravings for dAMPH after repeated drug use. While testing this hypothesis prospectively in humans would be difficult, further work with animal models may offer a more practical approach to better characterize how initial drug effects predict later drug wanting.

Caveats and limitations

While we believe the data presented here suggest the potential utility of exploring individual differences in the time course of subjective, pharmacokinetic, and physiological responses to psychostimulants, we note several limitations and their importance for follow-up work. In Study 1, we lacked early time points (< 60 minutes) post dAMPH and thus could not determine if the rise in DEQ_{H+L+F} in some subjects occurs earlier than 60 minute post administration, as appears to be the case in some early responders in Study 2. If the rapid rise in positive subjective effects make drugs of abuse highly reinforcing, obtaining measures of positive

effects early after drug intake will be critical to draw conclusions regarding their role in addiction liability. Furthermore, collecting subjective response data over fine-grained time points would allow for a more thorough determination of individual differences in peak subjective response. It is possible, for instance, that some subjects might have peak subjective responses somewhere between 60 and 90 minutes, and are inappropriately classified into the wrong peak DEQ group due to limited time resolution. Collection of additional subjective measure time points post dAMPH would allow for more sophisticated analyses of individual differences in the shape of responses over time (i.e. linear, curvilinear, hyperbolic, etc.). In addition, there could be instances where tracking a single subjective rating component such as liking or feeling, which differ in their level of positive connotations, could prove useful, although the current data indicate that liking, feeling and high, follow very similar time courses.

Prior work (Volkow et al., 2004) would suggest that the individual differences in subjective effects we observe here act via DA mechanisms in traditional reward circuitry in the striatum. We also note that rate of drug delivery affects the plasticity of circuitry involved in incentive sensitization, which extends beyond the striatum to the prefrontal cortex (Nestler, 2001). The ability for drugs to induce incentive sensitization is thought to be critical in their ability to promote their continual usage (Robinson and Berridge, 1993, 2000). Future investigation of a potential relationship between rate of drug delivery and variations in incentive salience to the drug could thus prove informative. It seems notable in this regard that the subjective variable closest to incentive salience, wanting, did not show a clear distinction between early and late peak responder groups, as it remained similarly elevated regardless of when the other subjective responses reached their peak. Whether or not our observed effects are related to differences in incentive salience, it would be surprising if DA signaling in mesocorticolimbic circuitry was not responsible for the individual differences in DEQ_{H+L+F} time course given the link between striatal DA and the positive subjective effects of psychostimulants (Volkow et al., 1999b, 1999c, Volkow et al., 2002) including self-reported drug “high” (Drevets et al., 2001; Laruelle et al., 1995; Oswald et al., 2005; Volkow et al., 1996, 1997). Identifying whether the subjective timing differences we observed here occur at the level of DAT, amphetamine-induced DA release, or some other regulator of DA signaling and the neural circuits involved in these differences will further our understanding of this potentially important individual difference measure of psychostimulant response.

Conclusion

In this study, we demonstrate three distinct patterns in the timing of peak positive subjective effects after acute oral dAMPH. The early peak DEQ_{H+L+F} responder group displays a faster peripheral absorption of amphetamine, a rapid rise in DEQ_{H+L+F}, POMS Elation, and ARCI Amphetamine subjective effects and elevated pulse after dAMPH. We speculate that these different patterns of positive subjective and physiological time courses across individuals may relate to individual differences in addiction risk and reflect different system level responses to dAMPH, potentially at the level of DA signaling. Our findings suggest the potential utility of incorporating analyses focused on time course differences in future studies of the subjective and behavioral response to psychostimulants.

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