Original Paper

Rewarding effects of physical activity predict sensitivity to the acute subjective effects of *d*-amphetamine in healthy volunteers

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Abstract

While individual differences in reward sensitivity are believed to generalize across drugs and alternative rewards, this notion has received little empirical attention in human research. Here, we tested whether individual differences in the subjective rewarding effects of physical activity were associated with the subjective response to *d*-amphetamine administration. Healthy volunteers (n=95; age 18–35 years) completed questionnaires measuring the self-reported pleasurable effects of physical activity and other covariates, and this was followed by two double-blind counterbalanced sessions during which they received either 20 mg oral *d*-amphetamine or placebo. Subjective drug effects measures were collected before and repeatedly after drug administration. Subjective *d*-amphetamine-related effects were then reduced via principal components analysis into latent factors of "positive mood," "arousal," and "drug high." Multiple regression models controlling for placebo-related scores, session order, demographics, body mass index, level of physical activity, and use of other drugs showed that degree of self-reported physical activity reward was positively associated with *d*-amphetamine-induced positive mood and arousal (βs≥0.25, ps≤0.04), but was not associated with *d*-amphetamine-induced changes in drug high (β=0.13, p=0.24). These results provide novel evidence suggesting that individual differences in reward sensitivity cross over between *d*-amphetamine reward and physical activity reward in humans.

Keywords

d-Amphetamine, physical activity, subjective effects, reward sensitivity, humans

Introduction

The rewarding effects of addictive drugs and alternative rewards (e.g. exercise or physical activity, food, sexual activity) appear to be mediated in part by a common neurobiological pathway–the mesolimbic dopamine system (Baik, 2013; Davis et al., 2008; Greenwood et al., 2011; Kelley and Berridge, 2002; Pitchers et al., 2010). *d*-Amphetamine and other psychostimulants robustly activate dopaminergic neurotransmission in mesolimbic reward pathways (Pierce and Kumaresan, 2006) and produce reliable subjective rewarding effects (i.e. increases in mood, arousal, and euphoria) in humans (Johanson and Uhlenhuth, 1980). There is substantial inter-individual variability in *d*-amphetamine response (Crabbe et al., 1983; Hart et al., 2012; Stoops et al., 2007; White et al., 2006), which may indicate that the subjective response to *d*-amphetamine may be a useful pharmacological probe for characterizing individual differences in brain reward system sensitivity (Tremblay et al., 2002). In this human laboratory study, we examine the potential relationship between two reward modalities: *d*-amphetamine reward (as measured by acute *d*-amphetamine-related subjective effects) and physical activity reward (as measured by baseline self-reported physical activity enjoyment).

Behavioral evidence from a relatively large range of preclinical literature indicates that there is considerable overlap between physical activity and stimulant drug reward. For example, in rats, wheel running has been demonstrated to be rewarding using drug-reward test methods, including conditioned place preference (Greenwood et al., 2011) and operant conditioning (Belke, 2000; Iversen, 1993). Additionally, wheel running attenuates both cocaine self-administration (Cosgrove et al., 2002) and oral *d*-amphetamine intake (Kanarek et al., 1995) when both physical activity and drug are available, suggesting that physical activity can at least partially replace drug as an alternative reward. Interestingly, while many studies indicate that chronic exposure to wheel running decreases subsequent cocaine reward in rats (Smith et al., 2008b; Thanos et al., 2010), Smith et al. (2008a) demonstrated that chronic physical activity produced increases in sensitivity to cocaine reward. These apparently conflicting findings could be the result of a number of differences in methodology, including rat strain, physical activity type, drug dose, and

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age of the animals. Overall, these preclinical data suggest that there is considerable overlap in physical activity and psychostimulant reward, but that the relationship between the two reward modalities is complex.

There are some data from the human literature that suggests a relationship between alternative rewards (including physical activity) and drug reward. For example, similar to *d*-amphetamine reward, the level of perceived rewarding effects from recreational exercise is stable over time (Dishman et al., 2010) and genetically determined (Bryan et al., 2007; Hart et al., 2012; Hooper et al., 2014). Additionally, responses to biologically based personality measures of propensity toward positive mood states, excitement (e.g. sensation-seeking, physical fearlessness, impulsivity), and other reward-related traits (i.e. reward-sensitivity) have been shown to predict greater *d*-amphetamine-induced subjective rewarding effects in healthy participants (Kirkpatrick et al., 2013, 2016; Stoops et al., 2007; White et al., 2006). Similar associations have been observed between some personality characteristics (e.g. sensation-seeking) and levels of physical activity (De Moor et al., 2006). Further, self-report mood questionnaires used to assess the acute subjective effects of *d*-amphetamine (such as the Profile of Mood States (POMS); Kirkpatrick et al., 2016; White et al., 2006) are also sensitive to the subjective effects of physical activity (Basso and Suzuki, 2017; Berger and Motl, 2000). However, although considerable preclinical literature supports an overlap between psychostimulant and physical activity reward, whether individual differences in self-reported physical activity reward and acute *d*-amphetamine-related effects covary with one another in humans remains unknown.

In order to address this gap in the literature, the current double-blind human behavioral pharmacology study investigated associations of individual differences in baseline self-reported perceptions of the rewarding effects of physical activity with the acute subjective effects of *d*-amphetamine in healthy young adults. Given that related trait personality measures similarly predict the intensity of *d*-amphetamine reward and levels of physical activity in humans, we hypothesized that greater self-reported physical activity reward would predict greater *d*-amphetamine subjective effects.

Methods

Participants

Healthy volunteers (n=105), aged 18–35 years old, were recruited from the Los Angeles area. Inclusion criteria required that participants (a) report having obtained a high school diploma or general education diploma; (b) be fluent in English; (c) have a body mass index (BMI) between 19–30; and (d) report normal to corrected-to-normal vision, including no color blindness. Participants were excluded if they (a) smoked more than 10 cigarettes per week; (b) consumed more than three cups of coffee per day; (c) reported night shift work; (d) had any current or past medical condition that was contraindicated for *d*-amphetamine (e.g. hypertension, abnormal electrocardiogram [EKG); (e) had a past or current psychiatric condition that increased risk of participation (i.e. current Diagnostic and Statistical Manual of Mental Disorders, 4th Edition *[DSM-IV]* Axis I psychiatric disorder, lifetime manic symptoms, lifetime substance use disorder [First et al., 2002]); (f) were currently pregnant, breastfeeding, or planning to become pregnant; (g) reported past 30-day use of any drug of abuse other than cannabis, caffeine, alcohol, or nicotine; (h) had a positive toxicology screen for any drug of abuse; or (i) reported lifetime use of any licit or illicit psychostimulant drug (e.g. methylphenidate, *d*-amphetamine, methamphetamine, cocaine) to isolate sensitivity to the *d*-amphetamine phenotype without confounding previous exposure. Ten participants were excluded from this report due to missing values for one or more study variables for the final analytic sample (n=95).

The study was reviewed and approved by the Institutional Review Board at the University of Southern California in accordance with the Code of Federal Regulations (Title 45, Part 46) adopted by the National Institutes of Health and the Office for Protection from Research Risks of the US Federal Government. The study was conducted ethically in accordance with the Helsinki Declaration of 1964 (revised 1989) and the National Advisory Council on Drug Abuse (2000) Recommended Guidelines for the Administration of Drugs to Human Subjects.

Design

The study used a within-subjects design, in which participants attended a baseline session, followed by two four-hour experimental sessions at which a 20 mg dose of oral *d*-amphetamine or placebo was administered under double-blind conditions (session order was counterbalanced). The present findings are a secondary analysis of a larger study examining individual difference factors that predict response to the acute effects of *d*-amphetamine (Kirkpatrick et al., 2016; Leventhal et al., 2017; Pang et al., 2016).

Procedure

After preliminary phone eligibility assessment, participants attended an in-person baseline session, involving written informed consent and an eligibility screening determined via urine toxicology; carbon monoxide (marker of tobacco exposure), alcohol breathalyzer, and pregnancy testing; health history and psychiatric interviews; and a physical examination and an EKG. Eligible participants completed baseline questionnaires assessing demographics, rewarding effects of physical activity, and level of recent physical activity (see Measures below). To control for expectancy effects as in prior research (de Wit et al., 2000, 2002; White et al., 2002), participants were informed that they would be administered any one of the following Food and Drug Administration drug classes during the subsequent sessions: stimulant, sedative, antidepressant, or a placebo.

For the two counterbalanced experimental sessions, participants were instructed to abstain from caffeine, alcohol, nicotine, and other psychoactive substances for 24 h and to fast after midnight the night before their session. The two sessions were completed in the morning from 09:00–13:00 and between 2–14 days apart from one another (Dlugos et al., 2007; Stoops et al., 2007; Weafer and de Wit, 2013). Pending negative drug toxicology, carbon monoxide, alcohol breathalyzer, and pregnancy screen (those with positive results were discontinued), participants continued with the session. Participants were tested individually and remained in a room for the four-hour session. They were administered a 20 mg dose of oral *d*-amphetamine or matching placebo

at 09:30 and completed repeated assessments of subjective drug reward before (pre-drug) and +30, +60, +90, +150, and +180 min post-capsule administration (Dlugos et al., 2007; Kirkpatrick et al., 2013; Stoops et al., 2007; Weafer and de Wit, 2013). In between assessments, participants were given the option to watch emotionally neutral movies or read. After completion of the study, participants were debriefed on procedures and remunerated US$185.

Measures

Baseline session measures. In addition to screening measures, which assessed past 30-day use of caffeinated beverages, alcohol, tobacco products, and other characteristics to determine eligibility (see above), participants completed a questionnaire assessing demographics, height and weight (for BMI calculation), and then the Physical Activity Enjoyment Scale (PACES) and the International Physical Activity Questionnaire (IPAQ).

Perceived rewarding effects of physical activity. The PACES (Kendzierski and DeCarlo, 1991) is a 14-item survey that was used to measure the degree to which a person enjoys being physically active or exercising (i.e. "It gives me energy," "My body feels good," or "I find it pleasurable"). Each item is rated on a five-point Likert scale (1=disagree a lot to 5=agree a lot). A composite reward index is calculated from the average rating per item for experiences indicative of positive responses that load onto a reward subscale (eight items; Leventhal, 2012).

Physical activity level. The IPAQ (Craig et al., 2003) is a well-validated 27-item questionnaire that was used to measure time spent being physically active at low, moderate, and high intensity levels in the last seven days. Each type of activity level has a specific ratio of work metabolic rate to a standard resting metabolic rate (metabolic equivalent of task (MET); i.e. walking=3.3 METs, moderate=4.0 METs, and vigorous=8.0 METs), derived from previous work (Ainsworth et al., 2000). A total physical activity MET min/week score is calculated based on the summation of walking (MET level*min/day*days/week), moderate physical activity (MET level*min/day*days/week), and vigorous physical activity (MET level*min/day*days/week). The physical activity level (MET min/week score) was included for descriptive information and as a covariate to rule out confounding by activity levels, per se.

Experimental session measures

Acute subjective drug response. The Drug Effects Questionnaire (DEQ), the POMS, and the Addiction Center Research Inventory (ARCI) were used to assess acute subjective drug effects at each time point. The DEQ (Fischman and Foltin, 1991) contains four visual 100 mm analog scales (range: 0–100), in which participants rate whether they "Feel the drug," "Like the drug," "Feel high," and "Want more." The left anchor is labeled as "no drug effect" and the right anchor is labeled as "strong effect." The POMS (Johanson and Uhlenhuth, 1980; McNair et al., 1971) is a 72-item adjective checklist of momentary mood states, yielding affect-specific subscale outcomes for anxiety, depression, vigor, fatigue, friendliness, anger, elation, arousal, confusion, and overall positive mood and negative mood composites. Participants rated affect adjectives on a five-point Likert scale from zero (not at all) to four (extremely) based on how they were currently feeling. A mean score was computed for each subscale. The ARCI (Martin et al., 1970) is a well-validated 49-item true–false survey that measures characteristic effects related to specific drug classes, yielding discrete subscale outcomes for the following: amphetamine (A;stimulant effects), benzedrine group (BG; energy and intellectual efficiency), morphine-benzedrine group (MBG; euphoria), pentobarbital-chlorpromazine-alcohol group (PCAG; sedation), and lysergic acid diethylamide (dysphoria and somatic complaints).

Drug

Four tablets of 5 mg of *d*-amphetamine (Amedra Pharmaceuticals) and dextrose were compounded into capsules. Placebo capsules were identical, however, they contained only dextrose. The 20 mg *d*-amphetamine dose was selected based on previous studies indicating differences in acute *d*-amphetamine response as a function of trait personality measures (Kirkpatrick et al., 2013; White et al., 2006). This dose produces reliable subjective effects in naïve participants (see time course graphs in Leventhal et al., 2017 and Pang et al., 2016), without increasing adverse effects associated with larger doses.

Data analysis

Preliminary analyses involved calculating descriptive statistics and intercorrelations between participant characteristics and study variables. As in prior work, area under the curve (AUC) was calculated for each subjective drug reward measure (DEQ, POMS, and ARCI) at placebo and *d*-amphetamine sessions to characterize overall *d*-amphetamine effects over the course of the session (see Kirkpatrick et al., 2016). Each outcome with a significant drug effect was then subjected to a principal components analysis (promax rotation, eigenvalue=1), following the procedures for data reduction detailed in Kirkpatrick et al. (2013). Outcome measures that loaded greater than 0.4 on a single factor, but did not cross-load on multiple factors were used to calculate factor scores. This process reduced the data into a more parsimonious set of three factor score outcomes, labeled "positive mood" (ARCI MBG; POMS elation, friendliness, positive mood, and vigor), "arousal" (ARCI A, BG, and PCAG; POMS arousal and fatigue), and "drug high" (DEQ feel, like, high, and more). The average of the AUC subjective drug reward measures at *d*-amphetamine sessions for each of the three factor scores served as outcomes.

In the primary analysis, physical activity reward was modeled as a predictor of drug effect using separate multiple regressions for each *d*-amphetamine AUC average factor score (i.e. positive mood, arousal, and drug high). Each regression was constructed in a two-step forced entry process. In the first step, the main predictor (PACES reward), as well as placebo AUC and session order were added simultaneously to the model. To rule out potential confounding factors that could explain the association between physical activity reward and drug effects, the second step simultaneously added age, sex, BMI, physical activity level, and use of other drugs (composite of caffeine, alcohol, and tobacco; scale of 0–3; 0=none, 1=less than weekly, 2=1–6 days

per week, 3=daily), given prior evidence of their associations with either *d*-amphetamine effects or physical activity reward (Ekkekakis et al., 2010; King et al., 2000; Paavola et al., 2004; Pate et al., 1996; Salmon et al., 2003; Trost et al., 2002; White et al., 2002; Zheng et al., 2014). Analyses were conducted in IBM SPSS Statistics for Macintosh Version 22 (IBM Corp., Armonk, New York, USA) and results are reported as standardized regression weights (βs). Significance was set to 0.05.

Results

Descriptive statistics for key variables and participant characteristics

On average, participants (69.5% female; female coded as zero, male coded as one) were 23.4 (standard deviation (*SD*)=4.2) years old with a BMI of 22.96 (*SD*=2.32). Overall the sample was ethnically heterogeneous (37.9% Asian, 12.6% Black, 6.3% Hispanic, 2.1% Middle Eastern, 11.6% Multiracial, 29.5% White). Participants reported having completed at least a high school education (2.1% high school, 44.7% some college or current enrollment, 53.2% college degree or higher). There were varied distributions of past 30-day use of caffeine (4.2% none, 7.4% less than weekly, 34.7% 1–6 days per week, 53.7% daily), alcohol (21.1% none, 58.9% less than weekly, 20.0% 1–6 days per week), and tobacco products (89.5% none, 7.4% less than weekly, 2.1% 1–6 days per week, 1.1% daily). The average score for other drug use (composite of caffeine, alcohol, and tobacco) was 3.5 (*SD*=1.2; range 0–9). On average, the score for reported physical activity reward was 3.8 (*SD*=0.8; range 1.3–5.0), and the score for reported physical activity level was 2864.4 (*SD*=2175.3; range 0.0–9600.0) MET min per week. Intercorrelations between study variables are presented in Table 1.

Relation between physical activity reward and d-amphetamine-induced increases in subjective drug effects

Parameter estimates for each regression model are reported in Table 2.

Positive mood. Physical activity reward significantly and independently predicted increases in positive mood in response to *d*-amphetamine (β=0.21, p=0.03) in the preliminary model including placebo response and session order as covariates (overall model R^2=0.15, F=5.13, p=0.003). In the model adjusting for placebo response and session order, and additionally controlling for age, sex, BMI, self-reported physical activity level, and use of other drugs, physical activity reward significantly and independently predicted greater increases in positive mood in response to *d*-amphetamine (β=0.27, p=0.02; overall model R^2=0.23, F=3.25, p=0.003; $R^2\Delta$=0.09, p=0.09).

Arousal. Physical activity reward significantly and independently predicted increases in arousal (β=0.22, p=0.03) after adjusting for placebo response and session order (overall model R^2=0.09, F=3.13, p=0.03). The association remained significant in the fully adjusted model including all covariates (β=0.25, p=0.04; overall model R^2=0.15, F=1.95, p=0.06; $R^2\Delta$=0.06, p=0.30).

Table 1. Intercorrelations of key variables and participant characteristics (n=95).

Variable		Intercorrelations (r)					
		1	2	3	4	5	6
1	Age	–					
2	Sex	0.27[a]	–				
3	BMI	0.11	0.13	–			
4	IPAQ level	−0.06	0.14	0.02	–		
5	Other drug use	0.15	0.001	0.07	−0.06	–	
6	PACES reward	0.04	0.13	<0.001	0.44[b]	0.14	–

BMI: body mass index; IPAQ: International Physical Activity Questionnaire; MET: metabolic equivalent of task; PACES: Physical Activity Enjoyment Scale.
IPAQ measured in MET min/week. Female sex coded as 0, male sex coded as 1.
Other drug use=composite of caffeine, alcohol, and tobacco, possible range 0–9.
[a]p<0.01, [b]p<0.001.

Drug high. Physical activity reward was not significantly associated with *d*-amphetamine-induced drug high in initial (β=0.10, p=0.31; overall model R^2=0.13, F=4.48, p=0.01) or fully adjusted (β=0.13, p=0.24; overall model R^2=0.28, F=4.14, p<0.001; $R^2\Delta$=0.15, p=0.01) models.

Discussion

Partially consistent with hypotheses, individuals who self-reported greater rewarding effects of physical activity on average reported larger *d*-amphetamine-induced increases on two of three measures of subjective drug effects. Previous data from the preclinical literature suggests a link between drug and physical activity reward, and that similar behavioral responses to both drug and physical activity reward may be indicative of shared underlying neurobiological mechanisms (Lynch et al., 2010; Olsen, 2011). Here, we extend these preclinical data by providing evidence using a human laboratory that individual differences in reward sensitivity may be expressed in two different modalities: acute subjective *d*-amphetamine response and self-reported physical activity enjoyment.

Overall, the current results are consistent with a relatively large preclinical literature indicating that there is overlap between physical activity and stimulant reward (Beiter et al., 2016; Hosseini et al., 2009; Segat et al., 2014; Smith et al., 2008b, 2011; Smith and Pitts, 2011; Thanos et al., 2010). Additionally, these data are consistent with previous findings indicating that similar biologically based personality traits may be related to both acute *d*-amphetamine response and physical activity reward. Evidence indicates that heavy recreational exercisers are higher on dimensions of sensation-seeking (De Moor et al., 2006), and individuals with high trait sensation-seeking are more sensitive to the rewarding effects of *d*-amphetamine (Kelly et al., 2006; Stoops et al., 2007). Further, both exercise dependence and acute *d*-amphetamine-related subjective effects are associated with greater levels of overlapping personality traits thought to measure reward sensitivity (i.e.

Table 2. Association of physical activity rewarding effects and covariates with *d*-amphetamine-induced drug effects.

	Factor 1				Factor 2				Factor 3			
	Positive mood				Arousal				Drug high			
	β	p	R^2	$R^2\Delta$	β	p	R^2	$R^2\Delta$	β	p	R^2	$R^2\Delta$
Model 1			0.15[a]				0.09[b]				0.13[a]	
PACES reward	0.21	0.03			0.22	0.03			0.10	0.31		
Placebo response	0.12	0.21			0.07	0.49			0.32	0.002		
Session order	−0.30	0.003			−0.19	0.06			−0.11	0.27		
Model 2			0.23[a]	0.09			0.15	0.06			0.28[c]	0.15[a]
PACES reward	0.27	0.02			0.25	0.04			0.13	0.24		
Placebo response	0.17	0.08			0.07	0.49			0.34	<0.001		
Session order	−0.24	0.02			−0.12	0.27			0.01	0.88		
Age	−0.18	0.07			0.01	0.96			−0.18	0.07		
Sex	0.10	0.35			0.17	0.12			0.35	0.001		
BMI	−0.18	0.08			−0.11	0.30			−0.22	0.02		
IPAQ level	−0.19	0.09			−0.15	0.18			−0.17	0.11		
Other drug use	0.09	0.35			0.11	0.29			0.01	0.93		

BMI: body mass index; IPAQ: International Physical Activity Questionnaire; MET: metabolic equivalent of task; PACES: Physical Activity Enjoyment Scale.
IPAQ measured in MET min/week. Regression parameter estimates for physical activity rewarding effects as predictor of *d*-amphetamine-induced increases in positive mood, arousal, and drug high, controlling for placebo response, session order, demographic variables, BMI, physical activity level, and other drug use (n=95). Other drug use=composite of caffeine, alcohol, and tobacco, possible range 0–9. Female sex coded as 0, male sex coded as 1.
[a]p<0.01, [b]p<0.05, [c]p<0.001 for R^2 and $R^2\Delta$.

social extraversion) (Aluja et al., 2003; Eysenck and Zuckerman, 1978; Hausenblas and Giacobbi, 2004; Kirkpatrick et al., 2013; White et al., 2006; Zuckerman et al., 1993).

In contrast with the findings for *d*-amphetamine-induced positive mood and arousal, individual differences in the rewarding effects of physical activity were not associated with the subjective drug high produced by *d*-amphetamine. The reason for the discordant results across outcomes is unclear. One reason for this pattern is that the measure of physical activity reward was focused on positive mood (e.g. "I find it pleasurable," "I enjoy it," and "It's very pleasant") and arousal (e.g. "It gives me energy" or "It's very exciting") reactions but did not have parallel items assessing physical activity "high." Whether a more comprehensive measure of rewarding effects from physical activity associates with each manifestation of *d*-amphetamine high indiscriminately is unknown and warrants future inquiry.

One limitation of this experimental study is that extraneous variables could explain the association between physical activity and *d*-amphetamine reward. We attempted to address this concern through design control and rigorous eligibility criteria to eliminate some confounding influences (e.g. previous stimulant exposure), and we statistically controlled for others (i.e. session order, demographics, BMI, physical activity levels, use of other drugs). However, it remains possible that unmeasured or uncontrolled variables influenced the associations demonstrated herein. Another limitation is that physical activity reward and levels were measured through retrospective self-report and did not account for the type of physical activity that the subjects were engaging in (e.g. aerobic exercise classes, yoga, weights, sprinting, swimming, contact sports). Different types of physical activities (e.g. social versus non-social, interval training versus continuous exercise, work-related versus recreational activity) may elicit different levels of reward and exertion within the same individual (Plante et al., 2001; Thum et al., 2017), and physical activity reward is likely to differ between athletes and non-athletes. Further, responses to the self-report questionnaire may have been affected by the recency of last physical activity. Thus, a precise measure of physical activity reward and exertion as a stable trait may be difficult to capture without accounting and controlling for the specific type of activity, or the individual's history and level of physical activity. Future research should assess the immediate rewarding effects of a variety of physical activities in a range of athlete and non-athlete populations, while carefully measuring and controlling for the actual amount of physical exertion.

Future research is also needed to examine the association between *d*-amphetamine and other alternative rewards (e.g. food, sexual activity), to determine whether the association is specific to physical activity reward. The rewarding effects from other non-drug rewards also share similar underlying neurobiological mechanisms with the subjective rewarding effects of stimulants, as demonstrated in rodent studies (Olsen, 2011) and neuroimaging research (e.g. examining activation of shared brain regions associated with overeating and compulsive drug taking; Wang et al., 2004). Based on such findings, we would expect individual differences in the rewarding effects of food, sexual activities, and other alternative rewards to predict inter-individual variation in the subjective effects of *d*-amphetamine. Of course, it is unclear whether the presence (or absence) of a positive (or negative) association between acute *d*-amphetamine subjective effects and self-reported pleasurable effects of alternative rewards would in and of itself clearly indicate overlap in underlying neurobiological mechanisms of these different reward modalities. Nevertheless, research examining these behavioral and subjective associations can be of value in providing further evidence to support the view that individual differences in reward sensitivity generalize across a subset of drugs and alternative rewards.

In sum, these findings provide novel evidence of a relationship between a drug of abuse (i.e. *d*-amphetamine) and an

alternative reward (i.e. physical activity), which has previously received very little empirical attention in human research. To further validate the concept that phenotypic variation in reward sensitivity generalizes across the broad domains of drug and alternative rewards, several further research avenues may be fruitful. Rewarding effects from physical activity or other hedonic responses (e.g. food response, sexual activity scale) may be worthy of study in association with *d*-amphetamine response.

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