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Asians compared to Whites show increased response to *d*-amphetamine on select subjective and cardiovascular measures

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Abstract

Objective—Identifying factors that moderate subjective response to stimulants is important for understanding individuals at risk for abusing these drugs. Some research suggests that Asians may respond differently to stimulants than other races, but controlled human laboratory research of stimulant administration effects in Asians is scant

Methods—In this double-blind counterbalanced within-subject study, healthy stimulant-naïve participants ($N = 65$; 55% Asian; 63% female; age 18–35) received a single dose of 20-mg oral *d*-amphetamine or placebo on separate days. At each testing day, subjective measures of abuse liability and cardiovascular assessments were administered at repeated intervals before and after drug administration over a 4-hour period.

Results—Asians (vs. Whites) demonstrated greater *d*-amphetamine-induced increases in diastolic blood pressure and ratings of ‘Feel High’ and ‘Like Drug’.

Conclusions—Asian and White healthy young adults may differ in certain subjective and cardiovascular responses to acute doses of *d*-amphetamine. Such individual differences could help explain between-person differences in abuse potential of *d*-amphetamine and other stimulants.

Keywords

race; Asian; *d*-amphetamine; drug response

1. INTRODUCTION

Nonmedical stimulant use has grown rapidly over the past several decades (Robison *et al.*, 1999, Robison *et al.*, 2002, Safer *et al.*, 1996, Setlik *et al.*, 2009), with important

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6. CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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differences in the prevalence of nonmedical stimulant use and disorders across different demographic groups (Substance Abuse and Mental Health Services, 2014, Substance Abuse and Mental Health Services Administration, 2014). A recent paper outlined the prospect that demographic differences in the psychopharmacological response to drugs of abuse could contribute to population-level disparities in addiction (Leventhal, 2015). Given that positive initial experiences with drugs may increase the likelihood of continued drug use (de Wit and Phillips, 2012), a better understanding of cross-population differences in the acute psychopharmacological effects of stimulants in naïve participants could provide evidence that certain drugs may be more reinforcing for certain groups.

Recent national estimates of adolescents and young adults (aged 12–34 years) in the United States indicated that lifetime nonmedical stimulant use was lower in Asians (3.83%) than Whites (11.68%) (Wu *et al.*, 2014). However, among those in the United States reporting past year stimulant use, the prevalence of past-year stimulant use disorder was similar in Asians (13.27%) and Whites (12.69 %) (Wu *et al.*, 2014). Also, another study found that in first-time substance use treatment clients, stimulant use was the primary drug problem in 57.3% of a combined Asian and Pacific Islanders ethnic group, which was twice as high as the percentage of Whites (28.5%) who endorsed stimulant use as their primary drug problem (Wong and Barnett, 2010). In addition, illicit stimulant use has been a rising concern in Asia (Global SMART Programme, 2013). A recent international study showed that Asian regions accounted for over half of the global amphetamine dependent disability adjusted life years, a measure of disease burden (Degenhardt *et al.*, 2014). Hence, it is clear that problematic use of stimulant drugs is a concern among people of Asian heritage.

Despite the importance of understanding factors that may contribute to stimulant use vulnerability in Asian populations, little is known about whether Asians (vs. other racial groups) differ in sensitivity to the pharmacological effects of stimulant drugs. A major reason for this gap is the limited sampling of this population in laboratory stimulant administration studies. However, the growing population of young Asians (Colby and Ortman, 2015, Hoeffel *et al.*, 2012) and use of non-prescription stimulants warrants investigation into characterizing pharmacological response to stimulants in Asian populations.

In the current double-blind within-subject study, we examined race (Asian vs. White) differences in subjective and cardiovascular response to a single oral dose of *d*-amphetamine (20 mg) and placebo. This study was carried out in healthy young-adult participants without prior history of stimulant use (except for nicotine or caffeine) to provide information about individuals at risk for experimentation and dependence in an age group when experimentation and escalation of stimulant use typically occur (Substance Abuse and Mental Health Services, 2014).

2. MATERIALS AND METHODS

Participants were recruited from the Los Angeles area via advertisements announcing the opportunity to participate in a study described as addressing individual differences in response to medications. Data from this sample have been previously reported in a

manuscript focusing on the relationship between stable emotional traits and acute amphetamine response (Kirkpatrick *et al.*, 2016). Inclusion criteria required that participants: (1) be 18–35 years old; (2) report having obtained a high school diploma or GED; (3) be fluent in English; (4) have a BMI of 19–30; and (5) report normal or corrected-to-normal vision, including no color blindness. Participants were excluded if they: (a) had any current medical condition requiring medication or any current or past medical condition considered to be a contraindication for *d*-amphetamine (e.g., hypertension, abnormal electrocardiogram [EKG]); (b) had any current Axis-I psychiatric disorder or a past psychiatric disorder contraindicated for *d*-amphetamine (i.e., psychotic disorder, panic attacks); (c) endorsed 1 past or current index (hypo)manic symptom; (d) reported smoking more than 10 cigarettes per week or consuming more than 3 cups of coffee per day; (e) reported working the night shift; (f) reported any lifetime use of licit or illicit stimulants (e.g., *d*-amphetamine, methamphetamine, MDMA, methylphenidate, cocaine), with the exception of caffeine and nicotine; (g) reported any history of substance use related problems, use of any illegal drug of abuse in the past 30 days, or a positive urine toxicology screen for any drug of abuse. Females were also excluded if they were pregnant or breastfeeding or planned to get pregnant. All experimental sessions in females not on hormonal birth control were scheduled during the follicular phase of the menstrual cycle (i.e., menstrual cycle days 2–10).

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 Recommended Guidelines for the Administration of Drugs to Human Subjects.

2.1 Design & Procedure

Following a screening session, this study used a within-subjects design in which single doses of oral *d*-amphetamine (20 mg) and placebo were administered in two separate, double-blind, counterbalanced experimental sessions.

After preliminary telephone eligibility screening, participants attended a screening session involving written informed consent, psychiatric interview, drug screening, and a physical examination with an EKG. Participants were told that the purpose of the study was to evaluate individual differences in medication response. In order to enhance blinding as in prior research (White *et al.*, 2006), participants were informed that they would be administered a capsule containing a standard dose of one of the following drugs: sedative/tranquilizer, stimulant/appetite suppressor, anti-depressant, or placebo.

Experimental sessions were conducted in the morning from 9:00 AM to 1:00 PM. Participants were tested individually and remained in a room with television and reading materials for the 4-hr session. During the sessions, participants could watch nature movies and read when measurements were not being taken. Participants were provided with a light breakfast after fasting from midnight the night before each session. To confirm drug and alcohol abstinence, participants provided urine and breath samples, and females were tested

for pregnancy. Participants testing positive were excluded from further participation. Next, the baseline (pre-capsule) subjective assessment was administered. At approximately 9:30 AM, participants ingested a capsule containing placebo or 20 mg *d*-amphetamine. Subjective measures and cardiovascular assessments were administered at 30, 60, 90, 150, and 180 minutes after capsule administration. Participants also completed computer tasks assessing emotional processing at the 90 minutes post-capsule administration time point, but results are not reported here. At the 180 minutes post-capsule administration time point, participants completed end-of-session ratings and were discharged either around 30 minutes later or when heart rate and blood pressure returned to baseline levels.

2.2 Predictor Variables

An author-constructed questionnaire assessed self-reported race/ethnicity. This questionnaire was used to distinguish participants who reported their heritage as Non-Hispanic White ($n = 29$) or Asian (including the Philippine Islands, Southeast Asia, and Indian, but not including Pacific Islander and Hawaiian, $n = 36$).

2.3 Outcome Measures

The Drug Effect Questionnaire (DEQ) assessed the extent to which participants experienced four subjective states: 1) Do you feel any drug effects (i.e., 'Feel Drug'); 2) Are you High (i.e., 'Feel High'); 3) Do you like the effects you are feeling now (i.e., 'Like Drug'); and 4) Would you like more of the drug right now (i.e., 'Want More'). Feel Drug, Feel High, and Want More were scored from 0 (*not at all*) to 100 (*a lot, very, and very much*, respectively) on a visual analogue scale. Like Drug was scored from 0 (*dislike*) to 100 (*like very much*) on a visual analogue scale. For Like Drug participants were instructed to mark neutral (=50) if they were not feeling any effects. The DEQ has been shown to reliably and sensitively measure the effects of stimulants (Morean *et al.*, 2013).

The 72-item Profile of Mood States (POMS) (Johanson and Uhlenhuth, 1980, McNair *et al.*, 1971) provided eight scales: five negative affect scales (Anger, Anxiety, Confusion, Depression, Fatigue) and three positive affect scales (Elation, Friendliness, and Vigor). We also reported composite scores for Arousal (i.e., Anxiety and Vigor minus Fatigue and Confusion), Negative Mood (i.e., mean of all negative affect scales) and Positive Mood (i.e., Elation minus Depression). Participants rated affect adjectives on a 5-point Likert scale from 0 (*not at all*) to 4 (*extremely*) based on how they were currently feeling. A mean score was computed for each subscale.

Heart rate and blood pressure were measured at each assessment time point by noninvasive computerized equipment.

2.4 Sample Characteristics

Sample characteristics were obtained at the screening session and reported in Table 1. Carbon monoxide (CO) was recorded to monitor smoking status. An author-constructed questionnaire assessed demographics including gender, age, height, weight, and usual caffeine consumption. BMI was calculated using height and weight.

2.5 Data Analysis

Mixed ANOVAs were conducted on each pre-capsule outcome measure with the between-subjects factor of Race (Asian, White) and the within-subject factor of Drug (AMPH, PBO). There was a significant effect of race on pre-capsule scores for POMS Arousal and POMS Vigor ($F_{1,63}=7.0-8.4$; $p<0.01$). Thus, to minimize the influence of variability between participants prior to capsule administration, subjective and cardiovascular scores were calculated as change from baseline in one of two ways: The pre-capsule score was subtracted from scores at all subsequent time points (for time analyses) or from the peak post-capsule score (for peak response analyses), as has been done in prior research (Justice and De Wit, 2000).

Preliminary analyses—Racial differences in sample characteristics were analyzed using t-tests and chi-square. To characterize the acute effects of *d*-amphetamine, data from cardiovascular and subjective measures were analyzed using repeated-measures analysis of variance (ANOVA) with two within-subject factors: drug condition (placebo, 20 mg *d*-amphetamine) and time (a five-level variable reflecting change from baseline at 30, 60, 90, 150, and 180 minutes post-capsule ingestion). Only cardiovascular and subjective outcomes with significant drug main effects or drug $\times$ time interactions were utilized in models examining race described below. This was done because the absence of such effects would suggest that these measures are insensitive to the pharmacological challenge.

Primary analyses—To determine whether the response to AMPH differed between Asians and Whites over time, mixed ANOVAs were used with within-subject factors of drug condition (placebo, 20 mg *d*-amphetamine) and time (a five-level variable reflecting change from baseline at 30, 60, 90, 150, and 180 minutes post-capsule ingestion) and one between-subjects factor (race [Asian, White]). Evidence of differences in pharmacological response to AMPH among Asians and Whites were indicated by a drug $\times$ race interaction or drug $\times$ race $\times$ time interaction. Additionally, we investigated whether the peak response (i.e., the pre-capsule score subtracted from the peak score post-capsule administration) to AMPH differed between Asians and Whites using mixed ANOVAs with one within-subject factor of drug condition (placebo, 20 mg *d*-amphetamine) and one between-subjects factor (race [Asian, White]). Evidence of differences in pharmacological response to AMPH among Asians and Whites were indicated by a drug $\times$ race interaction. For outcomes with evidence of racial differences in drug response, we conducted post-hoc simple effect analyses of the effect of drug condition within each race and race differences at each level of the drug. For significant outcomes, we conducted follow-up tests using ANCOVAs with the same factors of drug, time, and race that adjusted for other characteristics that could stratify by race and confound racial differences in drug response (i.e., gender, age, and BMI).

For all analyses, Huynh-Feldt corrections adjusted for violations of the sphericity assumption. Alpha was set at .05 for significance, and we did not correct for type-I error due to multiple testing because we did not want overlook possible effects that were of moderate magnitude. Data was analyzed using IBM SPSS Statistics version 22.

3. RESULTS

3.1 Sample Characteristics

Sample characteristics are reported in Table 1. Sample characteristics did not significantly differ by race.

3.2 Acute cardiovascular and subjective effects of d-amphetamine in the entire sample

d-Amphetamine significantly increased heart rate as well as systolic and diastolic blood pressure compared to placebo (Main effect of drug: $F(1,64)=26.6-111.3$; $p<0.001$). Additionally, *d*-amphetamine significantly increased ratings of DEQ 'Feel Drug', 'Feel High', 'Like Drug', and 'Want More', as well as POMS Arousal, Elation, Friendliness, Positive Mood and Vigor (Main effect of drug: $F(1,64)=9.3-31.1$; $p<0.005$). *d*-Amphetamine did not significantly alter ratings of POMS Anger, Anxiety, Confusion, Depression, Fatigue, or Negative Mood; thus, these measures were not included in the analyses of race.

3.3 Effects of race on acute effects of d-amphetamine

To demonstrate time course of drug effects, select subjective and cardiovascular responses by drug and race are depicted in Figure 1. In time analyses, there was a drug $\times$ race interaction for diastolic blood pressure ($F(1,63)=8.65$; partial $\eta^2=.12$; $p<0.01$) and ratings of DEQ 'Feel High' ($F(1,61)=6.67$; partial $\eta^2=.10$; $p=.01$) and 'Like Drug' ($F(1,62)=4.84$; partial $\eta^2=.07$; $p=.03$). *d*-Amphetamine increased diastolic blood pressure and ratings of DEQ 'Feel High' and 'Like Drug' to a greater extent in Asians compared to Whites. In models adjusted for gender, age, and BMI, significant drug $\times$ race interactions remained for diastolic blood pressure ($F(1, 58)=9.01$; partial $\eta^2=.13$; $p=0.004$), DEQ 'Feel High' ($F(1, 56)=6.87$; partial $\eta^2=.11$; $p=0.01$), and DEQ 'Like Drug' ($F(1, 57)=4.57$; partial $\eta^2=.07$; $p=0.04$).

Similar to the time findings, there was a greater effect of *d*-amphetamine peak response in Asians compared to Whites for ratings of DEQ 'Feel High' and 'Like Drug' (drug $\times$ race interaction: $F(1,62)=6.20-8.45$; partial $\eta^2=.09-.12$; $p<0.05$) and diastolic blood pressure (drug $\times$ race interaction: $F(1,63)=4.67$; partial $\eta^2=.07$; $p=0.03$). Least significant pairwise comparisons for peak difference analyses by race and drug are reported in Table 2. After controlling for gender, age, and BMI, drug $\times$ race findings in peak differences in diastolic blood pressure ($F(1, 58)=4.32$; partial $\eta^2=.07$; $p<0.05$) and DEQ 'Feel High' and 'Like Drug' ($F(1,57)=5.94-8.87$; partial $\eta^2=.09-.14$; $p<0.02$) remained significant.

4. DISCUSSION

This placebo-controlled study of stimulant-naïve young adults found race differences in response to a 20-mg *d*-amphetamine administration on a subset of subjective and cardiovascular indicators of amphetamine's abuse potential. Asians relative to Whites demonstrated greater amphetamine-induced increases in diastolic blood pressure, feeling high, and liking the drug. To the best of our knowledge, this is the first study to show differences in subjective and cardiovascular response to *d*-amphetamine between Asians and

Whites. The reasons why racial differences were found on only these outcomes are not entirely clear. It is possible that this study lacked power to detect small racial differences in drug effects. Alternatively, whatever mechanisms may be driving racial differences in drug response could be specific to these particular phenotypic expressions. Future work in larger samples is necessary to conduct head-to-head comparisons in whether Asians and Whites differ in sensitivity to certain drug effects but not others.

While these initial findings should be treated as preliminary until replicated, prior genetic studies suggest that these effects are biologically plausible: Asians are more likely to possess *SLC6A3* and *CYP2D6* genotype or allele variants that may increase sensitivity to amphetamine effects (de la Torre *et al.* , 2012, Kang *et al.* , 1999, Lott *et al.* , 2005). However, the current study did not directly assess genotype, and future work is needed to understand how inter-racial genetic differences might underlie differences in subjective and cardiovascular drug response.

This study focused on cardiovascular measures and self-report measures of subjective response and did not investigate whether these responses increase actual drug-taking behavior or drug reinforcement. There is some evidence that in the United States, Asians compared to Whites may have lower prevalence of stimulant use (Wu *et al.*, 2014). Differences in prevalence of use may relate to sociocultural processes in the United States that may deter drug use disproportionately in Asian Americans (vs. other groups), such as lack of cultural acceptance of recreational drug use (Hunt *et al.* , 2011, Moloney *et al.* , 2008). Though this study suggests that Asians (vs. Whites) may be differentially sensitive to the pharmacological effects of amphetamine, future research is necessary to further characterize the effects of sociocultural factors on substance use uptake in Asians and other races. Additionally, this study only investigated two racial groups: Asians (not including Pacific Islanders) and Whites. Future studies should also include other races. Another limitation of the current study is that we did not have a large enough sample size to detect small effects (e.g., some apparent amphetamine-related elevations on subjective measures in Whites). Further, we did not utilize a significance correction for multiple testing because we did not want to overlook any potentially meaningful effects that were medium in size; hence, current results should be interpreted with caution until replicated. Lastly, this study involved the administration of a single dose of *d*-amphetamine (20 mg). Although this dose of amphetamine reliably produces a range of physiological, subjective, cognitive, and behavioral effects in healthy participants, it is not clear if the relationships between race and acute drug response would be observed at higher or lower dose levels.

5. CONCLUSION

In conclusion, this study offers preliminary evidence that some subjective and cardiovascular responses to *d*-amphetamine in stimulant-naïve young adults may be greater in Asians compared to Whites. Given the overall dearth of controlled stimulant studies including an adequate number of Asians, current findings are also helpful in highlighting the need for future research examining acute pharmacological response to amphetamine in Asians relative to other racial/ethnic groups.

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Highlights

- *d*-Amphetamine increased diastolic blood pressure more in Asians compared to Whites
- Asians compared to Whites reported greater liking of drug following *d*-amphetamine
- Asians, but not Whites, reported greater 'Feel High' following *d*-amphetamine

Figure 1. Select figures of race effects on acute effects of *d*-amphetamine

Means and standard errors of data at each time point illustrates the effects of drug condition on diastolic blood pressure and selected subjective effects measures as a function of time and race. In general, peak drug effects occurred approximately 90 min post capsule administration in both Asians and Whites. AMPH = 20 mg. amphetamine; PBO = Placebo; mmHg = Millimeter of Mercury.

Table 1

Descriptives Statistics for Sample Characteristics by Race

Demographic Characteristic	Full Sample (n=65)		Asian (n=36)		White (n=29)		Race Differences	
	M(SD) or %(N)		M(SD) or %(N)		M(SD) or %(N)		t or χ^2	
Continuous Variables								
Age (years)	23.38 (4.39)		23.25 (4.19)		23.55 (4.70)		-0.27	
BMI	22.85 (2.24)		22.85 (2.64)		22.85 (1.69)		0.00	
CO Level at screening	2.11 (1.14)		1.92 (0.44)		2.36 (1.64)		-1.39	
Categorical Variables								
Gender							0.13	
Female	63.1% (41)		61.1% (22)		65.5% (19)			
Male	36.9% (24)		38.9% (14)		34.5% (10)			
Caffeine Consumption							1.33	
A few times a month or less	15.9% (10)		11.4% (4)		21.4% (6)			
A few times a week	33.3% (21)		37.1% (13)		28.6% (8)			
Daily	50.8% (32)		51.4% (18)		50.0% (14)			

Note. BMI = Body Mass Index; CO = Carbon Monoxide.

Table 2
Effects of race and drug on acute effects of amphetamine based on peak change from baseline.

Measure	Asian		White		Drug × Race	
	AMPH	PBO	AMPH	PBO	F	η_p^2
DEQ	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>		
Feel Drug	52.51 (4.69) ^{a‡}	25.77 (3.98)	32.38 (5.15) [#]	16.86 (4.38)	3.13	.05
Feel High	19.03 (2.53) [#]	3.00 (1.72)	12.28 (2.78)	6.35 (1.89)	6.20 [*]	.09
Like Drug	36.03 (4.75) ^{a‡}	7.26 (2.94)	15.38 (5.21)	6.90 (3.23)	8.45 ^{**}	.12
Want More	35.09 (5.44) [#]	10.63 (3.41)	25.21 (5.98) [#]	13.31 (3.75)	3.24	.05
POMS						
Arousal	1.32 (0.19) ^{a‡}	0.53 (0.17)	0.73 (0.21) [#]	0.06 (0.19)	0.13	.00
Elation	0.67 (0.13) [#]	0.14 (0.11)	0.30 (0.14)	0.02 (0.12)	1.79	.03
Friendliness	0.42 (0.11) [#]	-0.03 (0.09)	0.14 (0.12)	-0.05 (0.10)	2.49	.04
Vigor	0.79 (0.11) [#]	0.18 (0.10)	0.37 (0.13) [#]	-0.10 (0.12)	0.52	.01
Positive Mood	0.73 (0.14) [#]	0.19 (0.11)	0.31 (0.16)	0.05 (0.12)	2.00	.03
Cardiovascular						
Heart Rate	13.17 (1.91) [#]	2.17 (1.05)	11.00 (2.12) [#]	4.67 (1.12)	2.24	.03
Diastolic BP	13.39 (1.01) ^{a‡}	1.69 (0.90)	9.14 (1.12) [#]	1.93 (1.01)	4.67 [*]	.07
Systolic BP	20.14 (1.48) ^{a‡}	2.67 (1.16)	15.62 (1.64) [#]	1.17 (1.29)	1.07	.02

Note. AMPH = 20 mg. amphetamine; PBO = placebo; DEQ = Drug effects questionnaire; POMS = Profile of Mood States; Positive Mood = elation minus depression; BP = Blood Pressure. Pairwise comparisons of group differences are tested by least significant difference. For clarity, significant effects are shown only on the reference group (i.e., Asian for Asian vs. White and amphetamine for drug vs. placebo).

^a $p < .05$ for Asian vs. White pairwise comparisons;

[#] $p < .05$ for amphetamine vs. placebo pairwise comparisons.

^{*} $p < .05$,

^{**} $p < .01$ for Drug × Race.