Differential responses to drugs and sweet tastes

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Protocol Name: Differential responses to drugs and sweet tastes

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Background and Aims: Young people screened in late adolescence report surprisingly high rates of mood elevation or 'hypomanic' experience (Calabrese et al., 2003; Chandler et al., 2008). These experiences are characterized by intermittent periods of heightened activity, sleeplessness and reward-focused thinking. These experiences are also associated with increased risk of mental health problems, especially depression and anxiety (Calabrese et al., 2003). Even individuals who report these experiences but do not meet criteria for bipolar disorder show some of the same problems in cognitive and emotional function as individuals who do meet diagnostic criteria (Chandler et al., 2008; Rock et al., 2010). This strongly suggests that intermittent mood elevation per se in young people constitutes a trait marker for vulnerability to psychological disorders as a bipolar phenotype (BPP).

Individuals with the “bipolar phenotype” (BPP), defined as episodes of mood elevation and heightened activity, are at risk for several psychiatric disorders, including problem use of drugs and alcohol. Mood elevation has been linked to heightened alcohol consumption and alcohol use disorders. Individuals with BPP show elevated lifetime prevalence of alcohol use disorders (between 39%-61%), figures that exceed those reported in both major depression and schizophrenia (Regier et al., 1990; Kessler et al., 1997). Recently, we demonstrated in a controlled laboratory study that individuals with BPP report dampened responses to a single dose of alcohol, compared to placebo (Yip et al., 2012). Notably, these individuals were tested at ages 18 and 19, before they had extensive exposure to alcohol and other recreational drugs, suggesting that their responses reflect an underlying neurobiological risk factor. In addition, another recent study found that a genetic polymorphism associated with susceptibility to Bipolar Disorder was also associated with dampened neural responses to reward in healthy volunteers, using fMRI (Trost et al., 2016). These findings raise the possibility that individuals with BPP will exhibit dampened responses to *other* rewarding stimuli, including dampened feelings of well-being or euphoria from amphetamine, or less pleasurable experiences with a sweet taste.

In the present study, we will extend our previous findings and determine whether individuals with this phenotype also experience less positive effects from two other rewards: feelings of well-being from a single oral dose of d-amphetamine and preference for sweet solutions. This would suggest a mild dysfunction of the reward circuits in BPP individuals, possibly related to mesolimbic dopamine function.

Study Aim: To compare the rewarding effects of d-amphetamine (10 and 20 mg) and sweet tastes in young adults with low and high bipolar phenotypes. The rewarding effects of d-amphetamine in young adults will be measured using subjective self-report measures of euphoria and arousal. We will also obtain psychophysiological measures to provide an objective index of positive emotional responses. Based on our previous findings suggesting individuals with BPP display dampened subjective responses to alcohol, we hypothesize that individuals

with BBP, compared to matched controls without these symptoms, will be hypo-reactive to both amphetamine reward and sweet taste reward.

Method

Subject Recruitment and Screening: We will recruit 48 healthy men and women, aged 18 or 19. This age range matches the age of our previous study with alcohol, and minimizes the confounding influence of habitual alcohol consumption. Potential participants will complete the standardized Mood Disorders Questionnaire (MDQ)(Hirschfeld et al., 2000; Hirschfeld et al., 2003). We will recruit an even distribution of participants with higher or lower MDQ scores, totaling 48 individuals. Potential participants will be recruited either through our regular recruitment process (Protocol 13681B), or through targeted ads in which they are invited to complete the MDQ online. We will add the MDQ to our primary recruitment and screening protocol, and participants will come into lab for the in-person screening interview, under Protocol #13681B, which includes an EKG, physical exam, and clinical psychiatric interview.

Screening assessments: During the in-person screening interview, participants will be screened by a clinical psychologist and will complete several standardized questionnaires. They will undergo a semi-structured Clinical Interview for DSM-5 (SCID-5) (First, 1995) to exclude any major DSM-V psychiatric illness — including alcohol and substance abuse/dependence — with the exception of bipolar II or NOS for BPP participants. Other exclusion criteria will include: (i) any current psychotropic medication; (ii) any current non-psychotropic medication that might interact with amphetamine; (iii) history of cardiac or liver disease; (iv) high blood pressure; (v) night-shift work; (vi) more than 3-4 alcohol drinks per day for males and 2-3 drinks per day for females.

Group matching: As we enroll participants we will attempt to match the BPP and Healthy Control (HC) groups for sex, age, drug use history, and (non-verbal) cognitive ability (Raven et al., 1998).

Drugs: Oral d-amphetamine at 10mg and 20mg (Dexedrine; GlaxoSmithKline, Research Triangle Park, NC; 5mg tablets) will be placed in size 00 capsules with dextrose filler. Placebo capsules will contain dextrose only.

Self-report subjective measures: Subjective responses to amphetamine will be assessed using standardized scales.

The Drug Effects Questionnaire (DEQ) (Johanson and Uhlenhuth, 1980). Participants use 100mm visual analog scales (VAS) to provide ratings for four questions: 'Do you feel any drug effect?' ('None at all' to 'A lot'); 'Do you like the effects you are feeling now?' ('Dislike' to 'Like very much'); 'Are you high?' ('Not at all' to 'Very'); and 'Would you like more of what you consumed, right now?' ('Not at all' to 'Very much').

The Addiction Research Center Inventory (ARCI) (Haertzen, 1966). The ARCI is a 49-item true-false questionnaire that is sensitive to psychoactive drugs. Its 5 scales are sedation (Pentobarbital-Chlorpromazine Group; PCAG), stimulant-like effects (Amphetamine; A, and Benzedrine Group; BG), somatic and dysphoric effects (Lysergic Acid; LSD), and euphoria (Morphine-Benzedrine Group; MBG).

The Profile of Mood States (POMS) (McNair et al., 1971). The 72-item POMS will be used to assess momentary mood states across 8 subscales: Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness and Elation; participants indicating how they feel

at that moment in relation to 72 adjectives on a 5-point scale from 'Not at all' (0) to 'Extremely' (4).

Psychophysiology: Psychophysiological measures will be obtained to provide an objective index of responses to amphetamine and differences between the groups. Resting heart rate (HR) will be measured at 1000Hz before amphetamine and then for 2min at set intervals using a Biopac multi-channel device (MP150-BIOPAC Systems Inc., Goleta, CA). Recordings will be wireless via a (Biopac) BioNomadix RSP, (Biopac) ECG amplifier and (Biopac) BioNomadix respiration transducer while participants are seated with eyes closed. We will use disposable pre-jelled Ag–AgCl snap disposable vinyl electrodes placed in a modified Lead II configuration. Data analysis will proceed with AcqKnowledge v4 software. ECG signal will be converted to R-wave intervals (as interbeat intervals (IBI) to the nearest millisecond) and IBI values will be converted to beats per minute. Respiratory sinus arrhythmia (RSA) will be derived as a noninvasive index of cardiac vagal tone, or parasympathetic activity using the peak-valley method (Grossman and Taylor, 2007). Maximum HR expressed as milliseconds IBI during the expiration window will be subtracted from the minimum HR during the inspiration window of the respiration cycle to yield RSA (ms)(Grossman et al., 1990).

Study environment: The study will be conducted in the Human Behavioral Pharmacology Laboratory at The University of Chicago in secure, comfortable testing rooms. Medical assistance is readily available in the unlikely event of adverse drug experiences.

Consent Procedures: After screening, subjects will attend an orientation session in which they read and sign the consent form. Participants will be told that the study purpose is to investigate the effects of psychoactive drugs and food tastes on mood and behavior, and that they might receive a stimulant (such as amphetamine), a sedative (such as Valium) or an inactive placebo. Participants will agree not to use any drugs except for their normal amounts of caffeine for 24hr before and 6hr following each study visit. They will be informed that urine tests for stimulants, opioids and cannabis, breath samples for alcohol use, and pregnancy tests for women will be taken at the start of each visit and that positive tests may result in dismissal. Participants will be instructed to fast on the morning of the visit.

Orientation: During an initial orientation session, the study procedures will be explained, subjects will provide informed consent, and then practice study tasks. After practicing the study tasks, the participants will complete the following questionnaires: the Quick Inventory for Depressive Symptomatology (QIDS) (Rush et al., 2003); and neuroticism using the Eysenck Personality Questionnaire's Neuroticism subscale (EPQ-N)(Eysenck et al., 1985), and the cognitive ability assessment: Wechsler Abbreviated Scale of Intelligence-Second Edition (Wechsler & Hsiao-pin, 2011; WASI-II). For comparison to other studies, subjects will also complete the Lifetime Drinking History — Interview (Jacob et al., 2006) and the Timeline Follow-Back method (Sobell & Sobell, 1992; Hoeppner et al., 2010). Finally, participants will complete the revised Three Factor Eating Questionnaire (TFEQ) (de Lauzon et al., 2004), an 18-item questionnaire on eating attitudes and behaviors, with subscales to measure cognitive restraint, uncontrolled eating and emotional eating.

Design & procedure: Following orientation, participants will complete three 4-hour drug study visits and a final 1-hour visit. The 4-hour sessions will be conducted between 9am and 1pm separated by at least 48 hours in a double-blind, placebo-controlled, cross-over, within-subjects design. During these visits, they will consume capsules containing 10 or 20 mg d-amphetamine or placebo, double-blind in counterbalanced order. Women not using oral contraceptives will only be tested during the follicular phase (White et al., 2002).

Upon arrival at the laboratory, participants will provide BrAL and compliant urine tests for recent drug or alcohol use, and pregnancy (in females). Participants will then complete baseline questionnaires (DEQ, POMS, and the ARCI) and psychophysiological measurements. Participants will be given a snack (granola bar) to standardize food consumption, and then ingest a capsule containing placebo, 10mg or 20 mg d-amphetamine under double-blind conditions. The order will be randomized across subjects via Latin square design. Participants will complete the DEQ, POMS, and the ARCI scales at 30, 60, 90, 120, 150, 180, 210 and 240min time-points; HR will be taken at the same time. At 1pm, participants will complete a final set of questionnaires to collect their final state and subjective responses before being discharged to go home.

The Sweet Taste Test: On the final 1-hour study visit, participants will complete the sweet taste test and then the study will be explained. After BrAL and drug compliance tests, participants will complete the validated sweet taste test (Weafer et al., 2014). In this test, participants rate the sweetness intensity and liking of Kool-aid solutions of various sucrose concentrations. Participants will rate five concentrations equivalent to the molar sucrose concentrations typically used in sweet taste liking procedures (i.e. 0.05, 0.10, 0.21, 0.42 and 0.83M). The test will consist of five blocks, in which each of the five solutions will be presented in random order (i.e. a total of 25 taste trials). On each presentation, participants will receive a 2ml serving of solution in a small opaque cup, instructed to swish the solution for 5s and then spit it out. They rate the sweetness of the taste (from 'Not sweet at all' to 'Extremely sweet') and their liking of the taste (from 'Disliked very much' to 'Liked very much') on two 100-mm visual analog scales. Between trials, subjects will rinse and spit a small amount of water. Sweetness and liking ratings will be calculated by averaging ratings for each solution across the five presentations.

Data analysis and interpretation: First we will ensure that the BPP and HC groups are matched for demographic variables, and covariates will be identified if needed. Primary outcome measures will be the stimulant (A scale) and euphoria (MBG) subscales of the ARCI (Haertzen, 1966) and the Friendliness and Elation subscales of the POMs (McNair et al., 1971). These measures will be tested using GLMs with predictors of group (BPPs vs HCs), gender, treatment (placebo, 10mg and 20mg amphetamine) and time (0, 30, 60, 90, 120 and 150 and 180min). Sweet 'liking' responses will be tested using a GLM with the predictors of group, gender and concentration (i.e. 0.05, 0.10, 0.21, 0.42 and 0.83M). Participants will be classified as sweet-likers if their liking ratings were greatest for the highest concentration solution (0.83 M); all other participants will be classified as sweet-dislikers (Weafer et al., 2014). χ2-tests will test the supplementary prediction that there are more sweet-likers in the BPP group than in the HC groups.

Sample size: Estimations of sample/group size have been derived from our previous demonstration of blunted subjective response to alcohol in BPP compared to HC males (Yip et al., 2012). In that study, the effect sizes (f^2) for the two DEQ sub-scales of 'Feel high' and 'Feel effects' was 0.73 and 0.60, respectively. Taking the midpoint of these 2 values as our anticipated effect size (0.67), N=48 subjects would provide over 81% power (with $\alpha = .05$) to detect treatment differences between BPP individuals and HC individuals.

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