Exploring Predictors of Affective State during d-Amphetamine Intake

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Abstract

Possible predictors of positive and negative affective response to oral d-Amphetamine were examined in healthy adults using secondary data analysis on two datasets. The predictors examined included subjective response to the drug, midbrain D2/D3 binding potential, and stable personality traits. Using correlational analyses, D2/D3 binding potential and stable personality traits were found to not have significant associations with positive or negative affect. In contrast, subjective response to d-amphetamine was found to be positively associated with negative affect, though this finding did not replicate across datasets. In subsequent multiple regression models, one dataset showed a significant positive relationship between negative affect and the degree to which participants subjectively felt the effects of the drug, while the other dataset showed a significant positive relationship between negative affect and the degree to which participants subjectively disliked the effects of the drug. Though the lack of replication across datasets makes it difficult to draw definitive conclusions, these findings suggest that negative affect may play a major role in people's experience of drug use.

Exploring Predictors of Affective State during d-Amphetamine Administration

Psychostimulants are a class of drugs which act upon the dopamine (DA) system to produce feelings of heightened energy in those who take them. Specifically, they produce this effect by causing the dopamine transporter (DAT) to release dopamine into neural synapses and sustaining extracellular dopamine by blocking dopamine reuptake (Sulzer et al., 2005). While many drugs of abuse, such as cocaine and methamphetamine, are what people first think of when psychostimulants are mentioned, this class of drugs also includes more mild substances such as Adderall (which is a mixture of d-Amphetamine, or dAMPH, and amphetamine salts). While it is mostly used to treat cases of ADHD, Adderall has received increasing attention due to its status as a "study aid" and prevalent use among college students not prescribed the drug (Arria & DuPont, 2010; Bavarian, Flay, Ketcham, & Smit, 2015). According to national survey results released by SAMHSA in 2017, approximately 7 percent of U.S. adults aged 18-25, or 2.5 million people, have misused prescription amphetamines (including Adderall) in 2016 and 2017, which is a higher percentage of misuse than those found for people aged 12-17 (approximately 1.5 percent) and 26 or older (approximately 1 percent). While this relatively high level of psychostimulant misuse among young adults is concerning, not all people who use psychostimulants become addicted to them: while about 0.6 percent of U.S. adults (people aged 18 or older) used methamphetamine in 2016 and 2017, about 0.3-0.4 percent of adults required treatment for methamphetamine use disorder in 2016 and 2017 (SAMHSA, 2017). Certain biological and psychological factors may explain why some individuals become dependent on psychostimulants while others do not. Understanding what factors influence people's differential response to psychostimulants may help with the identificaiton of those with greater risk of developing substance use disorders.

Affect and its Relation to Drug Response

Positive and negative affect (PA and NA, respectively) describe general subjective states that reflect people's tendency to experience two overarching types of mood states. PA represents the degree to which a person experiences engagement with their environment, and is indicated by emotions such as alertness and interest (Crawford & Henry, 2004). NA represents the extent to which a person experiences subjective distress or displeasing engagement with their environment, and is indicated by emotions such as fear and guilt (Crawford & Henry, 2004). PA and NA are often measured using the Positive and Negative Affect Scale (PANAS). The PANAS is a self-report measure in which subjects rate to what degree they feel various affective states (such as attentiveness and fear) which differ from each other qualitatively and are associated with either PA or NA (Crawford & Henry, 2004).

Investigating how PA and NA relate to people's responses to drugs of abuse would add to our understanding of variables that may affect addictive liability. Previous research has demonstrated that individual differences in a number of variables, including personality traits and gender, affect people's responses to oral dAMPH (Smith et al., 2016b; Weafer & De Wit, 2013). Additionally, people use drugs of abuse for various reasons, which can include relieving negative affective states through self-medication or inducing positive affective states via a drug's pleasurable effects. Few studies, however, have investigated the relationship between PA and NA and responsivity to drugs of abuse during drug intake. It is worth investigating whether significant relationships may be observed with regards to people's affective response to dAMPH and psychological constructs known to be associated with the experience of drug use, as differences in variables such as personality and subjective drug response may relate to

differential affective responses to drugs of abuse that are associated with greater addictive liability.

This study used exploratory secondary data analysis on two datasets from the Affective Neuroscience Laboratory at Vanderbilt University to assess possible relationships between affective drug response and factors that are thought to be related to oral dAMPH drug response. We believe that this study reveals meaningful relationships that provide insight into people's experience of drugs of abuse, and that the results of presented here should be investigated further in future studies.

Neural Mechanisms of Drug Effects

This study used Positron Emission Tomography (PET) to investigate how differences in D2/D3 receptor availability & DA release may relate to individual differences in affective response during the course of drug intake. The properties of the PET radiotracers used determines the system one can measure in the brain. The datasets analyzed in this study use [^{18}F] fallypride, which is effective in measuring of D2/D3 receptor availability (Mukherjee et al., 1999, 2002). Since [^{18}F] fallypride is displaceable by endogenous DA, researchers can use it to measure DA release in response to a psychostimulant by comparing receptor availability under a placebo condition with that of the drug condition (Riccardi et al., 2008; Slifstein et al., 2010).

Recent research has confirmed that there is measurable DA release in response to dAMPH administration in the amygdala, ventral striatum (VS), ventromedial prefrontal cortex (vmPFC), and insula, which are brain regions involved in the evaluation of value (VS, vmPFC) and internal state (insula) (Smith et al., 2016a). DA release in the VS, vmPFC, and insula has been shown to positively correlate with ratings of subjective Wanting during dAMPH administration (Smith et al., 2016a). While it is known that all drugs of abuse affect DA

functioning in the brain, relatively little is known about how this change in DA functioning relates to people's affective state. This study examined the relationship between DA release and affective state during drug intake in order to clarify this relationship and provide a more concrete conception of how affect may contribute to addiction risk.

Subjective Response to Drug

Many studies examining individual differences in drug response have studied people's subjective response to drug using the Drug Effects Questionnaire (DEQ) (Morean et al., 2013), a self-report measure that assesses the strength of the subjective effects of a drug and the appeal of those subjective effects using unipolar ratings of Like, Dislike, Feel, High, and Want More. Importantly, these subjective responses differ from the emotional states measured by PANAS in that they are explicitly concerned with people's reactions to an administered drug while affect describes more emotional states that are not necessarily drug-related.

A large portion of available information regarding the subjective experience of drugs of abuse is based off of research focused on examining drug-dependent individuals (Kelly et al., 2009; Lambert, McLeod, & Schenk, 2006; Perry et al., 2013). Lambert et al. (2006) found that drug-dependent individuals have lower DEQ Liking scores relative to non-drug-dependent individuals, which is thought to be because of an accumulated tolerance to a drug and the association of the drug with subsequent unpleasant withdrawal symptoms (Robinson & Berridge, 1993, 2001; Wyvell & Berridge, 2000). Lambert et al. (2006) also found important evidence for the notion that subjective experience during initial use of psychostimulants can predict future drug use: in a retrospective study of 202 adults, they found higher levels of Wanting and lower levels of Liking relative to age-matched controls during initial use of cocaine (for which the mean age was 17.2) to be related to a history of tobacco or psychostimulant use. These findings

indicate that the subjective wanting of a drug is what drives long-term use following initial exposure to a drug.

A hypothesized mechanism for addictive drug use is that subjective wanting or craving of a drug begins to drive drug use as individuals become addicted, and often becomes associated with drug-associated cues that can result in DA release in the brain (Bradberry et al., 2000; Franken, 2003). These findings are consistent with rodent studies suggesting that the intake of DA-releasing drugs increases the incentive salience of rewards, increasing the likelihood of further drug use in the presence of drug-associated cues (Wyvell & Berridge, 2000). These studies have led to the proposed incentive salience theory of drug addiction, which states that DA release plays a significant role in instilling a drug and its associated cues with incentive salience, leading to wanting or craving for the drug by drug users (Robinson & Berridge, 1993, 2001).

There is also evidence suggesting that there are temporal differences in healthy subjects' DEQ response profiles to dAMPH (Smith et al., 2016b). These results are consistent with a rate hypothesis of addictive liability proposed by Fischman (1989) and Oldendorf (1992), which states that the rate at which a psychoactive substance binds to neurotransmitter receptor sites affects its addictive liability. In Smith et al. (2016b), there was some evidence of sex effects with respect to people's temporal response profiles, with males being more likely to be classified as early peak responders (individuals who experience the maximal subjective effects of dAMPH within 60 minutes of oral intake) and females being more likely to be classified as nonresponders (individuals who experience no significant difference in their subjective experience to dAMPH relative to placebo). There were also many "late peak responders" in the dataset (individuals who experience the maximal subjective effects of dAMPH at least 60 minutes after intake) (Smith et al., 2016b). These sex effects were observed in one dataset studied by Smith et al. (2016b) but

not another, larger dataset that the authors also investigated. Thus, sex differences in dAMPH responsivity remains an open question and more research will need to be conducted to discern if sex differences in subjective responses to dAMPH exist. Despite this, it is worth noting that sex differences have been found with regard to substance use disorders more generally: recent findings suggest that females have more severe consequences (e.g., medical, psychiatric) resulting from substance use disorders and experience drug-related illness at lower levels of exposure to psychostimulants (McHugh et al., 2017; Nolen-Hoeksema, 2004). This study analyzed sex effects to see if there is variation in affective response to dAMPH that may be sex-specific.

We hypothesized that high ratings of PA in response to dAMPH will be related to high ratings of DEQ Liking and Wanting after dAMPH administration. PA describes the degree to which a person experiences engagement with their environment and Liking describes the degree to which a person experiences pleasurable internal states, making it possible that subjects experiencing high PA (i.e., high alertness, interest, etc.) due to the effects of psychostimulants (e.g., pleasure, euphoria) may report higher Liking because they enjoy the positive affective states caused by the drug, as well as higher Wanting due to a desire to continue feeling these positive affective states. We also hypothesized that high NA ratings in response to dAMPH will be related to increased ratings of DEQ Wanting after dAMPH administration, as it is possible that dAMPH-induced DA release decreases participants' negative feelings and causes them to experience increased Wanting of dAMPH due to this relief from negative feelings. It is worth noting that there is less past research examining the second hypothesis, making it more exploratory in nature. The assessment of these possible relationships is intended to create a more

complete idea of a person's subjective experience of drug intake, which may clarify aspects of drug experience that affect individuals' addictive liability.

Personality and Trait Impulsiveness

Some studies of drug dependence have also been able to relate subjective response to drug with stable personality traits of individuals such as behavioral inhibition and approach, as measured using the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) scale (Carver & White, 1994), and DEQ responses (Weafer & De Wit, 2013). In particular, Weafer and De Wit's 2013 study investigated the role of inattention and impulsive action on subjective amphetamine response, with higher inattention being operationally defined as higher scores on a simple reaction time task (Reeves et al., 2006) and higher impulsive action as higher scores on the stop task (Logan, Schachar, & Tannock, 1997). They found that higher inattention was related to lower ratings of DEQ Like, Feel, and Want More in response to amphetamine while higher impulsive action was related to higher DEQ Want More scores (Weafer & De Wit, 2013). This shows that DEQ responses may differ based on stable personality traits, making it possible that other subjective responses to dAMPH are related to trait inattention and impulsive action. Additionally, Perry et al. (2013), found high NA to be significantly correlated with both BIS/BAS and BIS-11 among substance-dependent individuals, strengthening the idea that personality traits relate to negative affect and may differentiate substance abusers from controls.

In order to to investigate possible relations between affect and personality traits, this study assessed trait-level information about participants, such as behavioral inhibition and activation (using BIS/BAS) (Carver & White, 1994), and trait impulsiveness (using the Barratt Impulsiveness Scale Version 11, or BIS-11) (Barratt, 1965; Patton, Standford, & Barratt, 1995). The effects of sex and age were also investigated.

Based on Weafer and De Wit's (2013) findings that trait inattention is related to a weaker subjective response to amphetamine and Perry et al.'s (2013) finding that NA is significantly correlated with both behavioral inhibition and approach as well as trait impulsiveness, we hypothesized that high ratings of BIS-11 attentional impulsiveness would be related to low PA and low ratings of DEQ Liking and Wanting in response to dAMPH. Additionally, Weafer and De Wit (2013) found that high impulsive action was related to high sensitivity to the positive subjective effects of a drug reward (measured using the Profile of Mood States, or POMS), suggesting that high ratings of BIS-11 motor impulsiveness as well as high ratings of BIS/BAS behavioral activation will be related to high PA and DEQ ratings in this study. The investigation of these hypotheses was intended to clarify whether individual differences in stable personality traits are related to affective response to dAMPH, which would provide a broader view of the factors affecting people's experience of the drug.

Aims and Hypotheses

By using secondary data analysis in two datasets to investigate affective response to oral dAMPH, we assessed how affective response is related to factors associated with the addictive liability of dopaminergic drugs. This investigation built off of previous research by using evidence from studies examining factors demonstrated to be related to drug use, including various psychological constructs (subjective drug response and stable personality traits) and PET measures of DA signaling, to draw inferences about the possible role of affect in differences in personality, DA signaling, and subjective drug response that may associate with addiction risk.

We hypothesized that high DA release in mesocorticolimbic regions during dAMPH intake will be related to high general affective ratings in response to dAMPH, as these regions are heavily involved in interpreting value and reward (Baliki et al., 2013), which may involve the

integration of affective information about rewarding or aversive stimuli. We also hypothesized that high PA in response to dAMPH intake will be strongly related to high ratings of subjective Liking and Wanting of dAMPH, and that high ratings of NA will be related to high ratings of Wanting. Finally, we hypothesized that high ratings of trait attentional impulsiveness will be related to low PA and low DEQ ratings in response to dAMPH, and that high motor impulsiveness and general behavioral activation will be related to high PA and high DEQ ratings. We studied these relationships by performing iterative secondary data analyses on two datasets from the Affective Neuroscience Laboratory at Vanderbilt University.

Methods

Participants

All participants studied were healthy adults from the Nashville area. All possessed an estimated intelligence quotient greater than 80, and were capable of giving informed consent. Exclusion criteria included a history of substance abuse; current tobacco use; alcohol intake greater than the equivalent of 8 ounces of whiskey per week; psychotropic medication use for the past 6 months (other than the use of benzodiazepines as a sleeping aid); a history of major psychiatric illness or neurological problems; a history of head trauma; any condition which risks interfering with MRI or PET studies (e.g., metal implants, obesity, claustrophobia); pregnancy, lactation, or attempting to become pregnant during the time of the study; anemia; any condition preventing the participant from fasting for 6 hours (e.g., diabetes, hypoglycemia); recent participation in a study involving radiation or regular exposure to radiation through one's occupation; and extreme hypertension or an abnormal EKG which might put a participant at risk during amphetamine administration.

In Dataset 1, men and women aged 18-25 participated in the study. 44 participants were included in the analyses, for which there were slightly more female than male participants (21 male, 23 female). The mean age of participants in Dataset 1 was 22.12 years, with a standard deviation of 3.21 years.

In Dataset 2, men and women aged 20-30 (hereafter "young adults") and 50-65 (hereafter "middle-aged adults") participated in the study. Overall, 46 participants from Dataset 2 were included in the analyses, with slightly more males than females (24 male, 22 female). Among the young adults, 22 participants were included in the analyses, for which there were slightly more male than female participants (12 male, 10 female). The mean age of the young adults was 25.91 years, with a standard deviation of 2.60 years. Among the middle-aged adults, 24 participants were included in the analyses, for which there was an equal number of males and females. The mean age of the middle-aged adults was 55.79 years, with a standard deviation of 3.81 years.

Personality Assessment

In both datasets, subjects completed the following personality inventories: Barratt Impulsivity Scale-11 (BIS-11) (Patton, Stanford, & Barratt, 1995), the the Behavioral Inhibition System/Behavioral Activation System scale (BIS/BAS) (Carver & White, 1994), the Novelty-Seeking subtest of the Tridimensional Personality Questionnaire (TPQ-NS) (Cloninger, 1987), and the Revised NEO Personality Inventory (NEO-PRI; only the neuroticism, extraversion, and conscientiousness subscales were assessed in Dataset 2) (Costa & McCrae, 1992). These items took approximately 60-70 minutes to complete and were completed either in the Affective Neuroscience Laboratory or at the Vanderbilt University Medical Center (VUMC).

Fallypride PET Procedure

Participants completed two fallypride PET sessions, each of which began in the afternoon. Participants in Dataset 1, who were blind to drug administration order, received placebo for their first PET session and a target dose of 0.43 mg/kg oral dAMPH. The amount administered to each participant was rounded to the nearest 2.5 mg in order to achieve the target dose. In Dataset 2, 24 participants received oral placebo and 22 participants received a 0.43 mg/kg target dose of dAMPH during their first PET session prior to entering the scanner according to a double-blind, randomized administration order paradigm. Dataset 2 participants then received the opposite condition during their second PET session.

Participants were instructed not to eat for three hours prior to PET sessions in order to standardize drug absorption among subjects. Female participants were also tested for pregnancy before each PET session. Dots were placed on each subject's forehead and cheeks for periodic visual checks of alignment throughout the scan period, and for repositioning after breaks. Participants received a slow bolus injection of 5 mCi of [^{18}F] fallypride 3 hours after placebo or dAMPH administration, after which participants underwent fallypride scans which took place over 3 dynamic image acquisition periods (separated by breaks for participant comfort) that lasted approximately 3.5 hours.

PANAS-X Affect Assessment

A baseline PANAS-X rating was obtained prior to drug administration. PANAS-X ratings were then obtained at specific times post-drug which continued during the 2 breaks between fallypride PET acquisitions. The PANAS-X affective assessment was completed on a laptop computer. This 39-item scale was created using the PANAS (Watson, Clark, & Tellegen, 1988) with added elements of a labeled magnitude scale (Lishner, Cooter, & Zald, 2008) in order to have a more thorough assessment of participant affect. This scale evaluated to what degree

participants experienced various emotional states (such as drowsiness, fear, and alertness) on a visual analog scale ranging from 0 (not feeling the affective state described at all) to 100 (feeling the affective state to the greatest degree imaginable) (Crawford & Henry, 2004). Summary scores of Positive Affect (PA) and Negative Affect (NA) were calculated from the ratings of individual emotional states (Watson & Clark, 1999). Each PANAS-X rating after placebo was subtracted from the dAMPH rating taken at that same timepoint, and PANAS-X values were analyzed as ratings reflecting participants' responses to dAMPH relative to placebo (hereafter ΔPANAS-X). The means of the final two ΔPANAS-X rating timepoints (270 and 345 minutes post-drug for Dataset 1, 255 and 320 minutes post-drug for Dataset 2) for PA and NA were used in analyses due to subjects' presumably becoming familiar with the effects of the drug (after having the opportunity to experience its effects for the first time) and thus able to provide a more composed assessment of their affective state. Tables 1 and 2 provide detailed PANAS-X recording times for Datasets 1 and 2, respectively; note that cells marked "0" under the PANAS-X Recorded column denote the collection of data prior to placebo or dAMPH administration (pre-drug).

Drug Effects Questionnaire (DEQ)

At predetermined times during each PET session, participants used a laptop computer to complete the DEQ. For this measure, participants rated to what degree they: felt any effects of the substance they were administered (FEEL); felt high (HIGH); liked the effects of the substance (LIKE); disliked the effects of the substance (DISLIKE); and wanted more of the substance (WANT MORE) (Morean et al., 2013). In Dataset 1, the LIKE and DISLIKE scores were combined to create a single LIKE score measuring both constructs. Each subscale was rated using a visual analog scale ranging from 0 (not at all) to 100 (most imaginable). Similarly to the

PANAS-X, each response after placebo administration was subtracted from the dAMPH rating taken at the same timepoint, and the DEQ subscales were analyzed as ratings reflecting participants' responses to dAMPH relative to placebo. The means of the final two ΔDEQ measures were used in analyses due to subjects' presumably becoming familiar with the effects of the drug (after having the opportunity to experience its effects for the first time) and thus able to provide a more composed assessment of their subjective response to dAMPH. Tables 1 and 2 provide detailed DEQ recording times for Datasets 1 and 2, respectively.

Fallypride PET data acquisition

[^{18}F] fallypride was produced in the radiochemistry laboratory attached to the PET unit at VUMC. Synthesis and quality control procedures for [^{18}F] fallypride are described in U.S. FDA IND 47,245. Dataset 1 participants were scanned in one of two GE Discovery PET scanners at VUMC: a Discovery LS model or a Discovery STE system. Though the Discovery STE system allows for slightly thinner axial slices to be read, both scanners have similar in-plane resolutions and no differences in BPnd measures were observed between the scanners (Buckholtz et al., 2010; Smith et al., 2016a). All Dataset 2 participants were scanned on the Discovery STE system. Each subject underwent both their placebo and dAMPH scan on the same scanner system. Approximately 3 hours after being administered either placebo or dAMPH, participants received an injection of [^{18}F] fallypride and underwent PET scanning. Participants were scanned for approximately 3.5 hours during each PET session to collect estimates of both striatal and extrastriatal binding potential (specific scan times can be found in Smith et al., 2018). Participants were given two breaks during the course of scanning for their comfort at 270 and 345 minutes in Dataset 1 and at 255 and 320 minutes in Dataset 2. DEQ and PANAS-X ratings were assessed during these two breaks.

Fallypride PET data processing

Details on fallypride PET BPnd estimation procedures can be found in Smith et al. (2016a). Briefly, decay correction was performed using PMOD software (PMOD Technologies, Zurich Switzerland) and motion correction of PET scan frames was performed using SPM8 (Friston et al., 1994). Mean PET images for each subject were then created using the realigned image frames. These images were registered to each subject's T1 MRI image, which was nonlinearly registered to MNI space in FSL (Smith et al., 2004). The WFU Pickatlas (Maldjian et al., 2003) was then used to create the putamen and cerebellum reference region ROIs (regions of interest) such that contamination of signaling from nearby areas (such as the midbrain and occipital cortex) was minimized. FSL was used to warp these reference region ROIs back to each subject's PET space, which were then used in a simplified reference tissue model (or SRTM) (Lammertsma & Hume, 1996) in PMOD to estimate fallypride binding potential (BPnd), which is a ratio of bound fallypride to its free concentration, for both placebo and dAMPH PET sessions. BPnd was estimated voxel-wise in PMOD's PXMOD tool using a basis function fitting approach published by Gunn et al. (1997), with the cerebellum acting as a reference region due to its comparatively low quantity of D2/D3 receptors (Camps et al., 1989). Binding potential change between the placebo and dAMPH BPnd maps was calculated as %ΔBPnd = ([placebo BPnd – dAMPH BPnd]/placebo BPnd) x 100%. Placebo BPnd, dAMPH BPnd, and %ΔBPnd maps were then warped to MNI space using the same FSL transforms to create MNI-normalized images, which were then analyzed at a voxel-wise level in SPM8.

Data analysis

The key dependent measure in our analyses is affective response to dAMPH. We are interested in investigating how affective response to dAMPH relates to subjective ratings of

dAMPH as well as the relationship between affect and DA signaling as measured with fallypride PET. To work towards this, we used Dataset 1 as a discovery dataset to perform exploratory analyses and Dataset 2 as a test dataset to test specific predictions made based on findings in the first dataset. We tested for correlations between ΔPANAS-X PA/NA, personality, and ΔDEQ in SPSS; this was performed using Spearman's Rho, as the data for many of the variables included were not normally distributed. We also tested for relationships between ΔPANAS-X PA/NA and %ΔBPnd in mesocorticolimbic brain regions using SPM8. Independent samples t-tests were also performed for ΔPANAS-X PA and NA using sex (in both datasets), age group (in Dataset 2 only), and drug order (in Dataset 2 only) as grouping variables to understand how affective response may differ as a function of these categorical variables. The results of these tests were used to identify factors that are strongly related to ΔPANAS-X PA/NA and to determine which factors to include in follow-up multiple regression analyses (which were performed in SPSS). Factors which correlated significantly with ΔPANAS-X PA or NA after multiple comparisons correction were included in regression analyses as predictor variables in order to analyze to what degree ΔPANAS-X PA and NA are predicted by factors previously demonstrated to be related to drug response. For our analyses in these datasets, we considered any correlational relationship at $p < .05$ after performing multiple comparisons correction to be significant. The number of comparisons performed are detailed in the following section.

Results

Subjective Response to Drug

A total of 8 comparisons were made between affect and subjective response to drug in Dataset 1, as can be seen in Table 3.5. Significant positive correlations between ΔPANAS-X NA and ΔDEQ FEEL, LIKE, HIGH, and WANT MORE were found at $p < .05/8$ (using the

Bonferroni method). Scatterplots of these relationships (Figures 1-4) show the existence of some outliers which may contribute to these correlations, but they also show convincing positive relationships between ΔPANAS-X NA and ΔDEQ.

These results were not replicated in Dataset 2, as can be seen in Table 4.5. No significant relationships between ΔPANAS-X and ΔDEQ were found at $p < .05/10$. Note that in Dataset 2, DEQ LIKE and DISLIKE exist as separate measures, and were analyzed separately both in the correlations and in subsequent regression analyses.

Dopamine Receptor Availability

After correcting for familywise error rate (FWER), no significant correlations between ΔPANAS-X PA and NA and D2/D3 receptor availability were found at $p < .05$ in in mesocorticolimbic regions of the brain in either dataset. This runs counter to our hypothesis that high D2/D3 receptor availability in mesocorticolimbic regions during dAMPH intake will be related to high general affective ratings in response to dAMPH.

Personality and Trait Impulsiveness

No significant correlations between ΔPANAS-X PA and NA and stable personality traits were found at $p < .05$ after Bonferroni correction (.05/20 for BIS-11, .05/8 for BIS/BAS, .05/1 for TPQ-NS, .05/5 for NEO in Dataset 1, and .05/3 for NEO in Dataset 2) in either dataset, as can be seen in Tables 3.1-3.4 and 4.1-4.4. This runs counter to our hypotheses that high ratings of trait attentional impulsiveness will be related to low PA and low DEQ ratings in response to dAMPH, and that high motor impulsiveness and general behavioral activation will be related to high PA and high DEQ ratings.

Age and Sex

ΔPANAS-X PA and NA did not differ significantly as a function of sex or age group (which was assessed in Dataset 2 only), as can be seen in Tables 5-7. These variables were primarily analyzed because of their relationship with D2/D3 receptor availability (Kaasinen et al., 2000; Munro et al., 2006), and thus the lack of a relationship between ΔPANAS-X and D2/D3 receptor availability makes these results expected.

Drug Order

ΔPANAS-X PA and NA also did not differ significantly as a function of drug order (which was a factor in Dataset 2 only), as can be seen in Table 8. This indicates that this factor did not have a significant influence on affective response in Dataset 2, allowing us to have more confidence in our ability to compare the two datasets.

Multiple Regression Analyses

After obtaining the results of the correlational analyses and t-tests, multiple regression models were used to analyze whether DEQ ratings are predictive of ΔPANAS-X NA. This was done to examine whether DEQ ratings are predictive of ΔPANAS-X NA while controlling for stable personality traits, which may meaningfully influence people's subjective response to dAMPH in a way that explains its apparent relationship with ΔPANAS-X NA.

Significant relationships with ΔPANAS-X NA were found for ΔDEQ FEEL, LIKE, HIGH, and WANT MORE in Dataset 1, and so these variables were included in the multiple regression analyses for both datasets as predictors of ΔPANAS-X NA. Stable personality traits and D2/D3 receptor availability did not show any significant relationships with ΔPANAS-X, and so were not included as predictor variables. Given that BIS-11 Cognitive Instability, BIS-11 Attentional Impulsiveness, and BAS Drive showed statistically significant negative relationships with ΔPANAS-X NA before Bonferroni correction (and may influence the results of the

regression models), we controlled for these variables in our multiple regression models. Sex, age group, and drug order were not included in the models, as ΔPANAS-X NA did not differ significantly as a function of these categorical variables.

ΔDEQ FEEL, LIKE, HIGH, and WANT MORE were used as predictor variables of ΔPANAS-X NA in a stepwise regression model after controlling for the effects of BIS-11 Cognitive Instability, BIS-11 Attentional Impulsiveness, and BAS Drive. In Dataset 1, ΔDEQ LIKE, HIGH, and WANT MORE were found to not be significant predictors of the regression model and were excluded during analyses (see Table 9). After accounting for controlled variables, we found that ΔDEQ FEEL predicted .121 of the variance in the regression model (R = .489, F change = 6.052, p = .019). These results indicate that, after controlling for the aforementioned personality traits, ΔDEQ FEEL is a strong predictor of ΔPANAS-X NA during dAMPH intake in Dataset 1. The positive relationship between these variables suggests that feeling the effects of dAMPH more strongly may be associated with subjects experiencing a greater degree of distress, which could be due to a variety of reasons.

These results were not replicated in Dataset 2. The stepwise regression model in Dataset 2 used the same predictors and controlled variables as Dataset 1 (save for ΔDEQ LIKE, which is divided into ΔDEQ LIKE and DISLIKE in Dataset 2) and found that ΔDEQ DISLIKE predicted .237 of the variance in the regression model (R = .579, F change = 14.613, p < .001). ΔDEQ FEEL, LIKE, HIGH, and WANT MORE were found to not be significant predictors of the regression model and were excluded (see Table 11). These results indicate that, after controlling for stable personality traits, ΔDEQ DISLIKE is a strong predictor of ΔPANAS-X NA during dAMPH intake in Dataset 2. The positive relationship between these variables suggests that

subjects experiencing greater dislike for the effects of dAMPH may experience more distress at their current situation.

It is difficult to determine why this lack of replication across datasets is observed. One possible reason for it may that DEQ LIKE and DISLIKE exist as separate measures in Dataset 2 and as a single combined measure in Dataset 1, yet it is unlikely that this adequately explains the differences seen between the multiple regression models.

Discussion

Subjective Response to Drug

No significant positive relationships were found between ΔPANAS-X PA and ΔDEQ LIKE or WANT MORE in Dataset 1, which runs counter to our hypothesis predicting these relationships. Similarly, no significant positive relationship was found between ΔPANAS-X NA and ΔDEQ WANT MORE in Dataset 1, which runs counter to our hypothesis predicting this relationship. While significant positive correlations between ΔPANAS-X NA and ΔDEQ FEEL, LIKE, HIGH, and WANT MORE were found in Dataset 1, all but ΔDEQ FEEL were excluded as predictors of ΔPANAS-X NA in the stepwise regression model, indicating that their ability to predict ΔPANAS-X NA was not significant when ΔDEQ FEEL was also included as a predictor. The significant positive relationship between ΔPANAS-X NA and ΔDEQ FEEL suggests that people who feel the effects of dAMPH more intensely may experience greater negative affect (such as distress or fear). This may occur for a variety of reasons, such as a socially learned aversion to drug use, yet further research would be necessary to adequately investigate what this relationship might mean.

Similar to Dataset 1, the results of the correlation and multiple regression analyses in Dataset 2 did not support the relationships we predicted between ΔPANAS-X and ΔDEQ. No

significant correlations were found between ΔPANAS-X and ΔDEQ in Dataset 2, yet the subsequent stepwise regression model showed that ΔDEQ DISLIKE is a highly significant predictor of ΔPANAS-X NA after dAMPH intake. The significant positive relationship between ΔPANAS-X NA and ΔDEQ DISLIKE suggests that negative affect in response to dAMPH intake may be associated with a subjective dislike of the effects of the drug (which might produce unpleasant restlessness in some people). Further research is needed to clarify how these factors are related.

The relationships between ΔPANAS-X and ΔDEQ observed in each dataset were not replicated across datasets, which limits our ability to draw definitive conclusions concerning these relationships. This is likely (at least in part) due to the lack of a sufficient sample size to replicate the relationships observed in each dataset, as assessed using G*Power (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007). It is difficult to interpret what this lack of replication might mean, as the two datasets are similar in terms of the measures and protocols used and ΔPANAS-X NA did not significantly differ as a function of age group or drug order in Dataset 2. It is possible that the results obtained are due simply to random effects of sampling. Additional studies would be necessary to adequately investigate the possible reasons behind these results.

Dopamine Receptor Availability

No significant relationships were found between ΔPANAS-X PA and NA and D2/D3 receptor availability in either dataset, counter to our hypothesis that high DA release in mesocorticolimbic regions during dAMPH intake is related to high affective ratings in response to dAMPH. The lack of significant relationships between ΔPANAS-X PA and NA and D2/D3 receptor availability shows that people's affective experience of drug intake is not related to DA

release in the context of dAMPH intake. As a result, there is not enough evidence from these results to suggest that D2/D3 receptor availability is predictive of people's affective response to dAMPH. This suggests that people's affective response to psychostimulants may not be based on D2/D3 receptor availability, though our approach of modelling people's affective responses to dAMPH by analyzing timepoints during which subjects were inside of the PET scanner limits our ability to draw conclusions from these results, as the [^{18}F] fallypride radiotracer labels brain areas more according to D2/D3 receptor internalizing that occurred a few hours prior to the PET scans. As such, future studies examining relationships between affect and D2/D3 receptor availability would benefit from modelling affective response to psychostimulants based on earlier affective ratings (such as those recorded soon after psychostimulant intake) or a wider temporal range of ratings.

Personality and Trait Impulsiveness

No significant relationships were found between ΔPANAS-X PA and NA and stable personality traits in either dataset, counter to our hypotheses that high attentional impulsiveness is related to low PA and that high motor impulsiveness is related to high PA. Non-significant negative correlations were observed between ΔPANAS-X NA and BIS-11 Cognitive Instability, BIS-11 Attentional Impulsiveness, and BAS Drive in Dataset 1, which suggest that there may be meaningful relationships between these stable personality traits and negative affect during dAMPH intake (for example, high ratings on these personality traits may indicate personalities which are disposed towards experiencing less negative affect). Further research is necessary to investigate these questions more intensively.

Similarly, a non-significant positive correlation was found between ΔPANAS-X PA and BAS Reward Responsiveness in Dataset 1, which may meaningfully suggest that people who are

more sensitive to rewards such as those provided by psychostimulants (e.g., heightened energy, increased alertness) will show greater positive affect during dAMPH intake. It is difficult to draw definitive conclusions with the small sample sizes used in this study, however, making further research necessary to investigate this possible relationship.

Limitations and Conclusions

Limitations of the study include the small sample size for both datasets analyzed (44 and 46 for Dataset 1 and Dataset 2, respectively). This is of particular concern due to the exploratory nature of the analyses in this study, which would ideally be performed using a very large sample size so as to minimize the possibility of committing type I errors.

Additionally, this study only analyzed affective and subjective response to dAMPH while subjects were undergoing PET scans, which is a very limited amount of time relative to the length of time that the dAMPH remained in each subject's body. This study's examination of a fairly limited period of time during which subjects would experience the effects of the drug limits our ability to draw conclusions about other timeframes, which is a topic that is worth investigating in future studies. Additionally, the decision to examine these timeframes limited our ability to draw definitive conclusions about the relationship between affect and D2/D3 receptor availability in response to dAMPH.

In sum, the present study extends previous work investigating subjective response to drug in humans by raising the possibility that the degree to which people subjectively feel the effects of psychostimulants may predict the degree of negative affect that they experience in response to the drug. Additionally, the results of this study raise the possibility that negative affect in response to psychostimulant intake may associated with a subjective dislike of the drug's effects. Analyses of people's affective response to psychostimulants such as dAMPH may shed light on

factors that influence people's differential response to psychostimulants, which may in turn lead to greater understanding of factors that put people at greater risk of developing substance use disorders.

Table 1

Dataset 1 PANAS-X and DEQ Response Recording Times

Time post-drug (minutes)	PANAS-X timepoint recorded	DEQ timepoint recorded
0 (pre-drug)	0	-
60	1	1
120	2	2
180	3	3
270*	4	4
345*	5	5

* PANAS-X and DEQ data were collected while participants were inside the PET scanner for fallypride binding potential data collection.

Table 2

Dataset 2 PANAS-X and DEQ Response Recording Times

Time post-drug (minutes)	PANAS-X timepoint recorded	DEQ timepoint recorded
0 (pre-drug)	0	-
35	1	1
65	2	2
75	-	3
95	3	4
125	4	5
170	5	6
255*	6	7
320*	7	8

* PANAS-X and DEQ data were collected while participants were inside the PET scanner for fallypride binding potential data collection.

Table 3.1

Dataset 1 ΔPANAS-X/BIS-11 Spearman Correlations

	Attention	Motor	Self-Control	Cogn Complexity	Perseverance	Cogn Instability	Attentional Impulsiveness	Motor Impulsiveness	NonPlanning Impulsiveness	Total
ΔPANAS-X PA	-0.039	0.078	-0.096	-0.013	0.040	-0.046	-0.063	0.083	-0.091	0.011
ΔPANAS-X NA	-0.207	-0.021	0.022	-0.019	-0.107	-.364*	-.317*	-0.084	0.016	-0.148

Table 3.2

Dataset 1 ΔPANAS-X/BIS-BAS Spearman Correlations

	BAS Drive	BAS Fun Seeking	BAS Reward Responsiveness	BIS
ΔPANAS-X PA	0.133	0.192	.321*	0.252
ΔPANAS-X NA	-.303*	-0.218	-0.254	-0.025

Table 3.3
Dataset 1 ΔPANAS-X/TPQ Novelty-Seeking Spearman Correlations

	TPQ-NS Total
ΔPANAS-X PA	-0.045
ΔPANAS-X NA	-0.066

Table 3.4
Dataset 1 ΔPANAS-X/NEO Spearman Correlations

	N	E	O	A	C
ΔPANAS-X PA	-0.139	0.139	-0.074	-0.047	-0.111
ΔPANAS-X NA	-0.232	0.001	-0.026	0.131	-0.007

Table 3.5
Dataset 1 ΔPANAS-X/ΔDEQ Spearman Correlations

	Feel	Like	High	Want More
ΔPANAS-X PA	.195	.269	.164	.089
ΔPANAS-X NA	.507**	.396**	.493**	.449**

Note. Summary measures of the personality traits being measured are presented here.

* Results were significant at $p < .05$
** Results were significant at $p < .05$ after Bonferroni correction

Table 4.1
Dataset 2 ΔPANAS-X/BIS-11 Spearman Correlations

	Attention	Motor	Self-Control	Cogn Complexity	Perseverance	Cogn Instability	Attentional Impulsiveness	Motor Impulsiveness	NonPlanning Impulsiveness	Total
ΔPANAS-X PA	-0.003	0.193	0.082	-0.223	0.003	-0.194	0.167	-0.120	0.030	-0.022
ΔPANAS-X NA	-0.197	-0.149	-0.208	0.082	-0.044	-0.013	-0.069	-0.215	-0.129	-0.123

Table 4.2
Dataset 2 ΔPANAS-X/BIS-BAS Spearman Correlations

	BASDrive	BASFunSeeking	BASRewardResponsiveness	BIS
ΔPANAS-X PA	0.078	-0.116	0.067	0.046
ΔPANAS-X NA	0.086	0.055	0.203	0.271

Table 4.3
Dataset 2 ΔPANAS-X/TPQ Novelty-Seeking Spearman Correlations

	TPQ-NS Total
ΔPANAS-X PA	0.008
ΔPANAS-X NA	-0.052

Table 4.4
Dataset 2 ΔPANAS-X/NEO Spearman Correlations

	N	E	C
ΔPANAS-X PA	0.221	0.059	-0.038
ΔPANAS-X NA	-0.256	0.101	0.250

Note. Only the Neuroticism, Extraversion, and Conscientiousness subscales were assessed in Dataset 2.

Table 4.5
Dataset 2 ΔPANAS-X/ΔDEQ Spearman Correlations

	Feel	High	Dislike	Like	Want More
ΔPANAS-X PA	0.248	.307*	0.028	0.248	0.073
ΔPANAS-X NA	0.192	0.156	.342*	-0.068	-0.043

Note. Summary measures of the personality traits being measured are presented here.

* Results were significant at $p < .05$
** Results were significant at $p < .05$ after Bonferroni correction

Table 5
Dataset 1 Independent Samples T Test by Sex

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
ΔPANAS-X PA	Equal variances assumed	0.122	0.729	0.661	42	0.512	########	########	########	########
	Equal variances not assumed			0.666	41.814	0.509	########	########	########	########
ΔPANAS-X NA	Equal variances assumed	2.732	0.106	0.773	42	0.444	1.2418478	1.6056504	########	4.4821815
	Equal variances not assumed			0.796	32.797	0.432	1.2418478	1.5609979	########	4.4184675

Table 6

Dataset 2 Independent Samples T Test by Sex

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
ΔPANAS-X PA	Equal variances assumed	0.001	0.972	-1.406	44	0.167	########	########	########	########
	Equal variances not assumed			-1.401	42.738	0.169	########	########	########	########
ΔPANAS-X NA	Equal variances assumed	0.316	0.577	0.923	44	0.361	2.6377841	2.8564818	########	8.3946449
	Equal variances not assumed			0.923	43.465	0.361	2.6377841	2.8592671	########	8.4022607

Table 7

Dataset 2 Independent Samples T Test by Age Group

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
ΔPANAS-X PA	Equal variances assumed	1.255	0.269	1.173	44	0.247	########	########	########	########
	Equal variances not assumed			1.158	38.567	0.254	########	########	########	########
ΔPANAS-X NA	Equal variances assumed	0.937	0.338	-1.311	44	0.197	########	2.8292620	########	1.9915390
	Equal variances not assumed			-1.304	42.067	0.199	########	2.8451749	########	2.0310594

Table 8

Dataset 2 Independent Samples T Test by Drug Order

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
ΔPANAS-X PA	Equal variances assumed	0.026	0.874	1.469	44	0.149	########	########	########	########
	Equal variances not assumed			1.469	43.710	0.149	########	########	########	########
ΔPANAS-X NA	Equal variances assumed	0.039	0.844	0.101	44	0.920	0.2916667	2.8836936	########	6.1033693
	Equal variances not assumed			0.101	43.175	0.920	0.2916667	2.8900333	########	6.1192925

Table 9

Dataset 1 Stepwise Regression Model Summary

					Change Statistics				
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	R Square Change	F Change	df1	df2	Sig. F Change
1	.343[a]	0.118	0.050	5.1605353	0.118	1.739	3	39	0.175
2	.489[b]	0.239	0.159	4.8556195	0.121	6.052	1	38	0.019

a. Predictors: (Constant), Barratt Attentional Impulsiveness, BASDrive, Barratt Cogn Instability

b. Predictors: (Constant), Barratt Attentional Impulsiveness, BASDrive, Barratt Cogn Instability, DEQ_Feel_Amph_minus_plc_Scanning_Mean

c. Dependent Variable: PANAS_Negative_dAMPH_min_Plc_Scanning_Mean

Table 10

Dataset 1 Stepwise Regression Model ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	138.906	3	46.302	1.739	.175[b]
	Residual	1038.614	39	26.631		
	Total	1177.520	42			
2	Regression	281.593	4	70.398	2.986	.031[c]
	Residual	895.928	38	23.577		
	Total	1177.520	42			

a. Dependent Variable: PANAS_Negative_dAMPH_min_Plc_Scanning_Mean

b. Predictors: (Constant), Barratt Attentional Impulsiveness, BASDrive, Barratt Cogn Instability

c. Predictors: (Constant), Barratt Attentional Impulsiveness, BASDrive, Barratt Cogn Instability, DEQ_Feel_Amph_minus_plc_Scanning_Mean

Table 11

Dataset 2 Stepwise Regression Model Summary

					Change Statistics				
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	R Square Change	F Change	df1	df2	Sig. F Change
1	.313[a]	0.098	0.033	9.4012014	0.098	1.517	3	42	0.224
2	.579[b]	0.335	0.270	8.1699856	0.237	14.613	1	41	0.000

a. Predictors: (Constant),
First-order Factor: Cognitive Instability'=bis6+bis24+bis26,
Behavioral Approach System (BAS) Drive=bisbas3+bisbas9+bisbas12+bisbas21,
Second-order Factor: Attentional'=bis_attn_attn+bis_attn_cognitive_instability

b. Predictors: (Constant),
First-order Factor: Cognitive Instability'=bis6+bis24+bis26,
Behavioral Approach System (BAS) Drive=bisbas3+bisbas9+bisbas12+bisbas21,
Second-order Factor: Attentional'=bis_attn_attn+bis_attn_cognitive_instability, DEQ_Dislike_Amph_minus_plc_Scanning_Mean

c. Dependent Variable: Negative_dAMPH_min_PLC_Scan_Mean

Table 12
Dataset 2 Stepwise Regression Model ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	402.236	3	134.079	1.517	.224[b]
	Residual	3712.069	42	88.383		
	Total	4114.305	45			
2	Regression	1377.609	4	344.402	5.160	.002[c]
	Residual	2736.695	41	66.749		
	Total	4114.305	45			

a. Dependent Variable: Negative_dAMPH_min_PLC_Scan_Mean

b. Predictors: (Constant),
First-order Factor: Cognitive Instability'=bis6+bis24+bis26,
Behavioral Approach System (BAS) Drive=bisbas3+bisbas9+bisbas12+bisbas21,
Second-order Factor: Attentional'=bis_attn_attn+bis_attn_cognitive_instability
c. Predictors: (Constant),
First-order Factor: Cognitive Instability'=bis6+bis24+bis26,
Behavioral Approach System (BAS) Drive=bisbas3+bisbas9+bisbas12+bisbas21,
Second-order Factor: Attentional'=bis_attn_attn+bis_attn_cognitive_instability,
DEQ_Dislike_Amph_minus_plc_Scanning_Mean

Figure 1
Dataset 1 ΔPANAS-X NA/ΔDEQ FEEL Scatterplot

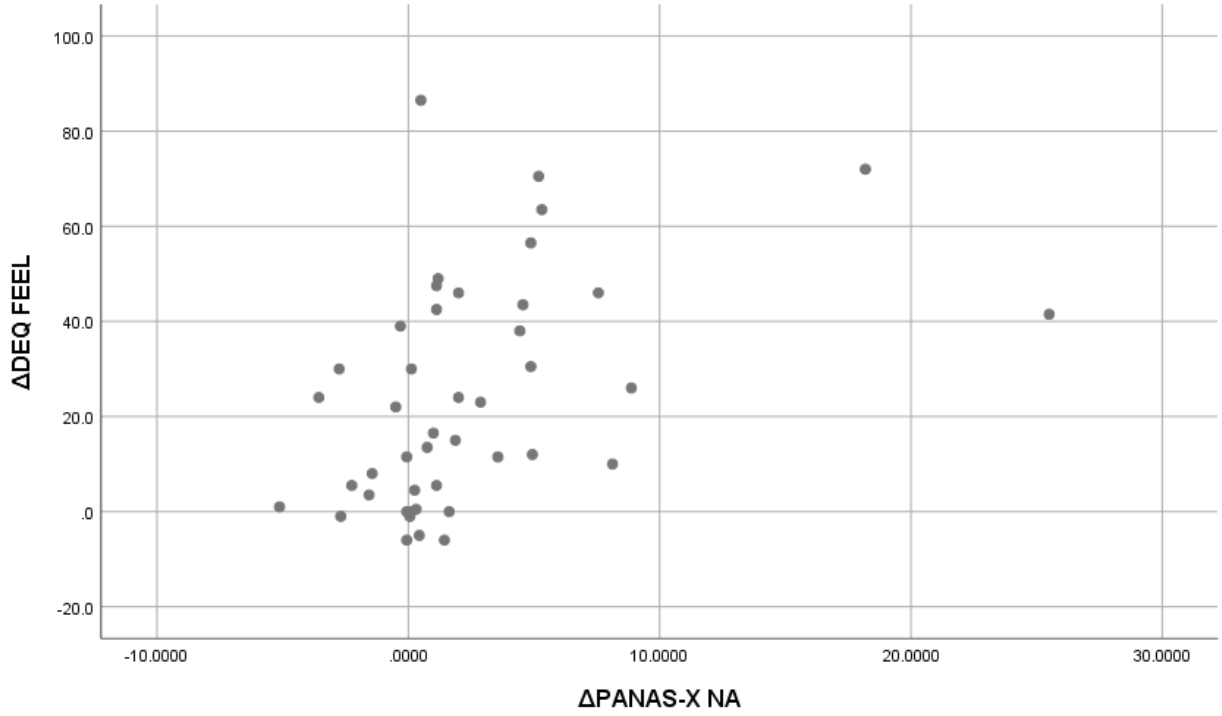


Figure 2
Dataset 1 ΔPANAS-X NA/ΔDEQ LIKE Scatterplot

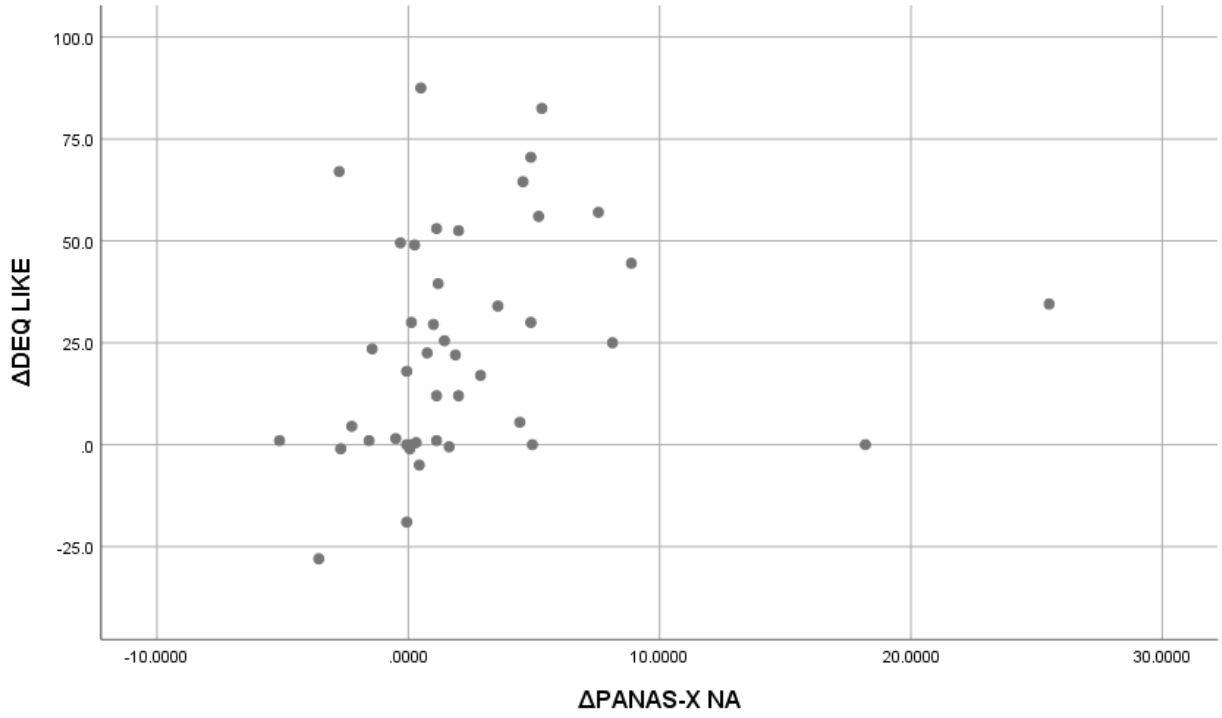


Figure 3
Dataset 1 ΔPANAS-X NA/ΔDEQ HIGH Scatterplot

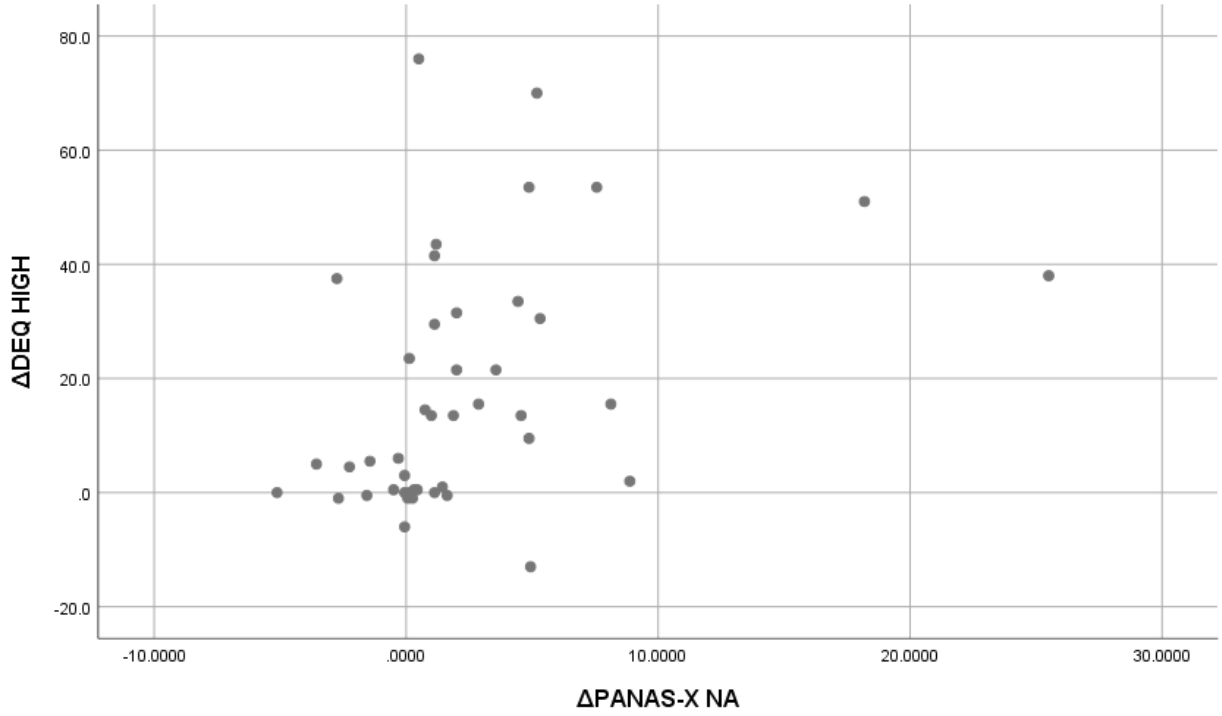
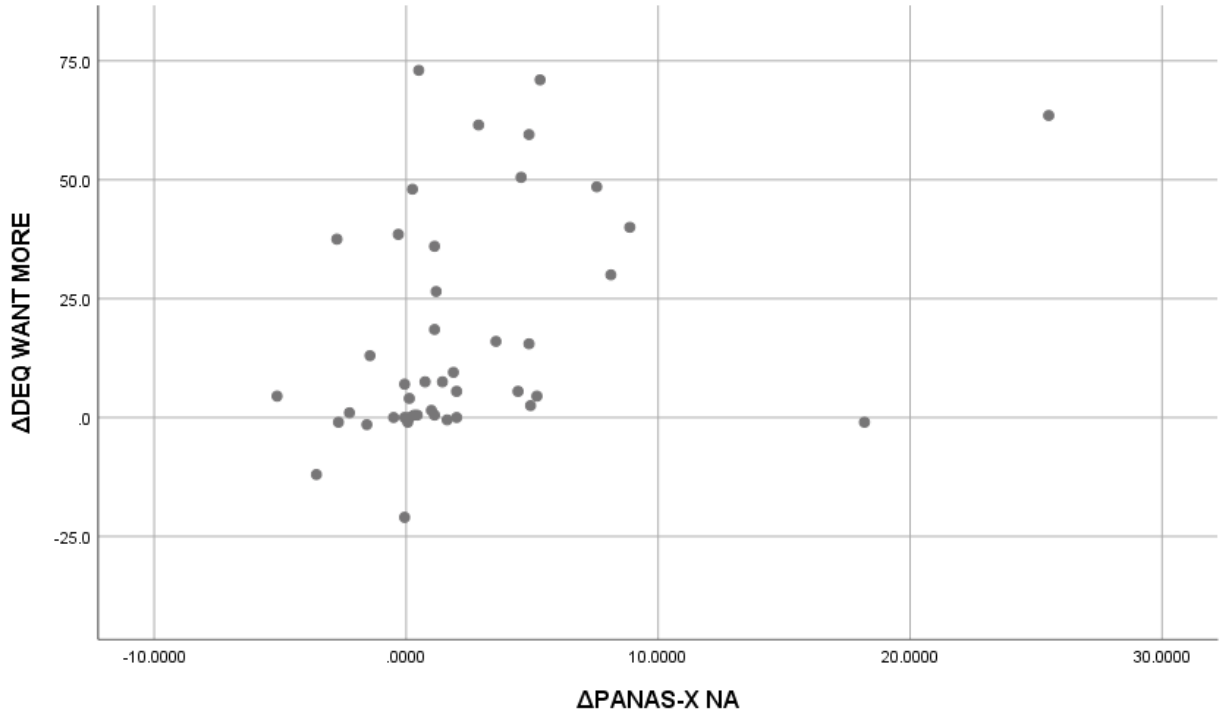


Figure 4
Dataset 1 ΔPANAS-X NA/ΔDEQ WANT MORE Scatterplot



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