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# The relationship between the subjective, behavioral, and physiological responses to methamphetamine administration in humans

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**Abstract**

It is important to investigate the factors contributing to continued use of methamphetamines (METH) considering the recent rise in psychostimulant deaths in the United States and health risks. While previous research has characterized specific responses to METH, such as increases in blood pressure and elevated mood, the current study aims to implement a multi-dimensional approach assessing behavioral reward related task responses, subjective questionnaire responses, and physiological blood pressure reads to understand the neurochemical basis of METH administration (20mg) in 51 healthy men and women between the ages of 18 and 35. We examined correlations comparing these three measures predicting the drug responses to be related to distinct underlying processes, dopaminergic and noradrenergic respectively. We found upon METH administration, participants experienced positive subjective responses, increased cardiovascular activity, and alterations in cognitive processes inducing a greater willingness to exert effort for reward. Our hypothesis was partially supported with marginally positive associations between subjective ratings and task-related responses. There were inconsistencies in the relationship between subjective ratings and blood pressure reads, with one questionnaire (Drug Effects Questionnaire), demonstrating a positive association, and another (euphoric measure) failing to demonstrate a relationship. Surprisingly, the behavioral reward-related task and blood pressure reads demonstrated a positive association. Based on these results, we conclude that the underlying processes associated with METH responses in drug taking behavior are not dissociable.

## The relationship between the subjective, behavioral, and psychological responses to methamphetamine administration in humans

Methamphetamine (METH) is the second-most popular illicit drug worldwide and achieves high concentrations within the brain producing feelings of alertness and wellbeing (Cruickshank & Dyer 2009). Health risks of METH use include, but are not limited to, cardiovascular and renal dysfunction, neurodegeneration, psychosis, and overdose. In the United States, psychostimulant related deaths have increased 5-fold between the years of 2012 and 2018 and continue to rise (Ciccarone & Shoptaw 2022). It is therefore important to investigate the factors contributing to repeated use including the drug responses METH elicits. Given the critical health risks psychostimulants pose for the population, it is vital to understand the neurochemical basis mediating the various behavioral and physiological effects and the extent to which they are related.

Single doses of METH increase measures of cardiovascular and subjective effects (Hart et al., 2008). The drug dose-dependently increases heart rate and produces positive subjective responses. The positive subjective effects are thought to contribute to continued use, but the relationship between subjective effects and excessive drug-taking behavior depends on other factors (Hart et al., 2000). The current research aims to characterize the acute drug response to METH by analyzing subjective, behavioral, and physiological measures to identify the actions of the drug that potentially contribute to drug taking behaviors.

### Molecular components of methamphetamine administration

Neurotransmitters, or chemicals involved in communication between neurons, mediate behavioral and physiological responses to stimulant drugs. METH acts mainly on neurotransmitter receptors of the catecholamines dopamine and norepinephrine. Dopamine, and

associated circuitry, is thought to mediate the positive reinforcing effects of stimulants. This neurotransmitter has been associated with regulating feelings of pleasure and the reward and motivational systems. It has also been linked to cognition and control of movement (SAMHSA 2021). Norepinephrine and associated circuits are recognized for their involvement in the processes of arousal, sleep-wake cycle, and stress and fear related responses through projections in a substantial number of brain regions implicated in wakefulness and reward (Aggarwal & Mortensen 2018, Kaye et al., 2007).

Stimulant drugs, such as METH, are known to modify dopaminergic, noradrenergic, and to a lesser extent, serotoninergic transmission at synapses (Cruickshank & Dyer 2009). The chemical structure of METH gives the substance a lipophilic quality enabling it to penetrate the blood brain barrier. METH acts as a substrate of monoaminergic transporters to promote the release and reverse transport of these neurotransmitters from storage vesicles to increase cytoplasmic concentrations. Additionally, METH inhibits the catalyzing enzymes of these catecholamines preventing uptake and stabilizing the increased levels. The net result of these processes is the increased neurotransmission of dopamine, noradrenaline, and serotonin (Kevil et al., 2019, Yamamoto et al., 2010).

**Physiological, behavioral, and subjective effects of methamphetamine administration**

Through its effects on the dopaminergic system, METH alters many cognitive processes such as memory, attention, task switching, and response inhibition. It is thought the acute METH-induced dopaminergic changes produce locomotor stimulation, sustained attention, feelings of euphoria, and behavioral disinhibition (Comer et al., 1996, Cruickshank & Dyer 2009). Further examination of these behavioral effects could potentially reveal the neurochemical basis of METH mediation.

Through its effects on the noradrenergic system, METH is thought to increase alertness, attention, and energy through alterations on adrenergic agonist receptors (Logan 2002, Tadrous et al., 2021). For example, peripherally, METH increases heart rate and blood pressure through facilitated vasoconstriction and arterial signaling (Kaye et al., 2007, Kevil et al., 2019, Westover & Halm 2012). The peripheral action of METH remains poorly understood, with conflicting reports regarding the relationship between METH-induced effects on noradrenaline and blood flow (Polesskaya et al., 2011). Centrally, METH increases feelings of energy and attention. Further examination of the physiological effects of METH could potentially reveal the basis of adrenergic and arterial mediation. With these known molecular functions in mind, the short-term behavioral and subjective effects of acute METH administration include alertness, euphoria, wakefulness, antifatigue effect, increased confidence, hyperactivity, loss of appetite, and locomotor stimulation through peripheral action and dopaminergic action (Moszczynska & Callan 2017).

**The current research**

As certain physiological effects of METH are thought to be caused by central or peripheral noradrenergic neurotransmission, and subjective and reward-related responses are understood to be caused by dopaminergic neurotransmission, the purpose of this study is to examine the relationships between these measures. Healthy adults (N=51) received either a moderate dose of METH (20mg) or a placebo, and three types of measures were obtained: subjective effect measures, behavioral measures on a reward-related task, and blood pressure measures. By examining correlations between pairs of measures in the three categories, we will test whether the responses are related to the same underlying processes or different processes. Following a single oral dose of METH, we hypothesize the reward-related behavioral effects and

the euphoric-like subjective experiences will positively correlate with each other, but these will not be correlated with the physiological measure of blood pressure. This prediction is based on the understanding that the cardiovascular effects are the result of adrenergic and arterial signaling, and the subjective and behavioral effects are the result of drug-induced enhancement of dopamine signaling.

## Method

### Subjects

Participants included 51 healthy men and women aged 18 and 35 years, with at least a high school education. Inclusion criteria were normal BMI (19 -26), no previous history of mental illness or substance use disorder, habitual consumption of not more than four alcoholic or caffeinated beverages a day, no prescription medications, a normal electrocardiogram (EKG), no history of cardiac disease or high blood pressure, and are not currently pregnant.

### Procedure

Participants attended an orientation session to ensure familiarity with procedures and tasks before commencing the individual study sessions. They provided informed consent, and the study was approved by the local Institutional Review Board. After orientation, participants attended two 4-hour sessions (9 A.M. to 1 P.M.) in which they received METH (20mg) or placebo under double blind conditions. On each session, participants completed urine screenings and completed baseline measures before ingesting a capsule (Table 1). During the remainder of the two sessions participants completed subjective ratings at regular intervals, and their heart rate and blood pressure were measured. At the expected time of peak drug effect, they completed the behavioral task described below. Subjects left the laboratory at 1 P. M.

Table 1.

*Individual timeline for single study session (behavioral-only)*

| **Ideal Time** | **Activity** |
|---|---|
| 9:00 A. M. | Arrival |
| 9:15 A. M. | Time Point 1: Blood Pressure (BP), Drug Effects Questionnaire (DEQ), Addiction Research Center Inventory Scales (ARCI) |
| 9:30 A. M. | Capsule |
| 10:00 A. M. | Time Point 2: BP, DEQ, ARCI |
| 10:20 A. M. | Time Point 3: BP, DEQ, ARCI |
| 10:30 A. M. | Tasks (block 1) – Effort Expenditure for Reward Task (EEfRT) |
| 11:00 A. M. | Tasks (block 2) |
| 11:30 A. M. | Time Point 3: BP, DEQ, ARCI |
| 11:45 A. M. | Tasks (block 3) |
| 12:30 P. M. | Time Point 5: BP, DEQ, ARCI |
| 1:00 P. M. | Time Point 6: BP, DEQ, ARCI, End of Session Questionnaire (ESQ) |

*Note:* Participants' baseline measures and post-capsule administration measures were taken before different task blocks. The current analysis focuses on Task Block 1. BP = blood pressure. DEQ = Drug Effects Questionnaire. ARCI = Addiction Research Center Inventory Scales with the current analysis focusing on the Morphine-Benzedrine scale (MBG) for euphoric measures.

## Measures

### *Behavioral Effects*

The behavioral effects of the drug were measured using the Effort Expenditure for Reward Task (EEfRT), which measures how much physical effort one is willing to expend for a monetary reward (Wardle et al., 2011, Treadway er al., 2009). This task is a multi-trial computer game in which participants are asked to choose between two difficulty levels for a high monetary reward in the high effort task or a low monetary reward in the low effort task. Effort was assessed by comparing their choice of low and high effort responding. The high effort task, or the hard choice, consisted of 100 button presses with the nondominant pinky finger within 21

seconds, and the low effort task, or the easy choice, consisted of 30 button presses with the dominant index finger within 7 seconds. Each button press raised the level of a "bar" viewed on the screen. Eligibility for reward depended on the ability of the participant to raise the "bar" to the "top" within the prescribed time-period. Subjects were instructed to complete as many trials as possible within a twenty-minute period. For the easy choice, subjects were eligible to win $1.00 for each successful completion. For the hard choice, amounts varied per trial ($1.24 - $4.30). The participants were instructed that successful "win" amounts would be added to their base compensation rate. To assist with determining which version of the task to complete, subjects were provided varying probability cues in receiving reward amounts. All trials were either "win" trials or "no win" trials with three levels of probability for being a "win" trial. High probability trials had 88% likelihood of being a "win" trial; Medium probability trials had 50% likelihood of being a "win" trial; Low probability trials had 12% likelihood of being a "win" trial. All probability levels were equally proportioned across the experiment. The comparison of the participants' choice of effortful responses in the series of high effort and low effort task conditions after METH and placebo provides the measure of willingness to exert effort in the present study.

We examined the percentage of the hard task choices vs total choices (hard plus easy) participants chose in the EEfRT after METH or placebo. We subtracted the percent hard choices after placebo from the percent hard choice after METH. Thus, for each subject we calculated the difference in hard choices between METH and placebo.

***Subjective Effects***

Subjective experiences were measured using the Addiction Research Center Inventory (ARCI-MBG) and the Drug Effects Questionnaire (DEQ) (Ciraulo et al., 2001, Morean et al.,

2013). The ARCI contains six subscales assessing the psychoactive effects of drugs. The Morphine Benzedrine Group (MBG) scale is a set of 17 questions measuring of drug-induced euphoric effects including "I feel as if something pleasant had just happened to me." One point is given to the answer "yes," and zero points is given to "no." The MBG scale then assesses elevated mood as a score between 0 – 17. The DEQ is a visual analog scale with questions assessing the acute subjective drug effects with questions including, "Do you like any of the drug effects you are feeling right now?" The participants responses ranged from 0 to 100 with 0 being not at all and 100 being maximum feeling. The participants' reports of euphoric and liking responses after METH and placebo administration provides the measure of subjective experiences in the present study.

For the DEQ 'liking' question and the ARCI-MBG responses (euphoric responses), we calculated the peak change in each type of response by finding the timepoint with the largest difference from the baseline. We then subtracted the peak change in liking and MBG during a placebo session from the peak change in liking and MBG during a METH session.

***Physiological Effects***

To assess the cardiovascular response of the drug, we utilized blood pressure measures from the six different time points, before administration of the capsule and periodically until the end of the session. For the purposes of this analysis, we analyzed only systolic blood pressure which measures arterial pressure when the heart beats rather than in between pulses. Systolic blood pressure is thought to be a more clinically significant measure of blood pressure compared to diastolic blood pressure. Previous research has shown that systolic blood pressure is a more robust measure to correctly classify blood pressure stages, especially in predicting cardiovascular disease risk (Izzo et al., 2000, Basile 2002). Indeed, we found average systolic blood pressure

changes for participants to be more sensitive to METH administration compared to diastolic blood pressure.

We averaged systolic blood pressure across each timepoint. This value was then transformed by subtracting the placebo results of systolic blood pressure from the METH session measurements of systolic blood pressure.

## Results

### *Effects of METH Administration*

On the DEQ, METH increased ratings of 'liking the drug effect' compared to the placebo condition. On the ARCI-MBG subscale, METH significantly increased peak change from baseline scores relative to placebo. On the EEfRT task, METH significantly increased participants' choice of the hard task, compared to placebo. Additionally, METH significantly increased peak change systolic blood pressure relative to placebo (Table 2).

Table 2

*Mean and standard error values for peak change from baseline on the four primary measures, in the METH versus placebo conditions.*

| **Measures** | | **Mean** | **SE** | | **P-Value** |
|---|---|---|---|---|---|
| **'Like' Peak Change from Baseline** | | | | | |
| | METH | 46 | 5.10 | $t = 4.79$ | $p < 0.001$ |
| | Placebo | 17.9 | 3.56 | | |
| **MBG Peak Change from Baseline** | | | | | |
| | METH | 6.69 | 0.65 | $t = 9.18$ | $p < 0.001$ |
| | Placebo | -0.22 | 0.38 | | |
| **Hard Choice Percentage** | | | | | |
| | METH | 0.54 | 0.03 | $t = 4.78$ | $p < 0.001$ |
| | Placebo | 0.46 | 0.04 | | |
| **Systolic BP Peak Change from Baseline** | | | | | |
| | METH | 6.86 | 1.49 | $t = 3.79$ | $p < 0.001$ |
| | Placebo | -0.63 | 1.31 | | |

### *Correlation Analysis*

Using Pearson correlation analyses, we tested for associations between the drug-minus-placebo scores on the liking and ARCI-MBG questionnaires (subjective effects), the drug-minus-placebo choice on the EEfRT (behavioral effects), and the drug-minus-placebo systolic blood pressure (physiological effects). Table 3 summarizes the correlations between the pairs of outcome measures. We found a positive correlation between systolic blood pressure and both liking of METH effects and the percentage of hard tasks selected in the EEfRT following METH administration. There was also a marginally significant positive association between euphoric ratings and the percentage of hard tasks selected in the EEfRT following METH administration. None of the other correlations were significant.

Table 3

*Correlations between subjective, behavioral, and physiological measures.*

| N = 51 | | **Systolic BP (drug – placebo)** | **MBG (drug – placebo)** | **% Hard Task (drug – placebo)** | **Like (drug – placebo)** |
|---|---|---|---|---|---|
| **Systolic BP (drug – placebo)** | **Pearson Correlation** | 1 | 0.073 | 0.317* | 0.386** |
| | **Sig (2-tailed)** | | 0.613 | 0.023 | 0.005 |
| **MBG (drug – placebo)** | **Pearson Correlation** | | 1 | 0.275 | 0.370** |
| | **Sig (2-tailed)** | | | 0.051 | 0.000 |
| **% Hard Task (drug – placebo)** | **Pearson Correlation** | | | 1 | 0.145 |
| | **Sig (2-tailed)** | | | | 0.309 |

*Note:* Data represent Pearson Correlation values for peak change scores on systolic blood pressure responses, euphoric responses (MBG), percentage hard task choices, and drug liking. Asterisks signify significant correlations.

## Discussion

Consistent with previous research, METH significantly increased ‘liking’ and euphoric effects. It also increased the willingness to exert physical effort in pursuit of reward and increased systolic blood pressure. These findings are congruent with previous studies

demonstrating positive subjective responses, increased cardiovascular activity, and alterations in cognitive processes associated with the dopaminergic system (Wardle et al., 2011, Hart et al., 2000, Kaye et al., 2007).

The primary purpose of this analysis was to examine relationships between pairs of outcome measures, including subjective, physiological, and task-related measures. We predicted that the effects of the drug on 'liking' and euphoria (DEQ and MBG) would be positively correlated with the percent of hard choices in the EEfRT. This hypothesis was based on the idea that all three of these measures might be related to the effects of METH on dopamine. Our hypothesis was partially supported. Effects of METH on ratings of drug 'liking' were not significantly correlated with the percent of hard choices. However, there was a marginally significant ($p<.051$) trend for a positive relationship between METH-induced euphoria and percent of hard choices. Defining subjective and behavioral changes induced by METH mediation on the dopaminergic system remains an open prospect. It can be argued that drug liking and drug-induced euphoria might be related, and indeed, there was a positive relationship ($p<.01$) between these measures following post-analysis correlation. Why MBG scores were (marginally) related to hard choices while liking was not is unclear. There is the possibility that MBG scores are a more robust measure of subjective experience due to its specificity. For example, participants who failed to report increases in 'liking' after METH still reported increases in MBG scores. The discrepancy may be explained by the small sample size, and unanticipated variability in liking ratings, which may have been due to ambiguities in the rating scales.

In addition, we predicted that 'liking' and euphoric effects would not correlate with the physiological measure of systolic blood pressure as these responses are understood to be

influenced by different underlying processes. Consistent with this prediction, we found no relationship between the euphoric (MBG) ratings and the increase in systolic blood pressure under METH. Surprisingly, however, the METH-induced 'liking' ratings were positively correlated with increased systolic blood pressure. The relationship between liking and blood pressure was contrary to the hypothesis, based on expected differences in the neurochemical mechanisms underlying the subjective rating and a cardiovascular effect. It is possible this finding may be related to the dynamical systems understanding that physiological arousal and emotional arousal may be coordinated through feedback mechanisms for organized behavioral responses (Thayer & Lane 2000). The affective response mechanism mediated by METH may be defined by changes in levels of physiological organization. Another possible explanation is that individual differences in plasma levels of the drug, related to absorption and distribution, might have accounted for the individual differences in both measures. Future work should consider measuring plasma levels to confirm if this discrepancy is related to individual sensitivities of the drug.

We also predicted that the METH-induced increase in percentage of hard tasks on the EEfRT would not be related to the increase in systolic blood pressure. However, a positive correlation was found between these two measures, meaning that greater willingness to exert effort after METH administration was associated with greater increase in blood pressure. This finding does not support the idea that these measures are mediated by different neurochemical mechanisms, and instead may be related to pharmacokinetic factors as described above. Elevated measures of systolic blood pressure may quantify the organization of physiological responses affecting goal-directed behavior according to feedback mechanisms in a dynamical systems perspective (Thayer & Lane 2000). There have been reports of individual differences in Heart

Rate Variability (HRV) being related to differences in cognitive performance and behavioral flexibility (Forte et al., 2019, Thayer et al., 2009). It is possible that changes in response selection upon mediation of METH is related to changes in vagal tone due to these potential central-peripheral feedback loops coordinating goal-directed behavior and individual pharmacokinetic differences (Thayer & Lane 2000). Future research should consider including other measures of vagal tone, for instance, pulse pressure, pulse wave velocity, and heart rate variability.

The strengths of this study include the multi-dimensional approach in characterizing the acute response to METH administration. Previous work primarily focuses on subjective, behavioral, and physiological responses individually or in pairs as opposed to a holistic analysis (Comer et al., 1996, Kaye et al., 2007, Kevil et al., 2019, Hart et al., 2001, Tadrous et al., 2021, Wardle et al., 2011, Westover & Halm 2012). This study used established reliable forms of measures in the ARCI-MBG scale, DEQ, and EEfRT responses (Ciraulo et al., 2001, Haertzen & Hickey 1987, Morean et al., 2013, Wardle et al., 2011)

However, this study had some limitations. The sample size used ($n$ = 51) is relatively small for a correlation analysis. There is also potential for individual differences in pharmacokinetics to influence these results as well as differences in interpretation of the subjective effects questionnaires. Future research should continue to evaluate the relationship between METH induced subjective and behavioral responses using different tasks or subscales of the ARCI that could more accurately measure these effects. Future research should also consider evaluating plasma levels to give clarity as to the relationship between physiological effects and other measures.

Overall, as systolic blood pressure increased, ‘liking’ of the drug effect and willingness to exert effort for reward increased. Otherwise, subjective responses remained unrelated to the cognitive behavioral task and provided inconsistent results compared to blood pressure. These findings suggest the relationship between cardiovascular effects and dopaminergic effects induced by METH is not dissociable. The neurochemical basis mediated by METH leading to non-discrete responses across physiological, subjective, and behavioral measures reveals that continued drug-taking behaviors may be informed by the coordination of these dynamic processes rather than by the effects of these systems separately.

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