

Short communication

## Residual effects of intranasal methamphetamine on sleep, mood, and performance

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### Abstract

Although intranasal methamphetamine abuse has increased, there are no published data investigating the residual effects of the drug under controlled conditions. Thus, the current study examined the residual effects of single-dose intranasal methamphetamine administration on a broad range of behavioral and physiological measures. Non-treatment seeking methamphetamine abusers ( $n = 11$ ) completed this two-week, in patient, within-participant, double-blind study. The study consisted of four two-day blocks of sessions; each block was separated by at least 48 h. At approximately 10:00 h, on the first day of each block, participants received one of four intranasal methamphetamine doses (0, 12, 25, 50 mg/70 kg). Lights were turned out at 23:00 h that evening and sleep measures were assessed. On the morning of the second day of each block, methamphetamine plasma levels, cardiovascular measures, mood, subjective reports of the previous evening's sleep, and psychomotor performance were assessed to determine residual drug effects. The larger methamphetamine doses (25 and 50 mg) markedly disrupted subjective measures of that night's sleep and some indices of next-day mood, but only the largest dose (50 mg) dose decreased objective measures of that night's sleep and increased next-day physiological measures. Methamphetamine did not produce any negative residual effects on early next-day performance. Future studies should assess methamphetamine-related residual effects following repeated doses administered over consecutive days.

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### 1. Introduction

Following several decades of dormancy, the abuse of amphetamines has again become an important public health problem in several countries, including Australia, Thailand, and the United States. In the United States, for example, treatment admissions for methamphetamine use disorders have steadily increased since 2000. Although acute administration of relatively low oral methamphetamine doses reportedly improves mood and cognitive performance (e.g., Johnson et

al., 1999, 2000; Hart et al., 2002), long-term abuse of larger doses, administered via routes other than oral, is associated with mood disturbances (London et al., 2004) and cognitive impairments (London et al., 2005). These deleterious effects appear to be exacerbated following abrupt discontinuation of methamphetamine use (Peck et al., 2005). In addition, hypersomnia, increased depression-related symptoms, anxiety and methamphetamine craving are reported after cessation of methamphetamine use (McGregor et al., 2005).

It should be noted, however, that there were a few methodological concerns that constrained the conclusions from studies indicating methamphetamine-related disruptive effects after discontinuation of drug use. For example, sleep behavior based on subjective reports may not correspond with objective sleep measures (e.g., Baker et al., 1999; Tworoger et al., 2005). Furthermore, previous studies relied on retrospective

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self-reported information regarding recency and amounts of methamphetamine use, making it difficult to precisely quantify patterns of methamphetamine use that are most likely to precipitate disruptive effects. Given these considerations, a systematic laboratory investigation, during which carefully controlled methamphetamine doses are administered and objective sleep measures are assessed, is needed. A better understanding of methamphetamine-related residual effects is an important initial step in developing effective methamphetamine abuse treatments because interventions can target specific symptoms. Therefore, we undertook a double-blind, inpatient, within-participant study to evaluate the residual effects of intranasal methamphetamine administration (0, 12, 25, and 50 mg/70 kg) on several dependent variables, including mood, cognitive/psychomotor performance, objective and subjective sleep behaviors. Residual effects were operationally defined as those occurring at least 12 h after drug administration, at a time when plasma levels of methamphetamine are declining and acute subjective effects are negligible. These participants were previously described in an investigation of the acute effects of intranasal methamphetamine on the behavioral and physiological measures in abusers (Hart et al., 2007).

## 2. Methods

### 2.1. Participants

Eleven research participants (2F, 9M) completed this two-week inpatient study: their age ranged from 22 to 45 years (mean age = 30.7). Prior to study enrollment, participants signed a consent form that was approved by the Institutional Review Board of The New York State Psychiatric Institute (NYSPI); each passed comprehensive medical and psychiatric evaluations and were within normal weight ranges according to the 1983 Metropolitan Life Insurance Company height/weight table [body mass index:  $24.1 \pm 4.4$  (mean  $\pm$  S.D.)]. All participants met DSM-IV criteria for current methamphetamine abuse or dependence and stated they were not seeking treatment at the time of study participation. No participant met criteria for any other axis I disorder. All reported abusing methamphetamine primarily via the intranasal route, although nine reported having used via the smoked route and one via the intravenous route. Participants reported using methamphetamine  $3.6 \pm 1.7$  (mean  $\pm$  S.D.) days/week. Six participants reported current cocaine use (1–4 times/week), seven reported current alcohol use (1.5–15 drinks/week), seven reported current marijuana use (1–6 times/week), and eight smoked 2–20 tobacco cigarettes/day.

### 2.2. Design and procedures

This two-week, double-blind, within-participant study consisted of four two-day blocks of sessions with each block of sessions separated by at least 48 h. On the first day of each block, at approximately 10:00 h, participants received one of four intranasal methamphetamine doses (0, 12, 25, 50 mg/70 kg). Methamphetamine dosing was counterbalanced across participants. Subsequently that evening, lights were turned off at 23:00 h for an 8-h sleep period and objective sleep was assessed. During this period, participants were instructed to remain in bed. On the second day of each block, at approximately 10:00 h, heart rate (HR), systolic (SP) and diastolic pressure (DP) and methamphetamine plasma levels were assessed. Then, a sleep questionnaire, subjective-effect ratings, and a cognitive/psychomotor battery were completed to determine residual drug effects.

At least two days before beginning experimental sessions, participants were admitted onto the General Clinical Research Service (GCRS) at the NYSPI, where they resided until study completion. This arrangement ensured a sufficient drug washout period before study commencement and decreased the likelihood that non-study drugs would be consumed during the study.

### 2.3. Sleep monitoring

Objective measures of sleep were obtained by tracking gross motor activity using Actiwatch<sup>®</sup> Activity Monitoring System (Actiwatch<sup>®</sup>: Respironics Company, Bend, OR), worn throughout the study by 6 of the 11 participants (Kushida et al., 2001). Actiwatch<sup>®</sup> data from the first five participants were not available due to equipment malfunctions with another portable sleep system. Each morning, all participants were asked to estimate the number of hours they slept the previous night and to complete a visual analog sleep questionnaire consisting of a 100 mm line labeled “not at all” at one end and “extremely” at the other end. The six items were: “I slept well last night,” “I woke up early this morning,” “I fell asleep easily last night,” “I feel clear-headed this morning,” “I woke up often last night,” “I am satisfied with my sleep last night.”

### 2.4. Subjective-effects and cognitive/psychomotor battery

The computerized visual analog questionnaire consisted of a series of 100 mm lines labeled “not at all” at one end and “extremely” at the other end (described in Hart et al., 2007). The lines were labeled with adjectives describing a mood (e.g., “Anxious,” “Depressed,” “Frustrated”), a drug effect (e.g., “Bad Drug Effect,” “Good Drug Effect,” “High”), or a physical symptom (e.g., “Headache,” “Muscle Pain,” “Stomach Upset”). Three items were also used to operationalize drug craving and were labeled “I want meth,” “I want alcohol,” and “I want a cigarette.”

Computerized psychomotor tasks (Haney et al., 1999) consisted of a 3-min Digit–Symbol Substitution Task (DSST; McLeod et al., 1982), a 3-min repeated-acquisition task (RA; Kelly et al., 1993), a 10-min divided attention task (DAT; Miller et al., 1988), a 10-min rapid information task (RIT; Wesnes and Warburton, 1983), and a 3-min immediate and delayed digit-recall task (Hart et al., 2001).

### 2.5. Drugs

Methamphetamine HCl, was provided by the National Institute on Drug Abuse (NIDA). Lactose (60 mg/70 kg) was used as a placebo and lactose was also added to each methamphetamine dose (12, 25, and 50 mg/70 kg) to achieve a final weight of 60 mg/70 kg. As a safety precaution, the maximum single methamphetamine dose administered did not exceed 60 mg. Three participants' weight exceeded 84 kg, and as a result, they were administered 41–48 mg/70 kg. Each dose was provided in a small medicine cup, along with a plastic straw (~7 cm) and participants were instructed to insufflate the entire dose within a 30-s period. All drug administrations occurred in a double-blind manner.

### 2.6. Data analysis

Repeated-measures analyses of variance (ANOVA) with planned comparisons were conducted to determine the residual effects of intranasal methamphetamine (0, 12, 25, 50 mg/70 kg) on sleep measures, subjective-effect ratings, cognitive/psychomotor performance, and physiological measures. For all analyses, ANOVAs provided the error terms needed to calculate planned comparisons that were designed to determine the effects of methamphetamine dose. Data were considered statistically significant at  $p < 0.05$ , using Huynh–Feldt corrections.

## 3. Results

Data collected from the three participants who weighed greater than 84 kg were consistent with the results of the other participants.

### 3.1. Sleep

Fig. 1 (upper left panel) shows that, relative to placebo, objective total sleep duration was significantly decreased by the

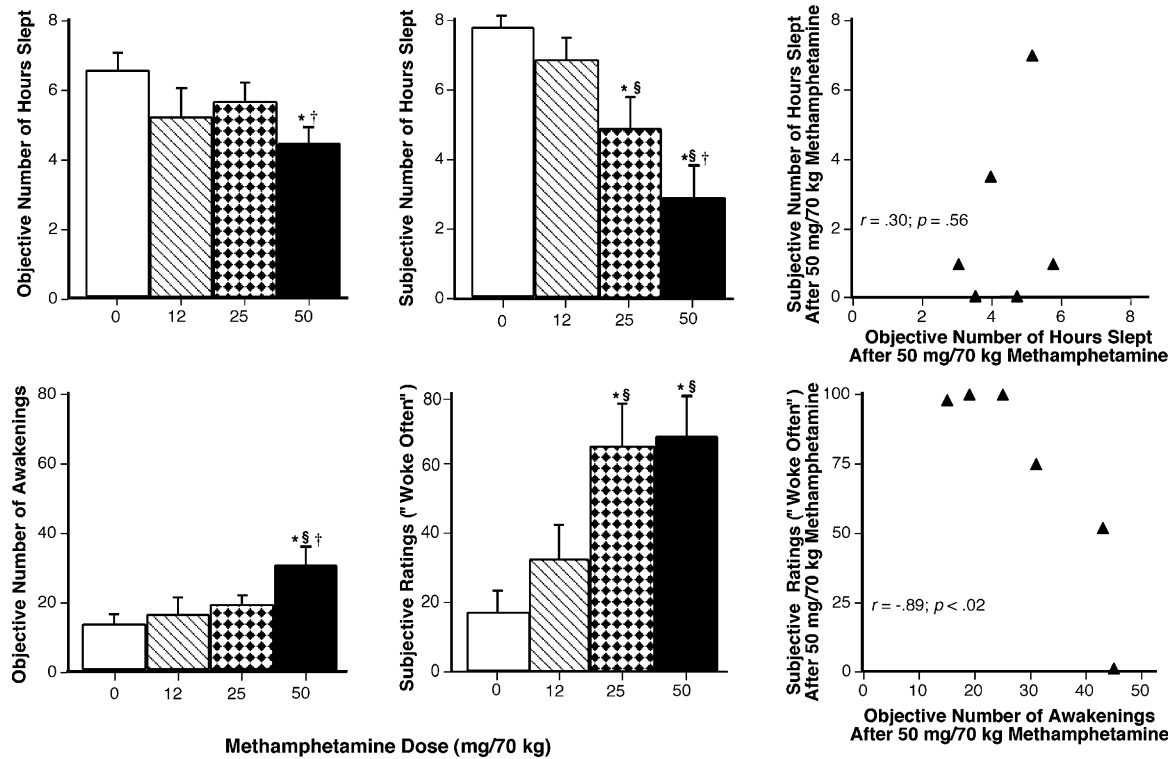


Fig. 1. Left panels: Mean values for total number of hours slept and number of awakenings as measured by the Actiwatch® Activity Monitoring System as a function of methamphetamine dose ( $n = 6$ ). Middle panels: Mean values for sleep questionnaire estimates of hour slept and ratings of “woke often” as a function of methamphetamine dose ( $n = 11$ ). Right panels: Values for subjective and objective number of hours slept for each participant and values for subjective and objective number of awakenings following 50 mg/70 kg methamphetamine ( $n = 6$ ). Error bars represent one S.E.M. An asterisk (\*) indicates significantly different from placebo ( $p < 0.05$ ). Symbol (§) indicates significantly different from 12 mg/70 kg ( $p < 0.05$ ). Symbol (†) indicates significantly different from 25 mg/70 kg ( $p < 0.05$ ).

Table 1  
Residual effects of methamphetamine on the sleep questionnaire, subjective-effect ratings, and physiological measures

Measure	Methamphetamine conditions						
	Placebo	12 mg		25 mg		50 mg	
	Mean (S.E.M.)	Mean (S.E.M.)	F value	Mean (S.E.M.)	F value	Mean (S.E.M.)	F value
<b>Sleep questionnaire</b>							
Clear-headed	78.20 (7.38)	71.17 (8.98)	0.39	63.80 (8.08)	1.64	49.44 (9.10)	6.55*
Estimated no. of hours slept	7.70 (0.31)	6.77 (0.56)	1.42	4.83 (0.85)	13.78*§	2.84 (0.89)	39.41*§,†
Fell asleep easily	57.50 (9.74)	56.06 (12.51)	0.01	27.40 (11.34)	4.38*	10.22 (4.56)	10.80*§
Satisfied with sleep	80.30 (7.75)	64.00 (10.77)	1.37	42.40 (12.43)	7.38*	25.33 (6.46)	15.53*§
Slept well	85.20 (3.82)	75.72 (8.57)	0.72	49.60 (11.68)	10.08*§	21.44 (7.41)	32.34*§,†
Woke often	16.50 (6.66)	32.28 (10.04)	1.15	64.80 (12.48)	10.78*§	67.56 (11.52)	12.04*§
<b>Subjective-effect ratings</b>							
Alert	55.55 (9.76)	51.09 (9.90)	0.32	53.36 (8.85)	0.08	38.09 (9.15)	4.40*
Content	53.91 (6.46)	46.09 (6.63)	1.56	42.09 (4.63)	3.56	37.36 (5.00)	6.98*
Energetic	35.20 (9.71)	45.00 (10.48)	1.04	29.20 (4.91)	0.39	22.80 (5.54)	5.33§
Friendly	65.00 (7.79)	60.36 (6.41)	0.48	59.09 (7.43)	0.77	43.00 (9.77)	10.69*§,†
Social	67.09 (7.59)	50.36 (6.17)	4.46*	55.82 (6.49)	2.02	40.82 (6.60)	10.99*
Talkative	58.46 (4.63)	47.00 (8.62)	2.11	55.64 (6.10)	0.12	37.36 (6.43)	7.16*†
<b>Physiological measures</b>							
MA plasma levels (ng/ml)	0.00 (0.00)	6.72 (0.42)	4.33	13.67 (2.90)	17.91*	38.08 (4.11)	139.00*§,†
Heart rate (bpm)	78.36 (2.28)	84.18 (2.90)	3.07	85.27 (3.09)	4.33	90.46 (4.44)	13.26*
Systolic pressure (mmHg)	118.00 (2.58)	119.64 (2.15)	0.42	123.00 (3.04)	3.96	124.00 (2.65)	5.70*
Diastolic pressure (mmHg)	69.00 (2.69)	71.36 (1.82)	0.84	73.82 (2.83)	3.51	78.55 (2.85)	13.76*§

MA: methamphetamine. d.f. = 1, 30.

\*  $p < 0.05$ , significantly different from placebo.

§  $p < 0.05$ , significantly different from 12 mg.

†  $p < 0.05$ , significantly different from 25 mg.

50-mg dose ( $p < 0.01$ ); the average reduction was 2 h (50 mg:  $4.4 \pm 1.03$  h vs. *placebo*:  $6.4 \pm 1.16$  h). Similarly, the number of awakenings was increased by the largest methamphetamine dose compared with all other doses ( $p < 0.01$ ; Fig. 1, lower left panel).

Fig. 1 (upper middle panel) shows that participants estimated that they had slept approximately 2.9 and 4.9 fewer hours the previous night when they received 25 and 50 mg, respectively, compared to when they had received placebo ( $p < 0.001$ ). Additionally, when participants received the larger methamphetamine doses (25 and 50 mg), they reported waking more frequently during the sleep period ( $p < 0.05$ ; Fig. 1, lower middle panel). Table 1 shows additional significant effects produced by methamphetamine on subjective sleep measures.

When the relationship between objective and subjective sleep measures was examined for the 25- and 50-mg dose, only the number of awakenings as measured by the Actiwatch<sup>®</sup> and subjective ratings of “Woke Often” following the 50-mg dose was significantly correlated ( $r = -0.89$  and  $p < 0.02$ ; Fig. 1; 25 mg data not shown). There were no significant correlations following the 25-mg dose.

### 3.2. Subjective effects

Table 1 displays the residual effects of methamphetamine on subjective-effect ratings. The 50-mg dose administered 24 h earlier, significantly decreased rating of “Alert,” “Content,” “Energetic,” “Friendly,” “Social,” and “Talkative” ( $p < 0.05$ ).

### 3.3. Cognitive/psychomotor effects

Methamphetamine did not produce any significant residual effects on cognitive/psychomotor performance.

### 3.4. Physiological measures

Table 1 summarizes next-day physiological effects of methamphetamine. Notably, all physiological measures were significantly increased by the 50-mg dose compared with placebo ( $p < 0.05$ ).

## 4. Discussion

The present data show that objective and subjective sleep behaviors were disrupted by a single intranasal methamphetamine dose administered to experienced methamphetamine users 12–14 h before bedtime. Objective measures of sleep (i.e., total number of hours slept and number of awakenings) reached statistical significance only following the largest methamphetamine dose (50 mg), whereas subjective measures (e.g., ratings of “Slept Well”) were markedly decreased by both the 25- and 50-mg doses. Consistent with objective sleep results, some measures of next-day mood (e.g., “Content” and “Friendly”) were decreased and next-day HR, SP, DP, and methamphetamine plasma levels were increased by the largest methamphetamine dose. Despite sleep and limited mood alterations caused by

methamphetamine, next-day cognitive performance was not negatively impacted.

The finding that methamphetamine-related effects on objective and subjective sleep measures were not entirely consistent is interesting and underscores an important limitation of past studies. Previous research investigating the residual effects of methamphetamine have relied exclusively on self-reports of sleep behavior (McGregor et al., 2005; Peck et al., 2005), despite the fact that a large database comparing subjective estimates of sleep with objective sleep measures suggests that the two modalities may tap different aspects of the sleep experience (e.g., Coates et al., 1982; Vitiello et al., 2004). Indeed, the current data demonstrate that self-reports may dramatically overestimate the extent of sleep disruptions produced by methamphetamine. For example, participants reported they had slept nearly five fewer hours the morning after they had received the 50-mg dose. Data from the Actiwatch<sup>®</sup>, however, showed that they had slept only two fewer hours. Similarly, participants reported a general decrease in sleep quality after the two larger methamphetamine doses, but objective sleep measures were significantly altered only following the largest dose. A caveat related to these observations is that objective sleep data was available for only 6 of the 11 participants, and this might limit generality of the current results. Despite this, the current results suggest that there may be a dissociation between objective and subjective measures of sleep disruption, a finding that should be assessed with a larger cohort of participants.

Although some next-day subjective ratings were decreased by the 50-mg methamphetamine dose, the overall pattern of effects produced by methamphetamine were limited and do not suggest that next-day mood disturbances are a major feature associated with a single intranasal dose administration. Importantly, ratings of “depressed,” “anxious,” and “I want meth” were not altered by the methamphetamine dose administered the previous day. Because no earlier study has assessed the residual effects of intranasal methamphetamine under laboratory conditions, it is difficult to relate the current findings to previous data. Nevertheless, the next-day performance data are congruent with the majority of next-day subjective ratings. That is, methamphetamine, administered 24 h earlier, did not produce disruptions in any of the cognitive domains assessed, including memory, reaction time, and sustained attention.

Anecdotally, illicit methamphetamine is used in multiple dose cycles, which may continue over the course of several consecutive days (Angrist, 1994; Cho et al., 2001). In the present investigation, the residual effects of methamphetamine were evaluated following only a single-dose administration, possibly decreasing the likelihood of observing methamphetamine-associated disruptions. A related point is that 24 h following methamphetamine administration (primarily the 50-mg dose), physiological measures remained significantly elevated and this might have potential implications for toxicity. For example, de Wit and co-workers showed that tolerance develops more rapidly to oral amphetamine-related subjective effects relative to physiological effects (Brauer et al., 1996). Thus, in the natural environment, some users may take repeated methamphetamine doses in order to achieve a certain level of intoxication, which

might increase the likelihood of physiological harm (e.g., cardiotoxicity). Future studies should determine the impact of the residual effects of methamphetamine following repeated dosing over consecutive days. Another caveat of this study was that next-day mood and performance were assessed at only one time point in the morning. It is possible that performance disruptions, for example, are subtle and require multiple assessments over the course of an entire day in order to be detected.

In conclusion, the present data show that a single intranasal methamphetamine dose produced marked reductions on measures of subjective sleep quality and, to a lesser extent, objective sleep. These findings highlight the importance of assessing both subjective and objective measures of sleep when determining the impact of methamphetamine-associated effects. Despite methamphetamine-related alterations of sleep and physiological measures, the drug produced few residual effects on mood and cognitive performance. Further study of the residual effects of methamphetamine following repeated dosing is needed to better understand the purported abstinence syndrome associated with methamphetamine abuse.

### Conflict of interest

The authors declare that, except for income received from our primary employer, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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*Contributors:* Drs. Hart, Foltin, and Silver designed the study, and Dr. Hart, Ms. Perez and Mr. Kirkpatrick wrote the protocol. Dr. Gunderson provided medical coverage and oversaw methamphetamine administrations. Ms. Perez and Marrone managed the literature searches and summaries of previous related work. Mr. Kirkpatrick and Ms. Marrone trained research participants on the task battery used in this study and undertook the statistical analysis. Ms. Perez wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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