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Short communication

Morning administration of oral methamphetamine dose-dependently disrupts nighttime sleep in recreational stimulant users

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ABSTRACT

Introduction: Use of amphetamine-type stimulants (e.g., methamphetamine) is associated with acute sleep disruptions. No prior reports have characterized the acute effects of methamphetamine on sleep using polysomnography, the gold standard for objective sleep monitoring.

Methods: Recreational stimulant users (n = 19) completed a baseline assessment, which included questionnaires assessing demographic and substance use characteristics, and the Pittsburgh Sleep Quality Index (PSQI), which assesses sleep quality over the past month. Participants were administered 0 mg (placebo), 20 mg, or 40 mg oral methamphetamine at 08:15 h on study days, using a double-blind, randomized, within-subjects design. Sleep was monitored using polysomnography from 22:20 that evening until 06:15 the following morning.

Results: PSQI scores indicated more than half of participants reported poor sleep quality at baseline. Methamphetamine dose-dependently increased sleep latency, and decreased total sleep time, sleep efficiency, time in NREM 2 sleep, number of REM periods, and total time in REM sleep. Sleep under placebo conditions was consistent with what would be expected from healthy adults.

Conclusions: Morning oral administration of methamphetamine produces robust disruptions in nighttime sleep. Future research should examine relations between stimulant use and sleep disruption in naturalistic settings, with regard to both stimulant abuse and licit prescription use.

1. Introduction

Amphetamine-type stimulants (e.g., amphetamine, methamphetamine) are among the most widely abused drugs worldwide (Degenhardt and Hall, 2012). Human laboratory studies have demonstrated that acute single and repeated administration of methamphetamine disrupts sleep among illicit stimulant users, even when administered 12 h or more prior to sleep assessment (e.g., Comer et al., 2001; Kirkpatrick et al., 2012a; Kirkpatrick et al., 2012b; Perez et al., 2008). One notable limitation of these prior studies is that they objectively measured sleep using wrist actigraphy (Kirkpatrick et al., 2012a; Kirkpatrick et al., 2012b; Perez et al., 2008) or the Nightcap® sleep monitoring system (Comer et al., 2001). Relative to polysomnogarphy, (PSG), wrist actigraphy underestimates total wake time and sleep-onset latency, overestimates total sleep time and sleep efficiency, and has demonstrated reduced sensitivity to detect drug-induced changes in sleep (Sivertsen et al., 2006). The Nightcap® system allows for discrimination between Rapid Eye Movement (REM) and non-REM sleep, but does not distinguish between the different phases of non-REM sleep (i.e., NREM stages 1, 2, and 3; Ajilore et al., 1995). PSG is considered to be the gold standard objective sleep monitoring (van de Water et al., 2011), and thus allows for the most detailed and accurate characterization of the acute effects of drugs on sleep continuity and architecture.

Although there have been several studies examining the acute effects of cocaine, another commonly used stimulant, on sleep using PSG (e.g., Post et al., 1974; Watson et al., 1992; Johanson et al., 1999), we are aware of only one PSG study that examined the effects of experimental methamphetamine administration on sleep (Miller et al., 1993). Miller and colleagues administered morning doses of oral methamphetamine to patients with narcolepsy and matched healthy controls. Both narcoleptic patients and matched controls showed modest reductions in sleep efficiency and REM sleep as a function of dose, with no significant effects on other measures of sleep continuity or architecture. However, it is uncertain whether these results generalize to recreational stimulant users. Doses administered to control participants (5–10 mg) were much lower than those typically used by recreational methamphetamine users (Simon et al., 2001). Narcolepsy patients received higher doses (20 mg and 40–60 mg), but these individuals have

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severely disrupted sleep-wake cycles relative to healthy adults (Roth et al., 2013), suggesting the relatively minor effects of these doses may be specific to this population.

The aim of this report is to provide the first double-blind, placebo-controlled polysomnographic characterization of the acute effects of a single morning administration of methamphetamine (20 mg and 40 mg) on nighttime sleep contiguity and architecture sleep among recreational stimulant users.

2. Material and methods

2.1. Participants

Participants were recruited from the greater Baltimore, MD area using media advertising and word-of-mouth. The primary purpose of the parent study was to examine the effects of methamphetamine on behavioral measures of decision-making and sexual HIV risk. Participants completed telephone and in-person screenings to determine eligibility. Screening included a general history (medical, psychiatric, and substance use), physical examination, electrocardiogram, blood chemistry and hematology, and urinalysis. Inclusion criteria included: (1) 21–55 years old, (2) recreational use of stimulants (e.g., amphetamine, cocaine, methamphetamine, methylphenidate) in the past six months, (3) within 20% of their ideal bodyweight according to the Metropolitan Life height/weight table, (4) having had sexual intercourse in their lifetime (relevant to measures not reported here), (5) literacy (assessed by having the participant read the consent document aloud). Exclusion criteria included: (1) physical dependence on any substance(s) except nicotine or caffeine, (2) seeking treatment for substance use, (3) daily licit prescription use of stimulants, (4) medical history, physical examination, or laboratory tests performed during the screening process revealing any significant illness or other contraindications to methamphetamine administration, (5) women who are pregnant, nursing, or not using birth control, (6) psychiatric hospitalization in the past 6 months, and (7) history of serious head trauma, dementia, or significant cognitive impairment.

2.2. Laboratory procedures

Participants completed three laboratory sessions, separated by at least one day in between. Participants were asked to abstain from stimulants starting on the day prior to the laboratory session. Participants arrived at the laboratory at 07:00, competed urine drug testing, and consumed a standardized low-fat breakfast. At 08:15, participants were administered 0 mg (placebo), 20 mg, or 40 mg oral d-methamphetamine hydrochloride (Mylan Inc.) in a randomized order. From 09:15-15:15, participants completed behavioral assessments not relevant to the present report. At 15:30, participants were escorted to an inpatient clinical research unit where they resided until the following morning.

2.3. Assessments

2.3.1. Demographic, substance use, and sleep characteristics

During the in-person screening interview, participants completed a 28-item questionnaire to assess demographic and substance use characteristics, and a checklist to screen for substance abuse and dependence (Hudziak et al., 1993) updated for DSM-IV criteria. Participants also completed the Pittsburgh Sleep Quality Index (PSQI), a validated 19-item self-report questionnaire that assesses sleep quality over the past month (Buysse et al., 1989). The PSQI yields seven component scores and a global score. Global scores of 5 or higher indicate poor sleep quality.

2.3.2. Polysomnograpy

Sleep was monitored nightly using an Embla N-7000 digital PSG data recorder (Broomfield, CO). A standard PSG montage was used: (1) five EEGs (F3-A2, F4-A1, C4-A1, C3-A2, O1-A2, O2-A1), (2) right and left electro-oculograms, and (3) three EMGs (submental and anterior tibialis muscles). See Vandrey et al. (2011) for a more detailed description of PSG monitoring procedures. Participants were allowed to retire between 22:20 and 23:10. Lights on was at 06:15.

2.4. Data analysis

PSQI individual component and global scores were calculated. PSG data were scored by a certified sleep technician following the standardized procedures of the American Academy of Sleep Medicine (AASM; Iber et al., 2007). Technicians responsible for recording and scoring PSG data were blind to study conditions. Outcome variables were defined using AASM guidelines (Iber et al., 2007), and included measures of: 1) *Sleep continuity:* time in bed, total sleep time, sleep latency, time awake after sleep onset (WASO), arousal index (i.e., mean number of arousals/hour) and sleep efficiency (i.e., total sleep time/time in bed × 100), and 2) *Sleep architecture*; total time in NREM 1, NREM 2, and NREM 3 sleep, REM onset latency, number of REM periods, and total time in REM sleep). These measures were examined across dose conditions using one-way repeated-measures ANOVA, with planned contrasts to compare individual dose combinations (i.e., 0 mg vs. 20 mg, 0 mg vs. 40 mg, and 20 mg vs. 40 mg). Significance was determined at $\alpha = 0.05$. Partial eta squared (n^2) values were calculated as a measure of effect size.

3. Results

3.1. Participant demographic, substance use, and sleep characteristics

Nineteen participants completed the study. Demographics, substance use characteristics, and PSQI scores are displayed in Table 1.

3.2. Laboratory sessions

Participants averaged 8.7 (± 5.9) days between laboratory sessions. All participants reported abstaining from stimulants for at least 24 h prior to study sessions. Ninety-one percent of urine drug tests results were negative for illicit stimulant use on session days; only 4 participants had one or more positive tests of illicit stimulant use (3 for cocaine and 1 for methamphetamine). Participants reported an average of 6.0 (± 1.3) hours of sleep on the evening before each study session.

3.3. Polysomnography

3.3.1. Sleep continuity

As shown in Table 2, methamphetamine significantly reduced time in bed ($F(2,36) = 3.70$, $p = 0.04$), total sleep time ($F(2,36) = 19.71$, $p < 0.001$), and sleep efficiency ($F(2,36) = 18.27$, $p < 0.001$), while significantly increasing sleep latency ($F(2,36) = 8.98$, $p = 0.001$). Planned contrasts revealed significant differences between individual doses for all measures of sleep continuity, except for arousal index.

3.3.2. Sleep architecture

As shown in Table 2, methamphetamine significantly decreased NREM 2 sleep ($F(2,36) = 6.28$, $p = 0.005$), number or REM sleep periods ($F(2,36) = 28.50$, $p < 0.001$), and total time in REM sleep ($F(2.36) = 36.08$, $p < 0.001$), and increased REM onset latency ($F(2,36) = 16.85$, $p < 0.001$), but did not significantly affect NREM 1 sleep ($F(2,36) = 2.46$, $p = 0.10$) or NREM 3 sleep ($F(2,36) = 2.03$, $p = 0.15$). Planned comparisons revealed significant differences between individual doses for time in NREM 2 and all three measures of REM sleep (all $ps < 0.05$; see Table 2).