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Acute, low-dose methamphetamine administration improves attention/information processing speed and working memory in methamphetamine-dependent individuals displaying poorer cognitive performance at baseline

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ABSTRACT

Abstinent methamphetamine (Meth) dependent individuals demonstrate poorer performance on tests sensitive to attention/information processing speed, learning and memory, and working memory when compared to non-Meth dependent individuals. The poorer performance on these tests may contribute to the morbidity associated with Meth-dependence. In light of this, we sought to determine the effects of acute, low-dose Meth administration on attention, working memory, and verbal learning and memory in 19 non-treatment seeking, Meth-dependent individuals. Participants were predominantly male (89%), Caucasian (63%), and cigarette smokers (63%). Following a four day, drug-free washout period, participants were given a single-blind intravenous infusion of saline, followed the next day by 30 mg of Meth. A battery of neurocognitive tasks was administered before and after each infusion, and performance on measures of accuracy and reaction time were compared between conditions. While acute Meth exposure did not affect test performance for the entire sample, participants who demonstrated relatively poor performance on these tests at baseline, identified using a median split on each test, showed significant improvement on measures of attention/information processing speed and working memory when administered Meth. Improved performance was seen on the following measures of working memory: choice reaction time task ($p \leq 0.04$), a 1-back task ($p \leq 0.01$), and a 2-back task ($p \leq 0.04$). In addition, those participants demonstrating high neurocognitive performance at baseline experienced similar or decreased performance following Meth exposure. These findings suggest that acute administration of Meth may temporarily improve Meth-associated neurocognitive performance in those individuals experiencing lower cognitive performance at baseline. As a result, stimulants may serve as a successful treatment for improving cognitive functioning in those Meth-dependent individuals experiencing neurocognitive impairment.

1. Background/Introduction

More people worldwide use amphetamine-type stimulants than any other illicit drug besides cannabis (UNODC, 2010). According to the most recent (2008) National Survey on Drug Use and Health (NSDUH), 314,000 residents of the US aged 12 or older used Meth in the prior month. Moreover, the number of recent new users of Meth was 95,000. While these numbers reflect a decrease from previous years of the survey, a significant segment of the population continues to experiment with this dangerous drug (SAMHSA, 2008). Meth use is associated with neurocognitive impairment (for review see: Kalechstein and Newton 2007; Quinton and Yamamoto 2006), including poor performance on measures of attention/information processing speed, learning and memory, and frontal lobe functioning. Also, a recently published manuscript reported that more than 40% of previously Meth-dependent individuals still experienced neurocognitive impairments after prolonged abstinence from Meth (Cherner et al., 2010). These neurocognitive abnormalities have been linked to deficits in presynaptic dopamine (DA) neuronal markers (Johanson et al., 2006; Volkow et al., 2001; Wang et al., 2004).

Given this association, it is reasonable to hypothesize that administration of dopaminergic agents such as Meth might ameliorate Meth-associated neurocognitive impairments. For example, a recently published study showed that, in those participants who experienced baseline working memory deficits, modafinil administration ameliorated them (Kalechstein et al., 2010). Furthermore, in a study of cocaine dependent individuals, it was reported that cocaine exposure improved cocaine users' neurocognitive performance (Woicik, et al., 2009; Johnson et al., 2005). Along similar lines, the administration of d-amphetamine has been proven effective to reliably improve aspects of cognitive function (Silber et al., 2006). Using the same reasoning, we assessed whether Meth administration improves neurocognitive functioning, specifically in those domains

Abbreviations: Meth, Methamphetamine; NSDUH, National Survey Drug Use and Health; S.D., Standard Deviation; BDI, Beck Depression Inventory.

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most affected in Meth-dependence: attention/information processing speed, learning and memory, and frontal lobe functioning.

2. Methods

2.1. Subjects

All subjects were non-treatment-seeking and met DSM-IV-TR criteria for current Meth dependence. They were 18 to 45 years old, smoked or injected Meth at least twice per week in 4 out of the 6 weeks prior to study entry, and provided a positive urine toxicology for Meth prior to admission. Furthermore, participants were in good health and had normal laboratory assessments and physical examinations. Potential participants were excluded if they were diagnosed with another Axis I psychiatric disorder, were currently dependent on any other drugs (including alcohol) aside from nicotine, and/or had a history of seizure disorder, head trauma, or concomitant use of any psychotropic medication. The Institutional Review Board of the University of California Los Angeles (UCLA) approved this study and all subjects gave informed consent after being made aware of the possible risks of participation. Subjects were recruited through advertisements in the community, and were paid for their participation.

Nineteen participants, 17 men and 2 women, completed the study. The average age of the participants was 35.58 ± 8.24 (mean $\pm$ S.D.). Twelve participants identified themselves as White or Caucasian, 5 as Hispanic or Latino, 1 as Asian, and 1 as African-American or Black. Participants in this study averaged 13.63 ± 2.14 years of education. Twelve of the 19 participants were cigarette smokers. With respect to Meth usage patterns, on average, participants used Meth for 8.50 ± 6.03 years, had used 16.78 ± 8.26 days out of the last 30 prior to study entry, reported using 3.25 ± 2.52 g of Meth per week, and had average Beck Depression Inventory-II scores of 6.65 ± 6.93.

2.2. Study design

This study was conducted as part of a medication trial conducted in the UCLA General Clinical Research Center (CRC) (De La Garza et al., 2008). Following admission to the CRC, participants completed baseline assessments, including the Addiction Severity Index (ASI)-Lite CF Version (McLellan et al., 1992), and the BDI-II (Beck et al., 1996). On the fourth day of the inpatient stay, participants received a single-blinded intravenous infusion of saline (placebo) and on the fifth day, subjects received a single-blinded infusion of Meth (30 mg, IV). One hour prior to drug (saline or Meth) administration, participants completed a baseline battery of neurocognitive tasks (described later). One hour following drug administration, participants completed the same battery of tasks that was administered at baseline, as well as the Hopkins Verbal Learning Task-Revised (HVLT-R) (Shapiro et al., 1999).

2.3. Drugs

A NIDA contractor (RTI International, Research Triangle Park, NC) provided sterile Meth solution for human use and a saline solution of equal volume and appearance was used as the control. An IND was obtained from the FDA for the use of Meth in this study. Meth or saline was administered over 2 min using an intravenous pump.

2.4. Neurocognitive Tasks

2.4.1. Simple reaction time task (SRT)

The SRT involves pseudo-random presentation of a series of letters (from the set *A*, *a*, *G*, *g*, *T*, *t*, *H*, *h*), one at a time, at the center of a computer screen. Participants were instructed to press a red button on the response box with their dominant forefinger as quickly as possible following presentation of the letter. Letters were black on a white background, subtended approximately $1.9° \times 1.6°$. Each letter was presented for 500 ms, with a subsequent letter presented 2500 ms later. A total of 32 trials were presented. The dependent variable was the difference in reaction time (msec) between the second and first administrations of the task (SRT2 − SRT1).

2.4.2. Choice reaction time task (CRT)

The CRT involves presentation of the same set of letters seen during the SRT. In this task, however, participants are instructed to press a red button on the response box with their dominant forefinger upon presentation of *G*, *g*, *H*, or *h*. Upon presentation of *A*, *a*, *T*, or *t*, participants were instructed to press a blue button on the response box. Letters were black on a white background, subtended approximately $1.9 \times 1.6°$. Each letter was presented for 500 ms, with a subsequent letter presented 2500 ms later. A total of 32 trials were presented. The dependent variables were reaction time (msec) and response accuracy, indexed as the ratio of actual accurate responses to total possible responses.

2.4.3. N-back task (working memory task)

The working memory task was a variation of an N-back that has been used previously (Smith et al., 1996). Participants were presented with a series of letters from the same set as seen on the SRT and CRT. In the 1-back condition, participants were to signal a 'yes' response (pressing a blue button with their dominant forefinger) if the presented letter matched the letter presented immediately beforehand. If the two letters did not match, a 'no' response (pressing a red button with their dominant forefinger) was required. In the 2-back condition, a 'yes' response was required if the presented letter matched the letter two trials previous. Otherwise, a 'no' response was required. Case of the letter was not relevant to matching verbal identity. Letters were black on a white background, subtended approximately $1.9° \times 1.6°$. Each letter was presented for 500 ms, with a subsequent letter presented 2500 ms later. After completing at least 20 trials of practice, participants completed a total of 32 trials for each condition. The dependent variables were reaction time (msec) and response accuracy, indexed as the ratio of actual accurate responses to total possible accurate responses.

2.4.4. Hopkins Verbal Learning Test-Revised (HVLT-R, verbal learning and memory task) (Brandt and Benedict, 2005)

The HVLT was administered with the above battery of neurocognitive tasks following Meth or saline administration. Participants were read a list of 12 words, and asked to recall as many as they could. This procedure was repeated two times (for a total of 3 learning trials). Following a 20–25 min delay, participants were asked to recall the words without the aid of cues (Delayed Recall). After delayed recall, participants were then read a list of 24 words, and had to identify the 12 words from the original list (Recognition). The dependent variables of interest for the HVLT-R were total words recalled during the three learning trials and number of words remembered on the delayed recall subtest. A different version of the test was administered pre- and post-infusion to eliminate the possibility of practice effects.

2.4.5. Order of test administration

The battery of neurocognitive tests were administered in the following order: The HVLT-R learning recall trials, SRT, CRT, the N-back tests, delayed recall of the HVLT-R, followed by re-administration of the SRT. Difference score between the two SRT administrations was used as a measure of psychomotor fatigue. The reaction time tests were programmed on a laptop computer using SuperLab (SuperLab 1997). All responses for computerized tasks were given using a RB-730 response box (Cedrus, Phoenix AZ). A standardized set of instructions was given to the participants both written and orally prior to administration of each