Published in final edited form as:
Am J Addict. 2010 ; 19(4): 340–344. doi:10.1111/j.1521-0391.2010.00052.x.

Modafinil Administration Improves Working Memory in Methamphetamine-Dependent Individuals Who Demonstrate Baseline Impairment

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Abstract

Modafinil improves working memory in healthy subjects and individuals diagnosed with schizophrenia and Attention Deficit/Hyperactivity Disorder, though the effects of modafinil have not been evaluated on working memory in methamphetamine-dependent subjects. This double-blind, placebo-controlled study evaluated whether a daily dose of 400 mg of modafinil, administered over three consecutive days, would enhance performance on a measure of working memory relative to test performance at baseline and following 3 days of placebo administration in 11 methamphetamine addicted, nontreatment-seeking volunteers. The results revealed that participants demonstrating relatively poor performance on the third day of a 3-day washout period (ie, at baseline), showed significant improvement on measures of working memory, but not on measures of episodic memory or information processing speed. In contrast, for participants demonstrating relatively high performance at baseline, modafinil administration did not affect test scores. The findings provide an initial indication that modafinil can reverse methamphetamine-associated impairments in working memory.

INTRODUCTION

In the last 10 years, an emergent body of research has consistently demonstrated that methamphetamine dependence is a risk factor for the onset of neurocognitive impairment in humans.[1] Specifically, a review of the extant literature on methamphetamine use and neurocognition revealed that 24 of 25 studies showed that methamphetamine dependence is associated with poorer performance on measures of attention and information-processing speed, learning and memory, and/or executive systems functioning (ie, frontal lobe functioning). The consistent observation of neurocognitive impairment in humans is not surprising given the decades of preclinical research that has successfully documented the stimulant-associated neurobiological changes in nonhuman primates[2,3] and rodents.[4] Moreover, several research groups have documented the association between methamphetamine dependence and disruptions in glucose brain metabolism. For example, Volkow and colleagues showed that long-term methamphetamine exposure in humans is associated with reduced metabolic activity in the striatum,[5] and that methamphetamine-dependence is associated with reduced dopamine transporter (DAT) expression in human users with varying lengths of abstinence.[6]

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Declaration of Interest
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Taken together, a variety of studies have consistently shown that long-term methamphetamine exposure is associated with neurocognitive impairment. Moreover, a subset of these studies have conclusively linked methamphetamine-associated neurocognitive impairments to reduced levels of DAT in the striatum,[6] reduced temporal lobe volume,[7] and increased theta wave activity, a quantitative electroencephalographic measure indicating the presence of an encephalopathic process.[8] Thus, it is necessary to ask new questions that capitalize on the results of these studies. One important, and as of yet unaddressed, question to be resolved is whether the neurocognitive impairments associated with long-term methamphetamine exposure can be reversed using pharmacological interventions.

For this study, modafinil was selected as the candidate medication, and a number of reasons underlay this choice. Namely, modafinil administration is associated with improved performance on measures of working memory in a variety of populations, including healthy controls[9] and individuals diagnosed with schizophrenia[10] and Attention Deficit/ Hyperactivity Disorder.[11] As previously noted, this same neurocognitive domain is likely to be affected in methamphetamine-addicted individuals. Furthermore, modafinil administration is associated with enhanced monoaminergic function and monoamines, particularly dopamine, are markedly diminished as a result of long-term, high-dose methamphetamine use.[2,3] Thus, we hypothesized that modafinil administration would be associated with improved performance on measures of working memory in those study participants that showed relatively poor performance at baseline.

METHOD

Study Participants

Research volunteers were recruited through advertisements in the community and were paid for their participation. All subjects were nontreatment seeking and met DSM-IV-TR criteria for methamphetamine dependence. Other inclusion criteria included being between 18 and 45 years of age, use of at least 2.0 g of methamphetamine per week in the 6 months prior to admission, positive urine toxicology for methamphetamine prior to admission, and a normal laboratory assessment and vital signs. Exclusion criteria included diagnosis of any other Axis I psychiatric disorder, dependence on any other drugs aside from nicotine, 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.

Fourteen participants were enrolled and 11 completed the study. One noncompleter presented with a previously undetected cardiovascular anomaly. Two other noncom-pleters were discharged after it was determined that they erroneously received modafinil instead of placebo. On average, study completers were 35.6 years in age (SD = 9.7), completed 12.7 years of school (SD = 1.3), used methamphetamine for 10.3 years (SD = 8.0), and had used methamphetamine 20.2 days (SD = 9.3) of the 30 days prior to study admission. Seven were men and four were women. Each of the 11 study participants smoked cigarettes.

Study Design

A double-blind, placebo-controlled, study design was employed. After the screening, in which participants provided a urine sample that was positive for methamphetamine, but not other drugs, they completed a 3-day washout period and underwent baseline neurocognitive testing. Using urn randomization to balance whether participants initially received placebo or modafinil, participants received oral modafinil, 400 mg/day for 3 days, or placebo,

underwent neurocognitive testing, and immediately crossed over to the opposite study arm. Following the crossover, study participants receiving oral placebo were given oral modafinil, 400 mg/day for 3 days, and vice versa, and then underwent neurocognitive testing. After both arms of the study were completed, participants were monitored for 24 hours, debriefed, and discharged from the study.

Drugs

An IND was obtained from the FDA for the use of modafinil in this study. Modafinil or placebo was administered orally on each morning at 9:00 a.m. for three consecutive days. As the half-life of modafinil is approximately 15 hours, steady state blood levels are reached after 2 days of dosing.[9]

Measures

Simple Reaction Time Task—The simple reaction time task (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° × 1.6°. Each letter was presented for 500 ms, with a subsequent letter presented 2,500 ms later. A total of 32 trials were presented. The dependent variable was difference in reaction time (ms) between the second and first administrations of the task (SRT2–SRT1).

Working Memory Task—The working memory task was a variation of an N-back that has been used previously.[12] Participants were presented with a series of letters from the same set as seen on the SRT. In the 1-back condition, if the verbal identity of the presented letter matched the verbal identity of the letter presented immediately beforehand, participants were expected to provide a “yes” response by pressing a blue button on the keypad with the dominant forefinger. If the identities of the two letters did not match, they were expected to provide a “no” response by pressing a red button on the keypad with the dominant forefinger. Case of the letter was not relevant to matching verbal identity. In the 2-back condition, participants were expected to provide a “yes” response if the verbal identity of the presented letter matched the verbal identity of the letter that was shown two trials earlier. Otherwise, a “no” response was required. Letters were black on a white background, subtended approximately 1.9° × 1.6°. Each letter was presented for 500 ms, with a subsequent letter presented 2,500 ms later. Participants completed at least 20 trials of practice, and a total of 32 trials for each condition were presented. The dependent variables were reaction time (ms) and response accuracy, indexed as the ratio of actual accurate responses to total possible accurate responses.

Verbal Learning and Memory Task—The Hopkins Verbal Learning Test-Revised (HVLT-R)[13] was used to assess verbal learning and memory. 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 three learning trials). Following a 20–25 minutes 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.

Order of Test Administration—The battery of neurocognitive tests were administered in the following order: The HVLT-R learning recall trials, SRT, the N-back tests (N-back), 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. All responses for computerized tasks were ascertained 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 task, and participants were always reminded to respond as quickly and accurately as possible.

Statistical Analysis

Median reaction time and mean percent correct were calculated and analyzed using SPSS 11.0. Reaction time cutoffs of shorter than 100 ms and longer than 1,500 ms for each computerized task were established to eliminate the possibility of anticipating the appearance of the stimuli, as well as the possibility of a delayed response intruding on the presentation of the subsequent stimulus.

Within subjects, repeated measures ANOVA was used to analyze the effects of modafinil on test performance across three conditions, baseline, placebo, and modafinil. Significance for all analyses was set at $p < .05$,[14] and effect size was indexed as eta squared. Subsequently, the sample was subdivided into high versus low performers based on performance at baseline using median split. Low performers ($n = 6$) demonstrated the slowest reaction times (ie, 1-back RT >875 ms; 2-back RT > 900 ms), lowest accuracy of responding (ie, 1-back accuracy < 90%; 2-back accuracy < 60%), and greatest level of fatigue at baseline (ie, SRT2–SRT1 > 0 ms), whereas high performers demonstrated the fastest reaction times, highest accuracy of responding, and lowest level of fatigue at baseline. The purpose of this approach was to determine if the lowest performers, those participants demonstrating greater levels of impairment at baseline, would be more likely to respond to modafinil administration than high performers.

RESULTS

Preliminary analyses revealed that order of medication administration, modafinil versus placebo, did not affect performance on the neurocognitive tests ($p > .20$). Moreover, demographic variables, such as age, education, and gender, did not moderate performance on the neurocognitive tests ($p > .20$). Hence, covariates were not included in subsequent analyses.

With respect to the low performers at baseline ($n = 6$), tests of within-subjects effects of accuracy of responses on the working memory tests increased significantly during the modafinil condition in contrast to baseline and placebo (Fig. 1). Specifically, the increase in response accuracy was significant for the 1-back test ($F[2,10] = 6.93$, $p \leq .05$, $\eta^2 = .46$) and the 2-back test ($F[2,10] = 8.15$, $p \leq .01$, $\eta^2 = .62$). There were differences in reaction time across the two conditions, but not to a level that approached significance ($p < .15$). In addition, similar results were observed on a measure of fatigue ($p < .15$). Furthermore, on a list-learning test, the HVLT-R, modafinil administration did not affect performance over three learning trials or recall of the list after a 20-minute delay period ($p > .20$).

With regard to the high performers ($n = 5$), neither accuracy of responding nor reaction time was affected by modafinil administration ($p > .20$). In addition, modafinil administration did not influence performance on an index of fatigue ($p > .20$). Finally, on a list-learning test, modafinil administration did not affect performance over three learning trials or recall of the list after a 20-minute delay period ($p > .20$).

DISCUSSION

To the best of our knowledge, this study is the first to demonstrate that treatment with a medication can reverse the working memory impairments that are common in methamphetamine-addicted individuals. Notably, a recently presented paper by Ghahremani, London, and colleagues showed that modafinil administration was associated with improved response accuracy on another executive functioning task, the reversal learning task, which requires the inhibition of an overlearned response.[15] The implications of these findings are several. One is that although methamphetamine is characterized as a "neurotoxic" substance,[16] it is unclear whether the residue of the neurotoxicity, indexed as neurocognitive functioning, can be improved with medication treatment.[6,17] These findings preliminarily show that methamphetamine-associated working memory impairments can be improved when the proper candidate medication is selected.

With respect to the selection of candidate medications for the treatment of methamphetamine-associated working memory impairment, modafinil was a logical choice. For example, modafinil modulates the release of monoamines, including dopamine.[9] Furthermore, nonhuman primate[2] and human[18] models of methamphetamine addiction have consistently revealed the presence of dys-regulated dopaminergic function. In addition, in a subset of studies, modafinil administration was associated with enhanced performance on measures of working memory in healthy controls[19] and individuals diagnosed with schizophrenia[10] and Attention Deficit/Hyperactivity Disorder.[11]

In terms of hypothesis testing, we predicted that modafinil would enhance performance on measures of working memory in those methamphetamine addicts that showed relatively poor performance at baseline whereas no effects would be observed in the relatively intact performance at baseline. This approach, which has been articulated in a recent manuscript,[20] is seemingly intuitive, but has not been applied in medication trials for methamphetamine addicts. For example, to our knowledge, trials designed for the purpose of determining whether a candidate medication can reduce craving for methamphetamine do not evaluate baseline levels of craving in the study participants before including/excluding them from the trial. From our perspective, the latter approach increases the likelihood of type II error and, as a result, limits the efficacy of these types of medication trials. Research from our lab has demonstrated the efficacy of this approach with respect to identifying anticraving medications in cocaine-dependent individuals.[21]

While these findings potentially have important implications with respect to the treatment of methamphetamine-associated neurocognitive impairment, it is important to specify the limitations of this study. For instance, the small sample size raises questions as to whether these findings can be generalized to the population of individuals experiencing methamphetamine-associated neurocognitive impairments, though it is important to note that large effect sizes were observed on each measure administered to the low performers, particularly on measures of working memory. In addition, the dosing regimen was limited to 400 mg/day, which precluded the determination of a dose effect. The assessment battery also included measures that focused exclusively on working memory, information processing speed, and episodic memory. Future studies might include other measures of executive function, such as inhibitory control. In addition, Volkow and colleagues showed that, in a subset of methamphetamine-addicted individuals, the neurocognitive impairments observed at baseline had resolved after 24 months of abstinence. Hence, it will be necessary to determine whether the resolution of deficits observed here would have occurred regardless of the intervention, though it is important to note that for low performers, scores on measures of working were consistently poorer during the placebo condition than that observed during the modafinil condition. Furthermore, for this study, impairment was

defined in a relative manner, for example, comparison of performance across washout, placebo, and medication stages, rather than an absolute manner, for example, comparison of participants' test performance to that of a normative data set. Finally, modafinil remediated some neurocognitive deficits, but not others, most notably, performance on measures of episodic memory (HVLT-R). Future studies might consider the administration of modafinil in conjunction with another medication that is associated with improved episodic memory.

These limitations notwithstanding, the results of this study support the hypothesis that modafinil treatment can remediate methamphetamine-associated neurocognitive impairment. While the functional consequences of methamphetamine-associated neurocognitive impairment have been inadequately studied, the effect(s) of neurocognitive impairment on day-to-day functioning for individuals diagnosed with other disorders, such as traumatic brain injury,[22] epilepsy,[23] HIV,[24] cocaine dependence,[25] and schizophrenia,[26] are well documented. Given that methamphetamine addiction is associated with widespread functional difficulties, such as unemployment and relapse to dependence, it is plausible that reversing the neurocognitive impairments associated with this disease will concurrently ameliorate these functional difficulties as well.

Acknowledgments

The authors acknowledge grants K24DA017754 (Dr. Newton) and R03DA020591–01 and RR00865 (Richard Rawson, PhD, UCLA) from the National Institutes of Health, Bethesda, MD.

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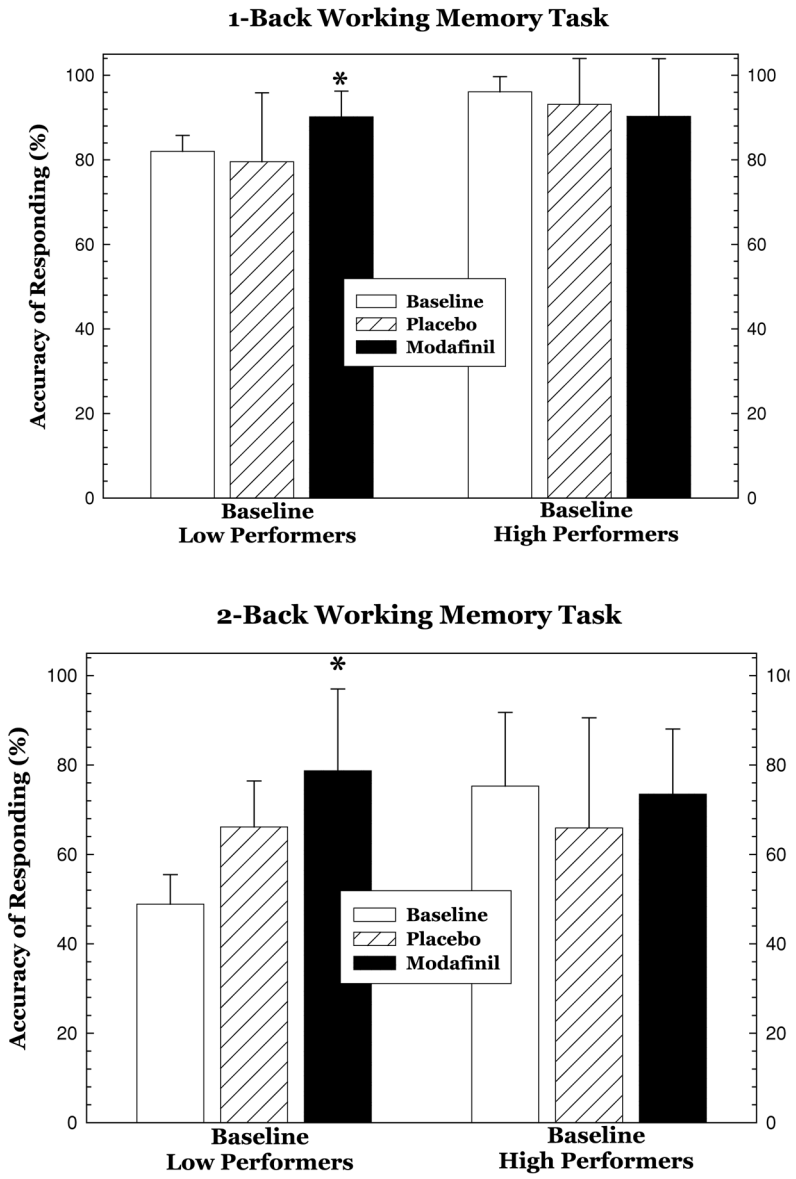

FIGURE 1.
Accuracy of responding on the N-back test for high and low performers at baseline.