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EFFECTS OF TOPIRAMATE ON METHAMPHETAMINE-INDUCED CHANGES IN ATTENTIONAL AND PERCEPTUAL-MOTOR SKILLS OF COGNITION IN RECENTLY ABSTINENT METHAMPHETAMINE-DEPENDENT INDIVIDUALS

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Abstract

Methamphetamine-dependent individuals often cite the need to maintain enhanced cognitive performance and attention as a reason for continuing or relapsing to drug-taking. Further, methamphetamine addicts might not comply with taking a potentially therapeutic medication if it had a profound effect on these cognitive processes. Topiramate, a sulfamate-substituted fructopyranose derivative, has been suggested as a putative therapeutic medication for treating methamphetamine dependence. Examination of topiramate's effects on cognitive performance and attention is a clinically and scientifically important component of understanding its potential therapeutic profile. In 10 male and female individuals who met DSM-IV criteria for methamphetamine dependence, we examined the effects of low (50 mg b.i.d.)- and high (100 mg b.i.d.)-dose topiramate — in both the presence and absence of low (15 mg)- and high (30 mg)-dose intravenous methamphetamine — on cognitive performance, attention, and concentration on the rapid visual information processing task and the digit symbol substitution test. Intravenous methamphetamine enhanced cognitive performance, attention, and concentration among recently withdrawn methamphetamine addicts — an effect that hitherto had not been well characterized. Topiramate's cognitive effects were mixed and rather paradoxical, with a tendency to improve attention and concentration both alone and in the presence of methamphetamine while worsening psychomotor retardation. No deleterious interaction occurred between topiramate and methamphetamine on any of these cognitive processes. While clinical studies with topiramate should

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prepare participants for possible psychomotor retardation, the cognitive-effects profile observed would not likely present an important obstacle to compliance in motivated patients. Topiramate's complicated cognitive effects among methamphetamine addicts need more comprehensive examination.

Keywords

Attention; Cognition; Humans; Methamphetamine; Performance; Topiramate

INTRODUCTION

Concern about the dramatic rise of methamphetamine in the U.S., particularly on the Pacific Coast (Hunt, 1995; U.S. Department of Health and Human Services, 2001), has spurred renewed interest in the programmatic development of efficacious treatment medications. While the main approach toward medications development has been to identify compounds that reduce methamphetamine's reinforcing effects associated with its abuse liability, the cognitive effects of potential compounds and their interaction with methamphetamine need to be fully characterized. This is because the need to increase cognitive performance is often cited as a reason for initiating or maintaining methamphetamine use (Brecht et al., 2004; von Mayrhauser et al., 2002). Hence, it might be difficult to maintain clinical compliance, even with an efficacious compound, should it have profound effects on cognitive performance either alone or in combination with methamphetamine.

Human laboratory studies form a bridge between preclinical and clinical studies that would allow accurate characterization of the effects of a putative therapeutic medication both alone and in combination with methamphetamine. Yet, while ample studies have demonstrated that d-amphetamine enhances cognitive processing on computerized tasks that test performance and attention (Gunne, 1977; Harvey, 1987; Johnson et al., 1996; Spiegel, 1979; Weiss and Laties, 1962), presumably due to enhancement of catecholamine (Cole and Robbins, 1987, 1992) and particularly dopamine release (Drachman, 1977), only one study has reported on the effects of intravenously administered methamphetamine on cognitive performance in methamphetamine-dependent individuals (Johnson et al., 2005b). In that study, intravenous d-methamphetamine produced dose-dependent increases in attention, concentration, and psychomotor performance. These results suggest that methamphetamine-addicted individuals, like healthy human volunteers (Johnson et al., 2000), experience measurable increases in cognitive performance with experimentally administered intravenous methamphetamine. This is the case despite the expectation of deteriorated cognitive functioning (Salo et al., 2002) due to presumed fronto-striatal damage (Ernst et al., 2000; Volkow et al., 2001). Replication of these results would not only establish this human laboratory paradigm for testing cognitive performance and attention among methamphetamine-dependent individuals but also provide added support for the notion that addicted individuals might continue taking the drug to maintain or enhance cognitive performance.

Topiramate, a sulfamate-substituted fructopyranose derivative, has been shown to be efficacious in the treatment of both alcohol (Johnson et al., 2003) and cocaine (Kampman et al., 2004) dependence, and to promote smoking cessation among alcohol-dependent individuals who smoke (Johnson et al., 2005a). These therapeutic effects have been attributed to its hypothesized potential to reduce levels of cortico-mesolimbic dopamine, the primary neurochemical substrate for the acquisition and maintenance of drug-seeking behavior for the majority of abused drugs including alcohol, cocaine, tobacco, and amphetamines (Hemby et al., 1997; Wise, 1998). Naturally, therefore, there is both scientific and clinical interest in testing topiramate as a potential treatment for methamphetamine dependence. Clinical

effectiveness of topiramate would, however, depend upon the demonstration not only that it can reduce methamphetamine-induced reinforcement but also that its use is not associated with a profound decrease in cognitive performance and attention.

Clinical studies with topiramate have, however, suggested that its administration is associated with decreases in executive functioning (Kockelmann et al., 2004), verbal fluency (Deutsch et al., 2003), and attention and concentration (Tatum et al., 2001). Importantly, these studies have been conducted in individuals with epilepsy, and there has been no formal testing, to date, of topiramate's effects on cognitive performance and attention in any addicted individuals, let alone the sub-population of those dependent upon methamphetamine. Hence, the effects of topiramate on cognitive performance and attention among individuals dependent upon methamphetamine are not known. Since individuals with methamphetamine dependence and chronic seizure disorder or epilepsy are prone to fronto-striatal damage (Fujikawa et al., 2000; Morioka et al., 2002; Soffer et al., 1986), we would predict that topiramate administration in individuals with methamphetamine dependence also would be associated with impairment of cognitive performance and attention. Nevertheless, the effects of topiramate on methamphetamine-induced enhancement of cognitive performance and attention are not known. Obviously, if topiramate was shown to impair methamphetamine-induced cognitive enhancement, this could be an important obstacle in the pairing of skills or cognitive-based therapies — presently the mainstay of psychosocial treatment for methamphetamine dependence (Rawson et al., 2004) — with topiramate treatment. In such an eventuality, the practical recommendation might be for clinical trials to pair topiramate with behavioral or simple compliance-based psychosocial interventions.

Therefore, in the present study, we determined — in recently abstinent methamphetamine-dependent individuals — whether intravenously administered methamphetamine would be associated with dose-dependent increases in cognitive performance, whether topiramate would impair or augment cognitive performance and attention, and whether topiramate would impair or augment methamphetamine-induced increases in cognitive performance and attention.

METHODS

Subjects

We studied 10 non-treatment-seeking, DSM-IV (American Psychiatric Association, 1994)-diagnosed methamphetamine-dependent individuals (7 males) between the ages of 31 years and 44 years (mean=37 years) who had been recruited by local newspaper, radio, and television advertisement. All subjects were recently abstinent in that they had been using methamphetamine up to a few days prior to study enrollment. These subjects did not meet diagnostic criteria for any other axis 1 psychiatric disorder except nicotine dependence. See Table 1 for additional demographic data. All subjects gave informed consent prior to their inclusion in the study. The same group participated in a study of the effects of acute topiramate dosing on methamphetamine-induced subjective mood (Johnson et al., in press). Subjects were compensated for study participation.

Experimental Design

This study was approved by the Institutional Review Board at The University of Texas Health Science Center at San Antonio and, therefore, was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. We conducted a double-blind, placebo-controlled, cross-over design, administering oral doses of topiramate (0 mg, 100 mg, and 200 mg) as a pretreatment before intravenous doses of methamphetamine (0 mg, 15 mg, and 30 mg). The 3×3 factorial combination of topiramate and methamphetamine resulted in a sequence of the nine treatments administered to each subject in an order that was determined

by a 9×9 Latin Square design. The designated topiramate dose (100 mg or 200 mg) was administered in two divided doses. The first dose (50 mg or 100 mg, respectively) was given at 2000 hours the evening before the session, and the second dose was given at 0830 hours on the morning of the session. Treatment sessions were conducted on a Monday, Wednesday, Friday schedule so that there was a 2- to 3-day interval between sessions. All subjects were hospitalized for the entire study (27 days) in the University Clinical Psychopharmacology Laboratory, a residential research unit at the University Hospital, the main teaching hospital of The University of Texas Health Science Center at San Antonio.

Choice of Medication Dose and Its Preparation

The high topiramate dose was chosen to correspond with the apparent minimal effective daily dose that was observed in the clinical trial for alcohol dependence (Johnson et al., 2003). Notably, however, this was an estimate because in that study, topiramate dose was confounded by the effect of time, as a paradigm of escalating dose over an 8-week period was employed. The lower topiramate dose was half of that effective dose. For methamphetamine, the high dose (30 mg) was approximately that which would have been achieved by a 70-kg individual, using data from a previous study in which robust subjective effects were observed (Johnson et al., 1999). The low methamphetamine dose was half of the maximum dose.

Twenty-five-milligram topiramate tablets were obtained from Ortho-McNeil Pharmaceutical, Inc. (Raritan, NJ, USA) and were over-encapsulated in royal blue size 0 capsules (Shionogi Qualicaps, Inc., Whitsett, NC, USA) and filled with cornstarch. Placebo topiramate capsules were identical in both color and size and contained only cornstarch. The intravenous methamphetamine doses chosen were in accordance with National Institute on Drug Abuse guidelines for methamphetamine administration. Methamphetamine-HCl as 20-mg/ml ampoules suitable for human intravenous administration was obtained from the National Institute on Drug Abuse. For injection, methamphetamine solution was mixed with sterile 0.9% w/v normal saline to produce 0-, 15-, and 30-mg/3-ml injection volumes. Placebo methamphetamine was 3 ml of 0.9% w/v saline without methamphetamine.

Laboratory Conditions

The study took place at the University Clinical Psychopharmacology Laboratory. Infusion procedures were performed in a testing room of approximately 18×11 feet. After insertion of a venous catheter with a three-way stopcock adapter into a non-dominant arm or hand vein, subjects were seated in a comfortable chair and instructed not to rise or talk during the experiment. Methamphetamine or placebo was infused through polyethylene tubing with an automated syringe pump. Cardiovascular function was monitored continuously, and the participants received close medical supervision at all times.

Experimental Measures

We evaluated cognitive performance using two standardized and well-validated methods.

Rapid Visual Information Processing Task—The rapid visual information processing task (RVIP) is a recognized computer-based test of attention and concentration (Johnson et al., 1996, 2005b; Silverstone et al., 1992). In the RVIP, subjects monitor digits that are presented sequentially on a computer screen at a rate of 100 per minute for 7.5 min. Subjects are instructed to detect and respond to targets of three consecutive even or odd digits as quickly as possible through a keyboard. Independent measures are made of both the speed and the accuracy of decision making. These measurements are recorded for each trial block: hits — correct responses within 600 ms; delayed hits — responses occurring between 600 ms and 1200 ms after the target; false alarms — incorrect responses, and reaction time for both hits and delayed responses.

Digit Symbol Substitution Test—The digit symbol substitution test (DSST) has been used frequently to measure sedative impairment of perceptual-motor function. A computerized version of the task (McLeod et al., 1982) has demonstrated dose-related impairment with psychoactive drugs such as ethanol (Mintzer et al., 1997; Roache et al., 1993). The task requires subjects to depress key positions on a numeric keypad to reproduce geometric symbol patterns displayed on the computer screen. The data are the number of patterns correctly reproduced out of the number attempted during a 90-s test session. Although this is an integrative task involving perceptual and motor components, its measures of both speed and accuracy are sensitive to the effects of drugs that can produce either psychomotor acceleration or retardation.

General Procedures

All subjects were caffeine abstinent while residing on the research unit, and cigarette smokers were limited to smoke breaks several times throughout the day but never within 1 h of the methamphetamine infusion. Generally, the limited smoke breaks resulted in the smoking of only 5 to 10 cigarettes/day. On a separate experimental day prior to double-blind testing, all subjects were trained in the performance of the tests of cognitive performance and attention. Also, during that session, a single-blind dose of methamphetamine (15 mg intravenously) was administered to ensure that the subject had clinical tolerance to the methamphetamine infusion procedures. This initial injection also familiarized subjects with the test room and conditions before the double-blind part of the experiment began.

All females were stabilized on the oral contraceptive pill before testing to control for menstrual cycle effects (Di Paolo, 1994; King et al., 1986) and to prevent pregnancy.

Test Day Procedures

In the evening before each session day, we administered the first dose of topiramate or matching placebo at 2000 hours and subjects were instructed to retire to bed at 2300 hours. On the morning of the test session, each subject provided a urine sample at 0700 hours before receiving a standard hospital breakfast. Using an OnTrak TesTcup® (Varian Inc., Palo Alto, CA, USA), we tested each subject's urine for the presence of opiates, amphetamines, cocaine, benzodiazepines, or barbiturates and took a breath alcohol concentration. The urine drug screen and breath alcohol concentration had to be negative and have a value of zero, respectively, for further testing to proceed. At 0800 hours, baseline scores on the RVIPT and DSST were recorded; then we placed a venous catheter in each subject's non-dominant arm or hand. Then, at 0830 hours, subjects took the second half of their topiramate dose. At 0945 hours, we attached electrodes (including chest leads) to each subject to perform a 12-lead electrocardiogram and to monitor the electrocardiogram and heart rate continuously. Additionally, we attached a blood pressure cuff to the subject to permit frequent (every 2 min) automated blood pressure measurements. All these cardiovascular parameters were collected electronically through a Spacelabs Ultraview® 1050, Module 90496 cardiac monitor (Spacelabs Medical Inc., Issaquah, WA, USA). Also, we used a 2.2-ml length of polyethylene tubing to attach the venous catheter to an automated infusion pump (Baxter International Inc., Deerfield, IL, USA). At 1000 hours, each subject completed the RVIPT and DSST. Then, at 1030 hours, the attending physician commenced the intravenous infusion of 3 ml of methamphetamine or matching placebo over a 60-s period by activating the syringe pump. At 1115 hours and 1200 hours, the RVIPT and DSST were re-ascertained. Lunch was provided at 1300 hours. At 1330 hours, RVIPT and DSST recordings were repeated. Then, at 1500 hours, the attending physician performed a second 12-lead electrocardiogram and a final assessment of subject health, and the electrodes were disconnected. We performed regular safety checks of each subject's health status throughout the test day until the time for the subject to retire to bed at 2300 hours.

Statistical Analysis

Multiple observations were made at different time points in the day for each combination of methamphetamine and topiramate for the RVIPT and DSST variables. For the RVIPT, each subject was instructed to detect and respond to targets of three consecutive even or odd digits as quickly as possible. Thus, there were three measures of hits, delayed hits, false alarms, and reaction time, respectively, recorded at each time point. We calculated total hits, total delayed hits, total false alarms, and average reaction time from these three measures of each variable. For the DSST, total responses and total correct were recorded.

To reduce the dimensionality, we used the area under the curve (AUC) and peak value in each day to summarize the observations. The AUC for each subscale from 0 to 8 h was determined by the trapezoidal rule. The peak value was taken to be the maximum value during that day. A mixed model (McCulloch and Searle, 2001) was used to compare the AUCs and peak values between different combinations of methamphetamine and topiramate while adjusting for the day effect.

All data were analyzed with SAS 9.1 (SAS Institute Inc., Cary, NC, USA) and S-PLUS® 2002 (Insightful Corp., Seattle, WA, USA).

RESULTS

Tables 2 and 3 provide the estimated means, their 95% confidence intervals, and analysis of variance for the AUC and peak values, respectively, on the RVIPT and DSST measures.

RVIPT

On the peak measure, methamphetamine increased the total number of hits significantly ($p=0.05$). Also, there was a non-significant trend for topiramate to increase the total number of hits. There was no significant effect of methamphetamine or topiramate on any of the other RVIPT measures.

On the AUC measure, methamphetamine increased significantly the total number of hits ($p=0.04$) and the total number of correct hits ($p=0.004$). Topiramate also had a marginally significant effect to reduce reaction time ($p=0.05$).

For both the peak and AUC measures, none of the interaction terms achieved statistical significance.

DSST

On the peak measure, topiramate decreased the total responses ($p=0.0008$) and total number correct ($p=0.0001$) significantly. There was no significant effect of methamphetamine.

On the AUC measure, topiramate decreased the total responses ($p=0.0001$) and total number correct ($p=0.0001$) significantly. Further, methamphetamine increased the total number correct ($p=0.004$) significantly.

For both the peak and AUC measures, none of the interaction terms achieved statistical significance.

DISCUSSION

Similar to our previous study (Johnson et al., 2005b), intravenous methamphetamine administration was associated with significant and orderly increases in psychomotor performance and attention in methamphetamine-dependent individuals.

Interestingly, topiramate's effects on cognitive performance and attention were mixed. Notably, topiramate decreased mean reaction time on the RVIPT significantly, and there was a non-significant trend for topiramate to enhance methamphetamine-induced increases in the number of hits on the RVIPT. On the RVIPT, reaction time is not a measure of raw performance but a measure of the minimum speed required to achieve an accurate response (i.e., hits) and is, therefore, more of an index of concentration. Hence, this somewhat unexpected effect of topiramate to increase concentration, and the tendency to enhance methamphetamine-induced increases in attention, must be balanced against its observed effect to decrease perceptual-motor function, which was measured on the DSST.

While this would, at first, appear paradoxical, we think that these findings could have five possible implications.

First, we considered the possibility that these methamphetamine-dependent individuals might have experienced considerable levels of anxiety, particularly in novel situations, which would have impaired baseline performance. Thus, through topiramate's reported sedating effects (Lathers et al., 2003) — as supported by the decrease in perceptual-motor function — there could have been a reduction in anxiety; this reduced anxiety could have improved attention and concentration. We did, however, consider this possibility unlikely because the extensive familiarization period should have expunged inordinate levels of anxiety to the initial novelty of the testing procedure.

Second, we considered the possibility that topiramate's suggested effects at reducing impulsivity could explain the apparent improvement in concentration. Even though we did not measure impulsivity directly, there was no indirect support for this proposal. For instance, inspection of the false alarm rate on the RVIPT — perhaps an index of impulsive-type responding — did not reveal a significant differential pattern of responding to either topiramate or methamphetamine.

Third, topiramate's effects on cognitive performance might depend upon the population and circumstances in which it is administered. While there was a general effect for topiramate to increase psychomotor retardation, as shown by the results of the DSST, its effects on concentration might be due to an anti-dysphoric effect. Although there has been little empirical study of the mood state of individuals recently withdrawn from methamphetamine, the literature on amphetamine withdrawal would suggest that mild dysphoric symptoms (Srisurapanont et al., 1999) are possible. Even though we did not clinically observe any obvious depressed mood in our study participants, and did not measure this directly, it is plausible that the stress of cognitive testing might have enhanced some dysphoric symptoms. Therefore, it might be that topiramate's reported mood-stabilizing effects (Maidment, 2002) could have improved concentration in this cohort by minimizing or preventing dysphoria.

Fourth, the rather standard paradigm of maintaining caffeine abstinence while in the human laboratory — to avoid sleep disruption in the evenings prior to testing or “over-stimulated” effects on experimental testing days — might be associated with some mild decreases in cognitive performance. Nevertheless, we do not consider this to be an important confound as all subjects were exposed to this paradigm. Therefore, any diminution in cognitive performance due to caffeine abstinence would be balanced across the treatment cells. Furthermore, caffeine-dependent individuals were not included in the study.

Fifth, it is possible that topiramate's effects on higher order and executive-type functions might be relatively confined to particular domains in methamphetamine addicts. Therefore, it would be important for future studies to characterize topiramate's cognitive profile more comprehensively in methamphetamine-dependent individuals using an extensive battery of cognitive tests.

Four limitations should be considered while placing the present study's results in context. First, the sample size is relatively small, and larger differences that are reported as trends might have emerged as significant differences with a larger cohort. Second, by testing topiramate in an acute dosing paradigm, we increased the likelihood of amplifying any potential enhancing or deleterious effects that might be less striking with chronic experimental dosing or in a clinical situation. Third, cognitive testing of methamphetamine-dependent patients being tested clinically with topiramate would be needed to appreciate fully the implications of our human laboratory results to real-world assessments of daily functioning. Fourth, it was beyond the scope of our experiment to compare methamphetamine-dependent individuals with normal controls on cognitive function at baseline. We are, therefore, unable to tell whether, and by how much, our results with methamphetamine-dependent individuals would differ from healthy controls under similar experimental conditions.

Future studies are needed to test higher topiramate doses, both acutely and chronically, among methamphetamine addicts to enhance our ability to correlate its cognitive effects in the human laboratory with the clinical situation.

CONCLUSION

Overall, as in healthy volunteers (Johnson et al., 2000), methamphetamine's effects on cognitive performance and attention in methamphetamine addicts appear to be similar to those of amphetamine but more prolonged. Given topiramate's mixed effects on cognitive performance and attention, this would not appear to be an obstacle *per se* that would have an important effect on clinical testing. It would, however, be prudent to advise clinical study participants of the possibility of some psychomotor retardation at least with initial acute dosing. We did not uncover any deleterious interactions between topiramate and methamphetamine on cognitive performance, attention, and concentration.

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Glossary

Abbreviations

AUC

area under the curve

DSM-IV

Diagnostic and Statistical Manual of Mental Disorders, 4th edition

DSST

digit symbol substitution test

RVIPT

rapid visual information processing task

Table 1
Demographics and Drug Use of 10 Non-Treatment-Seeking, Methamphetamine-Dependent Subjects at Intake

Age (years)*	37 (6.50)
Sex†	
Male	7 (70)
Female	3 (30)
Ethnicity†	
Hispanic	6 (60)
White	3 (30)
Black	1 (10)
Marital status†	
Single	5 (50)
Divorced	5 (50)
Married	0 (0)
Educational level†	
Partial college	5 (50)
High school	3 (30)
General equivalency diploma	2 (20)
Education years*	12 (1.49)
Employment status†	
Skilled worker	8 (80)
Unemployed	2 (20)
Days of methamphetamine use in last 30 days*	13.30 (7.86)
Days of alcohol use in last 30 days*	11.60 (10.55)
Cigarettes/day*	9.61 (7.02)

* Values are expressed as mean (SD).

† Values are expressed as number (%).

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Table 2

Means and Confidence Intervals of Area Under the Curve Effects of Methamphetamine (15 mg or 30 mg Intravenously) and Topiramate (100 mg or 200 mg Orally), Both Alone and in Combination, Among 10 Methamphetamine-Dependent Individuals

Rating Scales	Least Squares Means (95% Confidence Intervals)										ANOVA		Main Effect of Meth		Main Effect of Topa		Interaction of Meth and Topa	
	0 mg Meth + 0 mg Topa	0 mg Meth + 100 mg Topa	15 mg Meth + 0 mg Topa	15 mg Meth + 100 mg Topa	15 mg Meth + 200 mg Topa	30 mg Meth + 0 mg Topa	30 mg Meth + 100 mg Topa	30 mg Meth + 200 mg Topa	30 mg Meth + 300 mg Topa	30 mg Meth + 400 mg Topa	F	p	F	p	F	p	F	p
RVIPT																		
AUC total	179 (111–248)	179 (111–248)	201 (132–269)	189 (121–258)	209 (141–277)	189 (121–258)	229 (161–298)	208 (139–276)			3.9	0.04	0.7	0.53	1.3	0.29		
counts × h																		
AUC total	47.9 (24.6–71.3)	47.9 (24.6–71.3)	31.1 (15.2–47.0)	31.1 (15.2–47.0)	43.4 (20.0–66.7)	42.8 (19.4–66.2)	40.8 (17.4–64.2)				2.1	0.16	1.1	0.35	2.3	0.08		
delays																		
hits																		
counts × h																		
AUC total	25.0 (5.2–44.8)	25.0 (5.2–44.8)	28.0 (8.2–47.8)	24.5 (4.7–44.3)	31.0 (11.2–50.8)	18.2 (–1.7–38.0)	17.6 (–2.3–37.4)	20.7 (0.9–40.5)			2.5	0.11	0.06	0.94	0.5	0.76		
false alarms																		
counts × h																		
AUC	4182 (3762–4603)	4182 (3762–4603)	3995 (3573–4416)	4072 (3651–4494)	3980 (3558–4401)	4106 (3683–4528)	3982 (3560–4404)	3759 (3338–4181)			0.7	0.51	3.7	0.05	2.0	0.12		
average reaction time, ms × h																		
DSST																		
AUC total	327 (279–375)	311 (263–359)	329 (281–377)	318 (269–366)	309 (261–357)	345 (296–393)	325 (277–373)	296 (247–344)			1.6	0.23	16.4	0.0001	1.2	0.34		
responses, counts × h																		
AUC total	301 (253–348)	281 (233–328)	302 (254–350)	289 (242–337)	266 (219–314)	334 (287–382)	312 (265–360)	269 (221–317)			7.5	0.004	25.1	0.0001	0.9	0.47		
correct, counts × h																		

Negative values are due to model adjustments. All raw figures are positive.

Meth, methamphetamine; Topa, topiramate; ANOVA, analysis of variance; RVIPT, rapid visual information processing task; AUC, area under the curve; DSST, digit symbol substitution test.

Means and Confidence Intervals of Peak Effects of Methamphetamine (15 mg or 30 mg Intravenously) and Topiramate (100 mg or 200 mg Orally), Both Alone and in Combination, Among 10 Methamphetamine-Dependent Individuals

Rating Scales	Least Squares Means (95% Confidence Intervals)				Main Effect of Meth			Main Effect of Topa			Interaction of Meth and Topa					
	0 mg Meth + 0 mg Topa	0 mg Meth + 100 mg Topa	0 mg Meth + 200 mg Topa	15 mg Meth + 0 mg Topa	15 mg Meth + 100 mg Topa	15 mg Meth + 200 mg Topa	F	p	F	p	F	p				
RVIPIT	0 mg Meth + 0 mg Topa	29.6 (20.4–38.7)	27.3 (18.1–36.4)	30.2 (21.0–39.4)	32.7 (23.5–41.9)	30.5 (21.3–39.6)	32.5 (23.3–41.7)	29.7 (20.5–38.9)	34.9 (25.7–44.1)	33.9 (24.7–43.0)	3.5	0.05	0.6	0.56	1.4	0.26
	Peak total hits, counts	9.0 (4.9–13.1)	6.7 (2.6–10.8)	6.3 (2.1–10.4)	7.6 (3.5–11.7)	9.0 (4.9–13.2)	8.2 (4.1–12.3)	9.3 (5.1–13.4)	8.9 (4.7–13.0)	8.2 (4.0–12.3)	2.4	0.12	1.3	0.3	1.5	0.22
	Peak total false alarms, counts	5.6 (1.3–9.9)	5.6 (1.3–9.9)	6.0 (1.6–10.3)	6.2 (1.9–10.5)	7.0 (2.7–11.4)	6.7 (2.4–11.0)	5.4 (1.0–9.7)	4.0 (–0.4–8.3)	5.6 (1.3–9.9)	1.6	0.23	0.2	0.83	0.3	0.88
Peak average reaction time, ms	0 mg Meth + 0 mg Topa	564 (505–623)	541 (482–600)	540 (481–599)	539 (480–598)	552 (493–611)	529 (470–588)	550 (491–609)	533 (474–592)	529 (470–588)	0.9	0.43	2.5	0.11	1.0	0.45
	Peak total responses, counts	44.9 (39.6–50.3)	42.7 (37.3–48.0)	42.7 (37.4–48.1)	44.4 (39.1–49.8)	43.8 (38.4–49.1)	42.6 (37.3–48.0)	45.9 (40.5–51.3)	43.7 (38.3–49.1)	41.6 (36.2–46.9)	0.1	0.9	10.8	0.0008	1.2	0.35
	Peak total correct, counts	43.9 (38.4–49.3)	40.7 (35.2–46.1)	39.8 (34.3–45.3)	43.6 (38.1–49.0)	41.9 (36.5–47.4)	40.1 (34.6–45.6)	45.3 (39.8–50.8)	42.5 (37.0–48.0)	40.0 (34.5–45.5)	1.3	0.31	16.9	0.0001	0.5	0.77

Negative values are due to model adjustments. All raw figures are positive.

Meth, methamphetamine; Topa, topiramate; ANOVA, analysis of variance; RVIPT, rapid visual information processing task; DSST, digit symbol substitution test.