# Effects of intranasal methamphetamine on metacognition of agency

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**Abstract:** Although methamphetamine abuse has been associated with cognitive deficits, few studies have investigated the acute effects of the drug on complex cognitive performance. This study evaluated the acute effects of intranasal methamphetamine on a computerized task measuring metacognition of agency. Ten non-treatment seeking methamphetamine abusers (2F, 8M) completed this 4-session, within-participant, double-blind laboratory study; during each session, participants received one of four doses (0, 12, 25, or 50 mg/70 kg) and completed the metacognition of agency task. In this task, participants were instructed to "catch" falling targets with a mouse and then provide metacognitive judgments about their feelings of control. Following placebo, judgments of agency were greater under optimal task conditions compared with less than optimal task conditions. Relative to placebo, the 12-mg dose improved task performance, *increased* judgments of agency under the optimal condition, and *decreased* judgments of agency under the less than optimal condition. By contrast, the larger doses (25 and 50 mg) increased judgments of agency only under the optimal condition but disrupted performance under the less than optimal condition. These data show that a low intranasal methamphetamine dose enhanced judgments of agency and performance, while larger doses produced limited effects.

**Key Words:** methamphetamine abuse, amphetamine, cognitive performance, metacognition, humans

**Introduction**

Over the past decade, the possible deleterious effects of methamphetamine use on cognition have received a great deal of both empirical and popular attention. The majority of studies investigating the cognitive effects of the stimulant have focused on long-term illicit methamphetamine use (e.g., Simon et al. 2002; Gonzalez et al. 2004). Several studies have documented deficits in illicit methamphetamine users across a range of cognitive domains. For example, Kalechstein and colleagues (2003) reported that abstinent illicit methamphetamine users performed significantly worse than controls on some measures of executive function, attention, and learning and memory. Other researchers have observed that abstinent methamphetamine users performed worse than controls on measures of divided attention as measured by an auditory vigilance task (London et al. 2005), verbal memory as measured by the Rey Auditory-Verbal Learning Test (Hoffman et al. 2006), and selective attention as measured by the Stroop test (Salo et al. 2002, 2007). It is important to note, however, that in most of these studies, methamphetamine users' performance did not differ from controls on the majority of cognitive tasks employed (e.g., Kalechstein et al. 2003; Thompson et al. 2004). Furthermore, a minority of investigators has astutely pointed out that although methamphetamine users performed significantly worse than controls on some cognitive tasks, their performance remained within the age- and education-matched normal range (Chang et al. 2002; Johanson et al. 2006). Thus, the impact of illicit methamphetamine use on cognitive function is unclear.

One strategy employed by some researchers to examine methamphetamine-related effects on cognition is to assess cognitive performance before and after acute administration of the drug. The rationale guiding this approach is that if methamphetamine produces cognitive deficits one might predict that some methamphetamine-induced disruptions would be observed following

acute administration. Such laboratory investigations have yielded a wealth of empirical information about the acute effects of methamphetamine on human cognition. For example, data from previous studies showed that methamphetamine improved performance on measures of attention (Silber et al. 2006), learning and memory (Hart et al. 2002), and increased the rate of scanning for a target stimulus on a visual display (Mohs et al. 1978, 1980). Other researchers observed that the drug reversed vigilance and tracking performance decrements caused by sleep deprivation (Wiegmann et al. 1996) and attenuated visuospatial processing and attention disruptions produced by abrupt shift-work schedule changes (Hart et al. 2003, 2005). Finally, some investigators have reported that acute methamphetamine administration produced no effects on cognitive performance (Talland and Quarton 1965; Comer et al. 2001; Hart et al. 2001). Interestingly, methamphetamine-induced cognitive disruptions were not observed in any of the above studies.

It is conceivable that the lack of acute methamphetamine-associated deleterious effects on cognitive performance may be related to the doses previously examined. Many of the studies cited above, for instance, investigated relatively low methamphetamine doses that were within therapeutic range (e.g., 5-20 mg: Wiegmann et al. 1996; Mohs et al. 1978, 1980; Comer et al. 2001; Hart et al. 2001, 2002, 2003). Given that drug abusers' dose selection, in the natural ecology, may not be guided by clinical recommendations and may exceed doses tested in the laboratory (Griffiths et al. 2003), findings from the above studies may have limited generality in terms of better understanding methamphetamine-related cognitive impairments. Another potential caveat of the previous research examining cognitive performance following methamphetamine is that the overwhelming majority of studies have investigated the effects of oral methamphetamine, a route least often associated with drug abuse and toxicity. Route of

administration is a critical determinant of neurochemical consequences associated with stimulant administration, in part because neurochemical effects depend on the rate of the rise of drug concentrations and the maximum drug concentrations achieved (Gerasimov et al. 2000). Thus, it is possible that methamphetamine administered via routes other than oral, i.e., intranasal, intravenous, or smoked, might produce more disruptive effects on cognitive functioning.

In addition to the concerns raised above, few studies have examined the acute effects of methamphetamine on more complex cognitive performance, such as executive function. It is possible that methamphetamine-related cognitive disruptions are subtle and may be less likely to be detected using probes of simple cognitive functioning. One area of executive function research that has recently received increased experimental attention is metacognition, or cognitions about cognition. A major underlying assumption of metacognition research is that humans are able to monitor their own cognitive processes (Koriat 2002). Systematic examination of several metacognitive memory judgments, such as judgments of learning and feeling of knowing, has demonstrated that there is a high correlation between these judgments and subsequent performance on a recall task, suggesting that individuals can accurately evaluate what they know (Schwartz and Metcalfe 1994; Son and Metcalfe 2005). Recently, Metcalfe and Greene (2007) demonstrated that metacognition of agency, the ability to make judgments about one's own level of physical control, can be systematically evaluated under controlled laboratory conditions. Using a computerized task designed to examine metacognitive judgments of agency under varying conditions, Metcalfe and Greene (2007) reported that participants could accurately judge when they were 'in control' and when they were not.

Given these considerations, the present study examined the influence of a range of intranasal methamphetamine doses, including doses larger than those previously investigated (0, 12, 25, 50

mg/70 kg), on metacognitive judgments of agency in human research participants. Acutely, methamphetamine increases monoamine neurotransmission (Sulzer et al. 2005). Because dopamine plays a major role in the initiation of movement and locomotion, we hypothesize that methamphetamine will dose-dependently increase hand movements resulting in global performance disruptions following the largest dose (50 mg). Because acute increased activity of dopamine, norepinephrine, and serotonin enhances mood and feelings of well being, we further predict that methamphetamine will dose-dependently increase ratings of control under all task conditions, including conditions where actual control is minimal. This would suggest that under acute methamphetamine intoxication judgment of agency is disrupted. Findings from this study might contribute to a better understanding of methamphetamine-related effects on complex cognitive function, when the drug is administered via a route associated with abuse. The current experiment was part of a larger investigation of the acute and residual physiological and behavioral effects of methamphetamine (Hart et al. 2007).

## Methods

### *Participants*

Ten research volunteers (mean age 30.9 ± 6.7 [± SD]) completed this 4-session inpatient study. Two were female (1 Black, 1 White) and eight participants were male (3 Black, 3 Latino, 2 White). On average, they had completed 13.9 ± 2.0 (mean ± SD) years of formal education. They were solicited via word-of-mouth referral and newspaper and online advertisement in New York City. Before study enrollment, each participant signed a consent form that was approved by the Institutional Review Board of The New York State Psychiatric Institute (NYSPI). All passed comprehensive medical examinations and psychiatric interviews and were within normal weight

ranges according to the 1983 Metropolitan Life Insurance Company height/weight table (body mass index: 24.3 ± 4.5 [mean ± SD]). All met DSM-IV criteria for a current methamphetamine use disorder and none were seeking treatment at the time of study participation. No participant met criteria for any other Axis I disorder. They reported currently using methamphetamine 4 ± 1.8 (mean ± SD) days per week. All participants reported current methamphetamine use via the intranasal route, eight reported previous use via the smoked route, and one reported infrequent intravenous use. Participants reported using methamphetamine for 6.4 ± 5.5 (mean ± SD) years. Six participants reported current cocaine use (1-4 times per week), six reported current marijuana use (1-5 times per week), seven reported current alcohol use (1.5-15 drinks per week), and nine smoked 2-20 tobacco cigarettes per day. Urine toxicology analyses (UCP Drug Screening Test Kit; UCP Biosciences, San Jose, CA) completed during the screening process showed that all participants tested positive for methamphetamine. Additionally, 5 participants tested positive for the marijuana metabolite THC.

Upon discharge, each participant was informed about experimental and drug conditions and was paid for participation at a rate of $60 per day. Two additional male participants (both White) began but did not complete the study. One was dismissed after completing one session due to an unwillingness to follow study protocol and the other withdrew for personal reasons before completing a session.

*Design*

The study design and procedures have been previously detailed (Hart et al. 2007). Briefly, this was a 4-session, inpatient, within-participant, double-blind study. Over a two-week period, four intranasal methamphetamine doses were examined (0, 12, 25, 50 mg/70 kg). In order to

minimize the effects of a previously administered dose, each dose administration was separated by at least 72 hours. Each participant received the entire range of doses and presentation of methamphetamine doses was counterbalanced across participants. Participants completed the metacognition of agency task 45 min after drug administration.

*Procedure*

For the duration of the study, participants resided on the General Clinical Research Service at the NYSPI. They could not receive visitors and could not leave the unit unescorted by a staff member. Participants had access to tobacco cigarettes, but not caffeinated beverages, between sessions. Smoking was not permitted during the sessions and participants were asked to refrain from smoking at least one hour before the start of each session.

Each study day, sessions started at approximately 0915 and began with a baseline measurement of subjective effects, heart rate, and blood pressure (Sentry II-Model 6100 automated vital signs monitor; NBS Medical, Costa Mesa, California, USA). Methamphetamine was administered at approximately 1000 hours, and 45 min later, participants completed the metacognition of agency task. The task was completed on an Apple eMac computer (Apple eMac; Cupertino, California, USA).

*Metacognition of Agency Task*

Prior to admission, participants completed one 8-hr training session on the computerized metacognition of agency task, to familiarize them with the task and study procedures. The task and instructions have been described previously (Metcalfe and Greene 2007). During task completion, participants were required to use a response manipulandum ("mouse") to "catch" X's (targets) and avoid O's (distractors) that descended from the top of their computer monitor's screen. Immediately following the end of each trial, participants were asked to make a judgment of their feeling of control, or judgment of agency, using a 100-mm analog line labeled 'Very Little Control' at one end and 'A Great Deal of Control' at the other end. The task was comprised of two dependent measures: 1) judgment of agency and 2) performance, which was based on the target hit rate (proportion of targets "caught" to the total number of targets presented) and the number of errors of commission (proportion of distractors not avoided to the total number presented). *Enhanced judgment of agency* was operationally defined as increased ratings of control under optimal conditions (described below) and decreased ratings under less than optimal task conditions (described below). *Disrupted judgment of agency* was operationally defined as increased ratings of control under both optimal and less than optimal task conditions. Of course, enhanced or disrupted judgment of agency could only occur during active drug conditions because placebo was used as the comparator condition.

The task consisted of a 2x2x2 within-participant design with 3 replications, randomly ordered, for a total of 24 trials; there were three independent variables: 1) *Turbulence*: the responsiveness of the mouse was altered so that participants' actual level of physical control was manipulated. Under the no turbulence condition, the mouse accurately and appropriately responded to participants' movements. This was operationally defined as the optimal condition.

By contrast, under the turbulence condition, a programmed noise component was added so that the mouse responded unpredictably to participants' movements and therefore was not under the participants' full control. This was operationally defined as the less than optimal condition. 2) *Speed*: the rate of X and O descent was either fast or slow with the fast condition being the more difficult of the two. 3) *Magic*: in the magic-off condition, the participant had to make direct mouse contact with an X to receive credit for the hit. In the magic-on condition, hit rate was enhanced by making the criteria for a target hit more lenient. That is, instead of making direct mouse contact, the participant merely had to come close to an X (within 10 pixels) to receive credit for the hit.

In a recent study of undergraduates, Metcalfe and Greene (2007) found that although the participants' hit rate did not differ between the optimal and less than optimal conditions, their judgments of agency were significantly lower under the less than optimal condition, indicating that they were aware of whether they were or were not "in control."

*Drug*

Methamphetamine HCl, was provided by a National Institute on Drug Abuse (NIDA) contractor and prepared by the New York State Psychiatric Institute research pharmacist. Lactose powder was used as a placebo and 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, even if the participant weighed greater than 84 kg. Participants were instructed to insufflate the entire dose within a 30-sec period in either 1 or 2 nostrils. All drug administrations occurred in a double-blind manner.

*Data Analysis*

Repeated measures analyses of variance (ANOVA) with planned comparisons were used to determine the effects of intranasal methamphetamine on performance and judgments of agency on the metacognition of agency task. The dependent measures were analyzed using dose (0, 12, 25, and 50 mg/70 kg) as the main effect factor. Additionally, all significant interactions between dose and the three factors of the metacognition of agency task (turbulence, speed, and magic) were analyzed for simple dose effects. All comparisons were designed to determine the effects of dose (0 mg vs. three active doses, 12 mg vs. two larger doses, and 25 mg vs. 50 mg). Data were considered statistically significant at $p < 0.05$.

**Results**

*Metacognition of agency*

Under placebo, ratings of control were significantly higher in the no turbulence condition (0.540 ± 0.035 [mean ± SD]) compared with the turbulence condition (0.219 ± 0.022 [mean ± SD], $p < 0.0001$). Similarly, under active dose conditions, mean ratings of control were higher in the no turbulence condition (12 mg = 0.576; 25 mg = 0.558; 50 mg = 0.576) compared with the turbulence condition (12 mg = 0.173; 25 mg = 0.222; 50 mg = 0.230, all comparisons significant at $p < 0.0001$).

Figure 1 illustrates that there was a significant interaction of dose * turbulence * speed [$F(3, 27) = 4.969$, $p < 0.01$]. Under the optimal condition (slow speed and no turbulence) during which participants were in full control of the computer mouse, all active methamphetamine doses increased ratings of control compared with placebo ($p < 0.01$ for all comparisons). Under the less than optimal condition (slow speed and turbulence) in which participants had little control of the

computer mouse, the 12-mg dose decreased ratings of control compared with placebo ($p < 0.01$). Under the fast speed conditions (turbulence and no turbulence), ratings of control did not significantly differ between doses. There were no significant interactions between dose and magic.

*Performance*

Hit Rate. Figure 2 shows how methamphetamine altered hit rate on the metacognition of agency task. Relative to placebo, hit rate was improved only by the 12-mg methamphetamine dose ($p < 0.05$). There were no significant interactions between dose and any factor of the task.

Errors of Commission. Figure 3 illustrates that there was a significant interaction of dose * turbulence * speed [$F(3, 27) = 5.894$, $p < 0.01$]. Under the less than optimal condition (slow speed and turbulence), the 25- and 50-mg doses increased commission errors compared with placebo, as measured by the proportion of distractors not avoided to the total number presented ($p < 0.05$, $p < 0.0001$ respectively). There were no other significant interactions between factors.

**Discussion**

We hypothesized that acute administration of methamphetamine would disrupt judgments of agency, as measured by ratings of control. This was not borne out as the present data show that a single low dose of intranasal methamphetamine (12 mg) enhanced metacognition of agency, while larger doses (25 and 50 mg) did not disrupt judgments of agency and produced limited effects. Under optimal task conditions (i.e., no turbulence/slow speed), all active methamphetamine doses appropriately *increased* ratings of control, whereas under less than optimal task conditions (i.e., turbulence/slow speed), only the 12-mg dose *decreased* ratings of control. Because enhanced judgment of agency was operationally defined as increased ratings of control under optimal conditions and decreased ratings under less than optimal task conditions, only the 12-mg dose enhanced metacognition of agency. It is important to note, however, that no active dose disrupted judgments of agency. In addition, following placebo administration, participants' ratings of control were markedly higher under optimal conditions compared with less than optimal conditions. This result is congruent with data collected using healthy controls (Metcalfe and Greene 2007), and indicates that methamphetamine abusers appropriately recognized whether or not they were in control. Finally, the 12-mg methamphetamine dose improved task performance (i.e., hit rate) and the larger doses (25 and 50 mg) worsened performance (i.e., commission errors). While the demonstration that the 12-mg methamphetamine dose improved psychomotor performance replicates a large database investigating methamphetamine-related effects on performance (Mohs et al. 1978, 1980; Wiegmann et al. 1996; Hart et al. 2002, 2003, 2005; Silber et al. 2006), the finding that metacognition of agency, an executive cognitive domain, was enhanced by intranasal methamphetamine extends previous data.

The observation that the 12-mg dose enhanced judgment of agency, while the other active doses did not, is intriguing because intranasal methamphetamine has been reported to dose-dependently increase "positive" subjective-effect ratings (Hart et al. 2007). This suggests that judgment of agency is not simply a reflection of drug-induced euphoria. The reasons for the observed inverted U-shaped curve effect on judgment of agency, i.e., enhancement only at the lowest dose, are unclear, but several possible explanations exist. First, a large body of literature indicates that optimal dopaminergic activity is critical for improved complex cognitive performance (for review, see Remy 2003; Robbins 2005). For example, Cai and Arnsten (1997) demonstrated in rhesus monkeys that intramuscular administration of a $D_1$ receptor agonist produced dose-related effects on spatial working memory, with the low dose improving performance and the largest dose disrupting performance. Similarly, Zahrt et al. (1997) observed working memory disruptions in rodents after an infusion of a large dose of a $D_1$ receptor agonist into the prefrontal cortex. By contrast, the lower dose did not produce disruptive effects on working memory performance. Because methamphetamine is a potent releaser of monoamine neurotransmitters, including dopamine (Sulzer et al. 2005), it is possible that dopaminergic increases produced by the 12-mg dose were optimal and the increases produced by the larger doses were too excessive for sensitively judging control in the metacognition of agency task. This explanation is speculative and suggests avenues for further investigation.

Another possible explanation for the current findings on judgment of agency is that participants were over-stimulated when they received the larger methamphetamine doses, relative to when they received the 12-mg dose. That is, participants may have been too anxious and this decreased the ability to make sensitive judgments of agency. Data from subjective-effects ratings completed immediately after task performance (Hart et al. 2007) indicate that this

possibility seems unlikely because methamphetamine, at any dose, did not increase ratings of "Anxious," "Jittery," or "On edge." Furthermore, although ratings of "Stimulated" were systematically increased by methamphetamine, they were not near maximum levels (50 mg mean = 49.6), suggesting that participants did not experience adverse stimulant effects. Interestingly, there were no significant methamphetamine-related effects on ratings of "Can't concentrate," "Clumsy," "Confused," and "Unmotivated," further demonstrating that participants were able and willing to complete the metacognition of agency task. Finally, ratings of "Self-confident" were not significantly affected by methamphetamine, indicating that the enhancement of metacognition of agency is not merely associated with a stimulant-induced increase in self-confidence.

One prediction was that task performance would be globally disrupted by the larger methamphetamine doses. Only limited support for this hypothesis was observed as the 25- and 50-mg doses diminished performance under one task condition: the number of commission errors were increased in the less than optimal condition. While it is possible that the larger doses increased participants' hand movements resulting in even less control over the mouse, this seems unlikely because no concomitant decrease in hit rate was observed after these doses. A second potential explanation is that the metacognition of agency task is sensitive to methamphetamine-related effects on inhibitory control. The limited human literature investigating the acute effects of amphetamine on inhibitory control has been mixed. For example, using a Go/No-Go task, Fillmore et al. (2003) found that oral *d*-amphetamine increased the proportion of commission errors following presentation of a false "Go" cue, whereas de Wit and colleagues reported response inhibition improvements (e.g., de Wit et al. 2000, 2002). Further investigation is necessary to determine the impact of the amphetamines on inhibitory control.

The current results should be interpreted within the context of at least three potential limitations. First, only one measure of metacognition of agency was employed. In order to ensure construct validity and enhance the generality of findings, multiple measures probing metacognition of agency should be examined within the same experiment in future studies. Second, the current experiment did not provide a comparison between actual and perceived control because of the programmatic nature of the task. Future investigations should compare ratings of control to actual levels of control. Third, the dosing regimen employed in the current study, a single methamphetamine dose administered per session, appears inconsistent with how the drug is reportedly abused outside of the laboratory. Anecdotally, methamphetamine is commonly used in a binge pattern, consisting of several drug administrations across the day for several days (Gawin and Khalsa-Denison 1996; Cho et al. 2001). It is possible that metacognition of agency, as well as other executive functions, would be disrupted as a result of multiple doses of methamphetamine administered repeatedly. Future investigations should examine the effects of repeated intranasal methamphetamine administration on measures of executive function.

In conclusion, the current findings indicate that a single low dose of intranasal methamphetamine (12 mg) enhanced metacognition of agency and task performance, while larger doses (25 and 50 mg) produced limited effects. These data represent the first investigation of executive cognitive function following acute methamphetamine in abusers and are consistent with a growing database of research indicating that appropriate doses of methamphetamine enhance various cognitive domains. Although limited cognitive disruptions were observed, further study of methamphetamine, employing a dosing schedule that more closely models

methamphetamine use in the natural ecology, is necessary to better understand the cognitive effects of the drug.

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**References**

Cai JX, Arnsten AF (1997) Dose-dependent effects of the dopamine D1 receptor agonists A77636 or SKF81297 on spatial working memory in aged monkeys. J Pharmacol Exp Ther 283: 183-189

Chang L, Ernst T, Speck O, Patel H, DeSilva M, Leonido-Yee M, Miller EN (2002) Perfusion MRI and computerized cognitive test abnormalities in abstinent methamphetamine users. Psychiatry Res 114: 65-79

Cho AK, Melega WP, Kuczenski R, Segal DS (2001) Relevance of pharmacokinetic parameters in animal models of methamphetamine abuse. Synapse 39: 161-166

Comer SD, Hart CL, Ward AS, Haney M, Foltin RW, Fischman MW (2001) Effects of repeated oral methamphetamine administration in humans. Psychopharmacology 155: 397-404

de Wit H, Crean J, Richards JB (2000) Effects of *d*-amphetamine and ethanol on a measure of behavioral inhibition in humans. Behavioral Neuroscience 114: 830-837

de Wit H, Enggasser JL, Richards JB (2002) Acute administration of *d*-amphetamine decreases impulsivity in healthy volunteers. Neuropsychopharmacology 27: 813-825

Fillmore MT, Rush CR, Marczinski CA (2003) Effects of *d*-amphetamine on behavioral control in stimulant abusers: the role of prepotent response tendencies. Drug Alcohol Depend 71: 143-152

Gawin FH, Khalsa-Denison ME (1996) Is craving mood-driven or self-propelled? Sensitization and "street" stimulant addiction. NIDA Res Monogr 163: 224-250

Gerasimov MR, Franceschi M, Volkow ND, Gifford A, Gatley SJ, Marsteller D, Molina PE, Dewey SL (2000) Comparison between intraperitoneal and oral methylphenidate administration: A microdialysis and locomotor activity study. J Pharmacol Exp Ther 295: 51-57

Gonzalez R, Rippeth JD, Carey CL, Heaton RK, Moore DJ, Schweinsburg BC, Cherner M, Grant I (2004) Neurocognitive performance of methamphetamine users discordant for history of marijuana exposure. Drug Alcohol Depend 76: 181-190

Griffiths RR, Bigelow GE, Ator NA (2003) Principles of initial experimental drug abuse liability assessment in humans. Drug Alcohol Depend 70: S41-54

Hart CL, Ward AS, Haney M, Foltin RW, Fischman MW (2001) Methamphetamine self-administration by humans. Psychopharmacology 157: 75-81

Hart CL, Haney M, Foltin RW, Fischman MW (2002) Effects of the NMDA antagonist memantine on human methamphetamine discrimination. Psychopharmacology 164: 376-384

Hart CL, Ward AS, Haney M, Nasser J, Foltin RW (2003) Methamphetamine attenuates disruptions in performance and mood during simulated night-shift work. Psychopharmacology 169: 42-51

Hart CL, Haney M, Nasser J, Foltin RW (2005) Combined effects of methamphetamine and zolpidem on performance and mood during simulated night shift work. Pharmacol Biochem Behav 81: 559-568

Hart CL, Gunderson EW, Perez A, Kirkpatrick MG, Thurmond A, Comer SD, Foltin RW (2007) Acute physiological and behavioral effects of intranasal methamphetamine in humans. Neuropsychopharmacology Sep 12; [Epub ahead of print]

Hoffman WF, Moore M, Templin R, McFarland B, Hitzemann RJ, Mitchell SH (2006) Neuropsychological function and delay discounting in methamphetamine-dependent individuals. Psychopharmacology 188: 162-170

Johanson CE, Frey KA, Lundahl LH, Keenan P, Lockhart N, Roll J, Galloway GP, Koeppe RA, Kilbourn MR, Robbins T, Schuster CR (2006) Cognitive function and nigrostriatal markers in abstinent methamphetamine abusers. Psychopharmacology 185: 327-338

Kalechstein AD, Newton TF, Green M (2003) Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. J Neuropsychiatry Clin Neurosci 15: 215-220

Koriat A (2002) Metacognition research: An interim report. In: Perfect TJ, Schwartz BL (eds) Applied metacognition. Cambridge University Press, New York, pp 261-286

London ED, Berman SM, Voytek B, Simon SL, Mandelkern MA, Monterosso J, Thompson PM, Brody AL, Geaga JA, Hong MS, Hayashi KM, Rawson RA, Ling W (2005) Cerebral metabolic dysfunction and impaired vigilance in recently abstinent methamphetamine abusers. Biol Psychiatry 58: 770-778

Metcalfe J, Greene MJ (2007) Metacognition of agency. J of Exp Psych: General 136: 184-199

Mohs RC, Tinklenberg JR, Roth WT, Kopell BS (1978) Methamphetamine and diphenhydramine effects on the rate of cognitive processing. Psychopharmacology 59: 13-19

Mohs RC, Tinklenberg JR, Roth WT, Kopell BS (1980) Sensitivity of some human cognitive functions to effects of methamphetamine and secobarbital. Drug Alcohol Depend 5: 145-150

Remy P, Samson Y (2003) The role of dopamine in cognition: evidence from functional imaging studies. Curr Opin Neurol 16 Suppl 2: S37-41

Robbins TW (2005) Chemistry of the mind: neurochemical modulation of prefrontal cortical function. J Comp Neurol 493: 140-146

Salo R, Nordahl TE, Possin K, Leamon M, Gibson DR, Galloway GP, Flynn NM, Henik A, Pfefferbaum A, Sullivan EV (2002) Preliminary evidence of reduced cognitive inhibition in methamphetamine-dependent individuals. Psychiatry Res 111: 65-74

Salo R, Nordahl TE, Natsuaki Y, Leamon MH, Galloway GP, Waters C, Moore CD, Buonocore MH (2007) Attentional control and brain metabolite levels in methamphetamine abusers. Biol Psychiatry 61: 1272-1280

Schwartz BL, Metcalfe J (1994) Methodological problems and pitfalls in the study of human metacognition. In: Metcalfe J, Shimamura AP (eds) Metacognition: knowing about knowing. The MIT Press, Cambridge, pp 137-156

Silber BY, Croft RJ, Papafotiou K, Stough C (2006) The acute effects of d-amphetamine and methamphetamine on attention and psychomotor performance. Psychopharmacology 187: 154-169

Simon SL, Domier CP, Sim T, Richardson K, Rawson RA, Ling W (2002) Cognitive performance of current methamphetamine and cocaine abusers. J Addict Dis 21: 61-74

Son LK, Metcalfe J (2005) Judgments of learning: Evidence for a two-stage process. Memory & Cognition 33: 1116-1129.

Sulzer D, Sonders MS, Poulsen NW, Galli A (2005) Mechanisms of neurotransmitter release by amphetamines: a review. Prog Neurobiol 75: 406-433

Talland GA, Quarton GC (1965) The effects of methamphetamine and pentobarbital on the running memory span. Psychopharmacologia 7: 379-382

Thompson PM, Hayashi KM, Simon SL, Geaga JA, Hong MS, Sui Y, Lee JY, Toga AW, Ling W, London ED (2004) Structural abnormalities in the brains of human subjects who use methamphetamine. J Neurosci 24: 6028-6036

Wiegmann DA, Stanny RR, McKay DL, Neri DF, McCardie AH (1996) Methamphetamine effects on cognitive processing during extended wakefulness. Int J Aviat Psychol 6: 379-397

Zahrt J, Taylor JR, Mathew RG, Arnsten AF (1997) Supranormal stimulation of D1 dopamine receptors in the rodent prefrontal cortex impairs spatial working memory performance. J Neurosci 17: 8528-8535

**Figure Legend**

**Figure 1.** Judgment of agency ratings as a function of methamphetamine dose, turbulence, and speed. Error bars represent one SEM. An * indicates significantly different from placebo ($p < 0.05$).

**Figure 2.** Hit rate, defined as the proportion of targets 'caught' to the total number of targets presented, as a function of methamphetamine dose. Error bars represent one SEM. An * indicates significantly different from placebo ($p < 0.05$).

**Figure 3.** Commission Errors, defined as the proportion of distractors not avoided to the total number of distractors presented, as a function of methamphetamine dose. Error bars represent one SEM. An * indicates significantly different from placebo ($p < 0.05$).