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Preliminary evidence of reduced cognitive inhibition in methamphetamine-dependent individuals

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Abstract

Chronic methamphetamine abuse is associated with disruption of frontostriatal function involving serotonin and dopamine circuitry. Clinically, methamphetamine-dependent (MD) individuals are highly distractible and have difficulty focussing. Here, we used a computerized single-trial version of the Stroop Test to examine selective attention and priming in MD. Subject groups comprised eight MD men (31.7 ± 7.2 years of age), who had used methamphetamine for 15.75 ± 8.4 years but were currently abstinent for 2–4 months, and 12 controls ($35.7 + 9.7$ years of age). Compared with the control group, the MD group exhibited significantly greater interference ($P < 0.05$) despite intact priming. Error rates did not differ between the groups. This preliminary finding of reduced cognitive inhibition in MD individuals is consistent with the distractibility they show clinically. Furthermore, the dissociation between explicit attentional performance and priming effects suggests that some attentional functions are not as affected by long-term methamphetamine use as others.

Keywords: Methamphetamine; Cognition; Attention; Stroop

1. Introduction

Methamphetamine (MA) abuse is an increasingly serious problem in the US. Although MA abuse has, in recent years, been concentrated in the Western states, many indicators point to an impending pandemic use across the country (Hunt, 1995). The recent increase of MA abuse in the US and preliminary reports of subsequent effects on behavior and cognition add to the urgency of understanding how MA use affects the function and structure of the brain.

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Brain damage has been examined in multiple animal studies of high-dose MA administration. Studies based upon animal models of stimulant abuse have shown long-term changes in the dopaminergic system in animals, as well as behavioral abnormalities linked to damage of the dopaminergic system (Cadet et al., 1998; Eradiri and Starr, 1999; Ricaurte et al., 1980, 1983, 1984; Wagner et al., 1980). In contrast to animal studies, human studies have been infrequently conducted. Limitations of interpreting the findings from the animal literature include the possibility that brief high-dose administration to animals may not cause the same form of neural and behavioral damage as long-term human use of amphetamines. Consequently, it is essential to seek convergent evidence from studies that examine the neural and behavioral consequences of long-term use on the human brain.

Recent human imaging studies have reported that long-term MA use is associated with damage to both gray and white matter tissue within the frontostriatal regions of the brain (Ernst et al., 2000; Volkow et al., 2001). By understanding the distribution of damage within the cerebral cortex, targeted cognitive studies can then examine the cognitive sequelae of the neural changes. Cognitive tests that are sensitive to abnormalities within the dopaminergic and serotonergic rich frontostriatal regions may be well suited for understanding how MA dependence affects cognitive processing in humans.

Drugs that affect the monoaminergic system, such as amphetamines, can enhance or diminish selective cognitive processes. Some studies have reported that acute doses of MA administered to drug-naive subjects actually produce improvements in cognitive processing (Kornetsky et al., 1959; Seashore and Ivy, 1953; Soetens et al., 1995). Other studies have shown that chronic MA use is associated with impaired performance on tests of verbal memory, psychomotor function and the ability to manipulate information (Rogers et al., 1999; Sim et al., 2002; Simon et al., 2000, 2002; Volkow et al., 2001). These are all cognitive functions associated with frontostriatal regions, which are damaged following substantial MA exposure in both human and animal studies (Ernst et al., 2000; Ricaurte et al. 1984; Villemagne et al. 1998; Volkow et al., 2001)

The goal of the present study was to examine cognitive performance in MA-dependent individuals with a computerized test of selective attention, the Stroop task (Stroop, 1935). Although different versions of the Stroop task are available (MacLeod, 1991; Salo et al., 2001), the computerized single-trial version has been used successfully in clinical populations including schizophrenia (Carter et al., 1992; Salo et al., 1996; Taylor et al., 1996), Parkinson's Disease [PD] (Henik et al., 1993; Stam et al., 1993) and other psychiatric and neurological disorders (see Henik and Salo, submitted). Recent studies have employed the clinical version of the Stroop test to assess attentional performance in MA-dependent individuals (Simon et al., 2000, 2002; Sim et al., 2002), with longer reaction times emerging on the word-color sheet but no significant difference in Stroop interference. Because there are methodological differences between the clinical Stroop version and the single-trial version, the comparison of results from the two versions must be interpreted carefully (Boucart et al., 1999; Henik, 1996; MacLeod, 1991; Salo et al., 2001). Some methodological differences in using a computerized single-trial version as compared to the traditional clinical paper version are that: (1) more precise reaction times can be recorded in milliseconds; (2) reaction times are not summed across a large stimulus set, thus controlling for outliers; (3) errors can be recorded for individual stimuli; and (4) single stimuli can be presented without the presence of distractors that may affect attentional performance in clinical populations (Boucart et al., 1999). The single-trial Stroop version used in this study contained traditional word type conditions: congruent to test facilitation, incongruent to test interference, and neutral to serve as a baseline. This modified version also contained 'priming' sequences, which examined the effect of a previous trial on the next (Lowe, 1979). The analysis of the priming effects provided a measure of the persistence of inhibitory or facilitory processes. The Stroop task has been widely validated as a measure of response inhibition and assesses the ability to inhibit a prepotent response (word reading). Longer reaction times or

higher error rates reflect inefficient inhibition of task-irrelevant responses. Deficits on this task have been reported in patients with schizophrenia (Carter et al., 1992; Perlstein et al., 1998) and Parkinson's patients (Henik et al., 1993; Stam et al., 1993), suggesting an involvement of the dopamine system (Cohen and Servan-Schreiber, 1993).

Deficits in response inhibition and increased distractibility have also been documented in animals (Roberts et al., 1994) and in humans with damage to the dopamine system (Henik et al., 1993). Given the MA-associated disruption in dopamine function, we hypothesized that MA-dependent individuals would exhibit abnormal attentional performance compared to controls due to their lack of efficiency in ignoring distracting information. As the Stroop task has been widely validated as a measure of response conflict and distractibility in clinical populations, (Carter et al., 1992; Ochsner et al., 2001; Perret, 1974; Swick and Jovanovic, 2002), we used the Stroop task to assess attentional deficits in MA-dependent subjects

2. Methods

2.1. Subjects

Eight methamphetamine-dependent [MD] subjects were recruited through two sources: (1) a local substance abuse treatment center and (2) an ongoing NIDA-funded study of health risk factors associated with methamphetamine abuse. All eight subjects had been diagnosed MD according to DSM-IV criteria (American Psychiatric Association, 1994) determined from the Structured Clinical Interview [SCID] (First et al., 1995). Exclusionary criteria included the following: (1) history of significant head trauma or neurological injury; (2) co-existing Axis I disorder; (3) substance dependence other than methamphetamine (except nicotine) within the past year. All subjects reported normal color vision and normal or corrected to normal visual acuity. The eight MD subjects had been abstinent from MA use for a minimum of 8 weeks and a maximum of 16 weeks. Mean length of MA use was 17.25 years (S.D.= 8.46). MD subjects were men with a mean age of 33 years (S.D.=7.50). All MD-dependent subjects also completed a Methamphetamine Experience Questionnaire (MEQ) designed to assess symptoms of paranoia linked to the MA use. The MEQ asks subjects to report paranoid experiences associated with MA use and rate those experiences quantitatively as well as qualitatively and is based on a similar cocaine questionnaire (Gelernter et al., 1994).

Thirteen male controls were recruited from the surrounding community. One man was severely color-blind and thus was unable to perform the Stroop test. The mean age of the remaining 12 controls was 35.7 years (S.D.=9.72). Exclusionary criteria determined from the SCID included the following: (1) history of significant head trauma or neurological injury; (2) presence of an Axis I disorder; (3) history of drug or alcohol abuse within the last year. The MD and control groups did not differ significantly in age ($F<1$). There was a significant difference in education levels ($F_{1,18}=9.1$; $P<0.01$), with the controls having more education (mean=14.7 years; S.D.= 2.70) than the MD-dependent group (mean=11.3 years; S.D.=1.99). Demographic characteristics are reported in Table 1. All subjects signed informed consent and were paid a modest stipend for their participation in the study.

2.2. Stimuli

2.2.1. Stroop priming task

Four colors were employed: red, green, blue, and yellow. The incongruent stimuli were created by printing each of the four color names in the three other ink colors. The congruent stimuli were created by printing each of the four color names in its own color. The neutral stimuli consisted of strings of XXXXs printed in one of the four colors of ink. Each letter within the stimulus words and neutrals was upper case and subtended 1° vertically. The width of each word and neutral displayed varied as a function of the number of letters presented (range 3–6 letters; 2.4–5.4 visual degrees).

There were also three priming conditions: (1) Color–color sequence, the colors of the stimuli on trials *n*-1 and *n* were the same (the word RED in

Table 1
Demographic characteristics of the 8 men with methamphetamine (MA) dependence

Age (in years)	Education (in years)	Duration of MA use	Duration of MA abstinence prior to testing	Lifetime cannabis abuse	Duration of cannabis abstinence prior to testing	Lifetime alcohol abuse	Duration of alcohol abstinence prior to testing	Other abuse
39	12	12 years	90 days	No		No		None
27	12	10 years	90 days	Yes	1 year	No		Cocaine[a]
29	12	19 years	90 days	Yes	15 years	No		None
33	11	20 years	120 days	No		Yes	10 years	Cocaine[b]
28	7	12 years	60 days	No		No		None
43	14	30 years	120 days	Yes	20 years	Yes	8 years	LSD[c]
42	11	28 years	120 days	Yes	26 years	No		None
23	12	7 years	60 days	Yes	7 years	No		None

[a] Two years since last use.
[b] Ten years since last use.
[c] Twenty years since last use.

blue ink followed by the word GREEN in blue ink); (2) Unrelated control sequence, the two stimuli were different in both color and name (the word GREEN in yellow ink followed by the word RED in blue ink); and (3) the Word–color or Negative Priming sequence, the irrelevant word on trial *n*-1 was the same as the relevant color on trial *n*-(the word BLUE in red ink followed by the word GREEN in blue ink). Trial sequences are further described in Table 2.

There were two blocks of trials, each one composed of 162 stimuli: 58 neutrals, 54 congruent and 50 incongruent. The first trial (trial '*n*-1') was not analyzed for negative priming costs, thus served as a filler and was always an incongruent trial. In the critical pairs the leading stimulus was always incongruent and in the filler pairs it could be any one of the three congruency conditions. The trailing stimulus in each critical pair was further analyzed and will be referred to here as a critical stimulus. The practice blocks were not included in the analysis.

2.3. Procedure

Stimuli were presented on a 14″ VGA color monitor. An IBM-compatible computer controlled stimuli presentation and data collection. Voice responses were recorded via a voice-operated relay interfaced to the microcomputer. Response timing was to 1-ms resolution, and stimulus timing was linked to the vertical synchronous pulse. Subjects were instructed to say aloud as rapidly as possible the color of ink that the words were printed in while ignoring the word itself. Subjects were given instructions designed to avoid a speed-accuracy trade-off in that they were told to respond as quickly as they could without making too many mistakes. Each trial began with a blank screen followed by the stimulus at the center of the screen. The onset of the subject's voice triggered the voice-operated relay switch (recorded by the computer to the nearest millisecond) and terminated the stimulus display on the screen. The experimenter then typed in the first letter to record the subject's response accuracy, which also initiated the subsequent trial. The response stimulus interval employed (RSI) was 494 milliseconds (ms).

2.3.1. Methamphetamine questionnaire [MEQ]

The Methamphetamine Experience Questionnaire is a structured interview designed to assess symptoms of paranoia linked to methamphetamine use. The MEQ consists of 24 questions with a series of skip patterns that direct the questioner to the appropriate section. The MEQ asks subjects to report paranoid experiences associated with MA use and rate those experiences quantitatively as well as qualitatively. The MEQ is based on a

Table 2
Operational definition of each constraint

Within-trial stroop effects
Incongruent trials minus neutral trials=interference
Red printed in blue ink–XXXXX printed in green ink
Neutral trials minus congruent trials=facilitation
XXXXX printed in green ink–RED printed in red ink
Between-rial priming effects
Word–color pair minus unrelated pair=negtive priming
Word-color pair
'Trial *n*-1' RED printed in blue
'Trial *n*' GREEN printed in RED*
Unrelated pair
'Trial *n*-1' RED printed in blue
'Trial *n*' GREEN printed in blue*
Unrelated pair minus color-color pair=positive priming
Color-color pair
'Trial *n*-1' RED printed in blue
'Trial *n*' GREEN printed in yellow*
Unrelated pair
'Trial *n*-1' RED printed in blue
'Trial *n*' GREEN printed in blue*

* Reaction time for priming effects time calculated on trial '*n*'.

similar cocaine questionnaire (Gelernter et al., 1994).

2.4. Data analysis

2.4.1. Stroop priming task

Median reaction times (RTs) for correct responses for every condition were computed for each subject. Medians were used instead of means to reduce the influence of outlier responses, which can exaggerate group differences. Analysis of variance (ANOVA) for repeated measures was used to analyze the data in a $2\times3\times3$ mixed ANOVA with group as a between-subjects factor (MD individuals vs. controls) and word-type (congruent vs. incongruent vs. neutral) and priming: color–color (positive), word–color (negative), and unrelated (control) as within-subjects variables. Planned comparisons of within-trial effects for facilitation and interference were performed. Planned comparisons of between-trial effects for negative priming and positive priming were also performed.

3. Results

To calculate Stroop interference, the median RT of all neutral trials was subtracted from the median RT of all incongruent trials. To calculate the Stroop facilitation, the median RT of all congruent trials was subtracted from the median RT of all neutral trials. To calculate negative priming, the RT of the second trial of the unrelated pair (or control pair) was subtracted from the second trail of the word–color pair. To calculate positive priming, the RT of the second trial of the color–color pair was subtracted from the second trial of the unrelated pair (or control pair) (Table 3).

Analyses revealed main effects of group ($F_{1,18}=6.48$, MSe=120, 611, $P<0.05$), word type ($F_{2,36}=55.91$, MSe=10, 545, $P<0.001$) and priming ($F_{2,36}=34.86$; MSe=11, 138, $P<0.001$) as well as an interaction between word type and priming ($F_{4,72}=4.50$, MSe=6, 474, $P<0.005$). In addition, there was a significant interaction between group and word type ($F_{2,36}=4.76$, MSe=10, 545, $P=0.01$). The three-way interaction between group, word type and priming did not reach significant levels ($F<1$). Further analyses were carried out to examine the significant interactions.

Planned analyses revealed that interference effects were greater in the MD subjects (228 ms) compared with controls (122 ms) ($F_{1,18}=5.14$, MSe=15,801, $P=0.034$; Fig. 1). In contrast facilitation effects were virtually identical between the two groups and did not reach significance in either group ($P=0.69$). To control for type I errors, we employed the conservative Greenhouse–Geisser adjustment (Greenhouse and Geisser, 1959) and used the minimum possible degrees of freedom. The analysis survived this statistical adjustment, and the interaction between group and word type remained significant. We also carried out analyses of covariance (ANCOVA) controlling for differences in education and baseline RT. The group differences in interference endured with both education ($P<0.05$) and baseline RTs ($P<0.05$) as covariates (Fig. 1).

Analyses revealed that although there was a main effect of both negative ($F_{1,18}=8.279$; $P=0.01$) and positive ($F_{1,18}=28.893$; $P<0.001$)

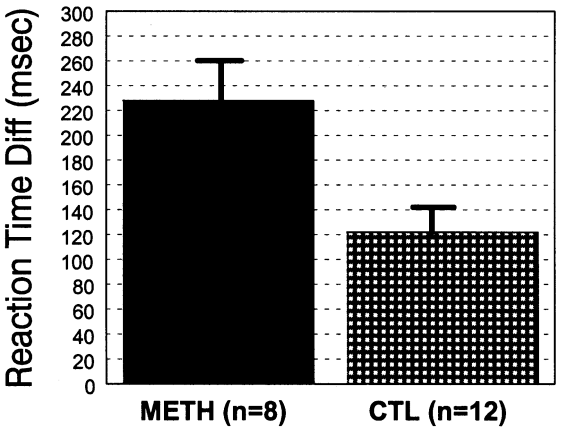

Fig. 1. Group differences in Stroop RT interference in milliseconds.

priming, the groups did not differ significantly on either priming measure ($F < 1$).

3.1. Error analyses

Although error trials were not included in the RT analyses, further analyses examined the effect of error responses on within- and between-trial effects. Analyses revealed a main effect of word-type ($F_{2,36} = 12.37$, MSe = 0.012, $P < 0.001$). Additional comparisons revealed that all groups made significantly more errors in the incongruent condition (11%) than in either the neutral condition (3%) or the congruent condition (2%). No other effects were significant. Analyses revealed no evidence of a speed-accuracy trade-off. In fact there was a positive correlation between reaction times and errors ($r = 0.47$). Subjects with faster reaction times made fewer errors than those with longer reaction times.

3.2. MEQ results

The results from the Methamphetamine Experience Questionnaire (MEQ) were evaluated as they related to the cognitive findings. The analysis showed that those subjects who reported experiencing frequent episodes of paranoia on a Likert scale (0–5) exhibited lower Stroop RT interference (98 ms) compared to those who reported infrequent episodes (307 ms). Although this finding with such a small N must be considered preliminary, it did reach statistical significance ($F_{1,6} = 6.4$; $P = 0.043$).

4. Discussion

Relative to controls, MD subjects exhibited longer reaction times in Stroop interference than in non-interference conditions. This difference in

Table 3
Median reaction times for between-trial and within-trial conditions across groups (in milliseconds)

	M (S.D.) Word–color	*M* (S.D.) Unrelated	*M* (S.D.) Color–color	% Errors
Controls				
Congruent	682 (93)	658 (73)	561 (56)	0.01 (0.02)
Incongruent	840 (170)	820 (146)	658 (75)	0.09 (0.14)
Neutral	693 (93)	651 (96)	608 (82)	0.02 (0.04)
Interference	147	169	50	
Facilitation	11	−7	47	
Error data	0.06 (0.14)	0.03 (0.03)	0.03 (0.03)	
MD subjects				
Congruent	829 (204)	745 (155)	641 (118)	0.03 (0.06)
Incongruent	1048 (253)	1068 (297)	810 (213)	0.13 (0.13)
Neutral	818 (154)	748 (122)	676 (137)	0.04 (0.06)
Interference	230	320	134	
Facilitation	11	−3	35	
Error data	0.08 (0.14)	0.07 (0.09)	0.05 (0.06)	

MD, methamphetamine-dependent.

Stroop interference held up when differences in education were taken into account. We interpret these prolonged reaction times to reflect a response-selection deficit arising from an impaired ability to suppress irrelevant information. This finding is consistent with the clinical observation that persons who use methamphetamine often appear distractible and have problems in concentration. The deficit in selective inhibition was present despite normal negative priming. Priming is considered an implicit or unconscious measure of processing that results from previous exposure to a stimulus or an event (Tulving and Schacter, 1990). Observed priming effects signify that the information has been processed at some level, but in some cases the information may not be accessible to conscious recollection or processing. In this case, although the increased interference observed in the MD subjects suggests that the conscious inhibition of the word reading was not efficiently carried out at the time of selection, there was at some level an inhibitory tag, which is believed to produce the negative priming observed in both MD subjects and controls (Neill et al., 1992; Salo et al., 1996). Intact priming effects are often preserved in patients with global amnesia or material-specific declarative memory impairment even when explicit memory deficits are evident (Graf et al., 1985; Squire and Zola-Morgan, 1988).

On this same Stroop negative priming task, unmedicated schizophrenia outpatients and medicated state hospital patients with a diagnosis of schizophrenia failed to exhibit negative priming but showed Stroop interference comparable to findings in matched controls (Salo et al., 1996, 2002). This pattern in the schizophrenia patients is the opposite of that seen in the MD subjects (i.e. increased interference in MD subjects, but normal interference levels in schizophrenia patients). Abnormalities of the dopamine system have been linked to schizophrenia and, acutely, some of the behaviors associated with methamphetamine abuse can mimic those of schizophrenia (e.g. paranoid delusions); thus a comparison of attentional performance between schizophrenia and MD individuals is relevant. Further to this point, the MEQ data suggest a possible relationship between the frequency of paranoid episodes and the magnitude of Stroop interference exhibited, and could suggest, if replicated, greater vigilance and focused attention in those MD subjects with a history of frequent paranoid episodes. Deficits on the Stroop task have also been observed as a result of Parkinson's disease (Henik et al., 1993; Stam et al., 1993). Because dopamine function may be altered in all three of these patient groups, the comparison of attentional abnormalities in Parkinson's patients, schizophrenia patients and MD subjects may contribute to our understanding of how dopaminergic systems modulate attentional performance.

Although the sample size ($N=8$) is a limitation of this study, it should be noted that the exclusionary criteria were stringent. All of the subjects were rigorously screened for co-existing Axis I disorders, and all eight MD subjects had been abstinent from MA use for a minimum of 8 weeks. The sample was subject to similar rigor in selection to minimize the presence of other substance abuse. Although five of the subjects met DSM-IV criteria for past cannabis abuse, the subjects tested reported no use of cannabis in the immediate period preceding the testing (see Table 1). This exclusionary criterion allowed us to minimize the effects of both co-morbid psychiatric disorders and other substances on the results.

Cognitive testing cannot dissociate whether dopamine alone mediates particular cognitive processes, but dissociations in cognitive performance can indicate whether certain brain regions are involved and are necessary to support particular cognitive processes. Even tasks that depend on selective brain regions or neurotransmitter systems commonly also require other brain regions and other neurotransmitter systems. By using a task that measured reaction time in milliseconds, we were, however, able to detect isolated cognitive deficits in MD subjects compared with matched controls. The use of a Stroop priming design allowed for both the measurement of explicit (Stroop interference) and implicit (priming) processes. This dissociation between conscious selective attention and priming, an implicit or unconscious measure of inhibition, suggests that

distinct systems or separate pathways are involved in accessing these different cognitive processes.

The finding of increased Stroop interference in MD subjects is consistent with the clinical observation that MD subjects appear distractible and have difficulty focussing attention. In addition a small but positive correlation between baseline RT and Stroop interference suggests that long-term MA use may contribute to slowing, which in turn may contribute to less efficient attentional processing. The convergent finding of damage to the frontostriatal networks in both human and animal MA studies suggests that the response-inhibition deficits observed in the MD subjects may be a result of altered functioning within cortical networks. Patients who have undergone surgical cingulotomies, patients with lesions to the anterior cingulate (ACC) and patients with lesions to the prefrontal cortex also exhibit increased Stroop interference (Ochsner et al., 2001; Perret, 1974; Swick and Jovanovic, 2002; Turken and Swick, 1999). Thus, the ability to efficiently monitor response conflict and suppress irrelevant information may be mediated by the prefrontal cortex and the anterior cingulate, areas within the frontostriatal region. Recent imaging studies have implicated the ACC as a region responsible for detecting response-conflict situations, while alerting other regions such as the prefrontal cortex to implement strategic processes to resolve the conflict (Carter et al., 2000; MacDonald et al., 2000). Thus, damage to the frontostriatal regions in MA-dependent users may result in deficits related to resolving conflict (Nordahl et al., 2001). Increased knowledge about the relationship of brain function to behavior can be a valuable tool to guide treatment strategies and pharmacological interventions, and should constitute an important contribution to the neuroscience of drug addiction.

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