

Overlapping Cognitive Patterns in Schizophrenia and Methamphetamine Dependence

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Objective: To examine whether overlapping cognitive deficits exist in currently drug-abstinent chronic methamphetamine (MA) abusers and schizophrenia (SZ) patients.

Background: Both SZ and chronic MA abuse are associated with frontostriatal disruption as well as deficits in cognitive control, such as selective attention. To identify overlapping cognitive profiles, we compared performance of the 2 groups on the Stroop attention task.

Methods: Data were analyzed from 69 MA abusers who had been MA-abstinent for differing periods of time and from 23 SZ patients and 38 non-substance-abusing controls.

Results: The MA abusers in early abstinence displayed more Stroop interference than the SZ patients ($P = 0.004$), long-term abstinent MA abusers ($P = 0.009$), and controls ($P = 0.002$). In the MA abusers, the magnitude of Stroop interference correlated positively with longer drug use ($P = 0.01$) and negatively with longer drug abstinence ($P = 0.04$). No correlations were found between psychotic symptoms and task performance.

Conclusions: On this task of attentional selection, only the MA abusers in early stages of abstinence showed performance deficits compared with controls. More research is needed to further elucidate overlapping patterns between MA abuse and SZ.

Key Words: schizophrenia, methamphetamine, selective attention, Stroop, cognition

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In the process of everyday functioning, human beings are confronted with many objects and events to which they must respond. Selection of task-relevant information is a critical element of successful behavior, and requires the engagement of top-down cognitive control mechanisms. Cognitive control can be defined as the ability to adapt behavior flexibly to current demands, by engaging attention to task-relevant information over time in the face of interference or competition from irrelevant information.¹ Deficits in cognitive control have been documented in a number of clinical populations, including those with psychiatric disorders such as schizophrenia (SZ)^{2–8} and those with long-term stimulant abuse, including methamphetamine (MA).^{9–15}

In addition to deficits in cognitive control, both SZ patients and MA abusers share a similar behavioral and neural profile, in that both groups (1) report hallucinations and delusions, (2) exhibit signs of distractibility, and (3) display altered patterns of neural activation that involve dopamine-rich frontostriatal brain regions.^{16–18} Given this overlapping profile across numerous domains, including cognition, it is surprising that relatively few studies have directly compared the 2 groups.¹⁹ As both MA abuse and SZ are linked to abnormalities within the dopamine system, the identification of overlapping as well as unique patterns between the 2 groups may give rise to a better understanding of the neural substrates involved in psychosis and cognitive deficits linked to the dopamine system.

Given that cognitive control deficits have been reported in both SZ patients and MA abusers, it was of specific interest to us to compare cognitive performance between the 2 groups.^{8,15,20–23} Many findings of reduced cognitive control have been linked to abnormal prefrontal function and reduced context processing in SZ and MA abuse.^{2,8,10,14,15,20,24–26} Although cognitive deficits have been linked to psychiatric symptoms and functional outcomes in patients with SZ,^{27–29} less work has been carried out in substance abuse. Current models of addiction propose that deficits in behavioral regulation and cognitive control may contribute to habitual and sustained drug abuse.³⁰ For example, substance abusers may be less able to engage cognitive control to overcome automatic, prepotent response tendencies (compulsive drug use), and are thus less likely to carry out behaviors associated with long-term rewards and positive outcomes (abstaining from drug use).

A number of tasks measure the ability to exert cognitive control, including the widely validated test of attentional selection, the Stroop color-word task. In the computerized single-trial version of the Stroop color-word task that we used, participants are presented with names of colors (eg, red, green, blue, yellow) that are printed in font colors that either match the word meaning (eg, red, printed in red ink) or are in conflict with the word meaning (eg, red, printed in blue ink). Participants are instructed to name the font color of the word that appears on the screen, and to ignore the meaning of the word. Thus, the Stroop task measures the ability to attend to task-relevant information (font color) and override a prepotent but irrelevant task response (reading the word rather than naming the color).^{31–33} Although multiple versions of the Stroop task are available,^{34,35} we chose to administer the computerized single-trial version because (1) more precise reaction times (RTs) can be recorded in milliseconds; (2) RTs are not summed across a large stimulus set, thus controlling for outliers; (3) errors can be recorded for individual stimuli; and (4) single-word stimuli can be presented without distractors that may impact attentional performance in clinical populations over and above a potential effect of response interference.^{35,36}

To measure overlapping cognitive patterns between long-term MA abusers during differing periods of MA abstinence and SZ patients, we combined previously published behavioral data from studies that compared 69 currently drug-abstinent MA-dependent subjects to controls, with previously published data from 23 subjects with SZ.^{22,23,37,38} All data reported in the current study were generated using the same computerized single-trial version of the Stroop attention task, with identical experimental parameters (eg, stimulus timing, display size). Our hypotheses were: (1) Stroop interference effects would not differ between the SZ patients and matched controls (consistent with Salo et al³⁹); and (2) we would find increased Stroop RT interference effects in the MA abusers.^{22,37}

Although early Stroop studies conducted in SZ patients did report increased Stroop effects, many of them used a card version that presented multiple words in a “cluttered field display.”^{40–43} In the card version, participants are presented with a series of cards containing 50 to 100 stimuli for one condition only (eg, incongruent stimuli), and are asked to name the ink color of each stimulus without stopping. The total time per card is the measure of performance.⁴⁴ Other studies conducted since have demonstrated that the form of the Stroop task administered can affect the magnitude of Stroop interference in both SZ patients³⁶ and healthy controls.³⁵ Because we collected our data with a single-trial Stroop design, we predicted no differences in Stroop interference between the SZ patients and controls.^{39,45,46} Furthermore, we predicted that the short-term MA-abstinent abusers would display more interference than the SZ patients. We based these predictions on the acute neurotoxic effects of MA on the anterior cingulate cortex and the prefrontal cortex that appear early in sobriety.^{47,48} We also predicted

positive correlations in the MA abusers between the magnitude of Stroop RT interference and years of abuse. Although our previous studies have not revealed a pattern of increased interference between SZ patients and controls, we analyzed the relationship between duration of illness and Stroop interference among the SZ patients as an analogous variable to duration of drug use in the MA abusers.

MATERIALS AND METHODS

Subjects

The data in this paper were pooled from our previously published studies. Thus, the recruitment methods described are those that we used for all the groups in the original studies.

MA Abusers

We recruited all 69 MA-dependent subjects (28 males and 41 females) through outpatient substance abuse treatment centers. Of the total, 41 had not used MA for between 3 weeks and 6 months before the study, and 28 had not used MA for at least 1 year before the study.

The short-term and long-term abstinent MA abusers did not differ from each other in age [$F(1, 67) = 1.14$; $P = 0.29$], years of MA use ($F < 1$), education ($F < 1$), or premorbid intelligence quotient as determined by the National Adult Reading Test ($F < 1$) (Table 1). The combined MA group did not differ significantly in age from either the controls ($F < 1$) or the SZ patients ($P = 0.10$). However, additional analyses revealed that the long-term abstinent group was slightly older than the controls ($P = 0.043$). There was also a significant age difference between the controls and SZ patients [$F(1, 56) = 8.03$; $P = 0.006$]. There was a significant group difference in education levels [$F(3, 128) = 10.9$; $P = < 0.0001$], with the controls having more education than the short-term abstinent group (mean = 12.6 y; SD = 1.8), the long-term abstinent group (mean = 12.6 y; SD = 1.6), and SZ subjects (mean = 12.8 y; SD = 1.7).

All 69 MA-abusing subjects had been diagnosed with MA dependence by the Structured Clinical Interview for DSM Disorders (SCID) and had been drug-abstinent for a minimum of 3 weeks (Table 2).⁴⁹ Random urine screens were performed at the referring sites to verify drug abstinence, and none of the screens yielded positive results. Exclusionary criteria were (1) a history of significant head trauma or neurological injury, (2) a co-occurring non-substance-related Axis I disorder, or (3) substance dependence other than MA (except nicotine) within the past year, or alcohol abuse within the past 5 years.

SZ Patients

The SZ group included 23 patients, 21 with SZ and 2 with schizoaffective disorder. The data from 2 male patients were excluded from the analysis because of an excessive number of errors on the Stroop task (> 25%).

TABLE 1. Demographic Characteristics of Participants

	Control Subjects (n = 38)	Recent Abstinent MA Abusers (n = 41)	Distant Abstinent MA Abusers (n = 28)	SZ Patients (n = 23)
Age (y), mean (SD)	33.8 (9.3)	36.2 (8.9)	38.4 (7.7)*	40.0 (8.3)†
Females	17	22	19	6
Education (y), mean (SD)	14.5 (2.1)	12.6 (1.8)†	12.8 (1.7)†	12.8 (1.7)†
NART score	114.0 (7.3)	107.0 (5.3)†	106.9 (5.7)†	—
Right handed	36	39	26	21

*Significantly different from control group at $P < 0.05$.

†Significantly different from control group at $P < 0.01$.

MA indicates methamphetamine; SZ, schizophrenia; NART, National Adult Reading Test.

The exclusion of these 2 patients did not significantly alter the demographic distribution.

All of the SZ patients had been diagnosed according to *DSM-IV* criteria, were medicated, and had used the same neuroleptic medication for at least 2 months before participating in the study, and at a fixed dosage for at least 2 weeks (Table 3). The SZ patients were interviewed by a psychiatrist and underwent an abbreviated version of the SCID. All of the SZ patients were administered the Scales for the Assessment of Positive and Negative Symptoms interviews to assess their psychiatric symptoms. Exclusionary criteria for this group were (1) a history of significant head trauma or neurological injury, (2) coexisting Axis II disorder, and (3) a history of drug or alcohol abuse within the past year.

Controls

We recruited 38 non-substance using controls (21 males and 17 females) from the surrounding community. Exclusionary criteria determined from the SCID were (1) a history of significant head trauma or neurological injury, (2) an Axis I disorder, (3) a history of drug or alcohol abuse within the past year, and (4) a family history of psychiatric illness.

All study participants reported normal color vision and had normal or corrected-to-normal visual acuity. They signed informed consent and were paid a modest stipend for participating in the study.

Apparatus

Stimuli were presented on a 14-inch VGA color monitor. A personal computer controlled stimulus presentation and data collection. Voice responses were

TABLE 2. Substance Use Characteristics of Abstinent Methamphetamine Abusers

	Recent Abstinent (n = 41)	Distant Abstinent (n = 28)
Duration (y), mean (SD)	14.2 (8.4)	13.3 (6.7)
Months abstinent, mean (SD)	2.7 (1.6)	51.9 (34.1)*
Age of first use, years, mean (SD)	19.3 (5.2)	18.8 (7.4)
Tobacco smokers	24	22

*Significantly different at $P < 0.01$.

MA indicates methamphetamine.

recorded through a voice-operated relay connected to the computer.

Stimuli

We used 4 colors: red, green, blue, and yellow. For the incongruent stimuli, we presented each of the 4 color names on the computer screen in each of the 3 other font colors. For the congruent stimuli, we displayed each of the 4 color names in its own font color. The neutral stimuli consisted of strings of XXXXs displayed in 1 of the 4 colors. All words were in upper-case letters and subtended 1 vertical degree. The width of each word display varied as a function of the word presented (range 3 to 6 letters; approximately 2.4 to 5.4 visual degrees). Supplemental Digital Content 1, <http://links.lww.com/CBN/A14> illustrates the color and word combinations.

Procedure

Subjects were instructed to name the font color while ignoring the word itself. They were told to avoid a speed/accuracy tradeoff. Each trial began with a blank screen, followed by the word 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

TABLE 3. Symptom and Medication Data from the 23 Schizophrenia Subjects

Symptoms		
Onset of illness (age)	24.5 (± 7.3)	
Chronicity (y)	15.9 (± 9.1)	
SAPS rating (mean)	17.8 (± 14.9)	
Medication		
	No. Patients	Mean Dose (mg)
Quetiapine	7	255
Sertindole	3	18.6
Clozapine	5	305
Risperidone	2	8
Haloperidol	3	7.5
Valproic acid	2	1500
Chlorpromazine	1	1500
Thioridazine	1	125
Loxapine	1	25
Thiothixene	1	20
Benzodiazepenes	3	—
Anticholinergics	4	—

The data from 2 patients were excluded due to excessive errors. SAPS indicates Scale for Assessment of Positive Symptoms.

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. The fixed response stimulus interval was 494 ms. There were 2 blocks of trials, each composed of 162 stimuli: 58 neutral, 54 congruent, and 50 incongruent. An introductory practice block was not included in the analysis.

Data Analysis

Median RTs for every condition were computed for each subject. Only correct responses were included in the RT analyses. Medians were used instead of means, to reduce the influence of outlier responses, which can exaggerate group differences, especially in patient studies.⁵⁰ Analysis of variance procedures for repeated measures were used to analyze the data in a 4 × 3 mixed design with "group" as a between-subjects factor (short-term abstinent vs. long-term abstinent vs. SZ vs. controls) and "word type" (incongruent vs. neutral vs. congruent) as the within-subjects factor. Further analyses were conducted to examine error responses and speed-accuracy patterns. Planned comparisons of interference (median incongruent RT minus median neutral RT) and facilitation (median neutral RT minus median congruent RT) were performed.

RESULTS

RT Analysis

Analyses revealed main effects of group [$F(3, 126) = 10.47$; $P > 0.0001$] and Stroop word type [$F(2, 252) = 588.11$; $P < 0.001$], as well as a significant interaction between group and word type [$F(6, 242) = 4.87$; $P < 0.001$]. Planned analyses revealed that interference effects (incongruent vs. neutral) were greater in the short-term abstinent MA abusers (177 ms) than in the controls (130 ms) ($P = 0.002$), SZ patients (120 ms) ($P = 0.004$), and long-term abstinent MA abusers (131 ms) ($P = 0.009$). RT interference effects did not differ significantly between the long-term abstinent MA abusers and the SZ patients ($P = 0.58$), between the long-term abstinent MA abusers and controls ($P = 0.95$), or between the SZ patients and controls ($P = 0.52$). No sex differences emerged within the MA abusers ($P = 0.33$) or within the controls ($P = 0.27$). We performed analyses of covariance controlling for differences in baseline RT, education, and parental education scores. The group differences in interference endured when baseline RT, age, and education were used as covariates. We examined facilitation effects (neutral vs. congruent); no significant group by Stroop interactions emerged [$F(3, 126) = 1.39$; $P = 0.25$]. Specifically, all groups showed the same pattern of faster RTs to the congruent stimuli than to the neutral stimuli.

Error Analyses

Although error trials were not included in the RT analyses, further analyses examined the effect of error responses on Stroop effects (Table 4). All 4 groups made significantly more errors in the incongruent condition

TABLE 4. Median Reaction Times and % Accuracy for Within-trial Stroop Conditions Across Groups

	Reaction Time in milliseconds (SD)	% Errors
Controls (n = 38)		
Incongruent	757 (94.0)	0.09 (0.09)
Neutral	627 (72.1)	0.01 (0.02)
Interference	130	—
Baseline reaction time	664 (104.8)	—
Short-term Abstinent MA Abusers (n = 41)		
Incongruent	852 (133.8)	0.10 (0.09)
Neutral	675 (87.9)	0.01 (0.01)
Interference	177*	—
Baseline reaction time	724 (138.4)	—
Long-term Abstinent MA Abusers (n = 28)		
Incongruent	780 (111.4)	0.07 (0.04)
Neutral	649 (63.6)	0.01 (0.01)
Interference	131	—
Baseline reaction time	684 (108.1)	—
SZ Patients (n = 23)		
Incongruent	900 (200.6)	0.07 (0.07)
Neutral	780 (150.9)	0.02 (0.02)
Interference	120	—
Baseline reaction time	808 (174)	—

*Significantly different from control group and distant abstinent MA abusers at $P < 0.01$.

MA indicates methamphetamine; SZ, schizophrenia.

(8%) than the neutral condition (1%). The error rates did not differ among the 4 groups ($F < 1$). Analyses revealed no evidence of a speed-accuracy trade-off for any of the 4 groups (short-term abstinent MA abusers: $r = 0.19$, $P = 0.23$; long-term abstinent MA abusers: $r = 0.24$, $P = 0.21$; SZ: $r = 0.04$, $P = 0.85$; controls: $r = 0.009$, $P = 0.96$). In fact, among the 69 MA abusers, there was a slight trend for those subjects with faster RTs to make fewer conflict errors than those with longer RTs.

Correlations with Symptoms and Drug Use Patterns

Given the range of symptoms in any study of psychiatric disorders, we wanted to examine whether drug use patterns and psychiatric symptoms correlated with cognitive performance in our 69 MA abusers and 23 SZ patients. Given our previously published finding of a relationship between duration of drug abstinence and cognitive performance,²² we examined whether a similar correlation existed in our current expanded data set of MA abusers. Consistent with our previous findings, regression analyses in the MA abusers revealed a positive correlation between Stroop interference and duration of MA use ($r = 0.30$; $P = 0.01$) and a negative correlation with months of MA abstinence ($r = 0.25$; $P = 0.03$). In other words, the MA abusers with longer periods of drug use performed worse on the task, whereas the MA abusers with extended periods of MA sobriety performed better. Similar analyses in the 23 SZ patients using

duration of illness as a regression variable failed to reach significance ($r = 0.13$; $P = 0.54$), perhaps because of the limited sample size.

As both the MA abusers and SZ patients reported psychotic symptoms, we wanted to examine whether these symptoms correlated with their cognitive performance. Among the 69 MA abusers, 68% ($n = 47$) reported a history of MA-induced psychotic symptoms, including paranoid delusions and hallucinations. Although weak correlations have been observed in SZ patients between positive symptoms (eg, delusions and hallucinations) and cognitive processes, less is known about such a relationship with drug-induced psychoses.⁵¹ Given that such a large percentage of MA abusers experience drug-induced psychosis, it was of interest to examine this relationship.

We observed no difference in Stroop interference effects between our MA abusers with a history of MA-induced psychosis and those with no history [$F(1, 67) = 0.14$; $P = 0.71$]. Furthermore, we examined the correlation between Stroop interference and the frequency of MA-induced psychotic episodes among those MA abusers with a history of MA-induced psychosis. We did not find a significant correlation between the frequency of MA-induced psychotic episodes and Stroop interference ($r = 0.008$, $P = 0.96$). We then examined the Scales for the Assessment of Positive Symptoms scores from our 23 SZ patients to determine if any relationship existed between scores of positive symptoms (delusions and hallucinations) and performance on the Stroop task. Analyses revealed no correlation ($r = 0.112$, $P = 0.62$). As these SZ patients were relatively high functioning, they did not have prominent negative symptoms.

DISCUSSION

We found that the MA abusers in early stages of abstinence (3 wk to 6 mo) exhibited greater deficits in attentional selection and cognitive control than the SZ subjects, controls, and MA abusers who had stopped abusing MA longer than 1 year before the study. Significant correlations were observed between duration of MA use, time of sobriety, and performance on the Stroop task. Longer periods of MA abstinence seemed to improve performance, while longer durations of use correlated with greater task deficits. These findings are consistent with other published studies that have reported cognitive deficits during the early periods of MA abstinence.^{52,53} Importantly, although the short-term abstinent MA abusers displayed significantly greater RT interference than the long-term abstinent MA abusers, they did not differ on baseline RT, demonstrating that overall slowing is not the underlying mechanism producing the group differences. Furthermore, it was only the SZ patients who were significantly slower than all the other subjects, yet their pattern of performance on the Stroop task was similar to both the controls and the long-term abstinent MA abusers.

It is perhaps unexpected that the MA abusers in early abstinence would perform worse than the SZ

patients. However, a careful review of the Stroop literature suggests that studies that have reported increased RT Stroop interference in patients with SZ used a different form of the Stroop task (ie, card version), which may have placed additional cognitive demands on the SZ patients. (For a review, see Henik and Salo.⁵⁴) The majority of single-trial Stroop studies have actually reported equivalent Stroop RT interference between SZ patients and controls.^{31,45,55-58} In several of these studies, SZ patients showed more facilitation than normal controls, but no difference in RT interference.^{31,59} Similar findings of equivalent Stroop RT interference in SZ patients have also been reported in priming experiments that used Stroop stimuli^{38,46,60,61} and in neuroimaging studies.^{62,63} Other studies that have measured top-down behavioral control have also failed to find deficits in SZ patients.⁶⁴ In a study that used the Attention Network Test, SZ patients displayed decreased alerting efficiency but no deficits in top-down control. Thus, the lack of increased Stroop RT interference observed in our study is indeed consistent with the literature.

Our data cannot answer why the short-term abstinent MA abusers exhibited greater RT interference than the SZ patients. Dysfunction has been observed within the anterior cingulate and prefrontal cortices of both groups; thus, one might predict similar performance deficits.^{8,15,21,25,62,65,66} One possible mechanism for the greater deficits in the short-term abstinent MA group than the SZ patients is that the acute neurotoxic effects of MA early in abstinence might have more profound effects on the anterior cingulate cortex and prefrontal cortex.^{45,47,67} This could explain the differences in Stroop RT interference observed between the short-term and long-term abstinent MA abusers. As mentioned, our 23 SZ patients were relatively high functioning. It is quite possible that more severely ill patients might have exhibited more pronounced deficits on the Stroop task. Nonetheless, our patients had been ill for an average of 16 years, and their average age was 40. More studies are needed to explore this issue.

We found no significant relationships between psychotic symptoms and cognitive performance across the clinical groups. These findings are consistent with findings in the SZ literature, in which weak correlations have been observed between cognitive performance and symptoms.⁵¹ Thus, neither the symptoms of SZ nor the drug-induced psychotic symptoms associated with long-term MA use seem to underlie our patients' cognitive patterns. More work is needed to examine this issue in substance abuse. It is important to keep in mind that the data in this study can address performance on only 1 aspect of attentional function, the ability to attend selectively and suppress a prepotent response within each trial. We do not claim that these results are generalizable to a broader range of cognitive processes.

Limitations

Among our 69 MA abusers, it is possible that a history of drug abuse other than MA, a common

comorbidity in such individuals, could have contributed to the cognitive patterns that we observed. To minimize this risk, we studied patients whose primary drug of choice was MA, with no dependence on other drugs beside nicotine, and who had not abused alcohol for at least 5 years before the study. It is also possible that differences in age and education could have impacted the results; however, statistical analyses covarying for these demographic differences did not alter the findings.

CONCLUSIONS

Although there are overlapping clinical and cognitive similarities between MA abusers and SZ patients, few studies have directly measured attentional performance between these 2 groups.¹⁹ A major strength of our study is that all 130 subjects across the 4 groups were tested on exactly the same computerized version of the Stroop attention task, using identical experimental parameters. We did not find that general slowing was a source of the group differences. Instead, for our task, the residual effects of MA during the first 6 months of abstinence seem to be causing the most pronounced cognitive deficits. We did not detect a relationship between psychotic symptoms and cognitive performance, although both groups reported such symptoms. Neither the drug-induced psychotic symptoms in the MA abusers nor the severity of symptoms in the SZ patients seemed to correlate with performance.

Although this was not designed as a clinical study, the improved attentional performance in the group who had stopped abusing MA for at least 12 months suggests that they can make adaptive changes. Specifically, their greater ability than the short-term abstinent MA group to shift attention from a prepotent response in the Stroop task may correlate with their ability to resist the prepotent response to use illicit drugs. Such cognitive improvements have the potential to be used to predict treatment outcome. The pattern of cognitive performance in the SZ patients is more difficult to interpret from a clinical perspective. Because our 23 SZ patients were high functioning, it is difficult to generalize across the disorder. Further studies using broader measures of cognitive function in larger groups of MA and SZ patients are needed to assess their overlapping cognitive patterns.

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