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THE IMPACT OF CLINICAL AND DEMOGRAPHIC VARIABLES ON COGNITIVE PERFORMANCE IN METHAMPHETAMINE- DEPENDENT INDIVIDUALS IN RURAL SOUTH CAROLINA

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Abstract

Inconsistencies in reports on methamphetamine (METH) associated cognitive dysfunction may be attributed, at least in part, to the diversity of study sample features (egg, clinical and demographic characteristics). The current study assessed cognitive function in a METH-dependent population from rural South Carolina, and the impact of demographic and clinical characteristics on performance. Seventy-one male (28.2%) and female (71.8%) METH-dependent subjects were administered a battery of neurocognitive tests including the Test of Memory Malingering (TOMM), Shipley Institute of Living Scale, Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), Grooved Pegboard Test, California Verbal Learning Test (CVLT), and Wisconsin Card Sorting Test (WCST). Demographic and clinical characteristics (egg, gender, frequency of METH use) were examined as predictors of performance. Subjects scored significantly lower than expected on one test of attention and one of fine motor function, but performed adequately on all other tests. There were no predictors of performance on attention; however, more frequent METH use was associated with better performance for males and worse for females on fine motor skills. The METH-dependent individuals in this population exhibit very limited cognitive impairment. The marked differences in education, Intellectual Quotient (IQ), and gender in our sample when compared to the published literature may contribute to these findings. Characterization of the impact of clinical and/or demographic features on cognitive deficits could be important in guiding the development of treatment interventions.

Introduction

In 2007, there were an estimated 529,000 current users of methamphetamine (METH) in the United States, 1 and substantial attention has been directed toward characterizing the chronic effects of METH use on neurobiological and neuropsychiatric functioning. Heavy METH use is associated with psychopathology, including mood and anxiety disorders,^{2–5} psychosis,^{3,6} and cognitive deficits.^{7–9} Neuroimaging studies suggest that METH can be neurotoxic, leading to changes in serotonin and dopamine function and alterations of cerebral blood flow.¹⁰ The neurotoxicity associated with METH use may contribute to continued use of METH and high propensity to relapse, as a result of neuronal alterations in reward pathways and changes in inhibitory control or other domains of cognitive function.

Findings from studies of chronic METH use are confounded by demographic differences in study populations, testing different domains of cognitive function (as well as the use of

different tests within each domain), METH use variables (egg, abstinent vs. using, period of abstinence, duration or amount of use, etc.), and the presence of psychiatric comorbidities. Multiple studies have assessed selective aspects of cognitive functioning in METH-dependent individuals, and a recent meta-analysis was constructed to evaluate the collective results of 18 studies comparing METH users versus controls.⁹ The largest effect sizes (i.e., the greatest deficits in METH users) were seen in the domains of executive function, learning, and memory; medium effect sizes were seen in information processing and motor skills; and slightly smaller effect sizes were seen in attention/working memory, visuoconstruction, and language.⁹

Analyses of explanatory demographic variables have yielded equivocal results. Some studies have reported that rates of cognitive impairment correlate with frequency¹¹ or amount¹² of METH use, while others show no associations of cognitive function with measures of the severity of METH dependence or the frequency, amount, or duration of METH use.^{13–16} In the recent meta-analysis of the neurocognitive effects of METH,⁹ gender had an influence on the magnitude of the METH-associated effect sizes, such that larger proportions of men in the METH sample was associated with greater levels of neuropsychological impairment. Interestingly, the authors point out that a 50% change in the gender composition of a METH sample would be associated with a difference in the effect size of .5 standard deviation units; thus, METH may differentially affect cognitive function in men and women.

Although METH abuse and dependence have been identified as particularly problematic in rural areas of the West, Midwest, and South, much of the research on cognition in METH-dependent individuals has been conducted in urban populations from cities such as Los Angeles. How the characteristics of urban versus rural METH-using populations impact cognitive functioning is unknown, although differences have been noted in other domains. For example, urban METH users from Kentucky have been shown to have greater exposure to multiple drugs, have more extensive criminal activity, and have higher levels of anxiety and psychoticism than rural METH users.¹⁷ In addition, rural METH users in the Midwest have been shown to initiate METH use earlier, be more likely to use intravenous route of administration, and have higher rates of alcoholism than urban Midwest METH users.¹⁸ The objective of this study was to investigate the influence of demographic and clinical characteristics on multiple domains of neurocognitive function in a group of METH-dependent individuals from rural South Carolina.

Methods

Subjects

Seventy-one men and women aged 18–50 years who met DSM-IV criteria for METH dependence within the past 6 months served as participants. The study was approved by the Institutional Review Board of the Medical University of South Carolina. All participants provided written informed consent after being fully informed of potential risks of participation before any study assessments were performed. Both treatment-seeking and nontreatment-seeking participants were recruited through referrals from local substance abuse treatment clinics or advertisements in the community. Subjects were compensated with retail vouchers for study participation (\$25 for the baseline assessment and \$25 for completing neurocognitive measures). All subjects were required to be abstinent from METH, alcohol, and all other drugs of abuse except nicotine as confirmed by breathalyzer and urine drug screening on the test day. Subjects could meet criteria for current (last 3 months) abuse, but not dependence, on any other substance with the exception of nicotine; past dependence on other substances was permitted. Individuals with history of or current psychotic disorder, bipolar affective disorder, current severe anxiety disorders or major depressive disorder requiring antidepressant pharmacotherapy, or presenting with significant

suicidal risk were excluded from study participation. Subjects with significant hematologic, endocrine (including diabetes mellitus), cardiovascular, pulmonary, renal, gastrointestinal, or neurological disease were also excluded.

Study Design

The cognitive assessments were administered as part of (1) a METH cue exposure/extinction study, reported elsewhere^{19, 20} or (2) an experimental Modafinil trial; cognitive tests were administered by trained research personnel before other experimental procedures began and took approximately 90 minutes. Cognitive assessment was administered and scored in accordance with published standardized test protocol and monitored by a licensed neuropsychologist (MTW). All study procedures were conducted at the research clinic of Behavioral Health Services in Pickens, South Carolina. After giving informed consent, potential participants were administered a brief physical exam and screened using the Mini International Neuropsychiatric Interview (MINI),²¹ a structured interview based on the DSM-IV for assessment of psychiatric and substance use symptoms. A subset of individuals (54/71) was assessed for Attention Deficit Hyperactivity Disorder (ADHD) using the MINI ADHD module. Quantitative METH and other substance use data for the past 90 days were assessed using the Time-Line Follow-Back (TLFB),²² a calendar based instrument used to assess daily self-reported substance use and breathalyzer and urine drug screening was conducted to assess recent substance use. Once all inclusion/exclusion criteria were satisfied, subjects were eligible to complete assessments.

Neurocognitive Measures

The following measures were used for the cognitive assessment:

Test of Memory Malingering (TOMM). The *TOMM*²³ is a brief visual recognition effort test designed to help discriminate between individuals with true cognitive impairment by ruling out inadequate effort as an explanation of impaired score performance. The published cut-off score was used to ensure valid effort.

Shipley Institute of Living Scale (Shipley). The *Shipley*²⁴ is designed as a brief screen of general intellectual functioning. The vocabulary and abstract subtests are combined to obtain a short-form global Intellectual Quotient (IQ) estimate to determine level of intellectual function.

Paced Auditory Serial Addition Test (PASAT). The *PASAT*^{25, 26} assesses working memory, divided and sustained attention, as well as calculation ability. Single digits are presented in two trials of 3-second or 2-second intervals, where the subject must add each new digit to the one immediately prior to it for this serial addition task.

Symbol Digit Modalities Test (SDMT). The *SDMT*^{27, 28} is administered as a measure of psychomotor function assessing information processing speed, divided attention, and motor speed. This measure can also sample response inhibition to assess executive functioning. The *SDMT* involves a simple substitution task, in which an individual is given a reference key and then has 90 seconds to pair specific numbers with given geometric figures.

Grooved Pegboard Test. The Grooved Pegboard^{29, 30} is a fine motor manipulative dexterity test consisting of 25 holes with randomly positioned slots to assess motor skills such as hand-eye coordination and motor speed. Pegs with a key along one side must be rotated to match the hole before they can be inserted.

California Verbal Learning Test (CVLT). The *CVLT-II*^{31, 32} is used to assess an individual's verbal memory and learning abilities. The examiner reads aloud a list containing 16 common words belonging to four categories. The subject is then asked to

recall as many of these items as possible over multiple trials, with and without cues for recall. The CVLT-II is able to capture immediate and delayed free recall retention.

Wisconsin Card Sorting Test (WCST). The WCST^{33, 34} is a neurocognitive measure of “set shifting,” that is the ability to display cognitive flexibility and is used as a general measure of executive functioning.³⁵ In this task, a number of stimulus cards are presented to the participant. He or she is given additional cards and asked to match each one to one of the stimulus cards. The participant is not told how to match the cards; however, he or she is told whether a particular match is right or wrong and must determine the correct sorting principle.

Statistical Analysis

Means and proportions for demographics and clinical variables of interest were calculated for the 71 subjects used in the analysis. Means are reported as means (standard deviation) and proportions as percentages (%). Due to the lack of a control group, we evaluated the distributions using standardized T-scores that were calculated for relevant variables for each of the cognitive assessments in the battery. These scores were compared to previously published normative standardized data using a one-sample *t*-test.

Gender, frequency of METH use in the past 90 days, and their interaction were considered primary predictors of cognitive performance outcomes. Frequency of METH use in the past 90 days was chosen for the use variable because it is continuous and has variability; other use variables either correlated strongly with the frequency variable or were not determined to be useful in the analysis. Other covariates considered for inclusion in the initial model were age, income, education, treatment status, and study cohort. For correlated cognitive outcomes within an assessment, linear mixed models were used. For these models, a subject-specific random effect term was included to model individual-level variation in test results; all other covariates were considered fixed effects. Covariates with initial significance level greater than .25 were carried forward into the model development stage while gender and frequency of recent use variables were retained in the model, regardless of significance. Akaike information criteria (AIC) was also assessed for each model with all variables included in the model and then with systematic stepwise removal of covariates ($p > .10$) and the interaction term ($p > .15$). Likelihood ratio tests were used to assess the final model fit to ensure that the reduced models were appropriate. Final reduced models included gender, frequency of use, as well as any covariates or interaction terms where at least a marginally significant effect ($p < .10$) was found. For all analysis, statistical significance was measured at $\alpha = .05$. No corrections for multiple comparisons were applied to presented *p* values. SAS software (Version 9.2, SAS institute, Cary, NC, USA) was used for all statistical analysis.

Results

Demographic and clinical characteristics of the sample are described in Table 1. Of the 54 participants assessed for ADHD, 3 positive diagnoses were made. Forty-one participants were enrolled in the METH cue study; 30 participants were enrolled in the Modafinil study. All 71 study participants were Caucasian and the majority were female (71.8%), enrolled in treatment (59.2%), reported active METH use in the past 90 days (71.8%), past 60 days (57.8%), and past 30 days (42.3%) prior to study enrollment. According to self-report, the percentage of subjects using, frequency, and total amount of use all declined in the sample on average over the 90 days prior to study enrollment. However, subjects who continued to use the drug during this period reported using stable dollar amounts of METH on using days. Gender differences in the total sample were noted in the percentage employed (21.6% female vs. 45% male, $p = .05$), level of income \$15,000 per year (93.7% females vs.

68.4% males, $p = .01$), and the percentage enrolled in drug treatment programs (74.5% female vs. 20% male, $p < .0001$).

All participants passed the cut-off criteria score on the *TOMM*, suggesting adequate effort on the cognitive measures. Figure 1 depicts cognitive test results where differences from the expected norm were noted. This study sample scored below average on the estimated IQ score provided by the *Shipley* (mean [SD] = 87.28 [9.93]). The *Shipley* is a global measure of general intellectual function indicating that this study sample fell below the national mean score of 100 (SD = 15). Because the study cohort IQ was below the average expected score [$t(70) = -10.79$, $p < .0001$; Fig. 1A], subsequent cognitive test T-scores were compared to an equivalent expected T-score of 43.82 instead of 50 to correct for this bias. On other cognitive measures, subjects performed significantly lower than expected on the *PASAT* Rate 1 and 2 (measures of sustained attention and vigilance) [37.9 (11.54), $t(70) = 4.34$, $p < .0001$ and 40.6 (7.29), $t(68) = -3.68$, $p = .0005$, respectively; Fig. 1B]. Scores on the *SDMT* (a measure of psychomotor function) and the *CVLT* (a measure of episodic memory) were not significantly different than expected (all $ps > .05$; data not shown), although performance on the *Grooved Pegboard* (a measure of fine motor dexterity) was lower than expected for the dominant hand [39.4 (15.70), $t(67) = -2.33$, $p = .023$] but not the nondominant hand ($p = .25$; Fig. 1C). Participants scored significantly higher than expected based on estimated IQ on the *perseverative response* [44.0 (9.46), $t(70) = 2.49$, $p = .015$] and the *perseverative error* [46.4 (8.66), $t(69) = 2.51$, $p = .015$] variables of the *WCST*; however, *total errors*, *nonperseverative errors*, and *conceptual level responses* were not different than expected (all $ps > .05$; Fig. 1D). The *WCST* is a general measure of executive function where subscales reveal different aspects of this construct.

Table 2 shows the results of the random intercept models used for the multivariate analyses, including the parameter estimates (beta), standard errors, and associated p values, all conditional on random effects. Higher level of education ($\beta = 1.713$, $p = .003$) and lower age ($\beta = -.281$, $p = .018$) were associated with higher scores on the composite *Shipley* (IQ) outcome. None of the variables proved predictive for the composite *PASAT* (attention/vigilance) score. Analysis of the composite *Grooved Pegboard Test* score revealed an interaction of gender and frequency of METH use on fine motor dexterity performance ($\beta = .29$, $p = .039$); more frequent METH use was associated with better performance for males and worse performance for females. Current enrollment in treatment was associated with better performance on the composite *WCST* variable, a measure of executive functioning ($\beta = 5.659$, $p = .007$).

Discussion

The cognitive functioning profile of METH-dependent individuals from rural South Carolina is consistent with some findings from previous studies focused on populations from various regions of the country, but dissimilarities were also found. The demographic summary of the METH dependent individuals in this study is different than what is typically reported in studies of METH-associated cognitive dysfunction, and may contribute to the differences found. For example, the average age (31.3 years) of our participants is similar to other reports (range 27.5–39.38 years).^{36–41} However, the mean number of years of education completed (11.14) is lower than what has been reported elsewhere (11.7–13.9 years).^{36–40,42–49} In addition, although epidemiological reports indicate that at least half of METH users are female, studies examining the effects of METH on cognition typically include a lower percentage of females (23–46%).^{38–42,50,51} Even in studies where the gender distribution is more equitable, sex differences are rarely examined.^{45,47,48,52} The current cohort included a considerably higher (71.8) percentage of females than other studies

in the literature. These demographic and educational differences may explain some of the discrepancies between our findings and those of other investigators.

The cohort in the present study had significantly lower estimated global IQ measure using the *Shipley Institute of Living Scale* than the general population, potentially confounding the results of other cognitive measures. The *Shipley* is widely used as a short-form estimate of IQ, and correlations between the *Shipley* and other intelligence tests are high.³⁵ Estimates of IQ are designed to test premorbid intellectual functioning and can therefore provide a gauge by which tests of more fluid cognitive functioning can be assessed. Many studies of cognitive function in METH users have assessed premorbid IQ and reported mean values ranging from 98.9 to 111.02,^{36,37,39–41,43,44} however, the mean IQ of the current cohort is substantially lower at 87.28 (Fig. 1A). Most studies have utilized IQ-matched subjects as comparative controls in more fluid measures of cognition; however, studies that compare IQ between METH users and healthy controls report no differences.^{42,53}

Since general intellectual functioning is so closely associated with educational achievement, it is possible that the lower IQ scores in this cohort reflect a lack of educational achievement (only half of the study participants completed high school) and educational quality (South Carolina is ranked poorly on a national scale of reading proficiency),⁵⁴ as is suggested by the association between the *Shipley* and education (Table 2). It is possible that the lower general intellectual functioning of the METH-dependent individuals in the current study makes it difficult to detect subtle deficits in cognitive performance that have been reported in other studies of METH-using populations, or that METH use is more damaging to cognitive function in individuals with higher baseline functioning.

METH-dependent individuals performed poorly on the *PASAT*, a test used to assess working memory, divided and sustained attention, and information processing speed (Fig. 1B). Since assessment of ADHD was limited to basic screening of a subset of subjects using the MINI in this study, contribution of ADHD to the poor *PASAT* performance in this cohort cannot be ruled out. At least one report has demonstrated that METH-dependent individuals with ADHD symptomatology have more severe cognitive deficits than those without.⁴⁹ In addition, it should be noted that performance on the *PASAT* is also impacted by calculation ability; since about half of this sample of METH dependent individuals did not earn a high school diploma, this demographic variable may have influenced the test outcome. Importantly, since performance on the *SDMT*, which measures *visual* information processing speed and attention, and *CVLT Trial 1*, which measures *verbal* working memory and attention, were not impaired in this cohort (data not shown), characterization of the performance of this METH-dependent sample on the *PASAT* as a true attentional deficit is difficult. In addition, attention and working memory deficits in METH users have been shown to have a smaller effect size than other domains of cognitive function,⁹ suggesting that deficits in attention and working memory may be dependent upon other variables (such as comorbidity or education level).

The most marked detrimental effects associated with METH use have been in the cognitive domains of learning and memory.⁹ Learning may be assessed by examining the *CVLT Total Free Recall* score over the five Trials, and memory may be assessed by the ability to recall words from the list after a period of time has passed. In the current sample of METH-dependent individuals, none of the variables for learning, memory, or recall were significantly lower than expected. The lack of deficits in the current cohort in these particular domains highlights a major difference between this population of METH users from the South and METH users who have been investigated from major U.S. cities (egg, Los Angeles, San Diego, Baltimore, Chicago).

The lack of motor deficits implied by adequate performance on the *SDMT* was in contrast to deficits in performance on the more complex test of visual-motor coordination with the *Grooved Pegboard Test*. This is congruent with studies demonstrating METH-associated neurotoxicity is associated with impaired fine motor skills,^{55–57} but inconsistent with results demonstrating otherwise.^{36,42,50} Chang and colleagues³⁶ examined sex differences in METH dependent versus control subjects on this task, and found a trend for better performance in control females versus control males, but no sex differences in the METH-dependent group. Our finding that men had better performance on the task with increased frequency of use in the last 90 days suggests that fine motor impairment in METH users may be more prevalent in females, or that females may take more time to recover after cessation of drug use. The METH dependent subjects in which sex differences were not noted had a mean pretest abstinence of 4.0 (6.5) months (median 2.0 months, range .25–36 months), but it is not reported whether frequency or recency of use was different between the groups or differentially influenced fine motor task performance.³⁶

In contrast to what has been reported in the majority of reports of cognitive function of METH-dependent individuals,⁹ the cohort in this study did not display impairment in executive function as assessed with the *WCST* and *SDMT*. Intriguingly, better performance on the *WCST* in our cohort was predicted by concurrent enrollment in community drug treatment programs (Table 2). This finding is consistent with reports that cognitive deficits predict higher treatment dropout and relapse rates in cocaine users.^{58–60}

Interestingly, an imaging study was reported in which performance on the *WCST* was worse in METH subjects than matched controls, and the number of errors was negatively correlated with cerebral glucose metabolism in the right frontal lobe of METH subjects.⁶¹ However, when the investigators examined each gender separately, males exhibited deficiencies in both frontal metabolism and frontal executive function (*WCST*) that were absent in the females. In another study,¹³ sex differences were not found in cognitive functioning of METH users, but compared to gender-matched controls, male METH users had more hypoperfused brain areas as assessed by perfusion MRI, suggesting greater METH-associated brain abnormalities as compared to female METH users. It has been hypothesized that estrogen is neuroprotective^{62,63} and may be responsible for the sex differences seen in preclinical METH-induced toxicity.^{64–68} The authors of the recent meta-analysis point out that a 50% change in the gender composition of a METH sample would be associated with a difference in the effect size of .5 standard deviation units.⁹ Thus, the high (71.8) percentage of females in our sample may at least partially account for the lack of cognitive deficits seen in these individuals.

Limitations and Conclusions

While some of the results of the current study are novel and contribute to the accumulating body of literature on cognitive functioning in METH users, there are a number of limitations that need to be acknowledged. This study did not consider other factors that are important with respect to cognitive performance among METH users (as reported in previous research) including: lifetime duration of meth use, polydrug or other substance use, previous treatments, route of use, and frequency of use as defined by daily use versus not. Although the demographic characteristics of the cohort examined in this study varied significantly from what is normally published on METH-dependent individuals, the lack of a demographically and IQ-matched control group makes it difficult to clearly attribute the findings of specific cognitive deficits to METH use. However, this is one of the first studies to test a significant number of female METH users and explore potential gender differences in the neurotoxic effects of METH.

Since cognitive-behavioral strategies are often employed in the treatment of substance dependence, cognitive deficits in METH users may interfere with their ability to respond to treatment. Characterization of cognitive deficits in METH dependent individuals as well as the impact of clinical and/or demographic features on these deficits could be important in guiding the development of treatment interventions.

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Figure 1.

Cognitive performance in METH-dependent individuals. Participants displayed below average IQ (A), scored lower than expected on one test of sustained attention (B), and one of fine motor dexterity (C) but performed adequately on measures of executive functioning (D) and all other tests.

Table 1

Demographic characteristics

	Total N = 71	Female N = 51	Male N = 20	P value *
Age (years, Mean [SD])	31.3 (7.5)	30.8 (7.1)	32.7 (8.3)	.49
Male (%)	28.2	—	—	—
Caucasian (%)	100.0	100.0	100.0	—
Smoker (%)	90.1	90.2	90.0	.69
Education (%)				
No HS diploma	29.4	45.1	25.0	.12
HS graduate	50.7	43.1	70.0	
Some college	9.9	11.8	5.0	
Employed (%)	28.2	21.6	45.0	.0483
Marital status (%)				
Married	18.3	15.7	25.0	.63
Sep/Divorced	40.9	43.1	35.0	
Never married	40.9	41.2	40.0	
Annual income (%)				
\$15,000	86.6	93.7	68.4	.0061
> \$15,000	13.4	6.3	31.6	
Treatment (%)	59.2	74.5	20.0	<.0001
Days used in the past 90 days (Mean [SD])	22.3 (26.3)	23.0 (26.2)	20.6 (27.2)	.76

* p values correspond to results of gender comparison.

TABLE 2

Predictive variables of cognitive performance multivariate mixed reduced model results

Dependent variable(s)	<i>n</i>	Independent variable	Parameter estimate	Standard error	<i>P</i> value	LRT(<i>p</i> value)
Shipley	71	Frequency of METH use	.009	.033	.786	$\chi^2_{df=4}$ 6.5 (.16)
		Male	−2.106	1.915	.275	
		Age	−.281	.116	.018 *	
		Education	1.713	.559	.003 *	
PASAT	70	Frequency of METH use	.015	.040	.704	$\chi^2_{df=6}$ 7.3 (.29)
		Male	−.443	2.339	.850	
Grooved pegboard	65	Frequency of METH use	−.12	.07	.097	$\chi^2_{df=4}$ 9.3 (.054)
		Male	−8.80	4.87	.076	
		Treatment	5.15	3.85	.186	
		Frequency of METH use × Male	.29	.14	.039 *	
WCST	67	Frequency of METH use	.040	.034	.245	$\chi^2_{df=5}$ 3.7 (.59)
		Male	.749	2.229	.737	
		Treatment	5.659	2.077	.007 *	

* A significant Wald test *p* value for covariate effects.