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Cytochrome P450-2D6 extensive metabolizers are more vulnerable to methamphetamine-associated neurocognitive impairment: Preliminary findings

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Abstract

While neuropsychological deficits are evident among methamphetamine (meth) addicts, they are often unrelated to meth exposure parameters such as lifetime consumption and length of abstinence. The notion that some meth users develop neuropsychological impairments while others with similar drug exposure do not, suggests that there may be individual differences in vulnerability to the neurotoxic effects of meth. One source of differential vulnerability could come from genotypic variability in metabolic clearance of meth, dependent on the activity of cytochrome P450-2D6 (CYP2D6). We compared neuropsychological performance in 52 individuals with a history of meth dependence according with their *CYP2D6* phenotype. All were free of HIV or hepatitis C infection and did not meet dependence criteria for other substances. Extensive metabolizers showed worse overall neuropsychological performance and were three times as likely to be cognitively impaired as intermediate/poor metabolizers. Groups did not differ in their demographic or meth use characteristics, nor did they evidence differences in mood disorder or other substance use. This preliminary study is the first to suggest that efficient meth metabolism is associated with worse neurocognitive outcomes in humans, and implicates the products of oxidative metabolism of meth as a possible source of brain injury. (*JINS*, 2010, *16*, 890–901.)

Keywords: Substance abuse, CYP2D6, Polymorphisms, Neurotoxicity, Metabolism, Cognition

INTRODUCTION

Heavy exposure to amphetamines has been associated with central nervous system (CNS) disturbances involving primarily dopamine (DA), but also serotonin, gamma-aminobutyric acid (GABA), and glutamate-dependent systems, leading to cerebrovascular (Citron, Halpern, McCarron, Lundberg, McCormick, & Pincus, 1970; Rumbaugh, Bergeron, Scanlan, Teal, Segall, & Fang, 1971) and neural pathology. Proposed processes for neurotoxicity include quinone formation, induction of transcription factors and oxidative stress, hyperthermia, and activation of neurochemical pathways implicated in neuronal apoptosis (Cadet, Jayanthi, & Deng, 2003; Quinton & Yamamoto, 2006). Methamphetamine (meth) use has become increasingly more prevalent throughout the United States and has been a commonly abused drug in Japan and other parts of Asia. Meth has been linked to abnormalities on brain imaging (Iyo, Namba, Yanagisawa, Hirai, Yui, & Fukui, 1997), decreased DA receptor and transporter densities (McCann, Wong, Yokoi, Villemagne, Dannals, & Ricaurte, 1998; Sekine, Iyo, Ouchi, Matsunaga, Tsukada, & Okada, 2001; Volkow, Chang, Wang, Fowler, Ding, & Sedler, 2001), and neuropsychological (NP) deficits consistent with alterations in abilities subserved by frontostriatal systems (Kalechstein,

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Newton, & Green, 2003; McKetin & Mattick, 1997, 1998; Rippeth, Heaton, Carey, Marcotte, Moore, & Gonzalez, 2004; Sim, Simon, Domier, Richardson, Rawson, & Ling, 2002; Volkow, Chang, Wang, Fowler, Leonido-Yee, & Franceschi, 2001). A recent meta-analysis by our group showed that meth dependence is most consistently associated with deficient executive functions, attention, information processing speed, episodic memory, verbal fluency, and motor skills (Scott, Woods, Matt, Meyer, Heaton, & Atkinson, 2007).

In a cohort of abstinent meth-dependent subjects, our group found that meth use characteristics, such as lifetime exposure, chronicity of use, mode of delivery, etc, did not predict who was found to have cognitive impairment (Cherner, Heaton, Gonzalez, Rippeth, Carey, & Grant, 2002; Cherner, Suarez, Casey, Deiss, Letendre, & Marcotte, 2010). The low predictive value of meth exposure parameters suggests that there are individual differences in vulnerability to meth-related neurocognitive deficits. Thus, the identification of factors that render some individuals vulnerable and others protected under conditions of similar drug exposure deserves investigation.

One such factor may be genetic differences in meth metabolism. The enzyme Cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6) is responsible for oxidative metabolism of several psychoactive substances, including methamphetamine (Lin, Di Stefano, Schmitz, Hsu, Ellis, & Lennard, 1997; Wu, Otton, Inaba, Kalow, & Sellers, 1997). In humans, depending on urinary pH, approximately 30–50% of meth is excreted unchanged. Hydroxylation by CYP2D6 yields the most abundant metabolite: 4-hydroxymethamphetamine, both as sulfate and glucuronide conjugates. N-methylation by CYP2D6 yields amphetamine, which is further metabolized into 4-hydroxyamphetamine and its conjugates, norephedrine, phenylacetone, benzoic acid, and hippuric acid (Caldwell, Dring, & Williams, 1972; Shima, Kamata, Katagi, & Tsuchihashi, 2006).

Variants of the *CYP2D6* gene have been well characterized, with over 80 polymorphisms identified (Dorado, Berec, Caceres, Gonzales, Cobaleda, & Llerena, 2005). These variants can make their carrier a "poor metabolizer" (PM) "intermediate metabolizer" (IM), or "extensive metabolizer" (EM). Ultra-rapid metabolizer (UM) phenotypes have also been described. Although research to date is not definitive, in humans some of these polymorphisms have been associated with motor neuron disease (Skvortsova, Slominskii, Shadrina, Levitskii, Levitskaia, & Alekhin, 2006), tardive dyskinesia (de Leon, Susce, Pan, Koch, & Wedlund, 2005; Tiwari, Deshpande, Rao, Bhatia, Lerer, & Nimgaonkar, 2005), and extrapyramidal symptoms in association with higher neuroleptic concentrations in plasma (Inada, Senoo, Iijima, Yamauchi, & Yagi, 2003), as well as vulnerability to Parkinson's disease (Singh, Khan, Shah, Shukla, Khaanna, & Parmar, 2008), each implicating effects on dopaminergic systems. Therefore, its role in methamphetamine metabolism and potential dopaminergic involvement makes *CYP2D6* a candidate for explaining individual differences in susceptibility to meth exposure that are manifested as cognitive impairment.

CYP2D6 Phenotypes

CYP2D6 phenotyping is increasingly indicated clinically to determine optimal dosing of pharmaceutical agents that use this metabolic pathway. Alteration of alleles from the normal wild-type (EMs) fall into several categories: one amino acid change or deletion, frameshift, splicing defect, stop codon, insertion, and entire gene deletion (Gonzalez, Vilbois, Hardwick, McBride, Nebert, & Gelboin, 1988; Gough, Miles, Spurr, Noss, Gaedigk, & Eichelbaum, 1990; Kimura, Umeno, Skoda, Meyer, & Gonzalez, 1989; Marez, Legrand, Sabbagh, Guidice, Spire, & Lafitte, 1997). PMs have no active *CYP2D6* alleles or only one that is partially active. As a result, they are at greater risk of drug-induced side effects due to diminished drug elimination. Approximately 5 to 14% of Caucasians are poor metabolizers. The four most common mutant alleles are *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*5*, and *CYP2D6*6* and account for 93–97% of the PM phenotypes in Caucasian populations. Individuals who are homozygous for PM alleles do not display *CYP2D6* enzyme activity, nor do any of those who carry combinations of these inactive alleles (Sachse, Brockmoller, Bauer, & Roots, 1997). IMs have one active and one inactive *CYP2D6* allele or two partially active alleles. Approximately 30% of Caucasians fall in the IM category (Raimundo, Fischer, Eichelbaum, Griese, Schwab, & Zanger, 2000). EMs correspond to the normal functional activity alleles, designated *CYP2D6*1* and *CYP2D6*2*. Genotypes consistent with the EM phenotype include two active *CYP2D6* alleles or one active and one partially active allele. This phenotype represents approximately 65 to 71% of Caucasians (Bradford, 2002). Ultra-rapid metabolizers have higher than normal rates of drug metabolism, and have three or more active alleles due to duplication or multi-duplication. Between 1 and 3% of Europeans fall in this category (Dahl, Johansson, Bertilsson, Ingelman-Sundberg, & Sjoqvist, 1995; Johansson, Lundqvist, Bertilsson, Dahl, Sjoqvist, & Ingelman-Sundberg, 1993). Ethnic and racial differences in the prevalence (Aklillu, Herrlin, Gustafsson, Bertilsson, & Ingelman-Sundberg, 2002; Aklillu, Persson, Bertilsson, Johansson, Rodrigues, & Ingelman-Sundberg, 1996; Bernal, Sinues, Johansson, McLellan, Wennerholm, & Dahl, 1999; Cascorbi, 2003; Dahl, Yue, Roh, Johansson, Sawe, & Sjoqvist, 1995; Gaedigk, Bhathena, Ndjountche, Pearce, Abdel-Rahman, & Alander, 2005), and possibly functionality (Gaedigk, Bradford, Marcucci, & Leeder, 2002; Inada et al., 2003) of specific alleles have been described in the literature. However, as the majority of the current study participants are of European Caucasian origin, we are limiting the description of population rates for the various phenotypes to those for that racial group.

In the present study, we set out to examine whether *CYP2D6* phenotype is related to cognitive impairment among meth-dependent individuals. We hypothesized that those with PM phenotype would exhibit worse neuropsychological performance and greater likelihood of cognitive impairment than phenotypes corresponding to higher *CYP2D6* activity because it was speculated that low or delayed clearance

of meth would result in greater net exposure in poor metabolizers for the same actual amount consumed, compared with extensive metabolizers. To our knowledge, this is the first investigation of this relationship.

MATERIALS AND METHODS

Participants

We analyzed retrospective data and fluids collected on 52 study participants who were evaluated at the HIV Neurobehavioral Research Center (HNRC) in San Diego, California, USA, as part of a federally funded, institutionally approved project on neuroAIDS effects of methamphetamine. Subjects were selected from a larger sample to be free of HIV or hepatitis C infection, as well neurologic, metabolic, or psychiatric conditions that might confound interpretation of neuropsychological findings. All gave written informed consent to participate in accordance with our Institutional Review Board requirements. To be eligible for the parent study, participants had to meet lifetime criteria for meth dependence, with use within the previous 18 months. Other substance dependence, except alcohol or cannabis, within 5 years, or abuse within the past 12 months was an exclusion. Alcohol dependence within 12 months was also exclusionary. No restrictions were placed on cannabis use, given its high prevalence in this population and minimal long-term effects on neuropsychological function (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003). Participants were requested to be abstinent for at least 10 days before testing and show negative urine toxicology for any nonprescribed substances except cannabis, as well as negative Breathalyzer test for alcohol on the day of NP testing.

Neurobehavioral and Drug Use Characterization

The methods of neurobehavioral and drug use characterization have been described elsewhere (Gonzalez, Rippeth, Carey, Heaton, Moore, & Schweinsburg, 2004; Rippeth et al., 2004). Briefly, participants were characterized as meth (and other substance) dependent based on DSM-IV criteria using a structured psychiatric interview (First, Spitzer, Gibbon, & Williams, 1994; Robins, Wing, Wittchen, Helzer, Babor, & Burke, 1988). History of mood disorder, attention deficit/hyperactivity disorder, and antisocial personality disorder were also evaluated according to DSM-IV criteria. A detailed history of meth and other substance use was gathered with a semistructured instrument covering onset, quantity, frequency, duration, and route of drug use over the participant's lifetime, previous 12 months, and previous 30 days. NP functioning was determined with a validated comprehensive battery of tests covering 7 ability domains (Learning, Memory, Attention/Working Memory, Verbal Fluency, Processing Speed, Abstraction/Problem Solving, and Motor Speed) with measures that have shown sensitivity to meth-related impairments. The specific tests in the battery are listed in the appendix. Raw scores were converted to demographically adjusted T-scores ($M = 50$, $SD = 10$), including adjustments for age, education, gender, and ethnicity as available for each test (Cherner, Suarez, Casey, Deiss, Letendre, & Marcotte, 2007; Heaton, Miller, Taylor, & Grant, 2004; Heaton, Taylor, & Manly, 2003). T-scores for each test were then converted into deficit scores based on half standard deviation (*SD*) increments, which reflect degree impairment by setting performances within the normal range at zero. The deficit scores range from 0 (T-score > 39; no impairment) to 5 (T-score < 20; severe impairment). The individual deficit scores were averaged to derive the Global Deficit Score (GDS), which reflects the number and the severity of deficits across the test battery (Carey, Woods, Gonzalez, Conover, Marcotte, & Grant, 2004; Heaton, Grant, Butters, White, Kirson, & Atkinson, 1995). For example, a GSD of 0.5 corresponds to scoring –1 *SD* on half the tests in the battery. Domain-specific deficit scores were also derived by averaging tests within an area of functioning. This method of data reduction is useful in avoiding multiple comparisons, as would be the case when considering individual tests, and has shown robust relationships with documented brain injury (Moore, Masliah, Rippeth, Gonzalez, Carey, & Cherner, 2006). Finally, level of premorbid ability was estimated with the Reading subtest of the Wide Range Achievement Test-3.

Genotyping and Phenotyping

CYP2D6 phenotype characterization was performed by an accredited commercial laboratory (Genelex, Seattle, WA, CLIA No. 50D0980559), using their standard *CYP2D6* mutation panel (Table 1). DNA was extracted from peripheral blood mononuclear cells that were stored at –70ºC, using a commercially available DNA extraction kit, QIAamp DNA Mini kit (Qiagen, Valencia, CA; Catalog #51185). Specimens were analyzed using the Tag-It™ Mutation Detection System for P450-2D6, which detects 12 nucleotide variants and two gene rearrangements in a multiplex polymerase chain reaction and allele-specific primer extension format. This method identifies 93–97% of PM phenotypes. Genelex provided the genotype, as well as the interpreted phenotype for each participant (see Appendix).

Statistical Analyses

Group differences in NP domain performance were analyzed with Wilcoxon Rank Sum tests, given the non-normal distribution of the variables. As individual NP test data were reduced by combining into ability domains, and given the exploratory nature of the study, we did not make experimentwise adjustments for multiple comparisons. Other continuous variables were analyzed with Student's *t* tests. Group differences in the proportions of NP impaired participants and discrete background variables were analyzed using Fisher's exact tests and χ^2 tests. Nonparametric correlations were computed between *CYP2D6* activity and NP performance.

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Table 1. Details of cytochrome P450-2D6 genetic analysis

	Cytochrome P-450 2D6 mutations detected	
CYP2D6 allele	Nucleotide change	Effect on enzyme metabolism
*1	None (wild-type)	Normal
*2	2850C>T	Normal
*3	2549A>del	Inactive
*4	1846G>A	Inactive
*5	Gene deletion	Inactive
*6	1707T>del	Inactive
*7	2935A>C	Inactive
*8	1758G>T	Inactive
*9	2613-2615 delAGA	Partially active
*10	100C>T	Partially active
*11	883G>C	Inactive
*12	124G>A	Inactive
*17	1023C>T	Partially active
*41	2988G>A	Partially active
Gene duplication	Duplication	Increased or decreased dependent on which allele is duplicated

RESULTS

Analyses yielded genotypes consistent with three meth metabolism phenotypes: EM (n = 32), IM (n = 17), and PM (n = 3). Given the small sample sizes and preliminary nature of the study, the IM and PM groups were combined for analyses. There were no significant differences in meth use characteristics between the groups (Table 2), with the exception of primary route of administration: The most prevalent mode among EMs was smoking, whereas the IM/PM group more often reported intranasal administration. Additionally, the IM/PM group had a greater proportion of injection users. Values for the PM group alone were comparable to those of the IM group alone, and results were essentially unchanged when PMs were excluded from analyses.

The EM and combined IM/PM groups were comparable with respect to demographic characteristics and estimated premorbid cognitive ability (Table 3).

Contrary to the initial hypothesis, EMs showed significantly worse overall NP performance, including significantly poorer scores in the areas of processing speed, abstraction/executive functioning, and learning (Table 4).

EMs were also more likely to obtain scores in the impaired range of cognitive functioning (Figure 1) compared with the combined IM/PM group, with significant differences in abstraction/executive functioning, and delayed recall, as well as trend level differences in learning, and global functioning. Although several of the comparisons did not reach statistical significance (which may be attributable to low power from small sample sizes), there was a consistent trend in the same direction in all domains, both in terms of level of performance, as well as proportion of subjects performing in the impaired range. Individual test T-scores and the proportion of participants in each group that performed at least one standard deviation below the mean appear in Table 5. In every case where statistically significant differences were detected, EMs showed worse performance.

As a *post hoc* exploratory analysis, we also investigated the strength of the relationship between participants' neuropsychological performance and their theoretical metabolic activity based on the combination of active, partially active, or inactive alleles present in their genotype. We recognize that this approach is speculative given the absence of data on the subjects' actual metabolic activity, but we believed that this exploration could be fruitful in corroborating our general finding that higher metabolic activity is associated with worse NP outcome. To this end, we used the data generated by Zanger, Raimundo, and Eichelbaum (2004) to rank-order metabolic activity from lowest to highest (1 to 5), as follows: 1 = two non-functional alleles; 2 = one decreased function and one non-functional allele; 3 = one normal function and one non-functional allele, or two decreased function alleles; 4 = one normal function and one decreased function allele; 5 = two normal function alleles. The appendix shows the number of participants with the various genotypes, corresponding phenotypes, and metabolic activity ranks. As shown in Table 6, and illustrated in Figure 2, higher purported metabolic activity was associated with worse cognitive functioning overall and in the areas of processing speed, learning, and abstraction/executive functioning.

Table 2. Methamphetamine use parameters by cytochrome P450-2D6 metabolic phenotype

Mean (*SD*) or %	Extensive n=32	Intermediate/poor n=20
Age of onset of meth use	22 (9)	23 (6)
Total years of meth use	12 (5)	12 (6)
Days abstinent from meth use	134 (107)	111 (75)
Density of meth use (grams/year)	419 (327)	342 (412)
Lifetime meth consumed (grams)	4875 (4295)	3690 (3876)
Meth in last 12 months (grams)	350 (318) (n=29/32)	277 (304) (n=20/20)
Binge use predominant	4%	5%
Primary administration route*		
Injection	6%	25%
Intranasal	27%	50%
Smoke	67%	25%

*Overall Chi Square $p < .05$.

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Table 3. Participant characteristics by cytochrome P450-2D6 metabolic phenotype

Mean (*SD*) or proportion	Extensive *n*=32	Intermediate/Poor *n*=20	*p* value
Age	35.5 (9.6)	37.9 (10.6)	NS
Education	12.5 (1.7)	12.6 (2.1)	NS
n (%) Male	24 (75%)	15 (75%)	NS
n (%) Non-white	8 (25%)	4 (20%)	NS
WRAT-3 Reading Quotient	98.4 (9.8)	101.5 (10.6)	NS
n (%) Lifetime alcohol dependence[a]	11 (33%)	8 (40%)	NS
Average daily alcohol (drinks, mean, *SD*)	6 (4)	8 (6)	NS
Years of alcohol use (mean, *SD*)	7.0 (6)	8.7 (6.0)	NS
n (%) Lifetime cannabis dependence	3 (9%)	8 (40%)	.009
Lifetime cannabis (grams, mean, *SD*)	4927 (6761)	7181 (6769)	NS
n (%) Lifetime cocaine dependence [b]	5 (16%)	4 (20%)	NS
n (%) Lifetime opioid dependence [b]	1 (3%)	0	NS
n (%) Lifetime sedative dependence[b]	0	0	—
n (%) Lifetime hallucinogen dependence[b]	0	0	—
n (%) Lifetime bipolar disorder	2 (6%)	1 (5%)	NS
n (%) Lifetime major depression	8 (27%)	9 (47%)	NS
n (%) Current major depression	2 (6%)	2 (10%)	NS
n (%) Ever on serotonin reuptake inhibitor	4 (12%)	7 (35%)	.05
n (%) ASPD	10 (31%)	4 (20%)	NS
n (%) ADHD/ADD	2 (7%)	3 (16%)	NS

[a]Greater than 12 months prior to assessment.
[b]Greater than 5 years prior to assessment and episodic in nature.
ASPD = antisocial personality disorder; ADHD/ADD = attention deficit disorder with/without hyperactivity; SSRI = Selective serotonin reuptake inhibitor; WRAT-3 = Wide-Range Achievement Test-3, estimate of premorbid ability; NS = not significant.

Because the IM/PM group had a greater prevalence of lifetime cannabis dependence, as well as somewhat greater lifetime exposure (not statistically significant), we explored the possible effects of cannabis on cognitive performance. In addition, we modeled the effects of meth exposure, given that EMs tended to have consumed greater amounts over their lifetime (again, not statistically significant). In linear regressions with phenotype, lifetime grams of meth consumption, and lifetime grams of marijuana consumption, only phenotype was a significant predictor of the global deficit score ($t = 2.05$; $p < .05$).

DISCUSSION

To our knowledge, this study is the first to suggest differences in vulnerability to methamphetamine-associated brain dysfunction linked to *CYP2D6* genotype in human users. The finding that the genotype associated with high metabolic activity is related to poorer cognitive performance was not expected, but it is consistent with the possibility that the metabolic products of methamphetamine oxidation may be a greater source of neurotoxicity than the parent compound. In fact, this has been demonstrated *in vitro*, where the metabolite 4-hydroxymethamphetamine showed significantly more cytotoxicity than unmetabolized meth (Clement, Behrens, Moller, & Cashman, 2000). In cultures exposed to other substituted amphetamines typically sold as "ecstasy" (methylenedioxy-methamphetamine: MDMA, methylthioamphetamine: MTA), cells expressing the active form of *CYP2D6* showed significantly greater toxicity than cells with less active forms or those devoid of *CYP2D6* activity.

Table 4. Global and domain-specific neuropsychological performance by cytochrome P450-2D6 phenotype

	Extensive		Intermediate/poor		Probability
	Mean	(*SD*)	Mean	(*SD*)	>|Z|
Neuropsychological Deficit Score					
Global	0.45	(0.43)	0.22	(0.25)	.04
Processing Speed	0.31	(0.43)	0.14	(0.33)	.13
Attention/Working Memory	0.39	(0.67)	0.18	(0.37)	.19
Verbal Fluency	0.36	(0.70)	0.10	(0.21)	.10
Learning	0.82	(0.73)	0.43	(0.55)	.05
Delayed Recall	0.53	(0.71)	0.33	(0.77)	.33
Abstraction/Executive Functioning	0.69	(1.00)	0.18	(0.49)	.04
Motor	0.69	(1.21)	0.45	(0.71)	.40

Note. Where differences are present, extensive metabolizers show worse performance.

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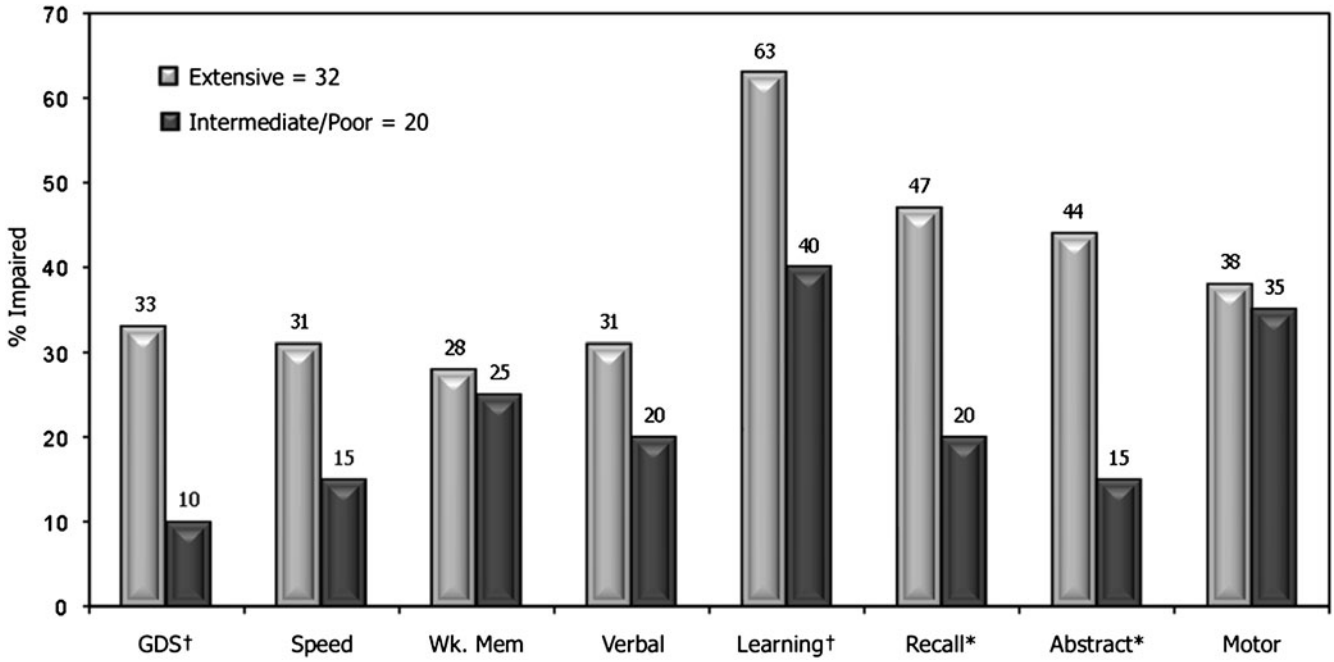

Fig. 1. Proportion of subjects performing within the impaired range of global and domain specific neuropsychological performance. Extensive metabolizers tend to have a greater likelihood of neuropsychological impairment than intermediate/poor metabolizers. *$p < .02$ †$p < .10$. GDS = Global Deficit Score; Speed = Speed of information processing; Att/Wk. Mem = Attention/working memory; Verbal = Verbal fluency; Abstr = Abstraction/problem-solving/executive functioning.

In these studies, toxicity was dependent on the formation of the oxidative metabolite N-methyl-α-methyldopamine, which was found to be 100-fold more cytotoxic than the parent substance (Carmo, Brulport, Hermes, Oesch, de Boer, & Remiao, 2007; Carmo, Brulport, Hermes, Oesch, Silva, & Ferreira, 2006). Furthermore, it has been demonstrated that stimulation of the P450 system in mice not only potentiates metabolism of MDMA but also increases the magnitude of neurotoxicity that can be observed (Monks, Jones, Bai, & Lau, 2004). These findings are discordant with results derived from an investigation of Dark Agouti rats, in which the females, considered a model for PM phenotype, exhibited greater acute MDMA-induced toxicity than males (Colado, Williams, & Green, 1995), and similarly in PM rats exposed neonatally to meth (Vorhees, Morford, Inman, Reed, Schilling, & Cappon, 1999f). However, translation of *CYP2D6* neurotoxicity findings from animals to humans has been criticized (de la Torre & Farre, 2004) as a result of evidence linking metabolism of amphetamines in rats to *CYP2D1*, which, while homologous to human *CYP2D6,* may be functionally different (Kobayashi, Murray, Watson, Sesardic, Davies, & Boobis, 1989). Additionally, significant inter-species differences have been described in the proportion of the various metabolites that are excreted in urine (Caldwell, Dring, Franklin, Koster, Smith, & Williams, 1977; Dring, Smith, & Williams, 1970; Shima et al., 2006). Thus, extrapolation of neurotoxicity findings involving the P450 system from animals to humans must be done cautiously. While no studies, to our knowledge, have investigated links between amphetamine metabolite concentrations and neurotoxicity in humans, it has been demonstrated that EM have greater urinary excretion of the hydroxy metabolite, followed by IM, and then by PM (Miranda, Sordo, Salazar, Contreras, Bautista, & Rojas Garcia, 2007).

Although our findings are intriguing, several limitations must be considered. First, the small sample size makes our results preliminary. For instance, because our sample only included three truly poor metabolizers, we were not able to test whether there is a "U" shaped function in CYP2D6 effects on meth-related neurocognition. It could be that extensive metabolism is deleterious because it results in the formation of large quantities of toxic metabolites, while complete lack of CYP2D6 activity could also be harmful because there is delayed clearance of the parent compound. Additionally, while meth consumption differences were not statistically significant, there tended to be a stair step increase in density of use (grams/year) with increasing metabolic efficiency. This raises the possibility that, although meth exposure was not related to NP deficits in these and previous analyses (Cherner et al., 2010), EMs evidence more impairment because they are indeed consuming larger amounts of meth. Future studies with larger samples will be required to address these possibilities with confidence.

Second, the lack of a drug-free control group precludes testing the possibility that *CYP2D6* genotype affects neurocognitive performance independently of meth use, for example, through some developmental effect. While it cannot be ruled out, there is no clear *a priori* reason to suspect such an effect, particularly because the EM phenotype is the most commonly occurring. Using our methods for determining cognitive

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Table 5. Demographically adjusted T-scores for neuropsychological tests and proportion performing within the impaired range (T-score < 40) in each group

	EM Mean *(SD)* % < 40	IM/PM Mean *(SD)* % < 40	*p value*
Learning			
Brief Visuospatial Memory Test-Revised (BVMT-R)	44.4 (11.9)	47.9 (10.1)	NS
	36%	20%	NS
Hopkins Verbal Learning Test-Revised (HVLT-R)	41.7 (6.4)	47.5 (8.9)	.008
	24%	20%	NS
Story Memory Test	44.0 (12.0)	47.6 (10.8)	NS
	45%	15%	.019
Figure Memory Test	37.6 (9.0)	41.5 (7.5)	NS
	70%	60%	NS
Memory			
BVMT-R Delayed Recall	47.8 (12.8)	49.0 (12.0)	NS
	24%	15%	NS
HVLT-R Delayed Recall	40.3 (7.7)	45.2 (8.8)	.039
	36%	30%	NS
Story Memory Test Retention	49.1 (12.4)	53.9 (10.1)	NS
	30%	10%	.073
Figure Memory Test Retention	53.0 (7.0)	51.0 (10.7)	NS
	3%	10%	NS
Attention/Working Memory			
Paced Auditory Serial Addition Task-200 item	41.9 (9.6)	49.2 (9.4)	.009
	30%	20%	NS
WAIS-III Letter-Number Sequencing	47.4 (7.6)	54.7 (10.1)	.004
	9%	10%	NS
Processing Speed			
Trail Making Test A	51.1 (9.3)	52.2 (7.8)	NS
	6%	5%	NS
WAIS-III Symbol Search	49.1 (10.2)	52.6 (8.1)	NS
	24%	11%	.051
WAIS-III Digit Symbol	46.8 (9.3)	49.8 (9.8)	NS
	27%	15%	NS
Executive/Abstraction			
Trail Making Test B	47.7 (10.3)	58.0 (10.9)	.001
	18%	5%	NS
Halstead Category Test Errors	43.9 (10.0)	50.7 (7.8)	.012
	39%	5%	.003
WCST-64 Perseverations	45.0 (12.4)	41.8 (9.3)	NS
	27%	30%	NS
Stroop Interference Ratio	48.0 (7.5)	47.3 (8.3)	NS
	12%	7%	NS
Verbal Fluency			
Letter Fluency (FAS)	48.5 (10.0)	49.6 (9.3)	NS
	15%	15%	NS
Category Fluency (Animals)	49.1 (11.2)	50.9 (8.4)	NS
	24%	5%	.051
Motor			
Grooved Pegboard Dominant Hand	46.0 (12.9)	48.1 (9.0)	NS
	33%	20%	NS
Grooved Pegboard Nondominant Hand	42.3 (9.1)	43.4 (8.5)	NS
	27%	30%	NS

EM = Extensive metabolizer; IM/PM = Intermediate/poor metabolizer; NS = not significant; WAIS III = Wechsler Adult Intelligence Scale-III; WCST-64 = Wisconsin Card Sorting Test 64-item computerized version.

impairment, which are based on the normal distribution of test performance, we would expect approximately 16% of a healthy normal population to perform in the impaired range (i.e., 1 *SD* below the mean). If the affected phenotype were the more rare poor metabolizers then we could not rule out that those members of a normative sample performing

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Table 6. Non-parametric correlations between neuropsychological deficit Scores and *CYP2D6* metabolic activity based on combination of alleles coded ordinally between 1 and 5

Deficit Score	Spearman ρ	Probability > |ρ|
Global	0.36	0.009
Processing Speed	0.31	0.025
Attention/Working Memory	0.16	NS
Verbal Fluency	0.18	NS
Learning	0.39	0.004
Delayed Recall	0.20	NS
Abstraction/Executive	0.35	0.010
Motor	0.02	NS

Note. Positive correlations indicate that higher metabolic activity is related to greater neurocognitive deficit. NS = not statistically significant.

below 1 *SD* did so because of an underlying genotype effect alone (i.e., in the absence of methamphetamine). However, between 65 and 70% of a Caucasian normative population would be expected to be extensive metabolizers. Thus, the norms that we use to interpret test performance ought to already reflect an underlying effect of genotype, given that EM would compose a majority of the normative sample. Nevertheless, future studies would benefit from including a control group to increase confidence in the findings.

Third, although several possible confounders of neuropsychological effects were controlled by use of demographic adjustments and careful exclusion criteria, factors that could potentially affect meth pharmacokinetics or pharmacodynamics, such as tobacco, herbal supplement, and prescription and non-prescription drug consumption, as well as diet (Wijnen, Op den Buijsch, Drent, Kuipers, Neef, & Bast, 2007) were not accounted for. These extrinsic factors may significantly affect the absorption, distribution, metabolism, and/or excretion of meth and thus should be examined in future work. For example, there was a higher proportion of lifetime depression in the IM/PM group, with an accompanying higher lifetime prevalence of serotonin reuptake inhibitor (SSRI) use. Because most SSRIs are substrates and inhibitors of CYP2D6, it would be important to determine the effects of concomitant meth and SSRI use, as this would presumably result in lower formation of meth metabolites. We unfortunately did not have the information required for this type of analysis but hope to tackle this question in future work.

Along the same lines, no study to our knowledge has examined how chronic exposure to meth may affect CYP2D6 metabolic activity. Although we have found that chronicity of meth use does not appear to predict cognitive impairment (Cherner et al., 2002, 2010), it is possible that chronic exposure to meth may alter metabolic activity and consequently our findings may not apply to the current literature, which has focused on acute exposure.

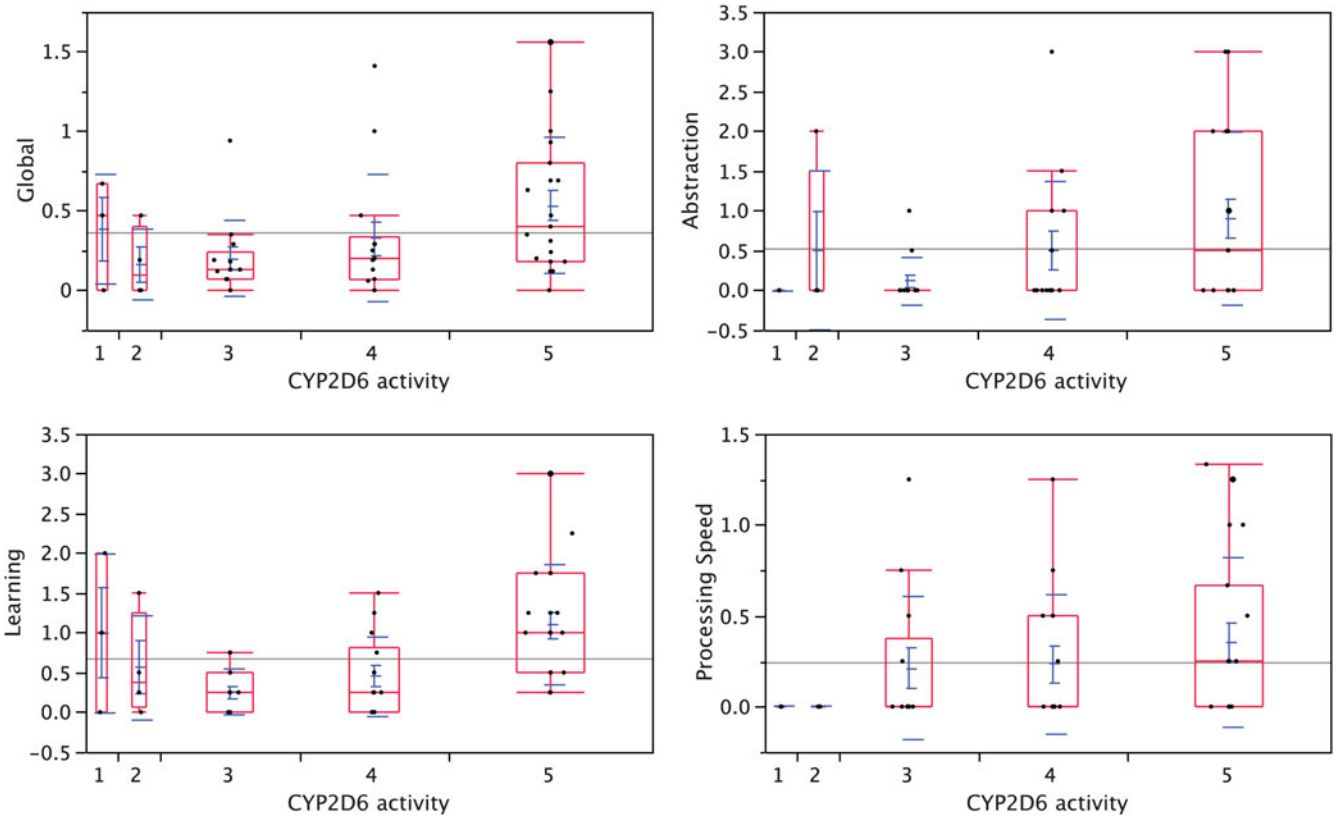

Fig. 2. Examples of the relationship between cytochrome P450-D6 (CYP2D6) activity and neurocognitive performance. The panel on the upper left shows increasing global impairment (GDS) with increasing CYP2D6 activity. The remaining panels show a similar relationship in learning, abstraction, processing speed.

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One factor on which the groups differed was history of cannabis dependence, with a greater prevalence among IMs/PMs (although 100% of study participants reported lifetime use). It is possible that cannabis conferred a protective effect on neurocognition. At least one study has shown that among meth-dependent subjects, those with coexisting marijuana dependence had somewhat better neuropsychological performance (Gonzalez et al., 2004). While further research will be needed to elucidate the effects of concurrent or historic cannabis exposure, analyses in our sample did not show evidence relating lifetime amount of cannabis consumed to global neurocognitive performance.

Another difference between groups that should be noted was route of meth administration. Although no study to our knowledge has examined the effect that different routes of administration may have on meth metabolism, recent work (Hendrickson et al., 2008) with pigeons suggests that administration of meth either intramuscularly or intravenously does not affect metabolism. Nevertheless, route of administration should be examined in future investigations, given that it results in differences in bioavailability.

Additionally, in this retrospective study of abstinent users, we were unable to test actual metabolic rates or metabolite concentrations. Such information would be useful to substantiate our hypothesis that meth metabolites are responsible for the neuropsychological manifestations observed. Finally, as individuals of Asian and African descent have a higher percentage (40–50%) of reduced function and nonfunctional *CYP2D6* compared with Caucasians (25–30%) (Bradford, 2002), generalization of these results to other racial/ethnic groups is not possible at this time.

These limitations notwithstanding, the current study found clear differences in neurocognitive impairment in meth-dependent adults in relation to their *CYP2D6* genotype and corresponding phenotype. While preliminary, our findings suggest differential vulnerability to meth-induced neurocognitive impairment in extensive metabolizers, specifically in learning, delayed recall, and executive ability domains, as well as overall global functioning. This differentiation was further demonstrated for these domains, along with performance in processing speed, during *post hoc* analysis using a linear measure of hypothetical metabolism. We also observed similar differential vulnerability at the trend level for the remaining ability domains, including attention/working memory, verbal fluency, and motor speed. Failure to find a significant association in these latter ability domains may be a consequence of the small sample size and limited power to detect significant differences. Again, further research with larger sample sizes will be required to determine whether a Type II error was committed.

If replicated, our findings may be of particular importance in guiding future development in the early identification of vulnerability to and prevention of neurocognitive impairment among meth-dependent individuals. Given the relatively high prevalence of extensive metabolizers in the general population and their putative vulnerability to meth-related neurocognitive dysfunction, there is potential public health impact in interventions to address brain injury in meth users. To date, several CYP2D6 inhibitors have been identified, including sertraline, fluoxetine, paroxetine, quinidine and ticlopidine (Hemeryck & Belpaire, 2002). Studies have investigated the efficacy of sertraline (Shoptaw, Huber, Peck, Yang, Liu, & Jeff, 2006), fluoxetine (Batki, Moon, Bradley, Hersh, Smolar, & Mengis, 1999), and paroxetine (Piasecki, Steinagel, Thienhaus, & Kohlenberg, 2002) on reduction of meth use, albeit with no significant effect. Thus, even though CYP2D6 inhibitors may not be efficacious for reducing meth use, future work might examine their influence on neurocognitive functioning.

Finally, future studies seeking to investigate or replicate relationships between meth use and indicators of brain disturbance may benefit from understanding the phenotypic makeup of their study groups to help interpret their findings as well as discrepancies among studies.

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APPENDIX

Cytochrome P450-2D6 genotype, phenotype, and rank-ordered hypothetical metabolic activity level for study cases

Metabolic activity was assigned as follows, based on data from Zanger et al (2004):

5: two normal function alleles

4: one normal function and one decreased function allele

3: one normal function and one non-functional allele, or two decreased function alleles

2: one decreased function and one non-functional allele

1: two non-functional alleles

Normal Function Alleles: *1, *2, *33, *35
Decreased Function Alleles: *9, *10, *17, *36, *41
Increased Function Alleles: *1xN, *2xN, *35xN
Non-Functional Alleles: *3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *15, *16, *18, *19, *20, *21, *38, *40, *42

No. of cases	CYP2D6 genotype	Phenotype	Metabolic activity
6	*1/*1	EM	5
11	*1/*2	EM	5
1	*2/*2	EM	5
2	*1/*9	EM	4
1	*1/*10	EM	4
1	*1/*17	EM	4
5	*1/*41	EM	4
2	*2/*10	EM	4
3	*2/*41	EM	4
5	*1/*4	IM	3
4	*2/*4	IM	3
3	*2/*5	IM	3
1	*2/*41	IM	3
1	*3/*41	IM	2
1	*4/*41	IM	2
1	*10/*41	IM	3
1	*5/*9	IM	2
1	*6/*10	IM	2
3	*4/*4	PM	1

Note. EM = extensive metabolizer; IM = intermediate metabolizer; PM = poor metabolizer.

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