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Methamphetamine Use Parameters Do Not Predict Neuropsychological Impairment in Currently Abstinent Dependent Adults

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Abstract

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²Contributors. All authors have materially participated in the research and/or manuscript preparation. All authors have approved the final manuscript. Mariana Cherner designed the study, including identifying the questions of interest, subject selection, and statistical analysis, and wrote the overall manuscript. Corinna Casey, conducted psychiatric and substance use interviews and analyzed data pertaining to these assessments. Robert Deiss provided a literature review for the discussion section. Paola Suarez, MA provided a literature review for the background section. Scott Letendre participated in the conceptual phase of the study, provided data regarding HIV and HCV infection status, and provided writing for the discussion section. Thomas Marcotte was instrumental in the design of the substance use history protocol employed in the study. Florin Vaida reviewed and commented on the study design and statistical analyses. J. Hampton Atkinson is a senior psychiatrist who conceptualized the neuropsychiatric and substance history protocols, as well as supervised the standardized training for collection of these data. He also provided substantive editing to the manuscript. Igor Grant is the Principal Investigator of the parent projects under which these data were collected. He conceptualized the overall scientific approach and hypotheses of interest from which the current analyses are derived. He also provided substantive editing to the manuscript. Robert K. Heaton is a senior neuropsychologist who designed the neuropsychological assessment battery and methods utilized in the current study. He worked closely with the first author to shape the analytic approach and contributed text to the discussion section.

³Conflict of Interest. All other authors declare that they have no conflicts of interest.

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Methamphetamine (meth) abuse is increasingly of public health concern and has been associated with neurocognitive dysfunction. Some previous studies have been hampered by background differences between meth users and comparison subjects, as well as unknown HIV and hepatitis C (HCV) status, which can also affect brain functioning. We compared the neurocognitive functioning of 54 meth dependent (METH+) study participants who had been abstinent for an average of 129 days, to that of 46 demographically comparable control subjects (METH-) with similar level of education and reading ability. All participants were free of HIV and HCV infection. The METH+ group exhibited higher rates of neuropsychological impairment in most areas tested. Among meth users, neuropsychologically normal (n=32) and impaired (n=22) subjects did not differ with respect to self-reported age at first use, total years of use, route of consumption, or length of abstinence. Those with motor impairment had significantly greater meth use in the past year, but impairment in cognitive domains was unrelated to meth exposure. The apparent lack of correspondence between substance use parameters and cognitive impairment suggests the need for further study of individual differences in vulnerability to the neurotoxic effects of methamphetamine.

Keywords

Methamphetamine; Stimulant; Motor impairment; Neuropsychological; Cognitive impairment; Drug exposure; Predictors

1. Introduction

Methamphetamine (meth) is a potent central nervous system (CNS) stimulant with high addiction potential. Persons who become dependent on meth often experience adverse psychosocial, psychiatric, and medical consequences. Abuse of meth and other amphetamines has been associated with brain abnormalities, including cerebrovascular damage such as arteritis (Rumbaugh et al., 1971), vasculitis (Bostwick, 1981), intracranial hemorrhage (Cahill et al., 1981), and increased prevalence of ischemic stroke, particularly in the subcortical white matter and basal ganglia (Yen et al., 1994).

While meth exerts effects on a number of neurotransmitter systems, including norepinephrine, serotonin, GABA, and glutamate (Burrows and Meshul, 1999; Nordahl et al., 2003), its influence has been most evident and extensively studied in dopaminergic systems. Meth increases synaptic concentrations of dopamine (DA) by stimulating its release into presynaptic terminals and decreasing striatal dopamine uptake (Hirata et al., 1996). There is substantial evidence that meth induces degeneration of dopaminergic terminals in the striatum (Cadet et al., 1995; Finnegan et al., 1982; Ricaurte et al., 1982; Ricaurte et al., 1980). Dopaminergic changes include reuptake inhibition, neurotransmitter depletion, and possible morphologic changes in frontostriatal pathways, such as dose-dependent loss of DA transporter and receptors in the striatum and nucleus accumbens (Hirata and Cadet, 1997). The increases in extracellular DA, with the accompanying increase in reactive oxygen-nitrogen species, as well as changes in glutamatergic transmission, may be major factors in the neuropathogenesis associated with meth use (Frost and Cadet, 2000; Larsen et al., 2002; Marshall et al., 1993; Pu et al., 1996; Stephans and Yamamoto, 1996; Yamamoto and Zhu, 1998).

More recently, studies have also demonstrated the importance of serotonergic changes in response to prolonged meth exposure. Kish et al (2009) described modest decreases in serotonin transporter (SERT) protein expression in the striatum of active meth users (compared to the robust DA transporter decreases that are typically observed), but more substantial changes in orbitofrontal and occipital cortex. Similarly, Sekine et al (2006) have shown reduced SERT density in a number of brain regions of currently abstinent meth addicts, and determined that SERT values in orbitofrontal, temporal, and anterior cingulate region were associated with

elevated aggression. Additionally, a functional polymorphism of the SERT gene (5-HTTLPR) has been implicated in risk for long-lasting meth-induced psychosis (Ezaki et al., 2008).

Cognitive studies of chronic exposure to meth and amphetamine have found deficits consistent with alterations in functioning of frontostriatal systems. These include worse test performance in verbal and visual learning and recall (Kalechstein et al., 2003; McKetin and Mattick, 1997, 1998; Sim et al., 2002; Volkow et al., 2001b), abstraction and cognitive flexibility (Kalechstein et al., 2003; Lawton-Craddock et al., 2003; Sim et al., 2002; Simon et al., 2000; Simon et al., 2002; Trites and et al., 1976; Trites et al., 1974), cognitive inhibition (Salo et al., 2002; Simon et al., 2002), working memory (Kalechstein et al., 2003), sustained attention (McKetin and Mattick, 1997, 1998), reaction time (Lawton-Craddock et al., 2003), psychomotor processing speed (Kalechstein et al., 2003; Lawton-Craddock et al., 2003; 2002; Sim et al., 2002; Simon et al., 2000); and motor speed (Toomey et al., 2003; Volkow et al., 2001b). Studies using decision-making and reward paradigms have also implicated the orbital prefrontal cortex in the poorer performance of meth users on such tasks (Paulus et al., 2003; Rogers et al., 1999).

A recent meta-analysis by our group (Scott et al., 2007) found that, across the literature, meth effects were strongest for episodic memory, executive functions, information processing speed, and motor skills, with smaller effects for attention/working memory and verbal fluency. The meta-analysis also pointed to certain short-comings in the literature that complicate interpretation of findings within studies as well as comparisons between studies. Among these is that a number of studies have identified the neuropsychological (NP) deficits mentioned in currently active, rather than abstinent meth users. Additionally studies have often been limited by suboptimally matched control groups, allowing for the confounding influence of differences in education or premorbid ability on NP results. Another important weakness in most of the existing literature is lack of documentation about HIV and hepatitis C (HCV) serostatus, as seropositivity for these viruses is prevalent among meth users (Alter et al., 1999; Bell et al., 1990; Frosch et al., 1996; Halkitis et al., 2001) and can be associated with neurocognitive problems in the absence of meth use (Bornstein et al., 1993; Cherner et al., 2005; Heaton et al., 1995; Hilsabeck et al., 2002). Finally, an important shortcoming of most studies is the use of raw score differences in test performance between meth users and control groups, which are not only susceptible to demographic influences (e.g., even seemingly small differences in education can affect test scores), but also do not indicate whether these performance differences correspond to actual cognitive impairment (as opposed to just lower level of performance) likely to have functional consequences.

To address these issues, in the present study we compared the NP performance of abstinent meth dependent subjects, who were seronegative for HIV and HCV, to that of demographically comparable control participants with similar levels of education and reading ability (as a measure of premorbid functioning and quality of education (Manly et al., 2002)). In order to help interpret our findings, we utilized demographically adjusted test scores, and applied data reduction techniques to arrive at global and domain-specific estimates of cognitive impairment, thus reducing the number of statistical comparisons. We predicted that even when excluding HIV, HCV, and premorbid ability as possible confounders, and accounting for demographic influences, individuals with a history of meth dependence would exhibit worse neuropsychological performance and greater prevalence of neuropsychological impairment than non-meth-using comparison subjects.

In addition, only a few studies have examined predictors of neuropsychological performance in meth addicts, such as the relationship between quantified exposure to meth and neurocognitive disturbances. Differences in meth exposure among participants in published studies may account for some of the discrepant findings in the literature. In an effort to shed

light on this issue, we report the results of a detailed survey of self-reported meth consumption, to explore meth-related predictors of NP dysfunction. We expected that meth use parameters, such as greater lifetime consumption and density of use, recency of use, binge use, and shorter length of abstinence would be associated with worse cognitive and motor test performance.

2. Method

2.1. Subjects

Study participants were 100 HIV and HCV seronegative men and women participating in the program project on NeuroAIDS Effects of Methamphetamine at the University of California San Diego (UCSD). All were recruited from substance dependence recovery programs and from the general San Diego community, and gave written informed consent according to the requirements of the UCSD Institutional Review Board prior to the start of their study visit. Participants were verified to be HIV and HCV negative by standard antibody testing. The methamphetamine dependent group (METH+) comprised 54 subjects who met criteria for a lifetime diagnosis of meth dependence according to the Structured Clinical Interview for DSM-IV (SCID-IV) (Spitzer et al., 1995), with meth use within the last 18 months. The METH-comparison group consisted of 46 participants who never met criteria for amphetamine use disorders and were not habitual users of any stimulant.

Potential participants were excluded from both groups if they met criteria for lifetime dependence on any other substance other than cannabis or alcohol, unless such dependence was episodic in nature and occurred more than 5 years ago, based on the SCID and substance use interviews. Alcohol and marijuana were admissible because of the high prevalence of use in the METH+ population. However, alcohol dependence in the past year constituted an exclusion, as did chronic, long-term alcoholism, determined by the clinician performing the interviews. Likewise, no substance abuse other than cannabis or alcohol was allowed in the past 12 months. Participants were requested to be abstinent from meth for at least 10 days prior to testing and show negative urine toxicology for any non-prescribed substances except cannabis, as well as negative Breathalyzer test for alcohol, on the day of assessment. Irrespective of toxicology results, participants were not allowed to undergo neuropsychological testing if they appeared to be intoxicated or experiencing withdrawal symptoms (assessed with structured guidelines). Additionally, subjects were ineligible if they had psychiatric, developmental, neurologic, or metabolic conditions of sufficient severity to confound the interpretation of NP findings (e.g., stroke, loss of consciousness > 30 minutes, psychosis, mental retardation).

Participants were selected from a larger study cohort (121 METH+ and 103 METH-) to obtain groups that had comparable mean values with respect to years of education and reading ability, two factors that are highly related to NP performance. By accomplishing similarity in background variables, differences in neurocognitive functioning that may be observed between the groups should not be attributable to premorbid factors such as learning disabilities or marginal quality of education or academic achievement. The resulting 54 METH+ and 46 METH- participants were statistically comparable with regard to age ($M_+ = 36.3$, $sd = 9.8$ vs. $M_- = 35.1$, $sd = 13.1$), years of education ($M_+ = 12.6$, $sd = 1.9$ vs. $M_- = 12.2$, $sd = 1.8$), reading ability (Wide Range Achievement Test -3 Reading Quotient: $M_+ = 99.8$, $sd = 10.0$ vs. $M_- = 100.6$, $sd = 10.0$), and proportion of subjects whose ethnic origin was not European-Caucasian (22% vs. 28%). The METH- group had a greater proportion of women (50% vs. 26%, $p < .05$).

2.2. Procedure

Participants received an initial screening interview by phone and/or in person at the HIV Neurobehavioral Research Center in San Diego. Those that met basic inclusion criteria were

invited to return for a full assessment. The study protocol was typically completed during one visit, but could be broken up into more visits if the participant's schedule required it. Urine toxicology and Breathalyzer testing were performed prior to the neuropsychological assessment and repeated if the testing had to be completed on a separate day.

2.2.1. Substance Use and Psychiatric Information—A structured substance use interview was administered to obtain a detailed history of quantity, frequency, and duration of use of methamphetamine and other recreational substances for the last 30 days and 12 months, and in 5-year epochs covering the participant's lifetime. The variables derived from this interview were age of onset, number of years of use, length of abstinence, preferred mode of use, prevalence of binge use, estimated lifetime grams of meth consumed, and average grams per year of use (which we have termed meth “density”).

The method for determining cumulative meth exposure has been reported previously (Gonzalez et al., 2004) and is as follows: Frequency of use was coded on a 6-point scale where 0 = “No use ever,” 1 = “Less than one day per month,” 2 = “Less than one day per week,” 3 = “1-3 days per week,” 4 = “4-6 days per week,” and 5 = “Every day.” The midpoint of each of these ranges was calculated in number of days per month, such that category 1 = .5 days (assigned arbitrarily); 2 has a range of 1 to 3 days, so the midpoint is 2; category 3 = 4 to 12 days per month (midpoint=8); 4 = 16 to 24 (midpoint=20), and 5 reflects daily use (30 days per month).

Participants were asked to estimate meth use quantity in terms of grams, “lines” (defined as .035 g per line), or common street names for specified quantities (e.g., “Quarter” = 0.25 g, “Teener” = 1/16 oz or 1.75 g, “8 ball” = 1/8 oz or 3.5 g). This information was translated onto a 5-point scale in grams per day of use and midpoints were similarly calculated, where 1 = less than 0.125 g (the lower level of the range was set arbitrarily at one “line” or .035 g, such that the midpoint becomes 0.08 g); 2 = 0.126 – 0.25 g (midpoint=0.19 g); 3 = 0.26 – 0.50 g (midpoint=0.38 g); 4 = 0.51 – 1.0 g (midpoint=0.76 g); 5 = “more than one gram” (maximum of range set at 3.5 g, with midpoint=2.25 g).

For each epoch of use, the midpoint of quantity in grams per day was multiplied by the midpoint of frequency in days per month, yielding grams per month. This figure was then multiplied by the number of months in each epoch (1 for last 30 days, 12 for previous 12 months, and 60 months for each subsequent 5-year epoch) to obtain the number of grams for each epoch. Then the number of grams consumed in each epoch was summed to compute total lifetime grams. Meth density was calculated as the average consumption per year of use by dividing lifetime grams by the total years of use. The pattern of use for each epoch was also described as characteristic of chronic use (high frequency irrespective of quantity) or binge use (low frequency but high quantity). The proportion of binge use was calculated as the number of years in which bingeing was the predominant pattern divided by the total number of years of meth use. Table 1 shows the meth use characteristics of the METH+ group as well as 12 METH- participants who reported having tried meth recreationally.

Participants also received a structured psychiatric assessment to determine eligibility for the study in terms of substance use diagnoses, as well as to obtain a history of lifetime and current (30-day) prevalence of major depressive disorder, bipolar disorder, and antisocial personality disorder using modules from the SCID-II and IV. Diagnosis of attention deficit disorder with or without hyperactivity (ADHD/ADD) was ascertained with the pertinent module from the Diagnostic Interview Schedule (DIS) (Robins et al., 1981). All psychiatric measures were administered by doctoral-level clinicians or trainees.

2.2.2. Neuropsychological Battery—The methods of neurobehavioral assessment have been described in detail elsewhere (Rippeth et al., 2004). Briefly, all participants completed a

neurocognitive evaluation with a comprehensive neuropsychological battery designed to assess functioning in 7 ability domains. Raw test scores were converted to T scores (standard scores with a mean of 50 and standard deviation of 10) using demographically corrected norms to account for the effects of age, education, gender, and ethnicity, as available for each measure. Individual test T-scores < 40 (more than one standard deviation below the mean) are considered impaired. A neuropsychologist then used a manualized rating system (Heaton et al., 1994; Woods et al., 2004) to assign blind clinical ratings of impairment according to a subject's performance in each neuropsychological domain based on the number and degree of impaired performances on individual tests for that ability area (e.g., learning, abstraction, etc.). The resulting clinical ratings for each domain were assigned on a nine-point scale ranging from 1 = above average to 9 = severely impaired, with 4 representing borderline performance and 5 representing definite mild impairment. Using the same scale, a rating of Global impairment was assigned to reflect overall level of NP functioning. In order to be deemed globally impaired, a participant would have to receive impaired ratings (≥ 5) in at least two ability areas. This method of ascertaining NP impairment has been used extensively by our group and in several national multi-site studies of HIV-associated deficits, as well as with schizophrenic (Heaton et al., 2001) and chronic obstructive pulmonary disease (Grant et al., 1982). It has the advantage of providing data reduction to minimize multiple comparisons, and it has shown robust relationships with documented brain injury (Cherner et al., 2002; Masliah et al., 1997).

2.3. Statistical analyses

Group comparisons on mean values for continuous variables were examined with t-tests. Differences in dichotomous variables were analyzed using contingency tables with Chi-square tests. Logistic regression was employed to discern the influence of third variables on neuropsychological impairment. Because of their skewed distribution, lifetime consumption of meth and "meth density" were square root transformed for use in analyses. For primary analyses examining group differences in neuropsychological performance, we utilized the data reduction technique mentioned above that combines individual scores into domain scores, thus reducing the number of comparisons. Follow-up analyses to determine differences in specific test scores are unadjusted for multiple comparisons, as they are meant for descriptive purposes only.

3. Results

3.1. Prevalence of other substance use

As shown in Table 2, the METH+ group exhibited greater prevalence of non-meth substance use disorders in the past. In particular, they reported higher rates of remote alcohol and cocaine dependence, as well as alcohol, cannabis, cocaine, and hallucinogen abuse. The rates of current (last 30 days) diagnoses of "allowed" substances were minimal. METH+ also had higher prevalence of other amphetamine use (61% vs. 15% in METH-), with 13% meeting abuse or dependence criteria, compared to none in the control group. Additionally, METH+ were more likely than METH- to have tried inhalants (31% vs. 11%) and dissociative drugs (PCP, Ketamine, 39% vs. 11%), although none met abuse or dependence criteria for these. Both groups had identical proportions of individuals who had used Ecstasy (9%), and none met diagnostic criteria. Finally, METH+ had a somewhat greater proportion of tobacco users than the METH- group (98% vs. 72%).

3.2. Prevalence of Non-exclusionary Psychiatric and Developmental Diagnoses

METH+ and METH- participants had comparable prevalence of major depressive disorder (MDD), with approximately one third of subjects in each group meeting lifetime criteria (METH+ = 33% vs. METH- = 31%). Only four METH+ and three METH- participants were diagnosed with current MDD (7% for both). The prevalence of bipolar illness was quite low

in this sample, with only 3 (6%) METH+ participants, and no METH- participants reporting the disorder ($p = .05$). Antisocial personality disorder was present in 26% of the METH+ group and completely absent in the METH- group ($p < .0001$). History of ADHD/ADD was slightly more prevalent among METH+ participants (10% vs. 2%, not significant).

3.3. Neuropsychological Performance

The overall NP performance of the METH+ group, as measured by the *Global* rating, was poorer than that of the METH- group: METH+ $\bar{X} = 4.1$ ($sd=1.2$) vs. METH- $\bar{X} = 3.4$ ($sd=1.2$), one-tailed significance level $p=.003$. The METH+ group obtained worse impairment scores in the areas of *Learning*: 4.1 (1.5) vs. 3.1 (1.5), $p=.0006$; *Motor Ability*: 3.1 (1.6) vs. 2.5 (1.3), $p=.02$; and *Attention/Working Memory*: 3.0 (1.4) vs. 2.5 (1.1), $p=.02$; with trends in *Speed of Information Processing*: 2.7 (1.4) vs. 2.3 (1.2), $p=.06$; and *Memory*: 2.9 (1.4) vs. 2.5 (1.2), $p=.09$. There were no differences in *Abstraction/Executive Functioning*: 3.6 (1.6) vs. 3.3 (1.5), $t=-0.68$; or *Verbal Fluency*: 2.7 (1.3) vs. 2.5 (1.1). Table 3 shows the individual demographically adjusted test T scores that contributed to the clinical ratings for each group. It should be noted that while the METH+ group generally obtained lower scores, the mean group level of performance was within normal limits (i.e., below a rating of 5) in most domains, with borderline-impaired scores in the Learning and Global ratings.

However, when we considered the proportion of individuals in each group whose scores fell in the impaired range (clinical rating ≥ 5), the METH+ group generally had at least double the rate of impairment seen the control group, although only the Global and Learning domain ratings reached statistical significance, with Memory and Motor ability showing trends (Figure 1).

As the METH+ group had a greater prevalence of other remote substance dependence, we used separate logistic regressions to account for the possible influence of alcohol, cocaine, and cannabis dependence diagnoses. In every case, other remote substance dependence did not account for the presence of global impairment, while meth dependence remained a significant predictor (alcohol: whole model test $X^2 = 6.99$, $p = .03$; alcohol effect $X^2 = 1.56$, $p = .21$; meth effect $X^2 = 6.37$, $p = .01$, odds ratio (OR) = 3.46 (95% confidence interval: 1.35, 9.44); cocaine: whole model test $X^2 = 5.60$, $p = .06$; cocaine effect $X^2 = 0.21$, $p = .62$; meth effect $X^2 = 5.28$, $p = .02$, OR=3.0 (CI: 1.20, 7.97); cannabis: whole model test $X^2 = 5.80$, $p = .05$; cannabis effect $X^2 = .44$, $p = .50$; meth effect $X^2 = 5.4$, $p = .02$, OR=2.83 (CI: 1.17, 7.30)). Rates of global NP impairment were likewise unaffected by presence of MDD (lifetime: $X^2 = .06$, $p = .81$; current $X^2 = .45$, $p = .50$), ASPD ($X^2 = .04$, $p = .85$), or ADHD ($X^2 = 0.02$, $p = .89$). Similarly, as there was a greater proportion of women in the METH- group, we conducted separate logistic regressions with METH group and sex as predictors of global and domain impairment. We found no effect of sex, or the interaction of METH group by sex, for any of the outcomes, while METH group remained a significant predictor of global ($p=.025$), learning ($p=.011$), memory ($p=.052$), and motor ($p=.037$) functioning. It should be noted that the demographic adjustments applied to generate test T-scores account for simple normative effects of sex on test performance.

3.4. Predictors of NP impairment among METH+ participants

Having observed higher rates of cognitive impairment in the METH+ group, we set out to examine which aspects of their meth use or background characteristics might differentiate between those METH+ participants who were cognitively impaired and those who were normal, based on the Global rating. NP normal ($n=32$) and NP impaired ($n=22$) meth dependent subjects did not differ with respect to demographic variables, lifetime prevalence of mood disorder, ASPD, ADHD, or other substance dependence. NP impaired participants had lower mean WRAT-3 reading scores (table 4), although mean scores for both groups were within the

average range. Individual NP test performances for the normal and impaired METH+ participants are shown in table 5. Globally impaired individuals were characterized by poorer scores in all domains except verbal fluency and motor functioning.

NP normal and NP impaired meth dependent subjects were comparable with regard to age at first use of meth, length of abstinence, total years of use, and density of use. This was true whether looking at global or domain-specific impairment. Likewise, primary mode of use (ingesting, injecting, snorting, smoking) and binge pattern of use were also unrelated to NP impairment. However, the average quantity consumed in the previous 12 months was greater among those with motor impairment (mean grams = 519.6, sd = 378.4 for impaired vs. 252.9, sd = 265.0 for normal, $p = .03$, but not significant when adjusting for multiple comparisons). This relationship was not observed for global impairment or for other domains of function (Figure 2).

We additionally explored whether length of abstinence was linearly related to test performance, even if it was not associated with meeting the threshold for impairment. Table 6 shows pairwise correlations between test scores and days since last use, with no significant associations emerging. In table 7 we show the mean test performance of subjects grouped according to increasing abstinence. The difference in proportion of impaired subjects between the group with the shortest (10-30 days) and longest (>180 days) abstinence was 11%. This difference was not significant, and there was no evidence of a monotonic trend. Similarly, there were no significant differences in mean performance on individual tests based on these (albeit small) abstinence groups.

4. Discussion

In the present study we set out to determine the prevalence and nature of neuropsychological impairment associated with methamphetamine addiction, as well as determinants of such impairment, when important confounders that have plagued the existing literature were minimized. We found that abstinent meth dependent individuals who were free of HIV, hepatitis C, and major psychiatric problems were still more likely to be neuropsychologically impaired than a control group having similar demographic characteristics and estimated premorbid ability. While they performed more poorly than control participants, on average the METH+ group's scores were within normal limits, suggesting that, at the group level at least, effects on cognition are mild. In addition, we found that quantified meth use parameters did not differentiate between those meth users who were cognitively impaired and those who performed within normal limits, pointing to the possibility of individual differences in susceptibility to the neurotoxic effects of meth.

Studies that attempt to establish non-acute effects of recreational substances on human cognition are fraught with the difficulty of differentiating the influence of the target substance from that of third variables and pre-morbid factors. A useful methodologic strategy for studies of this type is to obtain a comparison group that is closely matched to the study group on extraneous or confounding variables. In the current study, we made efforts to form groups that were comparable with respect to demographic composition, and particularly with regard to years of education and reading ability as an estimate of premorbid functioning. Additionally, we employed demographic corrections for NP test scores. While we attempted to sample from the same community as the meth users, we were less successful in our ability to find participants with similar remote histories of other substance dependence and ASPD, although our comparison group was still (purposefully) not as "clean" as typical healthy control groups. However, we were strict in excluding persons with recent or long-term addiction to other substances, and we were able to show that these background differences did not influence rates of neuropsychological impairment in this sample, nor did they differentiate between METH+

with and without NP impairment. In this regard, the present study confirms previous observations of neurocognitive compromise in meth dependent persons, after accounting for a number of confounding factors.

We conducted a detailed survey of meth use and found that indicators of meth exposure were largely unrelated to NP impairment. In part, this may have resulted from the manner in which substance use information was collected. Self-report estimates of drug quantities and events that occurred in past, and under conditions of intoxication, may be inaccurate. The use of temporal epochs and consumption ranges necessitating reduction to midpoint measurements may have introduced additional “noise.” While the self-report modality is not easily avoidable in this type of work, since these data were gathered we have modified our substance use instrument to allow for flexible entry of the actual quantity, frequency, and duration, rather than using pre-set ranges. We believe that this method improves the resulting estimates of substance exposure. Nevertheless, our findings are generally consistent with those of other groups who have used neurocognitive testing and other indicators of meth-related brain dysfunction. For example, Chang and colleagues (Chang et al., 2002) found that while performance on tests of reaction time were related to regional cerebral blood (rCBF) abnormalities in meth users, there was no relationship between quantity or duration of meth use with either rCBF or test performance. Similarly, Johanson (Johanson et al., 2006) reported no relationship between duration of use or length of abstinence and reductions in striatal vesicular monoamine transporter type-2 and dopamine transporter (DAT) availability observed among abstinent meth users, nor did they find relationships with test performance. Recently, McCann and colleagues (McCann et al., 2008) reported lower DAT binding potential in the caudate and putamen of meth users with an average of 6 years of abstinence. DAT values were related to learning and recall performance (but not to other domains); however, no meth use parameters were related to DAT values or to test performance. On the other hand, Volkow (Volkow et al., 2001a) demonstrated some recovery of DAT in the caudate and putamen of meth users after protracted abstinence, although this was not associated with concomitant NP improvement. In a group of current users, Simon (Simon et al., 2000) also found no relationship between days since last use and cognitive performance. Interestingly, in a subsequent study, meth users who remained abstinent or had periods of relapse tended to have worse cognitive performance than those who continued to use over a three to six month period (Simon et al., 2004).

It is possible that cross sectional designs are inadequate for detecting group-level improvements in neurocognition as a function of abstinence, but that well controlled longitudinal designs that account for normal practice effects may be able to uncover such changes. Some investigators have interpreted the general lack of relationship between length of abstinence and test performance or dopaminergic disturbances as evidence that, once incurred, the neurotoxic effects of meth are long-lasting (Johanson et al., 2006). This, however, still does not address the disconnect between cumulative meth exposure and neurocognitive outcomes found in this and other studies. Some studies have reported certain relationships between quantity of meth use and NP test performance. In the study of current users mentioned earlier, Simon (Simon et al., 2000) found that those reporting daily meth use fared worse on most tests than those who reported less frequent use --even including those who used 6 or fewer days per week. McKetin and Mattick (McKetin and Mattick, 1997) reported that estimated lifetime grams, period of heaviest use, and injection drug use were each correlated with performance on one (different) test in their battery. However, meeting criteria for amphetamine dependence was associated with worse performance on all tests. What these latter studies illustrate is that heavy use consistent with dependence is associated with worse test performance, but it may be that among those who meet dependence criteria, i.e., the heaviest users, the incremental explanatory value of the amount and pattern of meth exposure remains unclear.

This low predictive value of meth exposure parameters may point to individual differences in vulnerability to meth-related neurocognitive dysfunction. As with other agents that cause brain injury, it is almost never the case that 100% of those exposed to the risk factor end up manifesting signs of brain involvement. Thus, the identification of factors that render some individuals vulnerable and others protected in the face of similar drug exposure deserves concerted investigation. In the current study, cognitively impaired meth users had somewhat lower mean reading level than those who were cognitively normal. If NP impairment had been related to age of meth use onset, this finding could be interpreted as indicating poorer academic development as a result of early drug use. But since age at first use was unrelated to impairment (or to reading scores) in our sample, this explanation is unconvincing. Instead, if reading level can be taken as an indicator of premorbid functioning, then these results can be interpreted to support the role of cognitive reserve (Satz et al., 1993; Stern, 2002) in vulnerability to meth-related brain insult. According to this model, differences in “brain reserve capacity” (which might be manifest as degree of synaptic connectivity, flexibility in neural networks, or another factor that conveys advantage) could perhaps explain the differential susceptibility to similar noxious conditions.

Genetic and biomarker studies may also shed light on differences in susceptibility to the neurotoxic effects of meth. Among the candidates for study are genes involved in meth metabolism, such as polymorphisms of the liver enzyme cytochrome P450-2D6 (Cherner et al., 2008; Cherner et al., in review), as well as genes related to dopaminergic, serotonergic, and glutamatergic pathways (Ishikawa et al., 2005). Genetic variants in brain chemical signaling molecules that indicate immune activation and oxidative stress (Letendre et al., 2004) should also be considered. Genetic studies to date have focused on vulnerability to meth-induced psychosis (e.g. (Hashimoto et al., 2005; Nakamura et al., 2009; Ohgake et al., 2005; Suzuki et al., 2006; Ujike et al., 2006)), and addiction potential (e.g., (Hashimoto et al., 2008; Itoh et al., 2005; Iwata et al., 2004; Kanahara et al., 2009; Kinoshita et al., 2008; Kishi et al., 2008)), with most work coming from Japanese groups. To our knowledge, vulnerability to cognitive dysfunction has not received significant attention in genetic studies of meth users.

In this study, impairment in motor speed and dexterity was associated with greater meth use in the previous 12 months. Until this finding is replicated, it may be prudent to interpret it conservatively, especially given that only 10 METH+ participants scored in the impaired range. It is possible that this finding is spurious or unstable, given the number of statistical analyses that were performed. Alternatively, it could be that motor functions are more sensitive to meth use or take longer to recover, although the latter was not borne out in relation to length of abstinence. These relationships will have to be examined in larger samples in order to establish their stability. Similarly, animal work supports the notion that binge use is more likely to result in brain injury, as the organism likely mounts neuroadaptive responses to chronic meth exposure (Kuczenski et al., 2007; Segal et al., 2005). In our study, we did not find higher rates of impairment among individuals who reported periods of binge use. But again, as there were only 7 participants who met criteria for binge use (4 NP impaired, 3 NP normal), we cannot make statements about the significance of low frequency but high quantity meth exposure on NP functioning based on the present data.

In summary, the current results confirm neurocognitive impairments associated with methamphetamine dependence in the absence of coexisting conditions that have confounded interpretation of results in the literature. Careful characterization of methamphetamine use parameters revealed little with regard to likelihood of neuropsychological impairment, strongly indicating the need to study individual differences in vulnerability to methamphetamine-associated neurotoxicity.

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** p < .01 *p < .05 †p < .10

Figure 1.

Rates of neuropsychological impairment among methamphetamine dependent and control subjects based on blind clinical ratings from demographically adjusted test scores. Learn = Learning, Abstr = Abstraction/Executive functioning, Atten = Attention/Working, Memory SIP = Speed of Information Processing, Verbal = Verbal Fluency

* $p < .05$

† $p < .10$

Figure 2.

Average grams of methamphetamine used in the previous 12 months according to global and domain-specific neuropsychological impairment (METH+ subjects only). Learn = Learning, Abstr = Abstraction/Executive functioning, Atten = Attention/Working Memory, SIP = Speed of Information Processing, Verbal = Verbal Fluency

Table 1Methamphetamine use characteristics of the METH+ and METH-^{*} groups

Methamphetamine use	METH+	METH-
Mean (sd) or n (%)	(n=54)	(n=12/46 only)
Age at first use	22.5 (7.9)	25.6 (10.1)
Length of abstinence in days	128.8 (99.5)	3231.7 (2713.3)
Years of use	12.0 (5.3)	2 (1.5)
Lifetime grams consumed	4343.2 (4139.9)	14.2 (26.5)
Density (Average grams per year of use)	382.9 (360.1)	8.3 (13.8)
Using in the last 30 days	7 (13%)	0
Percent of time with binge use predominant	5 (13)	0
Primary mode of meth use		
ingest	1 (2%)	0
inject	7 (13%)	0
insufflate	19 (35%)	9 (82%)
smoke	27 (50%)	3 (18%)

* METH- use represents occasional experimental consumption.

Table 2

Lifetime prevalence of substance abuse and dependence per SCID-IV diagnosis

SCID-IV Diagnosis	Lifetime Prevalence Rate		
	METH+ (n=54)	METH- (n=46)	2-tailed p value
Alcohol abuse	47%	14%	.0003
Alcohol dependence	35%	7%	.0003
Cannabis abuse	47%	11%	.0001
Cannabis dependence	20%	7%	.04
Cocaine abuse	22%	2%	.002
Cocaine dependence	17%	0%	.0006
Opioid abuse	6%	0%	.05
Opioid dependence	2%	0%	NS
Sedative abuse	2%	0%	NS
Sedative dependence	0%	0%	--
Hallucinogen abuse	15%	2%	.01
Hallucinogen dependence	0%	0%	--
Ecstasy abuse	0%	0%	--
Ecstasy dependence	0%	0%	--
Inhalant abuse	0%	0%	--
Inhalant dependence	0%	0%	--
PCP or Ketamine abuse	0%	0%	--
PCP or Ketamine dependence	0%	0%	--
Polysubstance abuse	2%	0%	NS
Polysubstance dependence	0%	0%	--

SCID-IV = Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders –IV

Abuse and dependence diagnoses are non-overlapping (dependence supercedes abuse)

Dependence on all substances except cannabis and alcohol is remote (> 5 years ago) and episodic only. Alcohol dependence is greater than one year ago and episodic only.

Table 3

Performance on individual neuropsychological tests by methamphetamine dependence status using demographically adjusted T scores (mean=50, SD=10) based on normative standards available for each test. Higher T-scores indicate better performance.

Neuropsychological Test T-scores	METH+ Mean (SD)	METH- Mean (SD)	1-tailed p value*
<i>Learning</i>			
BVMT-R Learning	45.81 (11.42)	50.48 (11.69)	0.02
HVLT-R Learning	44.04 (7.92)	47.52 (9.53)	0.02
Story Memory Test - Learning	45.46 (11.51)	48.50 (10.44)	0.09
Figure Memory Test - Learning	38.69 (8.90)	43.04 (8.47)	0.007
<i>Memory</i>			
BVMT-R Delayed Recall	48.41 (12.32)	51.17 (8.54)	0.10
HVLT-R Delayed Recall	42.31 (8.36)	45.87 (7.31)	0.03
Story Memory Test Retention	50.76 (11.69)	54.72 (9.99)	0.04
Figure Memory Test Retention	52.31 (8.51)	50.52 (8.34)	0.15
<i>Attention/Working Memory</i>			
PASAT Total Correct	44.56 (10.01)	46.96 (8.53)	0.10
WAIS-III Letter-Number Sequencing	49.91 (9.36)	51.46 (8.91)	0.20
<i>Processing Speed</i>			
Trail Making Test A	51.41 (8.68)	53.98 (7.84)	0.06
WAIS-III Symbol Search	50.28 (9.49)	53.09 (9.82)	0.08
WAIS-III Digit Symbol	47.69 (9.58)	52.67 (9.33)	0.005
Stroop Color-Word Incongruent	45.40 (7.86)	49.89 (9.39)	0.009
<i>Executive/Abstraction</i>			
Trail Making Test B	51.35 (11.57)	52.89 (12.44)	0.26
Halstead Category Test Errors	46.31 (9.70)	49.70 (9.73)	0.04
WCST-64 Perseverations	43.74 (11.24)	46.17 (6.52)	0.09
Stroop Interference Ratio	47.81 (6.37)	51.86 (7.59)	0.004
<i>Verbal Fluency</i>			
Letter Fluency (FAS)	48.85 (9.57)	48.30 (8.67)	0.38
Category Fluency (Animals)	49.83 (10.10)	50.48 (8.69)	0.37
<i>Motor</i>			
Grooved Pegboard Dominant Hand	46.72 (11.41)	49.85 (10.51)	0.08
Grooved Pegboard Nondominant Hand	42.83 (8.81)	46.80 (9.76)	0.02

* p values for 1-tailed t-tests are not corrected for multiple comparisons. Instead, impairment was determined using a clinical rating method that combines individual tests into ability domains and a global impairment score.

HVLT-R: Hopkins Verbal Learning Test-Revised

BVMT-R: Brief Visuospatial Test-Revised

PASAT: Paced Auditory Serial Addition Task

WAIS-III: Wechsler Adult Intelligence Scale - III

WCST-64: Wisconsin Card Sorting Test - Computerized 64-item

Table 4

Characteristics of METH+ group stratified by global neuropsychological status

Mean (sd) or n (%)	NP Impaired n=22	NP Normal n=32	p value
Age	34.7 (8.8)	39.1 (10.8)	NS
Education	12.2 (1.5)	12.9 (2.0)	NS
Male	16 (73%)	24 (75%)	NS
Non-White	4 (18%)	8 (25%)	NS
WRAT-3 Reading Quotient	95.6 (10.1)	102.7 (9.0)	.001
Age at first meth use	21.6 (6.1)	23.2 (9.0)	NS
Length of abstinence in days	125.2 (96.1)	131.1 (103.2)	NS
Years of use	11.8 (5.2)	12.1 (5.4)	NS
Lifetime grams consumed	4234 (3421)	4415 (4603)	NS
Average grams per year of use	413 (395)	363 (340)	NS
Using in the last 30 days	3 (14%)	4 (13%)	NS
Primary mode of meth use			NS
ingest	0	1 (3%)	
inject	2 (9%)	5 (16%)	
insufflate	7 (32%)	12 (37%)	
smoke	13 (59%)	14 (44%)	
% Time with Binge Pattern	5 (12)	4 (12)	NS
Lifetime Alcohol Dependence	5 (23%)	14 (44%)	NS
Lifetime Cannabis Dependence	4 (18%)	7 (22%)	NS
Lifetime Cocaine Dependence	3 (14%)	6 (19%)	NS
Lifetime Tobacco Use	21 (95%)	32 (100%)	NS
Tobacco use last 30 days	18/20 (90%)	25/29 (86%)	NS
Daily cigarettes last 30 days	13.8 (7.8)	14.1 (7.9)	NS
Current Major Depression	2 (9%)	2 (6%)	NS
Antisocial Personality Disorder	6 (27%)	8 (25%)	NS
ADHD/ADD	2 (10%)	3 (10%)	NS

ADHD/ADD: attention deficit disorder, with/without hyperactivity WRAT-3: Wide Range Achievement Test –3

Table 5

Performance of METH+ participants on individual tests according to global neuropsychological status

Neuropsychological Test T-scores	NP Impaired Mean (SD)	NP Normal Mean (SD)	1-tailed p value*
<i>Learning</i>			
BVMT-R Learning	38.77 (12.14)	50.66 (7.99)	0.0002
HVLT-R Learning	39.32 (6.01)	47.28 (7.48)	0.0001
Story Memory Test - Learning	38.64 (10.91)	50.16 (9.50)	0.0001
Figure Memory Test - Learning	34.91 (5.57)	41.28 (9.86)	0.002
<i>Memory</i>			
BVMT-R Delayed Recall	40.41 (13.98)	53.91 (7.10)	0.0001
HVLT-R Delayed Recall	37.77 (8.51)	45.44 (6.76)	0.0006
Story Memory Test Retention	49.14 (13.60)	51.88 (10.26)	0.21
Figure Memory Test Retention	50.05 (10.03)	53.88 (7.03)	0.07
<i>Attention/Working Memory</i>			
PASAT Total Correct	38.32 (9.79)	48.84 (7.74)	0.0001
WAIS-III Letter-Number Sequencing	45.68 (7.98)	52.81 (9.22)	0.002
<i>Processing Speed</i>			
Trail Making Test A	49.14 (8.70)	52.97 (8.45)	0.06
WAIS-III Symbol Search	50.28 (9.49)	53.09 (9.82)	0.0001
WAIS-III Digit Symbol	44.55 (9.45)	49.84 (9.20)	0.02
Stroop Color-Word Incongruent	42.16 (9.26)	48.09 (8.81)	0.02
<i>Executive/Abstraction</i>			
Trail Making Test B	47.59 (13.89)	53.94 (9.02)	0.03
Halstead Category Test Errors	41.23 (8.46)	49.81 (9.02)	0.0004
WCST-64 Perseverations	40.82 (9.25)	45.75 (12.16)	0.05
Stroop Interference Ratio	47.73 (6.63)	47.87 (8.45)	0.48
<i>Verbal Fluency</i>			
Letter Fluency (FAS)	44.36 (10.23)	51.94 (7.84)	0.003
Category Fluency (Animals)	45.73 (10.36)	52.66 (9.03)	0.007
<i>Motor</i>			
Grooved Pegboard Dominant Hand	45.64 (12.32)	47.47 (10.88)	0.29
Grooved Pegboard Nondominant Hand	42.23 (9.00)	43.25 (8.79)	0.34

* p values for 1-tailed t-tests are not corrected for multiple comparisons and are shown to illustrate the instances of group differences.

HVLT-R: Hopkins Verbal Learning Test-Revised

BVMT-R: Brief Visuospatial Test-Revised

PASAT: Paced Auditory Serial Addition Task

WAIS-III: Wechsler Adult Intelligence Scale - III

WCST-64: Wisconsin Card Sorting Test - Computerized 64-item

Table 6

Pairwise correlations between test scores and length of abstinence.

Neuropsychological Test T-scores	Days Abstinent	
	r	p value
<i>Learning</i>		
BVMT-R Learning	0.22	0.11
HVLT-R Learning	-0.04	0.77
Story Memory Test - Learning	0.08	0.58
Figure Memory Test - Learning	0.02	0.89
<i>Memory</i>		
BVMT-R Delayed Recall	0.19	0.18
HVLT-R Delayed Recall	-0.02	0.87
Story Memory Test - Retention	0.09	0.54
Figure Memory Test - Retention	-0.01	0.96
<i>Attention/Working Memory</i>		
PASAT Total Correct	-0.06	0.69
WAIS-III Letter-Number Sequencing	-0.12	0.39
<i>Processing Speed</i>		
Trail Making Test A	0.01	0.96
WAIS-III Symbol Search	0.11	0.43
WAIS-III Digit Symbol	-0.01	0.95
Stroop Color-Word Incongruent	0.15	0.36
<i>Executive/Abstraction</i>		
Trail Making Test B	-0.18	0.20
Halstead Category Test Errors	-0.12	0.39
WCST-64 Perseverations	-0.05	0.74
Stroop Interference Ratio	0.07	0.66
<i>Verbal Fluency</i>		
Letter Fluency (FAS)	0.03	0.85
Category Fluency (Animals)	-0.01	0.96
<i>Motor</i>		
Grooved Pegboard Dominant Hand	0.10	0.47
Grooved Pegboard Nondominant Hand	0.04	0.79

Table 7

Mean neuropsychological test T-scores of METH+ group stratified by length of abstinence at the time of assessment. No statistically significant differences were found

NP Tests by Domain	days abstinent from methamphetamine use					
	10-30 n=7	31-60 n=10	61-90 n=9	91-120 n=7	121-180 n=9	180-400+ n=11
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
% Globally impaired	57%	30%	33%	29%	44%	46%
<i>Learning</i>						
BVMT-R Learning	44.0 (10.0)	44.3 (12.2)	47.8 (12.6)	42.9 (12.7)	43.1 (14.0)	49.6 (8.0)
HVLT-R Learning	41.3 (6.1)	44.6 (9.1)	47.6 (8.2)	41.4 (4.2)	46.2 (10.9)	42.0 (6.7)
Story Memory Test - Learning	42.4 (16.0)	47.3 (6.8)	45.8 (8.9)	45.3 (12.8)	46.8 (16.1)	46.6 (8.4)
Figure Memory Test - Learning	35.1 (6.1)	38.2 (10.9)	38.1 (8.3)	44.7 (11.2)	39.7 (4.9)	37.5 (10.2)
<i>Memory</i>						
BVMT-R Delayed Recall	43.7 (12.5)	47.9 (12.5)	49.8 (14.8)	49.9 (12.5)	43.4 (14.0)	52.6 (8.3)
HVLT-R Delayed Recall	41.0 (7.7)	42.5 (11.2)	45.7 (8.5)	42.0 (6.4)	40.7 (9.8)	42.0 (6.9)
Story Memory Test Retention	47.0 (10.3)	49.7 (13.0)	55.3 (8.1)	49.1 (16.2)	48.6 (11.8)	52.3 (11.8)
Figure Memory Test Retention	50.3 (12.1)	54.2 (4.9)	50.6 (6.7)	56.0 (2.7)	51.3 (11.3)	52.0 (10.6)
<i>Attention/Working Memory</i>						
PASAT Total Correct	45.6 (9.0)	47.9 (10.8)	42.1 (10.4)	43.1 (8.0)	47.1 (13.4)	42.8 (8.1)
WAIS-III Letter-Number Sequencing	42.6 (5.9)	52.0 (10.9)	50.3 (7.0)	57.3 (6.6)	54.6 (11.5)	44.6 (5.2)
<i>Processing Speed</i>						
Trail Making Test A	50.0 (10.7)	52.0 (10.3)	50.8 (6.7)	51.0 (5.5)	55.4 (5.0)	49.6 (11.7)
WAIS-III Digit Symbol	48.9 (9.1)	51.3 (9.9)	43.1 (7.2)	45.7 (11.1)	50.6 (11.3)	46.5 (9.3)
WAIS-III Symbol Search	47.7 (10.4)	52.4 (7.7)	46.3 (11.0)	49.6 (8.9)	54.9 (12.1)	49.6 (7.4)
Stroop Color-Word Incongruent	46.1 (5.9)	47.3 (10.7)	40.2 (7.4)	44.8 (7.2)	45.0 (9.5)	47.1 (13.3)
<i>Executive/Abstraction</i>						
Trail Making Test B	51.3 (17.0)	51.6 (12.2)	54.6 (8.6)	51.6 (6.2)	54.6 (13.9)	46.5 (10.7)
Halstead Category Test Errors	40.7 (8.6)	48.4 (9.0)	47.7 (7.5)	52.3 (10.2)	50.0 (10.8)	41.2 (8.5)
WCST-64 Perseverations	38.4 (9.1)	46.3 (22.2)	43.0 (6.9)	46.6 (6.7)	44.0 (7.3)	42.2 (4.1)
Stroop Interference Ratio	45.3 (9.5)	49.3 (7.2)	49.5 (4.8)	46.6 (7.3)	45.8 (8.1)	48.3 (9.1)

NP Tests by Domain	days abstinent from methamphetamine use					
	10-30	31-60	61-90	91-120	121-180	180-400+
	n=7	n=10	n=9	n=7	n=9	n=11
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<i>Verbal Fluency</i>						
Letter Fluency (FAS)	47.1 (4.9)	51.3 (11.1)	49.7 (9.8)	50.0 (5.0)	44.6 (13.3)	49.8 (10.0)
Category Fluency (Animals)	52.0 (12.1)	50.5 (9.3)	51.1 (12.6)	47.0 (12.3)	48.4 (10.1)	49.6 (7.9)
<i>Motor</i>						
Grooved Pegboard	46.7 (8.3)	47.7 (12.8)	44.6 (14.2)	40.0 (15.3)	50.8 (9.8)	49.4 (7.6)
Dominant Hand						
Grooved Pegboard	44.9 (9.8)	42.7 (13.8)	40.1 (9.4)	41.0 (6.9)	45.0 (13.8)	43.5 (10.6)
Nondominant Hand						