Pharmacology, Biochemistry and Behavior 99 (2011) 423–427

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Low dose, short-term rivastigmine administration does not affect neurocognition in methamphetamine dependent individuals

Ari D. Kalechstein [a,*], Jin H. Yoon [a], Daniel E. Croft [a], Susanne Jaeggi [b], James J. Mahoney III [a], Richard De La Garza II [a]

[a] Baylor College of Medicine, Menninger Department of Psychiatry and Behavioral Sciences, Houston, TX 77030, USA
[b] University of Michigan, Department of Psychology, Ann Arbor, MI 49109, USA

ARTICLE INFO

Article history:
Received 19 January 2011
Received in revised form 28 April 2011
Accepted 15 May 2011
Available online 23 May 2011

Keywords:
Methamphetamine
Cognition
Neurocognition
Neuropsychological impairment
Rivastigmine
Acetylcholine

ABSTRACT

Neurocognitive impairment is a well-documented consequence of methamphetamine addiction. Not surprising, methamphetamine-associated neurocognitive impairment has been identified as an important target of treatment. Thus, this study sought to determine whether rivastigmine, an acetylcholinesterase inhibitor and cognition enhancing agent, could improve neurocognitive performance in a sample of long-term, high-dose methamphetamine addicts who were not seeking treatment at the time of enrollment in the study. This double-blind, placebo-controlled study evaluated whether a daily dose 0, 3, or 6 mg of rivastigmine, administered over six consecutive days, would enhance performance on measures of attention/information processing speed, episodic memory, and executive/frontal lobe functioning relative to test performance at baseline. The results revealed that rivastigmine did not alter neurocognition in this cohort. There are a number of factors that may have mitigated the effects of rivastigmine in this particular study, including especially the short-term, low-dose treatment regimen utilized. The negative findings notwithstanding, the study serves as a springboard for future investigations that will examine whether other medications can alter neurocognition in methamphetamine dependent study participants.

1. Introduction

Long-term, high-dose methamphetamine use is a risk factor for the onset of neurocognitive impairment in humans (Kalechstein and Newton, 2007). A review of the extant literature on methamphetamine use and neurocognition revealed that 24 of 25 studies showed that methamphetamine dependence is associated with poorer performance on measures of attention/information processing speed, learning and memory, and/or executive/frontal systems functioning (Kalechstein and Newton, 2007). Two of these studies reported that 22 to 57% of participants were impaired, depending on the domain assessed (e.g., Cherner et al., 2009; Kalechstein et al., 2003). Moreover, methamphetamine-associated neurocognitive impairment is durable, i.e., unlikely to resolve with protracted abstinence (Volkow et al., 2001; Cherner et al., 2009). For example, the results of Cherner et al. showed that 5 of 11 participants continued to demonstrate global neurocognitive impairment after 6 months of continuous abstinence. In the one study that failed to detect differences between methamphetamine users and matched controls (Johanson et al., 2006), the lack of significant findings was at least partially attributable to the fact that the study relied on a test battery, the CANTAB, which demonstrated variable sensitivity in another study that examined the association between amphetamine use and neurocognition (Ornstein et al., 2000).

As a result of an accretion of articles on this topic, some researchers have identified methamphetamine-associated neurocognitive impairment as a neglected area of critical concern (Kalechstein et al., 2010; Sofuoglu, 2010). Sofuoglu (2010) highlighted the association between neurocognitive impairment and adverse functional outcomes, such as poor treatment retention in studies of cocaine-dependent and alcohol-dependent individuals, and also emphasized the need to identify and test candidate medications that potentially can ameliorate this condition.

It is noteworthy that stimulant-associated neurocognitive impairment can be ameliorated; for example, administration of 400 mg of modafinil for 3 days resulted in significantly improved response accuracy on measures of working memory in those study participants who demonstrated relatively poor performance at baseline (Kalechstein et al., 2010). A recent study by Ghahremani et al. (2011) showed that acute modafinil exposure improved performance on a reversal learning task in methamphetamine users. For the current study, rivastigmine was being evaluated for its safety and potential efficacy in a phase I clinical study in long-term, high-dose methamphetamine using volunteers. The effect of rivastigmine on neurocognitive impairment was identified as a secondary outcome.

Several reasons underlay the decision to focus on the remediation of neurocognitive impairment using rivastigmine. Namely, rivastigmine is classified as a cognition-enhancing agent (Hasselmo and Sarter, 2011)

* Corresponding author.
E-mail address: kalechst@bcm.edu (A.D. Kalechstein).

0091-3057/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2011.05.013

and, in some double-blind, placebo-controlled studies, administration of rivastigmine was associated with improved performance on tests of attention, memory in individuals diagnosed with Alzheimer's disease (Feldman et al., 2007; Frankfort et al., 2007) and traumatic brain injury (Silver et al., 2009; Tenovuo et al., 2009). In these studies, the efficacy of rivastigmine was greatest in studies that utilized higher doses, e.g., 7.9 mg per day for much longer period of times, e.g., 39 weeks (Silver et al., 2009); however, because the efficacy of rivastigmine has not been evaluated in samples of long-term, high-dose methamphetamine using individuals, we sought to determine whether relatively low-dose, short-term administration of rivastigmine would be associated with improved performance on measures of attention/information processing speed, episodic memory, and working memory.

2. Materials and method

2.1. Sample

Participants were English-speaking volunteers who were not seeking abstinence-focused treatment at the time of the study, between 18 and 55 years of age, met DSM-IV-TR (American Psychiatric Association, 2000) criteria for methamphetamine dependence, have a breathalyzer test indicating an undetectable blood alcohol level upon admission, had a medical history and brief physical examination demonstrating no clinically significant contraindications for study participation, and had a negative urine drug screen, with the exception of methamphetamine or marijuana. Exclusion criteria included having neurological or psychiatric disorders, as assessed by MINI (Sheehan et al., 1998), such as episode of major depression within the past 2 years, lifetime history of schizophrenia, other psychotic illness, or bipolar illness, current organic brain disease or dementia assessed by clinical interview, history of or any current psychiatric disorder which would require ongoing treatment or which would make study compliance difficult, history of suicide attempts within the past 3 months and/or current suicidal ideation/plan, or history of psychosis occurring in the absence of current methamphetamine use, meet DSM-IV-TR criteria for dependence on alcohol or other drugs, except for nicotine or marijuana. Data regarding demographic profile and substance use history are included in Table 1.

Table 1
Demographics and drug use.

Category	Total N = 17
Gender	
Male	14
Female	3
Ethnicity	
Caucasian	13
Hispanic	3
African–American	1
Age	34.4 ± 2.0
Education (in years)	13.2 ± 0.5
Estimated premorbid IQ	110.9 ± 2.2
Methamphetamine	
Years of use	10.2 ± 1.5
Recent use (last 30 days)	17.4 ± 2.4
Amount used per day (in grams)	0.8 ± 0.1
Nicotine (n = 14)	
Years of use	12.5 ± 2.0
Recent use (last 30 days)	26.7 ± 1.8
Number of cigarettes per day	16.7 ± 2.6
Alcohol (n = 14)	
Years of use	13.5 ± 2.6
Recent use (last 30 days)	2.2 ± 1.0
Marijuana (n = 11)	
Years of use	12.5 ± 2.9
Recent use (last 30 days)	8.0 ± 2.9

2.2. Procedure

The primary objective of the parent protocol was to characterize the effects of treatment with rivastigmine (0, 1.5, and 3 mg, twice per day) on the subjective and reinforcing effects produced by experimental administration of methamphetamine (0, 15 and 30 mg, IV) in the laboratory (data to be presented in a separate publication). A secondary objective, and the focus of this manuscript, was to determine the effects of rivastigmine treatment on cognitive functioning in long-term, high-dose methamphetamine using individuals. Participant reimbursement was not contingent upon performance on the neurocognitive tests.

This was a double-blind, placebo-controlled, within-subjects study. Participants resided in the Michael DeBakey VA Medical Center. Upon admission, study participants provided a negative urine toxicology screen, which reveals that they had not used methamphetamine for at least 3 to 5 days prior to that day. They completed neurocognitive battery assessments at 10:30 am on Days 1 (admission/pre-randomization) and 9 (discharge/post-randomization). On the dates of the neurocognitive assessments, participants were not allowed to smoke cigarettes during the 60 min prior to the test administration, during the assessment, or during the 60 min following the test administration.

On Days 2 and 6 participants received 3 double-blind methamphetamine infusion sessions in which the dose (0, 15 and 30 mg, IV) was randomized and separated by 3 h. They were randomly assigned to placebo or rivastigmine for days 3–8. On day 7, participants completed two sessions in which they received either placebo or 5 mg of IV methamphetamine. Infusions were separated by 15 min and the methamphetamine and placebo sessions were randomized in a double-blind manner. Additionally, each session was associated with a specific color (red or blue) and participants were informed to remember the color, as that color would be associated with the same dose of drug (placebo vs 5 mg of IV methamphetamine) for the sessions on the following day. On day 8, participants participated in a similar session to that of day 7, but they could now choose whether or not to self-administer each of the 10 infusions. On day 9, after completing the cognitive battery, they were discharged from the study and returned for enrollment and randomization to alternate rivastigmine dosing conditions after at least 1 week had passed.

2.3. Tests administered

The following tests were administered during the baseline and post-treatment phase of each study arm. Participants were provided with standardized instructions, both oral and written, prior to the administration of each task. Additionally, participants were always reminded to respond as quickly and as accurately as possible. The tests were selected based on studies demonstrating that these and or similar measures were shown to be valid and reliable with respect to differentiating between long-term, high-dose methamphetamine using individuals and matched controls (Cherner et al., 2009; Levine et al., 2006; Newton et al., 2003).

2.3.1. Wechsler Adult Intelligence Scale—III (WAIS-III; Wechsler, 2007)

The Vocabulary and Matrix Reasoning subtests of the WAIS-III were administered. These raw scores from these subtests were included in an algorithm, the Oklahoma Premorbid Intelligence Estimation algorithm (Schoenberg et al., 2002), which estimates level of intellectual function prior to the onset of drug use.

2.3.2. Continuous Performance Test—II (CPT-II; Conners, 2002)

The CPT-II measures sustained attention. Participants were instructed to press the space bar whenever any letter, except for 'X,' appeared on the computer screen. The letters were presented for 250 ms, and new letters appeared at intervals of 1, 2, or 4 s. The inter-stimuli time intervals varied pseudo-randomly. The variables of interest

were sensitivity (d′), response style (β), hit rate (response time in milliseconds), omissions (failure to press the space bar when required), and commissions (pressing the space bar when 'X' appeared). The indices were transformed into standard scores, i.e. T-scores.

2.3.3. Hopkins Verbal Learning Test—Revised (HVLT-R; Brandt and Benedict, 2005)

The HVLT-R is a measure of verbal learning and memory that includes six different forms. Participants were initially read a list of 12 words, approximately one word per second, and asked to repeat back as many words as possible. This procedure was repeated twice, for a total of three learning trials. Following a 20 to 25 minute delay period, participants were asked to recall the words without the aid of reminders. The dependent variables of interest for the HVLT-R were total words recalled during each of the three learning trials and the number of words remembered following the 20 to 25 minute delay period

2.3.4. Dual n-back task (Jaeggi et al., 2008)

For this working memory task, participants were presented with a series of visual stimuli (blue squares) and auditory stimuli (letters) simultaneously presented across 20 blocks of 20/+ n trials each. The visual stimulus was presented in one of eight locations on the screen, and the auditory stimulus was one of eight different letters. For each trial the stimuli were presented simultaneously for 500 ms, with a 2500 millisecond latency period between the presentation of stimuli.

Participants started with a 1-back condition, where they were required to provide a "yes" response (pressing a blue button with the left forefinger) if the location of the presented visual stimulus matched the location of the stimulus presented immediately beforehand. Similarly, if the auditory stimulus matched the stimulus presented immediately beforehand, the participants were required to provide a "yes" response (pressing a red button with the right forefinger). If both the visual and auditory stimuli matched those presented in the previous trial, then participants were expected to concurrently press the red and blue buttons, and finally, no response was required if none of the stimuli matched.

While completing the 20 blocks, the task difficulty varied as a function of participants' performance. Specifically, if participants achieved at least 90% accuracy rate for both visual and auditory modalities in a particular block, the n-back level increased by one (e.g. from 1-back to 2-back). Conversely, participants regressed to simpler conditions, e.g., from 2-back to 1-back, if they achieved less than 70% accuracy for either the visual and auditory modalities in a particular block. Finally, the n-back level stayed the same if participants performed at an accuracy level between 70 and 90%. For all levels, a "yes" response was required if the presented visual stimulus or auditory stimulus matched the stimulus that was presented n trials previously. The dependent variables were mean n-back level reached in those 20 blocks, visual and auditory accuracy (defined as the ratio of accurate responses to total responses), and response time (defined as mean response time over each of the 20 block administrations for the auditory and visual stimuli).

2.3.5. Order of test administration

The battery of neurocognitive tests was administered in the following order: the HVLT-R learning recall trials, the dual n-back tests, delayed recall of the HVLT-R, and lastly the CPT. The average duration of these neurocognitive procedures was an hour and a half. The reaction time tests were programmed on a laptop computer. The WAIS-III was administered on a separate day, following the cessation of withdrawal symptoms, and prior to randomization into the study arms.

2.4. Data analyses

Analyses were conducted using the Statistical Package for Social Sciences, version 18. Pearson, product moment correlations were used to evaluate the association between demographic and drug use variables and performance on the neurocognitive measures. Within-subjects, repeated measures analysis of variance (ANOVA) was used to evaluate the effects of rivastigmine on test performance. Values were considered significant at $p<0.05$.

3. Results

Preliminary analyses revealed that demographic indices, including age, years of education, estimated level of premorbid IQ, and substance use indices, including lifetime and recent use of alcohol, methamphetamine, and nicotine, did not correlate with performance on measures of sustained attention (CPT — d′, CPT — Response style (β), CPT — hit rate, CPT — commissions, CPT — omissions), learning and memory (HVLT-R Learning Trials, HVLT-R Delayed Recall), or working memory performance (n-back accuracy and response time for auditory and visual stimuli) (all p-values>0.05). Moreover, order of medication administration (0 mg, 3 mg, and 6 mg) did not affect performance on the measures of neurocognition (p>0.05). Thus, no covariates were included in the primary analyses.

Within-subjects, repeated measures ANOVA revealed that rivastigmine administration did not improve performance on measures of sustained attention (CPT — d′, CPT — response style (B), CPT — hit rate, CPT — commissions, CPT — omissions), learning and memory (HVLT-R Learning Trials, HVLT-R Delayed Recall), or working memory (n-back accuracy and response time for auditory and visual stimuli) (all p-values>.05) (Table 2).

Secondary analyses also focused on classifying participants as high or low performers on the CPT-II, the n-back test, and the HVLT-R using a median split for each of the performance indices, then determining whether the groups differed in terms of estimated premorbid intellectual functioning. Estimated premorbid IQ did not vary as a function of performance on the HVLT-R or the n-back test. On the CPT-II, higher sensitivity (d′) and fewer omissions were associated with higher estimated premorbid IQ; otherwise, no group differences were observed (Table 3).

Based on a previously used strategy, the study participants with the poorest baseline performance for each measure, operationally defined as scores within the bottom half of the frequency distribution for each test, were identified to determine if they might be most responsive to the medication (Kalechstein et al., 2010). Consistent with the results of the primary analyses, within-subjects repeated measures ANOVA showed that the relatively poor performers at baseline did not improve as a result of rivastigmine administration (p>.05).

4. Discussion

Although methamphetamine is associated with chronic changes to the human brain (Volkow et al., 2001; Cherner et al., 2009; Thompson et al., 2008), recently published studies suggest that these brain alterations, indexed as neurocognitive impairment, can be improved with the administration of cognitive enhancing agents, such as modafinil (Kalechstein et al., 2010; Ghahremani et al., 2011). That finding was not replicated in this study, and there are several potential explanations for that. The most likely explanation centers on the methodological limitations of this study. Specifically, rivastigmine administration was most likely to be associated with improved neurocognitive function in studies that utilized higher doses, e.g., 7.9 mg per day for much longer period of times, e.g., 39 weeks (Silver et al., 2009) in larger samples, i.e., samples in the cited studies included a minimum of 69 participants; for this study, the maximum dose was

Table 2
Baseline and post-treatment (post-tx) performance on tasks of attention, episodic memory, and working memory.

		0 mg		3 mg		6 mg	
Test	Index	Baseline	Post-tx	Baseline	Post-tx	Baseline	Post-tx
Continuous Performance	n=	17	17	16	17	17	17
Test–II	D′ (sensitivity)[a]	56.53 ±5.5	57.43 ±4.25	55.94 ±6.87	56.04 ±8.23	52.73 ±9.03	53.75 ±7.11
(T-scores)	β (response style)	48.84 ±3.07	49.68 ±3.30	48.61 ±3.17	49.44 ±6.89	47.73 ±3.12	48.66 ±3.80
	Hit rate − RT	45.92 ±8.89	49.82 ±11.8	43.85 ±10.11	44.64 ±13.62	43.48 ±9.74	45.63 ±15.66
	Omissions[a]	85.44 ±52.99	134.24 ±133.2	69.43 ±39.11	87.68 ±64.53	75.63 ±78.42	99.40 ±84.89
	Commissions	59.75 ±9.37	59.20 ±5.57	58.61 ±12.02	59.36 ±9.99	55.19 ±9.05	56.48 ±8.67
Hopkins Verbal Learning	n=	17	16	16	17	17	17
Test–Revised	Trial 1	6.59 ±1.73	6.38 ±2.90	6.88 ±2.16	7.06 ±2.63	6.35 ±1.87	6.41 ±2.21
(number of words recalled)	Trial 2	8.82 ±1.70	8.19 ±2.43	8.75 ±2.14	8.24 ±2.63	8.53 ±1.81	8.06 ±2.49
	Trial 3	10.06 ±1.52	8.25 ±3.17	9.63 ±2.03	9.18 ±1.98	9.12 ±1.45	9.06 ±2.56
	Trials 1–3	8.49 ±2.18	7.60 ±2.92	8.42 ±2.37	8.16 ±2.54	8.00 ±2.07	7.84 ±2.62
	Learning curve	3.47 ±1.77	1.88 ±2.39	2.75 ±2.59	2.12 ±1.83	2.76 ±1.75	2.65 ±1.73
	Delayed recall	8.71 ±1.65	6.94 ±3.64	8.47 ±2.77	7.56 ±3.52	8.35 ±2.40	7.88 ±3.44
n-back test	n=	17	17	17	16	16	17
(accuracy = percentage of	Auditory accuracy	0.62 ±0.11	0.53 ±0.18	0.58 ±0.09	0.56 ±0.12	0.59 ±0.11	0.56 ±0.12
accurate responses)	Visual accuracy	0.49 ±0.12	0.43 ±0.16	0.53 ±0.30	0.53 ±0.14	0.56 ±0.10	0.47 ±0.19
	n-value	1.73 ±0.43	1.56 ±0.50	1.99 ±0.36	2.01 ±0.40	1.86 ±0.46	1.83 ±0.48
(RT = reaction time in milliseconds)	Auditory RTs[a]	371.68 ±98.00	348.18 ±109.07	381.96 ±104.57	365.2 ±95.17	391.12 ±96.69	353.95 ±116.17
	Visual RTs[a]	335.77 ±111.51	336.44 ±136.82	352.20 ±92.08	346.87 ±88.12	353.56 ±92.18	321.13 ±138.20

[a] Higher scores are indicative of poorer performance.

6 mg for a period of 9 days. It is plausible that this aspect of the study design mitigated the efficacy of rivastigmine. Moreover, the mechanism of action for rivastigmine differs from that of modafinil, and this factor may explain why a negative finding was observed in this study.

There are other potential explanations for the study outcome. One possibility is that rivastigmine does not sufficiently target the neurochemical abnormalities that underlie methamphetamine-associated neurocognitive impairment; however, that explanation is inconsistent with research showing that rivastigmine administration modulates the acetylcholine system (Bailey and Lahiri, 2010), which also is adversely affected by methamphetamine (Kuczenski and Segal, 2001). A third possibility is that the efficacy of rivastigmine as a cognition enhancing agent is mixed. This point is well-taken as the result studies in participants diagnosed with Alzheimer's disease (Feldman et al., 2007; Frankfort et al., 2007) and traumatic brain injury (Silver et al., 2009; Tenovuo et al., 2009) yielded variable results in both cohorts. Although there were no prior studies specifically showing that rivastigmine might remedy methamphetamine-associated neurocognitive deficits, it is true that long-term, high-dose methamphetamine use is associated with the onset of neurocognitive impairment (Kalechstein and Newton, 2007) and that methamphetamine exposure is temporally associated with alterations to the cholinergic system in animal models of methamphetamine addiction (Kuczenski and Segal, 2001). Because rivastigmine is characterized as a cognition enhancing agent that modulates the cholinergic system (Bailey and Lahiri, 2010), it seemed reasonable to study whether low-dose, short-term rivastigmine administration might remedy, at least in part, methamphetamine associated neurocognitive impairment. A fifth explanation for the negative finding is that study participants generally did not show neurocognitive deficits at baseline, which would limit the efficacy of the medication given that there is insufficient data to support the use of these agents in individuals with relatively intact neurocognition. Finally, over 20 studies, including those conducted in our laboratory, have consistently detected neurocognitive impairment in methamphetamine-dependent individuals (Kalechstein and Newton, 2007). Therefore, the above-average premorbid IQ of the currently evaluated cohort, combined with the lack of impairment on various cognitive measures, makes this group of methamphetamine users atypical, particularly given their high levels of methamphetamine use.

Table 3
Comparison of estimated premorbid intellectual functioning based on performance on tasks of attention, episodic memory, and working memory.[a]

		High performers	Low performers	$p \leq .05$
Test	Index	OPIE[b]	OPIE	
Continuous Performance		n = 8	n = 9	
Test − II	D′ (sensitivity)[a]	116.10 ± 8.97	105.05 ± 10.00	**0.030**
(T-scores)	β (response style)	111.92 ± 6.66	109.75 ± 14.57	.692
	Hit Rate − RT	112.12 ± 9.49	109.53 ± 12.60	.637
	Omissions[a]	117.89 ± 5.96	104.68 ± 10.45	**0.007**
	Commissions	107.21 ± 11.11	115.05 ± 9.35	0.139
Hopkins Verbal Learning		n = 8	n = 9	
Test − Revised	Trials 1–3	114.43 ± 7.97	106.93 ± 12.62	0.158
(# of words recalled)	Delayed recall	115.58 ± 9.71	106.74 ± 10.42	0.092
n-back test		n = 8	n = 9	
(RT = reaction time in ms)	Auditory RTs[a]	109.98 ± 12.41	111.71 ± 9.81	0.753
	Auditory accuracy	108.06 ± 9.31	114.10 ± 12.03	0.262
	Visual RTs[a]	109.98 ± 12.41	111.71 ± 9.81	0.753
	Visual accuracy	113.84 ± 9.03	107.59 ± 12.2	0.245

[a] High and low performers based on median split.
[b] OPIE = Oklahoma Premorbid Intelligence Estimate.

Despite the current outcomes, we contend that methamphetamine-associated neurocognitive impairment remains an important target of treatment. This perception is consistent with that of other leading researchers in the field (Sofuoglu, 2010), particularly given the prevalence of methamphetamine associated neurocognitive impairment and the fact that the condition does not resolve with protracted abstinence (Volkow et al., 2001; Cherner et al., 2009). Furthermore, the association between neurocognitive impairment and functional outcomes, such as employment status for individuals diagnosed with other disorders, e.g., traumatic brain injury, epilepsy, and HIV, is well-documented (Kalechstein et al., 2003). Given that methamphetamine addiction is associated with widespread functional difficulties, such as unemployment and relapse to dependence, it is plausible that reversing neurocognitive impairments associated with this disease will concurrently ameliorate these functional difficulties as well.

Disclosure/Conflict of interest

There are no conflicts of interest to be declared.

Acknowledgments

Funding for this study was derived from a grant to R. De La Garza from the National Institute on Drug Abuse (DA 023964).

References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000.

Bailey JA, Lahiri DK. A novel effect of rivastigmine on pre-synaptic proteins and neuronal viability in a neurodegeneration model of fetal rat primary cortical cultures and its implication in Alzheimer's disease. J Neurochem 2010;112(4):843–53.

Brandt J, Benedict RH. Hopkings Verbal Learning Test — Revised (HVLT-R). Lutz, FL: Psychological Assessment Resources, Inc; 2005.

Cherner M, Suarez P, Casey C, Deiss R, Letendre S, Marcotte T. Methamphetamine use parameters do not predict neuropsychological impairment in currently abstinent dependent adults. Drug Alcohol Depend 2009;106(2–3):154–63.

Conners CK. Conners' Continuous Performance Test — II (CPT-II). Multi-Health Systems, Inc; 2002.

Feldman HH, Ferris S, Winblad B, et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study. Lancet Neurol 2007;6(6):501–12.

Frankfort SV, Appels BA, de Boer A, et al. Identification of responders and reactive domains to rivastigmine in Alzheimer's disease. Pharmacoepidemiol Drug Saf 2007;16(5):545–51.

Ghahremani DG, Tabibnia G, Monterosso J, Poldrack RA, London ED. Effect of modafinil on learning and task-related brain activity in methamphetamine-dependent and healthy individuals. Neuropsychopharmacology 2011;36:950–9.

Hasselmo ME, Sarter M. Modes and models of forebrain cholinergic neuromodulation of cognition. Neuropsychopharmacology 2011;36(1):52–73.

Jaeggi SM, Buschkuehl M, Jonides J, Perrig WJ. Improving fluid intelligence with training on working memory. Proc Natl Acad Sci USA 2008;105(19):6829–33.

Johanson CE, Frey KA, Lundahl LH, et al. Cognitive function and nigrostriatal markers in abstinent methamphetamine abusers. Psychopharmacology (Berl) 2006;185(3):327–38.

Kalechstein AD, Newton TF. Methamphetamine. Neuropsychology and substance use: state-of-the-art and future directions. A. D. K. a. W. G. v. Gorp. New York, NY: Taylor and Francis; 2007. p. 207–26.

Kalechstein AD, De La Garza R, Newton TF. Modafinil administration improves working memory in methamphetamine-dependent individuals who demonstrate baseline impairment. American Journal on Addictions 2010;19:340–4.

Kalechstein AD, Newton TF, van Gorp WG. Neurocognitive functioning is associated with employment status: a quantitative review. J Clin Exp Neuropsychol 2003;25(8):1186–91.

Kuczenski R, Segal DS. Caudate–putamen and nucleus accumbens extracellular acetylcholine responses to methamphetamine binges. Brain Res 2001;923(1–2):32–8.

Levine AJ, Hardy DJ, Miller E, Castellon SA, Longshore D, Hinkin C. The effect of recent stimulant use on sustained attention in HIV-infected adults. J Clin Exp Neuropsychol 2006;28(1):29–42.

Newton TF, Cook IA, Kalechstein AD, et al. Quantitative EEG abnormalities in recently abstinent methamphetamine dependent individuals. Clin Neurophysiol 2003;114(3):410–5. Mar.

Ornstein TJ, Iddon JL, Baldacchino AM, et al. Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. Neuropsychopharmacology 2000(2):113–26. Aug.

Schoenberg MR, Scott JG, Duff K, Adams RL. Estimation of WAIS-III intelligence from combined performance and demographic variables: development of the OPIE-3. Clin Neuropsychol 2002;16(4):426–37.

Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(Suppl 20):22–33. quiz 34–57.

Silver JM, Koumaras B, Meng X, et al. Long-term effects of rivastigmine capsules in patients with traumatic brain injury. Brain Inj 2009;23(2):123–32.

Sofuoglu M. Cognitive enhancement as a pharmacotherapy target for stimulant addiction. Addiction 2010;105(1):38–48.

Tenovuo O, Alin J, Helenius H. A randomized controlled trial of rivastigmine for chronic sequels of traumatic brain injury—what it showed and taught? Brain Inj 2009;23(6):548–58.

Thompson PM, Hayashi KM, Simon SL, Geaga JA, Hong MS, Sui Y, Lee JY, Toga AW, Ling W, London ED. Structural abnormalities in the brains of human subjects who use methamphetamine. J Neurosci 2004;24(26):6028–36.

Volkow ND, Chang L, Wang GJ, et al. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. Am J Psychiatry 2001;158(3):377–82.

Wechsler D. Wechsler Adult Intelligence Scale — III. TX, The Psychological Corporation: San Antonio; 2007.