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Preliminary findings of the effects of rivastigmine, an acetylcholinesterase inhibitor, on working memory in cocaine-dependent volunteers

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Abstract

Long-term cocaine use is a risk factor for the onset of neurocognitive impairment. This study sought to determine whether the cholinesterase inhibitor rivastigmine could improve neurocognitive performance in cocaine-dependent individuals. Cocaine-dependent individuals who were not seeking treatment at the time of enrollment in the study were randomly assigned to receive placebo (n = 16), rivastigmine 3 mg (n = 13), or rivastigmine 6 mg (n = 12). The baseline neurocognitive assessment, which included measures of attention/information processing (as measured by the Continuous Performance Task-II (CPT-II)), verbal learning/episodic memory (as measured by the Hopkins Verbal Learning Test-Revised (HVLT-R)), and working memory (as measured by the Dual N-Back Task), was conducted prior to the administration of study medication (Day 0). The follow-up assessment was conducted on Day 8 after the participants had received rivastigmine or placebo for 7 days (Day 2–8). Rivastigmine administration significantly improved performance on one measure of working memory span (mean n-back span). This study provides additional data showing that cocaine-associated neurocognitive impairment, specifically working memory deficits, can be remediated, at least to some degree.

Keywords

Acetylcholinesterase inhibitor; Cocaine; Neurocognition; Rivastigmine; Working memory

1. Background/introduction

Previous studies have reported that sustained cocaine use may result in neurocognitive impairment in humans (Bolla and Cadet, 2007; Jovanovski et al., 2005). Specifically, a meta-analytic review revealed effect sizes of moderate or greater magnitude in the domains of attention, episodic memory, and working memory (Jovanovski et al., 2005). These neurocognitive impairments may have detrimental consequences for cocaine-dependent individuals as they attempt to maintain successful daily functioning; for example, the

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presence of cocaine related neurocognitive deficits have been reported to be associated with poor treatment retention (Aharonovich et al., 2003, 2006, 2008; Sofuoglu, 2010).

Since cocaine-associated neurocognitive impairments adversely affect important outcomes for cocaine addicts, then an important area of research involves whether stimulant-induced neurocognitive impairment can be reversed or ameliorated by using cognition enhancing interventions. Recent publications suggest that such improvements are feasible. For example, following of 20 mg of oral methylphenidate (a medication used to enhance cognitive functioning in individuals with attention deficit/hyperactivity disorder), cocaine-dependent individuals made fewer errors on a computerized cognitive salience task (in which participants viewed a drug-related or neutral word on a screen written in blue, green, red, or yellow font, then pressed the matching colored button on a key pad) (Goldstein et al., 2010). Also, a recent study by our group revealed that modafinil (200 mg/day for 3 days) improved working memory in cocaine-dependent individuals, as measured by using a computerized n-back test (Kalechstein et al., 2013).

One class of medications that has demonstrated an indication for the reversal of neurocognitive impairment are acetylcholinesterase (AChE) inhibitors. Treatment with AChE inhibitors, acetylcholine (ACh) precursors, or cholinergic agonists can improve learning and memory in animals (Hasselmo and Sarter, 2011), healthy human subjects (Repantis et al., 2010), and in patients with Alzheimer's disease and other neuropsychiatric disorders (Feldman and Lane, 2007; Frankfort et al., 2007). Specifically, in double-blind, placebo-controlled studies, rivastigmine improved performance on tests of attention and memory in individuals diagnosed with Alzheimer's disease (Feldman and Lane, 2007; Frankfort et al., 2007). Furthermore, in samples of individuals diagnosed with traumatic brain injury, rivastigmine improved performance on tasks specific to information processing and episodic memory (Silver et al., 2009), as well as vigilance (Tenovuo et al., 2009). While there has been a great deal of research investigating the relationship between the dopamine system and the effects produced by cocaine, it is well known that cholinergic transmission is altered by drugs of abuse as well and that dopamine and ACh may affect the reinforcement of psychostimulants (Hurd et al., 1990; Mark et al., 1999a, 1999b). Specifically, the interaction between dopaminergic and cholinergic neurons in the nucleus accumbens results in the coordinated functioning of these neurotransmitter systems. Moreover, the impact of the ACh system on the effects produced by cocaine has been extensively reported by Adinoff and colleagues (Adinoff et al., 2010; Williams and Adinoff, 2008).

Based on the premise that rivastigmine enhanced neurocognition in other disorders, it is reasonable to hypothesize that this pharmacological compound will demonstrate similar effects in cocaine-dependent individuals. We hypothesized that rivastigmine would significantly improve various domains of neurocognitive functioning, including attention, verbal/episodic memory, and working memory, when compared to placebo.

2. Method

2.1. Participants

Participants were recruited from the Houston metropolitan area through newspaper and radio advertisements. The study was approved by the Baylor College of Medicine and Michael E. DeBakey Veterans Association Medical Center (MEDVAMC) Institutional Review Boards. All participants completed an initial telephone screen in order to assess basic eligibility. Candidates were then invited to complete an in-person assessment at the Research Commons of the MEDVAMC. During the in-person interview, candidates received an explanation of the study purpose and requirements and were allowed to review, inquire about, and sign the informed consent form. Eligible individuals were required to be between 18 and 55 years of age, provided at least one urine specimen that was positive for cocaine within the 2 weeks prior to study enrollment, met DSM-IV criteria for cocaine-dependence according to the Mini-International Neuropsychiatric Interview (M.I.N.I.), and were experienced with respect to smoking and/or injecting cocaine. Participants were excluded for any current psychiatric or medical illness (including depression, anxiety, etc.) based on the criteria set forth in the M.I.N.I. assessment, serious neurological or seizure disorder, use of any psychoactive medication, and drug or alcohol dependence excluding cocaine and nicotine. Women were classified as ineligible for the study if they were pregnant, breast feeding, or not using a reliable form of birth control. Inclusion/exclusion was based off of self-report, a cocaine-positive urine sample, and a performed history and physical conducted by a medical doctor. Participants were compensated with a $40 gift card for completing the in-person screen and were compensated $550 if they completed the inpatient phase of the protocol.

Overall, participants were predominately male, African American, approximately 40 years old, and averaged a high-school level of education. In terms of cocaine use, all participants were crack-cocaine users and most reported using cocaine approximately half of the days in the last month (Table 1).

2.2. Procedure

All study visits took place at the MEDVAMC Research Commons. Initial screening measures were assessed at the in-person screen interview, and included a medical and drug use history, electrocardiogram, and vital signs, which were conducted by trained research staff. Eligible participants were admitted to the Research Commons as inpatients and then randomized into one of three groups: rivastigmine (0, 3, or 6 mg) by the MEDVAMC Research Pharmacy in order to maintain the double-blind condition. During the enrollment period, participants were monitored 24 h a day by research staff and daily urine toxicology testing was performed to confirm drug abstinence. The participants were administered a low dose of 40 mg cocaine on Day 1 of the protocol but this was not considered a confound given that the half-life of cocaine is ~60 min and cognitive testing was performed 7 days following that low dose of cocaine.

2.3. Study medication

An Investigational New Drug was obtained from the Food and Drug Administration for the use of rivastigmine in this study. On days 2–8 of the study, commercially available rivastigmine or placebo were administered orally twice daily (BID) at 8:00 a.m. and 6:00 p.m. (0 + 0 mg, 3 + 0 mg, or 3 + 3 mg). We decided upon the 3 and 6 mg doses of rivastigmine based on previous research by our laboratory in methamphetamine users (De La Garza et al., 2008, 2012). On the basis of the information available, it is clear that the medication would have been at steady state levels after 2–3 days of administration and, more importantly, that cholinesterase inhibition would have also been achieved and maintained for several days during the protocol. According to the package insert, side effects of rivastigmine can include nausea, diarrhea, vomiting, indigestion, abdominal pain, loss of appetite and weight loss. Thus, to minimize the occurrence of these potential side effects, rivastigmine was administered BID. In addition, cognitive improvements in Alzheimer's disease patients receiving rivastigmine have been associated with central inhibition of both butyrylcholinesterase (BuChE) and AChE inhibition (Giacobini et al., 2002). These findings suggest that a greater effect on cholinergic transmission can be achieved through treatment with rivastigmine since it inhibits both enzymes.

2.4. Dates of test administration

The experiment utilized a between-subjects, double-blind, placebo-controlled design. Baseline neurocognitive testing was performed on Day 0 prior to randomization to study medication. As mentioned above, medication or placebo was administered twice daily beginning on Day 2. 13 participants were randomized to 3 mg rivastigmine, 12 participants were randomized to 6 mg rivastigmine, and 16 were randomized to placebo. The second and final neurocognitive testing was performed on Day 8 following 7 days of rivastigmine or placebo, which was sufficient for the drug to reach steady state levels. On the basis of the information available it is clear that the medication would have been at steady state levels after 2–3 days of administration, but more importantly that cholinesterase inhibition would have also been achieved and maintained for several days during the protocol. Notwithstanding, on the basis of published literature for Alzheimer's, we concede that longer testing regimens (i.e., several weeks) may have rendered more favorable outcomes. The current study was not designed to test the optimal duration of treatment needed to affect cognition, but merely to evaluate the safety of administration of these compounds in this patient population as part of an inpatient testing protocol.

2.5. Tests administered

Participants were provided with standardized instructions, both oral and written, prior to the administration of each task. Additionally, participants were 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 cocaine-dependent individuals and matched controls (Gooding et al., 2008; Verdejo-Garcia et al., 2006).

2.5.1. Wechsler Adult Intelligence Scale - III (WAIS-III; Wechsler, 2007)—The Vocabulary and Matrix Reasoning subtests of the WAIS-III were administered. Raw scores from these subtests were included in the Oklahoma Premorbid Intelligence Estimation algorithm (Schoenberg et al., 2002), which estimates level of intellectual function prior to the onset of drug use.

2.5.2. 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.

Dependent variables of interest included omissions – failure to press the space bar when letters other than X appear; commissions – pressing the space bar when 'X' appeared; and hit rate reaction time – amount of time in milliseconds for correct responses. The indices were transformed into standard scores, i.e. T-scores, where higher scores indicated greater impairment.

2.5.3. Hopkins Verbal Learning Test —Revised (HVLT—R; Brandt, 2005)—The HVLT—R is a measure of verbal learning/episodic memory that includes six parallel forms. In this particular study, participants completed 2 different forms (to minimize practice effects) of the HVLT—R, one pre-rivastigmine or placebo administration and one post-rivastigmine or placebo administration (it has previously been found that when alternate forms were used, practice effects were minimal (Barr, 2003; Benedict and Zgaljardic, 1998; Strauss et al., 2006). In addition, the forms were not counterbalanced as the manual for the HVLT—R shows that performance does not vary from one version to the next. 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 25 min delay period, participants were asked to recall the words without the aid of reminders. The dependent variables for the HVLT—R were total words recalled during each of the three learning trials and the number of words remembered following the 25 min delay period. The scores were transformed into T-scores.

2.5.4. Dual N-back Task (Jaeggi et al., 2008)—For this computerized working memory task, participants were presented with a series of visual stimuli (blue squares) and auditory stimuli (letters) simultaneously presented across 20 blocks of 21 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 ms latency period between the presentations of stimuli.

Participants started with a 1-back condition, where they were required to provide a "yes" response (pressing the left arrow key 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 the right arrow key 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 both arrow keys, 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 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 and maximum n-back level reached in those 20 + n blocks and visual and auditory accuracy (defined as the ratio of accurate responses to total responses).

2.5.5. Order of test administration—The battery of neurocognitive tests was administered in the following order: the HVLT—R learning trials, the dual n-back tests, delayed recall of the HVLT—R, and the CPT-II. The average duration of test administration was 90 min. The CPT-II and dual n-back tests were programmed on a laptop computer. The WAIS-III was administered on a separate day during the screening, after verifying that the volunteer was not experiencing withdrawal symptoms from cocaine, and prior to randomization into the study arms.

2.6. Data analyses

Analyses were conducted using SPSS, version 20. Pearson, product moment correlations were used to evaluate the association between demographic and drug use variables and performance on the neurocognitive measures. Mixed-model, repeated measures analysis of variance (ANOVA) was used to evaluate the effects of 3 and 6 mg rivastigmine versus placebo on test performance at baseline (day 0) and on Day 8. Review of the initial analyses revealed that, for the participants who received rivastigmine, dose did not moderate performance on the measures of neurocognition; hence, the participants administered 3 or 6 mg were combined into one group and their performance on the measures of neurocognition was compared with those participants who were administered placebo. In addition, based on a previously used strategy (Kalechstein et al., 2010, 2011), 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.

The p-value was set at 0.05 for all analyses. In addition, effect sizes are represented by partial eta squared (η^2) values where 0.01 = small effect; 0.06 = medium effect; and 0.14 = large effect (Cohen, 1973, 1988).

3. Results

Demographic and drug use characteristics of the 41 completers in the treatment groups are presented in Table 1. The treatment groups did not differ for any basic demographic or drug use variables (all *p*-values >0.05).

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, cocaine, marijuana, and nicotine, did not correlate with performance on indices of sustained attention, learning and memory, or working memory performance (all p's > 0.05). Thus, no covariates were included in the primary analyses. In addition, there were no differences in baseline performance across the 3 treatment groups and all were statistically similar during the pre-medication assessment.

Table 2 details participant's performance on the measures of neurocognition according to group (0, 3, and 6 mg of rivastigmine). Mixed-model, repeated measures ANOVA revealed that participants randomized to rivastigmine (3 or 6 mg) or placebo did not differ on measures of sustained attention as measured by the CPT, including hit rate ($F_{2,38}$ = 0. 233, p = 0.793, *partial* η^2 = 0.012), omissions ($F_{2,38}$ = 0.324, p = 0.725, *partial* η^2 = 0.017), and commissions ($F_{2,38}$ = 1.816, p = 0.176, *partial* η^2 = 0.087).

Participants randomized to rivastigmine (3 or 6 mg) were statistically similar to those randomized to placebo on the three learning trials of the HVLT—R ($F_{2,38}$ = 1.043, p = 0.362, *partial* η^2 = 0.052). Similarly, the groups did not differ with respect to performance on the delayed recall subtest of the HVLT—R ($F_{2,38}$ = 1.873, p = 0.168, *partial* η^2 = 0.090).

With regard to performance on the n-back, there were no significant differences observed for the following indices: mean length of the n-back trials for each block ($F_{2,38}$ = 2.617, p = 0.086, *partial* η^2 = 0.121), maximum block length during each assessment ($F_{2,38}$ = 0.854, p = 0.434, *partial* η^2 = 0.043), accuracy of responding to auditory stimuli ($F_{2,38}$ = 1.079, p = 0.350, *partial* η^2 = 0.054), and accuracy of responding to visual stimuli ($F_{2,38}$ = 0.177, p = 0.839, *partial* η^2 = 0.009).

As mentioned above, review of the initial analyses revealed that, for those participants that received rivastigmine, dose did not moderate performance on the measures of neurocognition; hence, the participants administered 3 or 6 mg were combined into one group and their performance on the measures of neurocognition was compared to participants who were administered placebo. In other words, there are times when the magnitude of the dose is not a moderating factor and this is one of them, thus we combined the groups to increase the power of the study. Table 3 includes the results of these analyses. Mixed-model, repeated measures ANOVA revealed that rivastigmine significantly improved performance on one index of working memory: mean length of the n-back trials for each block ($F_{1,39}$ = 4.202, p = 0.047, *partial* η^2 = 0.097). Rivastigmine and placebo groups did not differ on maximum block length during each assessment ($F_{1,39}$ = 1.745, p = 0.194, *partial* η^2 = 0.043), accuracy of responding to auditory stimuli ($F_{1,39}$ = 0.183, p = 0.671, *partial* η^2 = 0.005), accuracy of responding to visual stimuli ($F_{1,39}$ = 0.363, p = 0.550, *partial* η^2 = 0.009).

Rivastigmine administration did not affect measures of sustained attention as measured by the CPT, including hit rate ($F_{1,39} = 0.343$, $p = 0.562$, *partial* $\eta^2 = 0.009$), omissions ($F_{1,39} = 0.574$, $p = 0.453$, *partial* $\eta^2 = 0.015$), and commissions ($F_{1,39} = 2.224$, $p = 0.144$, *partial* $\eta^2 = 0.054$).

Participants randomized to rivastigmine were statistically similar to those randomized to placebo on the three learning trials of the HVLT—R ($F_{1,39} = 2.140$, $p = 0.152$, *partial* $\eta^2 = 0.052$). Similarly, there were no differences between groups on performance following a 20 min delay period ($F_{1,39} = 0.052$, $p = 0.821$, *partial* $\eta^2 = 0.001$).

Additional analyses were conducted to evaluate those individuals who demonstrated the greatest level of impairment during the baseline assessment (e.g. performed in the bottom half of the distribution). Participants who demonstrated impairment at baseline who were randomized to rivastigmine (3 or 6 mg) were statistically similar to those randomized to placebo on all measures of sustained attention, working memory, and episodic memory (all *p's* >0.05).

4. Discussion

This study demonstrated that rivastigmine administration improved span of working memory. That an effect was observed is noteworthy, particularly given that a short-term, low-dose treatment regimen was utilized in a sample of individuals who had been dependent on cocaine for approximately 16 years. These findings are consistent with those from other studies showing that, in cocaine-dependent individuals, administration of a cognition enhancing agent improved performance on measures of working memory (Kalechstein et al., 2013). It is apparent that some constructs, such as working memory, appear to be more amenable to modulation via medication than others. This may reflect that information processing speed is less prone to decline than other constructs, as borne out by the reaction time scores on the CPT-II. Moreover, the CPT-II scores were primarily within expected limits during pre-medication testing which may explain why there were no positive findings post-medication testing. HVLT—R learning scores were generally borderline impaired, i.e. approximately 61% of the sample had a t-score of 37 or less during pre-medication testing; hence, while this did not reach statistical significance, a trend towards a significant improvement in performance post-medication in the rivastigmine group, but not the placebo group, was apparent. Since the n-back is an experimental measure, there are no t-scores to use as a comparison. However, the n-back is considered to be a putative measure of dorsolateral pre-frontal cortex functioning which is affected adversely in cocaine-dependent individuals (Aharonovich et al., 2006).

These findings also buttress arguments suggesting that rivastigmine may be an effective treatment for cocaine dependence. Specifically, because rivastigmine reduced the positive subjective effects produced by methamphetamine, e.g., desire and likely to use (De La Garza et al., 2008, 2012), it is reasonable to infer that rivastigmine can target two consequences of addiction in stimulant users, i.e., craving and neurocognitive impairment. This line of thinking complements a current trend in the development of pharmacotherapies for cocaine-dependence; namely, medications are combined based on the notion that concurrent

modulation of multiple neurotransmitter systems may result in a synergistic outcome in which the benefit of the administration of both medications is greater than that associated with the administration of a single drug. Of course, the more parsimonious approach would be to identify a single medication that targets multiple outcomes. The benefits of the latter strategy are manifold, e.g., fewer side effects, less time titrating to the most effective dose because only one medication is prescribed, and a reduction in the potential for adverse outcomes as a result of medication interactions.

The positive findings of the study notwithstanding, the methodological limitations of the study need to be clarified. A primary limitation is that, in previously published studies, the duration of rivastigmine treatment was longer (approximately 39 weeks) and the doses were higher (up to 12 mg per day)(Silver et al., 2009). It is possible that this aspect of the study design mitigated the efficacy of rivastigmine, especially when considering the lack of effect of rivastigmine treatment on information processing speed, delayed recall on the HVLT—R, and some of the working memory indices. While an outpatient trial investigating the effects of rivastigmine on cocaine use has not yet been conducted, other trials involving AChE inhibitors as potential treatments for cocaine dependence have not been promising. Specifically, in a preclinical study in rats, rivastigmine did not produce reductions in cocaine-reinforced behavior (Grasing et al., 2011), while in an inpatient trial (Grasing et al., 2010) another AChE inhibitor, donepezil, increased ratings of ‘any’ and ‘good’ drug effect thus potentiating the effects of cocaine in dependent individuals. However, there are some critical differences between medications potentially leading to these conflicting findings. Rivastigmine inhibits both AChE and BuChE with equal potency (Williams et al., 2003). Other drugs, like donepezil, are centrally acting reversible inhibitors of AChE (but not BuChE). In a 10-week out-patient study was conducted using the Cocaine Rapid Efficacy and Safety Trial (CREST) study design, participants treated with donepezil did not reduce their cocaine use as compared to placebo (Winhusen et al., 2005). As mentioned above, this negative finding is supported by an inpatient laboratory study during which short-term treatment with donepezil increased positive subjective effects (Grasing et al., 2010). The available data may suggest that rivastigmine’s effect on BuChE may be critical in its potential efficacy as a treatment for cocaine or methamphetamine dependence or for improving cognitive functioning in these populations. In addition, neither of the studies using donepezil reported the impact of these drugs on neurocognitive functioning, thus it is unable to be determined whether cognition was a mitigating factor in the negative findings.

While the statistics regarding the effect size were clear, another limitation is the rather small sample size of 12–16 participants per group. A study with a larger number of individuals would add power to the findings and increase confidence in the results. While the statistics regarding effect size show that, despite the relatively modest sample size, the magnitude of the effect is large, future studies with larger sample sizes should be investigated. An additional limitation is that there was no demographically matched, non-drug using control group; we recruited only cocaine-dependent individuals to ensure that the placebo group closely matched the medication group. Moreover, the working memory span indices have been most responsive to cognitive enhancing medications whereas information processing speed, sustained attention, and episodic memory were not prone to modulation. Some potential explanations for this outcome include decent baseline performance prior to study

medication randomization (i.e., various indices on the CPT-II) and the nature of the treatment regimen (i.e., a more robust signal might be observed if a higher dose, longer treatment regimen was implemented). Thus, a study addressing these limitations would be needed to make any definitive conclusion of efficacy; however, the fact that a response was found in a short time is promising. Also, while we addressed concurrent substance use (e.g. the fact that the treatment groups were statistically similar with respect to alcohol and nicotine use), we excluded individuals during screening that had a co-occurring psychiatric disorder (e.g. depression, bipolar disorder). Thus, we suggest that future studies investigate co-occurring cocaine dependence and psychiatric disorders.

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

Future studies might also examine the degree to which improved neurocognition influences treatment retention in long-term cocaine users. It has previously been reported that there is an association between poor working memory function and an increased probability of treatment dropout (Aharonovich et al., 2008; Moeller et al., 2010; Streeter et al., 2008; Turner et al., 2009). In addition, specific to cocaine dependent individuals, studies have been conducted investigating the long-term treatment of similar AChE inhibitors (i.e. galantamine, donepezil) in multi-week outpatient trials with no severe or serious adverse events reported. Thus, given the facts that rivastigmine has been safely tolerated after being administered for several weeks in other populations, along with the fact that other AChE inhibitors have been safely tolerated in cocaine-dependent individuals over multi-week clinical trials, there is no evidence that there would be potential consequences of long-term exposure.

Taken together, while laboratory-based studies, such as the one reported on in this manuscript, provide insight as to the possibility of remediating cocaine-associated neurocognitive impairment, the ultimate determination of medication efficacy will be whether administration will result in continued abstinence from cocaine.

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Abbreviations

MEDVAMC	Michael E. DeBakey Veterans Association Medical Center
M.I.N.I	Mini-International Neuropsychiatric Interview
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
WAIS-III	Wechsler Adult Intelligence Scale - III
CPT-II	Continuous Performance Test - II
HVLT—R	Hopkins Verbal Learning Test —Revised
BID	twice daily
ACh	acetylcholine
AChE	acetylcholinesterase
BuChE	butyrylcholinesterase

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Table 1

Demographic and drug use characteristics.

Participant characteristics	Placebo (N = 16)	Riv 3 mg (N = 13)	Riv 6 mg (N = 12)
Demographics			
Females (%)	12.5	23.1	16.7
Caucasian (%)	0	7.7	16.7
African–American (%)	68.8	69.2	75.0
Hispanic (%)	12.5	23.1	8.3
Mixed	18.8	0	0
Age (years)	40.4 ± 2.0	43.9 ± 1.6	43.5 ± 1.6
Education (years)	12.1 ± 0.3	12.7 ± 0.5	13.3 ± 0.6
Estimated premorbid IQ	96.5 ± 3.8	98.8 ± 3.4	102.9 ± 3.0
Cocaine use			
Route of use-smoke (%)	100	100	91.7
Use in last 30 (days)	16.2 ± 1.9	18.6 ± 1.6	18.7 ± 2.7
Use lifetime (years)	15.6 ± 1.8	15.8 ± 2.4	15.8 ± 2.3
Grams per day	1.7 ± 0.3	2.9 ± 1.0	2.1 ± 0.4
Nicotine use	N = 14	N = 11	N = 10
Use in last 30 (days)	22.2 ± 2.6	21.2 ± 2.0	30.0 ± 0.0
Use lifetime (years)	17.4 ± 2.1	19.8 ± 2.2	21.8 ± 3.2
Cigarettes per day	9.3 ± 1.7	7.9 ± 1.6	14.3 ± 1.7*
Alcohol use	N = 15	N = 9	N = 10
Use in last 30 (days)	9.5 ± 2.1	10.8 ± 2.3	11.3 ± 3.0
Use lifetime (years)	19.1 ± 2.2	23.8 ± 0.8	19.1 ± 2.6
Drinks per day	3.1 ± 0.6	2.8 ± 0.4	2.4 ± 0.4

Values represent Mean ± SEM.

Number represents current users only.

Number represents days used in the part 30.

Number represents total number of years substance was used.

Table 2

Baseline and post-treatment (post-tx) performance on tasks of sustained attention, episodic memory, and working memory (0 mg, 3 mg, 6 mg rivastigmine).

	Placebo 0 mg (N = 16)		Rivastigmine 3 mg (N = 13)		Rivastigmine 6 mg (N = 12)	
Index	***Baseline***	***Post-tx***	***Baseline***	***Post-tx***	***Baseline***	***Post-tx***
CPT-II^						
Hit rate – RT^^	51.01 ± 3.96	46.58 ± 3.63	55.62 ± 4.88	52.46 ± 3.30	45.84 ± 4.10	44.26 ± 3.90
Omissions	79.66 ± 10.93	60.08 ± 4.76	100.46 ± 15.24	61.71 ± 6.95	87.95 ± 24.12	56.82 ± 7.37
Commissions	51.99 ± 2.35	52.46 ± 3.08	56.31 ± 3.04	50.59 ± 2.54	50.35 ± 2.79	48.76 ± 2.29
HVLT—R						
Trials 1–3 (scaled)	33.31 ± 2.78	32.13 ± 2.02	34.23 ± 2.54	37.69 ± 2.31	38.75 ± 3.31	42.08 ± 1.87
DR (scaled)	32.38 ± 2.65	31.38 ± 2.71	39.46 ± 2.43	34.92 ± 2.69	37.75 ± 2.72	39.33 ± 3.86
N-back						
Aud accuracy	0.50 ± .05	0.52 ± .05	.63 ± .03	.59 ± .03	.62 ± .05	.66 ± .03
Vis accuracy	0.43 ± .05	0.50 ± .05	.51 ± .02	.55 ± .02	.50 ± .06	.55 ± .06
N-value (mean)	1.46 ± .11	1.54 ± .10	1.51 ± .09	1.72 ± .12	1.60 ± .13	1.94 ± .11
N-value (max)	2.06 ± .19	2.06 ± .17	2.31 ± .13	2.54 ± .14	2.42 ± .23	2.67 ± .19

Values represent Mean ± SEM.

^Higher scores are indicative of poorer performance.

^^RT = reaction time.

Table 3

Baseline and post-treatment (post-tx) performance on tasks of sustained attention, episodic memory, and working memory (0 mg and collapsed 3/6 mg rivastigmine).

	Placebo 0 mg (N = 16)		Rivastigmine 3 mg and 6 mg (N = 25)	
Index	***Baseline***	***Post–tx***	***Baseline***	***Post–tx***
CPT-II^				
Hit rate – RT^^	51.01 ± 3.96	46.58 ± 3.63	50.92 ± 3.30	48.52 ± 2.62
Omissions	79.66 ± 10.93	60.08 ± 4.76	94.45 ± 13.78	59.36 ± 4.97
Commissions	51.99 ± 2.35	52.46 ± 3.08	53.45 ± 2.12	49.71 ± 1.69
HVLT—R				
Trials 1–3	33.31 ± 2.78	32.13 ± 2.02	36.40 ± 2.07	39.80 ± 1.53
Delayed recall	32.38 ± 2.65	31.38 ± 2.71	38.64 ± 1.79	37.04 ± 2.31
N-back				
Auditory accuracy	0.50 ± .05	0.52 ± .05	0.62 ± .03	0.63 ± .02
Visual accuracy	0.43 ± .05	0.50 ± .05	0.50 ± .03	0.55 ± .03
N-value (mean)	1.46 ± .11	1.54 ± .10	1.55 ± .07	1.83 ± .08*
N-value (max)	2.06 ± .19	2.06 ± .17	2.36 ± .13	2.60 ± .12

Values represent Mean ± SEM.

^ Higher scores are indicative of poorer performance.

^^ RT = reaction time.

* $p < 0.05$.