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Neuropsychological functioning in opiate-dependent subjects receiving and following methadone maintenance treatment

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Abstract

Objective—An accumulating body of research suggests that former heroin abusers in methadone maintenance therapy (MMT) exhibit deficits in cognitive function. Whether these deficits are present in former methadone maintained patients following discontinuation of MMT is unknown. This study tests the hypothesis that former heroin users who have detoxified from methadone maintenance therapy and are drug-free have less pronounced cognitive impairment than patients continuing long-term MMT.

Method—A series of neuropsychological tests were administered to three groups of subjects: 29 former heroin addicts receiving methadone maintenance treatment, 27 former heroin addicts withdrawn from all opiates, and 29 healthy controls without a history of drug dependence. Testing included Wechsler Adult Intelligence Scale-Revised Vocabulary Test, the Stroop Color-Word Test, the Controlled Oral Word Association Test, the Benton Visual Retention Test, and a Substance Use Inventory.

Findings—Both methadone-maintained and abstinent subject groups performed worse than controls on tasks that measured verbal function, visual-spatial analysis and memory, and resistance to distractibility. Abstinent subjects performed worse than their methadone maintained counterparts on tests measuring visual memory and construct formation. Cognitive impairment did not correlate with any index of drug use.

Conclusions—We confirmed previous findings of neuropsychological impairment in long-term MMT recipients. Both patients receiving MMT and former heroin users in prolonged abstinence exhibited a similar degree of cognitive impairment. Cognitive dysfunction in patients receiving methadone maintenance may not resolve following methadone detoxification.

Keywords

Methadone; Opiates; Dependence; Abstinence; Neuropsychological; Cognitive

1. Introduction

An increasing body of literature suggests that the prolonged use of opiates, such as heroin, is associated with a deleterious effect on intellectual functioning (Miller, 1985,1991). Active addicts may be hindered by poor impulse control, planning, and decision-making (Grant et al.,

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2000;Lee and Pau, 2002;Bolla et al., 2003;Hill et al., 1979;Gritz et al., 1975;Chastain et al., 1986;Strang and Gurling, 1989;Guerra et al., 1987;Tapert, 1999;Franken et al., 2000), suggesting that opiate-induced cognitive impairment may contribute to the relapsing nature of addiction (Gossop et al., 2002;Latowsky, 1996;Rogers and Robbins, 2001;Teichner et al., 2002;Aharonovic et al., 2003). Little is known about the course of opiate-associated cognitive deficits after cessation of opiate use. Increasing our understanding of cognitive impairment that occurs in chronic opiate use and especially in opiate abstinence may help in designing improved treatment strategies and reducing risk of subsequent relapses.

To date, only a handful of studies have investigated cognitive performance in opiate abstinent former heroin abusers (Verdejo et al., 2005;Lee and Pau, 2002;Pau et al., 2002;Davis et al., 2002;Mintzer et al., 2005). Three of the studies concluded that opiate-abstinent subjects demonstrate a lesser degree of neuropsychological impairment compared to subjects receiving methadone maintenance therapy (MMT) (Verdejo, 2005;Davis et al., 2002;Mintzer et al., 2002,2005). Verdejo et al. (2005) reported that methadone maintained subjects performed worse than abstinent heroin abusers on tests of processing speed and response inhibition (Five Digit Test), tests of visuo-spatial attention and cognitive flexibility (Oral Trails Test), and a test of reasoning (Wechsler Adult Intelligence Scale-III Similarities subtest). Verdejo et al. concluded that methadone consumption by itself may be associated with cognitive deficits. Davis et al. (2002) used a battery of 12 neuropsychological tasks and found a greater number of "cognitively impaired cases" (defined as a score of two or more standard deviations below published norms on two or more neuropsychological measures) among a group of methadone maintained patients compared to a group of abstinent drug-rehabilitation patients. Davis et al. concluded that the risk of neuropsychological impairment is greater in opiate abusers, and that recovery may occur during abstinence. Finally, Mintzer et al. (2005) reported that the performance of abstinent abusers fell between that of subjects receiving MMT and controls on a test of cognitive speed (Digit Symbol Substitution Test), and a measure of conceptual flexibility (Trail-Making Test), while abstinent abusers performed better than the methadone group on a measure of word memory (Recognition Memory). Mintzer et al. concluded that recovery of function may occur with opiate abstinence.

These studies had a number of methodological problems that limit the validity of their findings. Davis et al. (2002) included subjects who had been abstinent for only 6 weeks, and Verdejo et al. (2005) may have included subjects who had been abstinent for only 15 days: the duration of protracted abstinence in these studies was not well established. Only Mintzer et al. (2005) tested her subjects with urine toxicology and yet in this study subjects who had tested positive for cocaine or heroin were not excluded. Additionally, the cross-sectional studies that have directly compared opiate-dependent subjects in MMT with those who are opiate-abstinent lacked healthy controls (Verdejo et al., 2005), or used pain management subjects as controls (Davis et al., 2002). Finally, all three studies (Davis et al., 2002;Verdejo et al., 2005;Mintzer et al., 2005) report ample evidence of no statistical difference between test results of methadone maintained and opiate-abstinent subjects between levels and cognitive functioning. These non-significant differences in neuropsychological test performance argue against the resolution of methadone-associated cognitive impairments following abstinence.

Thus, the question of whether prolonged opiate abstinence is associated with better cognitive function than during MMT is still unresolved, and requires further investigation in a study that would use subjects rigorously screened for illicit drug use, and who have been abstinent for an extended period of time. To address this gap in our knowledge, we administered tests of cognitive function to former heroin addicts receiving methadone maintenance treatment (MMT), former addicts in protracted abstinence (PA), and controls without a history of drug dependence. Absence of concomitant illicit drug use was documented via urine toxicology tests in all subjects. A neuropsychological test battery was designed to assess functioning in a

variety of cortical areas, and consisted of: (1) the WAIS-R Vocabulary Test (frontal cortex) (Wechsler et al., 1982,1997); (2) the Stroop Color-Word Test (dorsolateral prefrontal cortex and anterior cingulate cortex) (Perret, 1974;Peterson et al., 1999); (3) the Controlled Oral Word Association (COWA) Test (left prefrontal cortex, left parietal cortex) (Ruff et al., 1996); and (4) the Benton Visual Retention Test (orbital prefrontal cortex) (Steffans et al., 2003). In accordance with previous literature reports, we hypothesized that both groups of the former opiate addicts would perform worse than the control group on the Vocabulary Test, Stroop, and COWA. We additionally hypothesized that the PA subjects will perform better on cognitive testing than would the MMT group.

2. Methods

Healthy male and female subjects, 21–55 years of age, were selected for inclusion in one of three groups based on their drug use history: (1) opiate-dependent subjects currently receiving methadone maintenance therapy (MMT); (2) opiate-dependent subjects who have received MMT, have undergone methadone detoxification and were in protracted abstinence (PA); and (3) control subjects without a history of opiate-dependence matched for age and ethnicity (C). For inclusion in the MMT or PA groups, participants were required to meet the DSM-IV criteria for opiate dependence in the 2 years prior to the study and to have been free of illicit drug use for the previous 18 months. Furthermore, both MMT and PA subjects were required to have negative urine toxicology screening tests (excluding methadone in the MMT group) as reported by their respective treatment programs. The PA subjects were recruited from the Su Casa Methadone to Abstinence Residence (7 Gouverneur Slip East, New York, NY 10002). The inclusion criteria for this group consisted of prior MMT for at least 1 year, followed by gradual methadone detoxification to complete abstinence, and no MMT for at least 6 months. The MMT subjects were recruited from either the Su Casa Short Stay Residence (7 Gouverneur Slip East, New York, NY 10002), or the Beth Israel Medical Center Methadone Maintenance treatment program. The inclusion criteria were enrollment in MMT program for at least 1 year, with a stable methadone dose for the previous 6 months. Control subjects were recruited through advertising in a local weekly magazine.

Exclusionary criteria for all participants were current or lifetime history of any Axis I diagnosis (other than opiate dependence for the MMT and PA groups, and nicotine dependence for all groups), current alcoholic intake of more than 15 drinks (1.5 oz liquor, 12 oz beer, or 5 oz wine equivalents) per week, history of head trauma, cardiovascular, pulmonary, other systemic, or neurological disease, and HIV seropositivity. Exclusion criteria for control subjects included current or remote history of significant drug abuse, however, neither moderate use of caffeine (<600 mg of caffeine per day), nor occasional marijuana use (≤ 1 marijuana cigarette/month and urine toxicology negative for THC) were exclusionary.

Initial screening was done in a telephone interview. Those subjects meeting initial criteria for inclusions and who continued to express interest in participating were invited for a face-to-face interview, consisting of the Structured Clinical Interview for DSM (SCID-I), conducted by personnel trained to adequate reliability (Williams et al., 1992). All subjects received a physical examination, routine laboratory testing, and a “surprise” urine drug screening exam. All interested subjects who met inclusion and exclusion criteria were entered into the study after signing a consent form, approved by the BIMC Institutional Review Board. In all, 29 subjects satisfied the criteria for inclusion in the MMT group, 27 subjects were included in the PA group, and 29 control subjects were enrolled. All subjects received financial reimbursement for their participation. All investigational procedures were reviewed and approved by the Institutional Review Board of Beth Israel Medical Center.

Subjects in both drug-using groups underwent repeated random urine drug screening examinations no less than once a month as part of routine monitoring at the Su Casa Short Stay Residence, the Su Casa Methadone to Abstinence program, and the MMT program at Beth Israel Medical Center, using established laboratory techniques (Wu, 1998). Routine screening tests provided for the detection of alcohol, amphetamines, barbiturates, benzodiazepines, benzoylecgonine (cocaine metabolite), cannabinoids, methadone, and opiates. Negative urine drug-screening test results are a condition of participation in the Su Casa treatment program.

Cognitive performance was determined by a small battery designed to probe different aspects of executive function. All tests were administered manually using paper and pencil testing. The testing battery included:

1. The WAIS-R Vocabulary Test (Wechsler, 1982): A test of verbal function and an estimate of general IQ. This is the WAIS-R subtest most highly correlated with full scale IQ. Scoring is based on subjects' correct definition of presented stimulus words, with an average score of 10 and a standard deviation of 3. The WAIS-R was used instead of the WAIS-III to be consistent with earlier data collection.
2. The Stroop Color-Word Test (Stroop, 1935; Perret, 1974; Fillmore et al., 2000): A test of sustained attention and resistance to distraction. The subjects are asked to name the printed color of displayed color-words, and control stimuli. The number of correct responses in the allotted time determines the score. Only Stroop Color-Word (CW) and Stroop Interference scores were used. The Stroop CW score is the number of colors correctly named, regardless of word stimuli presented. The Stroop Interference score is the increase in reaction time when the stimulus is a color-word printed in an incongruent color.
3. The Controlled Oral Word Association (COWA) (Benton, 1969; Ruff et al., 1996; Sumerall et al., 1997): A test of verbal fluency. Subjects are asked to name as many words possible beginning with the letters C, F, or L in a 60 s period. The total numbers of correct responses is recorded.
4. The Benton Visual Retention Test (BVRT): A test of visual memory, and visual construction. Subjects are presented an image for 10 s and then asked to draw it from memory. The numbers of total correct, total errors, right, and left-sided errors are recorded (Moses, 1986; Randall et al., 1988; Sivan, 1992).
5. Substance Use Inventory (SUI) (Sobell et al., 1980): A questionnaire about quantity and frequency of use of abused substances (opiates, cocaine, alcohol, marijuana, amphetamines, sedatives, PCP, and prescription medications). Respondents report years of heroin abuse, approximate dollars spent daily on heroin, years of methadone use, typical methadone dose, and for methadone-withdrawn subjects, years since methadone detoxification. Controls were asked to respond regarding the last 30 days and former opiate abusers were asked to refer to lifetime use.

Initial analyses compared groups on demographic and clinical measures (e.g. years of heroin abuse) with MANOVA's for continuous variables and χ^2 analyses for categorical variables. Any demographic or clinical variable that (1) significantly varied across groups and (2) correlated with a composite neuropsychological score was entered into later analyses as a covariate. Neuropsychological tests were compared across groups by MANCOVA, with follow-up univariate *F*-tests and Tukey's paired comparisons.

3. Results

Methadone maintained, protracted abstinent, and control groups did not significantly differ with respect to gender or ethnicity by χ^2 analysis. The three subject groups demonstrated

significant difference with regard to age, years of education, and mother's years of education. By Tukey's pairwise comparisons, PA subjects were older than either control or MMT subjects. MMT and PA subjects had fewer years of education compared with the control group. Furthermore, mothers of PA and MMT subjects had fewer years of education when compared with control subjects.

The MMT and PA groups did not significantly differ with respect to any measure of drug use history (age of onset of heroin use, years of heroin use, amount of money spent daily on heroin, years of methadone treatment, or highest dose level of methadone). Protracted abstinence subjects were methadone free an average of 9 months, with a range of .58–2 years. Thirteen PA subjects were opiate abstinent for 1 year or greater. These demographic and substance use data are summarized in Tables 1 and 2.

Neither subject age nor mother's years of education correlated significantly with the composite neuropsychological score. However, years of education was significantly correlated with composite neuropsychological score ($r = .398, p = .001$). Therefore, years of education was entered as a covariate in the MANCOVA comparing neuropsychological performance across groups. In a secondary analysis, subjects' age and mothers' education were entered as covariates.

By MANCOVA, there was an overall difference across all three groups (Wilk's $\lambda = .442$ (16,104), $p < .001$). With years of education entered as a covariate, this difference remained significant (Wilk's $\lambda = .580$ (16,102), $p = .02$); as it was with age entered as a covariate (Wilk's $\lambda = .413$ (16,102), $p < .001$). By univariate F -test with years of education entered as a covariate, groups differed on WAIS-R Vocabulary Test scores, the Stroop Interference scores, the Benton Visual Retention Test number correct, the Benton Visual Retention Test number of total errors, the Benton Visual Retention Test right errors, and the Benton Visual Retention Test left errors. There was no significant difference found among the three groups on the Controlled Oral Word Association Test (COWA) or the Stroop CW task (see Table 3).

By Tukey's pairwise comparisons, both MMT and PA subjects scored lower than control subjects on the WAIS Vocabulary Test and on the Stroop Interference task. They also had more total errors on the Benton Visual Retention Test than controls. PA subjects had significantly more BVRT right-sided and BVRT left-sided errors, and significantly fewer BVRT correct answers than either controls or MMT subjects. In addition, PA subjects had increased Stroop Interference scores than did controls.

In the secondary analysis with mother's years of education entered as a covariate, the groups differed marginally, but the univariate F -tests remained significant for the WAIS Vocabulary Test and all four Benton scores. With age entered into the model as a covariate, group differences continued to be significant, as did the F -tests for WAIS Vocabulary and the BVRT. Comparisons of the COWA and Stroop Interference scores were not significant in this analysis.

A composite neuropsychological score was calculated by summing the result of the WAIS Vocabulary, COWA total, Stroop Color-Word, and BVRT Correct scores for each subject. The composite NP score was correlated against each measure of drug use history (years of heroin use, average amount spend on heroin daily, years of MMT, and highest daily methadone dose). No significant correlations of drug use history and composite NP scores were revealed.

4. Discussion

The results of this study suggest that both methadone-maintained and opiate-abstinent subjects exhibit significant impairment of verbal intelligence, visual perception and memory, and divided attention with response inhibition when compared to healthy controls. Differences

between opiate-abstinent and methadone maintained subjects were minimal; the only difference being a significantly worse performance by opiate-abstinent subjects on the visual-spatial memory tests. This finding is unexpected and in distinction to the hypothesis that former heroin addicts in opiate-abstinence have better cognitive function than those receiving methadone. Additionally, we found no correlation of either the duration or intensity of opiate use with the degree of cognitive testing deficits on any of the studied measures.

Our findings of broad cognitive impairment in methadone-maintained subjects compared to controls are consistent with the previous literature reports (Mintzer and Stitzer, 2002; Darke et al., 2000; Davis et al., 2002; Rounsaville et al., 1982; Ornstein et al., 2000; Specka, 2000; Grant et al., 2000). Our results of inferior performance on the WAIS Vocabulary Test are similar to those of Darke et al. (2000), who reported significantly worse performance in subjects receiving MMT than controls on WAIS-III Vocabulary subtest. Similarly, Ornstein et al. (2000), Darke et al. (2000), and Davis et al. (2002) reported that MMT subjects performed worse on COWA than did control subjects. Although in our study MMT subjects performed lower on COWA than controls, the result was not statistically significant. Finally, as in Mintzer et al. (2002), our methadone-maintained subjects had impaired divided attention as measured by the Stroop Test.

Our findings that opiate-abstinent subjects have impaired vocabulary and verbal fluency is consistent with that of Davis et al. (2002) who reported that their group of abstinent subjects also had inferior performance on COWA and the WAIS Vocabulary Test. In contrast, Mintzer et al. (2005) reported no significant differences on the Digit Symbol Substitution Test (DSST) in abstinent opiate addicts, relative to controls. Both the WAIS-R Vocabulary Test and DSST are considered indicative of general cognitive functioning (Wechsler, 1997; Boone, 1992; Swan et al., 1995). Possible explanations for the discrepancy in our findings and those of Mintzer include possible confounding effect of illicit drug use (Davis et al., 2002), non-exclusion of subjects with positive urine toxicologies (Mintzer et al., 2005) and variations in the length of opiate abstinence (Davis et al., 2002; Mintzer et al., 2005).

We found little difference in cognitive abilities between subjects receiving MMT and subjects in protracted abstinence. This finding is largely consistent with one of the results from Davis et al. (2002), who reported no significant difference between former opiate abusers and controls on a test of verbal fluency (one of 12 measures of cognitive performance tested). Similarly, Mintzer et al. (2005) reported finding statistically significant differences between the test performance of MMT and PA subjects in only one of six different measures reported. Our results are also consistent with those of Verdejo et al. (2005), who found no difference in the test performance of MMT and PA subjects using a modified COWA, the Stroop Interference Test, and the Wisconsin Card Sorting Test, a test of executive function. The only statistically different result in our study was on the number of correct responses to the BVRT, on which subjects on PA performed significantly worse than MMT subjects.

To date, there have been no other studies of the Benton Visual Retention Test in either subjects receiving MMT or during protracted abstinence. Previous studies have associated performance on the BVRT to left orbital frontal cortex and hippocampus volumes (Steffans et al., 2003; Soininen et al., 1994). We have demonstrated that performance on the BVRT is associated with metabolic activity of the left parietal cortex (Galynker et al., 2005). The finding reported here of inferior performance in both drug use subject groups compared to healthy controls and the localization of associated cortical activity will have to await further research.

We did not find any correlation of neuropsychological test performance with measures of opiate use; i.e. years of heroin abuse, amount of dollars spent on heroin daily, or highest dose of methadone. This is consistent with the findings of Darke et al. (2000), Verdejo et al.

(2005), Guerra et al. (1987), and Rounsaville et al. (1981), who all reported absence of an effect of length or amount of drug use on neuropsychological measures.

One possible interpretation of this finding is that we are observing a ceiling effect in our drug-using subjects due to the very severe and long heroin abuse histories that may have masked any differential effect of chronic opiate use on cognitive function. Such a hypothesis could be tested by examining the cognition in heroin users with shorter and less severe addiction. Another possible explanation is that we collected drug use history measures based on our subjects' self-reports. Inaccuracies in these self-report may have skewed our findings.

There are several possible explanations for the findings of cognitive impairment in former opiate addicts. Cognitive impairment in opiate abusers may occur as a direct effect of opiate abuse. Numerous studies have documented cognitive deficits in a range of subjects using illicit or prescription opiates (Hill and Mikhael, 1979; Chastain et al., 1986; Strang et al., 1989; Guerra et al., 1987; Tapert and Brown, 1999; Franken et al., 2000; Grant et al., 2000; Banning et al., 1992; Sjogren et al., 2000), MMT (Appel and Gordon, 1976; Gritz et al., 1975; Lombardo et al., 1976; Darke et al., 2000; Ornstein et al., 2000; Specka et al., 2000; Curran et al., 2001; Mintzer et al., 2002). Opiates are known to cross the blood-brain barrier, and there is evidence for a direct neurocytotoxic effect of opiates on CNS in experimental animals (Kofke et al., 1996, 2000; Mao et al., 2002; Atici et al., 2004). However, to date, there is no evidence of neurocytopathology in human opiate addicts (Darke et al., 2000) and elsewhere, neuropsychological test scores have been shown to be independent of methadone dose (Specka et al., 2000).

Alternatively, it is fairly well recognized that opiate addicts may use and abuse a variety of different substances in addition to heroin (Sleznick and Prestopnik, 2005; Brooner et al., 1997; Flynn et al., 2003; Ornstein et al., 2000). It is therefore possible that cognitive deficits identified in opiate abusers occur due to the direct toxic effects of concomitant substance abuse, including adulterants, and/or the interactions of multiple drug use (Carlin et al., 1980; Grant et al., 1978; Darke et al., 2000). The evidence of the direct neurotoxic effect of substances such as alcohol and cocaine is stronger than that with opiates (Jung et al., 2005; Valles et al., 2004; McIntosh and Chick, 2004; Slikker et al., 2003; Ho and Segre, 2001; Fleckenstein et al., 2000; Ornstein et al., 2000). The extent to which associated drug use and abuse contributes to the neuropsychological deficits seen in opiate addicts has not been widely studied. Additionally, Darke et al. (2000) suggested that an indirect effect of opiates, such as lifestyle, poor nutrition, infections (notably HIV-dementia), or exposure to violence, may have a causative role in opiate addiction-associated cognitive impairment (Darke et al., 2000). A history of HIV-positive status, and head or brain trauma was an exclusionary factor in our sample selection process. We feel that none of these explanations adequately account for the differences in neuropsychological test performance we had reported here.

Contrary to our initial hypothesis, we have found little differences in the cognitive performance between those former addicts maintained on methadone and those who are opiate abstinent. The existence of negative effects that persist long after the biochemical detoxification, i.e., a "protracted withdrawal" effect (Satel et al., 1993; Ashton-Jones and Harris, 2004; Dole et al., 1966) has been posited. It is possible that cognitive impairments reported here and by others are another manifestation of the "protracted withdrawal" state. While our data suggest there is no change in cognitive function following cessation of methadone use, it is possible that such recovery may take place after a greater time interval following discontinuation from methadone. A different possibility is the cognitive testing deficits identified here and elsewhere may be a manifestation of a pre-existing condition that persists through drug use, abuse, and addiction treatment (Poon et al., 2000; Ozkaragoz et al., 1997; Koob and Le Moal, 2001). The notion that our finding of a similar degree of cognitive impairment in both subjects receiving

MMT and opiate-abstinent reflects a pre-existing condition that antedates drug use is intriguing and merits further investigation.

The results of this study have important clinical implications. As we have confirmed previous findings of the existence of cognitive impairment in chronic opiate users, it seems likely that participants in opiate abuse treatment programs will have difficulty with attention and memory, and these deficits may persist for months and years past detoxification. Recent studies have suggested that cognitive status may play a role in treatment efficacy (Miller, 1991;Gottschalk et al., 2001;Aharonovic et al., 2003;Teichner et al., 2002). Thus, the deficits we have demonstrated in both MMT and PA patients suggest that these populations may benefit from more personal effectiveness programs, adult daily living skills, remedial education programs, and concrete treatment planning to improve outcomes (Czuchry and Dansereau, 2004;Zinn et al., 2004).

Limitations to our study include a small sample size, some demographic differences between the MMT patients and subjects in protracted abstinence, and a possible selection bias among opiate abusers. Some neuropsychological testing measures, such as the WAIS, are normed across age and education levels and are less susceptible to demographic differences. However, to further control for differences, any demographic variable that varied across groups was entered onto analyses as a covariate. Recent reports in the literature have identified cigarette smoking as a possible factor on cognitive performance (Hill et al., 2003;Richards et al., 2003;Ascioglu et al., 2004). We did not control for cigarette use in our subject groups. Finally, we chose to perform a cross-sectional study on two sample groups rather than a longitudinal study of MMT patients pre- and post-detoxification because not all of the MMT patients will successfully continue in drug treatment, and of those that do; only a portion will elect methadone detoxification (Cushman, 1977;Fischer et al., 2005). This means however, that a self-selection bias is introduced into the PA group. We feel comfortable that the self-selection bias of our PA group is mirrored in the general U.S. population of heroin-dependent patients who have undergone and withdrawn from methadone maintenance treatment.

Nevertheless, our study is unique in that it provides (1) direct comparison of former addicts receiving methadone, former addicts off methadone, and healthy controls; (2) rigorous exclusion of comorbid Axis I and Axis II disorders; (3) long duration of abstinence in our PA groups; and (4) screening for illicit drug use at multiple time points, and exclusion of illicit drug users.

5. Conclusion

Despite its limitations, our study addresses the question of cognitive impairment in rigorously screened abstinent opiate addicts during a prolonged period of abstinence. Our results indicate that in patients detoxified from methadone to opiate abstinence, cognitive impairment is not improved. We believe additional investigations are warranted to better understand the development of changes in cognitive abilities over time in protracted opiate abstinence.

Uncited references

Appel and Gordon (1982) and Sivan (1991).

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Table 1
Demographic data and substance use history of methadone maintained, protracted abstinence, and healthy control groups

	Methadone maintained (<i>n</i> = 29)	Protracted abstinence (<i>n</i> = 27)	Controls (<i>n</i> = 29)	Statistic	Significance <i>p</i>
Gender					
Male	23 (79.3%)	20 (74%)	21 (72.4%)		
Female	6 (20.7%)	7 (26%)	8 (27.6%)	$\chi^2 = .49$, <i>df</i> = 2	.78
Ethnicity					
African American	6 (20.7%)	11 (40.7%)	10 (34.7%)		
European American	11 (37.9%)	7 (25.9%)	12 (41.4%)		
Hispanic	12 (41.4%)	7 (25.9%)	3 (10.3%)	$\chi^2 = 14.95$, <i>df</i> = 10	.134
Asian	0 (0%)	0 (0%)	1 (3.4%)		
Native Americans/Pacific Islands	0 (0%)	0 (0%)	1 (3.4%)		
Other	0 (0%)	2 (7.5%)	2 (6.8%)		
Age (mean $\pm$ S.D.)	37.93 $\pm$ 7.5	42.59 $\pm$ 5.4	34.00 $\pm$ 8.0	$F(2,84) = 10.21$	<.001
Education (years: mean $\pm$ S.D.)	13.03 $\pm$ 4.8	11.81 $\pm$ 2.2	15.51 $\pm$ 1.8	$F(2,84) = 9.32$	<.001
Mother's education (years: mean $\pm$ S.D.)	11.17 $\pm$ 2.8	8.80 $\pm$ 4.8	14.04 $\pm$ 3.0	$F(2,67) = 12.24$	<.001
Substance use history (years: mean $\pm$ S.D.)					
Age of onset	19.36 $\pm$ 5.5	23.32 $\pm$ 8.9	N/A	$F(2,51) = .18$	n.s.
Years of heroin use	15.14 $\pm$ 8.9	13.74 $\pm$ 8.9	N/A	$F(2,53) = .16$	n.s.
Daily dollar amount	93.33 $\pm$ 79.0	115.45 $\pm$ 88.02	N/A	$F(2,21) = .532$	n.s.
Years of MMT	6.44 $\pm$ 7.1	6.40 $\pm$ 7.0	N/A	$F(2,54) = .001$	n.s.
Highest methadone dose (mg/day)	73.79 $\pm$ 23.1	60.00 $\pm$ 43.2	N/A	$F(2,32) = .495$	n.s.
Years of abstinence	N/A	9 $\pm$.41	N/A	N/A	

Methadone maintained (MMT), protracted abstinence (PA), not statistically significant (n.s.), non-meaningful calculation (N/A).

Lifetime history of any substance use in former opiate abusers and control subjects who met inclusionary and exclusionary criteria (see Section 2) as a percent of group membership

Table 2

	MMT	PA	Controls	All subjects	χ^2
Methadone	100	100	0	59.6	N/A
Opiates	100	100	18.2	78.6	$\chi^2 = 32.3$, df = 2, $p \leq .001$
Cocaine	100	100	36.4	83.3	$\chi^2 = 23.7$, df = 2, $p \leq .001$
Stimulants	38.9	46.2	9.1	33.3	n.s.
Sedatives	78.9	69.2	18.2	60.5	$\chi^2 = 11.4$, df = 2, $p \leq .003$
Cannabis	100	100	81.8	95.2	n.s.
Alcohol (lifetime)	94.4	76.9	72.7	83.3	n.s.
Nicotine (lifetime)	94.4	69.2	63.6	76.1	n.s.
Alcohol (current)	0	0	46	8.3	$\chi^2 = 18.7$, df = 1, $p \leq .001$
Nicotine (current)	78.6	69.2	12.5	30.5	$\chi^2 = 15.5$, df = 2, $p \leq .001$

Current alcohol and nicotine use is included. Methadone maintained (MMT), protracted abstinence (PA), not statistically significant (n.s.), non-meaningful calculation (N/A).

Neuropsychological performance of methadone maintained, protracted abstinent, and healthy control subjects calculated with years of education as a covariate

Table 3

	Mean ± S.D.		Statistic	p	Paired comparison
	MMT	PA			
MANCOVA			Wilks' λ (16,102) = .580	.02	
WAIS Vocabulary	8.05 ± 2.19	8.6 ± 3.1	F = 21.49	<.001	A, B
COWA Total	35.35 ± 8.5	33.09 ± 13.5	F = 2.04	n.s.	—
Stroop Color-Word	39.55 ± 9.47	36.26 ± 10.8	F = 2.39	n.s.	—
Stroop Interference	−.15 ± 6.8	−2.52 ± 9.1	F = 2.91	.042	B
BVRT correct	6.7 ± 2.2	4.65 ± 2.4	F = 6.22	.001	B, C
BVRT errors	5.4 ± 3.78	7.82 ± 4.7	F = 8.33	<.001	A, B
BVRT Rt. errors	2.55 ± 1.87	3.96 ± 2.6	F = 8.39	<.001	B
BVRT L. errors	2.4 ± 2.09	3.22 ± 2.1	F = 4.09	.011	B

Tukey's pairwise comparisons: A = $p < .05$ for MMT vs. controls; B = $p < .05$ for PA vs. controls; C = $p < .05$ for MMT vs. PA. MMT: methadone maintenance treatment; PA: protracted abstinence; WAIS: Wechsler adult intelligence scale; COWA: controlled oral word association, BVRT: Benton Visual Retention Test.