Cognitive function during short-term abstinence from opioid dependence: a comparison to age, gender, and verbal intelligence matched controls

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Abstract

Background

Individuals with opioid dependence have cognitive deficits during abuse period. However, few studies have explored cognitive function during short-term abstinence. The purpose of this study was to study cognitive function of individuals with opioid dependence in early abstinence.

Methods

Fifteen patients with opioid dependence and fifteen controls matched for, age, gender, and verbal (crystallized) intelligence were tested with a comprehensive cognitive battery. Patients were tested between 5 to 15 days after cessation of opioid abuse. The results were analyzed with analysis of variance. When patients performed worse than controls correlations between cognitive performance and days of withdrawal, duration of opioid abuse, duration of any substance abuse, or opioid withdrawal symptom inventory score (Short Opiate Withdrawal Scale) were analyzed

Results

Short-term abstinent opioid dependent patients performed statistically significantly worse than controls in fluid intelligence, complex working memory, and executive function. Their fluid intelligence performance and working memory performance correlated statistically significantly with days of withdrawal.

Conclusions

The results indicate a rather general neurocognitive deficit in higher order cognition. It is suggested that cognitive deficit among individuals with short-term abstinence from opioid dependence is related to withdrawal induced neural cascade in the prefrontal cortex and is partly transient.

Key Words

Opioid dependence, opiate abuse, withdrawal, neuropsychological performance, higher order cognition
**Background**

Sudden cessation of opioid abuse leads to withdrawal symptoms. The somatic signs of withdrawal are flu-like symptoms and changes in heart rate and blood pressure. These typically peak within three days from the last dose of intravenous heroin and within five days from the last dose of intravenous buprenorphine [1, 2]. Peak withdrawal symptoms are followed by somewhat milder symptoms which last from two to three weeks. Among those who stay in treatment drug craving remains high in spite of withdrawal symptom relieving medications such as α-adrenergic agonist lofexidine or other psychotropic medications [3]. Even in specialized inpatient withdrawal programs treatment discontinuation rate rises to 30 - 60%.

During short-term abstinence from opioid abuse, usually considered lasting two or three first abstinent weeks, patients complain fatigue and poor concentrating. In agreement with this a cascade brain stress system dysregulations takes place during that time [4, 5]. Elevation of cortisol secretion has been found to be common during short-term opioid abstinence [6]. Experimental studies have shown that short-term elevation cortisol secretion may impair working memory transiently; and chronic hyperactivation impairs especially episodic memory [7, 8]. Against this background, it is surprising that only few studies have explored cognitive function during opioid abstinence.

In Guerra et al. study individuals with chronic heroin abuse were first tested at abuse period and then again after rapid detoxification treatment with lowering doses with either µ-opioid agonist methadone or non-opioid clonidine [9]. While using heroin they showed impairments in attention, verbal learning, and verbal fluency. At retesting 7-14 days after admission to rapid detoxification the performance of opioid withdrawal patients reached the level of controls. However, practice effects were not controlled for. Gerra et al. studied opioid abusing patients four months from detoxification [10]. Patients with antisocial personality disorder showed deficits in complex
attention and in executive function. Instead, patients with depressive symptoms or without psychiatric comorbidity showed no deficits. In Davis et al. study mean six month abstinent opioid abuse patients showed no specific cognitive deficits [11]. However, when individual cognitive profiles were inspected nearly third of drug-free patients scored two standard deviations below norms on at least two task. In a study by Lee and Pau mean eight month abstinent as well as in Pau et al. mean fourteen month abstinent heroin users showed deficit in executive function [12, 13] In a study by Mintzer et al. mean nine month abstinent patients showed normal cognitive performance expect in one task combining visual attention and flexibility [14]. Taken together, the association between short-term abstinence and cognitive function has been addressed in one study in which rapid recovery of function was found. Secondly, in studies concerning protracted abstinence executive function deficit has been found in some but not in all studies. Thirdly, individuals with antisocial personality disorder and opioid dependence may be more prone to cognitive deficits in attention and executive function than individual without this co-morbidity.

The purpose of this study was to explore cognitive function of individuals with opioid dependence during short-term abstinence. The sparse earlier research indicates that during short-term opioid abstinence deficits in attention and in executive function may appear though they may resolve rapidly. Therefore, we studied cognitive function of individuals with opioid dependence shortly after their typical peak somatic withdrawal from opioids had passed: between 5 to 15 days from detoxification. The battery covered wide range of cognitive functions: fluid intelligence, attention, memory and executive function. A comparison to age, gender, and verbal intelligence (VIQ) matched controls was made. Secondly, time-dependent neural responses due to opioid withdrawal syndrome as well as subjective withdrawal symptoms during opioid abstinence may associate with cognitive performance. Therefore, we analyzed correlations between cognitive performance and days of withdrawal; and between cognitive performance and subjective opioid withdrawal.
symptoms whenever patients in opioid withdrawal performed worse than controls. In addition, as long-term neurotoxicity related to substance abuse is possible correlations between duration of opioid abuse or any substance abuse were analyzed whenever patients performed worse than controls.

Methods

The participants of the study included 15 individuals with opioid dependence who were voluntary inpatients from Helsinki University Central Hospital drug detoxification unit and 15 controls. Inclusion criteria for all participants were age between 20 – 50 years. Participants with uncontrolled mixed substance abuse, acute alcohol abuse, and acute major psychiatric morbidity not related to substance abuse, severe brain injury, chronic neurological disease, with history of epileptic seizures, with human immunodeficiency virus (HIV), primary organic cognitive deficit, or magnetic objects contraindicative for magnetic resonance imaging (MRI) were excluded from the study. Each participant was evaluated by brain magnetic resonance imaging (MRI), and participants showing lesions indicating vascular pathology or brain injury were excluded. The study protocol was accepted by the Ethics Committee of Helsinki University Central Hospital. A written informed consent according to the Declaration of Helsinki was obtained from all participants. All participants with opioid dependence were voluntary patients from a series of consecutive patients admitted for potential methadone maintenance treatment. The patients were hospitalized for two weeks in a drug withdrawal unit before starting methadone substitution treatment. The criteria for this in our institute were a minimum age of 20 years, four years of documented opioid dependence, and failure of institutional or long-lasting outpatient opioid withdrawal. In the patient group there were several cases for all variants of hepatic viruses (A,B, or C). However, none of these were in acute phase. All those studied were negative for HIV. One patient refused to be tested for HIV. The patients had no neurological complains.
A control group matched for age, gender, and VIQ was recruited from the staff of our institution. The VIQ matching was based on Wechsler’s revised intelligence scale (WAIS-R) vocabulary subtest [15]. None of the controls had abused illegal drugs, but all of them had taken alcohol on social occasions. However, none of them met the criteria of abuse of or dependence on alcohol. The controls were screened by psychiatric interview of having no history of major psychiatric morbidity or substance abuse. Demographic variables of the groups are presented in Table 1. As a group the controls had more education than participants with opioid dependence.

The dependence and other psychiatric diagnoses were made according Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [16, 17]. All the patients met the DSM-IV criteria for opioid dependence. Nine patients also fulfilled the criteria for benzodiazepine dependence and four were cannabis dependent. One patient had all these three diagnoses. Self-reported recent month drug abuse was consistent with urine screening results. Table 2 shows recent month drug abuse in patient group.

During the inpatient period many participants with opioid dependence showed current mood or anxiety disorder symptoms. However, only two participants were classified as having other axis I diagnosis than substance-abuse. Both of these were depressive disorders not otherwise specified. When DSM-IV axis II diagnoses were evaluated all patients met criteria for at least one personality disorder. The most common of these was the antisocial personality disorder, which was diagnosed in all except three, who even so had some features of antisocial personality disorder.

**Cognitive tests**

A comprehensive battery of cognitive tests covering working memory, memory, executive function, and fluid intelligence was used. All tests were administered according to standard instructions.

**Working memory** was measured by The Digit Span subtest from the Wechsler Memory Scale-Revised (WMS-R) and a computerized version of the Paced Auditory Serial Addition Task
(PASAT) [18, 19]. The Digit Span measures auditory working memory storage in relatively simple form. In the PASAT more complex working memory functions are required: continuous storage of previous number, rapid arithmetical processing, and executive control of interference from previous items or from ongoing adding process. Presentation rate of a new number to be counted with the previous one was one in every 1.6 second.

**Verbal memory** was measured by The delayed Logical Memory subtest of the WMS-R and the Rey Auditory Verbal Learning Test (the RAVLT) [18, 20]. To avoid ceiling effect in the RAVLT only three learning trials of 15 word list were presented. The sum of the first three RAVLT trials was used as a parameter for immediate learning. **Visual memory** was measured by the Benton Visual Retention Test [21].

**Executive function** was measured by the modified Stroop task and by the Ruff Figural Fluency Test [22, 23]. The interference time of the Stroop task was calculated by subtracting reading time of 50 non-colored words from naming time of 50 colors printed in a different color than the one spelled by the letters. In the Stroop interference condition inhibition of routine action is required. The RFFT is a design fluency task measuring planning and fluency of action.

**Fluid intelligence** was measured by the Culture Fair Intelligence Test (CFIT) also known as Cattell’s Culture Fair test [24]. Version 2A was used. The CFIT includes a group of visuo-spatial reasoning tasks. The performance of the participant in these tasks reflects fluid or general intelligence needed in highly demanding novel problem solving situations. This test is sensitive to fluid intelligence deficit due to various origins. Dissociations between preserved standard intelligence measured by the Wechsler scales and by the poor CFIT scores have been shown in frontal lobe lesions as well as in normal ageing [25, 26]
**Procedure**

The psychiatric examination and diagnosis were made by trained psychiatrists at the detoxification unit. The cognitive testing was done in one day between 5 to 15 days from the last opioid dose. Tasks were presented alternating between difficult and easy one, and verbal and nonverbal ones, and memory and non-memory ones. To avoid fatigue on testing one pause was held. Patients showing positive urine drug screening at initiation of withdrawal period were tested after negative drug screening for other drugs than prescribed for them. On the test day morning at 8.00 patients completed the 10-item Short Opiate Withdrawal Scale (SOWS ) [27] measuring withdrawal symptoms. All patients were using symptom relieving or other psychotropic medications on the day of testing. Medication variables of the test day are presented in Table 3. The brain MRI scans were evaluated by two neuroradiologists. A consensus of opinion was formed in each case. Analyses of MRI results are reported separately [28].

**Statistical Analysis**

Analysis of variance (ANOVA) was used to compare the raw scores of each cognitive test. The effect sizes were calculated with partial eta-squared ($\eta^2$). Group difference in education was not covaried for, because the assumption of similar linear relation between education and cognitive performance in both groups needed for analysis of covariance (ANCOVA) was not met. All participants with opioid dependence had started substance abuse in their early teen years. Once the substance abuse history begins early-onset substance abusers start to skip school lessons at primary school, get poor grades, and only few of them get diploma from secondary education. Thus, as a group participants with opioid dependence had less education than their VIQ comparable controls; which however reflects only marginally their primary intellectual capacity. Whenever participants with opioid dependence performed significantly poorer than control participants correlations were analyzed by the Pearson product-moment correlation coefficient. Alpha was set at $<0.05$, and all
reported P values are two tailed. P-value of 0.05-0.1 was considered as a statistical trend. Statistical analyses were done by SPSS statistical software package, version 11.0.

Results

Table 4 shows that participants with opioid dependence performed significantly poorer than control participants in fluid intelligence, measured by the CFIT, in complex working memory, measured by the PASAT, and in one executive function test, the RFFT. After using the Bonferroni correction for multiple comparisons the group difference in the PASAT remained statistically significant \( (P = 0.02) \). In the CFIT the group difference still showed a statistical trend favoring the controls \( (P = 0.10) \).

Fluid intelligence performance associates highly with complex working memory performance and executive function, which was the case also in this study. The CFIT performance correlated between the PASAT strongly \( (0.65 \text{ for controls and } 0.66 \text{ for opiate withdrawal participants}; \ P = 0.009 \text{ and } 0.008, \text{ respectively}) \). The CFIT performance correlated with the RFFT performance in both groups moderately; \( 0.29 \text{ for controls; and } 0.30 \text{ for opiate withdrawal participants, both being statistically non-significant.} \) In order to determine the effect of fluid intelligence (the CFIT) on complex working memory (the PASAT) and executive function (the RFFT) we inspected the relationship between the measures employed among opioid withdrawal participants. ANCOVA was not used as assumption for similarity of slopes of the regression lines for performing an analysis of covariance was not fully met. Therefore, we first performed a median split on the CFIT. Low fluid intelligence group was formed out of the participants up to 32 points in the CFIT, and high fluid intelligence group out of those scoring at least 33 points. Then 2 x 2 ANOVA with two initial study groups (patients vs. controls) and two fluid intelligence related groups was performed. There were no significant interactions between the grouping factors, and therefore interaction was dropped from the models.
After this the initial group membership still explained statistically significantly the PASAT performance ($F = 7.1, P = 0.01$). For the RFFT performance the proportion of variance explained by the initial group membership was at a level of a statistical trend ($F = 3.1, P = 0.09$). The initial study group membership accounted, after adjusting for sample size, 19.6 % of the variance in the PASAT and 11.0 % in the RFFT. As expected, the fluid intelligence group membership (low vs. high) explained highly significantly performance on the PASAT ($F = 18.4, P = 0.0001$). This was not seen on the RFFT ($F = 1.9, NS$). The full model accounted for 57.5 % of the PASAT variance adjusted for the sample size and 17.8 % of the RFFT variance.

Finally, correlations between inferior cognitive performance and withdrawal variables were analyzed. Days of withdrawal correlated statistically significant with the CFIT performance and with the PASAT performance ($R = .65, P = 0.009$ and $R = .63, P = 0.01$, respectively). Figures 1 and 2 depict these correlations. The highest correlations between years of opiate abuse or years of any substance abuse and between inferior cognitive performances were found for the RFFT performance -.23 and -.31; respectively: Both of these were statistically non-significant. The correlations between the SOWS score and inferior cognitive performance ranged from 0.08 to -0.13 (NS). After correcting for multiple comparisons none of the correlations remained statistically significant.

**Discussion**

Short-term abstantent individuals with opioid dependence performed worse than normal controls in complex working memory, executive function, and fluid intelligence. After correcting for multiple comparisons the group difference in complex working memory and fluid intelligence remained statistically significant or at the border for significance, respectively. Fluid intelligence performance associates moderately to strongly with working memory and executive function performances [29, 30]. Thus, it may look like that group difference in fluid intelligence explains all other findings as
well. However, according to further analysis opioid withdrawal patient group membership gave still a statistically significant contribution to complex working memory performance. Thus, fluid intelligence difference between the groups does not totally account for working memory deficit in individuals with short-term abstinence from opioid dependence. After similar analysis the contribution of patient group membership showed a trend for statistical significance.

The relevance of neurocognitive study results comes often from dissociations found between different functions. In this study three dissociations merit further consideration. First, opiate withdrawal patients were inferior to controls in fluid intelligence task though the groups were matched for verbal intelligence. According to functional neuroimaging studies this indicates deficiencies in frontoparietal networks important for fluid intelligence.

Second dissociation was found between deficient performance in complex working memory task, the PASAT, and the normal episodic memory performance. It has been suggested that episodic memory impairment needs more chronic stress abnormality than working memory impairment; and this would hold especially among young adults [7, 8]. During opioid withdrawal high stress system activation as shown by elevated cortisol level is common; and especially pronounced this is among individuals with antisocial personality disorder [31]. Therefore, as nearly all patients studied were young adults (mean 31.5 years) and most of them (12/15) had antisocial personality disorder, an association between deficient working memory and elevated stress system activation related to antisocial personality disorder may be postulated. Thus, our results are in line with earlier research of opioid abstinence indicating cognitive deficits among individuals with antisocial personality disorder [10].

A meta-analysis of studies made in mixed clinical settings has shown executive function deficit to be common among individuals with antisocial personality disorder in spite of preserved intellectual capacity [32]. However, in contrary to earlier studies a recent large study concerning antisocial
personality disorder as such, among randomly selected community dwellers, could not evidence neither working memory (the PASAT), fluid intelligence (Block Design from WAIS-R) nor executive function deficit (verbal fluency or Wisconsin Card Sorting Test) deficits among them [33]. Thus, so far there is no convincing evidence that antisocial personality disorder as such, without high stress system activation, could account for the deficit profile observed in this study.

Third dissociation was found between deficient the complex and simple working memory performance: PASAT and the Digit Span, respectively. In the PASAT storage and central executive components of working memory are needed [34]. The Digit Span task demands especially storage of the several items and central executive is involved to a lesser degree. Thus, we suggest that central executive component of working memory is impaired in short-term opioid abstinence while storage is intact.

As the effect size of the figural fluency group difference was small (0.16) and the result may partly rely on the fluid intelligence deficit between the study groups, the argument for independence of specific executive function deficit in fluency performance is not very strong. However, the non-significant correlations between figural fluency performance and duration of opioid abuse or any substance abuse (-.23 and -.31) is in line with earlier research showing negative association between opioid abuse severity and figural fluency performance [35]. A larger sample study concerning the relationship between opioid abuse and other substance abuse variables and fluency performance is warranted.

According to current research the need for executive control is signaled from medial prefrontal cortex to anterior cingulate or to lateral prefrontal cortex which then implements the control [36, 37]. This may mean that right dorsolateral prefrontal cortex important for memory retrieval in “simple conditions” [38] is functioning normally while executive control system in more medial
areas is dysfunctional. This idea is consistent with the finding of disrupted synaptic connectivity in the medial prefrontal cortex after chronic opioid exposure [39]. Actually, a recent study showed an association between deficient executive function performance in opioid dependence and abnormal prefrontal and anterior cingulate function [40].

The observed deficits may be partly transient. First, we found more cognitive deficits than have been found in studies with comprehensive cognitive battery concerning protracted opioid abstinence – though this may partly reflect differences in sensitivity of measures too [11, 14]. Secondly, the positive correlations that were found between impaired performance and withdrawal length are in agreement with rapid recovery. In one study concerning opioid withdrawal aided with adrenergic agonist medication clonidine the elevated cortisol levels were found to normalize between third week and fourth month of abstinence [41]. Thus, we hypothesize that working memory deficit, and possibly also fluid intelligence deficit, during short-term opioid withdrawal is related to high cortisol responses during withdrawal and is at least partly transient. The correlations found between opioid withdrawal symptoms as measured by the SOWS and cognitive performances were practically zero. This may be due the finding that the individual SOWS scores and cortisol levels have been found to show only low correlations [6, 41].

**Clinical implications**

Higher order cognition and prefrontal cortex function are closely related. It has been suggested that when prefrontal cortex function gets “off line” in prolonged stressful situations more habitual responses start to regulate behavior [42]. Thus, reduced higher order cognition and impulsive behavior during opioid withdrawal are likely to be associated. Therefore, screening of higher order cognitive functions by highly sensitive task like the PASAT could be used for treatment planning. In addition, pharmacological and behavioral interventions to improve working memory performance may improve opioid withdrawal outcomes as well [43, 44].
Limitations

In most other studies concerning cognitive function under opioid withdrawal the frequency of personality disorder has not been reported or the reported proportion of personality disorders has been less frequent than in our study. However, according to meta-analysis prevalence of specified personality disorders ranges from 35% to 73% in substance abusing populations in treatment. The total figure rises even higher when personality disorders not otherwise specified are taken into account [45]. Thus, our sample of opioid withdrawal patients may not be as exceptional as it may look like in the first glance. Previous benzodiazepine abuse or cannabis abuse that was common among our patient group may also affect the results of this study. Long-term cannabis abuse and benzodiazepine abuse both have adverse effect on cognitive function [46, 47]. Thirdly, current benzodiazepine medication at test was common. In normal population benzodiazepines have adverse affect on several cognitive functions. On the other hand, norepinephrine α-2 agonist lofexidine, which was given to the patients of this study, may improve reduced working memory performance [43]. Finally, the suggestion for transient cognitive deficit due to high stress system activation is very preliminary. Neuroendocrine responses were not measured in this study.

Conclusions

Fluid intelligence, working memory, and executive function deficit observed in opioid withdrawal patients during first or second week from detoxification implicates a rather general cognitive deficit. We suggest that cognitive deficit during the opioid withdrawal may be associated with known opioid withdrawal related neural cascade in prefrontal cortex and relatively rapid substantial recovery after short-term abstinence is possible.
Competing interests

None.

Authors' contributions

PR was the main investigator collecting neuropsychological data. He was principally responsible for preparing the manuscript and performed statistical analysis. Together with authors TA, RK, and SK, he conceived the idea of this study.

HK and SK participated in the design of the study and also in writing the manuscript.

TA and RK carried out MRI investigations.

OJ and VP together with collaborators carried out psychiatric investigations.

All authors read and accepted the manuscript.

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References


**Figures**

**Figure 1.** Correlation between fluid intelligence performance and days of withdrawal among individuals with short-term abstinence from opioid dependence (N = 14) a

Note: CFIT = Culture Fair Intelligence Test.

a = One outlier performance (17 points) highly discordant to his other performance was dismissed due to poor collaboration during the CFIT administration.

**Figure 2.** Correlation between complex working memory performance and days of withdrawal among individuals with short-term abstinence from opioid dependence

Note: PASAT = Paced Auditory Serial Addition Test.
Fluid intelligence score in the CFIT

Days of withdrawal

R² = 0.4272
Complex working memory score in the PASAT

Days of withdrawal

$R^2 = 0.3908$
### Tables

#### Table 1. Group demographics

<table>
<thead>
<tr>
<th></th>
<th>Participants with opioid dependence (n = 15)</th>
<th>Controls (n = 15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years ($M, SD$)</td>
<td>31.6 (5.8)</td>
<td>31.3 (5.9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gender: females/males</td>
<td>9/6</td>
<td>9/6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Verbal intelligence $^a$ ($M, SD$)</td>
<td>98.7 (8.9)</td>
<td>98.5 (10.1)</td>
<td>n.s</td>
</tr>
<tr>
<td>Education, years ($M, SD$)</td>
<td>11.6 (1.2)</td>
<td>13.9 (1.6)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Duration of any substance abuse, years ($M, SD$)</td>
<td>15.2 (6.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of opioid abuse, years ($M, SD$)</td>
<td>8.6 (4.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of withdrawal, days ($M, SD$)</td>
<td>9.6 (2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Opiate Withdrawal Scale score ($M, SD$)</td>
<td>9.8 (5.7) (n = 13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Estimation based on WAIS-R Vocabulary score.
Table 2. Recent month drug abuse in patient group (number of patients)

<table>
<thead>
<tr>
<th>Main opioid abused</th>
<th>Buprenorphine</th>
<th>Heroin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

| Opioid only                             | 1             |
| Opioid with occasional benzodiazepine   | 3             |
| Opioid with frequent benzodiazepine     | 6             | 2      |
| Opioid with frequent benzodiazepine and occasional cannabis |   | 1      |
| Opioid use with benzodiazepines         |               |
| Opioid with frequent cannabis without other substances of abuse | 1 | 1      |

Note: Occasional = five to ten days of abuse. Frequent = more than ten days of abuse.

All who had abused mainly heroin within recent month did it were intravenously.

All but two abused buprenorphine intravenously.
Table 3. Medication within last 24 h before testing in patient group

<table>
<thead>
<tr>
<th>Medications used within 24 hours of test</th>
<th>Number of patients</th>
<th>Dose, range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxepine</td>
<td>2</td>
<td>50 – 100 mg</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1</td>
<td>150 mg</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1</td>
<td>150 mg</td>
</tr>
<tr>
<td><strong>Anxiolytics, sedatives and hypnotics (Benzodiazepines)</strong></td>
<td>15 (100%)</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>10</td>
<td>5 – 30 mg</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>4</td>
<td>15 – 60 mg</td>
</tr>
<tr>
<td>Tematzepam *</td>
<td>4</td>
<td>20 – 40 mg</td>
</tr>
<tr>
<td>Zolpidem *</td>
<td>1</td>
<td>10 mg</td>
</tr>
<tr>
<td>Zopiclone *</td>
<td>1</td>
<td>15 mg</td>
</tr>
<tr>
<td><strong>Neuroleptics †</strong></td>
<td>10 (67%)</td>
<td></td>
</tr>
<tr>
<td>Chlorprotixine/Truxal</td>
<td>1</td>
<td>75 mg</td>
</tr>
<tr>
<td>Promazine</td>
<td>9</td>
<td>100 – 200 mg</td>
</tr>
<tr>
<td>Melperone</td>
<td>3</td>
<td>75 mg</td>
</tr>
<tr>
<td><strong>Other opioid withdrawal symptom relievers</strong></td>
<td>15 (100%)</td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>6</td>
<td>100 – 300 mg</td>
</tr>
<tr>
<td>Lofexidine</td>
<td>6</td>
<td>0.2 – 1.2 mg</td>
</tr>
<tr>
<td>Naproxen/Alpoxen</td>
<td>6</td>
<td>1000- 1500 mg</td>
</tr>
</tbody>
</table>

* Used as a hypnotic the night before testing. † Used with anxiolytic indications.
Table 4. Comparisons of individuals with opioid dependence and controls on cognitive measures using ANOVA

<table>
<thead>
<tr>
<th>Domain</th>
<th>Test</th>
<th>Controls (n = 15)</th>
<th>Individuals with Opioid Dependence (n = 15)</th>
<th>F</th>
<th>df</th>
<th>η²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD (CI)²</td>
<td>Mean ± SD (CI)²</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Fluid intelligence</td>
<td>CFIT</td>
<td>34.0 ± 3.8 (32.5 – 36.7)</td>
<td>30.4 ± 4.2 (28.0 – 32.8)</td>
<td>7.97</td>
<td>1, 27</td>
<td>0.24</td>
<td>0.009</td>
</tr>
<tr>
<td>Attention</td>
<td>PASAT</td>
<td>47.5 ± 7.8 (43.2 – 51.8)</td>
<td>36.1 ± 10.1 (30.4 – 41.7)</td>
<td>12.00</td>
<td>1, 28</td>
<td>0.30</td>
<td>0.002</td>
</tr>
<tr>
<td>Memory</td>
<td>WMS-R Digit Span</td>
<td>15.4 ± 3.8</td>
<td>14.9 ± 2.7</td>
<td>0.15</td>
<td>1, 28</td>
<td>0.01</td>
<td>n.s</td>
</tr>
<tr>
<td>RAVLT, sum of learning trials 1-3</td>
<td>32.3 ± 6.1</td>
<td>28.9 ± 6.0</td>
<td>2.64</td>
<td>1, 28</td>
<td>0.09</td>
<td>n.s</td>
<td></td>
</tr>
<tr>
<td>RAVLT, delayed recall</td>
<td>10.7 ± 2.8</td>
<td>9.0 ± 2.8</td>
<td>2.65</td>
<td>1, 28</td>
<td>0.09</td>
<td>n.s</td>
<td></td>
</tr>
<tr>
<td>WMS-R Logical Memory, immediate</td>
<td>28.0 ± 5.5</td>
<td>25.9 ± 8.1</td>
<td>0.72</td>
<td>1, 28</td>
<td>0.03</td>
<td>n.s</td>
<td></td>
</tr>
<tr>
<td>WMS-R Logical Memory, delayed recall</td>
<td>25.1 ± 6.6</td>
<td>22.3 ± 7.3</td>
<td>1.20</td>
<td>1, 28</td>
<td>0.04</td>
<td>n.s</td>
<td></td>
</tr>
<tr>
<td>BVVRT, number of right figures</td>
<td>7.4 ± 1.3</td>
<td>6.8 ± 1.6</td>
<td>0.88</td>
<td>1, 28</td>
<td>0.03</td>
<td>n.s</td>
<td></td>
</tr>
<tr>
<td>Executive function</td>
<td>Stroop, modified interference time</td>
<td>24.5 ± 12.0</td>
<td>25.1 ± 8.8</td>
<td>0.30</td>
<td>1, 28</td>
<td>0.01</td>
<td>n.s</td>
</tr>
<tr>
<td>RFFT, unique designs</td>
<td>86.3 ± 22.6 (73.9 – 98.8)</td>
<td>68.1 ± 21.2 (43.2 – 51.8)</td>
<td>5.22</td>
<td>1, 28</td>
<td>0.16</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>RFFT, perseverative errors</td>
<td>2.8 (2.6)</td>
<td>3.4 (2.9)</td>
<td>0.34</td>
<td>1, 28</td>
<td>0.01</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

² CI = confidence interval
Note: CFIT = Culture Fair Intelligence Test; PASAT = Paced Auditory Serial Addition Task; WMS-R = Wechsler Memory Scale-Revised; RAVLT = Rey Auditory Verbal Learning; BVVRT = Benton Visual Retention Test; RFFT = Ruff Figural Fluency Test
Figure 1

Fluid intelligence score in the CFIT

Days of withdrawal

$R^2 = 0.4272$
Complex working memory score in the PASAT

$R^2 = 0.3908$