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

Pekka Rapeli\textsuperscript{1,8}, Reetta Kivisaari\textsuperscript{2}, Taina Autti\textsuperscript{2}, Seppo Kähkönen\textsuperscript{3,4}, Varpu Puuskari\textsuperscript{5}, Olga Jokela\textsuperscript{1}, Hely Kalska\textsuperscript{6}

\textsuperscript{1}Psychiatric unit for drug dependence, Helsinki University Central Hospital, Finland

\textsuperscript{2}Medical Imaging Center, Helsinki University Central Hospital, Finland

\textsuperscript{3}BioMag Laboratory, Engineering Center, Helsinki University Central Hospital, Finland

\textsuperscript{4}Cognitive Brain Research Unit, University of Helsinki, Finland

\textsuperscript{5}Department of Psychiatry, Helsinki University Central Hospital, Finland

\textsuperscript{6}Department of Psychology, University of Helsinki, Finland

\textsuperscript{8}Corresponding author: Pekka Rapeli, Psychiatric unit for drug dependence, Helsinki University Central Hospital, PL 590, FIN-00029 HUS, Finland
Phone: 358 50 4272403
Fax: 358 9 47163770
E-mail: pekka.rapeli@kolumbus.fi

Email addresses:
PR: pekka.rapeli@kolumbus.fi
RK: reetta.kivisaari@hus.fi
TA: taina.autti@hus.fi
SK: seppo.kahkonen@helsinki.fi
VP: varpu.puuskari@hus.fi
OJ: olga.jokela@hus.fi
HK: hely.kalska@helsinki.fi
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 intelligence were tested with comprehensive cognitive battery. Patients were tested between 5 to 15 days after cessation of opioid abuse. The results were analyzed with analysis of variance. Correlations between cognitive performance and days of withdrawal; and between cognitive performance and opioid withdrawal symptom inventory (Short Opiate Withdrawal Scale) were analyzed whenever patients performed worse than controls.

Results

Abstinent opioid dependent patients performed statistically significantly worse than controls in fluid intelligence, working memory, and executive function. Their fluid intelligence performance and working memory performance correlated statistically or nearly statistically significantly with days of withdrawal.

Conclusions

As fluid intelligence, working memory, and executive function are all related to higher order cognition the results indicate a rather general neurocognitive deficit. It is suggested that cognitive deficit among individuals with opioid dependence is related to withdrawal induced neural cascade in the prefrontal cortex and is partly transient.
Key Words

Opiod dependence, 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. Within this period dysphoric mood, restlessness, and impulsive behavior are still common. Even in specialized inpatient withdrawal programs treatment discontinuation rate rises to 30 - 60%. 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].

During short-term abstinence from opioid abuse the patients complain fatigue and poor concentrating. In agreement with this a cascade brain stress system dysregulations takes place during that time [4, 5]. Experimental studies have shown that transient hyperactivation of brain stress system as shown by elevated cortisol secretion may impair working memory transiently; and chronic hyperactivation impairs especially episodic memory [6, 7]. There is also preliminary neural evidence that opioid craving employs same neural circuits as attention, memory, and motivation. A reciprocal relationship between normal cognitive activity and drug-related craving has been suggested [8, 9]. Against this background, it is surprising that only few studies have explored the 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 [10]. 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 [11]. Only patients with antisocial personality 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 [12]. 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 [13, 14] 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 [15]. Taken together, the association between short-term abstinence and cognitive function has been addressed in only one study. Secondly, in studies concerning protracted abstinence executive function deficit has been found in some but not in all studies.

The purpose of this study was to explore cognitive function of individuals with opioid dependence during short-term abstinence. Therefore, we studied cognitive function of individuals with opioid dependence after their withdrawal from opioids with a comprehensive cognitive battery. A comparison to age, gender, and verbal intelligence (VIQ) matched controls was made. Secondly, time-dependent neural responses 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.

**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 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) [16]. 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) [17, 18]. 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 most 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) [19, 20]. In the PASAT sixty addition tasks were presented at 1.6 second intervals.

**Verbal memory** was measured by The delayed Logical Memory subtest of the WMS-R and the Rey Auditory Verbal Learning Test (the RAVLT) [19, 21]. 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 [22].

**Executive function** was measured by the modified Stroop task and by the Ruff Figural Fluency Test [23, 24]. 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 [25]. 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.

**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. Patients showing positive urine drug screening at initiation of withdrawal period were tested after negative drug screening for other drug than prescribed for them. On the test day morning at 8.00 patients completed the 10-item Short Opiate Withdrawal Scale (SOWS ) [26] 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 [27].

**Statistical Analysis**

Analysis of variance (ANOVA) was used to compare the raw scores of each cognitive test. The effect sizes were calculated with eta-squared ($\eta^2$). Group difference in education was not covaried for, because the assumption of similar relation between education and cognitive performance needed for ANOVA 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. Whenever participants with opioid dependence performed significantly poorer than control participants correlations were analyzed by the Pearson product-moment correlation coefficient.

**Results**

Table 4 shows that participants with opioid dependence performed significantly poorer than control participants in fluid intelligence, measured by the CFIT, in one working memory test, 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 ($P = 0.09$).

As fluid intelligence associates highly with working memory performance and executive function, and there was a group difference in this measure, fluid intelligence score was set as a covariate in the subsequent analyses. The group difference in the PASAT showed still a statistical trend favoring the controls ($F = 4.16, P = 0.05$) whereas the group difference in the RFFT reduced to statistically non-significant ($F = 2.26, NS$).

Finally, the correlations between reduced cognitive performance and withdrawal variables were analyzed. Days of withdrawal correlated showed statistically significant or nearly significant positive correlation with the CFIT performance and with the PASAT performance ($R = .65, P = 0.01$ and $R = .63, P = 0.01$, respectively). Figure 1 depicts the correlation between days of withdrawal and fluid intelligence performance measured by the CFIT. The SOWS score showed no significant correlations with the inferior cognitive performance. When correlations were corrected for multiple comparisons none of them remained statistically significant.
Discussion

Short-term abstinent individuals with opioid dependence performed worse than normal controls in working memory, executive function, and fluid intelligence. After correcting for multiple comparisons the group difference in working memory and fluid intelligence remained statistically significant or at the border for significance, respectively. As fluid intelligence performance associates strongly with working memory and executive function performances [28, 29] the independence of working memory and executive function deficits were analyzed. This was done by setting fluid intelligence score as a covariate in the further analyses. The working memory performance reflected by the PASAT was still at the border for statistical significance. 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 analysis of covariance the difference in the design fluency task was no longer significant. Thus, the argument for independence of specific executive function deficit in fluency performance is not very strong. Further study with a comprehensive battery of executive function measures is needed.

Fluid intelligence tasks like the CFIT places high demands for several cognitive processes: spatial perception, working memory, problem solving, and executive control of response selection. Working memory and attention task like the PASAT involve several similar cognitive demands. Actually, experimental studies have shown activation of highly overlapping neural networks while normal individuals perform cognitively demanding tasks [30, 31]. Therefore, our result indicates a rather general cognitive deficit during short-term opioid withdrawal.

The relevance of neurocognitive study results comes often from dissociations found between different functions. In this study two dissociations merit further consideration. First, there was dissociation among opioid withdrawal patients between deficient performance in working memory task, the PASAT, and the normal episodic memory performance. Deficient working memory
performance in relation to spared episodic memory performance fits well to the idea that elevated cortisol secretion during short-term abstinence from opioid dependence would affect 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 [6, 7]. Concerning opioid withdrawal high stress system activations as shown by elevated cortisol levels has been found especially among individuals with antisocial personality disorder [32]. 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 may be postulated. Secondly, it is possible that this deficit is partly transient. 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 [33]. In our study neuroendocrine responses were not measured. However, the positive correlations that were found between impaired performance and withdrawal length are in agreement with rapid recovery. 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. Whether the recovery of working memory or fluid intelligence is so rapid as studies showing nearly intact performance in other cognitive domains after half a year abstinence remains to be studied [12, 15]. 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 [33, 34]. Second dissociation was found between deficient the PASAT and intact Digit Span performance. Both tasks tap working memory – but differently. In the PASAT, storage of previous number, rapid arithmetical processing, and executive control of interference from previous items or from ongoing
adding process is required. The Digit Span task demands especially storage of the several items. Thus working memory storage is relatively spared among opioid withdrawal patients. Taken together, the results fit to the idea that the central executive component of working memory is impaired in short-term opioid abstinence.

According to current research the need for executive control is signaled from the medial prefrontal cortex to the anterior cingulate or to the lateral prefrontal cortex which then implements the control [35, 36]. This may mean that right dorsolateral prefrontal cortex important for memory retrieval in “simple conditions” [37] 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 [38]. Actually, a recent study showed an association between deficient executive function performance in opioid dependence and abnormal prefrontal and anterior cingulate function [39].

**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 [40]. 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 [41, 42].

**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. This complicates the comparisons between our study and earlier studies as personality disorders in clinical settings is associated with cognitive deficits [43]. 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 [44, 45]. 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 [41]. Finally, the linear correlation between cognitive performance and days of withdrawal may be a time-limited approximation of a curvilinear phenomenon. The relationship may be U-shaped during the first days of abstinence, then linear for some weeks and sigmoid during protracted abstinence.

Conclusions

Fluid intelligence, working memory, and executive function deficit observed in opioid withdrawal patients during first or second week from detoxification implicates 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.

Acknowledgements

This work was supported by the grants from the Alfred Kordelin Foundation and HYKS-Institute to the first author and from the Finnish Medical Foundation and the Yrjö Jahnsson Foundation to the R.K and T.A. We thank Professor VeijoVirsu for helpful comments during the research process and Senior Lecturer Pertti Keskivaara for statistical advice.

References


7. McEwen BS: Stress, sex, hippocampal plasticity: relevance to psychiatric disorders. *Clinical Neuroscience Research* 2001, **1**:19-34.


show enlarged cerebrospinal spaces but no signs of brain pathology of vascular origin. 


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.
Fluid intelligence score in the CFIT

Days of withdrawal

$R^2 = 0.4272$
## 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><em>n.s.</em></td>
</tr>
<tr>
<td>Gender: females/males</td>
<td>9/6</td>
<td>9/6</td>
<td><em>n.s.</em></td>
</tr>
<tr>
<td>Verbal intelligence $a$ ($M$, $SD$)</td>
<td>98.7 (8.9)</td>
<td>98.5 (10.1)</td>
<td><em>n.s.</em></td>
</tr>
<tr>
<td>Education, years ($M$, $SD$)</td>
<td>11.6 (1.2)</td>
<td>13.9 (1.6)</td>
<td><em>p&lt;0.001</em></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 (%)

<table>
<thead>
<tr>
<th>Drugs abused</th>
<th>Buprenorphine</th>
<th>Heroin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiod only</td>
<td></td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Opiod with occasional benzodiazepine</td>
<td>20</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Opiod with frequent benzodiazepine</td>
<td>40</td>
<td>13</td>
<td>53</td>
</tr>
<tr>
<td>Opiod with frequent benzodiazepine and occasional cannabis</td>
<td></td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Opiod use with benzodiazepines</td>
<td></td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>Opiod with frequent cannabis without other substances of abuse</td>
<td>7</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Total, opioids in any combination</td>
<td>67</td>
<td>33</td>
<td>100</td>
</tr>
</tbody>
</table>

Note: Occasional = five to ten days of abuse. Frequent = more than ten days of abuse. Bold number indicates sum. All who had abused mainly heroin within recent month did it were intravenously. abusers 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>Percent 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>26</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>13</td>
<td>50 – 100 mg</td>
</tr>
<tr>
<td>Venlaflaxine</td>
<td>7</td>
<td>150 mg</td>
</tr>
<tr>
<td><strong>Anxiolytics, sedatives and hypnotics (Benzodiazepines)</strong></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>67</td>
<td>5 – 30 mg</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>26</td>
<td>15 – 60 mg</td>
</tr>
<tr>
<td>Temazepam *</td>
<td>26</td>
<td>20 – 40 mg</td>
</tr>
<tr>
<td>Zolpidem *</td>
<td>7</td>
<td>10 mg</td>
</tr>
<tr>
<td>Zopiclone *</td>
<td>7</td>
<td>15 mg</td>
</tr>
<tr>
<td><strong>Neuroleptics†</strong></td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Chlorprotixine/Truxal</td>
<td>7</td>
<td>75 mg</td>
</tr>
<tr>
<td>Promazine</td>
<td>60</td>
<td>100 – 200 mg</td>
</tr>
<tr>
<td>Melperone</td>
<td>20</td>
<td>75 mg</td>
</tr>
<tr>
<td><strong>Other opioid withdrawal symptom relievers</strong></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>40</td>
<td>100 – 300 mg</td>
</tr>
<tr>
<td>Lofexidine</td>
<td>40</td>
<td>0.2 – 1.2 mg</td>
</tr>
<tr>
<td>Naproxen/Alpoxen</td>
<td>40</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>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><strong>Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid intelligence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>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>Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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>
</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>
</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>
</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>
</tr>
<tr>
<td>BVRT, 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>
</tr>
<tr>
<td>Executive function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>
</tr>
</tbody>
</table>

a 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; BVRT = Benton Visual Retention Test; RFFT = Ruff Figural Fluency Test
Figure 1

Fluid intelligence score in the CFIT

Days of withdrawal

$R^2 = 0.4272$