Reviewer’s report

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

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Reviewer: Antonio Verdejo-Garcia

Reviewer’s report:

General

The authors examined fluid intelligence, memory and executive functions performance on a group of 15 opioid abusers during short-term withdrawal from opiates, with regard to a group of 15 healthy comparison participants. Analyses of variance showed that opioid abusers performed poorer than healthy subjects on some measures of fluid intelligence and executive function, but not on episodic memory tests. Furthermore, they found significant correlations between executive functions and duration of withdrawal, indicating improved performance with increased duration. The authors discuss their findings in regards to a transient stress induced impairment on prefrontal cortex associated with withdrawal. This is an interesting study addressing a relatively non-explored issue.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

- Information regarding comorbid diagnosis is confusing. Early on Methods section the authors claim that participants with major psychiatric comorbidity were excluded, while they later inform that 12 out of 15 opioid abusers had comorbid antisocial personality disorder. The issue of antisocial personality may be critical to interpret results. Although the authors partially address this limitation in their discussion, they reckon that APD effects on elevated stress may contribute to explain the working memory dysfunction on the opioid abusers. However, APD alone has been consistently associated with executive dysfunction, and therefore it may be a more clear and consistent correlate of the observed deficits than stress-induced symptoms. In support of the proposed transient stress induced impairment are the correlations between duration of withdrawal and executive function improved performance, however, the authors acknowledge that medication may also partially account for this effect. I suggest that the authors address more in depth in their discussion the possibility that APD comorbidity can be an alternative or additional explanatory factor for their results.

- An additional factor that may impact results is opioid users previous severity of abuse of heroin, benzodiazepines and cannabis. The authors should report information regarding duration of abuse for these and other substances if available. Furthermore, several previous studies have documented a relationship between duration of use of these drugs and executive dysfunction. Therefore, it may be useful to conduct correlation or regression (although the sample size is limited) analyses to examine the relationship between duration and severity of cannabis, heroin and benzodiazepine use and executive function.

- An interesting finding of the study was that opioid abusers presented poorer performance on a figural fluency test. This is particularly consistent with apathy symptoms frequently observed on heroin abusers in clinical settings. However, the authors reported (according to analyses of covariance) that this effect was no longer significant after considering fluid intelligence effects. The authors should report if there was a correlation between RFFT and fluid intelligence, and discuss the pertinence of using ANCOVA (i.e., normality assumptions). In any case, the clinical implications of
defective fluency performance on opioid abusers may be independent of those of fluid intelligence. Therefore, the finding of a trend to poorer performance on fluency should be further elaborated on the Discussion.

- The Discussion of possible dissociations between opioid users performance on executive tests raise important interpretation issues. It is not clear which precise mechanisms are assessed in the PASAT that are not taxed by the Stroop or the Backward Digits test.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

- The procedures on the Stroop test seem not to be the standard ones (i.e., there was no color naming condition, 50 stimuli were used). The authors should further clarify the pertinence of the administration procedures selected.

- Tables may be improved by presenting more selective information (sums are not strictly necessary), filling blank cells, presenting numbers instead of percentages, and adjusting to APA format.

- A table or figure showing the correlation between PASAT and duration of withdrawal should be provided to be consistent with the presentation of this relationship in the case of fluid intelligence.

- Threshold levels of significance should be further clarified in the different comparisons.

- There are some minor typos and spelling errors.

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Discretionary Revisions (which the author can choose to ignore)

- On the Introduction section, it is not clear the relationship raised between craving, withdrawal and cognitive activity. Craving effects are observed even after protracted abstinence, and there is not reciprocal relationship between craving and cognitive activity. The authors may mean that craving is associated with neural circuits involved in motivation, memory and cognitive control.

- The error ratio scores of the RFFT may add significant information to performance on this task.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

'I declare that I have no competing interests'