Author's response to reviews

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

Authors:

Pekka Rapeli (pekka.rapeli@kolumbus.fi)
Reetta Kivisaari (reetta.kivisaari@hus.fi)
Taina Autti (taina.autti@hus.fi)
Seppo Kahkonen (seppo.kahkonen@helsinki.fi)
Varpu Puuskari (varpu.puuskari@hus.fi)
Olga Jokela (olga.jokela@hus.fi)
Hely Kalska (hely.kalska@helsinki.fi)

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Dear Editorial Team, Dear Reviewers Dear Dr Verdejo-Gargia and Dear Dr Lee

Thank you for your comments. The questions raised by the reviewers are the same that we have been struggling for with this manuscript. Our statistical means to resolve these issues are somewhat limited. Yet, we believe that in relatively non-explored phase of the research our study can give a contribution. Information about neurocognition during early opioid abstinence is sparse indeed.

Major compulsory revisions made: (in the order as received).

Revisions asked by Dr Antonio Verdejo-Garcia:

“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 personality disorder.”

Our revised text states that “participant with acute/ psychiatric comorbidity not related to substance abuse …. were excluded”. That is, opiate withdrawal patients had psychiatric comorbidity related to opiate withdrawal syndrome. The first criterion of DSM-IV opiate withdrawal syndrome states: “Dysphoric mood within few hours or few days of cessation or reduction of opioid use.”

Later in the method section more precise description is given.

“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.”

These symptoms observed indicate substance abuse induced dysphoric mood.

Personality disorders can certainly complicate opioid withdrawal symptoms. In our discussion section this issue is explicitly stated ….

“Concerning opioid withdrawal high stress system activations as shown by elevated cortisol levels has been found especially among individuals with antisocial personality disorder.”

]

… “The issue of antisocial personality may be critical to interpret results … 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.

In limitations paragraph we state: 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

1 Italics = new text.
abusing populations in treatment. The total figure rises even higher when personality disorders not otherwise specified are taken into account [46]. Thus, our sample of inpatient treated opioid withdrawal patients may not be as exceptional it may look like in the first glance. Secondly, a recent large population study concerning neurocognition in antisocial personality disorder as such, in 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) among them[47]. Thus, so far there is no convincing evidence that antisocial personality disorder as such, without high stress system activation, would account for the deficit profile observed in this study.

Abuse of heroin(opioids), benzodiazepines and cannabis. “The authors should report information regarding duration of abuse for these and other substances if available….it may be useful to conduct correlation or regression (although the sample size is limited) an analysis to examine the relationship between duration and severity of cannabis, heroin and benzodiazepine use and executive function.”

We have valid records of abuse histories of our patients. They look quite similar. Experimentation of substance use has usually started with alcohol, drugs at an early age from age of 8 years to age of 14-15. This is followed by mainly alcohol abuse during weekends from early teens onwards. Shortly after this “hard” drugs are experimented in random manner. Shortly after this opiate and benzodiazepine abuse/dependence is evident. From the records it is possible to determine the duration of opiate abuse as well the duration of any substance abuse. However, records concerning other substances of abuse show so much overlaps and uncertain information that they do not form basis for detailed description of duration of other substances of abuse. Therefore we give information concerning “only” duration of any substances of abuse in table 1. Then we conducted analysis of correlations between durations of opioid abuse or any substance abuse and inferior cognitive performance. There were mild to moderate correlations in the expected direction that would have reached statistical significance with sample size of twice as much we had. The highest correlation was -.31 between the duration of any substance abuse and figural fluency performance. As recent month abuse has potential implications for cognitive function information about it is given. Unfortunately this data was too variable for further analysis with our sample size.

“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, implications of defective fluency performance of 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 correlation between the RFFT and the CFIT (.30) is now given in the text. This correlation is in line with the reported moderate or strong (.25 -.69) correlations in the U.S. normative sample between the RFFT and Wechsler PIQ. In order to statistically elaborate this matter more in depth we re-checked all the assumptions needed for ANCOVA. The normality assumption was not violated. However, in the second glance the similarity of slopes appeared problematic. Therefore, instead of the ANCOVA we chose a statistically less problematic way of doing a post hoc factorial 2x2 ANOVA with categorical variables: study groups (patients vs. controls) and median splitted groups of based on fluid intelligence performance. In the RFFT it turned out that the study group was at the border for statistical significance. The issue of poor figural fluency performance is now briefly discussed on the Discussion.

The RFFT score variability across studies could be something worth considering in the future studies. In the U.S normative sample the mean performance is 82-83 unique designs with 7 errors.
for ages 25-39 with maximum 12 years of education. The ecstasy users from Hong Kong studied by Drs Lee and Yip scored mean 111-112 points with 14-15 errors. Yet, they had mean 10-11 of education! Thus, they outperform the nearly as educated poly-substance abusers of Spain who scored mean 79 u-designs (Studied by Dr Verdejo-Garcia.) Moreover, the Hong Kong ecstasy users (n = 100) outperform as well the U.S normative sample of those with 16 or more years of education. The Hong Kong sample makes only few more errors than the normative sample. The relative small Finnish control sample for this study could reach only 86 u-designs and made mean 3 errors. Yet, they had mean 14 years of education. According to U.S. normative sample score of 99-100 points with 8-9 errors could have been expected. This, it is possible that cultural predisposition for trade-off between speed and error contributes substantially to the variability of the results. Secondly, the effect of education on performance may also vary across countries. (Smaller in Hong Kong and Finland than in the USA?). As these issues are unresolved we are cautious in interpreting the RFFT findings more in detail. A multinational study with a control group on the relationship between executive function and substance abuse could be highly informative in this matter.

“It is not clear which precise mechanisms are assessed in the PASAT that are not taxed by the Stroop or the backward Digits test.

The PASAT is one of the most sensitive clinical measures of non-specific CNS dysfunction. It has ramifications on frontal, parietal, anterior cingulated, cerebellar and subcortical/white matter integrity. Stroop task is sensitive too (Lockwood et al. J Int Neuropsychol Soc 2004, 4:26-34.) However, it is likely that the Stroop interference phenomenon is more specific to frontal attention system dysfunction (Botvinick et al. Trends Cogn Sci 2004; 8:539-546). Concerning the backwards Digits Span it has not been convincingly shown that there would be a differentiation between forward and backward digit span performance in relation to their clinical sensitivity (The ecstasy study of Dr Lee is in line with this idea.) According to recent analysis of WMS-III normative sample analysis (Hester, J Int Neuropsychol Soc 2004; 4:475-481) it is plausible both task tap first WM storage and then in the longest versions central executive component of the WM is activated as well. Our conclusion is that the PASAT is the most sensitive measure of these. However, not to expand our discussion section we will not discuss this issue there.

Dr Lee:

The rationale for the speculated relationship between days of withdrawal and cognitive performance. “the authors may like to clarify the definition of “time-dependent neural responses” (p. 5 paragraph 2) and how it was related to cognitive performance as hypothesized”

The introduction section is now more precise in that matter. It is explained that the tests cover wide range of cognitive functions. Definition states now: …opioid abstinence related time-dependent neural responses …..

“The rational for choice of the tests is unclear”. … “The authors may also like to elaborate on the relationship between the different cognitive constructs studied and their effect of short-term abstinence from opioid dependence.”
The earlier studies give little advice for the test selection. Data was collected in 2001-2003. The tests were selected to be used for several substance abuse studies. One study concerning former amphetamine dependence has been published so far.

“The control for effect of testing was not addressed”…

Major principles of test administration are now given in procedure section. However in method section the test are presented in domains. Testing was done in the same order for all participants. The tests were given in two periods. As the PASAT may be anxiety provoking it was given as the last test of the first period. All participants showed good rapport.

“Further elaboration on the Short Opiate Withdrawal Scale may help clarify the nature of withdrawal symptoms and their relationship with cognitive functions”

We have SOWS score from all the patients. However, we do not have their SOWS profile. As the SOWS covers only physical symptoms analysis of these symptoms would not probably give much useful information in a small scale study.

“It is rather unclear why only verbal intelligence was matched for the clinical and control sample.”… “The unmatched education levels of the two groups further indicates that the baseline of the two groups may not be equivalent. The authors may consider re-analyzing the data by partalling out the confound variance by introduced by non-equivalent intelligence estimates of the two groups”.

We are aware that Dr Lee has done excellent contribution to research on cognitive effects of ecstasy use with a group matched for nonverbal intelligence. In our study, the rationale verbal/crystallized intelligence matching without fluid intelligence comes from well known studies by Duncan and colleagues. This is now told in the method section.

Quote: “….. brief measures of crystallized ability or verbal knowledge (e.g., the Vocabulary or Information subtests of Wechsler-derived batteries) can provide a broad sampling of the knowledge that has accumulated over one’s lifetime, and therefore can provide a rather accurate indication of an individual’s historic levels of fluid ability.” Ashton et al. J Person Ind Diff 2005; 39:999-1004.

The CFIT was chosen as a fluid intelligence measure because of well studied fluid intelligence tests it is the strictest. For instance Raven Matrices is non-timed pure and more a pure reasoning test. The reason for not converting the CFIT scores to IQ scores comes from the fact that there are no applicable norms for that. The CFIT has norms U.S and British co-norms from the sixties. However it known that even in well developed countries mean IQ scores have risen 2-3 IQ points per decade. This rise applies to crystallized as well as to fluid intelligence (Colom J Biosoc Sci 2003; 35:33-39; Personality and Individual Differences 1998; 25:927-935, 1,2). Therefore, Finnish norms for vocabulary performance based on early 1990’s are probably stricter than the CFIT norms from the 1960’s.

Matching for education would give too conservative results. In Finnish society young adults without secondary education are exceptions: either having luxurious sabbatical years before entering vocational schooling, having serious mental or social problems or special talents without formal education (performing artists, athletes etc). All of our patients had entered secondary education but due their substance abuse only few of them had finished it with diploma. Controls on the other hand many continued their studies in adult years with advanced diplomas.

The relationship between education, intelligence and substance abuse (specifically cannabis abuse) has been addressed in western societies has been reviewed by Lynskey et al. Addiction 2000, 95: 1621-1630. “In particular, early cannabis use appears to be associated with the adaptation of anti-
conventional lifestyle characterized by affiliation with delinquent and substance using peers….cannabis use occurs in peer group that rejects conventional values, such as educational achievement.” As most of our patients had entered in their vicious circle by early onset alcohol and cannabis abuse this applies to them as well.

“The length of period of opioid dependence may vary, which may become a confounding variable that affects their cognitive functioning.”

In general cognitive substance abuse studies have shown modest evidence for duration of abuse or dose-related effects on cognition. For revised version we looked the correlations of duration of opioid abuse or any substance abuse. The mild correlations were in the expected direction. However, running several correlations without specific hypothesis is not plausible.

“For the clinical population, opioid was not the only drug use. This makes it difficult to conclude that the identified cognitive profile was related to opioid use, but not the effect of the other substances of abuse”

The mixed substance abuse profiles of study participant are a general problem in Western addiction studies. In the Orient pure heroin abuse may traditional but in Finland it is rare. Actually this problem dates back to current diagnostic classifications. According to lay wisdom many opiate dependent individuals show polysubstance dependence. However, according to DSM-IV term polysubstance dependence has been defined in the way that is contradiction with common sense. This important problem has been reviewed by Schuckit et al. J Stud Alcohol. 2001, 62:54-61.

Quote: “The concept of polysubstance dependence (PD) has been defined several ways over the years. However, few clinicians and researchers appear to use this label in a manner consistent with any of the major diagnostic manuals.”

“the performance of the participants …may be confounded by their lack of motivation .. as a result of opioid craving..”

Only follow-up studies can tackle this question without doubts. In general, patients in inpatient settings are highly motivated to all activities that gives them chance to do something else than waiting for “release” from the ward.

Rather general cognitive deficits vs. a general cognitive deficit.

A rather general cognitive deficit. It may be transient. The follow-up neuropsychological studies I have made for sporadic clinical patients of this study are mainly in favour for transient hypothesis.

Minor Essential revisions:”

**Stroop test:**

“The authors should clarify the pertinence of the administration procedures selected”.

The Stroop effect is known to be very sensitive for administration format, administration procedures, and practice effects. This complicates the comparison of the results from thousands of studies in which Stroop task has been employed. The procedure we used is not the most conventional. The procedure dates back to work of well-known neuropsychologist CB Dodrill In (ed. Flickov SB & Boll TJ) Handbook of clinical neuropsychology, pp 366-395, 1981. Interference
is counted from subtracting word reading time form color-word reading time. Therefore both color naming speed and interference from inhibition from not reading words is affecting the result. This adds sensitivity but specificity is problematic. According to current research this procedure should be more prone to interference effect (Botwinick MM et al. Trends Cogn Sci 2004; 8:539-546.

“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.

Tables are simplified. Numbers are presented instead of percentages. In sums both are used. However, APA format is intended for printed journals; and simpler format is commonly used in the BMC journals.

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

Figure 2 depicts this correlation.

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

“There are some minor typos and spelling errors”

“What is the p-level after correction?”

All these have been checked for (Checking for cover letter somewhat superficial; U.S English)

“Opioid should be opioid”

Undoubtedly.

Discretionary Revisions

opioid craving and cognition

The discussion on the relationship between opioid craving and cognitive activity has been removed as non-compulsory for the matter.

the RFFT error ratio

the RFFT error scores are given in table 4. The error scores already show for interested reader that there is a small, and most likely statistically non-significant, group difference favouring controls in this measure. Checking ANOVA confirmed this.

With best wishes

Pekka Rapeli & research group