Author's response to reviews

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

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Author's response to reviews: see over
Dear Editorial Team, Dear Drs Verdejo-Garcia and Lee

Thank you for encouraging us to further elaborate our hypotheses and interpretations. We did find some new aspects. The Background section has been thoroughly rewritten. The relationship between opioid withdrawal neural cascade and its hypothesized cognitive ramifications is highlighted.

Major compulsory revisions

Further revisions asked by Dr Antonio Verdejo-Garcia:

Hypotheses at the end of the introduction section:
“(i) the existence of transient vs. stable cognitive executive deficits…”

This issue is clarified by referring to rapid recovery of opioid withdrawal neural cascade and associating these changes to possible neurocognitive deficits during opioid withdrawal.

“(ii) the relationship between withdrawal-induced stress dysregulations and cognitive-executive deficits…”

According to current knowledge catecholaminergic dysregulation in the prefrontal cortex may cause cognitive deficit.

“(iii) “the proposed relationship between fluid intelligence, working memory, and executive skills…”

This relationship has been elucidated in experimental research as reviewed by several eminent researchers. Contributions by Duncan and Conway are cited (refs. 30,54,60).

Description of the participants in the Methods section

By definition the DSM axis I disorders are conditions needing (acute) clinical attention. Axis II disorders are recorded to give information for additional intervention and treatment choices. In cases of personality disorders this may mean that they are always more or less acute though seldom put under diagnostic or treatment procedures. To be more precise, we changed the wording “participants with acute psychiatric comorbidity … ” to “participant with acute axis I diagnosis according to .. (DSM-IV) not related to substance abuse were excluded”.

Comprehensiveness of the cognitive battery

This expression has been reformulated.

A reference supporting the Stroop administration procedure

Information is now given in the Cognitive tests subsection.
ANOVAs in the Results section

We decided to focus our article on the hypothesis and issues raised in the Background section. Thus, these procedures without initial hypothesis stated were deleted. The decision of not using corrections for multiple comparisons is explained in the Method section.

Results of heroin vs. buprenorphine users

We did make a non-planned comparison addressing this issue. The group performances were nearly identical except in VIQ in which heroin users performed slightly better and in the PASAT in which they performed slightly worse than buprenorphine users. This may have heuristic value. However, as they were only 5 heroin users vs. 10 buprenorphine users, we are not reporting this.

Consistencies and discrepancies between the results of previous studies

These are shortly discussed in the beginning of the discussion section. However, only the Guerra et al. study has been made during early abstinence.

The potential impact of antisocial personality disorder (APD) on the study’s results... The authors should cite some evidence of increased executive dysfunction associated with stress + APD with regard to APD alone to support their strong conclusion.

This suggestion is now only “between the lines”

Dorsolateral vs. medial prefrontal cortex and working memory

This part of the discussion was removed as well.

Clinical implications …. assuming these deficits are mainly transient?

Opioid withdrawal is notorious for abrupt treatment cessations. Therefore, all efforts to understand the neurocognitive concomitants related to it are relevant. Only longitudinal studies can determine whether the transience hypothesis holds in the suggested domains.

Minor revisions

In the limitations subsection: the presence of APD … provides a potential confounding factor that should be acknowledged... Besides APD and co-abuse I would include the issue of non-matched educational level among the limitations of the study.

All these points are now mentioned in the Limitations subsection. In modern Finnish society young individuals need a vocational diploma to enter into labour market and often also further formal education to stay there. Even young addicts often start secondary education. Then they drop out from their schools due to non-attendance, not due to primary intellectual capacity deficit. Therefore, matching for VIQ was used as an estimate of premorbid IQ. The Nelson Adult Reading Test which is often used for this purpose is not available for Finnish language. In Finnish there are few words suitable for such a test. As a matter of fact, matching for premorbid IQ is not uncommon in opioid abuse studies either (eg. Davis, Ornstein refs. 6 & 11).

Season’s greeting from snowy Finland!

Pekka Rapeli & research group