Author’s response to reviews

Title: Gray-matter Structure in Long-term Abstinent Methamphetamine Users

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Answers to the comments

Comments to Author:

Thanks for the authors to give me the new information about the abstinent time effects in the gray-matter structure of methamphetamine (meth.) addicts. This study including 99 meth. and 86 healthy controls (HC), it was really hard work. The results also improve our knowledge about 'Compulsory detoxification' effects on meth addicts. But there are some problem should be clarified.

In the background

I can't find a hypothesis about this study. It makes me confused, what's the position of this study? what's a question the authors want to answer? For example, ref 15 shows a longitudinal study about abstinence of meth addicts to answer the relation between ABS and gray mater altered, so why you do this Cross-sectional study?

Answer:

As reviewed in the introduction, previous studies could not give a comprehensive conclusion about the effects of MA use and subsequently abstinence on gray-matter structures, possibly due to small sample size, multiple substances use, etc. In addition, results from the two longitudinal studies available are inconsistent. Therefore, we tested the effects of MA use and subsequently abstinence in a large
population of relatively pure MA users with long-range supervised abstinence. We now clarified our hypothesis in the last paragraph of the “Introduction”.

For the methods.
1. when you analysis the thickness you don't need to include the intracranial volume as the coveries;
   Answer:
   In MRI studies, the volume and thickness are commonly used to describe cortical morphology, while the volume of a certain brain region reflects its thickness and area. Winkler AM et.al: Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. NeuroImage 2010, 53(3):1135-1146. So, ICV was controlled both when analyzing the thickness and the volume.
   See supplementary methods.
2. the education years is most important value for group different, should be added in the ANCOVA analysis, please check https:// www.ncbi.nlm.nih.gov/ pubmed/27734304 and https://www.ncbi.nlm.nih.gov/pubmed/23796547;
   Answer:
   For two reasons we considered that the education should not be controlled in the analyses. First of all, within our knowledge, no study supports the view that general education influences morphological characteristics of gray-matter structures. We’ve read the two papers you recommended. In line with many other studies, these two implicate that longer education is a protective factor against age-related gray matter loss. But our sample is about 30 years old. Theoretically, they don’t have this kind of gray-matter loss which basically become obvious at about 40 years old. Peters R: Ageing and the brain. Postgrad Med J 2006, 82(964):84-88.
   Second, although the two groups were different in education, using which as a covariate would induce noises. In line with a previous report Mortimer JA, et.al.: Head circumference, education and risk of dementia: findings from the Nun Study. J Clin Exp Neuropsychol 2003, 25(5):671-679, the present study identified positive correlation between duration of education and ICV in healthy controls, suggesting that education reflects a developmental variation which could contribute to morphology of gray matter. However, this correlation was absent in users, suggesting that education did not reflect similar developmental variant in users. Schwartz et.al. have argued that less education (than healthy subjects) in users reflects a drop-out which is affected by drug use. Schwartz DL et.al. Global and local morphometric differences in recently abstinent methamphetamine-dependent individuals. NeuroImage 2010, 50(4):1392-1401. Therefore, using education as a covariate would induce noises by adjusting the data depending on a linear relationship formed mainly by the healthy controls.
   We didn’t show this part of results in the text as we considered that it’s distracting. Now we added them in the supplementary materials.
3. the times of Monte Carlo simulation, the version of the surfer should be reported;
   Answer:
   We used Freesurfer 5.3.1, and conducted 5,000 times of simulation. We have added them in the text. See the first paragraph of “MRI data processing” and the last paragraph of “Statistical methods”.
4. the history of smoking and drinking, maybe use the self-reported servility score to control the group difference is a choice?
   Answer:
   It is a limitation for this study because that we didn’t collect information about smoking and drinking so elaborately. And we have mentioned it in the limitation.
   See the “Statistical methods” and the last paragraph of the “Discussion”.
5. The quality of the image should be checked after preprocessing, and the report is deleted.
Answer:
We manually checked the quality of preprocessing and amended the mistakes. We have stated them in the methods section.
See the first paragraph of “MRI data processing”.

For the results
1. I am so curious about the scatter plots about the significant correlation between the ABS/MA use and Thickness/Volume.
Answer:
We provided the scatter plots in the text. See figure 2. The plots provided information same to table 2. So now we moved table 2 to the supplementary materials.

2. a little problem with the coordinate system.
Answer:
The two parts of the figure 1a showed the same alternations. The former showed the anterior and the latter showed the right anterior. And, the Freesurfer provides Talairach coordinates.

3. table 3 shows significant results between two groups, but I didn't find the corrected for multiple comparisons; the highest intensity = 3.7.
Answer:
Freesurfer provided -log10(p) as the intensity for each vertex. We have transformed these values of intensity to original p values. Additionally, we provided cluster p value for each significant cluster. Please see table 2.

4. also table 3 the intensity of group comparisons is t OR F?
Answer:
Same to the answer to comments 3. Freesurfer provided -log10(p) as the intensity. We have transformed them to original p values. See table 2.

For the discussion
Paragraph 3 "Providing this particular correlation reflects the effects of releasing from the pressure of MA, these results implicate that chronic MA use induces gray-matter loss in those regions that are recoverable subsequent to prolonged abstinence." I have 3 questions.
1. if the positively correlated reflect the recover, how about the negatively correlated?
Answer:
No negative correlation was identified in this study between cortical measurements and duration of abstinence. We have changed the confusing expression to: “Providing that correlation with duration of abstinence reflects the effects of releasing from the pressure of MA, these positive correlations implicate that abstinent users were experiencing a recovery from MA induced gray-matter reduction in volume and thickness. The effects of MA use suggested by these correlations……” See the third paragraph of “discussion”.

2. the group compare didn't show overlap in positive correlated, can your plot the correlated between abstinence duration and grey matter volume/thickness and add a line with 95%CI of health control, so we can easily see they have recovered.
Answer:
We have plotted the scatters. See figure 2.
3. In conclusion, you can't say a conclusion 'executive functions and decision-making' in a grey matter study.
Answer:
We have scaled back the claims in conclusions. In the new version of conclusions, we stated that: “Chronic methamphetamine use induces hard-to-recover cortical thickening in bilateral superior frontal gyri and recoverable volumetric reduction in right hippocampus, bilateral accumbens nuclei and bilateral cortical regions around insulae. These alternations might contribute to MA-induced neurocognitive disfunctions and reflect a regional specific response of the brain to MA.” See “Abstract” and the section “conclusions”.

By the way, authors can add newer ref, 16/42 nearly than 2014, like Okita, K., Morales, A. M., Dean, A. C., Johnson, M. C., Lu, V., Farahi, J., ... & London, E. D. (2018). Striatal dopamine D1-type receptor availability: no difference from control but association with cortical thickness in methamphetamine users. Molecular psychiatry, 23(5), 1320.
Answer:
We have added the reference you provided (Ref. 41). And we have refreshed the references as well. In the present version, twenty-three of them were no earlier than 2014.