Author’s response to reviews

Title: CASE REPORT: A GIANT ARACHNOID CYST MASKING ALZHEIMER’S DISEASE

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Version: 4 Date: 15 Jun 2019

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Our detailed responses to the reviewer’s comments are as follows:

Kayako Matsuo, Ph.D. (Reviewer 1): I am disappointed to learn that I failed to make me understood efficiently. I was not writing about the "volume-based" approach that authors referred to. Instead, I was writing about, I would say, a "slice-based" approach. This is a fundamental of clinical fMRI. I just asked the authors perform this basic fMRI procedure using the "native" (i.e., original EPI) slices without a spatial registration. In the processing of clinical fMRI, specifically that with a distortion, we often perform this kind of basic procedures first, and then apply an advanced approach. Otherwise, we cannot appreciate the real value of the advanced approach.

I have read the excellent PNAS paper from Dr. Van Essen's group (Coalson et al., 2018, "The impact of traditional neuroimaging methods on the spatial localization of cortical areas"). I found that the paper discussed the superiority of their surface-based method in spatial registration as compared to traditional methods. The spatial registration is crucial when we conduct a group analysis (with multiple subjects). Here, in this case study, the authors have only one patient. Actually, the "slice-based" approach has a minimum relationship with a spatial registration, or rather, in a sense, aims to avoid it. Instead, it will provide a direct view of a spatial relationship between the cyst and activation.
In addition, Coalson et al. (2018) only considered healthy young adult subjects from the HCP. These studies can never guarantee the accuracy of specific results by clinical population. Nevertheless, I recognize a significance of the authors' application of the surface-based method to the patient with a large cyst. For this reason, I would insist authors to follow a basic procedure of clinical fMRI. As the brain has a large distortion, we should first observe how activation manifests as it is at a very basic level using native EPI images.

As a matter of fact, we researchers often naturally feel a motivation to confirm the very basic behavior of the data. After that, we can apply high technologies that may include some of image processing errors. If we have these two, we can then estimate the validity of the whole results to obtain a conclusion.

I will explain more details about the "slice-based" method to make sure. The authors obtained 488 volumes of 22 slices from a patient's brain. Then, you have a number of voxels, each of which holds 488 time points. You could prepare a reference function of the task pattern (movement blocks vs. rest blocks) that have 488 time points. We typically convolve a hemodynamic response function to the reference function. Then, you could compute correlation coefficients between the reference function and each timeline from the voxels. Finally, you could visualize the significantly correlated voxels by overlaying them onto an average EPI. Many researchers usually conduct preprocessing including slice timing, realignment and/or smoothing before the correlation statistics, but I think it is up to you (I might avoid smoothing because of the cyst).

I hope the authors now clearly understand that the "slice-based" approach that I suggest is unrelated to spatial registration that Coalson et al. (2018) illustrated. This work could be completed within 1 or 2 hours. I would use SPM software (using a general linear model) because it's simple and straightforward, but other software will also do. I am not quite sure but I believe FMRIB software would include this kind of basic analysis tools. Or you can also do that by yourself on MATLAB if you are familiar with MATLAB programing. In this case, it might be easier to perform the preprocessing in advance using software you prefer (if necessary).

The resultant maps by the "slice-based" approach would be compatible with the current results (I believe they will), or unfortunately not compatible. Even when they were not compatible, this fact would not hurt the value of the paper at all. On the contrary, it would provide valuable information on the image processing of brains with a large distortion.

I believe that the "slice-based" analysis described above is mandatory in clinical fMRI with a distorted brain. I am sorry to disagree with the authors. I would prefer to adhere rigidity to the basics. I also believe that many of other neuroimaging researchers would agree with my opinion.
We would like to thank the reviewer for this clarification and his efforts to clear the misunderstandings. We agree that looking at data on a very basic level helps to judge the validity of results before publishing, and therefore is important for scientific quality assurance. We performed the SPM standard analysis proposed by the reviewer and as the reviewer expected the results are compatible with the surface based analysis. On revision we included an exemplary video of the results of the right digit no. 3. We did not revise the manuscript, because although this additional analysis is important to validate our own results before publishing, it does not add new information for the readers of the manuscript. As previously explained, we believe that the surface-based approach is the best possible treatment of the data and allows the reader to judge the data in a single picture. Including additional analysis on the same data would be redundant. We hope that the reviewer is satisfied with our efforts. We would also be happy to continue the dialogue on imaging techniques independent of the review process of this manuscript. If the reviewer is interested he can contact our imaging specialist directly via email (michaela.ruttorf@medma.uni-heidelberg.de).