Author’s response to reviews

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

Authors:

Anna-Sophia Wahl (Anna-Sophia.Wahl@zi-mannheim.de)
Martin Löffler (Martin.Loeffler@zi-mannheim.de)
Lucrezia Hausner (Lucrezia.Hausner@zi-mannheim.de)
Michaela Ruttorf (Michaela.Ruttorf@medma.uni-heidelberg.de)
Frauke Nees (Frauke.Nees@zi-mannheim.de)
Lutz Froehlich (Lutz.Froehlich@zi-mannheim.de)

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Author’s response to reviews:

Dear Dr. Cadar,

We would like to thank you and the reviewers for the valuable input on our manuscript. We think that the reviewers’ comments significantly improved the quality of this article. However, we have a serious issue with one of the comments on the fMRI results raised by reviewer #1. This comment addresses the presentation of a section view of the results and analyzing the fMRI data using a volume-based approach. This volume-based approach has several disadvantages and therefore does not represent a state-of-the-art procedure to evaluate fMRI data on the cortical surface, as is the case in our study. Up to date, better methods exist. We had previously explained to the reviewer that we used the Freesurfer software package for data evaluation, and with this software package we can draw on the surface-based stream, implemented by Freesurfer, which is used by a large number of publications.

In 2018, an article was published in PNAS by Coalson, van Essen and Glasser called "The impact of traditional neuroimaging methods on the spatial localization of cortical areas”. In this article, the authors discuss the traditionally used volume-based smoothing, the registration of the data to volume-based standard spaces, and the report of results relative to volume-based
parcellations, and show that these traditional processing steps, especially volume-based smoothing and registration, which is exactly what reviewer #1 wants us to do, substantially degrade cortical area localization compared with surface-based approaches.

We suspect that reviewer #1 might be prone to general procedures that he used in his previous publications. However, while these may be adequate for non-surface regions of interest, they do not fit with the purposes of our study. We suspect that it will be hard to explain this to the reviewer.

The reviewer never mentioned precisely why he thinks our fMRI results do not hold true. He states that "any image processing includes an error". This is too general and holds true for every (fMRI) result ever published. The reviewer fails to mention how this relates to our analysis explicitly. Further, he mentions that an image technologist warned him once to be careful. This is a good advice, but, again, does not relate to our analysis. Although this is an interesting topic, it reflects a general dispute on advantages and disadvantages of fMRI, which is not the topic/purpose of our paper.

This does not mean that we are not aware of the limitations of fMRI procedures. To avoid errors during acquisition, analysis or interpretation of the data we have consulted with experts in the field of neuroimaging methods (Ruttorf) and applied neuroimaging (Nees) at each step from data acquisition to analysis. Together, we have published >40 studies on imaging techniques and studies applying these methods.

Furthermore, as explained in detail in our response to the editor’s comments three authors of the manuscript are trained psychiatrists. Our memory clinic at the Central Institute of Mental Health, Mannheim, Heidelberg University – which is a large and well-known psychiatric clinic and research institute for psychiatric diseases- is run by psychiatrists with special training also in neurology and neuroradiology. The patient received a full psychiatric, neurological and neuropsychological assessment accompanied with further diagnostics searching for bio-markers explaining his cognitive decline.

We would like to thank you and the reviewers for all the helpful remarks. We believe that we have addressed all points raised and hope that you will find our manuscript now suitable for publication in BMC Psychiatry.

We are looking forward to receiving your response.

Best wishes,

Anna-Sophia Wahl
Our detailed responses to the editor’s and reviewer’s comments are as follows:

Editor Comments:

I received the reviews of two specialist in the area.

However, as you can see from the comments below one has expressed major concerns.

I think the following issues should also be cleared:

1. Did a psychiatrist examine the patient? If yes, what was the result of the clinical interviewing?

We would like to confirm that three trained psychiatrists (A.S. Wahl, L.H. Hausner, L. Frölich) examined the patient. The Central Institute of Mental Health in Mannheim, University of Heidelberg is a large and well-known psychiatric clinic and research institution in Germany. Our memory clinic at which the patient presented is run by psychiatrists with special training also in neurology and neuroradiology. To emphasis that, we have now stated in line 118 of the manuscript that the clinical examination was performed by trained psychiatrists.

The results of the clinical interviewing are presented in line 260ff of the manuscript. “Psychiatric examination was unremarkable except for mild cognitive dysfunction. At the time of evaluation, the patient’s mood was reported stable and euthymic (5 out of 60 points in the Montgomery-Asberg Depression Rating Scale).”

2. What was the psycho-social history of the patient?

We have stated in the manuscript line 236 ff: “He described a normal developmental history with no developmental delay or psychosocial abnormalities. He remembered that he was teased by other children because of his large head and that even as a small child he would have required headgears in adult size. He denied any history of head trauma, toxic exposure, chronic headaches or another neurological or psychiatric illness. The patient had never used any psychiatric drug before. There was no history of learning disorders, hyperactivity or significant academic difficulties as well as no form of substance abuse. He completed high school and professional training as a bank accountant, where he continued to work for 27 years followed by several years of work in a communication company. The patient has stable and good social relationships. He is retired but still assisting in a pharmacy by delivering medicine to clients.”

3. What was the result of the MMSE? The author should be presented the all of the test. I think that psychiatric results were missed.
The result of the MMSE was 28 out of 30 points. This is depicted in Table 2 together with the results of the extensive neuropsychological assessment using the CERAD test battery.

4. Did the patient use any psychiatric drugs?

We have included a statement that the patient had never used any psychiatric drug before in line 239 of the manuscript.

5. Did the patient have history of substance abuse?

We have included a statement that there was no history of substance abuse in line 241 of the manuscript.

Reviewer reports:

Kayako Matsuo, Ph.D. (Reviewer 1): I appreciate and found the manuscript greatly improved. However, I would like authors to work more because of the following points.

(1)

My first point is, again, their fMRI analysis procedure.

First of all, I apologize my rigidity in advance.

I have read authors’ responses to my previous first point as well as to my request to show a section view of fMRI results.

I am afraid I think authors might have a basic misunderstanding of fMRI processing or image processing in general.

While taking note of the reviewers suggestions and concerns, we realize and are likewise afraid the reviewer might have an outdated conception of fMRI data processing. We already explained in great detail that we used the surface-based stream of FreeSurfer software package – a software package which the reviewer does not seem to know. This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data thus are capable of
detecting submillimeter differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003; Salat et al., 2004). Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006; Reuter et al., 2012).

In the surface-based stream, FreeSurfer automatically reconstructs surface mesh representations of the cortex from individual subjects’ T1 images. The cortical surface mesh is inflated into a sphere, and registered to a common spherical coordinate system that aligned the cortical folding patterns across subjects (Fischl et al., 1999a, 1999b). The recon-all procedure generates corresponding volumetric (aparc.a2009s+aseg.mgz) and surface (lh.aparc.a2009s.annot and rh.aparc.a2009s.annot) parcellations of 74 sulci and gyri for each subject (Fischl et al., 2004b; Desikan et al., 2006; Destrieux et al., 2010). FreeSurfer assigns these labels based on probabilistic information estimated from a manually labeled training set (Destrieux atlas), as well as geometric information derived from the cortical model of the subject.

Please see the cited publications which explain very precisely the mathematics of the algorithms used.

Literature:


I would like authors to understand that not only segmentation (I appreciate the effort to provide the parcellation data) but also any image processing includes an error.

The authors are well aware that every image processing includes an error. This is a general remark which holds true for every fMRI result ever published (including the results in the reviewer’s own publications). It is for us not clear here how this comment relates to our manuscript and our analysis explicitly.

If you process images with a large distortion such as a giant cyst, the error might also become large. The activation shown in Figure 3 might be falsely enlarged or compressed because of the errors during the image processing.

Not in general. The size of the error depends on the quality of the algorithm used, primarily. If the algorithm is stable and robust the processing of a cyst will not lead to larger errors than the processing of a healthy brain. To allow the reader to evaluate the localization of our target regions we have added an additional Figure (Supplementary Figure 3), which depicts the localization of all regions, including the pre- and postcentral gyrus in volume and surface space.

In this regard, our image technologist once warned me that "be careful, image tells a lie." To minimize such a "lie" or error as much as possible, we usually perform fMRI statistics using slices in the native space of the patient, i.e., to avoid errors caused by warping procedures.
Again, this is a general remark. However it is unclear to us, how this remark is related to our manuscript and our analysis. We would like to emphasis that this review process cannot be a discussion on general concepts of standard and commonly used image processing methods as this would be off topic.

My misunderstanding previously was that I thought authors also followed such a standard procedure of statistics using slices, and then rendered the results on the surface base. For this reason, I requested authors to show a section view of fMRI results. But now, I understand that they only conducted a surface base statistics, as they wrote "whole analysis was done using a surface-based approach" in their comment.

The volume-based approach has several disadvantages and therefore does not represent a state-of-the-art method to evaluate fMRI data on the cortical surface, as is the case in our study. Up to date, better methods exist. In 2018, an article was published in PNAS by Coalson, van Essen and Glasser called “The impact of traditional neuroimaging methods on the spatial localization of cortical areas”. In this article, the authors discuss the traditionally used volume-based smoothing, the registration of the data to volume-based standard spaces, and the report of results relative to volume-based parcellations, and show that these traditional processing steps, especially volume-based smoothing and registration, substantially degrade cortical area localization compared with surface-based approaches.

While the general procedures proposed by the reviewer may be adequate for non-surface regions of interest, they do not fit with the purposes of our study.

If you performed fMRI statistics in the surface base, it inevitably included the image processing errors caused by the surface rendering (as well as errors by segmentation and parcellation). How did authors check the false activity ("lie") presented by an erroneous enlargement or compression during the surface rendering?

We would like to refer here to our first comment and the publications cited on page 2 of this document. The cited publications very precisely explain the mathematics of the algorithms we used in our analysis and which are also referred to from line 203 ff in the section “MRI data processing and analysis”.

I am sorry to be harsh. However, as a scientist, I would, again, like authors to show a section view of activation *after* performing a standard fMRI statistics using just slices in the native space without any warping. I mean, authors would conduct statistics using slices in a voxel-by-voxel manner as in a standard method and show the activation maps of slices including the
central sulcus. The maps would be informative in directly understanding a correspondence between the cyst and activation. I believe many clinicians would be eager to see the results.

We are sorry to contradict here, but as described and explained above in greater detail, we followed an up-to-date analysis method and to us it does not make sense to evaluate our patient in a way which is outdated and less precise than newly developed methods (see above). All the authors work in hospitals and all our clinician colleagues perceive the presentation of the results as optimal and they have no problems in understanding the results the way we presented them. The purpose of the fMRI analysis was to evaluate if the location of the sensorimotor representation of the hand was preserved in this particular patient. As mentioned above, the article by Coalson et al 2018 showed that the volume-based method performs worse in localization than the surface-based analysis.

(2)

I would like authors to clearly explain the fMRI procedure. What movement did the patient perform during fMRI? Perhaps, flex and extend back? The authors wrote: "All 5 digits were stimulated before any digit was stimulated again." It sounds that the fingers were stimulated by an experimenter using something, but I suppose the patient voluntarily moved his fingers. Am I right? I would like authors to rewrite this part to avoid misleading.

The reviewer correctly assumes that voluntary movements were performed instead of passive stimulation. We added this information to the manuscript (see line 137 ff in the manuscript).

How long did an fMRI run last and how many blocks did a run had? Thirty movement blocks and how many rest blocks? How many runs did the patient perform? Perhaps, 2 for left and right hands each?

We added this information to the manuscript, it now reads (line 150ff of the manuscript):

“In total the task consisted of 30 movement blocks (5 digits, 6 repetitions) and 31 rest blocks (1 in the beginning, 1 in the end of the experiment, 29 between movement blocks), summing up to a total of 12:12 min, which resulted in recording 488 functional volumes. This task was performed twice, once with the digits of the left and once with the digits of the right hand.”

Also, in the imaging method section, how many volumes did they acquire during fMRI?

I hope the authors clarify these points.
We acquired 488 functional volumes and added this information to the manuscript (see above).

(3)
I think that a case presentation part would come just after Introduction in many papers. What do you think?

The case presentation comes directly after the introduction or “background”. For the composition of the paper we followed the guidelines of the journal how case reports should be presented.

(4)
I am sorry again, but I would like to learn the discussion after the modifications concerning the above points. In any way, I perceive the whole manuscript including Discussion has been greatly improved. I appreciate their efforts. I would like to review this paper in the near future again.

We thank the editor and reviewer for the helpful comments and hope that we have now addressed all comments and concerns.