Author’s response to reviews

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

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Author’s response to reviews:

Our detailed responses to the referees’ comments are as follows:

Reviewer #1:

Kayako Matsuo, Ph.D. (Reviewer 1): My main concern is their fMRI analysis procedure. The authors processed fMRI data just as the same way as for a normal subject. However, the patient had a large distortion because of the giant cyst. In such a case, the image processing is challenging, and in many cases, some part of the processing (including segmentation and warping to the standard brain template space) may be given up. They should correctly recognize this problem in the image processing technology. At least, they should show the results on original native brain sections of the patient with the cyst.

The reviewer raises an important point in this comment. We fully agree that the processing of a distorted brain is complicated and manual editing may be necessary. We manually edited the segmentation and state this more specifically in the manuscript: “The segmentation was edited using control point procedures in freesurfer (semi-automated editing), which were followed up by manual editing.” (line 209ff of the manuscript)

In order to clarify a possible misunderstanding, we would like to give a more detailed description of how Freesurfer works. There are different approaches concerning space:
Volume space: this would be the original T1 measurement.

Surface space: here the calculation is done in grey-matter only and presented at the surface which can be white-matter surface, pial surface or inflated space. In inflated space, the brain gets blown up to get rid of the folding. This causes slight distortions, gyri and sulci are smoothed.

Native space: This is again the original T1 measurement, but it is possible to perform calculations surface-based (pial surface/white matter surface) as well as volume-based in native space without distortions.

Standard space: normalised to a template (e.g. MNI152)

We calculated all results in native space, but we present the functional activation in inflated space because the activation can be seen more clearly there. Otherwise, the activation would not be visible completely because of the gyri and sulci. Additionally, we have shown the activated areas in native volume space without distortions - as a complement to the inflated space.

All analyses were performed in native surface space, they were never normalized to standard space. The areas were labeled in native space. We decided to show them in inflated space because all areas are visible there. This would not be the case in the pial surface presentation mode.

We could change the presentation mode of results from inflated brain to pial surface which is native space. But then some of the activations are not visible as well as the border of sensory and motor cortex.

However, the reviewer is right, that there is some form of normalization, as the parcellation result is dependent on a standard atlas. This atlas is mapped on the individual subject and is used as initial parcellation solution, but the algorithm also iterates on the native space solution by using relative information between the neighbouring regions (https://www.ncbi.nlm.nih.gov/pubmed/16530430 & https://www.ncbi.nlm.nih.gov/pubmed/11832223). To avoid the impression that we manually put the labels at the region where our activation occurred, we refrained from manually correcting the parcellation results. However, we tried to be as transparent as possible by showing our parcellation results in volume space (see suppl. Figure 1+2) and also on the inflated brain surface (see Figure 3).
My next concern is that the authors have not yet organized their manuscript sufficiently. They failed to explain the purpose of the paper and the methods to achieve the goal in a comprehensible way. They may want to ask a senior researcher to give them a concrete and specific advice on the manuscript, and then ask a copy-editing company to correct the English writing.

We thank the reviewer for his suggestions: We have fully edited and re-organized the background section (line 91-116) stating the purpose for our case report. We also reorganized the results section including the review of literature into the results section (line 340). Furthermore we have fully restructured and reorganized the discussion section (line 386ff, see also all track changes). This revised manuscript has been edited by three senior researchers and has been also reviewed by a native speaking colleague concentrating on English spelling and grammar. We thus hope to have addressed this issue to the satisfaction of the reviewer.

I think this paper has some interesting points. I would like to review this paper again after they improve the manuscript sufficiently.

Introduction

*I would like to request authors to clearly describe their purpose of this paper in Introduction. They currently only explained about the background. They should also indicate why they performed various measurements shown in the following part of the paper.

We thank for this hint. We have rewritten the second part of the introduction/background to clarify the purpose of the paper and why different diagnostic tools were required to dissect Alzheimer`s disease rather than the arachnoid cyst as underlying cause for cognitive decline. We have stated the following (line 103 ff): “We here present the case of a 66-year-old man with a large left-hemispheric cyst and mild cognitive impairment. Although at first glance the slight cognitive decline seemed to be related to the anatomic anomaly, further extensive evaluation using different imaging modalities and biomarkers was required to reveal Alzheimer’s disease rather than the arachnoid cyst as underlying cause for the cognitive deterioration. With this case report we not only aim at presenting the coincidental finding of a large cyst and a neurodegenerative disease where the neurodegenerative component might have been overlooked without adequate diagnostic tools. We also discuss that arachnoid cysts mask and may further augment neurodegenerative processes and suggest a modus operandi for patients with arachnoid cysts and suspected cognitive impairment.”
Methods

* Table 1. Was it necessary to show the details of Edinburgh Inventory? We usually only report the handedness score.

The patient, we present here, was left-handed but trained to write with his right hand at school. Furthermore the patient kept preferentially using his left hand for all fine skilled motor function and sports (line 271). We provided the details of the Edinburgh Inventory to picture the ambidexterity of the patient as we think these details help to better interpret the fMRI results where we looked for hand presentation in both hemispheres using a sensorimotor task. We also discussed this issue in line 438: “Interestingly, bilateral representation in particular of the left hand was revealed and even pronounced in the right hemisphere, which might be explained by the ambidexterity of the patient, being originally left-handed but trained right-handed.”

* Sensorimotor task: They may want to use "a block-design" instead of "a block task" in line 143.

We have replaced “a block task” in line 151 of the revised manuscript by “a block-design” as suggested.

* Sensorimotor task: Why did they vary the duration of the rest blocks? Maybe, to avoid the synchronization of time and fMRI signals?

For clarification we have included the following sentence in the manuscript (line 152): “Duration of the rest blocks was varied to avoid synchronization of stimulation and fMRI signals”.

* I cannot understand the following sentence (line 145): To avoid time x signal interactions blocks were presented in randomized order, but movements of all five digits were performed before repetition of a digit.

In a group based analysis we would have randomized the order of the digit stimulation completely. However, as there is only one subject, we wanted to avoid effects of timing of digit stimulation on signal (e.g. due to habituation effects, vigilance of the subject, etc.). Therefore all 5 fingers were stimulated before another repetition was presented. Within each repetition, however, the order of digits was randomized. For clarification we have adapted the manuscript in the following way (line 155): “All 5 digits were stimulated before any digit was stimulated again. This was done to avoid timing effects on the BOLD signal. The order of digits within a cycle of repetitions was randomized.”

* fMRI data processing and analysis: authors may want to modify this subheading because this part also contains data processing of the structure images and DTI.

As suggested we have adapted the heading in line 209 to “MRI data processing and analysis”.
I would like authors to demonstrate the validity of the segmentation procedure of patient's brain with a large distortion.

This is an excellent point provided by the reviewer. However, demonstrating the validity of any procedure for case studies is hard, as they are by definition unique. For reasoning of our specific procedure we can explain it as above: The images of the fMRI results are not shown in standard space. Instead, we carried out the analysis in native space and present them on the inflated brain surface. However, the reviewer is right, that there is some form of normalization, as the parcellation result is dependent on a standard atlas. This atlas is mapped on the individual subject and is used as initial parcellation solution, but the algorithm also iterates on the native space solution by using relative information between the neighbouring regions (https://www.ncbi.nlm.nih.gov/pubmed/16530430 & https://www.ncbi.nlm.nih.gov/pubmed/11832223). To avoid the impression that we manually put the labels at the region where our activation occurred, we refrained from manually correcting the parcellation results. However, we tried to be as transparent as possible by showing our parcellation results in volume space (see suppl. Figure 1+2) and also on the inflated brain surface (see Figure 3).

We chose Freesurfer as a software tool, because it has robust algorithms (has e.g. been used to analyze data of patient H.M., see https://www.ncbi.nlm.nih.gov/pubmed/17016801) and allows automated parcellation.

* The journal name of the reference #12 is "Magnetic Resonance in Medicine". Please remove "official journal of the Society of".

As suggested we have removed “official journal of the Society of” in line 633.

* Review of literature: according to the main text, authors excluded studies in children. But Table 3 indicates <10 for Age of patients for Horiguchi, 2000. Isn't this a discrepancy?

We thank for this hint: We have removed the citation Horiguchi, 2000 from Table 3 and also adapted the specifications for the review of literature in the methods section as well as the results from our review of literature (line 348 ff) according to the removal of the citation.

Results

* At the outset, "A 66-year-old man" would be just "The patient" because authors had already mentioned the age etc. in Methods. The authors may want to make this part concise by avoiding lengthy description. Also, I wonder if the authors should put this case description here in the "Results" section; maybe, another part under a specific subheading.
We have replaced “a 66-year-old man” by “the patient” (line 240). In the revised version of the manuscript we also tried to avoid iterations and shortened the manuscript (see track changes in the revised manuscript).

* Legend of Figure 1. FlAIR should be FLAIR.

We thank for this hint and have replaced FlAIR by FLAIR in the legend of Figure 1.

* Figure 3. I want to see fMRI results projected on sections rather than rendering maps to see the correspondences with the cyst.

We are not quite sure, what the reviewer aims at by asking for fMRI results projected on sections. We assume the reviewer would like to see the results in volume space. However, there would be no point in that as the whole analysis was done using a surface-based approach. The mapping of the areas is evident due to the labels attached which are shown in volume space as well as in inflated surface space (see Figures 3 and Supplementary Figure 1 and 2). If the reviewer and the editor feel that this is important, we can include additional figures in supplementary material showing the results on white-matter surface or pial surface. Unfortunately, in this view the labels would not be visible any more. We also would like to refer to our first comment to this reviewer concerning the fMRI analysis procedure we applied on page 1.

Discussion

* I am sorry I would like authors to improve the points above first. I also would like them to organize the discussion more efficiently to show their scientific claims logically.

We have fully revised the manuscript according to the reviewer’s suggestions. We have also re-organized the discussion section (see discussion with track changes from line 386) and included the results from the search of literature in the results section as suggested by reviewer #6.

Konrad Beyreuther, Dr rer nat Dr med h c. (Reviewer 2): As correctly stated by the authors, patients with intracranial arachnoid cysts, most often present from childhood, may live their entire life without any overt symptoms from the cyst. However, several studies have shown that temporal cysts may impair several, mostly basic aspects of cognition and that cognition normalizes after surgical cyst decompression as early as 4 hours after surgery. This leads to the following questions. First, whether the case presented by the authors would not show cognitive improvements after surgery.
Indeed several studies e.g. by Wester et al., 1995 and Gjerde et al., 2013 have shown a cognitive improvement after surgery. However the lesion learned from our case study is that at first glance the arachnoid cyst might be the most obvious for being causally involved in cognitive decline—but our extensive work-up shows rather the neurodegenerative disease as underlying cause for the cognitive impairment. Our patient was seen several times by the same neurosurgeons for a possible surgical intervention. However further diagnostics using different imaging modalities and biomarkers revealed that pure clinical examination and structural MRI might be insufficient to triage patients either to neurosurgery or watchful waiting. Due to a very stable MRI report for the cyst seize over several years, only very mild cognitive decline without other neurological symptoms and results highly suggestive for Alzheimer’s disease the neurosurgeons decided against any neurosurgical intervention and recommended regular follow-ups in our memory clinic. We have addressed this point in the manuscript stating the following in the results section (line 262): “On repeated neurosurgical evaluation it was decided for watchful waiting and against surgical intervention because of the absence of focal neurological signs and size progression.” And in the discussion section: “Furthermore, the application of different imaging modalities and biomarkers helped the neurosurgeons to triage our patient: the patient was followed-up by the neurosurgeons several times for a surgical intervention as clinically a mild cognitive impairment became apparent. However, when Alzheimer’s disease was revealed as the leading underlying cause of cognitive decline rather than tissue damage from the arachnoid cyst, the neurosurgeons decided against a cystectomy. As there was no cyst size progression and no further neurological symptoms a benefit from the surgery was highly questionable for the patient. “(line 414 ff)

Second, is there a relationship between AD pathology and the cyst? The rather young age of the patient suggests that he carries one ApoEe4 allele or his early onset is possibly related to the cyst (reduced perfusion and metabolism in the surrounding cortical regions). Reduced clearance of Aβ is one hallmark of aging brains, and may lead to increased Aβ levels, thus increasing the risk of developing AD pathology (Randy Bateman et al.).

We thank this reviewer for this very interesting comment and aspect. We have discussed the relationship between AD and the arachnoid cyst in our discussion (line 452 ff): “Nonetheless a relationship between the onset of Alzheimer’s pathology and the arachnoid cyst might be plausible: As previously postulated by Silverberg et al., 2003(47) we speculate that the existence of the arachnoid cyst may modify intracranial pressure ratios, leading to reduced perfusion and metabolism in the surrounding cortical regions. Furthermore, the cyst might perturb CSF circulatory pathology which might result – along with genetic factors such as apolipoprotein E4 Aβ -in the accumulation of amyloid-β peptide, microtubular associated protein τ (MAP τ) and other toxins. An increase in the steady state concentration of Aβ influences Aβ aggregation which is causally und pathognomonic in Alzheimer’s disease (48, 49). In particular soluble Aβ is potentially neurotoxic affecting normal neuronal function and even causing cell death (50, 51).
Thus, longitudinal studies in patients with huge arachnoid cysts might become important to detect symptoms of cognitive decline early and thereby open a window of opportunity for early therapeutic intervention to prevent or slow down further cognitive deterioration (52).

We have also looked if the patient carries an apolipoprotein E4 allele. However he has an ε3/3 wildtype allele. Thus the APoE-Genotype did not suggest an advanced manifestation of Alzheimer dementia even more supporting our primary hypothesis that the cyst might have impaired CSF flow and caused reduced amyloid clearance inducing Alzheimer’s pathology.

The presentation of the careful and detailed neurological and neuropsychological examination as well as MRI and PET of the brain outlined in this paper would be improved by addressing the points mentioned above.

Regarding Table 3, with exception of one reference (Lebowitz, 2006), the remaining 14 references of these studies are not included under References. THIS NEEDS TO BE DONE.

We thank for this hint and how now included all missing references from Table 3 in the revised manuscript.

Mohammadrasoul khalkhali, M.D. (Reviewer 4): This is an interesting but very long case report that might confuse the readers and there is many unnecessary information in the manuscript that could be summarised or deleted. Although I believe that two different pathologies are involved and this is only a co-morbid clinical condition but the occurrence of arachnoid cyst in the patient with Alzheimer disease is a rare condition that can be reported.

We have tried to shorten the manuscript in its revised version and make it more concise. However, as other reviewers asked for more details in other parts a significant word reduction was not possible. Furthermore, we found it critical to discuss, why we used different diagnostics to dissect effects of the arachnoid cyst versus an underlying neurodegenerative disease on cognitive impairment. In addition, we aimed at highlighting in this case report that too often cognitive decline is just associated to the most obvious – such as an arachnoid cyst in our case. However our patient would not have benefited from a neurosurgical intervention: An extensive work-up suggested Alzheimer’s disease as the underlying cause for the cognitive decline. If the arachnoid cyst itself contributes or implies an increased risk for cognitive impairment remains a matter of debate.

Jacqueline Mogle (Reviewer 6): Overall this was a well-written manuscript that adds to an important literature on how other abnormalities such as arachnoid cysts may contribute to cognitive impairment. Two alterations would make this a stronger manuscript:
1. Please add a purpose statement to the introduction. What is the current case study intended to show? How does the review of existing case literature fit in with this purpose? It becomes clear as you read the paper but a strong purpose statement at the end of the introduction would guide the reader as they move on to the technical aspects of the paper.

We thank the reviewer for this advice. We have thus rewritten the last paragraph of the introduction including a purpose statement (line 103ff): “We here present the case of a 66-year-old man with a large left-hemispheric cyst and mild cognitive impairment. Although at first glance the slight cognitive decline seemed to be related to the anatomic anomaly, further extensive evaluation using different imaging modalities and biomarkers was required to reveal Alzheimer’s disease rather than the arachnoid cyst as underlying cause for the cognitive deterioration. With this case report we not only aim at presenting the coincidental finding of a large cyst and a neurodegenerative disease where the neurodegenerative component might have been overlooked without adequate diagnostic tools. We also discuss that arachnoid cysts mask and may further augment neurodegenerative processes and suggest a modus operandi for patients with arachnoid cysts and suspected cognitive impairment.”

2. I would advise moving the review of existing case literature into the results section. Where it is in the discussion, this valuable work gets lost in the paper. It would be important to have the case study first, and then present the review of the case literature next, and finally discuss the overlap of the two in the discussion.

As suggested we have included the review of literature in the results section (line 348 ff). We have also fully restructured and reorganized the discussion section to clarify our conclusions (line 386 ff). In the discussion section our emphasis was to discuss the different aspects of our case report with the two coincident pathologies (cyst and Alzheimer’s) and their possible interactions with each other.

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