We would like to thank you and the reviewer for the valuable input on our manuscript.

To satisfy the reviewer, we had performed the SPM standard analysis proposed by the reviewer and as the reviewer expected the results are compatible with our surface based analysis. On revision we included an exemplary video of the results of the right digit no. 3 (Video “digit3_right_fast”), which was not meant to be included in the publication. We did not revise the manuscript, because this additional analysis does not add new information for the readers of the manuscript. As you agreed and we had previously explained we believe that the surface-based approach is the best possible treatment of the data and volume-based analysis suffer from a number of drawbacks. Adding an analysis that is less suitable for the data than the one performed in the main manuscript would make the article less straight-forward to read and decrease the methodological quality of the paper. Including additional analysis on the same data would be redundant and confusing, leaving the impression, that we tried several methods and chose the one we liked most in terms of positive results. Furthermore, the paper is a case report about a patient with a large congenital cyst and fMRI was important for further clinical diagnosis and
interpretation. However, this paper is not about comparing different methods for analyzing fMRI data.

We believe that we have addressed all points 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 reviewer’s comments are as follows:

Kayako Matsuo, Ph.D. (Reviewer 1): I believe authors have considerably improved their manuscript since the first draft. Specifically, I appreciate the movie showing fMRI results on a slice by slice basis in the native space. I suggest authors to include this movie as a proper supplementary material to make rigorous researchers inspect the analysis. I believe that authors would agree with me, as they also encourage a rigorous use of neuroimaging modalities:

Our case report suggests the diagnostic value of rigorous neuroimaging modalities including DTI, fMRI and amyloid-PET imaging as well as ... (line 473-)

Indeed, and as also mentioned by the reviewer, in our case report we suggest “…the diagnostic value of rigorous neuroimaging modalities including DTI, fMRI and amyloid-PET imaging...” With this, we mean the use of different methodologies that add new information in terms of mechanisms and processes, as different imaging methods add different information to the diagnostic picture, e.g. the functional and structural organization of the brain or hints for amyloid burden of brain tissue. We do not mean multiple presentations or multiple testings of the very same construct (e.g.fMRI) – here we still want to follow the best possible way to analyze the data.

As also the Editor mentioned “…the surface-based approach is the best possible treatment of the data and allows the reader to judge the data in a single picture”. This is in line with our previous specifications that traditional processing steps, especially volume-based smoothing and registration, substantially degrade cortical area localization compared with surface-based approaches and backed up these arguments with citations (see previous response letters). In
addition, strong neural activations for hand motor tasks are distributed near the adjacent regions (omega knobs) of M1 and S1, leading to potential partial volume artefacts and erroneous signal intensity in volume-based approaches.

We have uploaded the video for the reviewers’ use only, and we are happy that he appreciates this action.

However, we refrain from adding the video to the supplement to use multiple methods based on a mechanistic and not presentation-related approach. This is further related to ethical restrictions to protect participant confidentiality, which prevent us from making such double-featured anonymised study data publicly available, and also refers to any advanced digital materials like videos. Readers seeking detailed access to the study data and materials should contact the corresponding author based on a formal collaboration agreement. This formal collaboration agreement indicates that data will be shared with other researchers who agree to work with the authors, and for the sole purpose of verifying the claims in the paper. The data and materials will be released to requestors after approval of this formal collaboration agreement by the local Ethics Committee of the Medical Faculty Mannheim.

I would also like authors to address the following points.

Major points.

(1) Authors maintain that the patient's memory function in the brain would not be affected by the cyst because the fMRI showed a seemingly normal spatial registration for the motor function in the injured side as well as in the intact side. For example, they wrote:

The results of the functional imaging made tissue damage and thus a consecutive cognitive decline due to the giant arachnoid cyst less probably. (lines 327-328)

The logic sounds to be a stretch by two issues. First, the motor function could be normal when the memory function got injured. Second, a normal spatial registration of fMRI could not ensure an absence of a tissue damage.

I would suggest that authors should clearly make a concession regarding these issues.

As written in our manuscript (line 308): The aim of the fMRI study was to gain knowledge if and how far the arachnoid cyst induced impairment of functional integrity in the left hemisphere. Structural MRI had already revealed a marked mass effect there. However, diffusion tensor imaging (DTI, Figure 2) provided a first hint of relative well-preserved structures of fiber bundles in the left hemisphere compared to the right one. As several studies have shown the reliability of motor maps in fMRI comparing individuals with different age and over time (McGregor et al., 2012; Weiss et al., 2013; Kolasinski et al. 2016), we decided for a motor task
in our patient. We agree that there is a broad variety of cognitive tasks for fMRI available. However, which of these tasks would be appropriate in our case would be another matter of debate. Furthermore, our case report suggests that the minimal cognitive dysfunction is caused by a developing Alzheimer’s disease and not by the cyst. Thus, it is valuable to examine the functional integrity in a domain (e.g. the sensorimotor domain) apart from the cognitive one.

As written in line 388 ff of the manuscript: “The often expansive lesions due to arachnoid cysts may cause a reorganization of cortical functions. This reorganization can vary to a large extent between patients, which is reflected in changes in a variety of cognitive functions. According to a review article (38), these functions encompass verbal perception and memory, complex verbal tasks, visuospatial functions and visual attention and dichotic perception and memory (7) of which not all have to be impaired in every patient.”

Furthermore, the variability of cortical response patterns to cognitive tasks is expected to be even larger than with a distinct motor task. We thus write in the discussion (line 419): “We chose a sensorimotor task for the functional magnetic resonance imaging to map in particular the left hemisphere, as the giant arachnoid cyst had a strong mass effect on this brain region. The goal of the fMRI was to detect any functional map shift and loss of functional integrity (together with structural alterations found in the DTI (Figure 2)), which could also impact cognitive functions. Since we did not aim at detecting the neuronal correlate of the cognitive decline but at understanding the structural and functional integrity despite the giant cyst, a cognitive task with fMRI would have been less helpful.”

We have also included in the discussion (line 425): “Although we cannot rule out that memory function is still impaired despite of the intact motor function, normal sensorimotor integration may be also correlative for cognitive performance as discussed by others (16, 18) and vice versa: Abnormal sensorimotor integration correlates with the cognitive profile in neurological diseases (41).”

We agree that a normal spatial registration of fMRI could not ensure an absence of a tissue damage. We have adapted our manuscript and removed “tissue damage” and added “loss/impairment of functional integrity” instead (line 308 ff, line 419 ff).

(2) In relation with the point #1 above, authors wrote:

Since we did not aim at detecting the neuronal correlate of the cognitive decline but at understanding the structural and functional integrity despite the giant cyst, a cognitive task with fMRI would not have been helpful. (lines 427-429)

The logic sounds flawed because many fMRI studies have revealed double dissociation of functions; a memory task should have been helpful for this study. I would suspect that they just
wanted to make excuses for their lack of cognitive tasks. There cannot be a perfect study in the world. Authors may want to rewrite this part in a modest and straightforward manner.

Please see our detailed response for (1). We have attenuated the statement in the following way: “Since we did not aim at detecting the neuronal correlate of the cognitive decline but at understanding the structural and functional integrity despite the giant cyst, a cognitive task with fMRI would have been less helpful.”

(3) Still in relation with the point #1 above, authors wrote:

fMRI revealed no map shift of the motor area for finger movements from the left to the right hemisphere (Figure 3) (lines 315-316)

This expression is awkward because the maps were distorted in reality because of the cyst. Authors may want to rewrite this sentence as explaining that the spatial registration by Freesurfer successfully mapped the functional areas quite similar to normal controls'. (Strictly speaking, authors should have statistically compared the patient's map with normal controls').

As suggested we rewrote the sentence in the following way (line 315 ff): “Preserved motor representation was shown by co-localization of the motor representation of the fingers and parcellation results for primary motor and sensory cortex in the left and right hemisphere (Figure 3), including an intact representation of the right fingers in tissue which was roughly localized at the position of the primary motor and sensory cortex (Supplementary Figure 1, 3). Although the cyst had a huge mass effect squeezing and smashing the left hemisphere towards the right one mapping of the functional areas was localized similarly in both hemispheres.”

(4) I would like authors to rewrite the following sentences in Methods because they are unclear:

Movements of all 5 digits were performed before the movement of any digit was repeated. This was done to avoid timing effects on the BOLD signal. The order of digits within one of these repetitions was randomized. (lines 146 to 148)

Authors may want to put the sentence with D2, D2, D2… (lines 148-150) first.

We rewrote the paragraph (line 138 ff) in the following way: “The patient performed visually cued voluntary movements of individual digits in the scanner. The movement performed was a button press (=flex and extend back) on an optical response keypad (LUMItouch) with five response buttons, with the respective digit: digit 1 (D1: thumb), digit 2 (D2: index finger), digit 3 (D3: middle finger), digit 4 (D4: ring finger), and digit 5 (D5: little finger). Movements were performed after a visual signal. For each digit the patient received visual cues in the form of a hand drawing with the respective finger being colored. We used a block-design with movement
blocks of 12s and rest blocks of 10, 11, 12, 13 or 14s (randomized) duration. The duration of the rest blocks was varied to avoid synchronization of stimulation and fMRI signals. During movement blocks, a visual cue instructed the patient to perform movements of a specific digit at 1 Hz (e.g., D2, D2, D2, D2, . . .). Each movement block was separated by a rest block. Six movement blocks per digit were acquired (30 movement blocks in total). One block of all 5 digits was performed before any block was repeated. This was done to avoid timing effects on the BOLD signal. The order of blocks within one of these repetitions was randomized. 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 minutes and 12 seconds, which equals 488 acquired EPI volumes (see below). This task was performed twice, once with the digits of the left and once with the digits of the right hand.”

Minor points.

(5) Line 139, "eypad" might be "keypad".

(6) Line 163, "coronar" might be "coronal".

We thank the reviewer for the hints. Both words were corrected.

References:

