Do quiescent arachnoid cysts alter CNS functional organization?

A fMRI and morphometric study

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Abstract—*Objective:* To investigate whether congenital and clinically quiescent arachnoid cysts (AC) in the left temporal fossa alter the functional organization of adjacent cortices. *Methods:* fMRI mapping was applied in five right-handed asymptomatic patients to determine the functional organization of language. Moreover, morphometry was performed in each patient to gain the size of cortical surface areas and cortical thickness values in the neighboring brain adjacent to the AC and explicitly in the left opercular region. *Results:* Four patients showed a clear left hemisphere language dominance regardless of the cyst size; a mixed laterality of language organization was found in the remaining patient. An interesting dissociation of morphometric data was assessed when comparing strongly language-related cortices in the inferior frontal gyrus with the entire neighboring cortices. Morphometry in the neighboring brain regions of the AC showed 1) overall reduced cortical surface areas and 2) a decrease in cortical thickness compared to the homologous right side. However, the surface area of the fronto-opercular region in the left inferior frontal gyrus—i.e., the pars triangularis and the pars opercularis—was larger on the left as compared to the right side. Both structures have earlier been identified to represent the morphologic substrate of language dominance in the left hemisphere. *Conclusion:* Arachnoid cysts do not disturb the normal asymmetry of hemisphere language organization despite delicate locations adjacent to the left inferior frontal gyrus.

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Arachnoid cysts (AC) are primarily congenital or develop secondary to trauma or infection.[1] In spite of delicate locations such as the left temporal fossa, many cysts remain asymptomatic. These silent cysts are regarded as incidental findings with no obvious functional significance. In contrast, others expand and cause symptoms by compressing adjacent brain or expanding the overlying skull.[2] So far, very little is known about the influence of AC on the functional organization in adjacent cortices. As these represent congenital maldevelopments, the associated anomalies are acquired early in contrast to those developing in later stages. Task-related functional neuroimaging has so far been almost exclusively performed in adults with newly acquired brain lesions. However, there is evidence that the potential for interhemispheric reorganization may be stronger in cases of early brain lesions. A considerable right-hemisphere shift of language-related activations in children and adolescents with left-sided brain lesions was described in a previous PET study.[3]

The relatively mild clinical effects of AC may be due to several causes. The first hypothesis is that AC do not invade the underlying tissue, which can therefore retain normal function. The second hypothesis is that congenital cysts cause reorganizational changes of cognitive functions toward other areas of the brain, mainly adjacent cortices or homologous contralateral cortices. It has been demonstrated that early lesions are less likely to cause permanent language impairment.[4]

We investigated whether and how AC influence the functional organization of the brain in neighboring cortices. Therefore, we investigated the functional distribution patterns of language processing in five patients with AC in the temporal fossa.

Materials and methods. Five patients with AC (three men, two women) aged from 19 to 51 years (mean ± SD 28.4 ± 12.9; median 25) were included in the study. All subjects gave their informed consent to participate in the investigation, which was approved by the local Ethics committee.

Each subject performed the Edinburgh Handedness Inventory (EHI) to assess the degree of handedness. The presence of aphasia was assessed by means of the Aachen Aphasia Test (AAT).[5]

Activation paradigms. A boxcar design was used; the length of each block was 40 seconds with alternation of target and baseline task. During the fMRI experiment, common German words composed of two syllables (length four to seven letters) were visually presented every 2 seconds in a word classification task with a stimulus duration time of 600 msec.[6] The words were half nouns or verbs and half abstract or concrete. The presentation was arranged

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in eight blocks per 20 words each with a pseudorandom presentation order and an overall length of 11 minutes. The patient was asked to make a semantic decision on each stimulus via button press: semantic (abstract or concrete) encoding was compared with a perceptual decision task (presentation of words with or without space between letters). Behavioral data (reaction times and number of errors) were recorded online during the fMRI experiment. A similar semantic encoding task has earlier been established to map inferior frontal language lateralization.[7,8]

fMRI recording. Functional MRI recording was performed on a 3-T whole body system (Medspec 300/100, Bruker, Ettlingen, Germany) using echoplanar imaging (eight axial slices: three below and five above the anterior commissure-posterior commissure line, 7-mm slice thickness, echo time 30 msec, repetition time 2 seconds, matrix 128 × 64, field of view 25 cm).

Image analysis. Data processing was performed using the software package LIPSIA.[9] The anatomic slices were coregistered with the individual three-dimensional brain scans of the patients. Functional images were created by generating statistical z-maps with z-values >3 on a single pixel level. A pixel was defined to be a local maximum if its z-value exceeded 3.09 and if it was largest within a 5-mm radius. Areas found to be significantly activated were subjected to a further post hoc analysis.

The regions of interest were characterized in size, volume, and mean activation strength. Lateralization indices (LI) were calculated by the number of activated pixels (P) reaching z-values >3 in predefined regions of functional activation—Broca area (BI) and superior temporal gyrus (TI)—as well as for the activations within the whole hemisphere (HI) [LI = $n_{\text{pixel left (Pl)}} - n_{\text{pixel right (Pr)}}/n_{\text{Pl}} + n_{\text{Pr}}$ (range ± 1)]. Thus, an individual distribution of hemispheric and interhemispheric language lateralization was assessed in each patient.

Cortical segmentation. Standard high-resolution three-dimensional brain MRI data sets of each patient were the basis of the segmentation analysis (128 sagittal slices, 256 × 256 matrix, field of view 192 × 192 mm, 1.5-mm slice thickness). Unless explicitly noted, all subsequent analysis steps were automated. Results were checked by an expert in imaging analysis. Slices were interpolated to an isotropic resolution of 1 mm using a fourth-order b-spline method[10] and aligned with the stereotactic coordinate system. The surface of the neocortex and the gray–white matter interface (GWMI) were extracted as triangular meshes and optimized by a deformable model approach.[11] The neocortical thickness was computed at each vertex of GWMI mesh as the shortest distance between both meshes. A brick-shaped region of interest (ROI) minimally enclosing the AC was defined in the left hemisphere of each patient. For comparison, another ROI of the same extent was positioned at the homologous position in the right hemisphere. The average cortical thickness, the cortical surface, and the gray and white matter volume were computed within both ROI.

In addition to this automated analysis, selected regions in the inferior frontal gyrus were manually outlined, following an accepted anatomic definition[12]: the right and left pars opercularis and pars triangularis of the inferior frontal gyrus. The manually drawn set of contours for each ROI was automatically connected to form a closed polyhedral compartment[13,14] and converted into voxel space to form a ROI mask. Each of the four ROI masks was then used to determine the enclosed cortical volume based on the segmentation produced as above. Cyst volumes were determined by summing the manually outlined areas on each slice and multiplying the result by the slice thickness.

Results. *Clinical characterization of patients.* All patients had been diagnosed with an AC of different extent in the left temporal fossa by anatomic MRI. The abnormality was discovered incidentally in all cases. At the time of the fMRI scan, neurologic examination was fully intact in all patients. None of the patients had aphasia as assessed by the AAT Token Test. EHI evaluation showed strong right-handedness in all patients with a mean degree of 91.3% (SD ± 4.31).

fMRI. Behavioral data. Analysis of performance during the word classification tasks showed mean reaction times of 722 ± 72 msec; the mean error rate was 19 ± 7%. Performance did not significantly differ from the earlier acquired normal control data (latency 713 ± 85; error rate 21%).[6]

Structural anatomy and functional activation patterns. *Patient 1.* Interesting activation patterns and an interhemispheric distribution of laterality were evident in Patient 1. The cyst had a volume of 24 cm^3. It originated in the temporal fossa and extended to the sylvian fissure, thereby mainly distorting the temporal pole and the fronto-opercular region. A differential interhemispheric recruitment of language-associated cortices was evident during the fMRI study: although the word classification task clearly recruited bilateral activation in the inferior frontal gyrus, temporal and superior frontal activation clearly showed a left hemisphere dominance. The distorted opercular region of the left hemisphere, and mainly of the pars triangularis, only showed little activation during the language task.

Patient 2. In this patient a small cyst (volume 8 cm^3) extended within the left sylvian fissure, causing no obvious distortion of the fronto-opercular region. Functional activation during word classification showed a clear dominance of the left hemisphere inferior frontal gyrus and superior temporal gyrus.

Patient 3. The cyst (volume 36 cm^3) was located in the temporal fossa, leaving the fronto-opercular region and the insular cortex structurally intact. Word classification was associated with dominant left hemisphere activation, although homologous right hemisphere cortices were recruited to a lesser extent.

Patient 4. A severe distortion of the fronto-opercular region, the insula, and the temporal pole was evident in Patient 4. The cyst had a volume of 90 cm^3 and again originated from the left temporal fossa. In spite of considerable structural distortions in the fronto-opercular region, a clear left hemisphere dominance was found in the fMRI study.

Patient 5. The AC (volume 85 cm^3) was mainly distorting the left temporal pole region, whereas the anatomic structures surrounding the sylvian fissure appeared morphologically unaffected. The functional activation patterns during word classification showed a clear preponderance for the left inferior frontal and superior temporal cortices.

Overall patterns. Taken together, language-related activation was mainly found in the left inferior frontal gyrus

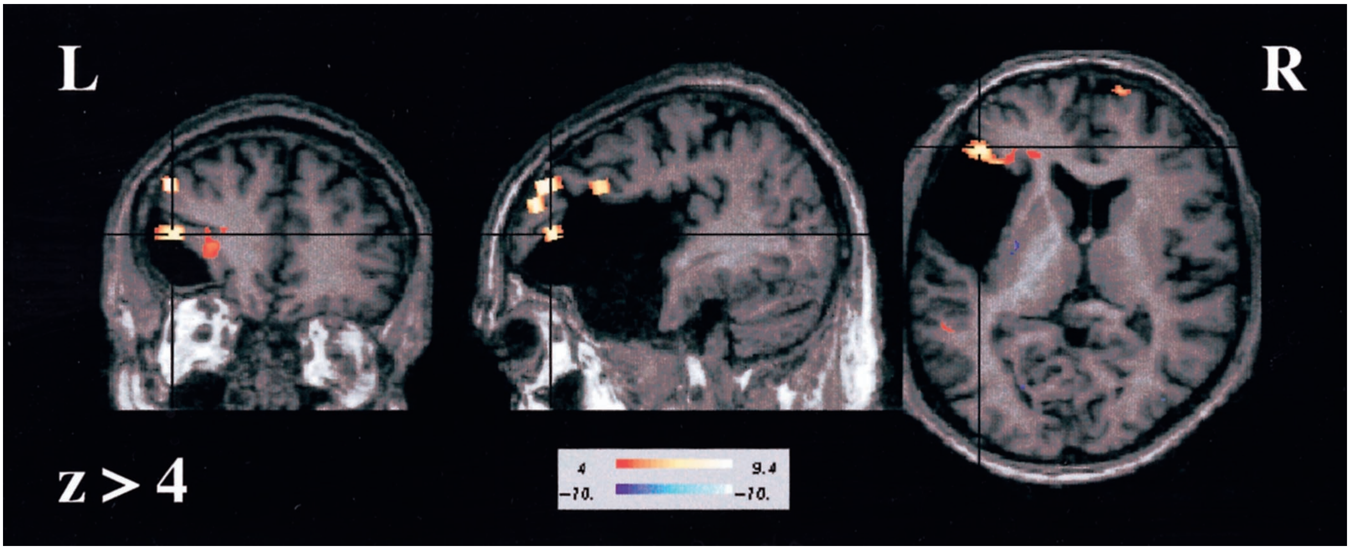

Figure 1. The individual z-map of a representative patient with a temporal arachnoid cyst is overlaid onto the morphologic three-dimensional dataset. The z-map was thresholded at z > 4, which corresponds to an alpha level of <0.001.

in four out of five patients, regardless of the volume of the AC and the associated distortion of anatomic structures. A representative z-map of one patient overlaid on the corresponding anatomic image is shown in figure 1. Independent of the degree of inferior frontal distortion through the AC, functional activation was mainly located in the pars triangularis (Brodmann area [BA] 44 and 45) and extended to the neighboring precentral gyrus (BA 6). Additionally, left dominant superior temporal activation was found in three of these four patients. A bilateral inferior frontal gyrus activation was found in the remaining patient, whereas superior frontal and superior temporal activation clearly dominated in the left hemisphere.

In comparison, the prototypical functional activation patterns in the control group of healthy right-handers during this task consisted of an extended activation of the left inferior frontal gyrus (pars triangularis/BA 44 and 45) and the neighboring precentral gyrus (BA 6). The left superior temporal gyrus was as well activated in the majority of controls.[6]

Calculation of the laterality indices based on significant activations (z-value >3) reflects the distribution of laterality within the language network (table): apart from Patient 1, all patients showed corresponding positive indices for superior temporal and inferior frontal language-associated cortices, indicating left hemisphere dominance within the language network. No significant correlation was found when relating the fMRI-gained LI to the EHI values. The size of the cyst did not significantly influence the distributional patterns of fMRI activation.

Morphometrics of AC. *Morphometric changes associated with AC.* In a first approach, the entire brain region neighboring the cysts was analyzed. The main finding was that the AC were associated with a reduction up to 33% in left hemisphere gray and white matter volumes of adjacent cortices in all patients, as compared to the right hemi-

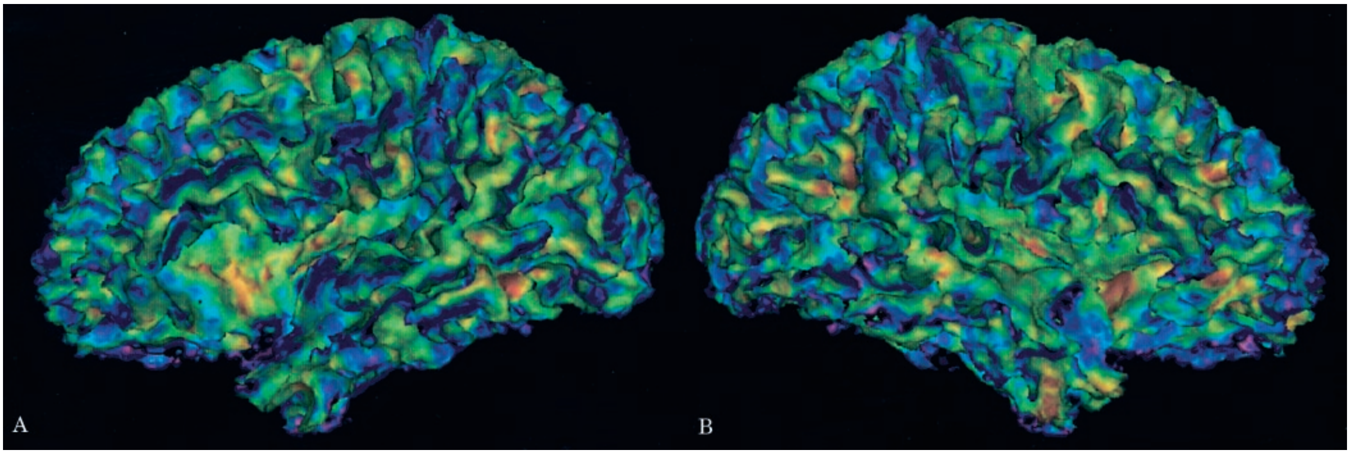

Figure 2. Left (left hemisphere) and right (right hemisphere) views of the gray–white matter interface of the sample Patient 1, which had shown a partially reversed language dominance in the functional MR study. The cortical thickness is color-coded on the surface (magenta, 1 mm; red, 5 mm). The region occupied by the cyst is easily visible adjacent to the inferior frontal gyrus on the left side. Note the difference in the cortical thickness in comparison with the right side.

***Table** Demographic data, morphometric results, and laterality indices gained from Edinburgh Handedness Inventory (EHI) and fMRI*

					Cortical thickness, mm		Surface area PTR, mm^2		Surface area POP, mm^2					
Patient	Sex	Age, y	EHI ± 100%	Cyst volume, cm^3	Left	Right	Left	Right	Left	Right	fMRI-BI ± 1	fMRI-SFI ± 1	fMRI-TI ± 1	fMRI-HI ± 1
1	F	25	92.5	24	2.64*	2.74	1,419	888	3,567	1,892	−0.25	+0.20	+0.25	+0.15
2	F	19	95.0	8	1.89	1.83	1,847	776	3,122	2,548	+0.94	+1.00	—	+0.95
3	F	21	85.7	36	1.87*	2.17	1,912	1,624	2,438	2,425	+0.30	+0.46	+0.40	+0.35
4	M	51	85.2	90	1.72*	1.93	1,731	1,030	2,931	1,980	+1.00	+1.00	+0.87	+0.99
5	M	26	87.9	85	2.36	2.37	2,144	762	1,526	1,074	+0.94	+1.00	+0.58	+0.76

The cortical thickness is displayed for the brain compartments enclosing the arachnoid cyst (in the left hemisphere) and the symmetric region of interest (ROI) in the right hemisphere. The cortical surface areas of the left and right pars opercularis (POP) and pars triangularis (PTR) are shown comparatively for the selected regions in both hemispheres.

* Significant interhemispheric difference ($p < 0.001$).

BI = Broca index; SFI = superior frontal index; TI = temporal index; HI = hemisphere index.

sphere homologous brain region. The same was true for the cortical surface area. The reduction of gray matter volumes was directly related to the size of the cyst ($r = 0.78$, $p < 0.05$). Moreover, the mean cortical thickness in the brain compartments neighboring the AC was significantly reduced as compared to the corresponding contralateral area. In one patient, only the left hemisphere cortex showed a larger thickness as compared to the right side. Notably, the cyst in this patient had the smallest size, with a volume of 8 cm^3. A prototypical example of the morphometric analysis of cortical thickness is displayed in figure 2.

More specifically, morphometry addressed in a second step the changes in strongly language-related cortices: the pars triangularis and pars opercularis of both hemispheres. Separate analysis for these ROI revealed one important finding. The cortical surface areas of the left pars triangularis and pars opercularis were found to be larger as compared to the right side in all patients, in spite of the presence of the cyst. The table summarizes the most important morphometric results of each individual patient.

Relation between morphometric parameter and blood oxygenation level-dependent signal changes. The comparison of morphologic characteristics and fMRI data did not reveal a significant relation between the fMRI-gained indices of laterality and morphometric values. In particular, the reduction of the cortical thickness did not interfere with the functional activation of the corresponding cortex during word classification. Even when the cortical thickness was significantly reduced through the AC in the left fronto-opercular region (Patient 4), dominant left hemisphere inferior frontal gyrus activation was assessed during the fMRI session. However, the asymmetry of surface areas in the pars triangularis and pars opercularis regions reflected the interhemispheric distribution of language dominance.

Discussion. This study examined the functional organization of language in five right-handed, asymptomatic patients with congenital AC using fMRI. The main issue was to determine whether and how functional language organization is influenced by an early acquired maldevelopment in the vicinity of eloquent cortices.

The main finding of this study was a clear left hemisphere dominance of language in four out of five patients, regardless of the size of the cyst, suggesting that the expected normal asymmetry was preserved. The language laterality profiles and functional activation patterns did not differ from a control group of healthy right-handed subjects addressed in an earlier study.[15] However, a displacement of inferior frontal activation was evident in the left inferior frontal gyrus in all patients. This seemed to be associated with a mere physical displacement of anatomic structures rather than reorganization within the left hemisphere. In one patient, the fMRI study assessed a mixed laterality; i.e., the fMRI-gained BI indicated a weak right hemisphere dominance, while all other laterality indices suggested a weak left hemisphere dominance.

Our study combined functional and morphometric data in patients with congenital and asymptomatic AC. The following main characteristics were found in brain areas neighboring the cysts: the global thickness of the cortex adjacent to the AC was significantly thinner and the corresponding global cortical surface area was reduced as compared to the homologous contralateral side in the majority of patients. The reduction in surface area even correlated to the overall volume of the cyst. Hence, in contrast to earlier pathologic studies claiming that overall brain volumes in AC remain normal,[16] we could demonstrate that a reduction of gray and white matter volumes of adjacent brain regions is accompanying AC. Moreover, the maturation of adjacent cortices may be influenced, resulting in a reduced cortical thickness of neighboring cortices.

In a more detailed analysis, the exclusive functional role of the left-sided fronto-opercular cortices was addressed and explicitly characterized by means of morphometry with interesting results: unexpectedly and in spite of the presence of a malformation, the surface areas of the pars triangularis and pars opercularis were larger in the left hemisphere as compared to the homologous right side. The frontoopercular region includes the third frontal convolution, which constitutes the classic Broca area. Much effort has been undertaken to demonstrate the close connection between morphology and language function in this ROI. A clear anatomic leftward asymmetry of the pars triangularis has been shown to highly correlate with language lateralization based on Wada testing.[17] The underlying concept suggests that functional asymmetry has a predefined morphologic substrate.[18,19] Our observations from a small number of patients with AC are in good agreement with this concept.

Previous research has addressed the functional impact of an early vs late brain malformation and hypothesized that early lesions are more likely to recruit the contralateral homologous brain region to compensate for the maldevelopment. We failed to demonstrate the assumed functional shift to the right in any of our patients. On the contrary, the expected asymmetry of a left hemisphere dominance was preserved, in spite of distorted anatomic structures and in spite of significant morphometric changes. This finding is in accordance with an earlier electrophysiologic investigation of language organization in patients with epilepsy,[20] which demonstrated that developmental lesions do not displace language cortices from prenatally determined sites when the language cortex is structurally intact. Similar results of a preserved language dominance in the left hemisphere in patients with left temporal AC were reported in a PET study.[21] None of the four examined patients with AC showed right hemisphere task-related activations. The mixed laterality—assessed in one patient with AC—is not contradictive to our conclusions, as it occurs in a smaller portion of the population of righthanders without penalty to function[15,22] and was not necessarily related to the AC.

The presented morphometric and fMRI data of our patients may be the starting point for further comprehensive research to determine the questions of a cytoarchitectonic concept of functional dominance.

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