TLE is associated with reduced folding of the temporal neocortex

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Introduction. Temporal lobe epilepsy (TLE) is the most common form of pharmacoresistant epilepsy in adults. Although hippocampal atrophy on MRI is a hallmark of the disorder, there is evidence for subtle structural brain damage that extends beyond the hippocampal formation. The vast majority of MRI studies dedicated to the examination of these abnormalities have been focused on assessing tissue volume. Other aspects of cortical morphology, such as sulcal shape, positioning and patterning, may give additional insights on disease-related structural brain changes. Indeed, there is growing evidence that developmental hippocampal abnormalities characterized by shape and positioning variants of the hippocampal formation are more prevalent in epileptics than in healthy individuals. Atypical morphologies of the collateral sulcus have also been described in TLE. Any disturbance of neural development, for instance during the formation of neural connections, may change mechanical properties of cerebral tissue that determine the gyrification of the cortical surface (1). Our purpose was to quantitatively analyze the gyrification of the temporal lobe in TLE and healthy individuals, and to investigate its relationship to underlying morphological and clinical parameters.

Methods. We studied 92 randomly selected patients with pharmacoresistant TLE and 33 age- and sex-matched healthy controls (HC). The seizure focus was right-sided in 41 (RTLE) patients and left-sided in 51 (LTLE). Using BrainVISA, a brain image analysis software that allows the reconstruction of surfaces corresponding to GM-WM and GM-CSF interfaces and to extract the brain sulci (2, 3), we automatically extracted skeletons that represent sulci and gyri of the basal and the lateral temporal lobe (*see panel A*). To measure gyrification complexity, we calculated the fractal dimension (*FD*) (4) and a 3D-based gyrification index (*GI*) (5) on the skeletons. Furthermore, we measured average sulcal depth and total sulcal length to quantify sulcal morphology (*See panel B*). We performed a group analysis and individual analysis by z-transforming patients with respect to the distribution of healthy controls. As FD and GI were highly correlated in all groups ($p<0.01$), we regressed only FD with sulcal morphology parameters. Correlations between FD and sulcal morphology did not differ across groups (ANCOVA: $F<1.3$, $p>0.1$), so we pooled groups together in this analysis step. We further regressed FD with disease duration, a history of secondarily generalized seizures and febrile convulsions. Tests for differences were two-tailed. Significances were adjusted using a Bonferroni-correction on the number of groups, ROIs, and hemispheres tested.

Results. Compared to HC, we observed a bilateral decrease of FD ($t<-2.94$, $p<0.04$) and total sulcal length ($t<-2.73$, $p<0.062$) in LTLE (*see panel D*). In RTLE, FD and total length were also decreased, but the difference failed to reach significance ($t<-1.31$,$p<0.1$, uncorrected). Average depth was not significantly different from HC in both patient groups. We did not find any significant difference between patients and HC in FD and total length in the basal temporal lobe. Results of the individual analysis are shown in the table below. HC displayed sparse abnormalities in all the measurements (0% - 6%), with a total (i.e. *left+right+bilateral*) not exceeding 6%. In the LTLE group, a high proportion of patients displayed abnormally low FD, total sulcal length, and GI in the lateral temporal lobes. In the RTLE group, proportions were smaller. In the lateral temporal lobes, FD was positively correlated with total sulcal length ($r>0.33$, $p<0.001$), but not with sulcal depth ($r<0.17$, $p>0.1$) (*see panel E*). There was no correlation between FD and any of the clinical parameters examined.

Discussion. In TLE, the lateral temporal lobes exhibit a simpler folding than that of HC. This simplified pattern is associated with shorter total sulcal length without decrease in average sulcal depth, suggesting that sulci have a shorter, but not necessarily shallower appearance in TLE than in HC. Findings were particularly prominent in LTLE. A "simplified" lateral temporal lobe may indicate an underlying subtle neurodevelopmental structural deviance making it more susceptible to insults, thereby triggering the epileptogenic process. An early nature of the precipitating event in our patients is supported by the lack of relation between sulcal morphology and history of febrile seizures or disease duration.

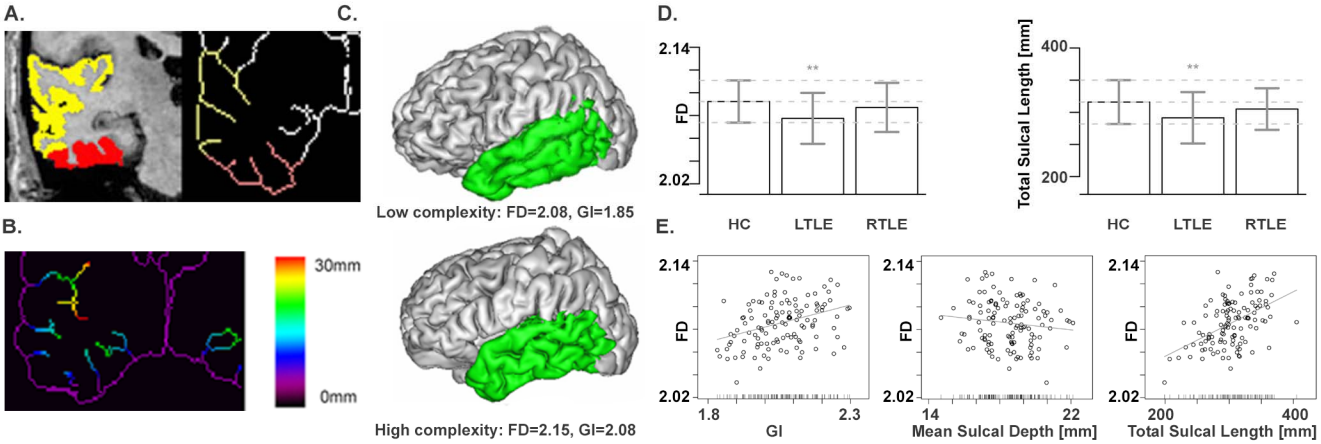

Figure. A) *ROI segmentation (yellow=lateral temporal lobe, red=basal temporal lobe) and surface skeletons.* ***B)*** *Geodesic depth map used to calculate mean average sulcal depth and total sulcal length.* ***C)*** *Two TLE cases with low (top) and high temporal lobe cortical complexity. Note the "simplified" sulco-gyral arrangement in the case with low complexity.* ***D)*** *Group comparisons FD and total sulcal length in [mm] in the left lateral temporal lobe. Stars indicate significant differences ($p<0.05$) with respect to controls.* ***E)*** *Scatter plots of GI, average sulcal depth and total length against FD. The least squares regression line is plotted.*

	LTLE			RTLE		
	left	**right**	**bilateral**	**left**	**right**	**bilateral**
FD	11%	8%	4%	7%	5%	0%
Total sulcal length	10%	2%	8%	2%	2%	4%
Average sulcal depth	2%	4%	2%	2%	0%	0%

Table. *Results of the individual analysis: Proportions of patients that show an abnormally low ($z < -2$) FD, total sulcal length, and average sulcal depth in the left lateral temporal cortex only (left), in the right side lateral temporal cortex only (right), or in both lateral temporal cortices (bilateral).*

References

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