Reduction of contralateral white matter volume after experimental focal epilepsy and hemispherectomy in rats

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Introduction

Focal epilepsies [1] as well as epilepsy surgery [2] result in changes in white matter volume not restricted to the epileptogenic area. However, the direction, extent and time course of these white matter volume changes – in particular in the contralateral hemisphere – remain largely unknown. Moreover, volume changes in patients who underwent epilepsy surgery may be the result of either the previous epilepsy, the surgical procedure, or both. In this study we aimed to characterize the pattern of white matter volume changes in the contralateral hemisphere under both conditions, i.e. epilepsy and epilepsy surgery, separately, using a well characterized rat model of focal neocortical epilepsy [3] and a model of hemispherectomy [4] We hypothesized white matter volumes in the 'healthy' contralateral hemisphere to be compromised as a result of the focal epilepsy or hemispherectomy.

Methods

We used Sprague-Dawley male rats weighing 283 ± 25 g at start of the study. Serial structural MRI was conducted in focal epileptic rats (E; n = 8), hemispherectomized rats (H; n = 8) and age-matched controls (C; n = 13), up to ten weeks after right M1 tetanus toxin microinjection, or microsurgical resection of the right hemisphere. MRI was acquired on a 4.7T Varian MR system at 7, 21, 49 and 70 days after epilepsy induction, and at 7 and 49 days after hemispherectomy, and included T_2- (TR/TE = 3600/15 ms; number of echo's = 12; matrix size = 256 × 128; FOV = 32 × 32 mm^2; 19 1-mm slices) and diffusion-weighted MRI (four-shot EPI; TR/TE = 3500/26 ms; b = 1250 s/mm^2 with diffusion-weighting in 50 directions; matrix size = 64 × 64; FOV = 32 × 32 mm^2; 25 0.5-mm slices). Sensorimotor performance scores (SPS) were measured weekly in the hemispherectomized rats. To select a robust rat brain white matter segmentation method, we first compared three, commonly used, optimized supervised segmentation approaches: the generalized linear model (GLM), support vector machine (SVM) and random forest (RF) [5]. White matter was manually delineated in twenty MRI datasets by an external neuroanatomist. Training data included both intensity (fractional anisotropy (FA), mean diffusivity (MD), T_2) and spatial (distance-to-brain-border, x-, y-, z-coordinates) features, and were randomly and equally divided in two subsets. The three methods were trained with one subset and validated (using the area under the curve (AUC) of the sensitivity versus specificity ROC curve on the other subset. Absolute (determined as the sum of all contralateral voxel probabilities × voxel size; $V_{Absolute}$) and relative (determined as $V_{Absolute}$ / hemispheric volume; $V_{Relative}$) white matter volumes were determined by restricting the prediction maps to the contralesional hemisphere masks. Group comparisons were made using a repeated measures linear mixed model (R, *nlme*) and included factors 'group', 'day' and 'group × day' with a continuous autocorrelation structure.

Results

SPS were significantly reduced ($p < 0.01$) after hemispherectomy, but restored to normal levels after 21 days ($p < 0.01$; relative to day 3 post surgery). The RF method obtained high predictability of white matter with an AUC of 0.992, which was significantly better than SVM and GLM ($p = 0.003$) and was therefore selected as the ultimate classification method. The RF method resulted in fast and accurate white matter segmentations in all datasets (Figure 1). Contralateral white matter volume increased progressively in healthy rats, up to 118 mm^3 at the last time point, or 9.8% of total hemispheric volume. In contrast, contralateral white matter volumes after one week of focal epilepsy declined significantly (group and day: $p < 0.001$ for both $V_{Absolute}$ and $V_{Relative}$, no interaction) (there was no difference with controls in body weights; $p > 0.4$) and remained as low as 100 mm^3 at the last time point (here again, no significant differences in body weight). After removal of the contralateral hemisphere in healthy rats, contralateral absolute and relative white matter volumes were unaffected at 1 week, but decreased at 7 weeks, and normal growth was lacking ($V_{Absolute}$ and $V_{Relative}$: group: $p = 0.003$ and 0.07; group × day interaction: $p = 0.01$ and $p = 0.001$).

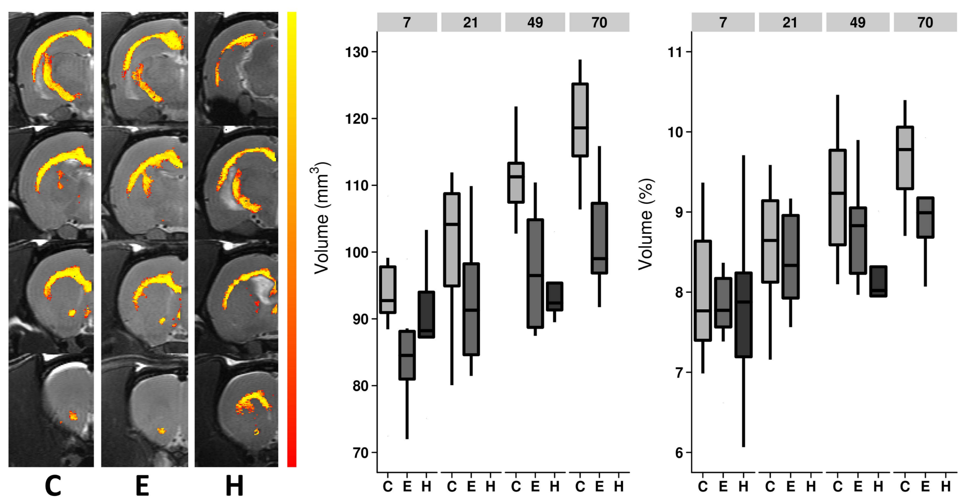

Figure. Representative examples of white matter segmentation (one dataset per group at day 49) overlaid on individual T_2-weighted images, with partial volume color bar (50-100%; left); and serial box plots for absolute (middle) and relative (right) contralateral white matter volumes in the control (C), epilepsy (E) and hemispherectomy (H) groups.

Discussion

Our study shows that white matter volume estimation in rat brain is feasible using probabilistic supervised segmentation based on multiparametric MRI data. Substantial reductions in white matter volume in the 'healthy' hemisphere were found in rats with an epileptic focus in the opposite hemisphere, supporting the hypothesis that location related epilepsy is not only a focal gray matter, but a global white matter disease as well. The absolute contralateral white matter volume was reduced as early as one week after experimental epilepsy induction (relative volumes at later time points), indicating the potency of frequent seizure propagation to affect major white matter bundles. Furthermore, and in agreement with our hypothesis, we found that the contralateral white matter volume was also reduced at a chronic time point after experimental hemispherectomy. Wallarian degeneration could be one of the underlying mechanisms that explain the absence of the normal age-related increase in white matter volume. These results imply that the interpretation of changes that occur in white matter volumes of patients who underwent epilepsy surgery is complicated by the fact that multiple factors, i.e. the pre-existing epilepsy and the consequence of the surgical procedure itself, influence structural alterations in the remaining brain. Interestingly, we found a discrepancy between the time courses of contralateral white matter volume changes and behavioral changes in the epilepsy as well as the hemispherectomy groups. In the first group, seizure activity peaked at seven weeks after induction but dropped significantly at ten weeks (data not shown) although white matter volume changes persisted. In the second group, SPS recovered substantially, while white matter volume remained reduced. This indicates that the adaptation processes probably are multifactorial and not restricted to the large white matter bundles.

References

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