Resting-state fMRI after experimental hemispherectomy in rats: changes in functional connectivity and network synchronization

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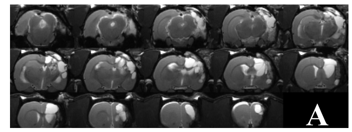
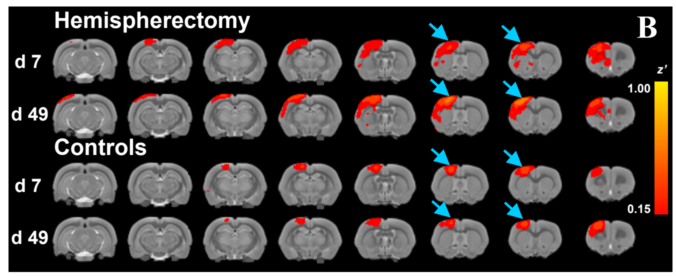
Introduction

Hemispherectomy is a last resort treatment for children with catastrophic hemispheric epilepsy. It abolishes seizures and improves quality of life. The remarkable motor recovery after hemispherectomy, observed in both clinical and experimental settings, reflects the plastic capacities of the brain, especially at young age. Direct cortical stimulation of the healthy hemisphere in adult rats two weeks after anatomical hemispherectomy has demonstrated that the latent capacity to control motricity bilaterally was brought into function after surgery[1]. Other studies have reported on the functional role of the basal ganglia in motor function improvement after hemispherectomy[2]. Recently it has been shown that the healthy brain features functional complex network properties, such as dense local clustering, highly connected hubs and optimal synchronizability, that are concordant with a small-world topology. Graph theoretical analysis of brain network properties improves our understanding of higher cerebral functioning, and the functional impact of focal lesions on global network configuration. In this study we assessed the functional consequences of right hemispherectomy on network characteristics of the contralesional hemisphere in rats, at an acute and chronic time-point after surgery, using resting-state functional MRI (rs-fMRI)[3], and interregional connectivity and graph theoretical analyses[4].

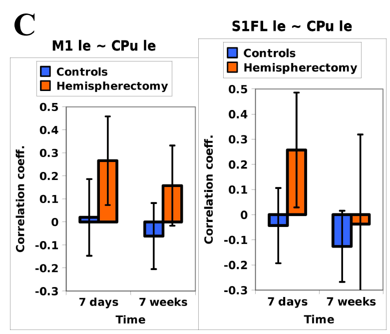


Methods

A hemicraniotomy, followed by opening of the dura mater and microsurgical hemispherectomy of the right hemisphere was performed in adult male Sprague-Dawley rats (n=7). The cortex, white matter, hippocampus and substantial part of the basal ganglia were resected with preservation of the diencephalon. In hemispherectomized rats, sensorimotor function was measured longitudinally by scoring neurological deficiency (NDS)[5].

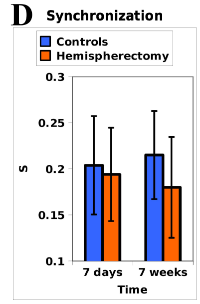


Structural MRI and rs-fMRI were conducted in hemispherectomized rats at 7 and 49 days after surgery, and in age-matched controls (n=10). Rats were mechanically ventilated with 2.5% isoflurane in air/O2 (2:1). MRI measurements were conducted on a 4.7 T horizontal bore Varian MR system. For at least 10 minutes, end-tidal isoflurane was reduced to 1%. Subsequently, rs-fMRI was performed during 10 minutes, using a T2*-weighted gradient echo EPI sequence (35° flip angle; TR/TE=500/19 ms; 64×64 matrix; 7 coronal slices; $0.5\times0.5\times1.5$ mm^3 voxels; 1200 images). In addition, gradient echo 3D MRI (GE3D; TR/TE=10/2.6 ms; 20° flip angle; 128×128×256 matrix; $0.3\times0.3\times0.3$ mm^3 voxels) and multi-echo multi-slice T2-weighted MRI (TR/TE=3000/17.5 ms; echo train length=8; 128×128 matrix; 19 coronal slices; $0.25\times0.25\times1.0$ mm^3 voxels) was included for registration purposes. Images from the rs-fMRI time-series were non-rigidly aligned to the high-resolution GE3D image. The GE3D anatomical images were registered non-linearly to a 3D model of a stereotaxic rat brain atlas[6]. The inverse b-spline transformations were estimated, which enabled mapping of atlas regions-of-interest (ROIs) to the original functional time-series space. Rs-fMRI preprocessing included spatial smoothing (1-mm FWHM kernel), rigid-body motion correction, band-pass filtering ($0.01<f<0.1$ Hz), and linear regression against rigid-body realignment parameters, deep white matter signals, ventricular system signals and global signal. Contralesional ROIs were selected within the sensorimotor network, i.e. the primary (M1) and secondary motor cortex (M2), forelimb region of the primary somatosensory cortex (S1FL) and caudate putamen (CPu). ROIs were projected from the atlas onto the functional time-series. Functional connectivity (FC) was measured as the correlation coefficient r and Fisher-transformed according to $z' = \ln((1+r)/(1-r))/2$. FC maps were obtained by calculating the voxel-wise correlation with the mean signal of a seed ROI. Averaging across subjects yielded group mean FC maps. A correlation coefficient $z' = 0.15$ was considered significant, and thresholded connectivity maps were overlaid on an anatomical template image. Interregional connectivities were obtained by calculating the correlation with the mean signals of both seed and target ROIs. For each left (contralesional) hemisphere functional dataset, a weighted graph was constructed with all cortical and subcortical gray matter voxels. Edges were defined between any pair of voxel time-series using Fisher-transformed correlation coefficients. We quantified the local and global graph structures via the weighted clustering coefficient C and the weighted characteristic path length L; self-connections and negative edges were excluded. For each functional dataset, L and C were normalized using ten surrogate (random) networks. Network synchronizability (S) was estimated from the eigensystem decomposition of the weighted Laplacian network matrix. S was defined as the ratio of the largest eigenvalue and the second smallest eigenvalue. Groups were statistically compared in a repeated measures linear mixed model (SPSS; data shown as mean ± SD).



Results

Fig A shows a multi-slice T2-weighted dataset that displays structural changes typically observed at 7 weeks after hemispherectomy; cerebrospinal fluid filled the empty spaces. One animal developed hydrocephalus one week after surgery and was terminated. After significant acute neurological deficits, NDS largely normalized in all animals within 2 weeks, although a pathological postural reflex remained up to 7 weeks. Average intrahemispheric FC maps with left M1 as seed ROI (blue arrows) are shown for both groups in fig. B (FC maps are superimposed on anatomical template). Removal of large part of the right hemisphere resulted in enhanced FC in the left hemisphere between cortical (M1, M2, S1FL) and subcortical (CPu) regions. Fig. C shows, as an example, the interregional connectivity pattern of mean FC between left M1 and CPu (group effect: $F(1, 15.5) = 11.14$, $P = 0.004$) and left S1FL and CPu (group effect: $F(1, 12.6) = 8.42$, $P = 0.013$; time effect: $F(1, 12.6) = 5.28$, $P = 0.035$). Hemispherectomized rats demonstrated higher increased FC appearing at 7 days, as compared to controls, that was persistent between M1 and CPu, but disappeared between S1FL and CPu in correspondence with a decrease in NDS. Graph analysis revealed that C and L did not differ significantly between groups, while synchronization (S; fig. D) was lowered in hemispherectomized rats at both time points ($F(1, 20.4) = 5.12$, $P = 0.035$).



Discussion

The sensorimotor cortex and striatum in the healthy contralesional hemisphere exhibited significantly increased functional connectivity at one week after surgery, which partially normalized after seven weeks. Removal of transcallosal inhibition may contribute to an enhancement of intrahemispheric FC. The inborn potential of each hemisphere for bilateral motor control is supported by the rapid motor recovery, correlating in time with an enhanced contralesional FC. In weighted graph analysis, scale-free networks have the highest synchronizability followed by random, small-world and regular networks[7]. Our synchronization results therefore assume a shift toward a more regular topology. We have shown that rs-fMRI, connectivity analyses and specific network measures can provide unique insights into functional reorganization in the remaining brain after experimental hemispherectomy.

References

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