Functional hippocampal networks changes in relation to spatial learning in hemispherectomized rats

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Purpose

Therapeutic hemispherectomy (that is, removal or disconnection of one hemisphere) hardly restricts the development and long-term gains in cognitive skills of children with refractory epilepsy [1]. However, our understanding of the plastic capabilities of the remaining hemisphere, in particular in relation to cognition, remains limited. We hypothesize that preserved cognitive outcome may be attributed to large-scale functional network reorganization in the contralateral hippocampus. Our goal was to characterize the functional hippocampal network organization in relation to the extent of spatial memory, following experimental hemispherectomy in rats.

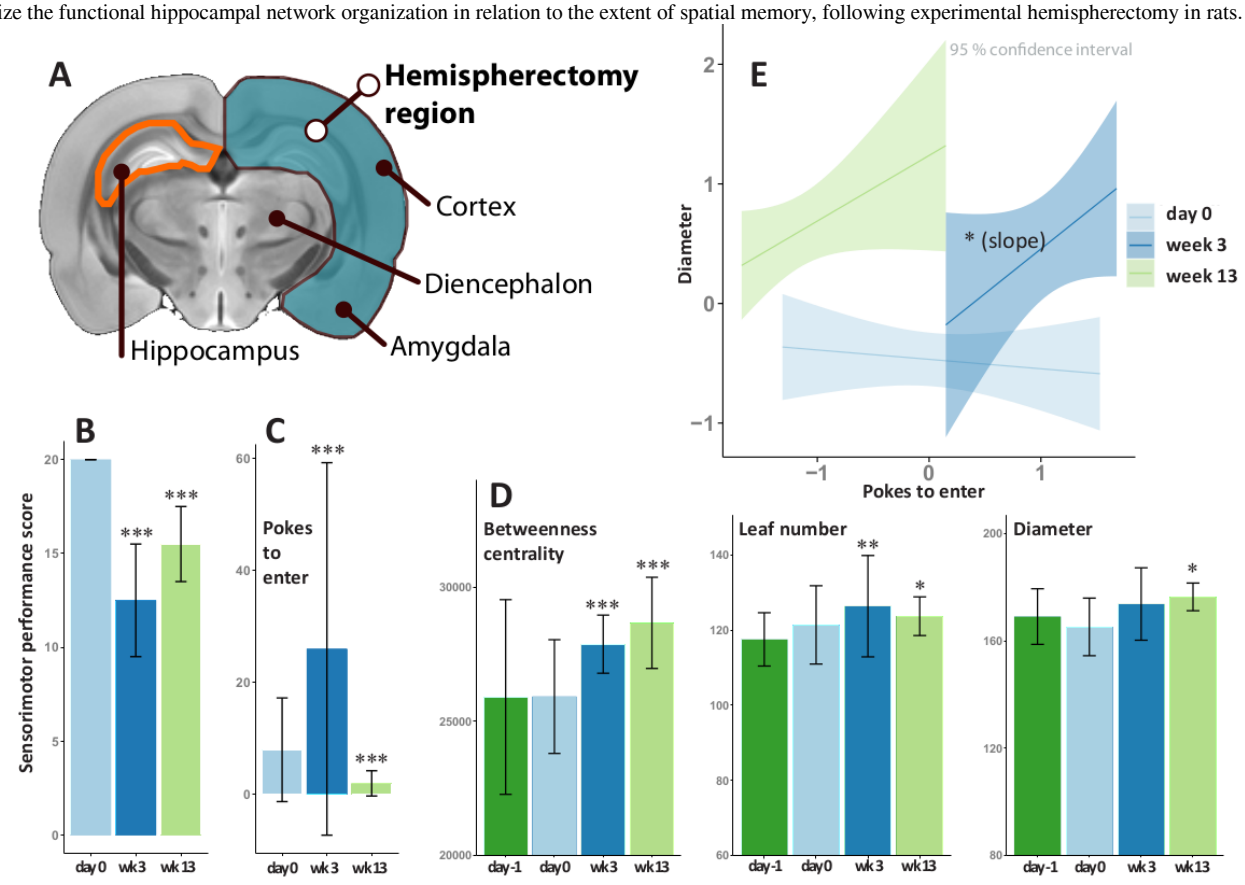

Figure * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ ('day 0' is reference in B, C and E, 'day -1' in D). Values as mean ± standard deviation (B as median ± iqr).

Methods

Seven young adult male Sprague-Dawley rats were trained in the Barnes maze spatial memory task. Spatial performance was measured before and after hemishperectomy, and inversely scored by the number of 'pokes to enter'. Resting-state fMRI was conducted on a 4.7T animal MR scanner, at one day before (labeled as: 'day -1') and after ('day 0') training [one-shot 3D EPI with ventilation-triggered non-Cartesian sampling; TR/TE 32/19 ms; flip angle 12°; 600 volumes, 10 min at 1% isoflurane anesthesia; 0.5 × 0.5 × 0.5 mm voxels]. Subsequently, the right hemisphere was microsurgically resected [2] (Fig A), followed by resting-state fMRI after 3 and 13 weeks. Sensorimotor performance was scored post-surgery. Functional images were motion-corrected, band-pass filtered (0.01—0.1 Hz), and nonlinearly matched with a common rat brain template, from which we manually delineated the contralateral hippocampus for functional connectivity analysis. Time series were extracted for all 299 hippocampal voxels in each dataset to calculate pair-wise functional connectivities (using Pearson's correlation coefficient). The maximum betweenness centrality, leaf number and diameter of the minimum-spanning tree (MST) of each hippocampal network were determined [3]. These measures, that capture several aspects of the network organization, were related to spatial memory outcome.

Results

Hemispherectomy caused significant sensorimotor deficits in all rats. One animal developed post-surgical hydrocephalus and was excluded. Rats recovered progressively within two weeks, however sensorimotor performance remained below baseline level ($p < 0.001$; B). Spatial performance was significantly disturbed at week 3. In contrast, the performance at week 13 had improved as compared to 'day 0' (C). The betweenness centrality, as well as the MST leaf number and diameter of the unilateral hippocampal functional network increased significantly after hemispherectomy (D). The MST leaf number and diameter also increased significantly (D). No association between spatial memory and network measures were found at day 0. However, post-hemispherectomy spatial memory significantly correlated with the hippocampal network's MST diameter (E), indicating that rats with a low functional network MST diameter value scored higher on spatial memory.

Discussion

Our study sheds new light on patterns of change in functional network organization in the contralateral hippocampus in relation to changes in spatial memory after hemispherectomy. Improved spatial memory after experimental hemispherectomy related to decreased diameter and increased leaf number of the network's MST, indicating a shift towards a more star-like MST network and an overall increase in hub-structure (measured as betweenness centrality). These data support the hypothesis that reorganization of large-scale neural networks in the hippocampus contributes to consolidation of spatial learning and memory after hemispherectomy.

References

[1] Thomas et al, *Childs Nerv Syst* 26 (2010); [2] Machado et al, *Epilepsia* 44 (2003); [3] Tewarie et al, *Neuroimage* Oct 22 in press (2013);