Spatiotemporal Network Alterations in Experimental Focal Cortical Epilepsy: MRI-based Longitudinal Functional Connectivity and Weighted Graph Analysis

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Introduction

The brain is increasingly recognized as a complex network of dynamically interacting subsystems with numerous functional interactions between local and more remote regions, where synchronization plays an important role in its dysfunctioning [1]. An example of a pathophysiologic neuronal synchronization disease is epilepsy, in which unprovoked recurrent seizures result from a complex interaction between distributed neural populations. The old concept of a localized epileptic focus, may possibly be extended with that of an epileptic network, which functional interactions extend to numerous remote brain areas. The importance of network organization for seizure spread has been emphasized in several modeling studies. Recently it has been shown, using complex network analysis, that epilepsy in functional brain networks produces specific patterns of altered functional connectivity (FC) among distant cortical regions [2]. During seizures, the neuronal network moves in the direction of a more ordered topology as compared to the interictal state, it has therefore been hypothesized that interictal networks in epilepsy are characterized by a more random organizations. In this study we aimed to evaluate experimental interictal focal epilepsy brain networks in rats longitudinally, and compare their spatiotemporal evolution with healthy control brains. To this end we assessed functional brain connectivity using longitudinal resting state functional MRI (rs-fMRI) [3] and graph theoretical analyses.

Methods

Chronic, mild, focal neocortical epilepsy was induced by intracortical injection of 120 ng tetanus toxin in the right motor cortex in male Sprague-Dawley rats (n=10) [4]. Resting state fMRI was acquired in epileptic rats and age-matched controls (n=10) at 7, 21, 49 and 70 days after epilepsy induction. Rats were mechanically ventilated with 2.5% isoflurane in air/O2 (2:1) during MRI. fMRI measurements were performed on a 4.7 T horizontal bore Varian MR system with use of a Helmholtz volume coil (90-mm diameter) and an inductively coupled surface coil (35-mm diameter) for signal induction. Rats were mechanically ventilated with 2.5% isoflurane in air/O2 (2:1) during MRI. MRI measurements were performed on a 4.7 T horizontal bore Varian MR system with use of a Helmholtz volume coil (90-mm diameter) and an inductively coupled surface coil (35-mm diameter) for signal induction. The tetanus toxin treatment induced frequent, mild, but persistent facial motor seizures in all treated animals. Four animals died due to a status epilepticus and were excluded from the study. Only EEG recordings at 0% isoflurane confirmed 5 sec discharges with discrete focal motor signs. We detected increased FC between bilateral sensorimotor (sub)cortical regions in epileptic rats at 1, 3 and 7 weeks after epilepsy induction as compared to controls. At 10 weeks, FC normalized, despite persistent but less frequent seizures in all six animals. FC maps of the left primary motor cortex (M1) (non-injected hemisphere) are shown in figure 1. Similar patterns were found in other cortical ROIs. Cratios and Lratios are shown in figure 2. The repeated measures linear mixed model (SPSS, v15) showed a significant interaction between group and time for both Cratio and Lratio (F(3, 48) = 3.22, P = 0.031; F(3, 48) = 4.58, P = 0.007, respectively).

Results

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Discussion

In this study we assessed changes in longitudinal resting state functional MRI in a rat model of focal cortical epilepsy and compared local and global networks properties with healthy controls. First, our results point out that functional changes extend beyond the seizure onset zone. Second, up to 7 weeks after induction the epileptic brain is characterized by a more ordered configuration, with higher Cratio and Lratio compared to the healthy brain. We repeated our analysis with binary graph analyses (data not shown) resulting in similar shifts to more ordered network configuration. This is the first study to compare the functional interictal epileptic network organization with the healthy brain, suggesting the previously suggested hypothesis to be false, at least in this animal model of focal epilepsy. The underlying pathophysiology of this epileptic network shift is not known. The temporal correspondence between the evolution of FC of (sub)cortical regions within the sensorimotor network and graph analytical measures (Lratio and Cratio) emphasizes the potential of resting state functional MRI to assess spatiotemporal characteristics of functional brain alterations in relation to pathophysiological disorders such as focal epilepsy.

References