Resting State Network Disruptions in Kainic Acid Model of Temporal Lobe Epilepsy

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TL; DR

- Functional MRI was performed on a rat temporal lobe epilepsy (TLE) model induced by kainic acid
- Functional connectivity increases in limbic and default mode networks of TLE model
- Graph topological properties differ significantly between epileptic and control rats
- TLE model shows increased clustering and small-worldness, but similar path length
- Isoflurane anaesthetic dose-dependently affects functional connectivity

Introduction

- Temporal lobe epilepsy (TLE) is a common type of focal epilepsy. It is characterized by spontaneously recurring focal dyscognitive seizures that originates from the temporal lobe, often from mesial structures such as the hippocampus and amygdala.
- Resting-state networks (RSNs) have been shown in awake/anaesthetized rats [1].
- Graph theoretical measures like clustering coefficient, centrality, modularity, and path lengths have been shown to be altered in TLE patients.
- We studied the graph topological properties of brain networks [2] derived from resting-state fMRI in a kainic acid induced model of TLE in rats.
- Ethical concerns prevent experimental studies in humans, although these studies are necessary to elucidate the underlying mechanisms. Thus, we used an animal model of TLE in an attempt to study the RSN disruptions in human TLE.

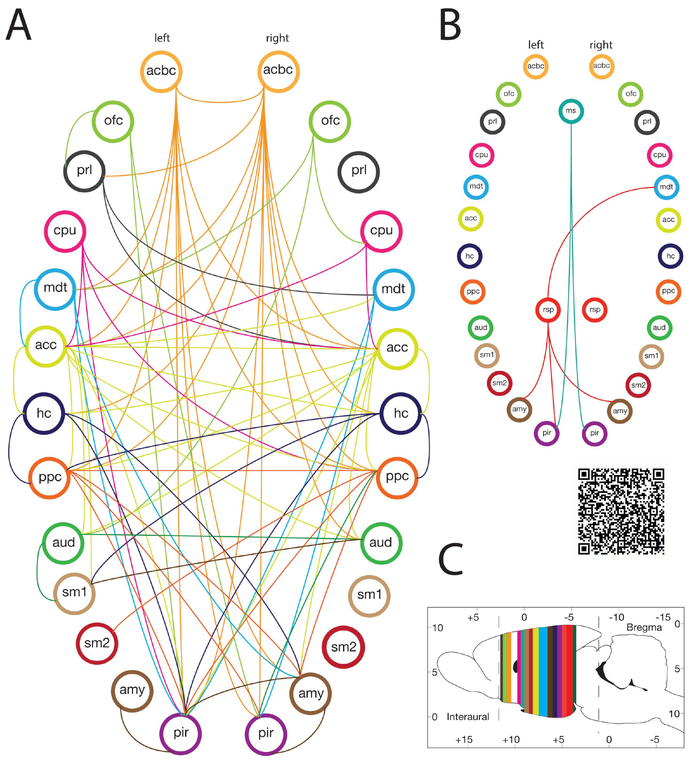

Figure 1: Connectivity graph (KA-treated > controls) for A: Isoflurane 1.5%, B: Isoflurane 2.0%, C: Approximate coronal location for the ROI (color coded). The circles with labels represent brain regions (nodes) and the line represents a significant connection between the two nodes. This sub-network was thresholded at t ≥3.5, with P < 0.05. Scan embedded QR code for node abbreviations; left and right pairs of a region are illustrated.

Methods

1. Long-Evans rats were injected with kainic acid (KA) according to induce spontaneous seizures [3].
2. 4-5 weeks following the KA injections, rats were anaesthetized using isoflurane, and structural and functional (10 mins each at 1.5% and 2.0% isoflurane end-tidal concentration) scans were acquired.
3. Functional connectivity was determined by temporal correlation of the resting-state Blood Oxygen Level Dependent (BOLD) signals between 33 pairs of regions of interest (ROIs) during 1.5% and 2% isoflurane, and analyzed as networks in epileptic and control rats.
4. Graph theoretical approach was implemented using Brain Connectivity Toolbox [4], and network comparison using Network-based Statistic (NBS) [5] toolbox in Matlab 2014a.

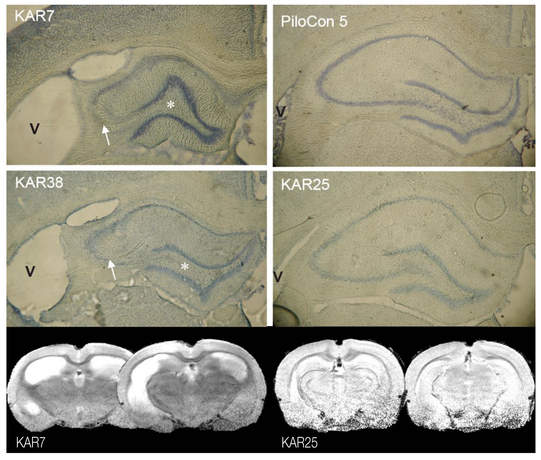

Figure 2: Hippocampal slices (top and middle row) and coronal structural scans (bottom row) in representative kainate-treated (left panel) and saline-treated (right panel) rats. CA3c lesion (*) was found in all kainate-treated rats, with less uniform CA3b (arrow) and CA1 lesion; V: lateral ventricle. Compared with saline-treated rats.

Results

Network Analysis

- At 1.5% isoflurane, the analysis revealed a single sub-network comprising of 23 nodes and 78 edges that was significantly higher in the kainate than the control group (Figure 1A). The network comprised of the limbic/subcortical system, the sensorimotor system and the default-mode system along with the mesiotemporal system.
- At 2% isoflurane, the analysis revealed a single sub-network comprising of 7 nodes and 6 edges that was significantly higher in the kainate than the control group (Figure 1B). The network is relatively sparse compared to 1.5% isoflurane concentration.

Graph Analysis

- At 1.5% and 2% isoflurane, clustering coefficient (C_w), global efficiency (E_{glob}), and local efficiency (E_{loc}) were significantly higher in the kainate than the control group (Figure 3).

Histology

- Figure 2 demonstrates the kainic acid induced damage in hippocampal slices (extended ventricles) and structural MRI (hyper-intensity).

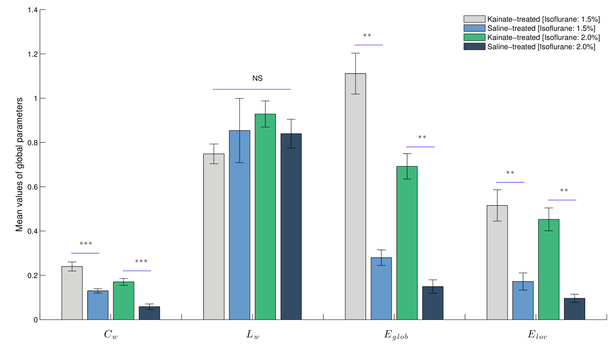

Figure 3: Statistical comparison of the global graph topology parameters C_w (clustering coefficient), L_w (path length), E_{glob} (global efficiency), E_{loc} (local efficiency) of the functional networks. Results are expressed as mean ± SEM. ** signifies P < 0.002, *** signifies P < 0.0001 and NS – not statistically significant.

Conclusion

These results suggest extensive disruptions in the functional brain networks and its organization, which may be the basis of altered cognitive, emotional and psychiatric symptoms in TLE.

References & Acknowledgements

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