

Functional consequences of network structure transformations in temporal lobe epilepsy

J. Dyhrfjeld-Johnsen¹, V. Santhakumar¹, R.J. Morgan¹, R. Huerta², L. Tsimring², I. Soltesz¹

¹Dept. of Anatomy & Neurobiology, UC-Irvine, Irvine, CA, USA.

²Inst. for Nonlinear Science, UC-San Diego, La Jolla, CA, USA.

Sclerosis of the dentate gyrus, a poorly understood consequence of repeated seizures in human patients and animal models of temporal lobe epilepsy, is characterized by cell loss and abnormal recurrent connections between granule cells. This study applied data-driven graph theoretical and computational modeling techniques to identify the nature and consequence of network reorganizations during the progression of sclerosis.

Based on anatomical data, we assembled a full-scale network graph of the dentate gyrus consisting of 1,064,000 excitatory and inhibitory neurons and their synaptic connections represented as nodes and directed links. Distributions of the links were constrained using Gaussian fits to reconstructed axonal distributions in the literature. We calculated the average path-length (L) and clustering coefficient (C) of the dentate graph and compared it to a randomly connected control graph. The relatively low L (high global connectivity) and high C (high local connectivity) established the “small world” structure (Watts & Strogatz, Nature 1998) of the healthy dentate. Parallel increases in the degree of hilar neuron loss and mossy fiber sprouting (i.e. sclerosis) resulted in enhanced C at lower degrees of sclerosis, followed by a decrease. The L remained low until severe sclerosis, indicating a high global connectivity, except after almost complete hilar cell loss. Compared to corresponding random networks, the small world features of the dentate network were progressively enhanced with sub-maximal sclerosis. The dentate graph was transformed into a primarily locally connected, regular network structure with high L and C when the last surviving hilar cells were lost.

Since previous studies have shown that small world topology enhances the propagation and synchrony of network activity, we examined whether the biphasic topological changes during sclerosis might influence the spread of seizure-like activity using a large-scale dentate network models that replicated the topology changes with sclerosis. The biophysically and topographically realistic network model contained multi-compartmental models granule cells (50000), mossy cells (1500), basket cells (500) and hilar interneurons (600) and implemented the connectivity distributions described for the full dentate graph. As predicted, in response to a single simulated perforant-path stimulation, both the duration and average activity of granule cells increased with sclerosis, peaked at 80% and then decreased at 100% sclerosis. Note that in the model network only 20% hilar cells survive at 80% sclerosis, similar to the degree of mossy cell survival reported in human temporal lobe epilepsy patients with hippocampal sclerosis (Blumcke et al. 2000). The local and long-range coherence in granule cell firing were similar at 40-60% sclerosis indicating a locally and globally connected network, followed by a decrease in the long-range coherence and dramatic increase the local coherence with maximal sclerosis.

In summary, we show that in the presence of at least a few surviving long-rang hilar cells the local, spatially restricted sprouting of mossy fibers can maintain global connectivity of the dentate gyrus while simultaneously increasing the local clustering. The resulting enhancement of the small world structure provides a structural framework for network hyperexcitability and propagation of epileptiform activity in the dentate gyrus during sclerosis.

Acknowledgement: Supported by the NIH (NS35915) to I.S.