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Graph Theory Signatures of Seizure Susceptibility in *scn1lab*$^{-/-}$ Zebrafish Networks

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Extended Abstract

Epilepsy is characterized by recurrent seizures, yet its underlying network mechanisms remain poorly defined. Conventional models, spanning humans, nonhuman primates, and rodents, offer limited access to single-cell dynamics across brain. To resolve how individual neurons contribute to emergent pathological states, an approach enabling brain-wide, cellular-resolution recording is essential. The larval zebrafish, combined with calcium imaging, provides such an opportunity, allowing simultaneous capture of neuronal activity and network interactions across the entire brain. [1].

Zebrafish share genetic and physiological similarities with humans [2] and can exhibit seizure-like behaviors in response to various drugs. One such drug is Pentylenetetrazol (PTZ), a pharmacological agent that blocks inhibitory GABAergic signaling, causing hyperexcitability and seizure-like activity [3]. Additionally, mutations in the zebrafish sodium channel gene *scn1lab*, homologous to mammalian SCN1A, recapitulate key features of Dravet syndrome [2]. In this study, we used light-sheet calcium imaging, brain-wide and at cellular resolution, on wildtype (WT) and *scn1lab*$^{-/-}$ mutant zebrafish larvae under baseline and post-PTZ conditions. Functional networks were constructed from neuronal Pearson's correlations, and eight graph-theory metrics drawn from the Brain Connectivity Toolbox [4] were applied to quantify topological features shown in Figure 1.

WT networks showed fewer fluctuations across the metrics following PTZ exposure, reflecting a more stable and resilient network structure. Assortativity, a measure of degree homophily and a potential biomarker for seizure-prone architecture, effectively distinguished genotypes at baseline, prior to any seizure activity. Mutant networks exhibited elevated assortativity values, consistent with core-periphery configurations commonly associated with pathological synchronization [5]. Differences in efficiency, modularity, and edge length further indicated fundamental disparities in information processing between WT and mutant networks. However, these distinctions largely diminished after PTZ administration, suggesting a convergence in network architecture during seizure onset.

To assess robustness, we conducted sensitivity analyses across correlation thresholds (5–25%) and compared results against Maslov-Sneppen randomized null models [6]. Genotype-specific differences were primarily driven by node degree, prompting a focused subregional analysis across 137 brain areas. This revealed spatially localized genotype-dependent alterations, notably in the pretectum, torus longitudinalis, and cerebellum. This suggests that seizure susceptibility in *scn1lab*$^{-/-}$ larvae arises from impaired network reconfiguration in specific brain regions. These findings demonstrate the value of graph-theory metrics in revealing hidden network vulnerabilities and identifying brain regions susceptible to seizure transitions, providing mechanistic insight into genotype-specific epileptic phenotypes.

References

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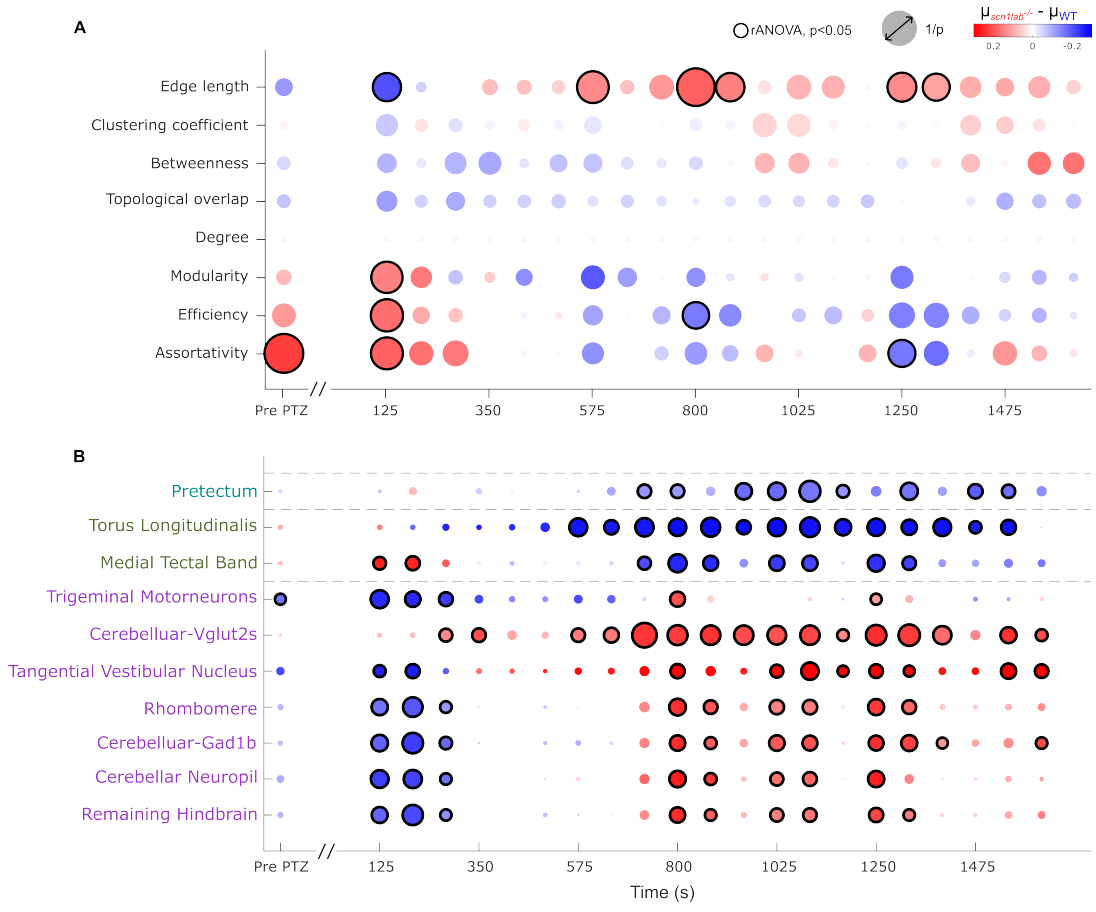

Figure 1: **Graph metrics across WT and *scn1lab*$^{-/-}$ brains.** (A) Genotype-specific differences in eight graph metrics tracked from pre- to post-PTZ. Blue/red circles indicate higher WT/*scn1lab*$^{-/-}$ means; black outlines mark significant effects ($p < 0.05$, rANOVA with Bonferroni correction). (B) Significant node degree differences across 137 subregions over time. Black rings denote significance ($p < 0.01$, rANOVA with Bonferroni correction).