

Unraveling mTORopathies: mTOR hyperactivation induces mutation-specific functional and structural phenotypes in human neuronal networks



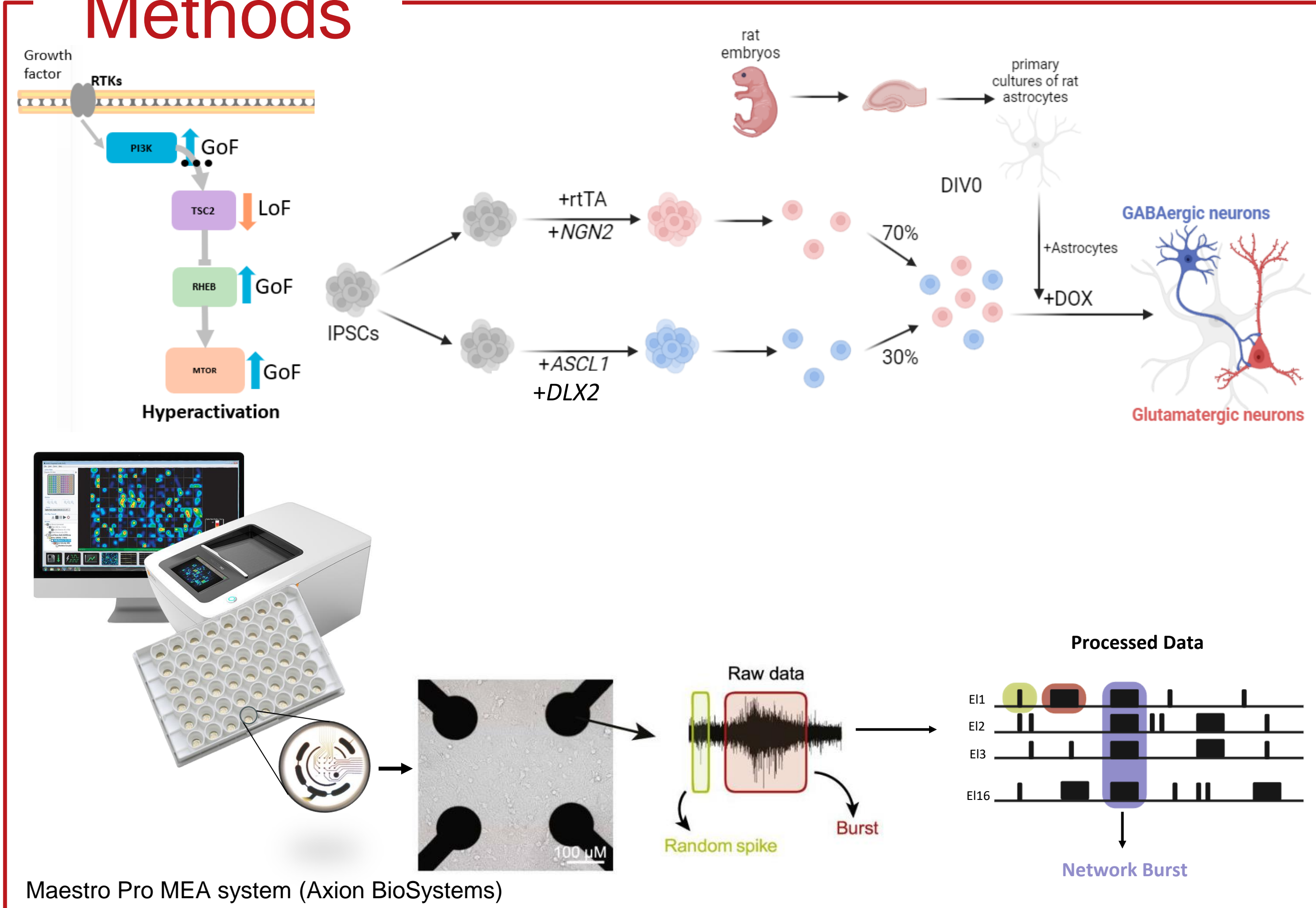
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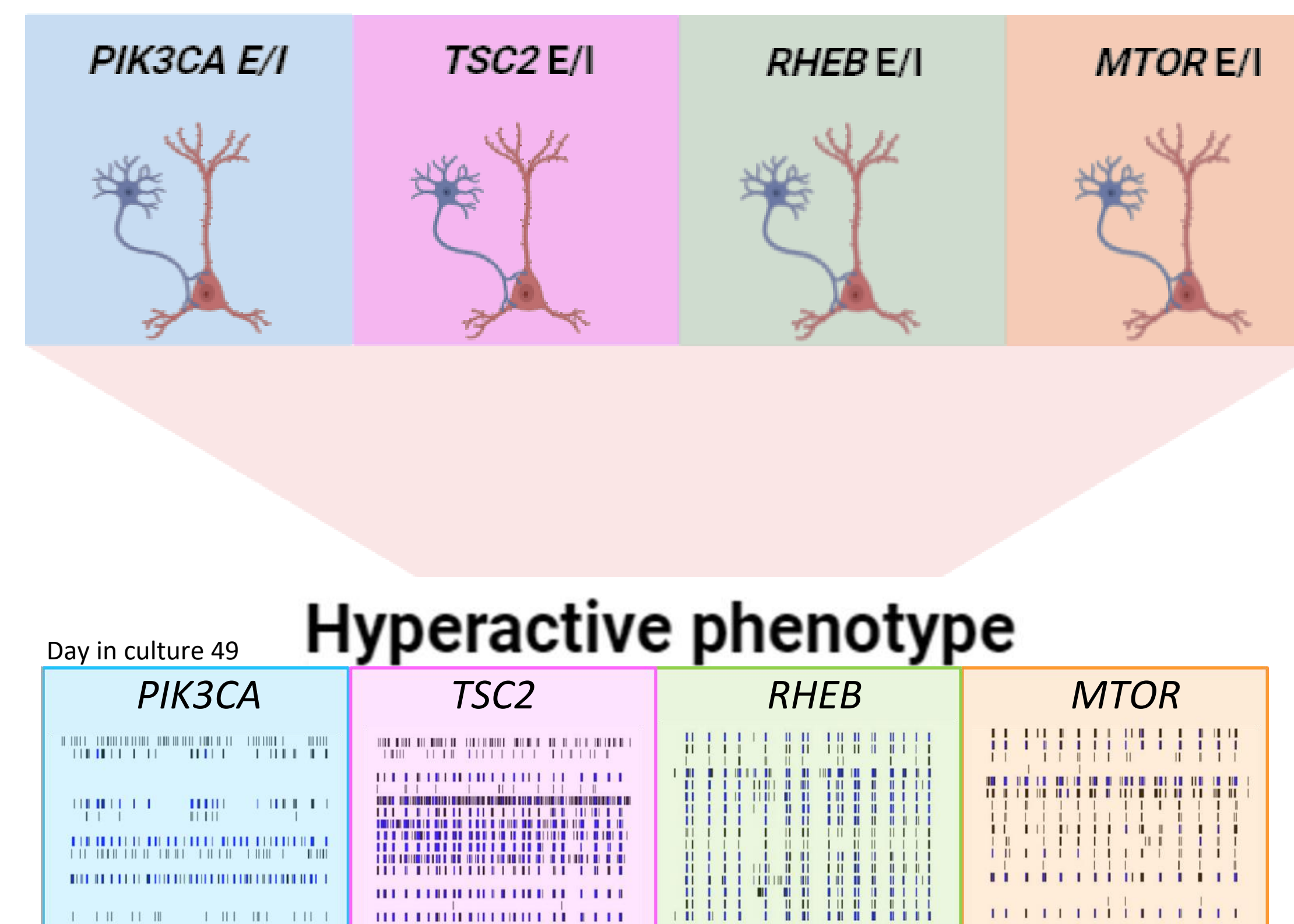
Introduction

The mTOR pathway is a pivotal cellular signaling pathway that impacts neuronal differentiation and function. Genetic disruptions leading to hyperactivation of the mTOR pathway, termed mTORopathies, represent rare genetic and systemic disorders that are associated with altered brain development and epilepsy. However, the precise mechanisms by which disrupted mTOR signaling affects neuronal network development and signaling remain poorly understood. In this study, we aimed to identify the structural and functional consequences of different mutations underlying mTORopathies on excitatory and inhibitory (E/I) neuronal network development.

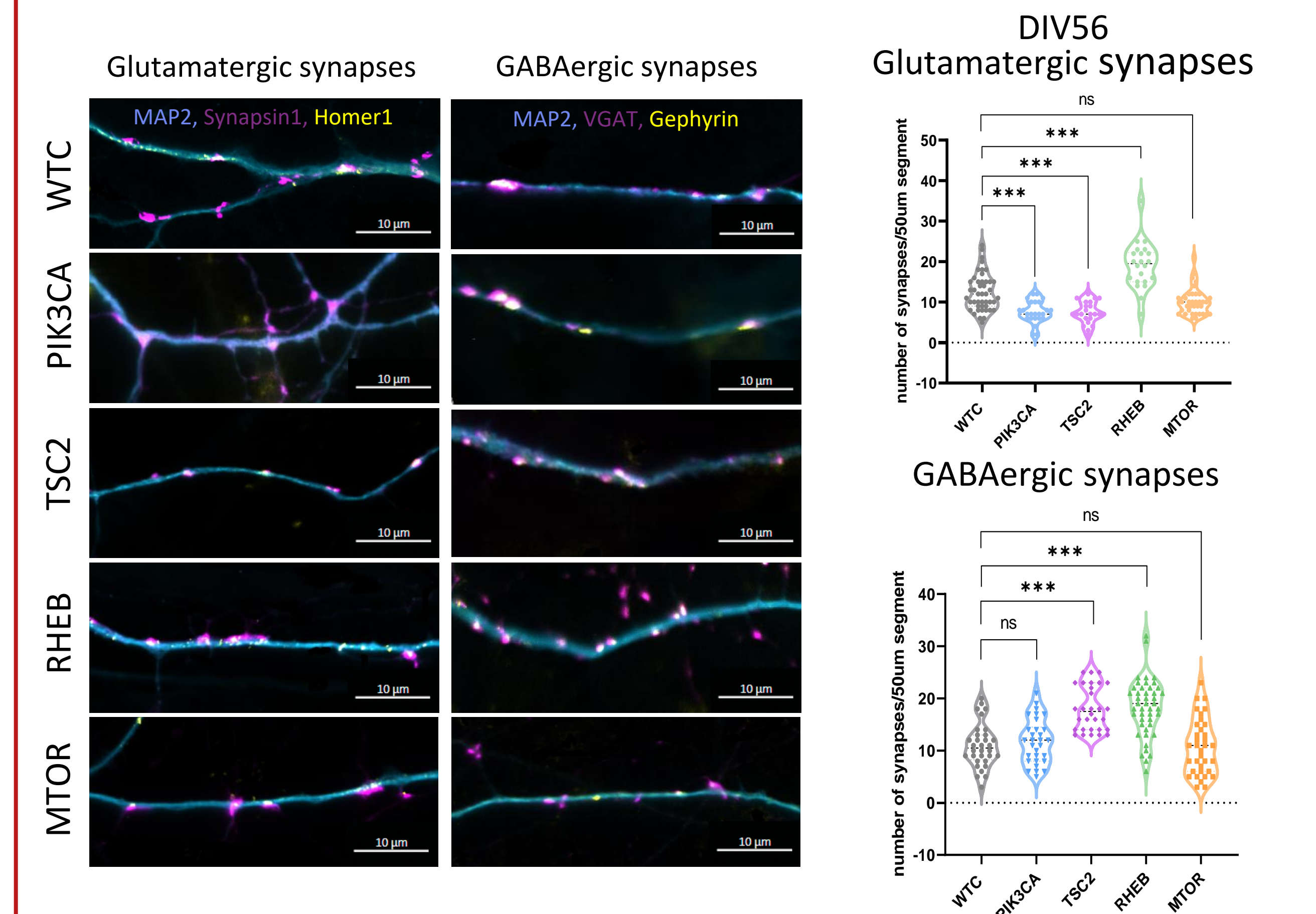
Methods



Graphical abstract

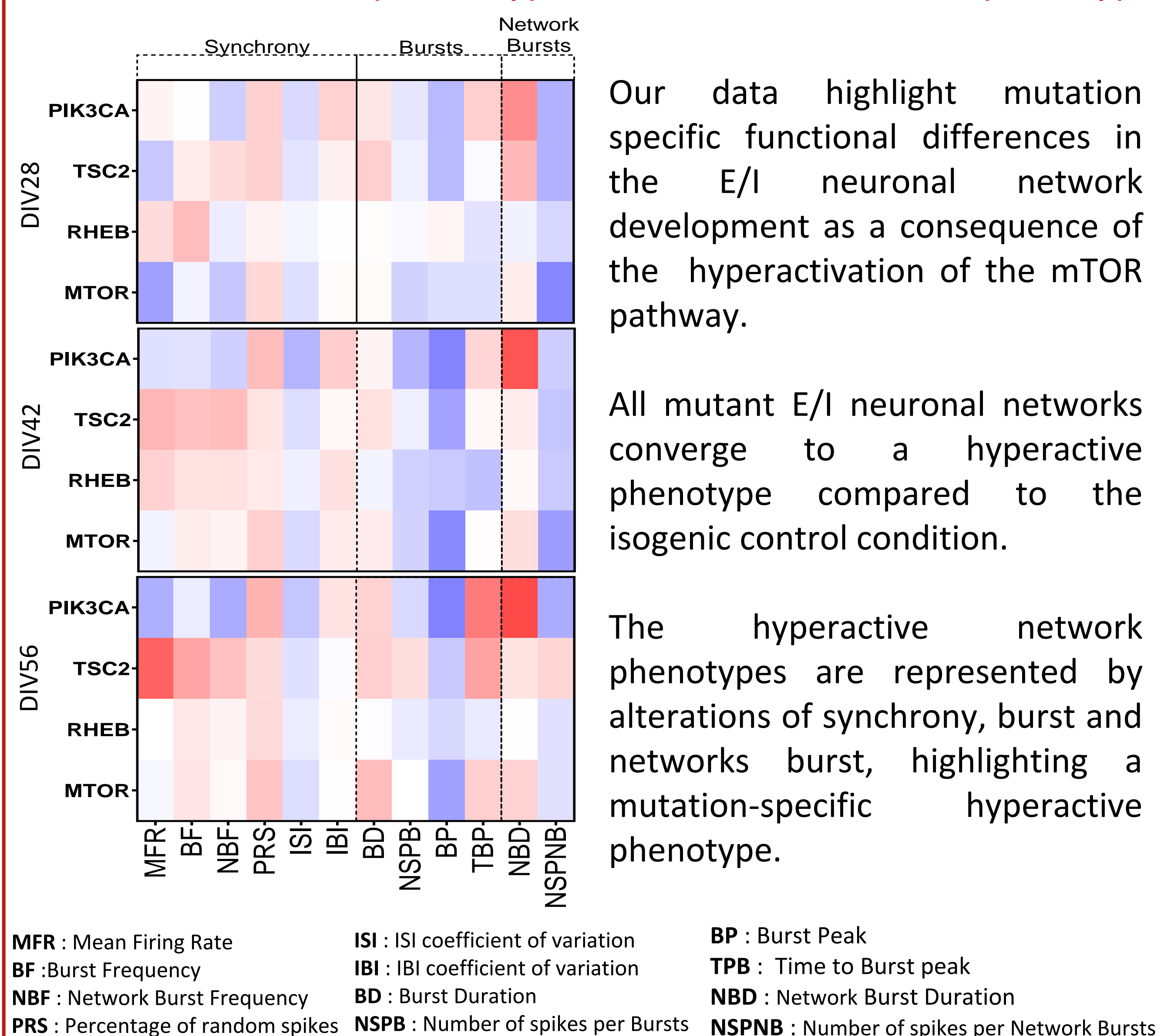


Results 2. Mutation-specific alterations of the synaptic connectivity

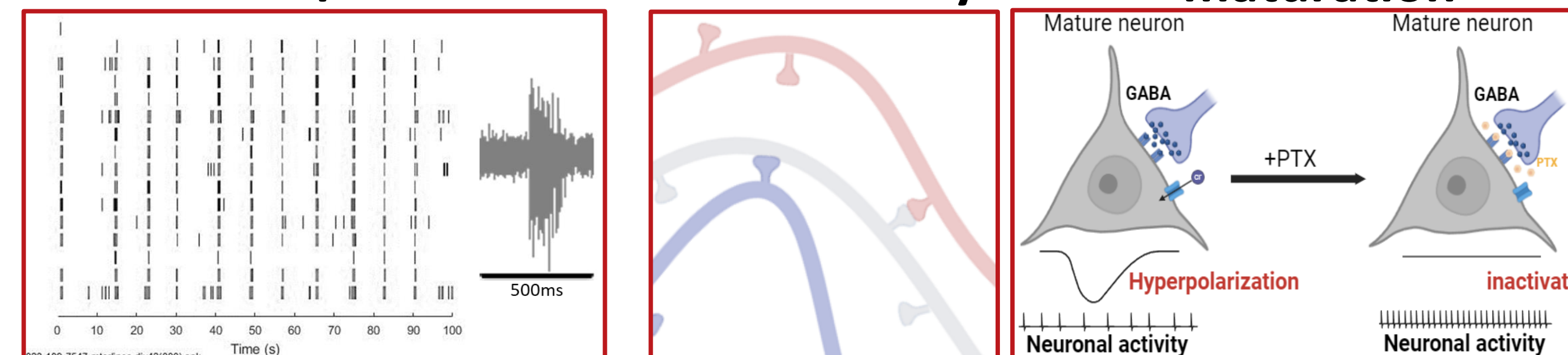


Quantification of glutamatergic and GABAergic synapses revealed mutation-specific alterations of the synaptic connectivity in the mutant E/I neuronal networks.

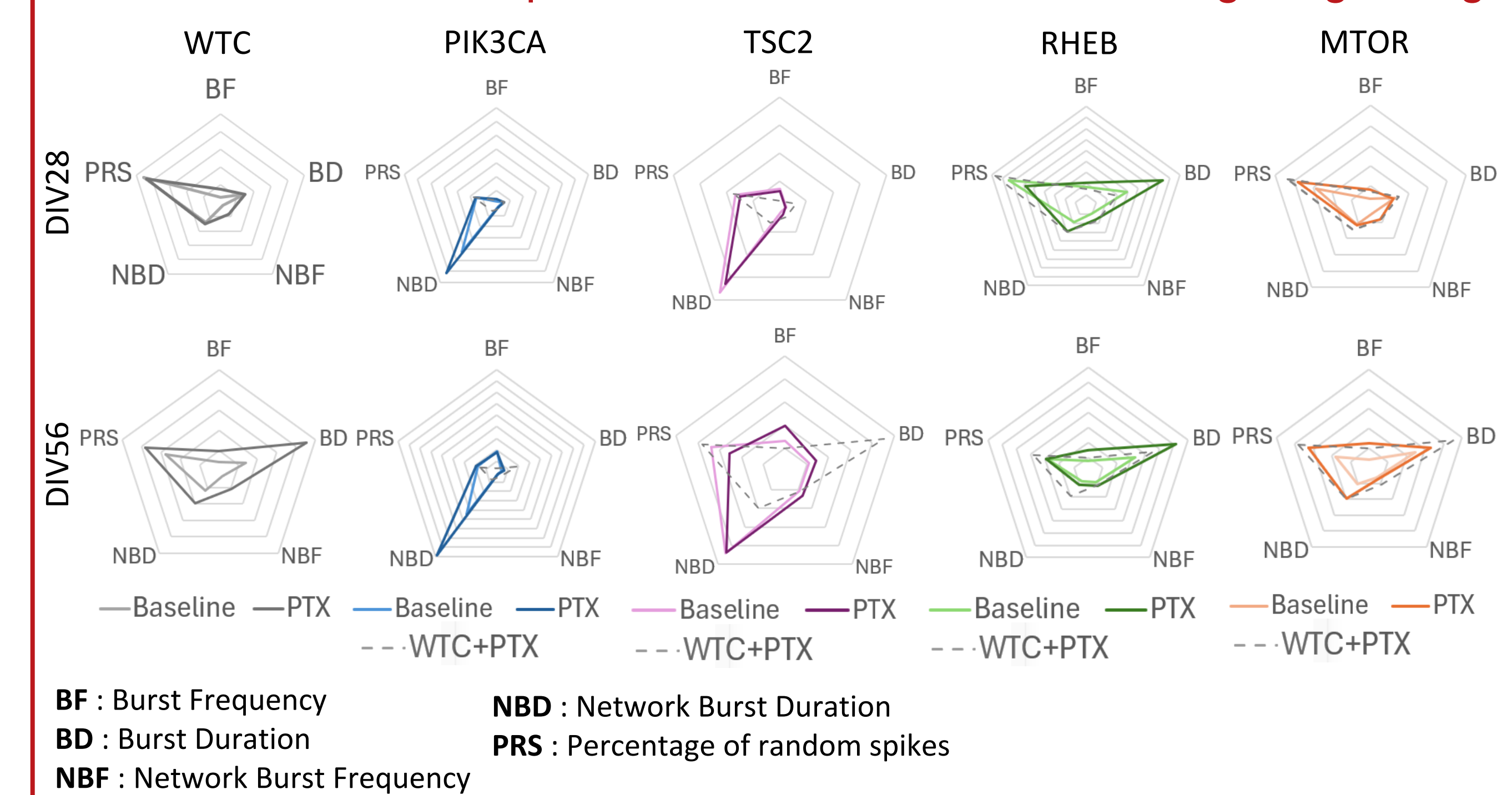
Results 1. Mutation-specific hyperactive neuronal network phenotype



1. Neuronal network development 2. Synaptic Connectivity 3. GABAergic signalling maturation



Results 3. Mutation-specific maturation of the GABAergic signalling



Pharmacological block of GABAergic signaling implies mutation-specific alterations in the maturation of GABAergic signaling in mTORopathy E/I networks.

Conclusion

E/I neuronal networks exhibiting hyperactivation of the mTOR pathway due to different mutations in the mTOR pathway generally converge to a hyperactive phenotype. However, the specific structural & functional aspects of network organization as well as the maturation of GABAergic signaling showed mutation specific differences. Taken together, our data imply mutation specific disruption in E/I balance in mTORopathy networks, possibly in association with delayed GABAergic maturation.