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TITLE

A multi-scale link between the structure and function of brain circuitries: from neuronal hubs to transcriptomics and diseases in brain networks

Abstract

In my talk I will tackle the multi-scale nature of brain circuitries through my most recent work[1,2].

First, I will introduce the multi-scale structural-functional nature of brain circuits and networks, the spontaneous dynamics which characterize them, and the complex networks as a mathematical theoretical framework to approach open questions.

Secondly, I will introduce the idea of networks' hubs, evidence of GABAergic neuronal hubs at the micro-circuits scale, and the concept of the "older gets richer".

I will then present a macro-scale model linking hubs, embryonic neurogenesis, transcriptomics and diseases in human brain networks[1]. This model provides a link between the genetic underlying major brain pathologies such epilepsy, Autism Spectrum Disorder, Parkinson's and Alzheimer's disease, and brain hubs.

Finally, I will talk about preventing the imprinting the epileptic state in micro-circuits by impacting the neuroinflammatory response[2] mediated by the JAK/STAT signaling. The link between epilepsy and JAK/STAT signalling emerges both at micro-circuit scale as evidenced by the STAT3[2], and at the macro-scale as shown by evidence from the Genome-Wide Association Studies on STAT4 and its expression in brain hubs[1].

REFERENCES

1. *Diez I, Garcia-Moreno F, Carral-Sainz N, Stramaglia S, Nieto-Reyes A, D'Amato M, Cortes JM,* ***Bonifazi P.*** "Older circuits get richer": neurogenesis timeline shapes hubness and neurogenetic profiles of the adult human brain *2022, Biorxiv. Cold Spring Harbor Lab. https://doi.org/10.1101/2022.04.01.486541*

Understanding the architectural principles that shape human brain networks is a major challenge for systems neuroscience. We hypothesize that the centrality of the different brain circuits in the human connectome is a product of their embryogenic age, such that early-born nodes should become stronger hubs than those born later. Using a human brain segmentation based on embryogenic age, we observed that nodes' structural centrality correlated with their embryogenic age, fully confirming our hypothesis. Distinct trends were found at different resolutions on a functional level. The difference in embryonic age between nodes inversely correlated with the probability of existence of links and their weights. Brain transcriptomic analysis revealed strong associations between embryonic age, structure-function centrality, and

the expression of genes related to nervous system development, synapse regulation and human neurological diseases. Our results highlight two key principles regarding the wiring of the human brain, "preferential age attachment" and "the older gets richer".

2. *Martin-Suarez S., Cortes JM,* ***Bonifazi P.*** Blockage of STAT3 during epileptogenesis prevents GABAergic loss and imprinting of the epileptic state. *BRAIN, awad055,* *https://doi.org/10.1093/brain/awad055*

Epilepsy, the condition of recurrent unprovoked seizures resulting from a wide variety of causes, is one of the world's most prominent neurological disabilities. Seizures which are an expression of neuronal network dysfunction occur in a positive feedback loop of concomitant factors, including also neuro-inflammatory responses, where seizures generate more seizures. Among other pathways involved in inflammatory responses, the JAK/STAT signaling pathway has been proposed to participate in epilepsy. We tested here an in vitro-model of temporal lobe epilepsy, the hypothesis that acute blockage of STAT3-phosphorylation during epileptogenesis, would prevent structural damages in the hippocampal circuitry, and the imprinting of both neural epileptic activity and inflammatory glial states. We performed calcium imaging of spontaneous circuits' dynamics in organotypic hippocampal slices previously exposed to epileptogenic conditions through the blockage of GABAergic synaptic transmission. Epileptogenic conditions lead to epileptic dynamics imprinted on circuits in terms of increased neuronal firing and circuit synchronization, increased correlated activity in neuronal pairs and decreased complexity in synchronization patterns. Acute blockage of the STAT3-phosphorylation during epileptogenesis prevented the imprinting of epileptic activity patterns, general cell loss, loss of GABAergic neurons and the persistence of reactive glial states. This work provides mechanistic evidence that blocking the STAT3 signaling pathway during epileptogenesis can prevent patho-topological persistent reorganization of neuro-glial circuits.