Research Interests – Prof. Dr. Julijana Gjorgjieva

The brain of a young baby needs to grow and acquire precise connections between individual nerve cells, called neurons, to be able to ultimately generate thoughts, percepts and behaviours. How does the brain do this? How do neurons in the developing brain grow and connect with remarkable precision and appropriate strengths to generate adult circuits involved in many tasks?

My research investigates how neural circuits undergo the transition from being weakly connected and non-functional to being appropriately connected and capable of executing diverse computations and behaviours. Various mechanisms drive the brain's self-organisation during early development. On one hand, interactions between different genes and molecules constitute a major aspect, guiding where neurons grow and to which other neurons they connect as they form networks. A second important factor are specific patterns of neural activity, which selectively strengthen or depress the synaptic connections between the neurons influencing the networks' computational properties. I use a combination of theoretical and computational approaches inspired by experimental data to build mathematical models of this process that allow us to dissect the individual influence of each involved mechanism. During adult life, the neural activity patterns are generated as we experience the sensory world around us, including things that we see, hear and smell. However, in early stages of development, which in humans is before babies are born, many of the sensory organs that perceive these sensory stimuli are immature. In these young brains, neural activity is spontaneously generated, providing training patterns to the brain to enable it to process sensory stimuli efficiently once the sensory organs mature. I investigate the patterns of spontaneous activity and their potential to generate appropriate connectivity and organisation in neural networks, and to ultimately guide thoughts, actions and behaviours. I am not only interested in development, but also in how these same principles apply to learning and memory formation in the adult.

My work is based on close collaborations with experimentalists who record patterns of neural activity in young animals, usually model organisms like mice and rats. We use machine learning approaches to identify features in these activity patterns that could instruct the high-level organisation of synaptic inputs on single neurons or entire networks. For instance, we have recently found that in the visual cortex of mice, spontaneous activity comes from two sources – transmitted from the eye and newly generated in the cortex. The activity from the

eye plays an important role in ensuring that the final circuit can transmit an ordered image of the visual world without scrambling nearby objects.

In contrast, the intrinsic cortical activity counterpart adapts during a prolonged developmental timescale to eventually prevent the propagation of large-scale epileptic activity while enabling efficient and distributed processing of sensory signals. These same activity patterns guide organisation at multiple scale: at the level of networks of neurons, and also at the level of synaptic inputs on the dendritic trees of individual neurons. Given the transient nature of developmental spontaneous activity, I am also interested in identifying the key factors that determine how this patterned activity is generated. For instance, inhibition is known to have a powerful role in controlling the total amount of excitation in adult circuits, and I am interested in how it becomes integrated as circuits grow and develop.

A second important question that interests me is how the brain transforms these non-random and unique patterns of spontaneous activity into specific patterns of connectivity that encode stimulus features and percepts. Various mechanisms of synaptic plasticity play an important part in this process. One of the most salient are so-called Hebbian mechanisms, which can potentiate or depress synaptic connection strengths depending on the patterns of activity experienced by the individual neurons that make the connection. My research aims to extract such plasticity mechanisms, also called learning rules, based on recorded patterns of neural activity, but also to build mathematical models that derive the functional implications of these learning rules. For instance, many learning rules modify synaptic connection strengths using precise combinations of spikes, which are the discrete signals that neurons use to communicate between each other. Our recent work has shown that synaptic plasticity can be decomposed into elementary connectivity motifs to drive organisation at the network level. A related aim of our research has been to identify the timescales at which these connectivity motifs interact to organise synaptic connectivity. We have proposed that the learning rules need to operate on timescales that match the timescales of the activity patterns they interpret into changes of connection strengths. How to obtain these timescales from the interactions among various molecules, receptors and proteins is a current and future focus of our research.

Despite being able to achieve specific connectivity, additional homeostatic mechanisms are needed to overcome the problem of unbounded synaptic potentiation or depression inherent in Hebbian synaptic plasticity mechanisms. Hence, in our work we also derive novel homeostatic mechanisms that control activity by enhancing inhibition or imposing non-local plasticity in the network. These mechanisms are indispensable to return network function to normal when neural circuits undergo external or internal perturbations. We also study their role in

enabling flexible learning when the carefully established excitatory-inhibitory balance needs to be temporarily disrupted.

Therefore, my work helps to characterise the complex synaptic, neuronal and network dynamics underlying developmental and learning trajectories. Knowing the timing and interaction of mechanisms during normal development, could have important implications for the understanding, treatment and prevention of developmental and psychiatric disorders. My group's theoretical approach can provide a key contribution in this process by identifying, modelling and analysing organisation principles across temporal and spatial scales, and brain regions, and integrating diverse experimental data.