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Regional and trans-regional heterogeneity of astrocyte morphology as a functional determinant of synaptic astrocyte-neuron interactions in the hippocampus

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Project description:

Synaptic transmission and its plasticity are modulated by fast reciprocal signal exchange between neurons and astrocytes on the synaptic level. This astrocyte-neuron signalling often involves diffusible signals. Therefore, its efficiency is likely to depend on the spatial proximity between neuronal structures and perisynaptic astrocyte processes and thus on astrocyte morphology. As a consequence, the heterogeneity of astrocyte morphology should have important implications for synaptic transmission. Indeed, we could demonstrate that the structural heterogeneity of astrocytes in the rodent CA1 stratum radiatum has important consequences for presynaptic release at the CA3-CA1 synapse, a standard model system in cellular neurophysiology. Using combinations of two-photon excitation fluorescence microscopy and novel electrophysiological approaches we could reveal that variations of the structural complexity of astrocytes determines presynaptic short-term plasticity via astrocytic glutamate receptors, likely through differential coverage of synapses by astrocyte processes. In this project, we will now build on this finding by first uncovering how regional intercellular heterogeneity of astrocyte morphology determines the local coverage of glutamatergic CA3-CA1 synapses and also GABAergic connections. To this end, we have established expansion microscopy. ExM enables us to super-resolve the structural relationship between synapses and perisynaptic astrocyte structures, which cannot be fully visualized by diffraction-limited microscopy. Second, we will extend our investigation to adjacent layers of the CA1 region, where astrocytes display different morphologies and cover other dendritic domains of the same CA1 pyramidal cell neurons and their incoming excitatory connections. By combining imaging and electrophysiological techniques with ExM we will reveal how trans-regional heterogeneity of astrocyte morphology determines the local properties of excitatory synapses received by a single neuronal cell type. Third, we will establish how astrocyte morphology and its intercellular and subcellular specialisation determines the responsiveness of astrocyte to synaptic activity. Here we will focus on how the proximity of astrocyte processes to glutamatergic synapses determines the likelihood that a synaptic stimulus results in a local astrocytic Ca2+ transients and how it affects their magnitude and underlying signalling cascades. These functional experiments will again be supported by structural analysis using ExM. Fourth, we will explore the relationship between astrocyte structure, its heterogeneity and synaptic astrocyte-neuron interactions in human tissue samples. In summary, we will establish how regional and trans-regional structural heterogeneity and specialisation of astrocytes determine local synaptic coverage by astrocyte processes and the functional relevance for astrocyte-neuron interactions.

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