A comprehensive and quantitative thalamocortical circuit diagram at the mesoscopic level

Awardee: Haining Zhong
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Awardee Institution: Oregon Health and Science University

As recognized by the NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, the precise wiring diagram of brain circuits is the missing link between our understanding of individual gene function and behavioral outcomes, serving as a focal point of current neuroscience research efforts. It is increasingly appreciated that brain circuits are organized around individual functional subdivisions and different neuronal subtypes. However, the complexity of brain subdivisions and cellular heterogeneity has presented major challenges in dissecting the precise circuit mechanisms underlying specific animal behaviors.
We have established a comprehensive mesoscopic circuit diagram, including both the sub-region and cell type components, of the thalamocortical pathway in mice. The thalamus relays both sensory and motor information to the cortex and is an integral part of all cortical executive functions. Dysfunction along this pathway plays a major role in schizophrenia and frontotemporal dementia. We employed a systematic, high-throughput viral approach to visualize thalamocortical axons with high sensitivity. We then developed algorithms to directly compare injection and projection information across animals. By tiling the mouse thalamus with 254 injections, we constructed the first densely-sampled comprehensive map of thalamocortical projections that described the thalamic subdivisions that target specific cortical sub-regions. Using cluster analysis, we identified new circuit properties that could only be revealed by such a large scale, complete dataset. We verified that the characterized projections formed functional synapses using optogenetic approaches. As an important application, we determined the optimal stereotaxic coordinates for targeting specific cortical sub-regions and expanded these analyses to localize cortical layer-preferential projections. This dataset will serve as a foundation for functional investigations of thalamocortical circuits. Our approach and algorithms also provide an example for analyzing the projection patterns of other brain regions.