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A connectomics approach to investigate mouse models of neurodegenerative diseases

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Abstract

Activity of a single brain structure alone typically is not sufficient to produce behavior. Instead, behaviors require the cooperative assembly of multiple neural circuits and networks. Therefore, in disease states, both individual structures and their projection sources and targets are affected. Such "connectopathies" have been implicated in neurological disorders such as Alzheimer's Disease (AD). However, currently little is known about the neuroanatomical wiring in neurological disease models and how these pathological connections correspond to cognitive deficits. To address this question, our research group adopted a high-throughput connectomics approach to systematically characterize the early and advanced alterations of hippocampal-subicular neuronal networks in a mouse model of AD, which expresses nonmutant human Tau isoforms in the absence of mouse Tau isoforms (htau mice). We found that across the progression of the disease, compromised connections correlated with neuropathological hallmarks (i.e., neurofibrillary tangle) and cognitive-behavioral impairments in a hippocampal dependent contextual fear conditioning procedure. We hope our approach will provide a novel strategy for exploring diagnostic and prognostic fingerprints not only for AD, but also for other disconnection syndromes.

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