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Early cell-autonomous mechanism of cellular hyperactivity in a rat model of Alzheimer's disease

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Neuronal network dysfunction is a hallmark of Alzheimer's disease (AD). However, the underlying pathomechanisms remain unknown. We analyzed the hippocampal micronetwork in a rat model of AD at a disease stage prior to extracellular amyloid beta (Aβ) deposition. We established two-photon Ca2+-imaging in vivo in the hippocampus of rats to reveal early neuronal hyperexcitability. This hyperexcitability was mediated by changes in the passive properties and intrinsic excitability of CA1 pyramidal neurons. We observed reduced dendritic complexity and length associated with increased neuronal input resistance and prolonged action potential width. Surprisingly, synaptic inhibition was intact in the hippocampus arguing for cell-autonomous deficits in CA1 pyramidal neurons. These data support the view that altered intrinsic excitability of neurons may precede inhibitory dysfunction at an early stage of disease progression.