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Effects of patient-derived pathogenic anti-NMDA receptor autoantibodies on synaptic function and network activity

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Over the last decade, a growing number psychiatric and central nervous system (CNS) disorders have been linked to autoantibodies against synaptic and neuronal cell-surface proteins. These autoimmune encephalopathies present with a wide range of symptoms, from prominent psychiatric and cognitive manifestations, such as psychosis, distorted thoughts and memory loss, to severe seizures and autonomic instability. Studies of patient cerebro-spinal fluid (CSF) revealed that in a population of patients the antibodies recognize an epitope situated within the N-terminal domain of N-methyl-D-aspartate receptor (NMDAR), likely causing receptor cross-linking and subsequent internalization. However, these studies could not discriminate between the effects of anti-NMDAR and various other anti-neuronal antibodies present in patient CSF. Moreover, the antibodies' specific mechanisms of action and how they affect different levels of neuronal and brain function are not fully understood.

To address these questions, we recently generated recombinant monoclonal antibodies cloned from single B cells from patients' CSF, which give us a unique tool to characterize the specific contribution of anti-NMDAR antibodies to disease pathology. Here, using a combination of in vitro cell imaging assays and electrophysiological recordings, we investigated the effects the antibodies on single neuron function and network activity. We are currently examining the specificity of the antibody to various receptor and neuronal subpopulation. These data could provide more insights into the specific mechanisms of anti-NMDAR encephalitis and possibly explain its multimodal symptomatology.