Cellular resolution circuit mapping in mouse models of autism with soma-targeted opsins

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Autism spectrum disorder is a range of complex neurodevelopment disorders, characterized by social impairment, communication difficulties, and repetitive patterns of behavior. Hundreds of candidate autism risk genes have been identified. The proteins coded for by these genes have very diverse molecular functions; ranging from synaptic scaffolding proteins and ion channels to transcription factors and translation modulators. How could mutations in genes coding for such diverse molecular functions result in such specific behavioral phenotypes? One hypothesis is that the convergence is at the circuit level. To search for circuitry endophenotypes among mouse models of autism, a method to map synaptic connectivity with higher throughput than paired patch-clamp recording is required. By expanding a two-photon beam in the imaging plane using the temporal focusing method and restricting channelrhodopsin to the soma and proximal dendrites, we are able to reliably evoke action potentials in individual neurons, verify spike generation with GCaMP6s, and determine the presence or absence of synaptic connections with patch-clamp electrophysiological recording. We evaluated synaptic connectivity in the lateral amygdala (LA) in the neuroligin3 R451C mouse model of autism using this method and quadruple patch clamp recordings. We found that feedback inhibition was enhanced due to a combination of increased connection probability from low threshold spiking (LTS) somatostatin expressing inhibitory neurons to LA principal neurons and increased excitatory synaptic connection probability and unitary strength from LA principal neurons to LTS inhibitory neurons. The distal dendrites of principal neurons in LA are under sustained inhibitory control by somatostatin interneurons that is transiently released to facilitate associative plasticity during fear learning. The neuroligin3 R451C mice show fear generalization in a two-tone differential cued fear conditioning test. This inability to learn specific contingencies between tones signaling shock vs safety may be due to the hyper-engagement and broadened connectivity of the somatostatin feedback neurons in these mice.