

Poster

CONNECTOMIC ALTERATIONS IN AUTISM: A STUDY OF HIPPOCAMPAL, CEREBELLAR AND COLLICULAR CIRCUITS IN AMBRA1$^{+/-}$ AND CHEMOGENETIC MOUSE MODELS

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Introduction. Autism spectrum disorder (ASD) is increasingly described as a disorder of brain connectivity. Evidence comes from macroscale diffusion and functional imaging and from region-level projection mapping, neither of which resolves which cell types lose which connections within a circuit. We reconstructed circuits at single-neuron resolution in two complementary mouse models. Ambra1$^{+/-}$ is a genetic model of female ASD characterised by hippocampal parvalbumin interneuron loss, while in a chemogenetic model DREADDs acutely silence CA1 parvalbumin interneurons.

Methods. Hippocampus, cerebellar cortex and superior colliculus were sectioned at 45 µm and immunostained for GABA, NeuroTrace, beta-tubulin and SMI-312, then imaged by confocal microscopy. These regions support social memory, motor coordination and multisensory integration, all affected in ASD. Neuronal structures were segmented with a deep learning model, reconstructed in three dimensions and converted into directed graphs carrying morphological class, neurotransmitter identity and Allen Brain Atlas region at each node.

Results. Relative to wild-type controls, both models were altered in cerebellum and hippocampus. The granule cell to Purkinje cell pathway was strongly reduced (−68% Ambra1$^{+/-}$; −75% chemogenetic), the interneurons modulating Purkinje cell firing were lost, and signals required 26% more steps to traverse the network. The pathway from the dentate gyrus into the memory circuit was disrupted in both models (−50%; −94%), with increased inhibitory neurons at the gate. Downstream the models diverged. CA1 was hyperexcitable in Ambra1$^{+/-}$ but hyper-inhibited in the chemogenetic model, where acute silencing triggers structural compensation. The superior colliculus was relatively spared in Ambra1$^{+/-}$, whereas the chemogenetic model lost 37% of its collicular inhibitory neurons, alongside increased excitatory feedback from the midbrain and a shift of inter-regional connectivity towards excitation.

Conclusions. The same endpoint, reduced CA1 inhibition, produced opposite network states depending on whether it arose developmentally or acutely, indicating that compensation shapes the outcome as much as the initial insult. Regional vulnerability also differed, with the colliculus reorganised only in the chemogenetic model. Comparable behavioural phenotypes in the two models conceal this divergent circuit organisation, accessible only through structural reconstruction.

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