Experience-dependent Plasticity of Cortical Organotypic Networks in Response to Days of Patterned Stimulation

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Synaptic plasticity is traditionally studied at the level of single synapses on the time-scale of minutes and hours. However, many forms of learning ultimately rely on changes in network function which occur over days. Indeed days of altered sensory input are often necessary to induce experience-dependent plasticity¹,²,³. In order to study these long-term forms of plasticity in a reduced system, and study the learning rules involved, we developed a method to administer patterned stimuli to cortical organotypic networks over the course of days. Here we examined how chronic patterned stimulation affects synaptic strength and network dynamics. We also explore whether an in vitro network can reorganize its response to reflect the patterns of sensory stimuli to which they are exposed. Specifically, we asked whether the network has the capacity to learn a stimulus pattern or time intervals.

First, we examined the predictions of cooperation/competition models of cortical plasticity, where coactive inputs are cooperatively potentiated while uncorrelated inputs compete in the ability to drive a neuron⁴,⁵. Two implanted electrodes were activated in-phase or out-of-phase. Subsequent whole cell-recordings did not reveal any bias in the form of pathway selectivity, indicating that the predictions of BCM were not observed in this preparation. However, we find that sequential stimulation of the two input pathways with a short delay interval (50 or 100 ms) produces synaptic and network plasticity as measured by differences in the initial EPSP slope and the integrated EPSP area. The response is modified so that the pathway activated last becomes dominant, which is opposite of what would be predicted by STDP rules. Additionally, the most robust change is in the polysynaptic response, suggesting that we are observing network reorganization in response to patterned stimulation. Mechanistically, the observed change could be explained by decreased strength of excitatory to inhibitory synapses in response to the second stimulation pathway; however, many mechanisms are likely operating in concert, including local changes in recurrent excitatory connections. Regarding the functional implications of the observed plasticity, the dominance of the response to the second input suggests that the sequence may be treated as a unitary spatial-temporal stimulus, and that the most salient feature of the stimulus pattern is the end.

In order to understand whether the networks were adapting to the patterned stimuli, we analyzed the timing of larger amplitude polysynaptic events after chronic stimulation. We found that exposure to the in-phase or sequential stimulation patterns produces different temporal profiles of activity, thus suggesting that networks are shaped by the specific temporal structure of the stimuli to which they are exposed.