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NEURAL DEVELOPMENT

Clustering connections

Repetitive bursts of spontaneous neural activity occur in the developing mammalian brain before sensory systems become functional, and these bursts are thought to have a role in the formation of neural circuits. How such bursts of activity travel across networks and individual neurons has been well described, but little attention has been paid to spontaneous activity patterns at the level of synapses. Through studying such patterns, Lohmann and colleagues now show that repetitive spontaneous activity in developing neural networks causes spatiotemporal clustering of functional synapses on dendrites.

To examine synaptic inputs during spontaneous activity, the authors conducted calcium imaging alongside patch-clamp recordings in hippocampal CA3 pyramidal neurons in neonatal rat brain slices. They confirmed that spontaneous bursts of neural activity occurred in these *in vitro* preparations and showed that the dendrites of the pyramidal cells exhibited spontaneous transient increases in cytosolic calcium levels (so-called calcium transients).

Approximately half of the calcium transients coincided with synaptic currents, and this co-occurrence was blocked by the application of ionotropic glutamate receptor inhibitors, indicating that such calcium transients reflected glutamatergic synaptic transmission events. The authors subsequently fine-mapped calcium transients along the dendrites of individual cells and defined synaptic and non-synaptic sites on the basis of the rate of coincidence of transients and currents. The application of ionotropic glutamate receptor inhibitors blocked calcium transients at the designated synaptic sites but not at the non-synaptic sites, supporting the authors' classification.

Using this method to define synapses, the authors investigated the spatiotemporal patterns of synaptic transmission at multiple synapses along individual dendritic trees during spontaneous bursts of activity. From one burst of activity to the next, patterns of activity differed between synapses along a dendritic tree, although synapses in close spatial proximity to each other — within 16 μm — were more likely to show co-activation during a burst of activity than synapses further apart from each other. This highly correlated activity of neighbouring synapses could not be attributed to individual axons forming multiple synapses on short stretches of dendrite.

These findings indicate that synaptic inputs of individual developing CA3 hippocampal neurons have a defined spatiotemporal structure. In the final part of the study, the authors investigated whether this structure was determined by spontaneous activity. They incubated slices for 3–4 days in normal medium or medium containing tetrodotoxin (TTX; which blocks action potential firing) and, after placing all slices in normal recording medium, assessed the pattern of synaptic inputs onto pyramidal cells during spontaneous activity. Pyramidal cells incubated in normal medium showed highly correlated activity in neighbouring synapses during bursts, but such correlated activity was absent in TTX-treated cells (overall activity was similar between the two groups), indicating that spontaneous activity directs the spatiotemporal clustering of functional synapses. This sorting process involves glutamatergic neurotransmission, as incubation of slices over a similar period with an NMDA receptor inhibitor also abolished synaptic clustering.

Taken together, these results show that spontaneous activity and NMDA receptor-mediated signalling influence the way in which neurons are connected during development.

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ORIGINAL RESEARCH PAPER Kleindienst, T. *et al.* Activity-dependent clustering of functional synaptic inputs on developing hippocampal dendrites. *Neuron* **72**, 1012–1024 (2011)