This Week in The Journal

Effects of Microglia on Synaptic Connections in Adult Cortex

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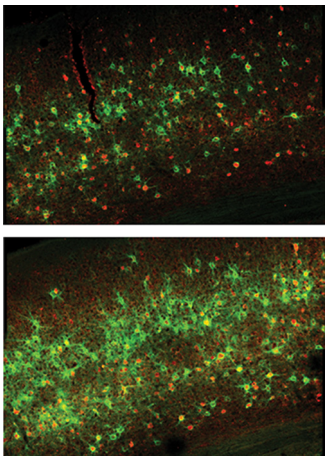
(see pages 1274–1287)

During development, neurons produce an overabundance of synapses, many of which are subsequently pruned. This pruning is mediated by microglia, which phagocytose less active synaptic elements. Although neural circuits become more stable over time, synaptic remodeling continues throughout life, allowing the incorporation of new information and the elimination of no-longer-relevant connections. Accumulating evidence indicates that microglia contribute to this circuit refinement as well. For example, depleting microglia increased the density of dendritic spines and caused mice to retain a memory that otherwise would be forgotten (Wang et al., 2020, Science 367:688), suggesting microglia promote synapse removal. Conversely, microglia can promote synapse formation and strengthening by digesting elements of the extracellular matrix (Nguyen et al., 2020, Cell 182:388). Liu et al. have now elucidated how these anatomical changes affect neuronal activity in mouse primary visual cortex.

Administering colony stimulating factor 1 receptor (CSF1R) inhibitors to mice for 3 weeks caused a ~95% reduction of microglia in visual cortex. Consistent with previous work, this decrease was associated with an increase in the density of extracellular perineuronal nets. In addition, microglia depletion led to a near doubling of the frequency of spontaneous EPSCs in layer 5 pyramidal cells, recorded in brain slices, and a near quadrupling of the number of excitatory inputs from local cells. Importantly, the number of inhibitory inputs to layer 5 pyramidal cells also increased substantially after microglia depletion. Consistent with these findings, the frequency of calcium transients in both pyramidal cells and parvalbumin-expressing interneurons in layer 2/3 was higher in microglia-depleted visual cortex than in controls during visual stimulation *in vivo*. Notably, in both cases, activity levels returned to baseline levels after treatment with CSF1R inhibitors was stopped and microglia repopulated the cortex.

These results support the hypothesis that microglia contribute to circuit remodeling and function in adult cortex. The finding that both neuronal connectivity and perineuronal-net density increase after microglia depletion is a bit surprising, because perineuronal nets are thought to limit synapse formation. Therefore, future work should determine which effects result directly from microglia depletion and which are secondary effects resulting from the attempts of the brain to restore synaptic homeostasis.



Compared with controls (top), visual cortex of mice treated for 5 weeks with a CSF1R inhibitor (bottom) had a greater density of perineuronal nets (green) and higher expression of parvalbumin (red). See Liu et al. for details.

Social Effects on Stress-Induced Facilitation of LTD

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(see pages 1317–1330)

In a stressful world, social interactions are a double-edged sword. On one hand, interacting with others can buffer the effects of stress. On the other hand, stressed individuals can transmit the effects of stress to their companions. Although behavioral and physiological manifestations of stress buffering and transmission have been well documented (Kiyokawa, 2017, Curr Top Behav Neurosci 30:47–65), little is known about the changes in neural circuitry that accompany these effects. Lee et al. addressed this by examining how social interactions affect one neural consequence of stress exposure in mice: an increase in the readiness of hippocampal synapses to undergo long-term depression (LTD).

Consistent with previous work, low-frequency stimulation—which was insufficient to induce plasticity in hippocampal slices from control mice—induced LTD in slices from males that had been subjected to restraint-and-shock stress. If mice were housed with an unstressed conspecific for 1 week before and 30 min after stress, however, approximately half of stressed mice did not exhibit LTD priming. Conversely, LTD priming was present in approximately half of unstressed mice that were housed with a stressed partner. Notably, unstressed mice that exhibited enhanced LTD also had elevated levels of corticosterone, as did all stressed mice.

Buffering and transmission of stress effects were influenced by social hierarchy and social interactions. Buffering did not occur—that is, all stressed mice showed enhanced LTD—if the stressed mouse was subordinate to its partner. In addition, buffering of LTD priming was associated with receiving more grooming from the unstressed partner. In contrast, transmission of LTD priming to the unstressed mouse was associated with more anogenital sniffing of the stressed companion. Importantly, ablating the olfactory epithelium or removing the adrenal glands of unstressed mice, or placing a barrier between cagemates after stress exposure, prevented stress buffering and transmission.

These results indicate that social interactions can both mitigate and transmit the effects of stress on synaptic metaplasticity in the hippocampus. These effects require direct contact, including sniffing, between stressed and unstressed mice, as well as an increase in serum corticosterone levels in the unstressed companion. Future work should determine how changes in hippocampal metaplasticity affect behavior, including subsequent responses to stress.

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