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NEURONAL CIRCUITS

The sound of fear

At the cellular level, the process of learning is associated with changes in synaptic strength, but much less is known about the neuronal circuits that underlie learning-induced changes in neuronal activity and ultimately in behavioural output. Reporting in *Nature*, Lüthi and colleagues identify a distinct circuit in the auditory cortex that is required for complex-sound associative fear learning.

Whereas the amygdala is known to be involved in the acquisition of fear memories, the role of the auditory cortex in this process has been debated. First, the authors showed that their fear conditioning protocol (in which a foot shock was administered along with complex auditory stimuli) required activation of the auditory cortex. Indeed, inhibition of neuronal activity by local injection of the $GABA_A$ receptor agonist muscimol into the auditory cortex abolished fear conditioning. They then used two-photon calcium imaging to investigate the neuronal circuit underlying this fear learning and found that foot shocks alone or foot shocks paired with tones, but not tones alone, strongly activated neocortical layer 1 neurons, which are mostly GABAergic interneurons. This activation depends on stimulation of nicotinic acetylcholine receptors (nAChRs), as the foot-shock responses were prevented when the cells were exposed to nAChR antagonists. As cholinergic afferents from the basal forebrain are the major source of cholinergic input in the mouse neocortex, it is likely that they are responsible for the activation of layer 1 interneurons during foot shocks.

Nicotinic activation of layer 1 interneurons had been hypothesized to lead to the inhibition of layer 2/3 interneurons, and electrophysiological recordings of parvalbumin-expressing (PV^+) layer 2/3 interneurons in head-fixed mice indicate that foot shocks lead to a prominent and long-lasting inhibition of these cells. Moreover, PV^+ cells are known to inhibit local pyramidal neurons, so disinhibition of PV^+ cells was predicted to cause pyramidal neuron excitation. Indeed, when the authors examined extracellular recordings in freely moving mice they found that tones associated with foot shocks excited pyramidal neurons much more than did tones alone. Finally, by expressing channelrhodopsin 2 in PV^+ neurons, they were able to confirm that the fear learning was strongly reduced in animals that were subjected to optogenetic stimulation compared to controls.

Together, these findings highlight that a disinhibitory circuit comprising basal forebrain cholinergic neurons, layer 1 interneurons, layer 2/3 PV^+ interneurons and pyramidal cells is essential for fear learning. Furthermore, this study shows that with existing technologies it is possible to start dissecting the circuits underlying different forms of learning and memory.

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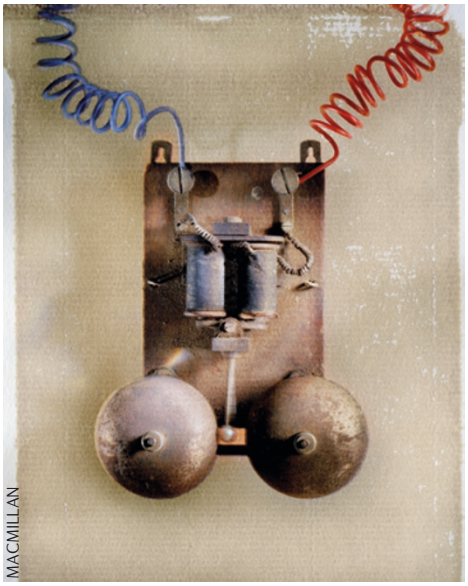
> “a distinct circuit in the auditory cortex … is required for complex-sound associative fear learning”

ORIGINAL RESEARCH PAPER Letzkus, J. J. *et al.* A disinhibitory microcircuit for associative fear learning in the auditory cortex. *Nature* 7 Dec 2011 (doi:10.1038/nature10674)



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