Research reveals 'exquisite selectivity' of neuronal wiring in the cerebral cortex

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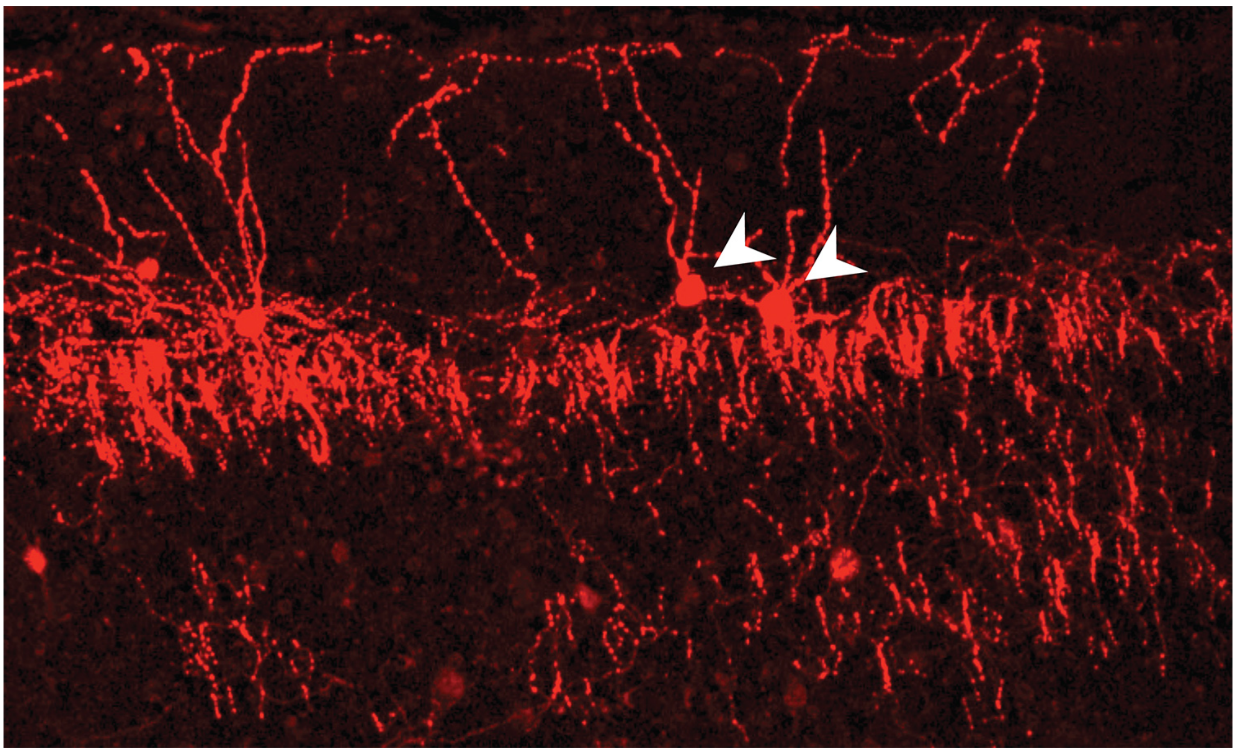


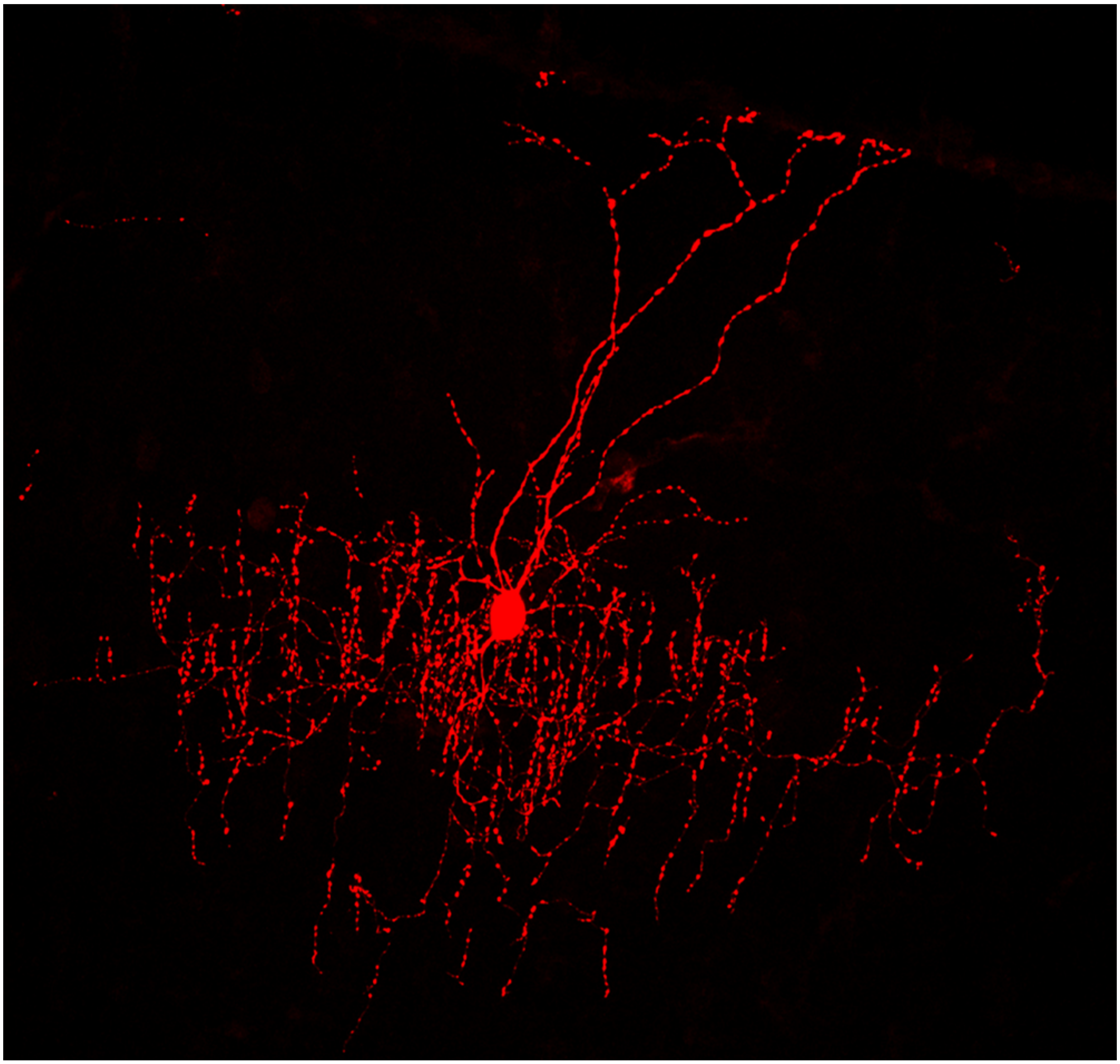
The CSHL team traced local and long-range connections of chandelier cells in the mouse brain. Arrow heads point to two of the chandelier cell soma or cell bodies, from each of which hundreds of candelabra-like arbors reach out to connect with local pyramidal neurons in a part of the cerebral cortex. These spatially intermixed excitatory neurons segregated into two groups, distinguished according to where in the brain they project to and their likely function. The chandelier cell can inhibit one group, causing a fear reaction to stop; from the other group it receives high-level information from elsewhere in the cortex that presumably informs its inhibitory activity. Credit: Huang Lab, CSHL

The brain's astonishing anatomical complexity has been appreciated for over 100 years, when pioneers first trained microscopes on the profusion of branching structures that connect individual neurons. Even in the tiniest areas of brain tissue, the pathways are tangled, almost indescribably dense. Today, neuroscientists are trying to figure out the workings of all those cells and the networks they form, the ultimate grand-challenge problem.

In a study appearing today in *Nature Neuroscience*, a team from Cold Spring Harbor Laboratory (CSHL) uses advanced technologies to illuminate the connectivity pattern of chandelier cells, a distinctive kind of inhibitory cell type in the mammalian brain. They reveal for the first time how this candelabra-shaped cell interacts with hundreds of excitatory cells in its neighborhood, receiving information from some, imparting information to others.

In the experiments just reported, these highly specific interactions are situated in the context of a larger global network regulating the fear response in mice. Chandelier cells play analogous roles in other networks, capable of inhibiting excitatory neurons in a variety of contexts. The research therefore suggests more broadly how communication hierarchies may be shaped in the brain, as diverse and often intermingled sets of neurons in "local" areas both receive inputs from and send outputs to distinct brain areas, near and far.

The team, led by CSHL Professor Z. Josh Huang and including researcher Joshua Gordon, M.D., Ph.D., director of the National Institute of Mental Health, focused on dense crowds of excitatory cells called pyramidal neurons - several hundred of which can connect with a single chandelier cell. Because each chandelier cell may control the firing of hundreds of pyramidal neurons, it has been suggested that they exert a kind of "veto" power over local excitatory messages. But there is more to the story. As this research shows, each chandelier cell also can receive inputs from hundreds of excitatory cells, input that influences whether or not it inhibits a circuit in which it is involved.

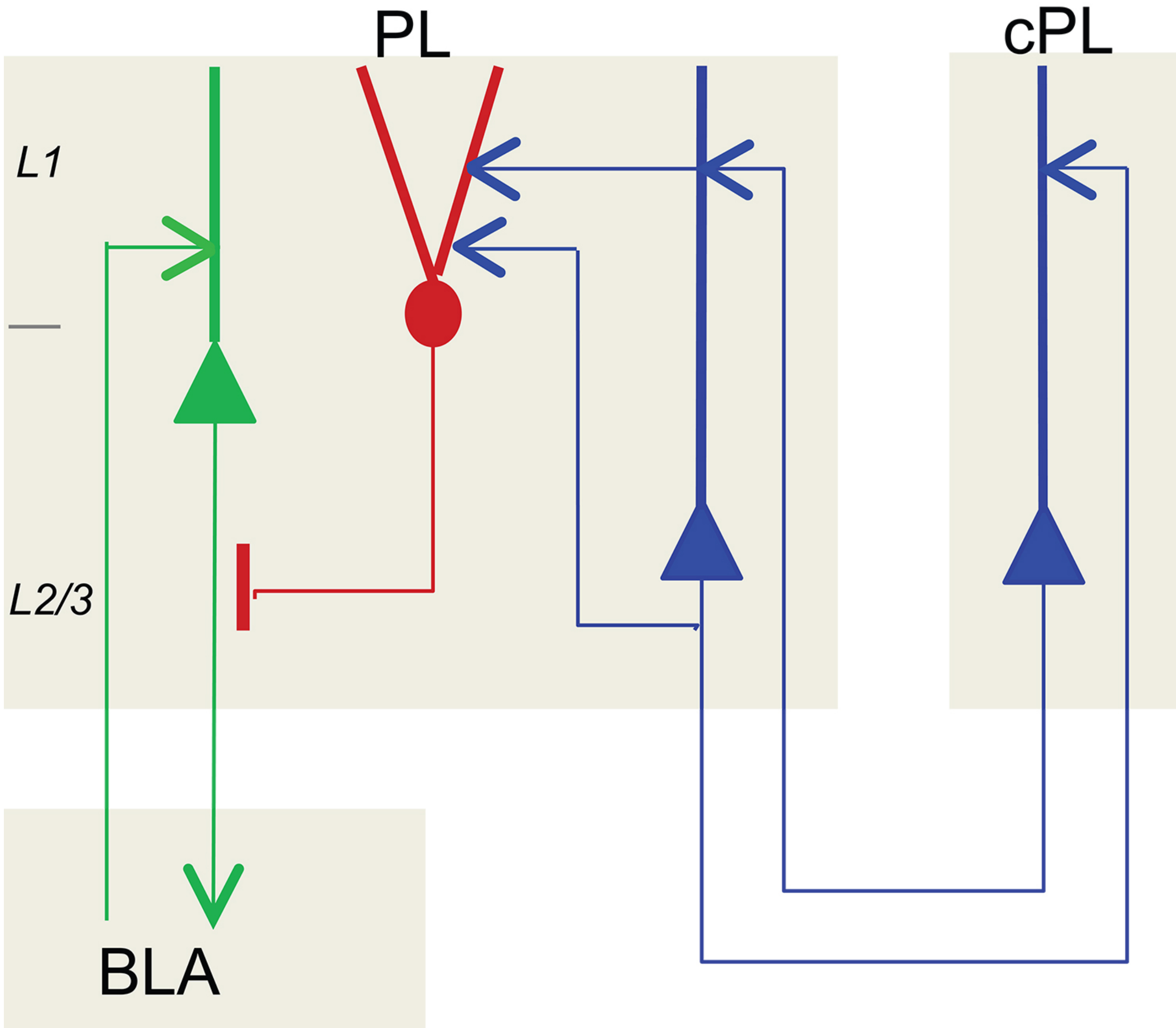


The chandelier cell, discovered only 45 years ago, is one of the most distinctive cells int he mammalian brain. Each one can synapse with hundreds of neighboring excitatory cells, accounting for its candelabra-like shape. New research is beginning to reveal how they work. Credit: Huang Lab, CSHL

The new research reveals how spatially intermixed pyramidal neurons that were associated with single chandelier cells in the mouse prelimbic cortex segregated into two groups. These were distinguished according to where in the brain they project to and their likely function.

One ensemble of these pyramidal cells was shown to transmit information to the amygdala, resulting in a fear response; this ensemble can be inhibited by the chandelier cell. A second ensemble projects to cortical areas conveying information from the thalamus, a relay station that Huang speculates is sending higher-order information to the chandelier cell. This information might reflect, for example, whether the individual (whether mouse, person, or other mammal) should be afraid of something that it has sensed in its environment, given past experience.

"This circuit highlights the exquisite selectivity of neuronal wiring with respect to inhibition in the most complex and heterogeneous part of the brain," Huang says. "It also illustrates the directionality of information flow in local and global brain networks. The messages move in a specific direction - the chandelier cell's overall inhibitory and information-routing role being the result of signals to it and from it by specific sets of neurons to which it is connected."



This circuit diagram summarizes the findings of Huang and colleagues. A chandelier cell (red) can inhibit excitatory pyramidal neurons (green) in a fear circuit that leads to the amygdala (BLA). A separate set of excitatory neurons (blue) provides input to the chandelier cell, most directly from the thalamus, and possibly reflecting high-order cortical information pertaining to the fear reaction. Credit: Huang Lab, CSHL

More information: Selective inhibitory control of pyramidal neuron

ensembles and cortical subnetworks by chandelier cells, *Nature Neuroscience* (2017). DOI: 10.1038/nn.4624

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