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Disinhibition plus instruction improve brain plasticity

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(PhysOrg.com) -- The healthy brain has balance of excitatory and inhibitory signals that stimulate activity but also keep it under control. Some brain diseases, like autism and Down's syndrome, have too much inhibition, which impairs cognitive functions. Reducing inhibition appears to improve cognition, and it can restore juvenile plasticity in the adult brain, making it more adaptable. Scientists want to recapture this plasticity to enhance recovery from stroke or brain injury and to treat people suffering from developmental or degenerative brain disorders. Now, a new MIT study using a common antidepressant that coincidentally reduces neural inhibition shows how this "disinhibition" works in ways that might be used therapeutically.

“It was previously known that the antidepressant fluoxetine, or Prozac, can improve plasticity and also reduce neural inhibition, but how this worked was unclear. We found that fluoxetine-mediated disinhibition permits neuronal rewiring, but it must be accompanied by an instructional cue for how the neurons should rewire themselves in a constructive, meaningful manner,” said Elly Nedivi, associate professor of neurobiology at the Picower Institute for Learning and Memory and senior author of the study in the May issue of *Nature Neuroscience*.

In normal development, the maturation of the inhibitory circuitry closes the “critical period” when the brain most easily rewires itself. The adult brain can still learn from experience, but more slowly. Scientists thought that ongoing learning does not rewire the brain structurally but only unmasks or re-weights existing connections. But five years ago, Nedivi

and colleagues showed that locally connecting neurons, called interneurons, actually do structurally remodel themselves on a daily basis, even in the adult brain.

“Interneurons are the primary inhibitory neurons in the cortex, so we thought that this structural rearrangement of the inhibitory circuit could be a mechanism for experience-dependent functional plasticity in the adult brain,” she said.

For the current study, Nedivi and colleagues used a standard visual manipulation — closing one eye — to induce plasticity in adult mice. Such monocular deprivation forces neurons to shift their allegiance from the closed to the open eye. This shift happens more slowly in adults than in juveniles, for reasons this study now explains.

The team used imaging technology developed by Peter T. So, professor of mechanical engineering and biological engineering at MIT, to obtain time-lapse 3-D reconstructions of entire interneurons, including the branching arbors of dendrites that relay signals from other neurons to the cell body.

In experiments led by Jerry Chen, a former graduate student in Nedivi’s lab, they saw the dendritic trees in the deprived zone almost quadruple their remodeling in response to visual deprivation.

This structural remodeling occurred in two phases. During the first few days, the inhibitory interneurons retracted their dendrites away from other neurons. This retraction reduced the inhibition of excitatory neurons, which then become more active. Later, the interneurons’ dendrites also grew outwards, forming new connections with neurons receiving input from the functioning eye — literally rewiring the circuitry.

The need to first retract before forming new connections explains the slow adaptation of the adult brain. “We realized we could speed up the constructive remodeling phase by artificially reducing inhibition with fluoxetine,” said Chen.

They found that giving the mice fluoxetine allowed the neurons to bypass the retraction phase and go right to the constructive phase. But this constructive remodeling had to occur at the same time as visual stimulation — an instructive clue — from the functioning eye.

“We think this finding could have clinical relevance,” Nedivi said. For example, during stroke rehabilitation, providing instructive activities with fluoxetine might accelerate a brain region’s adoption of a function previously performed by a damaged region.

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