

NEWS

# Brain's adaptability begins at single synapse

BY KELLY RAE CHI

10 AUGUST 2010

Plastic process: The steps that allow a neuron (red) to rapidly adapt to the outside world can take place at a single synapse (green).

Researchers have uncovered an important molecular piece of a learning mechanism that occurs at the junction between neurons. The findings, which may help understand how the brain is disrupted in disorders such as autism, appear in the 24 June issue of *Neuron*<sup>1</sup>.

Disruptions in synaptic plasticity — the ability of synapses, the connections between neurons, to change in strength — have long been linked to autism and related disorders, such as fragile X syndrome. But much less is known about 'metaplasticity,' the degree to which synaptic plasticity itself can strengthen or weaken.

Researchers believe that metaplasticity is controlled by molecular changes occurring in entire neurons and networks. Although its exact mechanisms are still unclear, the new study shows for the first time that it can also occur at a single synapse.

Without metaplasticity, neuronal activity would go haywire during early development. Strong synapses would strengthen at a constant rate, making them less sensitive to stimulation, and weak synapses would get steadily weaker until they are eliminated. Tweaks to the levels of plasticity

prevent these situations, creating stable yet flexible circuits that allow the brain to adjust to changes in the environment and learn new things.

Because the new study reveals that metaplasticity can be controlled at individual synapses, "it's the type of paper that's of fundamental importance for almost any [neural] disorder you can think of," says **Ben Philpot**, associate professor of cell and molecular physiology at the University of North Carolina at Chapel Hill, who was not involved with the study.

The work has particular relevance to autism, he adds, because dozens of studies have implicated **synaptic proteins in the disorder**. These or similar proteins could be involved in synaptic plasticity and metaplasticity.

"People haven't been looking at metaplasticity in existing mouse models of autism, and I think it's time that they do," Philpot says.

## Firing rate:

For decades, researchers have believed in Hebb's rule, a theory of synaptic plasticity established in 1949, which proposes that 'neurons that fire together, wire together,' — meaning the more that particular neurons are activated together, the stronger their synapses become. In the early 1980s, scientists first suggested that the plasticity of an individual neuron's synapses can change over time. The 'BCM rule' — named for its founders **Elie Bienenstock**, **Leon Cooper** and **Paul Munro** — hints that the activity of that neuron influences whether its connections strengthen or weaken<sup>3</sup>.

Since then, researchers have discovered that changes in the number of NMDA receptors — which respond to the excitatory neurotransmitter glutamate — help control metaplasticity. For example, in a neuron deprived of stimulation, the number of NMDA receptors may increase as a compensatory mechanism, which in turn would make the synapse more likely to strengthen in response to a stimulus.

In 2007, **Mark Bear**'s team at the Massachusetts Institute of Technology showed that depriving young rodents of stimulation to their visual cortexes — by keeping them in the dark — triggers an increase in NR2B, a protein component of the NMDA receptor, across the region<sup>4</sup>.

In the new study, scientists at Duke University labeled and selectively silenced synapses in neurons taken from the rat hippocampus, a brain area involved in learning and memory. They found that, compared with active synapses on a single neuron, silenced synapses on the same neuron are more likely to strengthen when given glutamate.

This suggests that metaplasticity can occur at a single synapse rather than the entire neuron. "This is an amazingly local level of control," says lead investigator Michael Ehlers, senior vice president and chief scientific officer for neuroscience at Pfizer. "These inactive synapses are primed to

undergo explosive increases in synaptic strength when they at last become strongly activated."

Because they are more sensitive to activation, silent synapses might be more responsive to newly forming connections compared with active synapses. That may help animals adapt to changing environments, Philpot says.

## Local control:

The study also found an underlying mechanism for metaplasticity: inactive synapses accumulate twice as many NMDA receptors containing the NR2B subunit than do active sites, allowing silenced neurons to become more sensitive to stimulation.

Researchers had assumed that all of a given cell's synapses respond uniformly to changes in plasticity. Now that they know otherwise, it will be interesting to see how a neuron instructs certain synapses to make more NR2B proteins than other synapses, notes **Mriganka Sur**, head of brain and cognitive science at Massachusetts Institute of Technology.

The amount of NR2B could be controlled by local protein synthesis at individual synapses, or through epigenetic changes to gene expression in the nucleus, Sur says.

Although the implications for autism are not yet clear, several lines of evidence hint at a link between the disorder and metaplasticity.

For instance, fragile X mental retardation protein, which is missing in some people with autism and in those with fragile X syndrome, **helps neurons make proteins** at the synapse.

What's more, synaptic proteins with autism-linked mutations — such as neuroligin and SHANK3 — bind to NMDA receptors at synapses. Other receptors that use glutamate have also been implicated in autism and **related disorders**.

The new findings need to be confirmed in animal studies, notes **Alfredo Kirkwood**, associate professor of neuroscience at Johns Hopkins University, who was not involved with the study. Cultured cells do not necessarily encounter chemicals that are ubiquitous in the brain. Magnesium, zinc and calcium, for instance, influence the activity of NMDA receptors.

One simple next step would be to do the same experiment in neurons from mouse models of autism, fragile X syndrome or Rett syndrome, says Philpot. Altering synaptic activity in these neurons could influence receptor expression in individual synapses, he says.

"I think with the advances in *in vivo* imaging, many of these questions will be able to be answered in a living animal," Philpot says.

## References:

---

1.

Lee, M.C. *et al. Neuron* **66**, 859-870 (2010) [Abstract](#)

2.

Abraham W.C. and M.F. Bear *Trends Neurosci.* **19**, 126-130 (1996) [PubMed](#)

3.

Bienenstock E.L. *et al. J. Neurosci.* **2**, 32-48 (1982) [PubMed](#)

4.

Chen W.S. and M.F. Bear *Neuropharmacology* **52**, 200-214 (2007) [PubMed](#)