Scientists get first close look at stimulated brain

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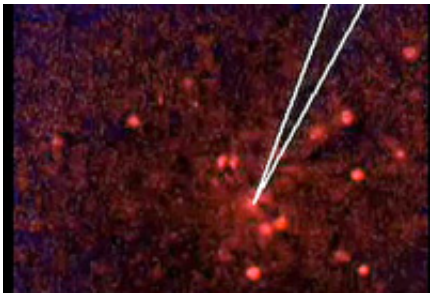

In this image, neurons fired by electrical stimulation are seen in bright red.

(PhysOrg.com) -- For over a century, scientists have been using electrical stimulation to explore and treat the human brain. The technique has helped identify regions responsible for specific neural functions -- for instance, the motor cortex and pleasure center -- and has been used to treat a variety of conditions from Parkinson's disease to depression. Yet no one has been able to see what actually happens at the cellular level when the brain is electrically prodded.

Now, with the aid of optical imaging technology, researchers in the lab of HMS neurobiology professor Clay Reid have taken the first look at this process. They found that the neural response to electrical currents isn't localized, as some had previously thought. That is, not all neurons immediately surrounding an electrode fire when a charge is delivered. Rather, a scattered and widely distributed set of neurons switch on.

These findings, which will appear in the August 27 issue of *Neuron*, promise to end a longstanding debate about how neurons react to electrical stimulation.

Traditionally, observing neurons during electrical stimulation has been problematic. First author Mark Histed, a postdoctoral fellow in Reid's lab, explains, "When you are stimulating electrically you are using relatively high voltages, and those high voltages make it almost impossible to record the very small currents that neurons produce."

To sidestep this obstacle, Histed, Reid and postdoctoral fellow Vincent Bonin used a relatively new form of optical imaging called two-photon microscopy. The technique allowed them to track calcium levels in the neurons of mice as they were being exposed to electrical stimulation. When calcium levels increased, a chemical that had been introduced into the tissue brightened. Since calcium levels spike every time a neuron fires, the team could literally see the neurons flash each time they were activated. More importantly, they could monitor which neurons were being triggered.

According to Histed, these findings run counter to a long-standing hypothesis. "One prior theory was that at low currents, the neurons in a tiny ball around the electrode would activate, and if you increased the current, a larger ball would activate, but you would still only activate cells within that ball. What we showed was that, even at the lowest currents, you have cells very far away that are activated, so it's not just a tiny ball around the electrode tip that increases in size, but instead a very large, sparse pattern that fills in as the current is increased."

The researchers suspect that this sparsely distributed activation pattern results because it's really the axons—the long, thin fibers that transmit electrical signals in the nerve cells—that are being stimulated, not the cell bodies. To prove this, they moved the electrode tip 10 microns from

the site of their first stimulations. That's a distance smaller than the width of just one nerve cell. Reid says, "you might guess that the same neurons would light up. But, in fact, the same number of neurons lit up, but they were entirely different neurons, and that really proved to us the hypothesis that we're exciting just a tiny little ball of neural processes, not neurons. We think we're exciting the axons in that 10 micron sphere."

Histed compares the neural mass to a box of unwound yo-yos. If you stick a pencil into that box, the tip of the pencil would touch only a few strings. Follow those strings all the way to their respective disks, and you would be "activating" only a few, scattered yo-yos within the knotted heap. Move the pencil tip just a quarter of an inch, and it touches a completely different group of strings, leading to an entirely different set of bodies.

The researchers believe that this study establishes optical imaging as a vital tool for any scientific and clinical research that involves electrical brain stimulation. Reid hopes that it will also "be very important in understanding, rationalizing, and designing neural prostheses." Such prostheses are already being used to cure deafness and to treat movement disorders, and Reid's lab has itself conducted research into the use of electrical stimulation to restore vision. This study, by shedding light on how electrical stimulation acts on the brain at the cellular level, could lead to the reinterpretation and refinement of earlier research in the field, and may help guide experiments.

Source: Harvard Medical School (news : web)