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Neuronal Recordings Predict Decision to Move

BY JEFF EVANS

FROM NEURON

Investigators for the first time have used electrode recordings of the firing patterns of small clusters of neurons to predict voluntary movement in people more than 1 second before they are even aware of their decision or urge to act.

The experiment, conducted by Dr. Itzhak Fried of the University of California, Los Angeles, and his associates, detected sets of neurons in the supplementary and presupplementary motor areas and the anterior cingulate cortex (ACC) with firing rates that would progressively increase or decrease before the participants had even reported the urge to push a button on a laptop.

The investigators then constructed algorithms that could successfully predict the impending decision to move at a rate of 70% or greater, depending on the location and size of the set of neurons chosen (Neuron 2011;69:548-62).

Dr. Fried and his colleagues recruited 12 patients with drug-refractory epilepsy who had chronic depth electrodes implanted to determine their seizure focus for possible surgical resection. While the patients sat in bed, they watched an analog clock on a laptop computer and were instructed to push a button after at least one rotation of the clock's hand whenever "they felt the urge to do so." Each time that the individuals pushed the button, called time P, the researchers asked them to indicate where the clock handle had been when they first felt the urge to move, called time W.

The participants reported a mean W time of 193 ms prior to P, but this varied from trial to trial. In the trials, the greatest proportion of neurons that changed their activity before W was located in parts of the medial frontal lobe of the brain: the supplementary motor area (SMA), the pre-SMA, and the dorsal and rostral regions of the ACC. In some of

these areas, the researchers observed rises in neuronal firing rates beginning several hundreds to several thousands of milliseconds prior to W, whereas progressive declines in firing rates were recorded in a similar time span prior to W. The number of neurons that changed their firing rate also increased as W approached.

The study data did not indicate that the subjects were cued to respond by the completion of the clock hand's first rotation. To sort out concerns related to potentially inaccurate reporting of W and the subjective nature of its determination, the investigators manipulated the timing of W either forward or backward in time by fixed amounts or by adjusting its timing by a random amount. These analyses indicated that small temporal shifts in W on the order of 200 ms or less are still compatible with the changes in firing rates seen in recorded neurons and matched what was observed within each participant's trials.

With an algorithm that considered the responses of electrodes to be independent of each other across all participants, Dr. Fried and his associates found that they could predict W on a trial-by-trial basis across all participants. The algorithm could detect changes in the neural activity of 512 neurons in frontal lobe regions 500 ms before W in nearly 90% of the trials. The changes in activity could be detected in more than 70% of trials at 1,000 ms before W.

When the algorithm was constructed on the basis of firing patterns from 256 neurons in the SMA, it detected the neurons' change in activity at 500 ms before W in more than 80% of the trials. In comparison, the change in activity of 256 neurons in the ACC at 500 ms before W could be detected in only 70% of trials.

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ADVISER'S VIEWPOINT

Minding Your Brain's Free Will

Neurologists, physiologists, and philosophers were tossed a hot potato in 1983 with Benjamin Libet, Ph.D., and his colleagues' publication of the first attempt to measure the time of the perception of intent to make a "voluntary" movement (Brain 1983;106:623-42). Called W, it happened about 250 ms prior to the movement itself. They compared this time to the onset of the Bereitschaftspotential or Readiness potential (RP), an EEG potential that had been previously described by Dr. Hans Kornhuber and Dr. Lüder Deecke (Pflugers Arch. Gesamte Physiol. Menschen Tiere 1965;284:1-17). The RP starts about a second prior to movement. This was a shock. It appeared that the brain was preparing to make a "voluntary" movement before the person was aware of it! The experiment has been repeated many times, so there is no disputing the data; the controversy is the interpretation.

In this new paper by Dr. Fried and his colleagues, they have first repeated the experiment using recording from neurons in the brain rather than the EEG. Their finding about the timing of W was similar to all the other experiments. Since the EEG comes from neuronal activity, it should not be a great surprise that they were able to find neurons that changed their activity in the second or so prior to movement. They then took the data one step further. By analyzing a small number of the neurons, they could predict with a high degree of accuracy, prior to W, when a movement would occur. Hence, it appears that the neuronal activity prior to awareness of intention is marching toward the motor command. Recently, our group, led by Ou Bai, Ph.D., has done the same thing using EEG, although not with the same high degree of accuracy (Clin. Neurophysiol. 2011;122:364-72).

So what does this mean? If people have free will in making voluntary movements, doesn't the decision have to be made before the motor command? Here, it looks like the motor command is being made before the "decision." The situation is actually easy to resolve, but it does involve some careful thinking. The first point to settle is that the

mind is generated by the brain; it is not separate from the brain. Most people agree with that, even though it is easy to fall into dualistic thinking. We are our brains; what the brain is doing, we are doing. Hence, it appears that the decision to make a movement, in this circumstance, arises unconsciously. The decision becomes conscious, or at least we have the impression it becomes conscious, just slightly before the movement. The priority is important. That we have the perception of willing before the perception that the movement occurs allows us to draw the conclusion that we are causal in the production of the movement; that is, that we freely willed the movement.

Is this compatible with the idea that we actually have free will? It depends on what that means. If we are our brains, and our brain is choosing to do this without external coercion, then the movement is free. We become aware of this, in fact, only some of the time. Much of the time, we go about our business without worrying whether our movements are freely chosen or not. But, if we think about it, we can appreciate a sense of willing, or intention, that does occur prior to the movement. In fact, the timing of when we can appreciate the upcoming movement may depend on how we interrogate our brain. Dr. Masao Matsuhashi and I showed that if you probe a person, the knowledge that the movement is coming can be earlier than if you ask after the fact when the intention occurred (Eur. J. Neurosci. 2008;28:2344).

All of this has relevance for the clinical practice of neurology. My favorite example in this regard is trying to understand why patients with psychogenic movement disorders believe their movements to be involuntary when they look so voluntary.

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Continued from previous page

infusion of the gene product," the researchers wrote.

Although the study findings are promising, questions remain as to how long the effects of the gene therapy will last and what advantages it might have over deep brain stimulation, Dr. Michael Hutchinson of New York University, wrote in an accompanying editorial. The added value of the study is that the placebo effect is not large enough to explain the benefits of gene therapy seen in open-label surgical trials, he said (Lancet Neurol. 2011 March 17 [doi:10.1016/S1474-4422(11)70041-2]).

A separate investigational gene therapy treatment for Parkinson's disease, called CERE-120, proved to be safe

but lacked efficacy in a recent randomized, sham-controlled, phase II trial that was sponsored by Ceregene Inc. (Lancet Neurol. 2010;9:1164-72). The investigators of that trial blamed its results on the failed delivery of the therapy (consisting of the AAV2 viral vector and the gene for neurturin, a member of the same protein family as glial-derived neurotrophic factor) to dopaminergic neurons.

In the trial, AAV2-neurturin was injected into an area of the brain called the putamen in patients with Parkinson's disease, where the nerve terminals of degenerating dopaminergic neurons reside. However, the investigators realized that neurturin was not being transported effectively to the cell bodies of the dopaminergic neurons, which reside in the substantia

nigra (Mov. Disord. 2011;26:27-36).

A new treatment protocol that delivers a larger dose of AAV2-neurturin to the putamen, as well as directly to the substantia nigra, is currently being tested in a new randomized, sham-controlled, phase II trial of approximately 52 Parkinson's disease patients at 11 U.S. centers. The new treatment protocol was successfully given to six patients with Parkinson's disease in a phase I trial and has not been associated with any serious adverse events after 7-13 months of follow-up, according to Ceregene.

The new phase II trial of AAV2-neurturin is partially funded by the Michael J. Fox Foundation. ■

Jeff Evans contributed to this report.