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COGNITIVE NEUROSCIENCE

In search of lost time

Electrical stimulation of the human brain does not enhance memory, according to a report that is in apparent conflict with earlier work. But this discrepancy could enable deeper insight into brain dynamics by stimulating basic research.

NOAH P. YOUNG & KARL DEISSEROTH

In the first century AD, when methods of recording information were limited, the Roman philosopher Pliny the Elder described[1] memory as the "greatest gift of nature, and most necessary of all others for this life". Technology now enables easy immortalization of every moment, but Pliny's insight still rings true: when memory is lost, the essence of the individual also seems lost. New strategies for the preservation or restoration of memory are urgently needed, and researchers have sought to explore electrical stimulation of the brain as a therapy, but results have been mixed. Writing in *Neuron*, Jacobs *et al.*[2] report that deep brain stimulation (DBS) of memory-associated brain areas impairs memory in humans.

An initial question when considering DBS for memory enhancement is where to place the electrodes that provide the stimulation. Memories of various types have been linked to distinct regions in the vertebrate brain, including the hippocampal and entorhinal areas[3]. Most early studies found that stimulation in the hippocampus caused memory impairment, for instance by reducing recognition of previously seen images[4]. But evidence for DBS-elicited memory enhancement in rats has also been found[5]. In 2012, a promising study by Suthana *et al.*[6] reported that memory was enhanced in seven people when the entorhinal area was stimulated while the participants took part in a spatial learning task in which they navigated a virtual environment.

Jacobs and colleagues' study is the largest of its type, involving 49 participants. It focuses on a different form of spatial memory from the 2012 study (which involved traversing a multi-stop route). The volunteers were placed in a virtual location in which they were shown a hidden object, and learnt the location of the object relative to nearby landmarks while being subjected to either electrical or sham stimulation in the entorhinal region or hippocampus. They were then placed at another location and asked to return to where they had been initially placed, to find the now-hidden object. Stimulated individuals were less accurate at pinpointing the position of the hidden object than unstimulated individuals. The authors also performed a test of verbal memory, in which the participants attempted to memorize 12 words that appeared in succession while they received electrical or sham stimulation. Again, performance in this task was degraded by stimulation in the hippocampal or entorhinal areas.

Thus, unlike Suthana and colleagues, Jacobs *et al.* report that electrical stimulation causes memory impairment, leaving the field at a crossroads. There are many other regions of the brain in which DBS-based therapies could be explored, but these, too, might yield inconsistent results without a deeper understanding of the basic underlying principles. For instance, reports of memory improvement following DBS in the fornix (a structure that links hippocampi across brain hemispheres, among other connections) led to a trial of one-year-long continuous stimulation of the fornix in people with Alzheimer's disease[7]. But although the treatment powerfully altered cerebral metabolism, no improvement was found in the primary outcome being measured — memory.

"Identification of informative differences between studies of deep brain stimulation might unveil a fruitful path forward."

As Jacobs and colleagues discuss, identification of informative differences between DBS studies might unveil a fruitful path forward. For instance, does electrode placement differ between studies? Assessing electrode placement is challenging, because the computed tomography scans used to check electrode placement post-operatively have poor resolution compared with the magnetic resonance imaging (MRI) used for pre-operative planning. It can be hard to define whether electrodes are in white matter (tracts of neuronal projections called axons that send information between brain regions) or grey matter (the neuronal cell bodies and local circuitry). This is important because the entorhinal area includes both the grey matter of the entorhinal cortex and white-matter tracts that project to the hippocampus. Differences in targeting might explain the discrepancies between Suthana and colleagues' and Jacobs and colleagues' results. Unpublished data from Suthana *et al.* suggest that memory-improvement effects are specific to white-matter targeting.

Indeed, optogenetics — a technique in which genetically defined elements of the neuronal circuitry are controlled by light — has revealed that there are certain advantages to targeting axonal projections[8,9], and clinical evidence is in agreement[10]. White-matter stimulation can be more potent, efficiently modulating bundled collections of axons before they disperse across grey matter. Moreover, when axonal projections are stimulated, downstream neurons are modulated by the synaptic connections formed by long-range projections, more closely emulating normal brain communication than does the less-specific stimulation of grey matter. These insights from optogenetic work (which enables direct control of projections defined by their origin and target[9]) could guide clinical DBS by defining specific projections, rather than simply locations, that enhance memory when modulated in animals. A white-matter-based strategy guided by patient-specific MRI could then target the corresponding tracts in humans.

The next generation of DBS treatments may also require more-precise timing. Both Jacobs *et al.* and Suthana *et al.* used tasks wherein the timing of memory encoding and thus stimulation were defined by the researchers, but it seems less than ideal to ask patients to decide when they want stable memory formation. Precision timing might be achieved using closed-loop techniques in which stimulation is guided by signals from the brain itself[9] — for example, by locking to the phase of naturally occurring electrical oscillations in the hippocampus. Examples of such systems remain few and primitive, but technological advances could improve their feasibility in the future. This approach may become especially promising when combined with patient-specific spatial targeting, and with a precise knowledge of the timing and amplitude of neuronal activity that causes changes in memory (that is, knowledge derived from optogenetics that can be used to elicit activity that matches naturally occurring activity timing and amplitude[9]).

DBS is nonspecific for cell type, and therefore might cause abnormal dynamics within neural networks, as is the case with pharmacological and magnetic interventions in the clinic, and with less commonly used optical strategies in animals that target all neurons indiscriminately[11,12]. But knowledge gained from standard cell-type-specific optogenetics already has clinical value for DBS — for instance, cell-type-nonspecific neurostimulation in people addicted to cocaine can be

targeted to a particular brain region thanks to optogenetic experiments, reducing drug use[13,14]. Moreover, insights from optogenetics have enabled the tuning of cell-type-non-specific electrical stimulation to generate neuronal activity features involved in memory[15]. Finally, the technique has provided insight into how localized interventions can elicit brain-wide activity states that modulate behaviour — natural events are known to cause altered activity in brain-wide networks, and an optogenetic study similarly demonstrated that moderately increased excitability of a cell type in the prefrontal region of the rat brain resulted in tuning of reward-related behavioural preferences, owing to specific alterations in the activity relationships across brain-wide networks[16].

Thus, Jacobs and colleagues' study pushes the field forward by highlighting the need to study fundamentals of brain dynamics. The epidemiology of memory-related diseases suggests that our world will bear a higher burden from memory loss than Pliny's (notwithstanding his account of memory loss due to brain trauma and illness[1]), but despite the urgency for treatments, the next steps in clinical memory neurostimulation may be best rooted in basic neuroscience. ■

Noah P. Young *and* **Karl Deisseroth** *are in the Department of Bioengineering, Stanford University, Stanford, California 94305, USA.* **K.D.** *is also at the Howard Hughes Medical Institute and in the Department of Psychiatry and Behavioral Sciences, Stanford University. e-mail: deissero@stanford.edu*

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