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What We've Got Here Is Failure to Communicate: Improving Interventional Psychiatry With Closed-Loop Stimulation

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Through the early 1950s, nearly 20,000 children were born each year with congenital heart defects. The majority of these “blue babies” would die almost immediately. The pioneering surgeon C. Walton Lillehei performed the first successful repair of a ventral septal defect. But even after this miraculous intervention, Lillehei’s patients were not in the clear. The team discovered that after surgery, the children’s hearts could still unpredictably stop beating if there was damage to the vulnerable electrical conduction system. A solution existed, but it was far from ideal. Cardiologist Paul Zoll had recently developed a large pacemaker machine that could deliver periodic electrical impulses through electrodes strapped to the chest. Though it saved lives, the treatment was painful, and the child’s mobility was limited to the length of the electrical cord.

So, in 1958, frustrated by the lack of options, Lillehei reached out to a friend, an electrical engineer named Earl Bakken. He asked Bakken to design a portable, comfortable, battery-operated pacemaker. Bakken took on Lillehei’s request with enthusiasm, and in less than a month he had both designed the device and witnessed its first use with a patient (1).

The device still had major limitations. Under ordinary circumstances, the heart rate naturally adjusts to the body’s needs; Bakken’s device operated at a fixed frequency. This meant not only that a paced heart could not respond to increasing physiological demands, but also that high levels of exertion could induce a dangerous arrhythmia if natural and artificial rhythms conflicted. Without a mechanism for the heart and machine to communicate, patients’ bodies could come into lethal conflict with the ostensibly life-saving devices. The solution to their problem came the following decade when engineers figured out how to guide (or synchronize) pacing by incorporating an internal electrocardiogram into the device. An explosion of research followed, and soon devices could enhance cardiac functioning with few adverse effects.

Today, the field of psychiatry faces similar challenges to Lillehei’s, but the stakes are much higher. Whereas Lillehei was working with a small cohort of children, depression is the leading cause of disability worldwide. Each year, more than 5 million Americans struggle

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with treatment-resistant depression, and suicide rates continue to climb. The need for new treatments could not be greater. In this wide-open space, one of the most exciting growth areas is the burgeoning field of interventional psychiatry.

The brain, like the heart, is an electrical organ. Modern psychiatrists are increasingly appreciating both the intrinsic electrical properties of a healthy brain and the role of aberrant circuit functioning in disease. From this perspective, the idea of neurostimulation seems obvious. But developing a “pacemaker of the brain” is a daunting prospect. While there are approximately 40,000 neurons in the heart, there are approximately 100,000,000,000 neurons in the human brain. While the heart serves the single function of pumping blood through the body, the brain serves functions as diverse as motor control, vision, emotion processing, and consciousness.

The first formal electrical intervention for psychiatric illness, developed in the 1930s, was electroconvulsive therapy. Like defibrillation, the large electrical impulse of electroconvulsive therapy was thought to effectively “reset” the brain. It remains the most effective therapy in psychiatry; about 70% of patients with treatment-refractory depression will remit (2)—a number that dwarfs the 30% remission rate with typical antidepressants (3). Yet its use has been limited by misconceptions, stigma, side effects, and high relapse rates.

Efforts to develop a less invasive and more focal treatment have led to new forms of brain stimulation therapies. Transcranial magnetic stimulation, which received approval by the U.S. Food and Drug Administration for the treatment of depression in 2008, uses a series of magnetic pulses applied to the scalp to induce an electric field within a focal area of the cortex (4). Other new approaches include transcranial direct or alternating current stimulation and low intensity focused ultrasound. Like the early pacemakers, though, these treatments all share the goal—and intrinsic challenges—of trying to apply energy, across a barrier, to induce change in a specific location.

A more direct approach, paralleling the first implantable cardiac pacemaker, would be to apply current directly within the relevant organ. Deep brain stimulation (DBS) offers this opportunity: electrodes are surgically implanted with precision targeting cortical or subcortical structures; stimulation is regulated by a small device placed under the skin on the chest. The first study of DBS for major depression was conducted by Mayberg *et al.* (5) in 2003. Targeting an area of the brain termed the subcallosal cingulate, they successfully treated 4 of 6 patients with severe, unremitting major depression. Positive results from 14 additional patients over the next few years instilled hope and excitement within the psychiatric community.

But early optimism soon gave way to frustration and disappointment. A large, double-blind, multicenter trial of subcallosal cingulate DBS was halted prematurely by the device company after a 6-month futility analysis in 2012. A second blinded, randomized trial of ventral capsule/ventral striatum DBS also failed to demonstrate a significant difference between the active and sham groups (6). A shadow of doubt was cast on the whole field of targeted intracranial stimulation. What happened?

Several factors may have contributed to the study failures. There are a vast number of technical parameters (e.g., stimulation intensity, frequency, and pulse width), to say nothing of where, precisely, to actually apply the current. There seemed to be a large placebo effect, thus making it difficult to interpret the potential benefits of the treatment. The primary end point may have been too early, preventing a true effect from being observed. And, of course, every individual is unique and may therefore require different interventions. Trying to account for all these factors would be financially prohibitive, if not impossible.

At its core, though, the problem with these first forays into interventional psychiatry may be the same as that with early pacemakers: they all seek to apply an external stimulus without being guided by any signal back from the diseased tissue. To quote the film *Cool Hand Luke*: “What we’ve got here is failure to communicate.” The new frontier for addressing this problem is an approach termed “closed-loop” stimulation. An intervention is made, feedback from the system is recorded, and this feedback is then used to alter the next intervention—thus setting up a continuous iterative loop of feedback and stimulation. Modern cardiac care was revolutionized by closed-loop pacing. Could the same approach work for the brain?

In fact, it already does. Closed-loop DBS has been proven to work in both epilepsy and Parkinson’s disease. In these systems, electrodes continuously record and analyze an intracranial electroencephalogram. Features detected from this signal (such as the early signs of seizure activity) can then be used to guide interventions (such as inhibitory stimulation). In epilepsy, such a system is approved by the U.S. Food and Drug Administration and in widespread clinical use today (7). For Parkinson’s disease, early research studies have shown promise; using a biomarker of motor symptoms in the subthalamic nucleus, researchers have achieved better outcomes using less total stimulation (8).

So, what about depression? Here, the challenges remain. Foremost, what biomarker can be used to guide treatment? Early work focused on alpha frequency coherence over prefrontal regions, but this did not yield consistent results (9). Subsequent studies that attempted to combine several features from one or more electroencephalograms similarly failed (10). Despite extensive efforts on the part of scientists, a quantifiable and reproducible biomarker of depression remains elusive.

In the end, it may be that the problem is solved by not solving the problem at all—at least not in the traditional sense. Newly developed machine learning algorithms and advances in computing power may ultimately extract complex biomarkers on their own. These biomarkers may rely on hundreds of features from high-density electrodes that cover an entire neural network. Such methods have been applied successfully to detect disease processes in the fields of ophthalmology and oncology. They are at the heart of a new field of computational psychiatry. Clinical trials are now underway by several groups across the world to examine the effects of noninvasive closed-loop systems that use electroencephalography features to drive transcranial magnetic stimulation or direct electrical stimulation.

Other challenges will remain. Most notably, successfully implementing this type of approach will entail collecting, storing, and analyzing a staggering amount of data. Each device would

need to have both extraordinary signal processing capabilities and, with it, a means of ensuring a stable energy supply. Nonetheless, if and when the technological demands can be met, the potential benefits would be transformative for our field.

When Earl Bakken made the first portable pacemaker, he had recently turned his hobby for medical electronics into a small struggling company. He never imagined that this company, Medtronic, would become a leader in stimulation devices of both the heart and the brain. Given the relative complexity of these organs, it is no surprise that cardiology has achieved success so much more quickly. But the lessons from their field stand as an inspiring vision for psychiatry: personalized and fully integrated interventions that could save the lives of our sickest patients.

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