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Brain Stimulation, Revolutions, and the Shifting Time Domain of Depression

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Brain stimulation methods are changing, some might even say revolutionizing, the way we think about neuropsychiatric disease.(1) As we lift our heads up out of the synaptic cleft and free ourselves from explaining everything in terms of neurotransmitters, compelling new perspectives are abundant. We can re-remember that the currency of the brain is indeed electricity, and that all synaptic activity merges onto the all-or-none decision at the axon hillock, modifying whether or not an action potential will be sent crashing down an axon that connects to other neurons and passes the signal along.(2,3) We can dream about patterning electrical stimulation through focal brain stimulation or even focal pharmacology, where, cleverly using frequencies that change circuit activity (long-term potentiation (LTP) or long-term depression (LTD)), we can locally excite one area while inhibiting another. The potentials for brain stimulation are enormous.(4)

The two articles in this issue of *Biological Psychiatry* draw attention to the key issue of durability of antidepressant response. The brain stimulation therapies have helped shift the timeframe of analysis of antidepressant response – a minor revolution. Formerly, in the oral medication neuropsychopharmacology model, we studied largely treatment naïve patients, administered oral medication for 6–12 weeks, counted responders and remitters, and then compared notes about which medicines were effective, or not. The monumental STAR-D study has forced us to remember that many, if not most, patients do not do well with first-line medications, and that frequent relapse and incomplete response are common in depression. (5,6) Many patients have treatment-resistant depression, and even when they respond to medication, they often have break-through episodes that some have labeled tolerance. (7,8) The great news about electroconvulsive therapy (ECT) is that it is remarkably effective in achieving response and remission for acute episodes, but we struggle to keep even half of the patients well for a full 6 months after treatment. (9,10)

The two studies in this issue stand in stark contrast to the doom and gloom of the new epidemiology studies and the transient, non-durable outlook for oral medications and ECT. Perhaps because brain surgery, or implantation of medical devices, is so invasive, researchers

have focused more attention on the long-term outcome in patients with devices or following brain surgery. We should remember the controversial and largely uncontrolled work of Freeman and others who reported that the clinical effects of frontal lobotomies for depression were not transient, and that mood and life quality improvements lasted for many, many years. (11) Because these were open-label longitudinal studies of patients with lobotomies, we do not know how much of the sustained response is due to spontaneous recovery or placebo, and we should be cautious in interpreting durability data from open-label studies. The article by Shields and colleagues resurrects the hypothesis that responses to brain surgery (or brain stimulation) for depression are more durable than other treatments. The Shields article also suggests a dose-response relationship in terms of the size or location of the lesion and the overall response and durability of response. Those who did not respond by 6 months to a single bilateral anterior cingulotomy (about half the subjects) went on to have another surgical procedure, either a repeat and expanded anterior cingulotomy, or a subcaudate tractotomy. In this case, more was better. Shields and colleagues found, in this very treatment resistant group, about a 70% response rate at 30 months. These follow-up results of the modern stereotactic lesions are remarkably consistent with reports from 30 years ago following ablative surgery in and around the subgenual cingulate (Brodmann Area 25). The earlier neurosurgical cingulate ablation studies also reported about 70% partial or full response at 2–3 year follow-up, which foreshadowed the recent cingulate deep brain stimulation (DBS) studies.(12–15)

However making conclusions from long-term open label treatments is notoriously risky. For example, antidepressant medications are extremely effective with high durability of benefit in open-label uncontrolled trials. It took carefully controlled randomized trials to show that a large part of the efficacy of antidepressant medications can be accounted for by spontaneous recovery or placebo effect. Designing and implementing the appropriate control condition for the brain surgery or stimulation techniques opens up many new challenging and difficult questions. How do you make a sham TMS system that fools everyone, patient and treater alike?(16,17) Is it ethical to implant brain stimulation devices and not turn them on? Can you go for several years without turning a device on? We have recently launched a new journal, *Brain Stimulation*, in order to stimulate discussion of these highly important, and critical, methods and issues, and to promote consilience in this new field.

Given these promising, and seemingly durable, results from neurosurgical lesions, it is not surprising that the initial method of DBS for Parkinson's Disease, dystonia, and, most recently for depression, has largely mimicked and modeled the methods and approaches of resective neurosurgery. The DBS electrodes are turned on at high frequency (>100 Hz) and are constantly on, 24/7, mimicking a surgical lesion.(18,19) Because this is an artificial prop of the system, symptoms typically return rapidly if the device is turned off, or a lead breaks or the battery dies. If the knowledge from other areas of systems neuroscience is correct, then intermittent stimulation of these same areas should provoke longer-term neuroplastic brain changes in these circuits (LTD or LTP), thus moving brain circuits into a more resilient and healthy mode, making symptom recurrence less likely if stimulation is stopped or withdrawn. Exciting trials with intermittent deep brain stimulation are underway testing these new hypotheses.(20,21)

Vagus nerve stimulation (VNS) is a most interesting form of brain stimulation, heralded and prophesied by some of the founders of Biological Psychiatry such as Paul MacLean, Karl Pribram and others.(22) As currently performed, cervical VNS is delivered intermittently, within a fairly rigid neighborhood of repeated identical stimulation [0.25–5 mAmp intensity, 5–20 Hz, 130–500 millisecond pulse-width].(23,24) After the disappointing acute trials of VNS for treatment-resistant depression, where active treatment was not statistically different from sham treatment, researchers were struck by the durability of the clinical benefit, when achieved. (25) Overall, the acute response and remission rates were modest, albeit in a treatment resistant group. In general there appeared to be a 60–70% probability of maintaining response and

remission over periods of 12–24 months. (26) The article by Nierenberg and colleagues shows that the durability of response does not differ between unipolar and bipolar depressed patients. Finding better, and durable, treatments for the depressed phase of bipolar illness is an important and needed area.

The two articles in this issue thus provide soft support of the tentative hypothesis that one of the benefits of neurostimulatory treatments might be an enhanced durability of benefit, at least for depression. But we must remember that the database is very limited to support this hypothesis. If these uncontrolled long-term studies are correct, why would the clinical response to intermittent brain stimulation, or ablative resective neurosurgery, be so different from our experience with medications? The answer likely lies in better understanding the mechanisms of antidepressant medication tolerance, and the neuroplastic changes induced by electrical stimulation. When taking a medication, the brain becomes ‘bathed’ in the molecule, with constant exposure. Over time the brain can adapt or respond or become tolerant to the ‘artificial’ neurochemical milieu. But remember that electricity leaves no trace or residue. There is no constant neurochemical environment to react against. If our thinking is correct, then the stimulation parameters that would be the most durable, and least likely to develop tolerance, would be those within a therapeutic space, but which were always slightly varying, jittered to provide stimulation within a range of parameters, but with no stimulus train being exactly like the one before, constantly fooling the brain and preventing tolerance. It is an exciting and ‘stimulating’ time for our field to begin addressing the issues raised in these two articles surrounding the translational neurobiology of acute antidepressant response, durability, resilience, or tolerance and relapse.

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Dr. George currently receives funding from 5 R01 MH069887-04, 5 P20 DA022658-02, 1 R21 MH078046-01. Dr. George owns no stock or equity in any device or pharmaceutical company. He is a paid consultant to several device manufacturers, including Neuropace (DBS) and Cyberonics (VNS). He is an unpaid consultant to several TMS manufacturers (Neuronetics, Brainsway), and served as head of the DSMB for a trial by Aspect Medical. For the past decade, his entire yearly compensation from all manufacturers and speaking engagements is less than 20% of his annual university salary. He is the editor-in-chief of a new journal published by Elsevier, entitled *Brain Stimulation* and has written several books in this area. MUSC holds several patents in his name involving brain stimulation and imaging, one using fMRI (not EEG) to determine the best dose of VNS for a patient.

Dr. Sackeim is a consultant and serves on the scientific advisory board of Cyberonics, Inc. and Neuronetics, Inc. He is also a consultant to the MECTA Corp.

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