The COBRE Center for Neuromodulation (CCN) at Butler Hospital: Clinical-Translational Research in Human Brain Stimulation

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ABSTRACT

The COBRE Center for Neuromodulation (CCN) at Butler Hospital supports clinical research in neuromodulation and investigators' career development in this field. The work couples brain stimulation methods with readouts of brain activity (e.g., using various neuroimaging, behavioral, and physiological assessment methods) in clinical or clinically relevant populations. Its guiding principle is that for noninvasive brain stimulation to gain efficacy and implementation, it is essential to better characterize clinically relevant target circuits and mechanisms of action. The CCN includes a Design and Analysis Core (DAC) to support rigorous and innovative experimental design and data analytic strategies and a Neuromodulation and Neuroimaging Core (NNC) to facilitate the acquisition and processing of high-quality data using noninvasive neurostimulation and neuroimaging methods. This article will describe the CCN's research focus and how it enhances research capacity in neuromodulation in our state. It will introduce our current investigator Project Leaders, their projects, and our pilot project program. It will also detail the CCN's links to Centers and research cores in Rhode Island researching allied areas of clinical neuroscience, neurology, psychiatry, and psychology, current collaborative efforts across those centers, and opportunities to collaborate in research and training.

KEYWORDS: neuromodulation, TMS, tTDS, neuroimaging, neuronavigation

INTRODUCTION

To quote this issue's Introduction, "the impact of behavioral and mental health problems on the overall health of individuals and populations has become increasingly recognized" (Padbury and Cho). Neuromodulation is typically used in combination with pharmacotherapies and psychotherapies to address the burdens mental illness (and other brain disorders) impose on individuals, families, and population health. Here, we use CCN members' work to illustrate important aspects of the therapeutic and research contexts of neuromodulation. And we highlight the new infrastructure and resources that the CCN has made available to enhance work in this promising area, and to help train and support the new generation of neuromodulation researchers in Rhode Island.

"Neuromodulation" might be any method modifying the nervous system. So, medications, devices, psychotherapies, mind-body approaches, and more might qualify. The term, however, has a narrower definition: device-based methods affecting the CNS. Typically, devices emit energy (e.g. electrical, magnetic, ultrasonic) to modify brain activity directly or via peripheral nervous system components. This definition of neuromodulation dovetails with the use of brain networks as a fundamental unit of analysis in understanding brain-behavior relationships in health and disease. A network can be thought of as a collection of nodes that are structurally and functionally related. This, in turn, lends itself to translational research involving an exchange between cognitive and affective neuroscience and clinical disciplines. Models of illness pathophysiology envision dysfunction at multiple levels: within regions, within networks, and in the smooth flow of information across networks. For an example of how brain functional architecture might relate to illness symptoms (in this case of post-traumatic stress disorder, PTSD). see Barredo et al.[1] Regarding how neuromodulation might be understood to act at the level of brain networks in PTSD and major depression, see Philip et al. [2]

Another translational aspect of neuromodulation is using clinically relevant affective or cognitive processes as the basis for research (complementing the focus on anatomical networks). Examples include studies by CCN Project Leaders, e.g., by Nicole McLaughlin on response inhibition in obsessive-compulsive disorder[3], or Mascha van't Wout-Frank and colleagues on affective elements in decision-making. [4] The abilities to flexibly inhibit responses, or to incorporate the experience into decision-making, are essential to adaptive behavior in health or illness. Another example is using brain stimulation to augment extinction of conditioned fear, thought to underlie therapeutic change in PTSD.[5] These studies represent essential steps guiding development of brain stimulation methods for eventual clinical use, and will generate results that advance fundamental knowledge in cognitive and affective neuroscience.

Neuromodulation is seeing the application of increasingly powerful tools, both in the array of devices used and their combination with neuroimaging, electrophysiology, and computational modeling to understand impacts of

stimulation on brain and behavior. Mechanistic insights, in turn, guide research refinement, with each next step addressing goals and hypotheses relevant to health and therapeutics. These include identifying specific brain regions, circuits, or oscillatory signals to be engaged and modulated; establishing efficacy and safety of a neuromodulatory treatment at a group level; selecting specific stimulation methods for individuals most likely to benefit; tailoring neuromodulation to optimize effects in each participant or patient; and developing technologies and implementation steps required for widespread dissemination of a new treatment to meet the large and manifest clinical need. This research can exemplify multiple stages along the translational research continuum, and its success requires an ongoing interplay between clinicians, clinical researchers, basic and cognitive neuroscientists, and biomedical engineers.

Devices used can be invasive (implanted) or noninvasive. An example of the former is deep brain stimulation, currently used clinically in Parkinson's disease, essential tremor, dystonia, and obsessive-compulsive disorder (OCD; see Greenberg, et al.[6] for the latter). The CCN's focus, in contrast, is noninvasive methods. The best-known noninvasive therapy is transcranial magnetic stimulation (TMS, also 'repetitive TMS'), a standard-of-care treatment for severe major depressive disorder (MDD). The other non-invasive method we will describe here, which thus far has not gained regulatory approval for clinical treatment, is transcranial direct current stimulation (tDCS).

TRANSCRANIAL MAGNETIC STIMULATION

Here, a pulsed magnetic field delivered through the scalp and skull stimulates relatively superficial brain. The magnetic flux generates electrical activity in the cerebral cortex, producing both local and, via networks, distant effects. TMS is "supra-threshold," meaning that enough energy is delivered to induce action potentials in target neurons. TMS research in MDD began in the early 1990s, with subsequent development through extensive clinical trials. Results converged on the effectiveness of TMS. In practice, patients come to the clinic for repeated TMS therapy sessions, delivered in each session as brief "trains" of pulses with rest between trains. Typically these are once per weekday for up to six weeks, often followed by several weeks during which TMS is tapered. See Carpenter et al.[7] for an example of research on clinical effectiveness and also a recent update on TMS in depression.[8]

During each session, a patient receives many TMS pulses over a defined region, usually left or right dorsolateral prefrontal cortex. Researchers continue to develop new devices, one of many examples being a device using a multiple electromagnetic coil array[9] instead of the single-coil design of all currently approved devices. Novel approaches for selecting stimulation parameters and new methods for identifying the best brain targets are under investigation, many informed by electroencephalography and neuroimaging findings generated by senior CCN researchers. TMS treatment protocols have shown preliminary clinical efficacy for numerous neuropsychiatric and behavioral disorders; randomized clinical trials recently led to the US FDA approvals for TMS to treat OCD and for smoking cessation. TMS is increasingly available across healthcare systems in the United States and elsewhere.

In Rhode Island, there are active neuromodulation clinical programs (or TMS clinics) at Butler Hospital, the Providence VA Medical Center, and Rhode Island Hospital, with several others in private-practice settings. Despite increasing public awareness that TMS therapy is an option for patients who do not achieve adequate benefit with more traditional depression treatments, it has remained underutilized since its 2008 FDA approval. The substantial time commitment required may be one reason for slow uptake. Recent research has led to the approval of a novel stimulation pattern, intermittent "theta-burst" TMS, which can be delivered in the clinic much more rapidly than "traditional" TMS (2-3 minutes rather than 20-30 minutes per session). Research applying the theta burst TMS method to other conditions, like PTSD, has generated substantial interest.[10]

TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS)

tDCS involves low-energy electrical current, following the principle that applying current to the skin generates an electrical field. Although there are commercially available devices for transcranial electrical stimulation (largely marketed directly to consumers), here, we restrict ourselves to tDCS, which delivers a constant ("direct") current waveform. See Philip et al.[11] for a comprehensive review of tDCS and related methods. Devices deliver a predefined intensity of electric current of several milliamperes, using a variety of electrode arrays for current "focusing." For example, a single anode typically using multiple smaller cathodes around a single anode (or vice versa), for more focal tDCS. While the skin and skull are transparent to the magnetic pulses delivered by TMS, there is resistance to energy flow between electrodes during tDCS. The electrical fields used in tDCS are considered subthreshold, i.e., stimulation at the intensities used does not independently cause neuronal depolarization. Rather, it is thought to bias neurons' activity to influence the ongoing flow of information in a pathway. The factors involved are complex, but the basic point is that even a small tDCS-induced change in membrane voltage may impact activity. An example is a pilot study by CCN investigators who evaluated tDCS concurrently with psychotherapy in depression. Most tDCS devices are relatively inexpensive, have a good safety profile, and can be deployed either in a clinical research laboratory or in a nonresearch

environment; recently tDCS devices have been designed for self-administration at home, with remote "supervision" functions to support investigation of their effects in randomized controlled trials comparing active or sham stimulation.

THE COBRE CENTER FOR NEUROMODULATION (CCN) AT BUTLER HOSPITAL

The CCN (https://www.butler.org/services/cobre/) was established in 2019 as part of the NIH-NIGMS-funded IDeA (Institutional Development Award) program. CCN has a primary focus on device-based neuromodulation, and particularly that using noninvasive methods. A guiding principle of our Center is that for neuromodulation methods to gain acceptance and implementation by the clinical community, it is necessary to understand their mechanisms of action (requiring clinical-translational research) and their therapeutic efficacy (the domain of clinical trials). That, in turn, opens an interplay between our understanding of mechanisms underlying impairments in mental health or neuropsychiatric conditions more broadly. These can either be understood as traditional diagnostic categories (a categorical diagnosis requires that an individual "meets criteria" for an illness; the person either has it or not) or be based on a dimensional view of maladaptive behavior. In the latter view, clinically significant problems emerge when actions that occur along a continuum in the general population are expressed with problematic severity or frequency.

Our Center's components is overseen by the CCN Administrative Core, aided by three advisory committees. One of these committees' overall work is based at the home institution, Butler Hospital. Its members are leaders in various hospital departments required to facilitate and support core operations of the CCN; the second committee also includes representatives of local research institutions, and finally, an External Advisory Committee composed of leading national experts in neuromodulation research. The CCN Administrative Core works closely with our program partners in the state.

CCN is a "Phase 1" COBRE, built around multiyear projects in human neuromodulation, each led by a Project Leader developing a research career. Currently, there are four Project Leaders, each advised by mentors providing scientific, technical, and career guidance. The projects and leaders are: 1) Brain Circuitry of inhibitory control in young adults: Modulation with tDCS, Nicole C. McLaughlin, PhD; 2) Effects of tDCS timing on safety memory in PTSD, Mascha van't Wout-Frank, PhD; 3) Modulating prefrontal circuits underlying behavioral flexibility in OCD: a TMS study, Sarah Garnaat, PhD; and 4) Determining whether TMS changes the brain through brain synaptic plasticity, Joshua Brown, MD, PhD.

The projects are supported and facilitated by two CCN research cores. The cores are also designed to serve a separate Pilot Project Program, which allows faculty researchers at Rhode Island institutions to collect preliminary data in clinically relevant neuromodulation studies to support external grant proposals. The Design and Analysis Core (DAC; Director Richard Jones, PhD; Co-Director Jennifer Barredo, PhD), as its name implies, supports the experimental design, data processing methods, and general statistical aspects appropriate to human subject's research. Given that understanding possible mechanisms underlying effects of neurostimulation on the brain and behavior is central to the mission of CCN, this core also specifically addresses needs particular to neuroimaging and neurophysiology research (e.g., fMRI, brain connectivity or evoked responses measured with EEG or electromyography). A new high-capacity CCN computing center at Butler Hospital houses dedicated workstations for MRI and for EEG analyses with internet access, software, external storage devices, and direct connection to a dedicated data storage server.

The aspects of "hands-on" brain stimulation training and data acquisition are the Neuromodulation and Neuroimaging Core (NNC, Director, Linda Carpenter, MD; Co-Director, Noah Philip, MD). The NNC hosts an array of TMS equipment, including several different devices and "neuronavigation" platforms that permit stimulation to particular brain regions with an individual's MRI. There are TMS coils for both active and sham stimulation to permit controlled studies. The TMS coils themselves have different designs producing different magnetic field shapes for stimulating brain regions that differ in location and extent, and the TMS stimulators have various features as needed for the application of theta-burst stimulation or electrophysiological studies of cortical excitability; the latter is used in combination with pharmacological probes to investigate plasticity mechanisms of TMS action (see Brown et al.[12,13]) Similarly, there are multiple tDCS devices available in the core, allowing investigators to select different electric field geometries as needed for their research purposes. There are also computational modeling platforms available via the NNC, which use neuroimaging and/or brain models to design the optimal montage for the desired stimulation effect with either TMS or tDCS; such models ensure the resulting electrical current will engage particular brain targets with a degree of selectivity. The NNC also supports EEG recording with several research-grade electrophysiology platforms, with additional modules and accessories to permit collection of other psychophysiological data (e.g., cardiac data, galvanic skin response, and other physiological responses). Both the NNC and DAC work closely with the Brown MRI Research Facility to support the collection of high-quality neuroimaging data in concert with neuromodulation procedures.

It is to our great advantage that senior researchers at CCN also lead active neuromodulation clinical programs in Rhode Island, the TMS Clinic at Butler Hospital, directed by one of the authors (Carpenter), and the Neuromodulation Clinic at the Providence VA Medical Center, led by another

(Philip). The NNC is, in fact, adjacent to the space used by the Butler TMS Clinic. This has allowed it to draw upon and utilize additional clinically trained staff support and other resources from Butler's TMS clinical service. Researchers in the core facility at Butler thereby have immediate access to the infrastructure of the TMS Clinic and other clinical service resources including a pool of physicians, technicians, and a nurse trained in TMS and other neuromodulation techniques, access to medical equipment, emergency response teams, and physician supervision for management of potential adverse events as well to address any clinical issues that may arise in the patient populations under study. This arrangement allows our Center and the NNC specifically to be an essential resource for the safety and success of projects involving clinical samples, particularly in cases where the principal investigator is not medically trained and/or does not have access to neurostimulation-trained physicians on his or her research team. The two research cores collectively host training in brain stimulation and neuroimaging methods, including the safe and experimentally rigorous use of brain stimulation devices, MRI, EEG, data acquisition, data management, quality control and analytic methods.

CCN's cores have worked hard during the COVID-19 pandemic to implement procedures ensuring safe research in this evolving environment, a complex and ongoing task involving multiple institutions and facilities, and IRBs. Our personnel's dedication has enabled research protocols to be adapted flexibly as needed, and to be restarted as soon as possible after a pandemic-imposed pause. We share tremendous optimism regarding our Center's capacity to enhance research in this exciting and rapidly developing field, and welcome interest and engagement by the research community.

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