

Brain Stimulation And Therapeutic Modulation

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Overview

The Brain Stimulation and Therapeutic Modulation (BSTM) Division specializes in the use of emerging electromagnetic means of modulating brain function to study and treat psychiatric disorders. The ability to stimulate targeted brain structures non-invasively has opened for the first time the potential to probe the circuitry underlying brain-based disorders and represents a powerful new tool for treating disorders that fail to respond to conventional therapies. The BSTM encompasses research programs (preclinical, translational, and clinical) and clinical services utilizing existing and emerging brain stimulation and neuromodulation interventions at NYSPI and NYPH. These techniques include deep brain stimulation (DBS), electroconvulsive therapy (ECT), magnetic seizure therapy (MST), transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and vagus nerve stimulation (VNS). These techniques are applied as probes of brain function, as therapeutic interventions, or in conjunction with functional imaging (simultaneous TMS/fMRI, TMS/PET, TMS/MRS). The clinical research facilities include the Brain Behavior Clinic at NYSPI, the Brain Stimulation Service at NYPH, 2 newly constructed human TMS treatment suites at NYSPI, the TMS Unit of the fMRI Center, Stimulation/Imaging facilities (TMS/fMRI, TMS/PET, TMS/MRS), and the ECT suites at NYSPI and NYPH. The pre-clinical research facilities include the Nonhuman Primate Brain Stimulation Lab, the Primate Cognition Lab, and the Brain Stimulation Technology Development Laboratory specializing in novel device design and implementation.

The BSTM pulls together expertise in the neuroanatomical, cognitive and neurophysiological assessment of the impact of stimulation on brain function in the nonhuman primate model and in the clinical setting. Close collaborations with the Department of Neuroscience (Drs. Arango, Dwork, Underwood) provide the platform for neuroanatomical and neuropathological studies on the impact of brain stimulation on hippocampal plasticity (including neurogenesis, synaptic remodeling, and gene expression). The Primate Cognition Laboratory (Dr. Terrace) provides custom neurocognitive batteries to assess the impact of brain stimulation on a rich variety of cognitive functions in monkeys (including anterograde and retrograde amnesia, working memory, spatial memory, serial list learning, ordinal position, numerosity, and meta-cognition). The Nonhuman Primate Brain Stimulation Lab, coupled with the physiological expertise of Dr. Charles Schroeder, performs intracerebral recordings of the neurophysiological effects of brain stimulation. Finally, our Technology Development Laboratory enables us to design, model, construct, and test novel devices for brain stimulation that are purpose-built to match the physiology of the human brain.

The BSTM serves as a resource for other groups wishing to utilize brain stimulation techniques to investigate

other research questions. We have active collaborations with the Sergievsky Center in Neurology with Dr. Yaakov Stern (DARPA), Barnard Psychology with Dr. Peter Balsam (DARPA), fMRI Center with Joy Hirsch, Hatch Center with Truman Brown (DARPA), Columbia Psychology (Drs. Tor Wager and Ed Smith), Brain Imaging with Drs. Larry Kegeles and Dikoma Shungu (Dana funded TMS/MRS study) and Dr. Brad Peterson, the Anxiety Disorders Group (Drs. Fallon and Simpson), and the Substance Abuse Division (Drs. Vorel and Bisaga).

Current Research

Active research in the BSTM ranges from basic neuroscience studies on brain behavior relationships, to novel intervention development, to clinical trials. Recent work with magnetic seizure therapy, transcranial magnetic stimulation, transcranial direct current stimulation, vagus nerve stimulation, and brain stimulation technology development is summarized below.

Magnetic Seizure Therapy (MST)

A focus of our work is on the development of MST as a less invasive means of performing convulsive therapy. Our results demonstrate that MST can induce seizures from focal regions of the cortex that have less involvement of deeper brain structures (such as medial temporal cortex) that are implicated in the amnesic side effects of ECT. Parallel studies in a preclinical model (R01 MH60884, PI: Lisanby) and in patients with depression (supported by grants to Dr. Lisanby from NARSAD, Stanley Foundation, and American Federation for Aging Research) are testing its feasibility and safety. Results include the first publications on the safety of MST (and ECT) in a preclinical model, the finding that MST has a better acute safety profile than ECT in patients with depression, neurophysiological evidence that MST-induced seizure are more focal and result in relative sparing of deeper brain structures compared to ECT, and a publication on the anesthetic considerations for MST. We also found that ECT significantly induces the proliferation of new cells and aberrant sprouting of mossy fibers in the dentate gyrus in a preclinical model. These results have implications for the mechanisms of action of convulsive therapy, and for antidepressant pathways in general. We completed the first trial of the antidepressant efficacy of MST in patients with major depression. We are now engaged in a Stanley supported 2 center trial of MST in the US, and launched an international cooperative trial with sites in Wales and Scotland (supported by the Medical Research Council Brain Sciences II) using a novel MST device design capable of higher output than the original device. The first human to receive 100 Hz MST was treated this summer as part of this international collaboration.

Transcranial Magnetic Stimulation (TMS)

Our work with subconvulsive levels of TMS encompasses basic studies using TMS in conjunction with functional imaging as a mapping tool, and clinical trials in the treatment of depression and other disorders. Our basic work with TMS includes active studies on working memory, classical conditioning, deception, visual masking, self-awareness, and language processing. One of our basic cognitive neuroscience projects funded by DARPA (co-PIs: Lisanby and Stern) utilizes fMRI and TMS in the study of the effects of sleep deprivation on working memory circuits. This work has isolated brain networks expressed during task performance, affected by sleep deprivation, and differentially affected as a function of cognitive susceptibility to sleep deprivation. We published our results that TMS stereotaxically applied to nodes in these networks facilitates working memory performance in a frequency- and time-dependent fashion, work led by Dr. Bruce Lubner. We further found that TMS was able to remediate the effects of sleep deprivation on working memory. In the past year Dr. Lisanby received three more grants from DARPA: (1) to develop field implementation strategies for TMS using classical conditioning, (2) to probe the neurocircuitry underlying deception using TMS, and (3) to enhance the restorative properties of sleep using TMS-induced slow wave oscillations. In another series of basic studies on the use of TMS to probe visual information processing, we published our work led by Dr. Lubner revisiting the significance of visual masking deficits in schizophrenia in *Biological Psychiatry*. In collaboration with Dr. Joy Hirsch and John Ferrera, we are using fMRI-guided rTMS as a probe of language processing.

Our clinical work with TMS includes active trials in depression, schizophrenia, OCD (led by Dr. Antonio Mantovani, in collaboration with Drs. Fallon and Simpson), and depersonalization disorder (led by Dr. Mantovani in collaboration with Dr. Simeon of Mount Sinai). This year we completed the industry-sponsored (Neuronetics, Columbia PI: Lisanby) pivotal multicenter trial of TMS in the treatment of depression, the results of which will be reviewed by an FDA panel hearing in January 2007. We are midway through a similar NIMH sponsored 4-center trial of TMS for depression (R01 MH069895, Columbia PI: Lisanby). We have taken the opportunity to spearhead some add-ons to this trial, examining genetic polymorphisms relevant to treatment response and fMRI and DTI measures of prefrontal cortex function before and after the course of rTMS treatment (both efforts led by Dr. Alexandra Sporn). We also received with Dr. George a NIDA supplement to study the impact of prefrontal rTMS on measures relevant to nicotine craving, in collaboration with Drs. Vorel and Bisaga of the Substance Abuse Division. We also have an active program with TMS in schizophrenia, led by Dr. Arielle Stanford. Dr. Stanford received a NARSAD Young Investigator Award, a Janssen Translational Neuroscience Fellowship, and an NIMH K23 award to use rTMS in the study and treatment of the negative symptoms of schizophrenia. This work dovetails with the Dana supported collaborative grant with Drs. Larry Kegeles, Dikoma Shungu, Arielle Stanford, and SH Lisanby, to map abnormal excitatory and inhibitory neurochemical circuitry in schizophrenia with rTMS and MRS. That project should inform the selection of rTMS dosing to alter GABA/glutamate balance in schizophrenia, and will also serve as a probe of GABA/glutamatergic transmission in schizophrenic patients as compared with controls. Also this year Dr. Mantovani published his original finding of efficacy of rTMS in the treatment of OCD and Tourette's syndrome, work we are now following up in a controlled trial.

Transcranial Direct Current Stimulation (tDCS)

tDCS is a noninvasive means of altering endogenous firing rates of cortical neurons using polarization with weak direct currents applied to the scalp. Reports suggest tDCS may have antidepressant properties, and may enhance some forms of memory. We receive a grant from DARPA (PI: Lisanby) to test the ability of tDCS to affect working memory. Dr. Peter Bulow received a NARSAD Young Investigator Award to test the antidepressant properties of tDCS applied to prefrontal cortex.

Vagus Nerve Stimulation (VNS)

VNS was approved for the treatment of resistant major depression last summer, but questions remain regarding patient selection and dose-response relationships. We received contracts to participate in the two multicenter postmarketing trials to address some of these questions (Treatment Resistant Depression Registry and D21 Dose Finding Study, PI: Lisanby). We also received an investigator-initiated contract to study of the impact of VNS on TMS measures of cortical excitability in patients with treatment resistant depression (PIs: Mantovani and Lisanby).

Technology Development

We opened a new brain stimulation technology development laboratory, led by Dr. Angel Peterchev who has a background in power electronics and electrical engineering. Dr. Peterchev used this new facility to design, construct, and test a working prototype of a novel TMS device that expands the functionality of available stimulators. The physiological response to TMS depends on the shape and width of the induced current pulses, however, existing TMS devices allow limited, if any, control over these parameters. The cTMS device induces near rectangular pulses with continuous control over pulse width and shape, allowing the pulses to be physiologically optimized for specific applications. Dr. Peterchev's R21 to support cTMS development received a score of 166 on the first submission, and the revision has been submitted. Dr. Lisanby received the 2006 NYSTAR Faculty Development Award to support this and other neuromodulation technology development projects. Additionally, DARPA support has funded our implementation of fMRI/TMS interleaving, allowing noninvasive, in vivo measures of the blood flow response to TMS with excellent temporal and spatial resolution.

Primate Cognition Laboratory

Led by Dr. Terrace and supported by R01s MH040462 (Terrace) and MH60884 (Lisanby), the primate cognition laboratory continues to innovate new paradigms to probe the impact of brain stimulation on various aspects of nonhuman primate cognition. This year we published the first study on the impact of a full course of MST on cognition, finding that it had less of an effect than electroconvulsive shock (ECS). Other major publications from Dr. Terrace's lab this year focused on ordinal numerical comparisons and aspects of serial learning.

Physiology

We were joined this year by Dr. Charles Schroeder who brings expertise in multichannel electrical recording in awake primates, multisensory integration, and the functional significance of oscillations in information processing. His addition has greatly enhanced our ongoing primate studies of the physiological impact of brain stimulation, and has enabled us to apply for new grant applications to guide brain stimulation dosing strategies to be optimally tuned to ongoing endogenous physiological properties. For example, Dr. Schroeder is a co-investigator on the NYSTAR award that supports the development of EEG-synchronized TMS delivery. Dr. Schroeder's R01s are on the physiology of visual dysfunction in schizophrenia (MH060358), somato-auditory convergence (MH061989), and the neurophysiological basis of fMRI (MH067560).

Education and Training

In the past year the BSTM has provided rotations for 2 undergraduates, 2 medical students, 3 graduate students, 6 residents, and 1 visiting fellow from Columbia and other universities. We currently support 3 postdoctoral fellowship lines on our DARPA grants. In the past year we had our first Columbia graduate student successfully defend her PhD on a Brain Stimulation topic (Dr. Moscrip, co-mentored by Drs. Terrace and Lisanby), and currently we are mentoring a second graduate student on a TMS/fMRI language study (John Ferrera, co-mentors Drs. Hirsch and Lisanby). We also offer CME programs in TMS and ECT, which are provided free of charge to Columbia trainees and faculty.

Clinical Services

Brain Behavior Clinic (BBC)

The BBC at NYSPI specializes in the evaluation and treatment of pharmacotherapy resistant disorders, including mood, anxiety, and psychotic disorders. We enroll patients into approved research protocols where appropriate, and provide post-protocol clinical care following study termination.

Brain Stimulation Service (BSS)

Opened this year, the BSS at NYPH is a unique specialty program offering expert consultations, treatment, and research into innovations in therapeutic brain stimulation. The BSS is uniquely poised to transition new therapeutic devices into clinical application, given our translational research program that ushers novel treatments from device development through pivotal multi-center clinical trials. As novel device-based therapies become FDA-approved, they are added to the spectrum of treatments offered in the BSS. The BSS represents a mutually beneficial bridge between NYPH and NYSPI, enhancing the quality of the clinical care, while increasing patient access to research protocols.

Electroconvulsive Therapy (ECT)

The ECT services at NYSPI and NYPH provide state of the art clinical care to patients referred for ECT. The services also support approved research studies on novel forms of convulsive therapy.

Awards/Honors

2005 NARSAD Young Investigator Awards

Jason Scalia, PhD (mentor: V. Arango, co-mentor: SH Lisanby): The Neurobiology of Depressive Disorder: Hippocampal Neurogenesis and Serotonin Replacement Therapy

Arielle Stanford, MD (mentor: SH Lisanby; co-mentor: D Malaspina): Restoring function: Repetitive transcranial magnetic stimulation for the negative symptoms of schizophrenia. The Brian Bass named award.

Robert Berman (mentor: H Sackeim; co-Mentor: SH Lisanby): Testing neurocircuitry of antidepressant response using focal brain stimulation

Raj Narendran (mentor: M Laurelle; co-Mentor=Lisanby): Probing the connectivity between the dorsolateral prefrontal cortex (DLPFC) and striatum in schizophrenia

2006 NARSAD Young Investigator Awards

Peter Bulow, MD (mentor: SH Lisanby): Transcranial Direct Current Stimulation for the Treatment of Depression

K23 Award to Arielle Stanford, MD (mentor: SH Lisanby; co-mentor: D Malaspina): Negative symptoms of schizophrenia: From phenomenology to targeted treatment

Janssen Translational Neuroscience Fellowship to Arielle Stanford, MD (mentor: SH Lisanby; co-mentor: C Schmauss)

NY State Office of Science, Technology and Academic Research Faculty Development Award to Dr. SH Lisanby. Shaping The Future of Therapeutic Neuromodulation

Dr. Lisanby appointed to the 2005-2007 Defense Sciences Study Group; DOD and Institute for Defense Analysis

2005 Career Development Institute, Stanford University and University of Pittsburgh Colloquium to Dr. Stanford

2005 ACNP/Pfizer Summer Fellowship to Dr. Stanford, to work in the laboratory of immediate Past President Carol Tamminga, MD

2006 Research Colloquium for Junior Investigators, APA/APIRE, to Dr. Stanford

2006 Travel Fellowship Award, Society of Biological Psychiatry, to Dr. Stanford

NIH Predoctoral (NRSA) Fellowship awarded to Tammy Moscrip (priority score = 104; percentile = 0.1).

Promotion to Assistant Professor of Clinical Psychiatry – Dr. Stanford

DARPA grant: “From the Lab to the Field: Transcranial Direct Current Stimulation for Memory Enhancement.” (PI: Lisanby)

DARPA grant: “Deception disruption.” (PI: Lisanby)

Cyberonics contract: “Randomized trial of different levels of electrical charge in VNS treatment of depression (D21 study).” (PI: Lisanby)

Cyberonics contract: "Treatment Resistant Depression Patient Registry Study." (PI: Lisanby)

Cyberonics contract: "Intracortical inhibition following VNS for the treatment of depression." (PIs: Mantovani and Lisanby)

Dana Foundation: "Mapping abnormal excitatory and inhibitory neurochemical circuitry in schizophrenia with MRS and rTMS." (PI: Kegeles, coIs: Lisanby, Stanford, Shungu)

Stanley Foundation: Magnetic Seizure Therapy (MST) for the Treatment of Depression." (PI: Lisanby)

Medical Research Council Brain Sciences II (PI:Ebeiemer, coI: Lisanby) 151,796 Pounds, Reducing adverse ECT effects on memory by magnetic stimulation

Neuronetics contract: "Compassionate use of rTMS for the treatment of Depression." (PI: Lisanby).

Highlights

K23 Award received by Arielle Stanford, MD (mentor: SH Lisanby; co-mentor: D Malaspina): Negative symptoms of schizophrenia: From phenomenology to targeted treatment

Patent application submitted for a novel technology developed by Dr. Angel Peterchev (cTMS, a novel TMS device with controllable pulse shape)

New York State Office of Science, Technology and Academic Research (NYSTAR) Faculty Development Award received by Dr. Lisanby, entitled "Shaping The Future of Therapeutic Neuromodulation"

Publications

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