## AGENDA: DAY ONE

### 2:00pm - 2:05pm
**Welcome Remarks**
Bin He, PhD
Symposium Chair

### 2:05pm - 2:40pm
**Plenary Talk: Physiology of Deep Brain Stimulation: Lessons from the Primate Model of Parkinson's Disease**
Jerrold Vitek, MD, PhD
McKnight Professor and Chair
Department of Neurology
University of Minnesota School of Medicine
Moderator: Bin He, PhD (University of Minnesota)

### 2:40pm - 2:45pm
**Moderator: Bin He, PhD (University of Minnesota)**

### 2:45pm - 2:40pm
**Plenary Talk: Next Generation Strategies to Refine and Optimize DBS for Depression**
Helen Mayberg, MD
Professor of Psychiatry, Neurology and Radiology
Dorothy Fuqua Chair in Psychiatric Neuroimaging and Therapeutics
Member, National Academy of Medicine
Emory University
Moderator: Sophia Vinogradov, MD (University of Minnesota)

### 3:15pm - 3:40pm
**Invited Talk: From Brain Observatories to Scientific Payloads: Strategies for Catalyzing Translational Neuroscience to Address Disease**
Timothy Denison, PhD
Vice President, Research & Core Technology
Restorative Therapies Group
Medtronic, Inc.
Moderator: Matt Johnson PhD (University of Minnesota)

### 3:40pm - 3:45pm
**Moderator: Matt Johnson PhD (University of Minnesota)**

### 3:45pm - 4:00pm
**Coffee Break**

### 4:00pm - 4:30pm
**Poster Highlights I**
This session consists of brief highlight talks of poster presentations.

- **MNS-208:** Closed-loop Optogenetic Control of Neural Circuits: Tracking Dynamic Trajectories of Firing Rate in Vivo
  - Michael Bolus, Georgia Institute of Technology & Emory University
- **MNS-111:** Chronic Cortical Stimulation for Treatment of Focal Epilepsy with Interictal Discharges as a Biomarker
  - Brian Lundstrom, Mayo Clinic
- **MNS-201:** Stress Relief Can Improve Neuromodulation Outcomes and Consistency
  - Cory Gloeckner, University of Minnesota
- **MNS-152:** Tremor Suppression in Parkinson's Disease by Cutaneous Afferents Evoked by Transcutaneous Electrical Nerve Stimulation
  - Ning Lan, Shanghai Jiao Tong University, China
- **MNS-138:** Subthalamic Nucleus Deep Brain Stimulation Alters Kinesthetic Information Processing in Primary Motor Cortex
  - Luke Johnson, University of Minnesota

### 4:30pm - 4:55pm
**Invited Talk: Advances in Neuromodulation Technology and Opportunities from the BRAIN Initiative, SPARC, and NINDS**
Nick Langhals, PhD
Program Director for Neural Engineering, Repair and Plasticity Cluster
National Institute of Neurological Disorders and Stroke (NINDS)
National Institutes of Health (NIH)
Moderator: Hubert Lim, PhD (University of Minnesota)

### 4:55pm - 5:45pm
**Panel Discussion: Opportunities and Challenges in Neuromodulation**
Panelists:
- Stephen Carcieri, PhD, Fellow Research Scientist, Boston Scientific
- Timothy Denison, PhD, Vice President of Research and Core Technology, Technical Fellow, Medtronic
- Nick Langhals, PhD, Program Director, NIH
- Helen Mayberg, PhD, Professor of Psychiatry, Emory University
- Lalit Venkatesan, PhD, Senior Principal Scientist, Abbott
- Jerrold Vitek, PhD, McKnight Professor and Chair of Neurology, University of Minnesota
Moderator: Bin He, PhD, University of Minnesota

### 5:45pm - 8:00pm
**Reception**
### AGENDA: DAY TWO

**8:30am - 9:05am**
**Plenary Talk: The Logic of Non-Invasive Neuromodulation**
Mark Hallett, MD  
Chief, Human Motor Control Section  
National Institute of Neurological Disorders and Stroke (NINDS)  
National Institutes of Health (NIH)  
President, International Federation of Clinical Neurophysiology  
Moderator: Tim Ebner, MD, PhD (University of Minnesota)

**9:05am - 9:40am**
**Plenary Talk: Transcranial Electric Stimulation Techniques**
Walter Paulus, MD, PhD  
Professor of Clinical Neurophysiology  
Director of the Department of Clinical Neurophysiology  
University Medical Center Gottingen, Germany  
Moderator: Kelvin Lim, MD (University of Minnesota)

**9:40am - 10:10am**
**Poster Highlights II**
This session consists of brief highlight talks of poster presentations.

**MNS-130: Closed-loop Neuromodulation of Vagus Nerve for the Hemodynamic Stability After Asphyxial Cardiac Arrest**  
Qihong Wang, Johns Hopkins University

**MNS-197: Transcranial Direct Current Stimulation Alters Brain Connectivity During BCI**  
Bryan Baxter, University of Minnesota

**MNS-139: tACS Impacts Detection of Change in Visual Task and its Ongoing Neural Oscillations**  
Giulio Ruffini, Neuroelectrics Corp.

**MNS-144: Spinal Cord Stimulation Reduces Freezing of Gait Episodes and Improves Gait in Advanced Parkinson's Disease Patients**  
Olivia Samatus, University of Western Ontario, Canada

**MNS-240: Continuous Restoration of the Human Vestibulo-Ocular Reflex via a Multichannel Vestibular Implant**  
Peter Boutros, Johns Hopkins University  
Moderator: Wei Chen, PhD (University of Minnesota)

**10:10am - 10:30am**
**Neuromodulation Research at UMN**
Bin He, PhD  
Director, Institute for Engineering in Medicine  
Director, Center for Neuroengineering  
Medtronic-Bakken Endowed Chair for Engineering in Medicine  
Distinguished McKnight University Professor of Biomedical Engineering  
Moderator: Wei Chen, PhD (University of Minnesota)

**10:30am - 1:00pm**
**Poster Session**

**12:30pm - 1:30pm**
**Lunch**
Box lunches will be provided

**1:30pm - 2:05pm**
**Plenary Talk: Neuromodulation for Real World Applications**
William Tyler, PhD  
Associate Professor  
School of Biological and Health Systems Engineering  
Arizona State University  
Moderator: Bin He, PhD (University of Minnesota)

**2:05pm - 2:40pm**
**Plenary Talk: Neurotechnologies for Peripheral and Visceral Neuromodulation**
Nitish V. Thakor, PhD  
Professor of Biomedical Eng, Electrical Eng, Neurology  
Director, Neuroengineering Training Program  
Johns Hopkins University  
Editor in Chief, Medical and Biological Engineering and Computing  
Moderator: Kip Ludwig, PhD (Mayo Clinic)

**2:40pm - 3:05pm**
**Oral Session**
**Noninvasive and Alternative Neuromodulation Approaches Towards Healing the Mind and Body**  
Hubert Lim, PhD, Associate Professor of Biomedical Engineering, University of Minnesota

**Clinical Trial of the Intracortical Visual Prosthesis (ICVP): Preparation and Trial Design**  
Phil Troyk, PhD, Professor of Biomedical Engineering and Associate Dean of Engineering, Illinois Institute of Technology

**Enhance Intra-cortical Stimulation with Implantable Micro-coils**  
Shelley Fried, PhD, Associate Professor in Neurosurgery, Harvard Medical School  
Moderator: Teresa Kimberley, PhD (University of Minnesota)

**3:40pm - 3:55pm**
**Awards Ceremony**
INVITED LECTURES
From Brain Observatories to Scientific Payloads: Strategies for Catalyzing Translational Neuroscience to Address Disease

Abstract: Neurological disease has a significant economic and societal impact. While promising in-roads for treatment have been made for some conditions, many disorders continue to be plagued by limited understanding of the underlying pathophysiology and the therapeutic mechanisms of existing and potential treatments. To address this issue, teams are creating investigational research tools, with advanced bioelectronic designs, that can be chronically implanted to study the nervous system. These tools permit the active probing of malfunctioning neural circuits with novel instrumentation, enabled by a system architecture that leverages an existing neurostimulator’s potential “scientific payload” to provide a chronic conduit to the nervous system. Deployed with clinician-researchers, these instrumentation toolkits bootstrap off existing clinical care pathways to facilitate exploration of therapeutic concepts. This strategy enables a new approach to translational research, merging engineering design methods with basic neuroscience to help catalyze the next generation of neurological therapies. This talk will provide a technical perspective on the state-of-the-art for this work, some promising areas for exploration, and the significant challenges that remain.

Timothy is the Vice President of Research and Core Technology, Implantable Systems, for the Restorative Therapies group of Medtronic PLC. He was named a technical fellow in 2010, received Medtronic’s highest technical and scientific award, membership in the Bakken Society in 2012 and was honored with the Wallin Leadership Award in 2014. Timothy was named to the College of Fellows for the American Institute of Medical and Biological Engineering in 2015. Timothy Denison received his M.S. and Ph.D. in Electrical Engineering from the Massachusetts Institute of Technology, and his A.B. in Physics from the University of Chicago. He is currently completing an MBA at the University of Chicago. His extracurricular pursuits include serving as an adjunct professor at Brown University, volunteering as an assistant editor for the IEEE Transactions on Biomedical Circuits and Systems/Biomedical Engineering, and on the editorial board of the Journal of Neural Engineering.

The Logic of Non-Invasive Neuromodulation

Abstract: Brain stimulation can change brain networks during stimulation and this is generally the logic of deep brain stimulation which requires continuous operation to be effective. Non-invasive brain stimulation depends on inducing a plastic change in the brain. If done in the passive state, as usually done, the logic has often been to create facilitation or inhibition of the stimulated region. Long term plastic change appears to require repeated stimulation. Looking to the future, it might be more sensible to combine brain stimulation with a behavioral intervention that could lead to more specific brain changes.

Dr. Hallett is the President of the International Federation of Clinical Neurophysiology. He is now the Chief of the Human Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland. From 1976 to 1984, Dr. Hallett was the Chief of the Clinical Neurophysiology Laboratory at the Brigham and Women’s Hospital and Harvard Medical School. From 1984, he has been at the National Institute of Neurological Disorders and Stroke where he also served as Clinical Director until July 2000. He is past President of the American Association of Neuromuscular and Electrodiagnostic Medicine and the International Parkinson and Movement Disorder Society. He has served as Editor of Clinical Neurophysiology. His work mainly deals with principles of motor control and the pathophysiology of movement disorders.
Nick Langhals, PhD

Advances in Neuromodulation Technology and Opportunities from the BRAIN Initiative, SPARC, and NINDS

Abstract: Nick B. Langhals, Ph.D. serves as the Program Director for Neural Engineering at the National Institute of Neurological Disorders and Stroke (NINDS), where he manages a portfolio of grants focused on the development and translation of neurotechnologies. He is heavily involved in the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative focused on both implantable and non-invasive technologies for recording and modulating neural activity. He also serves as the NINDS lead for the Bioengineering Research and Stimulating Peripheral Activity to Relieve Conditions (SPARC) programs at NIH. Within this talk, he will discuss some of the recent advances in neuromodulation that have been developed through NIH funding in many of these areas. Further, he will also discuss a vision for future opportunities in research and development in these areas and where the neuromodulation community could play an active role.

Nick B. Langhals, Ph.D. serves as Program Director for Neural Engineering within the Repair and Plasticity Cluster at the National Institute of Neurological Disorders and Stroke (NINDS). He is heavily involved in both the BRAIN Initiative as well as the SPARC program. Prior to arriving at the NIH in 2015, Dr. Langhals served as a Research Assistant Professor in the Plastic Surgery Section of the Department of Surgery and Assistant Research Scientist of Biomedical Engineering at the University of Michigan, Ann Arbor. Dr. Langhals served as Co-Director of the Neuromuscular Laboratory, which has developed a regenerative peripheral nerve interface (RPNI) to extract prosthetic control signals and restore lost sensation to amputees for the control of replacement upper and lower extremity prostheses. His previous research activities have spanned in a wide range of topics including neural engineering, neuroprosthetics / neuroprostheses, neuromodulation, sensory restoration, neural decoding algorithms, brain-machine / brain-computer interfaces, and drug delivery in the brain.

Helen Mayberg, MD

Next Generation Strategies to Refine and Optimize DBS for Depression

Abstract: Deep Brain Stimulation (DBS) is an emerging treatment strategy for patients with intractable depression with selection of the subcallosal cingulate (SCC) as a stimulation target based principally on converging findings from resting-state PET studies of conventional antidepressant interventions. At present, surgical implantation of DBS electrodes relies on high resolution structural images to localize the SCC grey matter-white matter border followed by trial-and-error behavioral testing of chronic stimulation at individual contacts. Clinical response may however be optimized by more precise targeting along specific white matter tracts as evidenced by recent diffusion tensor imaging and tractography analyses of DBS responders and non-responders. Catalyzed by availability of next generation devices that allow ongoing recordings of local field potentials in the targeted circuit of interest, recent work now combines multimodal neuroimaging with real-time behavioral and electrophysiological measurements, providing a more precise method to identify the optimal target location and stimulation parameters for individual patients. Strategic integration of neuroengineering innovations and selective animal models offers potential complementary perspectives to fully delineate critical pathways and mechanisms mediating antidepressant effects of SCC DBS and inform on the pathophysiology of treatment resistant depression more generally.

Helen Mayberg, M.D. is Professor of Psychiatry, Neurology and Radiology, Dorothy Fuqua Chair in Psychiatric Neuroimaging and Therapeutics at Emory University. Over the last 25 years, her multi-disciplinary depression research team has worked to integrate cutting-edge imaging strategies, quantitative behavioral and psychophysiological metrics, and experimental treatment trials to define brain-based biomarkers that can optimize treatment selection for individual patients. This work was foundational for the first studies of subcallosal cingulate deep brain stimulation for treatment resistant depression and remains the cornerstone of current studies to both refine and optimize DBS implementation and characterize network mechanisms mediating its antidepressant effects. Dr. Mayberg is a neurologist, trained at Columbia’s Neurological Institute in New York, with fellowship training in nuclear medicine at Johns Hopkins. She is a member of the National Academy of Medicine, among other honors, and participates in a wide variety of editorial, advisory and scientific activities across multiple fields in neuroscience.
Transcranial Electric Stimulation Techniques

Abstract: Transcranial electric stimulation techniques have been developed as cheap and efficient tools for modifying cortical plasticity. Repetitive transcranial magnetic stimulation (rTMS) allows increasing or decreasing the excitability of corticospinal or cortico-cortical pathways depending on the intensity and frequency of short stimulation pulses in the range of 100 µs. Here magnetic stimulation is the vehicle which allows transferring transcranially short-pulsed electric energy without inducing skin pain. Direct transcranial electric stimulation of the human brain can be used painlessly if less steep voltage gradients are involved. Weak transcranial direct current stimulation (tDCS) with a homogenous DC field fulfills this requirement ideally (Nitsche and Paulus, 2000). TDCS induces plastic aftereffects via membrane polarization: cathodal stimulation hyperpolarizes, while anodal stimulation depolarizes the resting membrane potential, whereby the induced after-effects depend on polarity, duration and intensity of the stimulation. Transcranial alternating current (tACS) (Antal et al, 2008) and random noise stimulation (tRNS) intend to interfere with ongoing cortical oscillations (Terney et al., 2008). Using these techniques, we can induce and modify differently neuroplastic changes with different advantages and disadvantages of tDCS, tACS and tRNS. Plastic aftereffects need a minimal stimulation duration time and may reverse with too long stimulation. Whereas in the normal stimulation duration range of about 10 minutes tDCS allows for excitability increase and decrease, tACS and tRNS induce only excitability increases in particular with higher frequencies between 100 and 600 Hz or in the low kHz range. TACS and tRNS induce less skin sensation than tDCS and accordingly can be blinded better. They are also no longer current flow direction sensitive. These effects are strongly modified by neuropharmacological co-application: L-DOPA leads to a focusing effect in analogy to its otherwise found U-shaped dose dependency. Dopamine agonists may reverse anodal excitatory tDCS into inhibition, SSRI provide the opposite effect. In conclusion transcranial electrical stimulation techniques allow for targeted modulation of cortical plasticity in man.

W. Paulus—studied medicine at the University of Düsseldorf and was awarded the MD with his thesis on “Psychophysics of color vision deficiency”. After specialist training in neurology in Düsseldorf and a 6-month research residence at the National Hospital for Nervous Diseases, University College London, he was in the Department of Neurology and Clinical Neurophysiology at the Alfred-Krupp Hospital and transferred then to the Neurological University Hospital in Munich with a scientific focus on human posture regulation. In 1987 he was habilitated (German professorial qualification) in neurology and clinical neurophysiology and, in 1992, was appointed Director and chair of the Department of Clinical Neurophysiology at the University Medical Centre of the University of Göttingen. In 1997 he was President of the German Society of Clinical Neurophysiology. He has been the coordinator of various research networks and was speaker of the international graduate school “Neuroplasticity: From Molecules to Systems”. At present he is Chairman of the European Chapter of the International Federation of Clinical Neurophysiology. In 2016 he obtained the Hans-Berger Price from the German Society for Clinical Neurophysiology for his lifework on clinical neurophysiology encompassing now some 550 publications.
Nitish Thakor, PhD

Neurotechnologies for Peripheral and Visceral Neuromodulation

Abstract: Peripheral nerve or muscle function modulation, involving recording and stimulation, has been shown to be effective in restoring limb functions in animal models and selectively in humans. Both motor function and sensory input perceptions have been demonstrated. Visceral nerve modulation has been shown to be effective treating a variety of disorders including depression, epilepsy, inflammation, bladder function, etc. While much of the work is demonstrated in animal models, some clinical effectiveness has also been demonstrated. The overall goal of this talk is to present state of the art technologies for nerve modulations. The essential technologies can be grouped into electrode interfaces to the nerves (recording and stimulation), integrated circuits for low noise recording and effective stimulation or blocking, power and data delivery to the implant. The integrated solutions developed by our group as well as the state art will be described with applications to both peripheral visceral nerve modulation. This field is poised for a significant growth: In view of the therapeutic potential, NIH is supporting this field through the SPARC initiative, and many industrial and startups venturing into this field as well.

Nitish V. Thakor is the Director of the Singapore Institute for Neurotechnology (SINAPSE) at the National University of Singapore and the Professor of Electrical and Computer Engineering and Biomedical Engineering since 2012. He has also been the Professor of Biomedical Engineering at Johns Hopkins University since 1983. Prof. Thakor’s technical expertise is in the field of Neuroengineering, where he has pioneered many technologies for brain monitoring to prosthetic arms and neuroprosthesis. He is an author of more than 328 refereed journal papers (H Index 62; I-10 Index 210), more than a dozen patents, and co-founder of 3 companies. He is currently the Editor in Chief of Medical and Biological Engineering and Computing, and was the Editor in Chief of IEEE TNSRE from 2005-2011. Prof. Thakor is a recipient of a Research Career Development Award from the National Institutes of Health and a Presidential Young Investigator Award from the National Science Foundation, and is a Fellow of the American Institute of Medical and Biological Engineering, IEEE, Founding Fellow of the Biomedical Engineering Society, and Fellow of International Federation of Medical and Biological Engineering. He is a recipient of the award of Technical Excellence in Neuroengineering from IEEE Engineering in Medicine and Biology Society, Distinguished Alumnus Award from Indian Institute of Technology, Bombay, India, and a Centennial Medal from the University of Wisconsin School of Engineering.

William Tyler, PhD

Neuromodulation for Real World Applications

Abstract: The engineering of non-invasive neuromodulation platforms for everyday use in research applications, biomedical systems, and consumer electronics is leading neuroscience into uncharted territories. A globally emerging sensosphere provides an opportunity to collect human physiological and behavioral data on unprecedented scales. The first part of the talk will describe our science and engineering efforts on developing neuromodulation methods. A portion of this discussion will be devoted to describing our work on pulsed ultrasound as an approach to non-invasively and mechanically interface with brain circuits for neuromodulation purposes. The second part of the talk will transition into a discussion of how non-invasively modulating established and highly characterized deep-brain pathways in freely behaving humans while simultaneously acquiring data from connected sensors and devices in real world environments will markedly advance our understanding of brain and behavior, as well enable the optimization of human performance.

Dr. Tyler is an Associate Professor at Arizona State University in the School of Biological and Health Systems Engineering. He received his B.S. and Ph.D. from the University of Alabama at Birmingham before conducting a postdoctoral fellowship in the Department of Molecular and Cellular Biology at Harvard University. Dr. Tyler was a National Institutes of Health, National Institute of Neurological Diseases and Stroke predoctoral and postdoctoral fellow. After completing his postdoc in 2006, he began as an Assistant Professor of Neurobiology and Bioimaging at Arizona State University, then spent a few years as an Assistant Professor of Biomedical Engineering at Virginia Tech before returning to ASU.
Abstract: Deep brain stimulation has been a highly successful surgical therapy for patients with Parkinson’s disease, dystonia and tremor and is being explored for other neurological and psychiatric disorders. In order to optimize this therapy for PD and insure its successful application to other disorders, we need to understand how DBS works to improve motor function in movement disorders, its effect on neural circuits that underlie the development of these disorders, and how we can predictably modulate these circuits to improve function. Human studies have provided some insights into these questions but have limitations that can only be addressed using nonhuman primate models of disease. Nonhuman primate studies have provided us with the ability to explore in depth the changes that occur within and across neuronal structures during stimulation revealing critical pieces to the puzzle of DBS mechanisms. Studies in animal models have demonstrated that contrary to early hypotheses stimulation activates rather than inhibits output from stimulated structure, that improvement during DBS may be related in part to activation of adjacent fiber pathways and that stimulation in one node of the basal ganglia thalamo-cortical (BGTC) circuit induces network wide changes. In this lecture we will discuss the insights into DBS mechanisms gained from these studies.

Jerrold L. Vitek is McKnight Professor and Head of the Department of Neurology at the University of Minnesota. Dr. Vitek was on faculty at the Johns Hopkins University, Emory University and Cleveland Clinic, and accepted the Chair of Neurology position at the University of Minnesota in June of 2010. He has been working for decades on the development of new applications for DBS, improving current application and advancement of functional surgery and DBS techniques for the treatment of neurological disease. He continues to see patients specializing in the diagnosis, treatment and management of movement disorders, performing electrophysiology and mapping during DBS surgery and DBS programming. Dr. Vitek is also the Director for the Center for Neuromodulation Research at the University of Minnesota and a principal investigator on numerous basic, preclinical and clinical studies investigating the pathophysiology of movement disorders, mechanisms of DBS and the application of DBS for the treatment of neurologic disorders.
ORAL SESSION
PRESENTATIONS
Noninvasive and Alternative Neuromodulation Approaches Towards Healing the Mind and Body

Hubert H. Lim, PhD, Associate Professor of Biomedical Engineering, University of Minnesota

Over the past decade, a variety of novel stimulation approaches have been developed for modulating the nervous system and body towards treating different health conditions. Stimulation technologies are expanding beyond just electrical stimulation to incorporate magnetic, optical and ultrasound modalities. Additional factors, such as the placebo effect, stress and attention levels, are also being explored in their ability to alter or enhance therapeutic effects. In my talk, I will present several new directions in my lab towards developing alternative and combined stimulation approaches for treating deafness, phantom sound pain (tinnitus), and inflammatory pain (rheumatoid arthritis). We are developing noninvasive methods using ultrasound stimulation, peripheral nerve modulation, and stress relaxation techniques to better target and more consistently induce therapeutic effects for treating different types of pain. We are also exploring the ability to co-stimulate multiple nerve pathways with varying delays to drive and steer modulatory effects within the nervous system. The initial success and future challenges of these noninvasive approaches towards developing individualized treatments for patients will be presented.
Clinical Trial of the Intracortical Visual Prosthesis (ICVP):
Preparation and Trial Design

Philip R. Troyk1,6,7, Stuart Cogan2, Gislin Dagnelie3, Janet Szlyk4, Martin Bak5,
Glenn DeMichele6, V. Leo Towle7

1Illinois Institute of Technology, USA; 2University of Texas, Dallas, USA; 3Johns Hopkins University, USA;
4The Chicago Lighthouse, USA; 5MicroProbes for Life Science, USA; 6Sigenics, Inc, USA; 7University of Chicago, USA

Background: The Intracortical Visual Prosthesis has a long history of development dating back to the late 1960s. Following numerous extramural contracts by NINDS, through the Neural Prosthesis Program (1970 – 1998), technology for intracortical stimulation of the visual cortex was developed in conjunction with safe methods of neural stimulation. The NIH effort culminated in a demonstration of 38 electrodes implanted in a volunteer for four months. In 2000, IIT created the ICVP project team that now comprises seven institutions, as listed above. The functional basis for the ICVP is that through multiple implanted 16-channel wireless intracortical stimulator modules, temporal- and spatially-coordinated stimulation of the visual cortex can provide useful visual perception for individuals with blindness. The current clinical trial, funded under the BRAIN Initiative, seeks to explore how this unique cortical interface might be used for visually-guided tasks, wayfinding, and improvement of quality of life. Here we briefly describe the basic technology and the clinical trial plan.

Methods: The wireless-floating-microelectrode-array (WFMA) stimulator (5mm diameter x 0.5mm thickness) combines integrated electronics, inductive wireless powering and communication, and iridium oxide microelectrodes into a single implantable module. A collection of these comprise a multichannel ICVP system. Prior to implantation in five human volunteers, the ICVP system will be submitted for FDA approval under an early feasibility study IDE. Building upon our earlier demonstrations of WFMA reliability, preclinical work (2 years) will involve GLP large animal, ISO10993 biocompatibility, and engineering laboratory qualification testing. Subsequent clinical testing (3 years) will involve studying the stability of the artificial neural interface, determination of phosphene thresholds and mapping, and study of the integration of distinct phosphenes into higher-level visual perceptions. Subjects will be implanted in three groups (1, 2, 2) starting with about 10-15 WFMA, then doubling the devices for each group up to a maximum of about 40 devices (640 electrodes).

Results: Prior in-vivo testing of the WFMA was done through rodent and non-human primate models; WMFA has been implanted for over 1 year in both. Engineering evaluation employed highly-accelerated temperature-humidity-bias and temperature cycling tests; WMFA have survived over 1 year of the brutal environmental exposure. Additional in-vivo and engineering tests are on-going. External hardware to control the implanted WMFA uses high-power Class-E magnetic transmission technology at 4.8MHz. The external telemetry control units will be configured for use in the psychophysics laboratory and for home use by the subjects.

Conclusions: After decades of preparation, the available technology has matured to allow for a clinical trial of the ICVP system in five volunteers. The clinical demonstration of this multi-channel neural interface may enable other cortical neuromodulation applications.

Funding: The ICVP project is supported by the National Institute Of Neurological Disorders And Stroke of the National Institutes of Health under Award Number UG3NS095557, Gifts to IIT, and Sigenics internal R&D. The content here is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
Enhance intra-cortical stimulation with implantable micro-coils

Shelley I. Fried\textsuperscript{1,2,3}, Seung Woo Lee\textsuperscript{2,3}

1. Boston VA Healthcare System, USA; 2. Massachusetts General Hospital, USA; 3. Harvard Medical School, USA

**Background:** Cortical stimulation from implanted micro-electrodes is under evaluation for the treatment of a wide range of neurological and psychological disorders. The long-term effectiveness of this approach has been limited however, in part due to the complex biological and chemical reactions that diminish the effectiveness of implants over time as well as by the inability to selectively stimulate specific sub-populations of neurons. Magnetic stimulation can theoretically overcome these limitations, e.g. even severe glial scarring will not impede magnetic fields, and, the spatially asymmetric magnetic fields can be harnessed to preferentially target specific cell types. Here, we report the development of a new micro-coil design that can be implanted cortically and demonstrate its effectiveness in physiological experiments [1, 2].

**Methods:** Computational modeling was used to compare different coil designs and the most promising were fabricated for use in electrophysiological experiments. The sensitivity of individual Layer 5 pyramidal neurons (L5PNs) was tested during \textit{in vitro} experiments in mouse brain slices. Coils were also implanted into mouse motor cortex \textit{in vivo} to explore whether behavioral responses could be induced.

**Results:** Modeling revealed that even simple bends of micro-wires generated supra-threshold fields and \textit{in vitro} testing of fabricated prototypes confirmed effectiveness. Sensitivity mapping in individual L5PNs revealed that the proximal axon had the highest sensitivity to individual pulses but that the apical dendrite was more sensitive to repetitive stimulation. Only those coil orientations that induced a strong electric field along the length of the L5PN were effective; as a result, coil-based activation was confined to a relatively small region of vertically-oriented L5PNs around the coil. In contrast, the spread of activation with electric stimulation was considerably more extensive. Coils implanted into whisker cortex \textit{in vivo} induced movements of single whiskers; consistent with previous electric stimulation experiments [3], the direction of movement was dependent upon the frequency of stimulation.

**Conclusions:** The reduced susceptibility to encapsulation, the ability to better confine activation to a focal region around the coil and the demonstration that coils drive behavioral responses suggest that coil-based implants may be an attractive alternative to conventional electrode implants. In addition to allowing for more precise targeting of cortex during research studies, they may also help to enhance the performance of cortical prostheses that require precise resolution, e.g. those that target visual cortex or those that provide a feedback signal to somatosensory cortex.

**References:**


**Funding:** Rappaport Foundation, NIH R01 EY023651 and U01 NS099700 (BRAIN Initiative), VA RR&D 1I01RX001663.
POSTER
HIGHLIGHT TALKS
Closed-loop Optogenetic Control of Neural Circuits: Tracking dynamic trajectories of firing rate in vivo

Michael F. Bolus¹, Adam A. Willats¹, Clarissa J. Whitmire¹, Christopher J. Rozell², Garrett B. Stanley¹

1. Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA 30332, USA; 2. School of Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, Georgia 30332, USA

Background: Understanding how to interface with the nervous system effectively has become increasingly important as the role of neuromodulation expands in the treatment of a variety of disorders including Parkinson’s disease (PD), loss of sensation, and epilepsy. However, most devices rely on physician intervention at the timescale of weeks to months to fine-tune stimulation. An alternative strategy is to ‘close the loop’ around the activity being controlled, using feedback to guide stimulation in real-time. Optogenetics enables control of neuronal activity at fast timescales with cell-type specificity and can be easily coupled with electrophysiological recordings for use as feedback. Therefore, it is an appealing technique for gaining scientific insight, developing closed-loop stimulation strategies, and identifying targets for clinical intervention. As such, we are developing methodologies for closed-loop optogenetic control (CLOC) of neural activity in vivo [1]. Here, we develop a systematic methodology for designing closed-loop optogenetic systems for the control of dynamic trajectories of firing rate.

Methods: An optrode (80 µm tungsten electrode; 200 µm optic fiber) is advanced into somatosensory thalamus of anesthetized female Sprague-Dawley rats. Spikes from a single unit are isolated from extracellular recordings. Firing rate is estimated online and used as feedback for a proportional-integral (PI) controller which modulates optical stimulation of cells expressing the excitatory opsin channelrhodopsin (ChR2, AAV-CaMKIIα). During a phase of system identification, a linear-nonlinear-Poisson (LNP) model is fit to data. Using this model, controller gains are tuned for tracking sinusoidal trajectories in simulation, and the resulting parameters are used experimentally to elicit the desired firing rate trajectory: a naturally relevant, non-sinusoidal pattern.

Results: We demonstrate that PI control is effective for tracking time-varying firing rate patterns in individual neurons. Moreover, compared to open-loop control, we find that there is a reduction in across-trial variability conferred by feedback, even in cases where open-loop pulsed or continuous stimulation performs well on average. Importantly, closed-loop stimulation also has the capacity to reject disturbances such as input from other brain regions (Figure 1B). Finally, we show that a design procedure built around sinusoidal patterns of firing rate can generalize to a more complex, band-limited target signal of interest (Figure 1C).

Conclusions: Our results illustrate the ability of closed-loop control to reduce variability in response to stimulation on rapid timescales without manual intervention. Therefore, CLOC has the potential for real-time titration of stimulation to elicit target patterns of activity while rejecting pathological changes that occur in PD or in epilepsy.

Figure 1. (A) Physical diagram for controlling thalamic firing rate. (B) Example of closed-loop control vs. open-loop pulsatile stimulation. Control is subject to a disturbance in the form of noise applied to the whisker driving the isolated thalamic neuron. Light lines correspond to single-trial estimates of firing rate; bold lines correspond to trial-averaged. (C) Controlling a naturally relevant, non-sinusoidal target trajectory after the design procedure. Average firing rate achieved, spike rasters, and control input (light intensity) are shown in the top, middle, and bottom panels, respectively.

References:

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**Chronic cortical stimulation for treatment of focal epilepsy with interictal discharges as a biomarker**

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**Background:** Approximately 1 to 3 in 1000 people have drug resistant focal epilepsy. Resective surgery is the most effective treatment but may not be feasible if the seizure focus is in eloquent cortex. Here, we respectively assess the clinical efficacy of chronic focal cortical stimulation in reducing seizure frequency and severity for patients with focal drug resistant epilepsy (DRE).

**Methods:** Thirteen patients with DRE were deemed unsuitable for resective surgery since the seizure focus was located in eloquent cortex. A trial of therapeutic continuous cortical electrical stimulation was given via the surgically implanted subdural grid and depth electrodes used for intracranial electroencephalography (iEEG) monitoring. Parameters of cortical stimulation were adjusted to minimize the frequency of interictal iEEG spikes. Permanent stimulation hardware was implanted when iEEG electrodes were explanted. Three hours of iEEG data were analyzed retrospectively for each patient. Interictal spike rates were detected by a previously validated automated method for iEEG spike detection. Assessment of epilepsy severity, life satisfaction, and frequency of disabling seizures was based on retrospective patient report.

**Results:** The mean decrease in disabling seizures was 80% (range 33-100%) following chronic stimulation (Lundstrom et al, JAMA Neurology, 2016). Ten (77%) of the 13 patients reported improvement for both epilepsy severity and life satisfaction. iEEG spike rates decreased significantly for all analyzed patients. The mean spike rate decreased from 0.61 to 0.08 IED/s (p=0.002). Additional analyses showed that spike heights were significantly decreased during stimulation and away from the seizure onset zone by 9% and 21%, respectively (p<0.001).

**Conclusions:** Continuous subthreshold cortical stimulation may be a suitable treatment for focal epilepsy patients with lesions involving critical cortical areas or those with a localized seizure onset zone for whom a potentially reversible procedure is attractive. iEEG spike rate could be a useful biomarker for treatment efficacy. Spike height may be correlated with seizure probability.

**References:**

Stress Relief Can Improve Neuromodulation Outcomes and Consistency
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Background: Many neuromodulation methods rely on inducing long-term plasticity in specific brain regions. However, most of these methods show at least some inconsistent results across patients, especially for neural disorders like tinnitus which result from abnormal spiking patterns. Recently, Multimodal Synchronization Therapy (mSync), a novel neuromodulation technique pairing two different sensory stimuli at specific inter-stimulus delays, has been found to induce plasticity in auditory cortex that may be useful for treating tinnitus. We investigated how stress affects the quality of outcomes for plasticity induction during mSync, which might imply effects of stress on neuromodulation in general.

Methods: We positioned a 32-site electrode array in primary auditory cortex (A1) of 6 ketamine-anesthetized guinea pigs. Needle electrodes were used to electrically stimulate the pinnas, paired with broadband noise auditory stimulation with varying inter-stimulus delays (-25 to +25 ms in 10 ms steps). Plasticity induction was determined using a two-tailed, unequal variance, ranked t-test (p<0.01) to compare acoustic-driven spike activity before, immediately after, and 30 minutes after paired stimulation to indicate long-term changes in neural responses. This paradigm was repeated in 10 awake animals with chronic recording arrays, 5 of which received Healing Touch for stress-relief treatment, and 5 of which received no treatment. An elevated plus maze behavioral test was used to determine the stress levels of all awake animals.

Results: Under anesthesia, an inter-stimulus delay of +15 ms (acoustic stimulation preceded body stimulation) consistently induced significantly more suppression of neural activity than facilitation across all animals, while no other delay showed a significant difference (see figure, control indicates no stimulation). Results in stressed awake animals were inconsistent with no statistical significance. However, in the stress-relief awake group, the +15 inter-stimulus delay was significantly suppressive (matching anesthesia results) and the +5 inter-stimulus delay was significantly facilitative, which matches previous literature on timing-dependent plasticity in the auditory system. Using an elevated plus maze, we determined that the stress-relief group exhibited less stress than the stressed group with statistical significance (p<0.05).

Conclusions: The results of the stressed group were extremely inconsistent across animals, with fewer neurons showing significant changes. Meanwhile, the results of the stress-relief group not only showed the same result as the anesthetized group, but also showed spike timing-dependent plasticity effects consistent with other studies. This implies that stress plays a key role in the ability to consistently and systematically induce plasticity with mSync, and might imply the need for low-stress subjects for neuromodulation in general.

References:

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Tremor Suppression in Parkinson’s Disease by Cutaneous Afferents Evoked by Transcutaneous Electrical Nerve Stimulation

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**Background:** Resting tremor is one of the primary motor symptoms of patients with Parkinson’s disease (PD). Tremor signals in PD are originated from cortical central oscillators at single and double tremor frequencies and transmitted to extremities, causing involuntary cyclic movements, or tremor. In this study, we investigated the inhibition effects of cutaneous afferents evoked by transcutaneous electrical nerve stimulation (TENS). Cutaneous afferents presumably inhibit the propriospinal neurons (PN) in spinal circuits, thus alleviating tremor symptom. The central signal of double tremor frequency was found to correlate more directly to individual muscle EMGs (Timmermann et al. 2003), while the central oscillation at tremor frequency contributes mainly to synchronize peripheral muscles in the modulation of tremor intensity (He et al. 2015). This change in frequency content implies that spinal circuits play an important relay in corticospinal transmission of tremor signals. We proposed that the propriospinal neuron (PN) network generates the alternating pattern of antagonistic muscle bursts from central oscillation signals (Hao et al. 2013). We further hypothesize in this study that inhibiting propriospinal neurons by cutaneous afferents could disrupt tremor signals, and thus, inhibiting tremor in PD patients.

**Methods:** We tested this hypothesis by activating cutaneous afferent in the dorsal hand skin innervated by superficial radial nerve using transcutaneous electrical nerve stimulation (TENS), which is known to inhibit PNs. 8 PD patients with tremor dominant symptom were recruited to participate in the randomized block design of this study. Kinematic data of 7 degrees of freedom and EMGs of six muscles in the one side upper extremity of these PD subjects were simultaneously recorded while surface stimulation was applied to the dorsal skin of hand of them.

**Results:** At stimulation intensity of 1.5 ~ 1.8 times of radiating sensation threshold, complete or incomplete suppressions of tremor at wrist, forearm and upper arm and in the EMGs were observed immediately at the onset of stimulation. After termination of stimulation, tremor and rhythmic EMG bursts reemerged gradually. Statistical analysis of peak spectral amplitudes showed a significant reduction in most joint tremors and EMGs prior to and during stimulation in all 8 PD subjects.

**Conclusions:** Our results support the hypothesis that the spinal PN network transmits cortical tremor signals to peripheral muscles in PD patients. And tremor in the upper extremity of PD patients can be inhibited to a large extent with evoked cutaneous reflex. A non-invasive method of tremor suppression may be achieved.

**References:**

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Subthalamic nucleus deep brain stimulation alters kinesthetic information processing in primary motor cortex

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Background: Primary motor cortex M1 is not only responsible for controlling voluntary limb movement, but is also integral to sensory processing of kinesthetic information [1]. In this study we examined the effect of subthalamic nucleus (STN) deep brain stimulation (DBS) on information processing of passive limb movements in M1 of a non-human primate rendered parkinsonian by systemic injections of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). We tested several hypothesized mechanisms of DBS: 1) DBS increases M1 specificity to opposing joint articulations [2], 2) DBS causes an “informational lesion” which may be reflected by reduced responsiveness to passive movement [3], and 3) DBS acts to narrow receptive fields (i.e. reduces the number of joint movements to which M1 cells respond).

Methods: A 96-channel microelectrode array was chronically implanted in the arm area of M1 to record single units, and a scaled version of the human DBS lead was implanted in STN to deliver electrical stimulation. Two methods for testing passive movement responses were implemented. The first was an automated arm rigidity testing device consisting of a torque motor and force transducers to measure the force required to move the forearm about the elbow joint, which also enabled objective quantification of rigidity. The second was experimenter controlled passive limb movement about shoulder, elbow and wrist joints. Spike times were aligned to movement events (e.g. maximum flexion) and perievent time histograms were compared between off-DBS and on-DBS conditions.

Results: Therapeutic STN DBS altered the response to passive manipulation in the majority (70%) of M1 cells. However, there was considerable heterogeneity in the responses. The specificity of joint elbow joint articulation increased in some cells (10/49) but decreased in other cells (22/49). DBS changed the number of joints M1 cells respond to in 50% of cells. STN DBS evoked putative antidromic firing in ~30% of cells, evidenced by short, fixed latency response after DBS pulses. Based on peristimulus time histograms (PSTH) aligned to DBS pulses, the median PSTH of the population revealed significant suppression of firing rates at therapeutic DBS current levels.

Conclusions: Based on these findings it is apparent that STN DBS alters the representation of passive limb movements in M1. DBS changed the degree to which M1 cells respond to a given joint movement, though that change was heterogeneous across the population. Our working hypothesis is that one of the therapeutic mechanisms of DBS is that it serves to decrease abnormal/excessive kinesthetic information in M1.

References:

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Closed-loop Neuromodulation of Vagus Nerve for the Hemodynamic Stability after Asphyxial Cardiac Arrest

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Background: Poor neurological outcome of cardiac arrest (CA) arises from the inability of resuscitation and therapies to stabilize the heart and brain (1, 2). The asphyxial cardiac arrest rat model has high clinical relevance for resuscitation research. Recently, we have developed a bidirectional closed-loop peripheral nerve interface which performed targeted heart rate control via neuromodulation of vagus nerve (3). In the present study, our hypothesis is that closed-loop neuromodulation of vagus nerve (CNVN) will improve hemodynamic stability during resuscitation after asphyxial cardiac arrest.

Methods: Male Wistar rats were randomly assigned to two groups: CA with and without (control) CNVN treatment (n=6 each group). The global asphyxial CA was induced by stopping the ventilator and clamping the ventilator tube for 7 min. Cardiopulmonary resuscitation (CPR) was initiated by unclamping the tracheal tube, restarting mechanical ventilation with 100% Oxygen, one dose epinephrine (0.005mg/Kg, i.v.) and consistent sternal chest compression (200/min). Attempts to generate systolic arterial pressure >50mmHg is considered to have achieved return of spontaneous circulation (ROSC). A tripolar micro-cuff electrode was placed on left vagus nerve through a ventral incision in the neck. 30 minutes CNVN was performed beginning at 30 min post-CA. Vital signs including heart rate, mean arterial pressure (MAP), electroencephalogram (EEG) were recording consistently. Neurological outcomes were quantified by the Neurological Deficit Scale (NDS, 0 worst to 80 best) at 4 and 24 hours post-CA.

Results: All animals arrived at ROSC after CPR within 2 min. Compared with the control group, the treatment group demonstrated significantly lower fluctuation of MAP, higher MAP value and earlier return to normal range during treatment and post-treatment periods. The heart rate was controlled stably by dynamic vagus nerve stimulation frequency outputs via the closed-loop interface. EEG data showed a similar pattern of cortical activity recovery but NDS at 24 hours post-CA demonstrated higher score in treatment group compared with control group (P<0.05). (Fig. 1)

Conclusions: Closed-loop neuromodulation of vagus nerve improved hemodynamic stabilization including heart rhythm stability, system arterial pressure recovery and reduction of hemodynamic fluctuation during early post-CA phase compared to controls. It may contribute to better neurological outcomes after global ischemic brain injury following asphyxial CA.

References:


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Transcranial direct current stimulation alters brain connectivity during BCI

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Background: A challenge for broad applications of sensorimotor rhythm based brain-computer interface (BCI) is the need for extensive training to acquire useful control of a cursor or physical object [1-2]. Transcranial direct current stimulation (tDCS) has been used to alter the excitability of neurons within the cerebral cortex to improve motor imagery-based BCI performance [3]. Neural connectivity following transcranial current stimulation during task performance has not been well studied. We test the hypothesis that applying high definition tDCS (HD-tDCS) alters the neural connectivity during sensorimotor rhythm based BCI performance.

Methods: Five healthy subjects naïve to BCI control received three experimental sessions of anodal tDCS stimulation while performing 1-dimensional left/right hand motor imagery-based BCI. A 64-channel EEG system was used to record and a 4x1 HD-tDCS was used to stimulate, with the center electrode located between C3 and CP3, over the left sensorimotor cortex, and return electrodes located between adjacent EEG electrodes. Subjects performed BCI tasks before, during, and after 20 minutes of 2mA tDCS stimulation. Source imaging using a weighted minimum norm approach was used to map scalp activity to cortical dipoles. Regions-of-interest (ROIs) were selected as peak dipoles based on the mean power in the alpha band (8-13 Hz) during task performance combined across all subjects. As right hand and left hand imagination involve different brain regions, ROIs were calculated separately for each direction. Connectivity was calculated by fitting a multivariate auto-regressive model to the dipole time courses and calculating the directed transfer function.

Results: We report increased connectivity between regions of interest both unilaterally and bilaterally in the alpha (8-13 Hz), beta (15-30 Hz), and gamma (31-40 Hz) bands following anodal stimulation during right hand imagination (Figure 1). Significant increases in inflow from surrounding ROIs to the left postcentral gyrus, under the anodal stimulation electrode, were found across all three frequency bands. The right premotor ROI also had increased output to the majority of other ROIs in both the alpha and gamma bands. There was a decrease in connectivity in the alpha band for left handed trials from the left to the right postcentral gyrus.

Conclusions: Unilateral HD-tDCS alters connectivity during BCI performance based on task specific neural activation, where anodal stimulation over the left sensorimotor cortex preferentially altered connectivity during right hand imagination trials. Connectivity effects of localized stimulation should be considered when applying noninvasive brain stimulation during motor imagery-based BCI tasks or other cognitive tasks.

References:

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Figure 1: Changes in connectivity between peak dipoles in regions-of-interest following stimulation. Arrows indicate statistically significant changes in connectivity between ROIs (circles) following stimulation. Blue arrows indicate a decrease in connectivity; Red arrows indicate an increase in connectivity. LH: Left Hand imagination trials. RH: Right Hand imagination trials.
tACS impacts detection of change in visual task and its ongoing neural oscillations

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Background: Little is known about the precise neural mechanism by which tACS affects the human cortex. Current hypotheses suggest that tACS can either directly entrain brain oscillations and/or induce synaptic plasticity. Entrainment has been reported in studies in-vitro that required invasive interventions, while its presence in non-invasive human studies is still under debate [1]. Here, we aim to investigate the immediate and short-term effects of tACS bursts on the occipital cortex and its impact in behavior while volunteers are conducting a visual detection-change task.

A.

Figure 1. A: Cognitive task associated to tACS burst stimulation. Subjects conducted 240 trials of the speed-of-change detection task. B: Electric field resulting from the multisite tACS stimulation (normal to the cortical surface). Positive values indicate that the field is directed into the cortical surface, which oscillates according to the frequency of tACS stimulation applied.

Methods: Thirty healthy subjects participated in a randomized, sham-controlled crossover study and were required to respond with a keypress to the change of speed of the inward-moving visual stimulus in a reaction time visual task paradigm (Figure 1A). Visual stimulus span 5° of the visual field and is centered at the fixation point (fixation required). Feedback was provided with an OK/KO (correct response is defined as keypress within 0.2-0.8s after speed increase). tACS (Starstim, Neuroelectrics) was applied in 240 5 second bursts of alpha (10Hz) and gamma (70Hz) frequencies using a multi-electrode optimized montage (Stimweaver [2]) with 1.2mA intensity (Figure 1B, sham has 0mA intensity). Bursts were delivered to the occipital cortex at the onset of visual stimulation to interfere with the dominant γ-band (60-80Hz [3]). EEG signals were recorded from five electrodes located across the occipito-parietal cortices. Statistical analysis of the tACS effects was conducted via generalized linear mixed-effects regression models (GLMM).

Results: tACS significantly increases the reaction time associated to the detection of a change in the speed of a moving-grating (RTsham=423.85(± 1.27), RT10=432.1(± 1.17), RT70=429.7(± 1.11), mean ± ste, p<0.001), although this difference is not tACS-frequency specific (p=0.1741). A significant increase in α-power is found in occipital electrodes after tACS10 as compared to tACS70 and tACSsham while γ-power is significantly decreased after tACS70 as compared to tACS10 (p<0.001). Oscillatory response phase-locked to tACS stimulation was also analyzed in terms of the spectral response (FFT), where we found that tACS-locked γ-power is statistically increased after tACS10 as compared to tACSsham, while α-band power remains unaffected.

Conclusions: Our study provides behavioral and electrophysiological evidences for an interaction of tACS stimulation with cortical oscillations. This interaction seems to be frequency independent in terms of behavior, while modulations of oscillatory activity are frequency-specific. This study opens the door to frequency-dependent effects of tACS and furthers the understanding of tACS modulations of cortical excitability.

References:

Funding: Biogen Inc. Cambridge MA, USA.
Spinal cord stimulation reduces freezing of gait episodes and improves gait in advanced Parkinson’s disease patients

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Background: Dopaminergic therapy and deep brain stimulation (DBS) alleviate motor manifestations in Parkinson’s disease (PD) however, their effects on axial features such as gait dysfunction reduces with disease progression.1 Epidural spinal cord stimulation (SCS) may be a new therapeutic approach for levodopa-resistant motor symptoms in PD.2,3 The primary objective was to investigate the therapeutic effect of SCS on gait dysfunction including freezing of gait (FOG) in advanced PD patients. The secondary objectives were to determine the effects of pulse width and frequency SCS parameters on FOG and spatiotemporal gait parameters.

Methods: A total of five advanced PD male patients (mean age of 71±10 years with 14±4 years with PD) not eligible for DBS, with significant gait disturbances, FOG and postural instability underwent mid-thoracic SCS. A range of SCS settings at 200-500 microseconds and 30-130 Hz at suprathreshold intensity were tested in eight study visits over a six-months period. A 20-foot Protokinetics Zeno Walkway measured dynamic gait characteristics, such as step length, stride width, stride velocity, step, stance and swing times. Timed sit-to-stand and automated FOG detection using foot pressures were also analyzed. FOG questionnaire, Unified Parkinson’s Disease Rating Scale (UPDRS) motor items, Activities-specific balance confidence scale (ABC), and Parkinson’s disease questionnaire (PDQ-8) were completed at each study visit.

Results: Three patients found SCS setting combination of 300 microseconds and 60 Hz provided the best improvement in timed sit-to-stand, stride velocity and step length with a mean improvement of 63.8%, 76.2% and 91.1%, respectively. Two patients found a combination of 130 Hz with 200 or 300 microseconds more beneficial with a mean improvement by 58.4% for timed sit-to-stand, 36.6% for stride velocity and 56.7% for step length. Six-months post-implantation, there was a mean improvement by 39.4% in the UPDRS motor score, by 26.8% in the FOG questionnaire, and by 116.9% in the ABC score. The mean number of FOG episodes reduced significantly from 16 pre-surgery to 0 at six-month period while patients were “ON” levodopa and OFF stimulation.

Conclusion: By using objective measures to detect dynamic gait characteristics, the therapeutic potential of SCS was optimized to each patient’s characteristics. This pilot study demonstrated the safety and significant therapeutic outcome of SCS in advanced PD patients and thus, a larger clinical study will be utilized to investigate the neurophysiological changes that occur at different SCS parameters.

References:

Continuous Restoration of the Human Vestibulo-Ocular Reflex via a Multichannel Vestibular Implant

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Background: The inner ears’ vestibular labyrinths play a major role in stabilization of visual gaze, posture, and spatial orientation via sensation of head movement and tilt. The 3D angular vestibulo-ocular reflex (VOR) stabilizes vision during head rotations by generating eye movements that keep retinal images stable. Individuals with bilateral vestibular hypofunction (BVH) due to inner ear dysfunction suffer poor visual acuity during head motion, chronic disequilibrium and postural instability [1,2]. Affected individuals who fail to compensate despite rehabilitative exercises currently have no adequate treatment options. Electrical stimulation of surviving vestibular afferent neurons to partially restore the VOR has been effective in animal models of BVH [3,4]. Based on that foundation, the Labyrinth Devices/MED-EL MVTM Multichannel Vestibular Implant was designed to sense 3D head motion and continuously provide artificial stimulation to individual branches of the vestibular nerve that normally encode different components of that motion. Here we describe initial results from a first-in-human early feasibility study of the MVTM as a treatment for BVH.

Methods: One adult male with BVH was implanted with the MVTM stimulator, which comprises a modified MED-EL GmbH cochlear implant stimulator with an array of intralabyrinthine electrodes inserted into each semicircular canal in the left ear. An earth vertical rotary chair was used to provide en bloc sinusoidal rotations of the subject in darkness over 0.1–2Hz at peak velocity 100°/s. Eye movements were recorded using 3DBinoc™ video-oculography goggles (Labyrinth Devices, LLC) pre-operatively, post-op/pre-activation, and up to 8 weeks post-activation.

Results: VOR gain during sinusoidal whole body rotations before implantation in response to 100°/s peak velocity sinusoids at 0.1, 0.2, 0.5, 1 and 2 Hz was 0.07±0.009, 0.09±0.009, 0.13±0.01, 0.3±0.02 and 0.25±0.02, respectively. After device activation, the subject reported improvement in visual and postural stability with prosthetic stimulation, which so far has persisted throughout >4 mo of continuous use. VOR measurements while the MVI device actively encoded head rotation revealed a modest but significant increase in gain above preimplantation levels. After 8 weeks of continuous use, the subject’s VOR gain at the same frequencies was 0.11±0.02, 0.15±0.02, 0.19±0.03, 0.28±0.04 and 0.37±0.02, respectively.

Conclusions: Coupled with durable and significant subjective benefit, an increase in VOR gain over an initial 8 week period of MVTM use supports the hypothesis that prosthetic vestibular nerve input effectively drives the vestibulo-cerebellar VOR circuits.

References:

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POSTER
PRESENTATIONS
INVASIVE
NEUROMODULATION
Deep Cerebellar Stimulation to Treat Degenerative Cerebellar Ataxias

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**Background:** Degenerative cerebellar ataxias, both Mendelian and sporadic in form, affect as many as 1 in every 5,000 people worldwide, leading to incoordination, tremor, and falls. Despite more than twenty years since the first ataxia-causing genes were found, treatment strategies are limited. Notwithstanding a large amount of etiologic variation, the various forms of degenerative cerebellar ataxia universally share the loss of cerebellar Purkinje cells, a major source of input to the deep cerebellar nuclei. Thus, we are working to develop an electrical stimulation-based approach based in the dorsal dentate nucleus, the major motor output from the cerebellum, to treat the motor symptoms of degenerative cerebellar ataxias.

**Methods:** We are testing this therapeutic strategy in the Wistar Furth shaker rat, which presents with a shaking ataxia, full-body tremors, and frequent falling, each progressive in nature. We have developed a methodology to directly quantify each of the above symptoms in an operator-independent manner, enabling easy validation of symptom relief and comparison of stimulation parameters. We have bilaterally, stereotactically implanted a small cohort of shaker rats with stimulating electrodes to test the hypothesis that electrical stimulation of the dorsal dentate nucleus can reduce each of these motor symptoms, and we have quantified each symptom in comparison to wild type rats.

**Results:** We first tracked the motor performance of cohorts of shaker and wild type Wistar Furth rats from 7 weeks, prior to the onset of symptoms, to 35 weeks, at which point the symptoms have stopped progressing, to quantify the progression of symptoms in our model in comparison to unaffected animals. We next tested a number of stimulation parameters in a small cohort of young (~15 week) affected animals, and our preliminary results have indicated that electrical stimulation at approximately 30 Hz most effectively reduced tremor and fall rates. These animals did not yet present with much incoordination of gait, so we have not yet tested treatment for this symptom. We have recently implanted a small cohort of older (>30 week) animals, each with severe incoordination of gait, and we will present our findings in regard to treatment of this symptom as well.

**Conclusions:** Preliminary results indicate that electrical stimulation of the dorsal dentate nucleus may provide a novel method for treating the motor symptoms of degenerative cerebellar ataxias.

**Funding:** Utah Neuroscience Initiative Collaborative Pilot Project (awarded to Pulst and Dorval); National Ataxia Foundation Post-Doc Fellowship (awarded to Anderson)
Using vagus nerve stimulation to treat hypertension and hypertension-induced heart disease

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Background: Vagal nerve stimulation (VNS) is an autonomic neuromodulation therapy that involves delivering electrical pulses to the vagus nerve. VNS is an FDA-approved treatment for intractable epilepsy and treatment-resistant depression. However, VNS therapy may have the potential to treat cardiovascular and metabolic diseases through modulation of parasympathetic activity and reestablishing the cardiac autonomic balance that is usually impaired in these diseases. This study investigates the therapeutic potential of low-level intermittent VNS to treat hypertension (HTN) and HTN-induced heart disease.

Methods: The effects of VNS on the physiological properties and survival of HTN dahl salt sensitive rats were evaluated through in-vivo and ex-vivo studies. During VNS therapy, continuous cardiovascular data acquisition through DSI transmitters was performed in-vivo to obtain real-time ECG and arterial blood pressure (Fig 1A). In addition, weekly tail vein blood draws were performed to investigate levels of inflammatory markers. At the end of the study, ex-vivo optical mapping studies were performed to study the electrophysiological remodeling in the heart due to HTN and VNS therapy (Fig 1B).

Results: The in-vivo analysis showed that long-term low-amplitude intermittent VNS treatment of HTN rats significantly attenuated the increase in mean arterial pressure and decreased the number of in-vivo arrhythmia episodes. Preliminary findings show an improvement in the long-term survival rate of the VNS treated rats. In ex-vivo optical mapping studies, the rats receiving VNS showed electrical remodeling, through an increase in conduction velocity (CV), a decrease in action potential duration (APD), and a decrease in ventricular APD heterogeneity, µ, suggesting the heart is less arrhythmogenic.

Conclusions: These results suggest that chronic, intermittent VNS can be used as a potential therapy for HTN and HTN-induced heart disease.

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Figure 1. A) Schematic illustration of in-vivo procedures. VNS stimulators were implanted with bipolar cuff electrodes placed around the right cervical vagus nerve. DSI transmitters were implanted to allow for continuous blood pressure and ECG recordings. B) Schematic illustration depicting ex-vivo optical mapping procedure which allows for the detection and analysis of cardiac action potentials for effects of VNS on electrophysiological properties, such as APD, CV, and µ.
Opposite Arterial Pressure Responses to Renal Afferent Nerve Stimulation in Unanesthetized versus Anesthetized Rats: Implications for the Neural-Renal Axis and Hypertension

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Background: Autonomic neural control of the kidney remains a primary focus of treatment of cardiovascular and renal disease, including hypertension (HTN). Moreover, recent studies support a role of renal afferent nerves in the modulation of sympathetic nerve activity (SNA), and in turn, arterial pressure (AP). We recently reported resting afferent nerve activity (ARNA) is elevated in the DOCA-salt hypertensive rat, and that targeted afferent renal nerve ablation attenuates this model of hypertension (Banek et al. Hypertension 2016). These findings suggest that increased ARNA contributes to the pathogenesis of HTN. Previous investigations of the responses of AP and SNA to renal afferent nerve stimulation have been conducted in anesthetized animals have reported a sympatho-inhibitory response. The present study was designed to measure the acute AP response to increased ARNA in anesthetized and unanesthetized preparations.

Methods: Male Sprague Dawley rats (300-400g) underwent acute renal afferent stimulation while under 2% isoflurane anesthesia (ISO; n=12) or in the absence of anesthesia following a cortical decerebration (DEC; n=12). Animals were instrumented to measure AP, heart rate (HR), and ARNA. To activate renal afferent nerves, a ureteral catheterization was performed to perfuse the renal pelvis with vehicle 0.9% saline (VEH) or with the TRPV1 agonist 50μM capsaicin (CAP). Following instrumentation and a 30 minute stabilization period, ARNA and cardiovascular responses to VEH or CAP stimulation were recorded. Peak responses in ARNA, AP, and HR were quantified and compared between ISO vs. DEC preparations by a Student’s t-test (α=.05). ARNA responses were calculated as percent change from baseline (%ARNA). Data presented as mean±SEM.

Results: There was no difference in resting ∫ARNA, AP, or HR prior to afferent stimulation between ISO and DEC groups. VEH perfusion of the renal pelvis elicited no response in both ISO and DEC groups. In contrast, CAP administration resulted in marked increase in %ARNA that was similar in magnitude in both groups (ISO 214±31% vs. DEC 239±40%). More importantly, whereas the CAP-induced increase in ARNA elicited a depressor response in ISO rats (-17±6mmHg), CAP evoked an opposing pressor response in DEC rats (+54±9mmHg).

Conclusions: These findings suggest the existence of a renal afferent nerve-dependent sympathoexcitatory reflex in the rat, and anesthesia may directly interfere in this signaling pathway. Currently, it is unknown whether this acute reflex translates to long-term regulation of SNA and AP. While the mechanisms within this neural-renal axis are yet to be elucidated, these studies suggest targeted ablation or neuromodulation of renal ARNA may be a novel alternative strategy for cardiovascular and renal disease treatment.

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Entrainment of M1 activity to thalamic deep-brain stimulation

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Background: Deep brain stimulation (DBS) targeting the motor thalamus has been shown to be effective in reducing tremors in patients with movement disorders, but the physiological mechanisms of this therapy are not fully understood. It has been shown in essential tremor patients that DBS is especially efficacious when (1) targeting the ventral motor thalamus and (2) using high frequencies (such as above 100Hz) [1]. As the motor thalamus has reciprocal connections with the motor cortex (M1), it is likely that therapeutic stimulation parameters should modulate the thalamocortical and corticothalamic circuit significantly. We proposed to study how location and frequency of motor thalamic stimulation modulates neuronal activity in motor cortex.

Methods: An 7-channel DBS lead was implanted in a naïve primate such that contacts spanned motor thalamus on a dorsoventral axis. Extracellular unit-spike activity in the motor cortex was recorded in a resting condition before and during DBS of motor thalamus. Two experiments were conducted, 1) a location-experiment and a frequency-experiment in which M1 neuronal firing was recorded during 130Hz pulse-stimulation through electrode contacts C6 (dorsal) through C0 (ventral); and 2) a frequency experiment testing stimulus pulse trains between 10-130Hz at contact C0 exclusively. Based on peristimulus time histograms (PSTHs) of unit-spike activity, two entrainment detection methods were used: 1) Standard deviation threshold: spiking activity was deemed entrained if a peak in the PSTH exceeded a pre-DBS level by 6 standard deviations; 2) Entropy threshold: spiking activity was deemed entrained if the calculated entropy of the PSTH was less than an experimentally-corrected uniform distribution (p<0.05).

Results: Null Hypothesis: Entrainment of M1 neurons is not contingent upon stimulation location/frequency.

Location experiment: Null hypothesis rejected for both 6-STD-method and Entropy-method, using Chi-squared test for independence.

Frequency experiment: Null hypothesis accepted for both 6-STD-method and Entropy-method (Chir-squared).

Conclusions: In the ventral motor thalamus, cerebellar afferent fibers are relatively close to the more ventral DBS contacts that may have resulted in more widespread thalamic modulation and thus cortical entrained activity. Since DBS likely recruits axonal fibers more readily than cell bodies [2], it is likely that the recruitment of cerebellothalamic afferents directly influences the entrainment of cortical neurons. However, our results do not suggest entrainment is stimulus-frequency dependent. Comparing our two entrainment-detection methods: while they both allowed for the same conclusions, the Entropy-method provided a more nuanced analysis of entrainment, and thus gave stronger conclusions than the 6-STD method.

References:


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Deep Brain Stimulation of Afferent Axon Terminals

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Background: Deep brain stimulation (DBS) of the subthalamic region is an established clinical therapy for patients with late stage Parkinson’s disease. However, despite its clinical successes, the therapeutic mechanisms of DBS are largely unknown. Computational models of axonal stimulation are commonly used to study the neural response to DBS therapy in attempts to identify potential mechanisms. However, the accuracy of these simulations is dependent on the structural detail of the axon model, and small modifications to the axon structure can result in large changes in the simulated neural response. This is especially relevant for subthalamic DBS, as axons projecting to the subthalamic region exhibit a complex terminal branching structure¹. Activation of these axon terminals is likely to play a major role in the therapeutic mechanism of DBS², yet the response of branched axonal structures to DBS has rarely been considered. The goal of this work is to evaluate how branching at the axon terminal affects action potential generation in response to DBS.

Methods: Multi-compartment cable models of structurally idealized branched axon terminals were created with various degrees of branching complexity³. A finite element model of the voltage distribution generated by the DBS electrode was calculated using a finite element volume conductor model of the DBS electrode in an isotropic, homogeneous medium. Axon models were stimulated by applying this voltage distribution to the extracellular surface of the branched axon structure. Activation thresholds were determined for a range of conditions by identifying the lowest stimulus amplitude that elicited an action potential which propagated to the main branch of the axon. Strength-duration and current-distance curves were generated.

Results: The activation threshold was directly dependent on the branching complexity, where more complex branching structures resulted in higher thresholds.

Conclusions: Preliminary results suggest that extracellular stimulation thresholds of branching axon terminals are dependent on the complex anatomical relationships of the axonal arbor and its position relative to the DBS electrode.

References:

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Brain Machine Interfaces Neuromodulate Remote Brain Regions

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Background: It is becoming increasingly evident that neurons used to control an external device (direct neurons) in a Brain Machine Interface (BMI) task modulate their activity to enhance performance (control of the external device) in the task. Research has also shown that neurons not directly linked to the BMI (i.e. indirect neurons) may also modulate their activity but their role and the extent of modulation is unclear. Understanding the role of these indirect neurons is especially important when considering nervous system injuries such as spinal cord injury (SCI) in order to optimize performance in the injured state.

Methods: Rats were chronically implanted with microwire arrays, bilaterally, into the hindlimb sensorimotor cortex (HLSMC) and then subjected to different types of whole-body rotational tilts in the lateral plane. This task engaged neurons bilaterally, regardless of whether the tilt was to the left or to the right and a real-time decoder classified the type of tilt from the neural activity of one hemisphere (direct neurons) while the neural activity in the opposite hemisphere was simply recorded (indirect neurons). Rats then received a spinal transection (SCI) and were reevaluated in the task. Offline, changes in the firing patterns of direct and indirect neurons in response to the tilt, both before and after SCI were assessed.

Results: Before SCI, performance was above chance and increased for the first 8-10 days. Correspondingly, a subset of both direct and indirect neurons changed their firing properties in response to the tilt when compared to their activity before training. Therefore, indirect neurons as remote as the opposite hemisphere can be modulated by training in a BMI task. After SCI, neurons continued to provide information sufficient to discriminate between tilts.

Conclusions: Recent studies of the impact of BMI on indirect neurons has yielded conflicting results with some suggesting BMI influences indirect neurons and some suggesting they do not. This study demonstrates that if neurons are engaged in the BMI task (i.e. bilaterally in this case), then indirect neurons can be modulated by BMI training, even if the cortical region is far from the direct neurons. Furthermore, while SCI-related cortical effects are likely, the ability of these neurons to encode information about the task remain. These widespread effects should be considered in designing decoders and furthers our understanding of the potential for BMI technology after severe injury.

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Modeling Dynamic Oscillations in Deep Brain Stimulation of the Subcallosal Cingulate

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Background: Deep brain stimulation (DBS) is a promising investigational treatment for patients with treatment resistant depression (TRD). Previous studies using diffusion tensor imaging (DTI) have identified key white matter tracts, passing through the subcallosal cingulate (SCC), that when stimulated, are associated with TRD recovery [1]. However, the mechanism by which stimulation modulates network level pathological activity in the SCC network has not been clearly established. Local field potential (LFP) recordings of the left and right SCC in TRD patients implanted with DBS have shown the emergence of dynamical oscillations, or chirps, following specific stimulation conditions. These chirps are a reproducible response in the SCC that may help to constrain neural circuit dynamics impacted by DBS, and be used as a metric to assess SCC neurophysiology. Understanding why and how stimulation causes this electrophysiological behavior in the SCC network is an important step in increasing the efficiency and success rate of treatment for patients with TRD.

Methods: Network connection models informed by the SCC network can be used to understand the dynamics of groups of neurons that would cause the observed signals in LFP recordings. A group of neurons can be modeled as a single population of neurons with a subpopulation of excitatory neurons and a subpopulation of inhibitory neurons. The classic example of this mean field approach is the Wilson Cowan (WC) model [2]. Each of the neuron population was modeled with a set of WC equations and white matter tracts connecting each neuron population were modeled as measures of excitatory-inhibitory subpopulation connectivity.

Results: A single WC population showed the emergence of chirps when the phase plane trajectory reaches a homoclinic orbit (Fig. 1a). This orbit is caused by specific excitatory-inhibitory neuron balance. It was found that connecting the two modeled neuron populations together via excitatory-excitatory subpopulations, a transient chirp could be induced by decreasing the connectivity between these two populations. Expanding the two-population model into the topologically guided 6 region network, it was found that stimulation of the white matter tract between populations 1 and 3 induced the appearance of chirps in populations 2, 5, and 6 (Fig. 1b).

Conclusions: These findings demonstrate that decreasing the connectivity between populations of neurons and shifting the excitatory-inhibitory neuronal firing balance of these neuron regions could generate the empirical chirps seen during DBS. These findings further predict that DBS of white matter tracts near the SCC could induce responses from connected upstream or downstream regions. These conclusions show a need to conduct further cortical measurements from related structurally connected regions to fully understand the network.

References:

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Reinforcement learning for phasic disruption of pathological oscillations in a computational model of Parkinson’s disease

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Background: Deep brain stimulation (DBS) is an effective therapy for motor symptoms of PD, and is often used as a complement to medication in patients who have progressed to severe stages of PD. However, programming these devices is difficult and time consuming, and DBS therapy is limited by side effects and partial efficacy 1. Furthermore, traditional continuous DBS (cDBS) does not account for fluctuations in motor symptoms caused by factors such as sleep, attention, stress, cognitive and motor load, and current drug therapy 2, and as the patient’s state changes, so does the need for stimulation. Current cDBS strategies are incapable of adapting to the needs of patients: once the clinician sets the parameters, they do not change until the next programming visit. In this study, we have created a reinforcement learning (RL) algorithm capable of learning online how best to stimulate to reduce pathological oscillations in silico.

Methods: We have developed the reinforcement learning DBS (RL-DBS) algorithm for tuning DBS parameters, and have tested it on a biophysically realistic mean-field model of the basal ganglia-thalamocortical system (BGTCs) 3, simulating parkinsonian neural activity. The RL-DBS algorithm decides when to deliver stimulus pulses based upon the real-time amplitude and phase of the pathological oscillation in order to reduce the amplitude of that oscillation. The algorithm learns which actions lead to the highest cumulative reward (i.e. reduction of oscillation amplitude).

Results: After training on the model, the RL-DBS algorithm is able to learn both phase and amplitude selectivity to optimally reduce the pathological oscillation. The algorithm learns the expected reward for both actions (not stimulating and stimulating) as a function of the phase/amplitude of the oscillation (Fig. 1a, Fig. 1b). The algorithm then decides which action to execute based upon the action difference (Fig. 1c). Additionally, the algorithm learns to deliver bursts of stimulation phase-locked to the oscillation.

Conclusions: We created an adaptive RL-DBS algorithm capable of learning on-line how to reduce the power of a pathological oscillation in a computation model of PD. The algorithm has the potential to deliver individualized, adaptive DBS therapy that can improve the quality of life for PD patients.

References:

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Fig. 1. Learned reward maps (a), (b) and action difference (c) as a function of the phase and amplitude of the oscillation. (a) and (b) show the learned reward for no stimulation and stimulation respectively, while (c) shows the action difference. The algorithm selects the action that with the highest expected reward. The action difference reveals that the algorithm learns both phase- and amplitude-selective stimulation.
Closed-Loop Deep Brain Stimulation for Essential Tremor

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**Background:** Deep brain stimulation (DBS) is an important therapy for treating movement disorders, such as essential tremor (ET). Currently, DBS therapy delivers continuous stimulation pulses to a deep brain nucleus, regardless of whether the patient is experiencing symptoms. In ET, tremor is typically only present during movement, so there can be extended periods where stimulation is unnecessarily delivered, depleting battery life and potentially causing unwanted side-effects. Closed-loop DBS could mitigate some of these issues by only delivering stimulation when movement is detected. Using experimental DBS technology that allows recording of cortical neural activity, we implemented a closed-loop DBS system for detecting movement and delivering stimulation in two ET patients.

**Methods:** All experiments were approved by the University of Washington IRB and the FDA (IDE received). The subjects for this study were two ET patients who had been implanted with the Medtronic Activa PC+S DBS system and a 4-contact electrocorticography (ECoG) strip electrode. The DBS electrode was implanted in the ventral intermediate nucleus of the thalamus and the ECoG electrode was implanted over the central sulcus in hand/motor area. During the experiment, each subject engaged in a prompted movement task designed to elicit tremor. Movement periods of 1-30 seconds were interspersed with rest periods of a similar duration. During the task, cortical data from the PC+S and movement data from a wrist-worn commercial smartwatch were streamed onto a laptop computer. After engaging in the task for approximately 3 minutes with DBS off, a logistic regression classifier was trained offline using features extracted from the neural signal and labels from the movement data. This process was repeated with DBS on, yielding OFF- and ON-stimulation classifiers (two classifiers were used due spectral changes induced by stimulation). Then, the patient repeated the movement task, and the classifiers used the streaming cortical data to detect movement and turn stimulation on and off in real time. For comparison, the task was repeated with continuous stimulation and no stimulation.

**Results:** The system of classifiers had an accuracy and sensitivity of 77% and 82% for patient 1, and an accuracy and sensitivity of 52% and 77% for patient 2, respectively. The average stimulation voltage for patient 1 was 0.83 V, or 41% of the continuous stimulation level. The average stimulation for patient 2 was 1.58, or 53% of the continuous stimulation level. For patient 1, closed-loop DBS resulted in a 68% reduction in tremor amplitude from no stimulation, compared to an 87% reduction for continuous stimulation. For patient 1, closed-loop DBS resulted in a 4% reduction in tremor amplitude from no stimulation, compared to a 27% reduction for continuous stimulation. Closed-loop system performance for both patients can be seen in the figure below.

![Figure 1](image.png)

**Conclusions:** Using cortical recordings from ET patients, we were able to detect tremor-inducing movement and change stimulation in real-time. This closed-loop DBS reduced power consumption of the device, compared to continuous stimulation. It also decreased tremor amplitude, although not as much as the reduction seen with continuous stimulation. Although there is much room for improvement, these results suggest that closed-loop DBS therapy for treatment of ET is a promising technology.

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Model-Based Identification of Candidate Optimal Stimulation Settings in Subcallosal Cingulate Deep Brain Stimulation for Treatment Resistant Depression

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Background: Major depressive disorder (MDD) is a disabling chronic illness that affects at least 10% of the world population and is now the leading cause of years lost due to disability worldwide. Of the estimated 30 million Americans with MDD, approximately 10% do not respond to standard treatments, and deep brain stimulation (DBS) of the subcallosal cingulate (SCC) is an emerging experimental therapy for treating these individuals. Tractography has helped delineate the putative white matter targets mediating therapeutic effects in SCC DBS [1], but we have yet to establish a systematic methodology for how to choose the initial parameters and make adjustments over time.

Methods: We used the methodology summarized in our previous works [2, 3] to construct a detailed image-based bioelectric field model of a patient that underwent bilateral SCC DBS for treatment resistant depression, and a combination of probabilistic tractography and cable theory was used to simulate responses of forceps minor (FM) and three pathways in each hemisphere: cingulum bundle (CB), a medial portion of uncinate fasciculus (mUF) that connected the subgenual region to the orbitofrontal cortex, and a lateral portion of uncinate fasciculus (lUF) that connected the temporal cortex and amygdala to the orbitofrontal cortex. Stimulation frequency was held constant at 130 Hz, and we considered 732 possible settings: the 61 electrode configurations that are programmable with Medtronic’s devices, and 12 pulse widths between 20 μs and 450 μs. Axonal responses were evaluated for each setting, and the most energy-efficient and target-selective settings were identified.

Results: The clinical/therapeutic setting activated CB and mUF in both hemispheres, and FM. Among the myriad settings, we identified a bilateral stimulation setting that activated more axons than the clinical setting but using markedly less energy; energy savings for this setting was estimated to improve battery life or recharge intervals by > 50%. Additionally, there were three settings for each lead that preferentially activated CB, mUF, or FM, with the left lead activating more of FM than the right. There were no settings that selectively activated lUF.

Conclusions: Model-based design helped us identify candidate optimal settings for SCC DBS, albeit in one patient. Future work will focus on streamlining the process for optimizing the stimulation settings and extending our analysis to a larger population of subjects.

References:

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Figure 1. Candidate optimal stimulation settings for SCC DBS.
(a) Pathways identified with probabilistic tractography. (b) Clinical setting. (c) Energy-optimal setting. (d) Optimal settings for preferentially activating FM, left CB, or left mUF with left lead only. Right and left leads are Medtronic’s Model 3387. Red, light blue, and black colored contacts denote anode, cathode, and inactive, respectively.
Conceptual Design of Flex-DBS, a Mechanically Reconfigurable Deep Brain Stimulation Probe

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Background: Deep Brain Stimulation (DBS) has demonstrated outstanding results for the treatment of medically intractable Parkinson’s disease (PD), essential tremor and other neurological and psychiatric disorders, such as Obsessive Compulsive Disorder (OCD) and major depression. Despite widespread proliferation, DBS efficacy is limited primarily because of two key limitations: (a) non-specific activation of regions implicated in DBS side effects, and (b) inefficient neurostimulation due to complex anatomical structure and axonal orientations of target regions. Recent efforts in target selection has focused on shaping the stimulation field by using multichannel electrodes for current steering. These multichannel electrodes are limited to cylindrical lead configurations, only correct for small spatial localization errors, and do not utilize the direction of the electrical field’s gradients to stimulate neurons depending on their orientation. Thus, there is critical need for new DBS architectures that enable spatial steering and stimulation field orientation tuning. Here we present Flex-DBS, a novel electrode architecture that harnesses recent advances in flexible probe fabrication and precision guidance to mechanically reconfigure electrodes within anatomically complex tissue, enabling spatial steering and field orientation tuning.

Methods: The architecture is grounded in our previous work using a tri-polar electrode to stimulate the corpus callosum (CC) of the rat. In this study, we demonstrated the concept of Rotational Field Phase Steering (RFPS) which allowed us to control the direction of the stimulating electric field on a plane while monitoring the neuronal response using functional magnetic resonance imaging. Our experiments demonstrated that maximum stimulation efficiency occurred when the electric field was aligned with the axon fibers of the CC. Using preliminary experimental and simulation results as design inputs, we developed the conceptual design for a reconfigurable device architecture with flexible leads containing dense arrays of electrodes that can precisely deliver spatially steered and orientation tuned stimulation fields.

Results: The overall concept and architecture of the Flex-DBS device (Fig. 1) consists of an array of flexible 50-100µm diameter multi-channel stimulators that are actuated independently and housed inside a 1.5mm diameter implant. The proximal end of the implant terminates at a coin-sized electronics housing. Each individual multi-channel stimulation fiber terminates inside this housing at a circuit board, which can slide in the axial direction of the corresponding stimulator.

The stimulators can be automatically positioned in an automated manner using an array of 3mm diameter micro-miniature brushless DC motors that push or pull the corresponding stimulation lead via a leadscrew, thus setting the final position of the electrodes at the distal end of the implant. The position is fixed with a clamping screw, and the motor array module is removed. The custom fabricated multichannel leads slide inside guide conduits that span the length of the implant. A precision tip at the distal end of the implant flares the fibers to a controlled exit angle, spreading the electrodes as the motor array drives them distally. The mechanical forces and positioning accuracy can be well characterized, as we have shown with preliminary experimentation.

Conclusions: Our preliminary experimental results, simulation, and design efforts show that we can realize the required mechanical packaging and activation scheme required to produce Flex-DBS implants that enable spatial steering and stimulation field orientation tuning capabilities. We expect this technology to result in novel, efficient, and safe DBS paradigms in well-established targets and also currently difficult to target nuclei of interest. We will implement the fabrication of a proof of concept device in the near future.

Figure 1: Flex-DBS concept design. (a) Overall mechanical architecture showing electronics at proximal end and reconfigurable stimulating leads at the distal end. (b) Actuation scheme of the flexible multicore probes. (c) Preliminary experimental data relating actuator displacement to actual lead tip displacement with micrometer-scale resolution. (d) A removable motor array drives and positions individual stimulation leads.

References:


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Human Memory Enhancement through Electrical Brain Stimulation in the Temporal Cortex
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Background: Direct electrical stimulation of the human brain can elicit sensory and motor perceptions as well as recall of memories. Stimulating higher order association areas of the lateral temporal cortex in particular has been reported to activate visual and auditory memory representations of past experiences1. We hypothesized that this effect could be utilized to modulate memory processing. Recent attempts at memory enhancement in the human brain have focused on the hippocampus and other mesial temporal lobe structures, with a few reports of memory improvement in small studies of individual brain regions2 that have not been reproduced3. Methods: Here, we investigated the effect of stimulation in four brain regions thought to support declarative memory: hippocampus, parahippocampal neocortex, prefrontal cortex and temporal cortex. A classic verbal memory task was used to assess the effect of bipolar 50 Hz stimulation during encoding of word lists on subsequent free recall. Results: We show enhanced recall of words from lists with electrical stimulation in the temporal cortex, but not in the other three brain regions tested (Figure 1). This selective enhancement was observed on the level of individual subjects, subjects stimulated in the temporal cortex, and across the four brain regions studied. Stimulation targets in the other brain regions had a negative effect on memory compared to targets in the temporal cortex. These differential behavioral effects were paralleled by modulation of neural activities in high gamma frequency band (60-120 Hz) during memory encoding. Conclusions: This study shows that electrical stimulation in specific brain areas can modulate neural processes induced during memory encoding and enhance memory performance.

References:

Funding: DARPA Restoring Active Memory (RAM) program (Cooperative Agreement N66001-14-2-4032).

Figure 1. Behavioral effect of stimulation in the four brain regions studied. a). Brain surface maps show localization of all bipolar electrode pairs tested in a total of 23 patients. Red indicates electrode pairs in the temporal cortex. b). Behavioral effects of stimulation are grouped and color-coded according to the brain region tested (PH – parahippocampal/perirhinal/entorhinal cortex, HP – hippocampus, TC – temporal cortex, PF – prefrontal cortex). Each bar represents stimulation-induced change in memory performance in one subject. Asterisks mark subjects with a significant change (p<0.05, permutation test); right-side panel summarizes group effect of stimulation in specific brain regions (p<0.01, ANOVA with Tukey-Kramer post-hoc comparison). Notice that stimulation had overall a negative effect on memory performance except in the temporal cortex, where consistent enhancement was observed.
Relationships between cocaine-related synaptic plasticity and optogenetic self-stimulation behavior

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Background: Experience-dependent synaptic plasticity in brain-reward circuits plays an important role in addiction. Plasticity at glutamatergic inputs onto medium spiny neurons in the nucleus accumbens shell (NAcSh) has been reported during abstinence from chronic cocaine exposure, but also after acute cocaine re-exposure in abstinence, a primary trigger for relapse1-2. While changes in synaptic plasticity during cocaine abstinence are known to be input-specific2, the effects of cocaine re-exposure on input-specific plasticity is unknown and the functional relevance of these changes in reward-related behavior is unclear. In drug-naïve mice, optogenetic self-stimulation of NAcSh inputs is typically rewarding and input-pathway independent, suggesting that glutamate non-discriminately supports behavioral reinforcement3. However, how cocaine-related plasticity may impact the ability of glutamate from individual inputs to reinforce behavior has not been examined. Therefore, the goal of this study was to identify input-specific changes in plasticity that occur after cocaine re-exposure in abstinence and to examine the effects of cocaine-related plasticity on optogenetic self-stimulation behavior.

Methods: C57Bl/6J mice were virally infected with the blue light-sensitive activation opsin channelrhodopsin in the infralimbic cortex (ILC), ventral hippocampus (vHPC), or basolateral amygdala (BLA), and optical fibers were implanted over the NAcSh to allow for selective stimulation of these inputs during behavioral or physiological testing. Mice were exposed to cocaine (15 mg/kg i.p.) for 5 days, underwent abstinence for 10-14 days, and a subset of mice were acutely re-exposed to cocaine in late abstinence. Synaptic plasticity was assessed using whole cell patch clamp electrophysiology to measure AMPAR/NMDAR ratios. Self-stimulation behavior was assessed using an open-field spatial task in which entry into a contextually distinct “active zone” resulted in acute optogenetic activation (10 Hz, 5 ms pulse width) of individual NAcSh inputs. Competition between ILC-NAcSh and vHPC-NAcSh inputs was also examined to further understand the integration of these inputs in the NAcSh and the effect on reward-related behavior.

Results: Both synaptic plasticity and self-stimulation at IL-NAcSh inputs was enhanced during cocaine abstinence but reversed by acute cocaine re-exposure during abstinence. In contrast, self-stimulation of vHPC-NAcSh inputs was mildly enhanced by cocaine abstinence, and further augmented by cocaine re-exposure. Competition experiments revealed that mice preferred to self-stimulate IL-NAcSh over vHPC-NAcSh inputs during abstinence, but that this preference was reversed after cocaine re-exposure.

Conclusions: Together, our findings indicate that input-specific changes in plasticity occur during cocaine abstinence as well as after cocaine re-exposure and these changes directly modify the reinforcing effects of glutamate in the NAcSh.

References:

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Astrocytic activation can reduce harmalin-induced tremor in rats

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Background: DBS is known to be highly effective for movement disorders, but its mechanisms are not well understood. Its therapeutic success in movement disorders has led to its consideration for rapidly expanding neurologic and psychiatric conditions. The pressure to expand DBS applications makes it all the more critical that we improve understanding of its underlying mechanisms and that all potential molecular and physiologic processes that bear on its therapeutic action be investigated. To date, basic research has focused on DBS-driven changes in neurons and their projections around the DBS lead. And, while the physiological actions of astrocytes, the most numerous cell type in the brain, have been extensively investigated, little attention has been paid to their functional role in therapeutic DBS. Thus, here, we investigated astrocytic functions in DBS for tremor. Tremor was used to quantify astrocytic function in behavior level and optogenetic tools were used to selectively stimulate astrocytes.

Methods: A force plate actimeter was used to measure tremor. Animals were placed on the force plate actimeter before and after harmaline injection (7.5-20 mg/Kg, i.p.). For optogenetic modulation, AAV-GFAP-ChR2 and AAV-CaMK2α-Chrimson were injected at the VL thalamus. While tremor was monitoring, optical stimulation was applied at the ventral lateral (VL) thalamus. Single unit electrophysiology recording was performed to determine neuronal activity changes in the VL thalamus. To record neuronal activity modulated by optical stimulation, eight tetrodes were positioned next to the optic fiber.

Results: Harmaline induced 8-12 Hz tremor in rats. In the behavioral study, harmaline-induced tremor was significantly reduced by high frequency light stimulation (HFSlight) in GFAP-ChR2 rats (HFS, 130Hz; p-value<0.05, t-test between stimulation off vs. on), while tremor was not affected by HFSlight in CaMKIIα-Chrimson rats. In the electrophysiological study, we found that harmaline significantly modified the neuronal activities of the VL thalamus in anesthetized animals. Then, to identify a cellular function, we selectively activated either astrocytes or neurons. Astrocytic activation reduced neuronal firing rates of 50% of neurons and increased them of the other 30% of neurons in normal condition. On the other hand, neuronal activation increased firing rates of 61.1% of neurons in both before and after harmaline injection.

Conclusions: Harmaline could induce tremor in rats and increase neuronal firing rates in even anesthetized rats. The harmaline-induced tremor was significantly reduced by optogenetic astrocyte activation but not by optogenetic neuronal activation. Electrophysiology data suggest that astrocytic activation has a trend in decreasing neuronal firing rates. These results suggest that astrocytic activation in the VL thalamus may contribute to the therapeutic effect of DBS by modulating hyper neuronal activities.

References:

Funding: NIH R01 NS 88260
**Functional MRI during DBS in rats using MB-SWIFT**

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**Background:** Being able to detect brain activity during deep brain stimulation (DBS) is essential for understanding the mechanisms underlying the neuromodulation. For this purpose, simultaneous functional magnetic resonance imaging (fMRI) and DBS studies have been conducted in humans and animals using echo planar imaging (EPI), however, the electrode can cause significant artefacts and signal loss in EPI pulse sequences due to susceptibility variations. In this work, we demonstrate that fMRI maps nearly free of susceptibility artifacts can be collected using Multi-Band Sweep Imaging with Fourier Transform (MB-SWIFT) during DBS of the rat brain.

**Methods:** Three-channel tungsten electrodes (diameters 200 µm per channel) were implanted into the rat ventral posteromedial nucleus (vpm; ML 2.8 mm, AP -3.4 mm, DV -5.8; n = 5). The stimulation paradigm consisted of 3 blocks of 60 s of rest and 18 s of stimulation, ending with an additional rest period. The electrode was driven monopolar using 50 µs square pulses repeated at 20 Hz with an amplitude of 0.5 mA/channel.

The parameters of MB-SWIFT were: TR = 0.97 ms and 3076 spokes per volume, resulting in temporal resolution of 3 s, and bandwidth (BW) = 192 kHz. Separate trials were made with flip angle = 2°, 4° and 6°. Spin-echo EPI (SE-EPI) parameters were: TE = 35 ms, TR = 1.5 s, two shots, resulting in temporal resolution of 3 s, and BW = 250 kHz. MB-SWIFT and SE-EPI were set to have the same voxel size. The resulting functional data were post-processed in SPM.

**Results:** MB-SWIFT exhibited dramatic improvement of the image quality in the presence of an implanted electrode as compared to SE-EPI (Figure 1A-C). The activated areas obtained with MB-SWIFT and SE-EPI were similar. The time series of the activation in the ipsilateral side also exhibited similarity between MB-SWIFT and SE-EPI, although a clear flip angle dependence of the activation amplitude was seen with MB-SWIFT (Figure 1D, E).

**Conclusions:** MB-SWIFT shows great potential for fMRI studies in the presence of strong susceptibility variations such as those occurring around implanted leads. In this work we demonstrated that good temporal resolution and robust activation maps can be achieved with MB-SWIFT around implanted electrodes. Further research is needed to investigate whether inflow is the major mechanism generating the observed fMRI contrast with MB-SWIFT. MB-SWIFT may also aid in post-operational structural imaging for assessment of DBS electrode implantation.

**References:**

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![Figure 1. Examples of imaging slices with the implanted electrode using (A) SE-EPI, (B) MB-SWIFT and (C) Fast-Spin Echo (FSE). The respective activation maps are overlaid in (A, B). Mean time series from the somatosensory cortex rostral to the electrode artefact as seen by (D) SE-EPI and (E) MB-SWIFT.](image-url)
Stimulus artifact removal for closed-loop electrical brain stimulation

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Background: Closed-loop neuromodulation will adapt stimulation parameters based on biomarkers to tune stimulation or adapt the stimulation with patient state. However, stimulation during recording, even if stimulation is applied to electrodes separate from the recording electrodes, can corrupt the neural biomarkers extracted from the local field potential (LFP) recordings. The current industry standard to remove these stimulation artifacts is to “blank” the data by holding the potential at zero during the stimulation epoch [1]. If stimulation artifact is long and overlaps with the neural biomarker, blanking may remove the biomarker of interest. Here we compare different stimulation artifact removal methods that can applied in real-time during recording and compare their efficacy in removing the stimulus artifact while preserving the underlying neural signals.

Methods: We compare stimulation artifact removal by: 1) blanking, 2) template subtraction 3) comb filter, 4) adaptive FIR filter, 5) adaptive IIR filter, and 6) Kalman filter. All algorithms are tested on a simulated data set where we simulated a neural signal, stimulation artifact, evoked response, and measurement noise. Pearson R was measured between the extracted neural signal and the underlying neural signal and evoked response to estimate the efficacy of the reconstruction. Stimulation was applied periodically, but to address problems that may arise from aperiodic stimulation we also applied stimulation using a Poisson process where interaction between stimulus artifacts are variable. To simulate the non-stationarities observed during experiments, we changed the stimulus artifact midway through the experiment. All correlation coefficients are then averaged over the number of stimulation artifacts removed.

Results: For non-stationary stimulation artifact amplitude, regardless of stimulation paradigm, the adaptive algorithms obtained the largest Pearson R value with the adaptive FIR filter performing the best. Similarly, for stationary stimulation artifact amplitude, the adaptive FIR filter performed the best. However, for the periodic stimulation paradigm, the template algorithm performed better than the adaptive IIR and Kalman filter. In all cases, blanking had the lowest Pearson R value.

Conclusions: Non-adaptive removal algorithms, such as blanking and subtraction methods, are effective at removing the stimulation artifact under stationary recording conditions and if the evoked neuronal response is clearly separable from the stimulus artifact. Adaptive stimulation artifact removal methods, such as the adaptive FIR, and adaptive IIR filter, work well when stimulus artifact are non-stationary. The Kalman filter is computationally more intensive, but can be very accurate in stimulus artifact removal and measurement noise removal.

References:

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Dynamic Synchronization State Discrimination in Deep Brain Local Field Potentials of Neuropathic Pain

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Background: In neuropathic pain, the neurophysiological and neuropathological function of the sensory thalamus and the periventricular gray/periaqueductal gray (PVAG) involves multiple frequency oscillations [1, 2, 3]. Moreover, the oscillations related with pain perception and modulation are dynamically change together with pain [2, 3]. Therefore, dynamic identify the neural state is the key to coding brain function of neuropathic pain. This work aims to dynamically identify the neural state of the sensory thalamus and the PVAG of neuropathic pain by dynamically discriminate the synchronization state of theta and alpha oscillations.

Methods: A pattern extraction model based on wavelet packet transform was developed to characterize the synchronization activity of the oscillation. The wavelet packet coefficients were calculated in running window and represented the synchronization degree of theta and alpha oscillations. And then a state discrimination model was designed to compute adaptive threshold to distinguish the synchronization state and de-synchronization state of oscillation. The strategies of state discrimination were divided into two steps. Firstly, the threshold in a specific time-window was calculated with priori data. Secondly, the state was identify compare to the threshold and modified using post-hoc test. The parameters of the two models were optimized with sensory thalamus and PVAG LFPs recordings from eighteen neuropathic pain patients. The performance of the approach was verified with computing the sensitivity and specificity of simulation signals. Then the theta and alpha oscillations in deep brain LFPs were dynamically and simultaneously discriminated, then their states with synchronized or de-synchronized were identified.

Results: The performance of theta oscillation state identification in simulation signal with -9dB noise achieved 93% sensitivity and 86% specificity. The performance of alpha oscillation state identification in simulation signal with -11dB achieved 80% sensitivity and 86% specificity. The synchronization states were correlated to the pain relief level. In PVAG LFPs, the average frequency of theta oscillation at synchronization state while alpha oscillation at de-synchronization state is positively correlated to the pain-relief (r=0.644, p=0.009). In sensory thalamus LFPs, the average frequency of theta oscillation and alpha oscillations at both de-synchronization state is inversely correlated to the pain-relief (r=−0.51, p=0.07).

Conclusions: This study provided an approach to reliably identify the neural state by using sparse representation of wavelet packet transform to characterize the activity of oscillations and adaptive discrimination strategy to dynamically determine the synchronization state. This approach can be used to explore the mechanisms of pain perception and modulation, therapy.

References:

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Effect of levodopa on neuronal activity in primary motor cortex in the MPTP non-human primate model of Parkinson’s disease during rest, passive manipulation and active movement

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Background: Primary motor cortex (M1) is a key component of the basal ganglia-thalamo-cortical (BGTC) network and likely plays a significant role in the manifestation of motor symptoms in Parkinson’s disease (PD), yet relatively few studies have characterized the firing patterns of M1 neurons in PD. M1 is not only responsible for controlling voluntary limb movement, but is also integral to sensory processing of limb position and movement. It is believed that the loss of dopaminergic cells in PD disrupts this kinesthetic information processing leading to broadened receptive fields of cells throughout the BGTC network. In this study, we examined the effect of levodopa, the most common medication used for treatment of PD symptoms, on neuronal activity in M1 of two non-human primates (NHPs) rendered parkinsonian by systemic injections of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) during rest, passive manipulation and active movement.

Methods: A 96-channel microelectrode array was chronically implanted in the arm area of M1 to record populations of single units in two NHPs. Recordings were made both in the “off” and “on” levodopa state during rest, passive manipulation of the arm and while the animal performed an active reach & retrieval task.

Results: In the resting condition, we saw an inconsistent response to levodopa. Across the cell population we observed both increases and decreases in firing rates as well as no change.

During passive manipulation levodopa narrowed receptive fields (reduction in the number of joints to which cells responded) in 43% and 47% of the cells in NHPs K and J, respectively. Moreover, the degree of firing rate modulation and temporal dynamics of the response to a given joint manipulation differed between the on and off drug state, though the details of these differences were not consistent between cells across the population.

Initial analysis of the active reaching task data suggests a heterogeneous response to levodopa. 50% of the M1 neurons increase in their specificity to either the reach or retrieval portions of the active task. This specificity was achieved by suppression (35%) or an increase in firing rate (15%) during either the reach or the return portion of the movement.

Conclusions: Levodopa therapy that improves parkinsonian motor signs leads to narrowed receptive fields together with complex changes in M1 neuronal responses to passive joint articulation and active movement, supporting the hypothesis that information processing in M1 is disrupted in PD and improved by dopaminergic medication.

Figure. Raster plots and perievent time histograms are shown, aligned to the reach start of the reach & retrieval task. These three cells exemplify the heterogeneous changes observed in the on-levodopa condition. (A) Suppressed activity during the reach and return. (B) cell shows suppressed reach and increased return activity. (C) increased activity during return.
Neural models for in-the-loop testing of implantable neural stimulators

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**Background:** The next generation of neuromodulation devices will have the ability to deliver stimulation as well as measure the neural response. These devices will enable closed-loop adaptive therapies that may modulate stimulation based on the patient’s state. These adaptive devices may improve efficacy by optimizing therapy to the patient as well as adapting to the patient as their need changes over time. Testing safety in adaptive devices produces new challenges. Here we demonstrate a platform using a computational model to simulate neural signals and respond to stimulation for testing adaptive neural stimulation devices. This computational model and neuromodulation hardware loop can be used to test hardware as well as closed-loop algorithms at the bench greatly reducing the need for animal studies.

**Methods:** An efficient computational model of seizure activity (Jirsa et al., 2014) was used simulate local-field potential (LFP) recordings that may be observed with surface or depth electrodes during seizures. These models were implemented in Lab View and were simulated at 1kHz in real time. The LFP signal was converted to a voltage using a National Instruments analog to digital converter and applied to two titanium plates submerged in a saline tank. A Nexus RC Implantable Neural Stimulator (INS) was submerged in the tank and was used to record the signal generated by the model and the digitized signal was sent through wireless telemetry to be processed through Lab View to detect events and trigger stimulation. Voltage delivered to the stimulation electrodes were then digitized and delivered to the computational models to simulate neuronal response to stimulation in real-time.

**Results:** This closed-loop computational model in the loop was able to generate seizures that were detected by the INS, which then delivered stimulation to suppress the seizure.

**Conclusions:** Coupling the computational model to the INS provided a level of real world problems that did not occur during open-loop playback of neural signals for seizure detection. Primarily, closed-loop algorithms must distinguish between signals they deliver and the neural signals in real time. This hardware in the loop algorithm provided the opportunity to identify hardware and software bugs at the bench, as well as unique problems that arise in closed-loop stimulation algorithms. Models simulating pathological parkinsonian activity observed in the basal ganglia (van Albada and Robinson, 2009) have also been implemented.

**References:**


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A Programmable Fully-Integrated Microstimulator for Neural Implants and Instrumentation

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Background: Electrical microstimulation (EMS) has been widely used in neuroscience research to manipulate neural activity and understand neural circuits’ function. It has also been used to treat diseases and improve the quality of life. There are recent exciting applications such as neuromusculoskeletal to restore motor, sensory, and organ function; neurorehabilitation to aid rehabilitation from brain injuries; and neurotherapeutic to treat neurological disorders. Although EMS has been studied and used for decades, there is little understanding of its exact impact on the nervous system and the underlying signaling. To better understand the mechanism, it requires new technology that allows interrogating neural circuits with a higher precision, more flexibility, and most importantly bidirectional.

Methods: We propose a fully-integrated microstimulator chip which can support high-precision current-mode stimulation with a versatile waveform, amplitude, timing, and pattern [1, 2]. The stimulator has two complementary charge-balancing mechanisms integrated, which reduce the amount of residual charge and prevent leakage. Our circuits have been validated and characterized on an in vitro preparation using E18 rat embryonic cortical tissues grown on a microelectrode array (MEA). A variety of stimulation protocols and conditions with different amplitude, timing, and frequency have been tested, where we are able to modulate neural activity and acquire neural signals during and immediately after stimulation.

Results: The device is designed in a high-voltage process that allows up to 20V power supply and 19V output voltage compliance. A broad range of current-mode stimulation waveforms and patterns can be generated, including symmetrical/asymmetrical, biphasic/monophasic, and pulse train stimuli. The current amplitude, pulse width, and stimulation rate are adjustable from 0.5µA to 2mA, 100µs to 4ms, and 0.1Hz to 200Hz, respectively. Two complementary charge-balancing techniques are shown to successfully reduce residual voltage and stimulation artifacts. In in vitro experiments, the stimulator is demonstrated to trigger neural spikes, modulate neuronal firing rate, and alter mesoscopic neuronal activity.

Conclusions: This work presents a fully-integrated microstimulator that can support high voltage compliance and perform precise stimulation. The stimulator has passive and active charge-balancing schemes integrated to reduce the residual charge and stimulation artifacts. The circuit specification and functionality have been validated in both benchtop testing and in vitro preparations. Translation of the technology for human use is ongoing. Successful completion of the project will lead to a new microstimulation technology that can support both scientific studies and clinical trials utilizing closed-loop neuromodulation.

![Diagram of the microstimulator](image1)

Figure 1: (A) Simplified functional diagram of one stimulation channel. (B) Examples of stimulation waveforms and patterns used in experiments. (C) Micrograph of the prototype chip. (D) In vitro preparation using neuronal cell culture grown on a microelectrode array. (E) Recorded neural data during an experiment session. (F) Average firing rates of a neural spike cluster before, during, and after stimulation.

References:
A Bio-inspired Redundant Sensing Architecture for High-Precision Neural Data Acquisition Under Electrical Microstimulation

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Background: The effectiveness of electrical microstimulation (EMS) can be studied by applying a controlled amount of charge to a targeted nervous system while precisely monitoring neural responses. This task is challenging with existing sensors because EMS can generate artifacts that are many orders of magnitude larger than neural signals. For example, acquiring autonomic nerves’ biopotentials with microvolt-amplitude under 1-volt stimulation artifact requires a 24-bit equivalent precision. Implementing such data acquisition systems in practice presents many challenges due to the presence of imperfections, especially mismatch error. Even with high-end commercial devices, it is uncommon for a 24-bit analog-to-digital convert (ADC) to have 18-20 bits effective resolution.

Methods: This work presented a novel redundant sensing architecture which was inspired by a highly efficient biological sensor: the human eyes [1]. Redundancy was generated by integrating the information between two arrays of components embedded in the sensor’s internal structure, resembling the human eyes’ binocular structure. A mathematical model was derived to show how redundancy can be utilized to remedy mismatch error and accomplish a significant precision enhancement. As a proof-of-concept demonstration, we designed a high-resolution ADC in integrated circuits employed with the proposed architecture and a heuristic mechanism that allowed unsupervised estimation and calibration of mismatch error [2].

Results: Simulations suggested the architecture can suppress large mismatch error and permit a precision approaching the Shannon limit which was otherwise not possible with conventional structures. The data showed that 24-bit and beyond effective resolution was feasible even in the presence of a large mismatch ratio. Measurement results of the prototype chip also demonstrated the proposed technique’s efficacy, which can increase the effective resolution by 2-5 bits and linearity by 4-6 times while occupying only one-third the chip area and consuming one-half the power comparing to other sensors with a similar resolution in the literature.

Conclusions: We presented a redundant sensing architecture and derived the mathematical model to demonstrate its structural advantages in removing sensors’ mismatch error and enhancing sensing precision. Both simulations and actual measurements of the prototype ADC chip confirmed the proposed structure’s effectiveness. Redundant sensing could be applied to design high-resolution sensors that assist the study of EMS by precisely capturing neural activities which are otherwise masked by artifacts. Moreover, the framework could be generalized to handle higher-dimensional data and apply to a variety of applications beyond the field of neuromodulation such as digital imaging, fMRI, 3D data acquisition, etc.

References:
Electrochemical Method for Vagus Nerve Stimulation Evoked Catecholamine Release at End Organs
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Figure 1: FSCV recordings of known norepinephrine in vitro and norepinephrine-like signals in vivo at the kidney during vagus nerve stimulation before and after injection of desipramine, a norepinephrine reuptake inhibitor. (A) In vitro FSCV recording of 1 μM norepinephrine. (B-C) In vivo FSCV recordings of a norepinephrine-like signal elicited at the kidney during Hering-Breuer Reflex following vagus nerve stimulation before (B) and after (C) desipramine injection.

Background: Bioelectronic medicines are an emerging area focused on treating diverse disease/disorders using precise, minimally invasive electrical stimulation to modulate autonomic nerves controlling end-organ function. To this end, there is a need for quantifiable, real-time feedback of stimulation. Vagus nerve stimulation is known to cause a variety of physiological changes throughout the body, but there is no measure of the immediate neurochemical changes at end organs. Fast scan cyclic voltammetry (FSCV) is an electrochemical technique that has been used in the central nervous system to measure norepinephrine with subsecond and submillimeter precision [2]. Here we used FSCV to measure changes in norepinephrine concentration during Hering-Breuer Reflex (HBR), which is sympathetic activation in response to significant slowing of breathing caused by vagus nerve stimulation [3].

Methods: We used homemade nerve cuffs, adapted from [1], to stimulate the cervical vagus in order to elicit the HBR. Mayo developed WINCS Harmoni was used to apply FSCV at the tip of a homemade carbon fiber microelectrode (CFM) implanted in the cortex of the kidney. FSCV works by cycling the voltage such that electroactive molecules near the CFM oxidize and reduce at potentials specific to those molecules, producing a “fingerprint” signal shown here as a color plot [Figure 1A]. Desipramine, a norepinephrine reuptake inhibitor, was injected to pharmacologically verify that the evoked signal was norepinephrine.

Results: Vagus nerve stimulation resulted in cessation of breathing and activation of HBR as confirmed by reinstatement of breathing during continued stimulation. FSCV measurement of catecholamine release was recorded approximately fifteen seconds following beginning of stimulation and coincided with reinstatement of breathing. Injection of desipramine caused an apparent increase in the amplitude and duration of the measured FSCV signal, indicative of norepinephrine measurement [Figure 1B-C].

Conclusions: FSCV can be used to measure the neurochemical correlates of the HBR elicited by vagus nerve stimulation in real-time at the kidney. These results are significant in that they provide deeper understanding of a well-known reflex, and provide support for the use of FSCV for measurement of biomarkers associated with bioelectronic medicines therapy.

References:

Funding: The Grainger Foundation
**Thalamic-DBS-Induced Cortical Perfusion Is Dependent On Baseline Cortical State**

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**Background:** Deep brain stimulation (DBS) has revolutionized the treatment of movement disorders and is under investigation for other conditions as diverse as epilepsy, pain, and psychiatric conditions. Despite the widespread use of DBS, how it achieves benefit is unclear [1]. Our previous work applying DBS in ventrolateral (VL) thalamus, used to treat tremor clinically, increased perfusion in rodent primary motor cortex (M1) [2]. Here we examined electrophysiological activity and cortical perfusion using optical imaging. We tested the hypothesis that baseline neural activity will affect the thalamic-stimulation induced cortical perfusion.

**Methods:** In urethane-anesthetized rats (n=6), we applied electrical stimulation (10-100 Hz) using a concentric bipolar electrode to VL thalamus. Stimulation involved biphasic, constant current pulses for a 3 s train, while recording neural activity and perfusion in M1 through a cranial window. Tissue reflectance (which is proportional to tissue perfusion) was measured using intrinsic optical imaging under green illumination (~570 nm) while neural activity (spikes and local field potential) was recorded using a microelectrode placed into layer V of M1 where maximal perfusion change occurred.

**Results:** In 3 of 6 animals, perfusion increased linearly with frequency to 60 Hz and plateaued above 60 to 100 Hz (group#1). In the other 3 animals, perfusion changes were flat or decreased (group#2). For example, in group#1, percent change in reflectance with 10 Hz DBS applied was 0.77±0.1 (mean± SEM) and using 100 Hz, it was 3.05±0.22. In group#2, percent change in reflectance with DBS applied at 10 Hz was 2.3±0.53 and using 100 Hz the change was 2.28±0.13.

Baseline spiking activity was low and tonic in group#1 (3/3) while it was bursty in group#2 (3/3). Bursting was identified as a minimum of 3 spikes with a maximum interspike interval of 15 ms. DBS induced antidromic responses were present in all group#1 animals, whereas they were absent in 2 of the 3 group#2 rats.

VL thalamus is reciprocally connected to M1 thus its stimulation will generate both antidromic and orthodromic evoked responses in M1. We found antidromic evoked responses only in group#1 sites, and their presence resulted in greater increases in perfusion.

**Conclusions:** Baseline spiking activity of the cortex affected the perfusion response of cortex to thalamic DBS. Moreover, antidromic activation of fibers was associated with greater cortical perfusion in our model. These data will provide insights into the circuit mechanisms of DBS for essential tremor and epilepsy.

**References:**


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**Fig 1.** Relationship between percent change in reflectance (Mean ± SEM) and frequency of DBS applied in VL thalamus. Blue circles indicate results when baseline spiking was low or tonic (N=3) while the red circles show data when the baseline spiking was bursty (N=3).
Cortico-thalamic Based Responsive Deep Brain Stimulation for the Treatment of Essential Tremor

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Background: Essential Tremor (ET) is defined as a rhythmic, involuntary oscillatory movement of the limbs. Intention tremor is present mostly in the upper limbs (with slow oscillations at ~4-12 Hz) during the initiation and execution of goal-directed reaching motions, while it is absent at rest. Although the pathophysiological basis of ET remains unknown, it has currently been suggested that a synchronous pathological oscillation is present in Ventral Intermediate Thalamic Nucleus (VIM) and cerebellum “tremor cells” (1), affecting their network with Premotor (PM) and Primary Motor (M1) Cortex. The goal of this study is to develop a responsive Deep Brain Stimulation (DBS) therapy for ET that would use movement intention and pathological activity as markers for an implanted neurostimulator (Medtronic PC+S). The rationale is that it would be possible to decrease the side effects caused by DBS such as speech and balance impairments, decrease battery usage, while delivering an equally effective treatment.

Methods: Two patients were implanted in both cortical (PM, M1) and thalamic (VIM) regions and recorded during a DBS implantation surgery. Other 2 patients (non ET) were implanted with PC+S Neurostimulators, which will be also used for our ET cohort. Together with inertial and EMG collected data, it was possible to explore biomarkers related to movement intention/execution, and to tremor. Leveraging the presence of specific biomarkers we show that it is possible to reliably deliver responsive DBS.

Results: Pilot data collected from cortical strips, implanted for a different cohort (non ET, Tourette’s), and from M1 and VIM, during DBS implantation surgeries for ET, show reliable detection capabilities using a simple LDA classifier to discriminate upper limb movements compared to rest. Hence, this work shows the feasibility of a responsive DBS therapy implemented within Medtronic PC+S devices.

Conclusions: Our results suggest that a reliable control of responsive DBS, completely embedded in the neurostimulator device, is possible with the use of a single or a combination of targeted brain areas. This enhanced DBS therapy solution is expected to improve the quality of life of the population affected by ET by responsively tackling and quenching tremor occurrences, while decreasing possible patient’s side effects, such as balance and speech impairment, and slowing down battery depletion, by being inactive during non-tremor events.

References:


Funding: University of Florida start-up funds, NIH BRAIN Initiative.

Normalized spectrogram of right VIM (top spectrogram) and motor cortical activity (bottom spectrogram) collected in an ET DBS implantation surgery in human during volitional cup grasping (middle), along with contralateral (bottom) and ipsilateral (top) hand accelerations. The GO signal (shown in green at the top and bottom panels) represents when the patient moved to reach the target (cup). The movement detection is based on the top features obtained with Fisher score feature selection (22Hz-26Hz from cortical activity, 18Hz-25Hz from VIM activity) and then classified with an LDA classifier, with an approach similar to the one implemented in Activa PC+S.
Kinetic characterization of stimulation-evoked striatal dopamine release in a 6-hydroxydopamine-lesioned parkinsonian rodent model.

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\textbf{Background}
Dopamine (DA) is an important neurotransmitter, exhibiting critical roles in neurologic function during Parkinson’s disease (PD). As such, the ability to characterize DA responses to therapeutic interventions such as deep brain stimulation (DBS) has important implications for studying the pathophysiology of disease. The non-linear and time-varying dynamics of stimulation-evoked DA responses have been characterized using mathematical models of DA release in healthy anesthetized animals. However, the complex relationship between electrical stimulation and subsequent stimulation-evoked DA release has yet to be characterized in a Parkinsonian animal model. Thus, this study characterizes DA responses in the striatum of 6-hydroxydopamine (6-OHDA) lesioned rats in response to medial forebrain bundle (MFB) DBS.

\textbf{Methods}
The MFB was electrically stimulated in urethane-anesthetized 6-OHDA lesioned male Sprague-Dawley rats using a comprehensive range of stimulation parameters. Concurrently, striatal DA release was measured using fast scan cyclic voltammetry in combination with carbon fiber microelectrodes. Evoked responses were characterized using a multi-compartment parametric model of DA release. The resulting kinetics were then compared to the kinetic responses from healthy anesthetized rats.

\textbf{Results}
The results from intact animals suggest that the kinetics of stimulation-evoked DA release can be described using compartmental models and that these models can describe the forward relationships between electrical stimulation parameters (i.e., stimulus pulse width and amplitude) and stimulation-evoked extracellular dopamine responses. Further analysis will determine whether these relationships are altered following 6-OHDA lesioning.

\textbf{Conclusions}
Characterization of DBS induced DA release in a model of PD is an important step towards understanding neurotransmitter dynamics in the context of neurologic disease and therapeutic interventions. Ultimately, this work will aid in understanding the neurochemical effects of DBS and further the development of novel therapeutic strategies.

\textbf{Funding}
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Individualized Tractography-Based Parcellation of the GPI at 7T in PD Patients prior to DBS Surgery

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Background: Success of DBS surgery relies on accurate placement of an electrode within the motor portion of subcortical brain targets; however, it is estimated that 15-34% of DBS procedures require revisions¹. We have previously generated reproducible, individualized, parcellation of the STN into functional territories using 7T MRI data². Here, we developed methods to uncover patient-specific functional territories of the GPI, prior to surgery, to aid DBS targeting.

Methods: Nine patients were imaged using a 7T MRI scanner. The protocol included high-resolution anatomical images and DTI². The GPI was manually segmented and the cortex was divided into limbic, associative, motor and “other” regions using standard atlas². Anatomical studies have shown that the GPI does not have direct connections to the cortex³; therefore, we executed the parcellation in two steps: 1) Identifying functional territories of the Thalamus using tractography to the cortex² parcellation of the GPI using the thalamic defined territories. The thalamus was extracted from an atlas. DTI preprocessing included motion, susceptibility artifact, and eddy current correction, and three-fiber model estimation of the diffusion parameters. Tractography-based connectivity was computed at each voxel of the Thalamus (step1) and the GPI (step2) and performed unilaterally. To obtain the targets for GPI parcellation, masks were derived based on the thalamus parcellation from step1. Lastly, final electrode and contact location was extracted from a post-operative CT scan in order to assess clinical significance of our results.

Results: A reproducible topographic functional organization of the GPI was observed in all patients. The motor territory is located posteromedially followed anteriorly by the associative and limbic territories. Physiological validation of our results was achieved by registering the post-operative CT lead location with the anatomical model. The electrode confirmed to be placed in the motor region. The clinically optimized DBS settings indicate that best motor improvement was seen with the active contact located in the motor territory.

Conclusions: Our results demonstrate, visually, the existence of multiple functional territories within the GPI in humans. This organization pattern is similar to that previously described in the STN and thalamus² which may reflect a common architecture of structures of the basal ganglia. Our results are further validated by the post-operative electrode location and clinically optimized DBS programming settings. These new findings provide better understanding of the fundamental organization of target structures for DBS surgery and neuromodulation therapy.

References:

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Adaptive and automated closed-loop stimulation of pelvic nerve for bladder emptying

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Background: The use of neural stimulation to restore bladder function has traditionally relied on tonic stimulation that is manually activated and terminated by the user [1]. However, due to the open-loop nature of the stimulation, partial voiding or nerve habituation due to overstimulation can occur [2]. Our preliminary work showed that pelvic nerve stimulation was able to evoke voiding, however voiding efficiency was less than 75%. In this study, we used bladder pressure signals and pelvic nerve stimulation to create a closed-loop system for more complete bladder emptying. Our results showed that our closed-loop system achieved >75% voiding in anesthetized rats. This novel approach could be useful in cases where overstimulation of the nerve is a concern, and thus multiple epochs of stimulation are necessary.

Methods: All procedures were performed in accordance with protocols approved by the IACUC of NUS. Adult female Sprague-Dawley rats were anesthetized and maintained with ketamine/xylazine. To expose the bladder and the pelvic nerve, a ventral incision of the lower abdomen was made. The bladder was filled at a constant rate using an infusion pump, which allowed us to measure the urine output to quantify the residual bladder volume. Intra-bladder pressure was measured via a saline-filled catheter (Instech Laboratories), inserted into the bladder, and connected to a pressure sensor. The pressure was monitored using a closed-loop algorithm written in LABVIEW. Identification of voiding events was based on thresholds derived from linear discriminant analysis. Bipolar stimulation was carried out with an A-M Systems stimulator connected to platinum hook electrodes implanted onto the left pelvic nerve. The amplitude of the stimulation current was controlled by the closed-loop algorithm through a custom designed current shunt. The pressure-volume relationship and the threshold current amplitudes needed to evoke voiding were established for each animal at the start of the experiment.

Results: The figure below shows an epoch of our closed-loop stimulation. Our results showed that online processing of pressure was able to correctly guide adjustments in the stimulation amplitudes, which resulted in consistent and more complete voiding in a rat (79.2 ± 1.0 % voided, 3 trials).

Conclusions: Our closed-loop system, which uses only pressure signals to initiate, adjust, and halt pelvic nerve stimulation, can safely and effectively achieve almost complete voiding of the bladder. Future work could apply this automated system to rats with spinal cord injury where voiding is impeded [3].

References:


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Human Models of Particle Swarm Optimization for Programming Deep Brain Stimulation

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Background: The efficacy of Deep Brain Stimulation (DBS) for neurological and neuropsychiatric disorders relies on precise activation of therapeutic brain targets and simultaneous avoidance of non-therapeutic regions. Recent developments in commercial DBS systems aim to enhance precision of stimulation by introducing capabilities such as current steering. However, as DBS systems provide more control over stimulation parameters, assistive programming algorithms will be essential to help clinicians identify effective stimulation settings in an efficient manner.

Methods: Here, we extend a Particle Swarm Optimization (PSO) DBS programming approach, previously developed for use with translational animal models¹, to identify a range of optimal stimulations settings in human subjects. We developed subject-specific anatomical models of DBS in the subthalamic nucleus (STN) in four humans with Parkinson’s disease who had previously received STN-DBS implants (Medtronic 3389). The human models leveraged T1-weighted whole-brain MRI, ultra-high field (7T) susceptibility-weighted and T2-weighted MRI of the basal ganglia, and diffusion-weighted images for probabilistic tractography of the basal ganglia. We incorporated multiple regions of interest (ROI) that are known to be therapeutic (i.e. motor part of STN, tracts between STN and globus pallidus, tracts from globus pallidus to thalamus), as well as multiple regions of avoidance (ROA) that can lead to side effects if stimulated (i.e. internal capsule, limbic and associative parts of STN).

Results: The original PSO algorithm¹ was not able to accommodate multiple ROIs and ROAs in its objective function, which led to development of a dominance-based PSO approach that was able to simultaneously accommodate multiple subject-specific regions of interest and regions of avoidance. This new method was shown to efficiently identify a range of non-trivial electrode configurations that maximized the number of neurons and axons activated in the regions of interest, minimized the number of neurons and axons activated in the regions of avoidance, and minimized power consumption overall.

Conclusions: This work demonstrates the application of new algorithmic approaches for programming DBS devices using a dominance-based PSO approach fit to retrospective imaging data from human PD subjects. Such algorithms have potential to more efficiently and effectively identify therapeutic DBS settings in patients, but will need to undergo extensive validation in future studies.

References:


Funding:

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Effects of Vagus Nerve Stimulation (VNS) Paired with Rehabilitation in Upper Limb Motor Function After Stroke

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Background: Vagus nerve stimulation (VNS) paired with motor training can significantly improve recovery of forelimb function compared to training alone in a rat model of cortical ischemic stroke. A first-in-human open study showed that VNS paired with upper limb rehabilitation was safe and feasible in adults up to 5 years after ischemic stroke.1 The goal of this randomized blinded sham-controlled preliminary trial was to further assess the effects of VNS combined with rehabilitation on upper extremity function after chronic stroke.

Methods: Seventeen participants (8 female) with moderate to severe upper extremity hemiparesis due to supratentorial ischemic stroke were enrolled. Mean±SD age and time since stroke was 59.8±10.4 years and 1.5±1.0 years, respectively. All participants were implanted with a VNS device and randomized to one of two groups: real VNS paired with rehabilitation (n=8) or control VNS paired with rehabilitation (n=9). Patients, treating therapists and testers were blinded to group allocation. The rehabilitation intervention consisted of 18 sessions of intensive, goal-oriented, and task-specific upper extremity exercises (~3x/week for 6 weeks). During upper extremity task practice, each repetition of movement was paired with a VNS pulse (real: 0.8mA; control: 0.0mA) for 300-500 repetitions/session. Three months after completion of therapy, participants in the control group crossed over to the VNS group and received real VNS paired with rehabilitation. The primary outcome measure was change in the Upper Extremity Fugl Meyer (UEFM) score with a clinically meaningful change of ≥6 point increase from baseline. Assessments occurred at 1 and 30 days after therapy completion. Long term effects will continue to be assessed up to three years after treatment completion.

Results: Study related serious adverse events included a wound infection, dysphagia, and two vocal cord paralyses (3 resolved, 1 ongoing). In the intention to treat analysis, 75% of VNS participants had a clinically meaningful improvement in UEFM (mean change: 7.6±4.8 points) compared to 33.3% in the control group (mean change 5.3±3.2 points; p=0.21). Improvements in the VNS group continued up to 6 months after therapy was completed. Full statistical results will be presented at the meeting as not all participants have completed the protocol.

Conclusions: The findings suggest that VNS paired with rehabilitation is feasible and safe in adults after chronic stroke. A pivotal study will be undertaken for commercial approval in the US based on power analyses from these results.

References:

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Neural Suppression with Deep Brain Stimulation using a Linear Quadratic Regulator

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Background: Current neuromodulation techniques for seizure suppression, such as vagus nerve or deep brain stimulation, have shown some clinical efficacy. Yet their application is complicated by the large parameter space of electrical stimulation settings inherent to these systems. A physician must skillfully choose stimulation parameters such as frequency, amplitude, and pulse width for each individual patient in order to effectively reduce their incidence of seizures. We demonstrate an algorithm capable of automatically generating a continuous stimulation waveform to suppress neural activity and minimize total stimulation energy.

Methods: We treat the suppression of neural activity as a linear-quadratic-Gaussian (LQG) control problem. The resulting optimal controller consists of a Kalman filter and a linear-quadratic regulator (LQR). The effectiveness of the LQG controller in suppressing seizure biomarkers was first verified in a computational model of epilepsy called Epileptor1, which simulates local field potential (LFP) recordings within a seizure focus. We built a model of the generated LFPs using the Ho-Kalman algorithm2 for subspace system identification. The Kalman filter estimated the state of the system and a feedback control signal provided by the LQR successfully prevented seizures during stimulation, even while varying the Epileptor model parameters.

We then implemented the LQG controller in an in vivo rodent model. We stimulated the ventral hippocampal commissure while recording in the hippocampus. The Ho-Kalman algorithm was again used to build a dynamical systems model of the LFP activity based on the evoked response to Gaussian white noise stimulation. We used a three phase experiment to test the LQG controller: 2 minutes of baseline activity; 2 minutes of closed-loop neural stimulation; and 2 minutes post-stimulation to check if LFPs return to baseline levels. This same stimulation waveform was then replayed in “open-loop,” without state estimation from the Kalman filter. The LFP power from 1-100Hz was used to measure performance.

Results: Our results show a significant decrease in LFP power during closed-loop stimulation. Open-loop stimulation produced negligible change in LFP power.

Conclusions: The LQG controller was confirmed to be an effective tool for minimizing LFP activity within a selected frequency band. The mathematical models of neural dynamics it uses are subject specific and determine stimulation waveforms based on state to suppress neural activity.

References:

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STN or GPI Deep Brain Stimulation for Parkinson’s disease: The STOP PD DBS Clinical Trial

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Background: The objective of this study was to compare the effects of unilateral DBS in the subthalamic nucleus (STN) to unilateral DBS in the internal segment of the globus pallidus (GPI) for the treatment of patients with advanced Parkinson’s disease (PD). A secondary objective was to assess the relative benefit of unilateral versus bilateral stimulation and whether there was a difference between those patients receiving unilateral STN or GPI DBS in the number of patients who required second side surgery. Although early studies demonstrated stimulation in both sites as effective in the treatment of motor symptoms associated with PD¹, the majority of open label studies suggested STN provided greater clinical benefit. Currently most clinicians regard the STN as the surgical target of choice based on the relatively greater improvement in motor symptoms and the ability to reduce antiparkinsonian medications. However, more recent blinded randomized trials of STN vs GPI DBS have reported maximal improvement in motor symptoms is similar in GPI and STN and several of these studies have reported increased neuropsychological and behavioral side effects with STN stimulation².

Methods: We conducted a prospective, double-blinded, randomized DBS clinical trial in 123 patients (64 STN and 58 GPI) with medically refractory PD. The primary outcome was the mean change in total score on the UPDRS from baseline (OFF medications) to the six-month outcome (OFF medications, with stimulation ON). Secondary measures included indicators of severity of PD, reduction in antiparkinsonian medications, and surgical complications/adverse events. Neuropsychological, psychiatric, functional status and quality of life measures were all obtained. Data was collected at baseline (a month before DBS surgery), and at 6, 12, 24, 36, 48, and 60 months after surgery.

Results: There was no significant difference between STN and GPI in the change of UPDRS III motor subscale scores from baseline OFF to 6mo OFF meds/ON stim.; mean percent (SD) change was -29.2% (26.7%) for GPI and -21.9% (28.5%) for STN; F(1,99)=1.757, p=.188. Sleep improved in both groups at 6 months, however subjects who underwent STN DBS were less likely to report sleep disturbances (28 of 53 participants; 13 of 54 STN participants); X²(1)=9.358, p=.002. GPI participants showed more improvement (from Baseline OFF to 6mo OFF/ON) in ipsilateral modified UPDRS motor items (20-26), a decrease from mean (SD) 9.9 (4.1) to 7.5 (3.8) points, as compared to the STN group’s decrease from 10.1 (4.6) to 9.5 (4.8) points; a significant main effect for time point (F(1,98)=17.292, p=.000, partial η²=.150) and significant interaction between time point and site (F(1,98)=6.613, p=.012, partial η²=.063). A similar interaction was not seen in contralateral UPDRS items.

The Schwab & England activities of daily living patient-assessed scale showed greater improvement in GPI (60% to 75%) than STN (62% to 68%) participants from baseline OFF to 6mo OFF/ON. A 2x2 ANOVA was significant for time point (F(1,101)=33.486, p=.000) and the interaction of time point and DBS site (F(1,101)=6.832, p=.010).

Conclusions: STN is generally regarded as the “standard” target site for DBS implantation in treatment of PD. However, our 6 month results suggest that GPI may have some advantages in quality of life and ipsilateral improvement in motor symptoms. Analyses of our long-term follow-up data will help determine whether these differences persist over time.

References:

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Long-term recording from multiple sites in basal ganglia for DBS Targeting in children with secondary Dystonia

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Background: The optimal target for neurostimulation in children with secondary dystonia varies depending on the etiology and anatomic distribution of injury in each child.

Methods: We present 5 cases of a new technique for identifying DBS targets. 10 Adtech ™ MM16C depth electrodes are implanted in bilateral subthalamic nucleus (STN), internal globus pallidus (GPI), ventrolateral nucleus of the thalamus (VL), ventral intermediate nucleus of the thalamus (Vim), and ventroposterolateral nucleus of the thalamus (VPL). Each electrode has up to 10 high-impedance “micro” contacts capable of identifying single unit extracellular potentials, and 6 “macro” contacts capable of identifying local field potentials. Test stimuli can be applied through the macro contacts. Children are admitted to the epilepsy monitoring unit for 5 days with continuous recording from 96 intracranial channels and 8 EMG channels (AlphaOmega Inc. NeuroOmega ™ recording system), continuous video recording, and intermittent stimulation at bilateral macro contact pairs during attempts at movement.

Results: No single consistent pattern of activity was found. Single-unit recording showed high firing rates that were spread throughout GPI. Activity in both VL and Vim was partially correlated with dystonic movements. The optimal stimulation target varied between children. When effective, stimulation in thalamic targets caused immediate response, whereas stimulation in Gpi did not show immediate effects. In one child, stimulation in STN caused a significant improvement in sleep. Based on the recording and stimulation results, 4 of the children were implanted with up to 4 permanent stimulation leads (Medtronic 3387 or 3389) connected to implanted Activa™ pulse generators. Preliminary results suggest significant reduction in dystonia in all 4 children.

Conclusions: The new method of DBS targeting identified targets that varied between children. Clinical response suggests a beneficial effect greater than what would be expected for GPI stimulation alone. This method may increase the effectiveness of DBS in secondary dystonia and may allow it to be applied to children with a broader range of diagnoses.

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Phase-Offset Sinusoidal Stimulation to Increase Therapeutic Windows for DBS Applications

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Background: Pulse patterns used in Deep Brain Stimulation (DBS) therapy are thought to induce non-specific axonal activation surrounding active electrodes. Given the proximity of active electrodes to regions implicated in side effects of DBS as well as high levels of directionality in white matter DBS targets such as the subcallosal cingulate for depression [1], there is a need to develop more selective stimulation approaches. Previous work has shown orientation selectivity of stimulation by varying the electrode shape [2] and controlling the primary electric field direction using multichannel electrodes [3]. In this work, we introduce a novel spatiotemporal approach based on Rotating Field Phase Steering (RFPS) paradigms for enhancing orientation selectivity of axonal activation. We evaluated these RFPS approaches using computational models of DBS across a range of axonal orientations using (1) a standard 4-channel DBS lead and (2) an 8-channel segmented DBS lead.

Methods: Computational tissue conductance models were developed using COMSOL and coupled with multi-compartment axonal models in NEURON to estimate axon activation thresholds for each electrode design. Two commercially available DBS leads were modeled in this study: a 4-annular-contact DBS lead (Medtronic) and an 8-contact array with two annular contacts separated by two rows of 3 segmented contacts (St. Jude Medical). Stimulation was applied in varying electrode combinations using phase-offset (0-2π) 1 kHz sinusoids. Axonal activation thresholds were analyzed for axons radially distributed 1-3 mm adjacent to the central axis of the leads.

Results: Sinusoids applied the Medtronic lead with no phase-offset between two adjacent contacts resulted in a lower activation threshold for axons perpendicular versus parallel to the lead (1:2.2). In contrast, sinusoids with a phase-offset of π between two adjacent contacts showed the lowest threshold for parallel axons with a 9.1:1 threshold ratio. Coupling the St. Jude Medical array with π-offset sinusoids applied to two segmented contacts improved orientation selectivity to ±60° relative to the central axis of the lead (Figure 1). A threshold ratio of 1.2:1 was found for axons aligned with the active contacts (-60° relative to the lead central axis) compared to axons antiparallel to the active contacts (+60°).

Conclusions: This study provides a novel stimulation framework for generating orientation-selective activation with potential to improve DBS efficiency as well as widen the therapeutic window between stimulating pathways of interest and pathways implicated in side effects. RFPS combined with multichannel electrodes provides a wide spectrum of variables for more efficient, flexible, and selective neuromodulation.

References:


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Figure 1: Surface plot of the effect of RFPS using a segmented lead (St. Jude Medical 6172). An axon angle of 0° is perpendicular to the lead, and 90° is parallel to the lead.
Deep Brain Stimulation That Mimics Endogenous Synchrony Rapidly Terminates Temporal Lobe Seizures in Rats

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Background: Deep brain electrical stimulation (DBS) is a treatment modality being explored for many neurological diseases and is a potentially potent means for disrupting the aberrant rhythms that arise during the epileptic seizures that afflict over 1% of the population [1]. However, current DBS protocols typically employed are formulated a priori and do not reflect the electrophysiological dynamics within the brain as seizures arise which may underlie their limited efficacy. Furthermore, most stimulation paradigms in therapeutic devices seek to reduce the frequency of seizure onset but are not specifically tailored to terminate a seizure once ictal activity has initiated simply because past efforts at this goal have not yet shown strong efficacy. This study investigates how the efficacy of DBS to terminate seizures could be improved using endogenous dynamics to inform stimulation protocols.

Methods: Multi-site brain dynamics within the circuit of Papez were calculated in a chronic rat limbic epilepsy model induced via LiCl/pilocaprine i.p. injections. Stimulation/recording electrodes were placed in the CA3 region of left and right hippocampi and the anteromedial nucleus of left thalamus. Deconvolution of local field potentials using empirical mode decomposition (EMD) and phase synchrony analysis revealed multisite coherence as seizures approached natural termination that could not be detected with Fourier analysis [2]. Multisite stimulation used charge-neutral biphasic square waves at frequencies observed during natural seizure termination.

Results: Synchronization of electrical activity across sites occurred as both spontaneous and evoked seizures naturally terminated in freely-moving rats. Further, the location and frequency (from 7 Hz to 300 Hz) of the synchrony varied between subjects but was stable in time within each animal. DBS efficacy was significantly more effective at rapidly stopping seizures when the frequency and location of multi-site stimulation reflected the endogenous synchrony dynamics observed in each subject as seizures naturally terminated [3]. Furthermore, applying the same analytical techniques to intracranial recordings from human limbic epilepsy patients revealed the same type of coherence at natural seizure termination suggesting that this approach in rats to tailoring stimulation protocols to specific subject dynamics may also be relevant to humans. Conclusions: These results strongly support the approach of tailoring DBS protocols to individual endogenous rhythms that may represent how brains naturally resolve epileptic seizures. This methodology can significantly improve the overall efficacy of this potentially important therapy for seizure termination and may also show improved efficacy for seizure prevention.

References:

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**Wireless Stimulation of Single Neurons and Nerve Fibers Using Neural Slurries**

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**Background:** Microscale, wireless paradigms offer significant advantages of high-throughput stimulation and localized selectivity for obtaining high degrees of freedom in peripheral nerve control. The main objective of this study is to develop a novel approach for wireless stimulation that demonstrates microstimulation of the peripheral nerve *in vivo* using potentially injectable combinations of microscale elements of piezoelectric elements and rectifying circuits.

**Methods:** Three different experimental models, namely single neurons derived from abdominal ganglion of *Aplysia californica*, *ex vivo* models of bull frog derived sciatic nerves, and *in vivo* models of rat sciatic nerves were used for testing. Ultrasound (300 kHz-1 MHz) incident on piezoelectric elements such as PZT were used to generate cathodic stimulation pulses using free-floating rectifying circuits placed adjacent to the sciatic nerve. Downstream compound action potentials (CAPs) and electromyograms (EMGs) were recorded using Intan™ recording system.

**Results:** Initial bench top models showed the feasibility of energy transfer from ultrasound driven piezoelectric elements to free floating rectifying circuits. In response to this cathodic extracellular stimulation, stimulus-locked, intracellular action potentials were observed in single neurons of *Aplysia* in a voltage dependent manner. *Ex vivo* frog sciatic nerve experiments showed that high frequency, AC stimulation generated by ultrasound modulation of PZT routed through freely floating rectifying circuits modulated the amplitude of CAPs in a voltage dependent manner suggestive of nerve fiber recruitment. *In vivo* rat sciatic nerve experiments showed that high frequency, AC stimulation in combination with free floating rectifying circuits are capable of modulating the amplitude and selectivity of compound muscle potentials derived from needle based EMG recordings. Finally, generation of muscle twitches (n=3 rats) in response to ultrasound induced PZT-based AC stimulation of the rat sciatic nerve suggests the energy transfer between ultrasound driven, piezoelectric material and rectifying circuits is capable of generating CAP/EMG events.

**Conclusions:** We demonstrate proof-of-concept of wireless stimulation and selective neuromodulation of single neurons, nerve fibers and muscle fibers. *In vivo* rat sciatic nerve experiments showed that ultrasound induced AC stimulation in combination with free-floating rectifying circuits are capable of wirelessly stimulating nerve fibers.

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Oscillatory Activity in the Supplementary Motor Area (SMA) and Motor Cortex (MC) in the MPTP Nonhuman Primate (NHP) Model of Parkinson’s Disease

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Background: Deep brain stimulation (DBS) has been shown to prevent the transmission of pathologic bursting and oscillatory activity within the basal ganglia thalamocortical (BGTC) network thought to underlie the motor signs in Parkinson’s Disease (PD). Understanding these processes will be critically important if we are to reach the full potential of DBS. Although studies have targeted subcortical activity, little is known about cortical activity in the parkinsonian brain. We hypothesized that neurophysiological activity in the supplemental motor area (SMA) and Motor Cortex (M1) in PD would differ from those of the Naïve condition.

Methods: We recorded local field potentials (LFP) in Naïve and parkinsonian conditions via two microelectrode recording chambers implanted over the bilateral SMA and the right-side pre-motor and motor cortex of our NHP subject. A modified UPDRS clinically evaluated the effectiveness of our MPTP induced mild-hemiparkinsonian state. Our NHP performed a randomized eight target center-out reaching task. Oscillatory activity collected over regions of interest was downsampled and lowpass filtered and parsed into individual trials, further divided into discrete epochs—baseline, reaction and reach time. A signal processing toolbox for spectral density estimation analyzed data from all trials, channels, and recording days prior to averaging and graphically presenting as time frequency color plots.

Results: Our data show elongation of both reaction and reach time. High (21-30 Hz) and low beta band (13-20 Hz) desynchronization corresponding to reach initiation in the SMA of the Naïve condition is diminished in the parkinsonian condition. An inverse relationship exists in M1 in which high beta desynchronization is time-locked to reach initiation to a greater degree in PD. Specificity across the bilateral SMA is shown to be significantly attenuated in the PD state. Additionally, beta band synchrony between SMA-M1 brain areas is increased during movement from startpad to touchscreen in PD.

Conclusions: This study showed marked differences in brain activity between Naïve and PD state in motor planning and initiation regions. It is possible that loss of specificity in motor regions across and within hemispheres is responsible for the observed change in reaction time, reinforcing that chronic pathological oscillations throughout the BGTC network interfere with normal non-synchronous activity between nodes of the network. Changes in the relative power between high and low beta, and the ability to synchronize and desynchronize neuronal activity within and across brain areas, appears to play a key role in the development of parkinsonian motor signs.

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Selective Peripheral Neuromodulation through Organ-Specific AAV-Mediated Gene Transfer

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**Background:** Peripheral neuromodulation has been pursued for conditions such as chronic pain and dysfunctions of pelvic organs. While peripheral nerves are accessible and amenable to electrophysiological manipulation, they often innervate multiple organs, have complex composition of efferent and afferent axons, and participate in complex neural circuits that are not completely understood. These neuroanatomical challenges hinder the expansion of therapies based on peripheral neuromodulation. The introduction of methods for manipulation of neural activity through genetically engineered chemogenetic and optogenetic receptors and channels creates an opportunity for the development of tools for targeted neuromodulation through viral vector-mediated cell-specific gene transfer. Targeted expression of engineered receptors and channels in peripheral neurons is likely to enable neuromodulation of afferent or efferent systems of individual organs, dissection of peripheral neural circuits, and potentially development of neuromodulation approaches beyond electrical stimulation. Our long-term objective is to develop strategies for peripheral neuromodulation through cell-specific delivery of neuromodulatory transgenes to peripheral ganglia using adeno-associated viral (AAV) vectors. As proof of concept for this approach, we are in the process of establishing a strategy for selective neuromodulation of colon-innervating sensory neurons based on dual-vector AAV vector targeting, using a Cre-activated vector that carries the inhibitory chemogenetic receptor hM4Di and an AAV-Cre vector. Here we describe the anatomical characterization of this approach using the reporter gene tdTomato.

**Methods:** AAV9 carrying tdTomato was injected in the colon wall of mice as previously described (Christianson et al., 2006). tdTomato expression in lumbosacral and thoracolumbar dorsal root ganglia (DRG) was analyzed by imaging whole-mount preparations with a multiphoton imaging system. For dual-vector combinatorial targeting, AAV9-Cre was injected intrathecally and AAV9 carrying Cre-dependent tdTomato was injected in the colon wall.

**Results:** Consistent with the distribution of neuronal tracers injected in the colon wall, transduced sensory neurons were abundant at the lumbosacral level when the vector was injected in the distal colon, while labeling in thoracolumbar DRG was more sparse. Injections in proximal colon resulted in sparse labeling in both lumbosacral and thoracolumbar DRG. Analysis of dual-vector combinatorial targeting is in progress.

**Conclusions:** These results demonstrate that AAV9 is able to transduce primary afferent neurons following uptake into peripheral terminals within the colon wall and provide proof-of-concept for organ-selective AAV-mediated gene transfer to the afferent visceral innervation. The use of dual-vector combinatorial targeting and cell-specific promoters has the potential to provide further selectivity in delivery of neuromodulatory genes to efferent and afferent peripheral neurons.

**References:**


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The Duration and Intensity of High Frequency Alternating Current Influences the Degree and Recovery of Nerve Conduction Block

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Background: Blockade of axonal conduction through nerves can be accomplished with delivery of charge-balanced high frequency alternating current (HFAC)(1). Such modulation has much clinical utility in pathologies related to activity of peripheral nerves. Energy requirements for delivery of sustained HFAC are considerable and necessitate development of efficient blocking algorithms. Many studies have demonstrated that nerve conduction can recover in milliseconds after HFAC-induced block(2). However, recent work has also demonstrated that, under certain conditions, recovery of nerve function can take minutes to hours. This prolonged recovery time has been termed a “carry-over” effect (3). It is of practical significance that no energy is being consumed during this carry-over period of nerve blockade. HFAC amplitude and duration have been shown to contribute to prolonged conduction block, however, different combinations of HFAC amplitudes and durations have not been explicitly tested with the intent to extend recovery times. In this study, conduction block of Aδ and C waves in electrically-evoked compound action potentials was assessed with an isolated rat vagus nerve preparation following the application of different combinations of HFAC duration and amplitude.

Methods: The HFAC signal consisted of charge-balanced square waves delivered at 5000 Hz to an isolated rat vagus nerve with a bipolar hook electrode (blocking electrode). The blocking electrode was positioned between stimulation and recording hook electrodes. A total of 25 combinations of HFAC amplitudes (1-10 mA) and durations (1-120 seconds) were tested.

Results: It was determined that both degree of conduction block and time of recovery of function were dependent on HFAC amplitude and duration, and that 30 seconds of HFAC at 10 mA was the most energy efficient method to achieve full block of Aδ waves with a prolonged recovery. For C waves, HFAC amplitude of 10 mA and duration of 120 seconds were the most efficient and effective parameters for induction of prolonged conduction block.

Conclusions: We established that the degree of nerve conduction blockade and time of recovery can be influenced not only by HFAC amplitude, but also the duration of HFAC delivery. There are certain combinations of HFAC amplitude and time which are optimal to produce the greatest amount of block during recovery, while maximizing efficiency.

References:

Funding: EnteroMedics Inc., St Paul, MN, USA
Evolution in the modulation of passive responses in primary motor cortex during prolonged STN DBS in the parkinsonian monkey

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Background: Deep brain stimulation (DBS) in the subthalamic nucleus (STN) has been a therapeutic treatment for Parkinsonian motor symptoms for decades. Some studies have characterized the neuronal activity responding to passive movements of the limbs in parkinsonism [1-3], however, the effect of DBS on this type of neuronal activity in the primary motor cortex (M1), a key nodal point in the basal ganglia-thalamo-cortical network, is not well understood. Moreover, the alteration of this neuronal activity during long-term STN DBS has not yet been explored. In the present study, the M1 neuronal responses to passive manipulation of the arm during prolonged STN DBS were studied in the MPTP non-human primate (NHP) model of Parkinson’s disease.

Methods: A NHP (female, 6kg) was implanted with an 8-contact scaled-down DBS lead in the STN and a 96-channel Utah array in the arm area of M1. Optimal stimulation contacts and parameters (0.2mA, 130Hz, 125μs) were determined by standard practice. Prolonged (4 hours) STN DBS was applied and the modified UPDRS (mUPDRS) score was assessed to confirm the efficacy of the DBS. Passive manipulations of elbow and shoulder extension-flexion were performed pre, at multiple times during and post DBS. Single unit activities recorded from the array were sorted and analyzed to investigate the modulation of passive responses.

Results: A 30-35% improvement of mUPDRS was observed during the prolonged DBS. A total of 56 well isolated single units were sorted from the array data. The modulation of M1 units responding to passive movements was altered during therapeutic STN DBS. Moreover, the alterations were different during the early (minutes after DBS onset) versus late (hours after DBS onset) stage of STN DBS. (1) The proportion of modulating units were reduced shortly after DBS onset but partially recovered as DBS continued. (2) Modulation depth increased with prolonged DBS. The change in modulation depth correlated with the magnitude of passive movement about the elbow but not the shoulder. (3) DBS suppressed the modulatory activity of some cells over the duration of stimulation but this was not correlated to whether or not the cell was antidromically activated.

Conclusion: Broadened receptive fields have been reported in the parkinsonian state and considered to represent a defocusing effect in the dopamine depleted state [1-3]. The reduced proportion of units responding to elbow or shoulder movement together with an increase in the depth of modulation of the remaining cells could indicate a refocusing effect during stimulation.

References:

Funding:
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2) MnDRIVE Neuromodulation Postdoctoral Fellowship;
3) Parkinson’s Disease Foundation Postdoctoral Fellowship PDF-FBS-1550.
**Improved Spatial Resolution of Local Field Potentials in The Globus Pallidus And Subthalamic Nucleus For Use In Closed-Loop DBS Applications**

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**Background**: The basal ganglia are known to have a functional topography composed of motor subcircuits and oscillatory networks that are likely to be critically important for the identification of biomarkers for Parkinson’s disease (PD), and the successful application of closed-loop deep brain stimulation (DBS) therapy. Oscillatory activity, particularly in the 12-30 Hz range, has drawn much attention as a potential biomarker for PD [1], though results have varied. To accurately measure oscillatory dynamics using local field potentials (LFPs), the bipolar pair of recording electrodes should match the geometry of the target neural activity so that the electrodes do not shunt the underlying heterogeneity of sinks and sources. We hypothesized that there is spatially heterogeneous oscillatory activity in the globus pallidus (GPe/GPi) and subthalamic nucleus (STN) at a scale smaller than that observable with conventional clinical DBS leads.

**Methods**: DBS arrays (DBSAs), with 8 rows of 4 radially-oriented electrodes [2], were implanted in the GPe/GPi and in the STN in two non-human primates. LFP recordings were performed in the resting-state, during reach and retrieval, and in the naïve and mild Parkinsonian state across both arrays, and bipolar LFP recordings were performed along and around each DBS array.

**Results**: Multiple oscillatory dipoles were found across both DBS arrays. Notably, when simulating a conventional DBS lead with four cylindrical electrodes – i.e. by shorting two rows of electrodes along the DBS array and taking the differential between shorted rows – oscillatory dipoles were not observed in the STN and a single oscillatory dipole was found for the GPe/GPi lead at the border between nuclei. Additionally, the differential LFP signal amplitude was 4x larger between individual electrodes around or along the DBS array than in the case of the differential signal between two virtual macroelectrodes (Figure).

**Conclusions**: Together, the data suggest that closed-loop DBS and PD biomarker identification will benefit from using DBS leads that consist of a more spatially refined distribution of electrodes along and around the lead shank.

**References**:


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NON-INVASIVE NEUROMODULATION
Bottom-Up Modulation of Cognition Through Electrical Stimulation of Cranial Nerves

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Background: The cranial nerves are the pathways through which environmental information (sensations) are directly communicated to the brain, leading to perception, and giving rise to higher cognition. As cranial nerves determine and modulate brain function, the consequences of activating these pathways with electrical stimulation are relevant in both the clinical and cognitive domains. Thus, invasive and non-invasive cranial nerve electrical stimulation methods intend to modulate brain function, and by extension behavior. Other “transcranial” stimulation techniques, such as transcranial direct current stimulation, may also modulate cranial nerve activity because they produce significantly higher current density in the skin than in the brain.

Methods: An investigation of existing literature with regards to cognitive changes induced by electrical stimulation of cranial nerves was made. We amalgamate extant knowledge of 1) cranial nerve anatomy and biophysics and 2) evidence of modulatory effects on cognition by cranial nerves 3) integrated clinical and behavioral studies.

Results: In regards to anatomy and biophysics, our investigation points to a need for subtle and integrated mechanisms since activation of just one cranial nerve is often impractical or unlikely without precise targeting. Also, even isolated targeting of a single nerve is nuanced as each nerve is composed of functionally distinct axon-types that differentially branch and overlap in space with other nerves. On cognition, the cortical targets of each cranial nerve, which are several if not one synapse away, are widespread and modulate cognition via a bottom-up manner.

Conclusions: There is evidence that there are pathways to modulating higher cognitive processes by electrically stimulating cranial nerves. We have characterized the sensory systems for each cranial nerve from existing bioengineering, clinical and cognitive domain knowledge in a holistic manner to better inform future electrical stimulation studies.
Human dorsolateral prefrontal cortex functional connectivity with transcranial focused ultrasound

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**Background:** Transcranial focused ultrasound (tFUS) is an emerging technology for non-invasive neuromodulation that confers high spatial resolution with adjustable focal lengths. Previous research (Legon et al., 2014) has demonstrated tFUS modulating the excitability of cortical circuits with high spatial specificity. This study examines the effect of tFUS on resting state fMRI data in the targeted dorsolateral prefrontal cortex (DLPFC) region, close proximity regions of DLPFC, contralateral hemisphere, and functionally connected regions in the parietal cortex.

**Methods:** Two healthy volunteers with no history of neurological disorders participated in this study. A single element 0.5 MHz focused ultrasound transducer was used for tFUS stimulation targeting the middle frontal gyrus (MFG). Targeting of tFUS stimulation was achieved using a stereotaxic neuronavigation system and the subject’s T1 MRI. Resting state fMRI data was collected in a 7T Siemens scanner during tFUS stimulation (150 stimulations) and sham conditions.

The resting state fMRI data was processed using Analysis of Function NeuroImages (r threshold = 0.75). A 6mm diameter sphere seed region was placed at the location of tFUS stimulation. To test the spatial specificity of tFUS, data from seed points in close proximity (<15mm) to the tFUS target area (anterior, posterior, inferior, and superior directions) were also used for resting state analysis.

**Results:** Subject 1 showed strong connectivity of DLPFC to ipsilateral parietal cortex that the tFUS condition abolished; subject 2 showed strong connectivity to bilateral DLPFC that was not observable during the tFUS condition (Fig 1). At the site of stimulation, subject 1 showed a decrease in activation size (434 vs 589 voxels), but subject 2 did not show a change. In seed regions <15mm away from the tFUS stimulation target, there were no observable connectivity changes in either subject between both conditions.

**Conclusions:** Based upon these preliminary results, it is possible to use tFUS for stimulation of the DLPFC to probe connecting neural networks. This study shows tFUS stimulation of the MFG results in elimination of resting state activity in subjects. Differences seen in affected networks are likely due to differences in underlying connectivity between individuals. These data also demonstrate the spatial specificity of tFUS stimulation, where resting state activations < 15 mm away do not appear to be affected by stimulation. The preliminary results show it is possible to probe networks of the DLPFC with high spatial selectivity using tFUS not possible with other neuromodulation methods in common use.

**References:**

**Funding:** University of Minnesota start-up funds
**Transcranial focused ultrasound of thalamus in humans**

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**Background:** Transcranial Focused Ultrasound (tFUS) is an emerging technology for non-invasive neuromodulation that confers high spatial resolution with adjustable focal lengths. Unlike other electro and electromagnetic technologies, tFUS also has the ability to be focused deep to the cortex with high spatial resolution for potential stimulation of discrete deep neural structures. This study examines this possibility by using a deep focused single element ultrasound transducer targeted at the thalamus in humans.

**Methods:** Five neurologically healthy volunteers participated in this study. A single element 0.5 MHz focused ultrasound transducer with a focal length of 55mm (-3dB ± 11mm) was used to target the sensory nuclei of the thalamus, including the ventral posterior lateral nucleus (VPL). A total of 300 stimulations were delivered. Targeting of tFUS stimulation was achieved using a stereotaxic neuronavigation system, the subject’s T1 MRI, and the Oxford thalamic connectivity atlas. Thalamic activity was induced using median nerve stimulation and recorded as the somatosensory evoked potential (SEP) using four EEG electrodes placed in 10-20 electrode locations C3, CP3, P3 and CP1. SEPs were derived by median nerve (MN) stimulation (300 total delivered, jittered 3-5 sec) on the right wrist using a 0.2 msec square wave pulse. Ultrasound stimulation was time-locked 100 msec prior to MN stimulation. The N20 component was also analyzed. Sham and ultrasound blocks were delivered for each participant with the order counterbalanced across participants.

**Results:** Ultrasonic stimulation of the sensory nuclei of the thalamus resulted in a 17% attenuation of the P14pp (Sham: 2.3 ± 0.56 µV; US: 1.9 ± 0.38 µV). This inhibitory effect also translated to the N20pp (8% attenuation; Sham: 3.4 ± 1.5 µV; US 3.1 ± 1.0 µV).

**Conclusions:** Based upon these results it is possible to target nuclei of the thalamus in humans. Focused ultrasound directed at the sensory nuclei of the thalamus resulted in reduced amplitude of the P14 suggesting an inhibitory effect. This result is commensurate with previous work (Legon et al., 2014). The P14 attenuation also translated to the N20 SEP, suggesting downstream effects of tFUS though to a lesser extent. This study demonstrates that it is possible to directly target neural structures deep within the human brain non-invasively with tFUS, something that current noninvasive neuromodulation techniques (TMS or tDCS) cannot do. Focused ultrasound provides a promising new means to achieve stimulation with high spatial resolution anywhere in the brain.

**References:**


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Using Neuro-Imaging to Measure Effects of Non-Invasive Brain Stimulation as an Intervention for Alcohol Use Disorder

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Background: New interventions are needed to improve high relapse rates in alcohol use disorder (AUD). We have neuroimaging evidence showing that individuals with AUD with long-term abstinence have higher resting functional connectivity (FC) in a network including prefrontal cortex, thalamus and nucleus accumbens than those with short-term abstinence (Camchong, Stenger, & Fein, 2013b, 2013c). Low FC in this network during early abstinence predicts subsequent relapse (Camchong, Stenger, & Fein, 2013a). Literature shows that thalamus-prefrontal FC can be enhanced with transcranial direct current stimulation (tDCS). The purpose of this study is to investigate whether resting FC within a network known to mediate abstinence in alcohol use disorder can be enhanced with tDCS.

Methods: We investigated whether thalamus-prefrontal FC can be enhanced in AUD with a double-blind longitudinal study design. Intervention: 10 cognitive training sessions combined with either sham-tDCS or active-tDCS (anode on left dorsolateral prefrontal cortex). Rest fMRI data was collected pre- and post-intervention. Two AUD subjects undergoing active tDCS were compared to two AUD subjects undergoing sham tDCS. Preprocessing used FSL-FEAT and Melodic-ICA denoising. We hypothesized that individuals assigned to receive stimulation on left dorsolateral prefrontal cortex would show increases in thalamus-prefrontal FC when compared to individuals assigned to receive sham-tDCS.

Results: Preliminary analyses examining FC between left thalamus and left dorsolateral prefrontal cortex showed that subjects assigned to active-tDCS had a significant within-group FC increase (t=20.87, p=0.037) while subjects assigned to sham-tDCS did not (t=0.27, p=0.832). Group x Time effects was eta-square η²=0.116.

Conclusions: These pilot data suggest tDCS can improve thalamocortical connectivity. Larger sample size and treatment outcome information will provide crucial evidence supporting the therapeutic use of interventions targeting both cognitive and underlying neural mechanisms that support abstinence.

References:

Funding: University of Minnesota, Clinical and Translational Science Institute - KL2 scholar
Background: Short interval intracortical inhibition (SICI) is a widely adopted motor cortex excitability assessment technique using paired pulse transcranial magnetic stimulation (TMS). It consists of a conditioning pulse and a test pulse. By adjusting the intensity of the conditioning pulse, the inhibition level of the SICI response can be modulated and a conditioning intensity stimulus-response (S-R) curve can be measured. The inhibitory phenomenon of SICI is thought to be a reflection of the gamma-aminobutyric acid-A receptor mediated inhibition process of the brain. It has been reported that repetitive TMS (rTMS) can modulate the excitability of the brain. However, how the SICI changes in response to low-frequency (inhibitory) rTMS remains inconclusive. It has been reported that SICI responses are increased (Modugno et al. 2003), unchanged (Fierro et al. 2010) and decreased (Khedr et al. 2004) after low-frequency rTMS. The aim of this study was to systematically investigate the role of the conditioning intensity in SICI responses before and after low-frequency rTMS.

Methods: 15 participants were recruited to participate a three-part experiment, including a pre-test, an intervention and a post-test. For the intervention, participants received 900 single-pulse subthreshold (90% of RMT) 1-Hz rTMS. Pre- and post-tests included 10 trials of SICI conditioning intensity S-R curve (50% - 95% of resting motor threshold) with test stimulus at 1mV threshold and 20 trials of the cortical silent period (CSP).

Results: Significant CSP differences were observed between pre- and post-tests (p<.0001), meaning CSP was increased, suggesting more inhibition secondary to the inhibitory rTMS intervention. However, SICI did not demonstrate any difference between pre- and post-tests, meaning SICI was not modulated by the intervention at any conditioning intensity.

Conclusions: SICI may not be modulated by low-frequency subthreshold rTMS according to the results demonstrated in this study. Further parameter setting of SICI needs to be explored.

References:

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Feasibility of Performing TMS assessment of Infants with Perinatal Stroke by Incorporating Stereotactic Neuronavigation with EMG intensity threshold-triggered TMS

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Background: The overall purpose of this study is to use transcranial magnetic stimulation (TMS) to understand brain reorganization in infants with perinatal stroke. Many studies have used stereotactic neuronavigation guidance to assist the location of the TMS coil when targeting a specific brain area in children and adults; however, no studies have reported the use of this system when performing TMS with infants. To evaluate brain excitability from TMS-evoked motor potentials during infancy when the corticospinal tracts are not fully developed and thresholds are high, active motor threshold (AMT) is more likely to provide an attainable measure of cortical excitability than motor threshold. The feasibility of the above-mentioned components during TMS assessment, as presented in this poster, may be critical to the successful assessment of infant brain development.

Methods: A T1-weighted structural MPRAGE scan was obtained in one infant with perinatal stroke (4-month old female) before participation in the TMS session. The T1 scan was reconstructed as a 3-dimensional (3-D) image to guide TMS assessment (Figure). To locate the infant’s head position in space during coil navigation, a lightweight head tracker was made using a 3-D printer. Electromyography (EMG) intensity threshold-triggered TMS technique was used to obtain AMT in the wrist flexor. With this method, the investigator can deliver the TMS stimuli only when EMG amplitude was between 40-50 μV. The targeted muscle and threshold were chosen from data obtained during preliminary testing.

Results: Modifications to our TMS/Stereotactic protocol has allowed for feasibility of assessment of infant stroke. Our new lightweight version of the head tracker placed on the forehead was well tolerated by the infant. Even with a smaller head size compared to children and adults, the infant’s head was registered to the neuronavigation system without errors. With the guidance of the neuronavigation system, and using a 70-mm figure-of-eight TMS coil, we successfully and rapidly located the brain area that might control upper extremity muscles The infant’s EMG activity reached pre-defined threshold easily while the infant was engaged in play-activity guided by the investigator.

Conclusions: Stereotactic neuronavigation with a lightweight head tracker is feasible for guiding infant TMS assessment. Wrist flexor activity level and contraction duration is sufficient for performing TMS assessment in infants with perinatal stroke. By confirming the feasibility of our infant TMS assessment protocol, we will be able to obtain information about cortical reorganization in infants with perinatal stroke support the needs of timely interventions.

References:

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Neuromodulation of Peripheral Nerve Excitability using Ultrasound

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Background: Ultrasound has been observed to have neuro modulatory effect on peripheral nerves[1]–[3]. This study investigates the effect of short burst of 5MHz ultrasound on the excitability of amphibian sciatic nerve.

Methods: Sciatic nerve of American Bullfrog is harvested and mounted in a ringer's bath. It is suspended using two stimulating silver hook electrodes spaced about 1cm apart. CAP events were evoked by electrical pulses from an AM Systems Model 2500 constant current stimulator and detected by a pair of silver silver-chloride electrodes placed 3.5inches distal to the site of stimulation. Ultrasound from a 1/2” diameter 5 MHz focused transducer is operated in the pulse power range of 50 mW/cm² to 300 mW/cm² Ispta and focused between the two stimulating electrodes. Thus the electrical and ultrasound stimulation occur at the same site on the nerve. The electrical nerve stimulus was set in amplitude so that the CAP events evoked were about 50% of their maximum amplitude and this was held constant. A computer controlled data acquisition system written in LabVIEW first triggered the ultrasound pulse and then followed it by electrical stimulating pulses at varying tens of millisecond-order delay times after. Thus, changes in the nerve excitability by preceding ultrasound pulses showed as changes in CAP event amplitude around a nominal 50% value.

Results: Nerve excitability was found to be generally suppressed by ultrasound pulses, with a lingering persistence of ultrasound effect for tens of milliseconds depending on applied ultrasound power. At higher levels of ultrasound power, near-total suppression of nerve excitability was possible to an electrical stimulus that would otherwise produce a 50% amplitude of maximum CAP.

Interestingly, during the recovery time of the nerve, we observe that its excitability overshoots nominal to a higher level where a given electrical stimulus produces a relatively larger effect. Fig. 1 shows the plot of the evoked CAP peak to peak amplitude as a function of delay following ultrasound pulses. It shows the nerve is suppressed immediately at ultrasound pulse cessation but transitions to an excitatory response after 30-80ms delay depending on the ultrasound power. This effect suggests that nerve sensitivity to electrical stimulation can be modulated by preceding ultrasound pulses.

Conclusions: Ultrasound is seen to have both suppressive and excitatory effect on the excitability of amphibian sciatic nerve. The effects seen could be a result of radiation force of ultrasound causing mechanical stress on the nerve thereby causing suppression and excitation.

References:
Characterizing Variation in Responses to Transcranial Magnetic Stimulation using Electroencephalography

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**Background:** Transcranial magnetic stimulation (TMS) is a form of noninvasive neuromodulation that uses large transient magnetic fields to induce electrical current in targeted brain regions. Individual TMS pulses can be used to characterize cortical excitability and other factors [1], while extended trains of TMS pulses can induce temporary changes in neural plasticity, with implications for various clinical therapies [2]. However, a major limitation of current TMS methods is large variability in responses to stimulation, both across individuals and across stimulation pulses within an individual. This study aims to characterize some of this variability using electroencephalography (EEG) data recorded concurrently during TMS.

**Methods:** Healthy human volunteers participated in multiple TMS-EEG sessions, during which both real and sham rTMS at 1 Hz was applied at 90% resting motor threshold (RMT) for 15 min each. Each session targeted a particular motor-related cortical area. Motor cortex excitability was measured before and after rTMS with trains of pulses applied to left primary motor cortex at 0.333 Hz at 120% RMT. EEG and EMG data were recorded throughout using a TMS-compatible system with a 64-channel EEG cap and bipolar EMG electrodes places on the left and right FDI muscles of the hands. TMS-evoked potentials (TEPs) were extracted from the recorded EEG data and stimulation artifacts were attenuated using a multi-step ICA preprocessing pipeline similar to that described in [3]. Hierarchical agglomerative clustering was used to separate TEPs into groups with differing spatial topographies and/or temporal evolutions. Several forms of clustering were explored based on single-channel, multi-channel, or source-space features, both within and across subjects. Self-consistent clusters were identified by their silhouette values.

**Results:** Agglomerative clustering methods were able to extract multiple self-consistent groups of TEPs with differing spatial topographies and temporal evolutions, even when these TEPs were recorded during identical stimulation conditions within a single experimental session. Multi-subject analyses resulted in some clusters that could be clearly attributed to individual subjects or sessions, while other clusters consisted of TEPs distributed more uniformly across subjects and sessions.

**Conclusions:** Most common methods for TMS-EEG rely on interpretation of grand average TEPs from data recorded across multiple subjects. The results of this study suggest that it may be justified to examine subtypes of evoked responses, in order to better characterize variability in the propagation of neural activity after stimulation. Overall, a more comprehensive understanding of the brain’s response to TMS will enhance future neuromodulation therapies.

**References:**

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Electrophysiological mechanisms of tDCS modulation of executive functions

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**Background:** Cognitive deficits are common across neuropsychiatric disorders and a primary cause of functional disability. Nevertheless, clinicians have limited therapeutic options to facilitate cognitive enhancement, particularly of executive functions. tDCS is emerging as a promising tool for the treatment of neuropsychiatric disorders, and dysexecutive syndromes in particular [1]. The successful development of novel therapies requires an understanding of its mechanisms of action and the key targets that, when engaged, drive the therapeutic response. In this sense, Event-Related Potentials (ERPs) recorded on the scalp have established scalp-recorded signatures of executive functions [2].

**Methods:** We investigated the role of tDCS in modulating executive functions in 20 healthy adults, who received three different tDCS stimulation conditions over three separate visits: sham, anodal tDCS on the right DLPFC and the left DLPFC. Participants performed the Flanker task and Multisource Interference Task with International Affective Picture System (MSIT-IAPS) before and after receiving 30 minutes of tDCS at 2mA. We measured behavioral responses and EEG during the task, and calculated ERPs over Fz.

**Results:** For Flanker incongruent trials, Anodal Left tDCS lead to faster RT and an increase in P3 amplitude, while Sham lead to no significant changes in RT or ERPs. For congruent trials, Anodal Left and Right tDCS lead to no improvement in RT but P2 amplitude was significantly increased after Left stimulation. For incorrect trials, Error Related Negativity (ERN) amplitude was significantly decreased after Left stimulation compared to Right and Sham. For the MSIT-IAPS task, the effect of tDCS stimulation is not significantly different for Interference and Non-Interference trials, nor for Positive/Neutral/Negative trials. For all types of trials, Right stimulation lead to a significant decrease in RT and an increase in P2 amplitude, related to attention.

**Conclusions:** Our results show that specific working memory and attention-related ERPs are modulated by anodal tDCS applied over DLPFC in healthy adults. This modulation is correlated with an improvement in the behavioral performance, suggesting tDCS as a possible method to improve executive function. Furthermore, the correlation between behavioral performance and ERP modulation presents these ERPs as potential biomarkers and therapeutic targets of executive function modulation.

**References:**
Priming to Alter the Effects of Paired Associative Stimulation

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Background: Neuroplasticity governs mechanisms of cortical reorganization, adaptation and recovery following neural injury. Paired associative stimulation (PAS) induces a long-lasting change in neuroplasticity by pairing a peripheral nerve stimulus with a cortical stimulus. However, preceding PAS treatment intended to induce neuroplastic change in one direction (e.g. facilitatory) with a PAS treatment intended to weight synaptic plasticity in the opposite direction (e.g. suppressive) may deploy homeostatic synaptic mechanisms that prime the motor cortex to better respond to the second treatment, resulting in a larger and more consistent change in cortical excitability. Exploring principles of homeostatic synaptic plasticity by priming and conditioning of human motor cortex using PAS, this study aims to explore whether or not primed PAS will augment neuromodulation.

Methods: Twenty people were randomized into two groups, Group A (n=7) and Group B (n=13). Data collection is ongoing so group assignment remains blinded. Individuals in each group received four interventions in a randomized order with one-week washouts. One group received interventions to assess the effect of primed facilitatory PAS (PAS_LTP) and the other group received interventions to assess the effect of primed suppressive PAS (PAS_LTD). The four interventions applied to the PAS_LTP group are 1. Sham priming of PAS_LTP, 2. PAS_LTD priming of PAS_LTP, 3. PAS_LTP priming of PAS_LTP and 4. Sham priming of sham PAS. Interventions applied to the PAS_LTD group are 1. Sham priming of PAS_LTD, 2. PAS_LTD priming of PAS_LTD, 3. PAS_LTP priming of PAS_LTD and 4. Sham priming of sham PAS. Change in corticospinal excitability was measured using the average of 20 motor-evoked potentials recorded from abductor pollicis brevis immediately prior to intervention and at 0, 10, 20, 30, 40, 50 and 60 minutes following intervention. A repeated measures ANOVA with factors intervention and time statistically assessed data for each group.

Results: There was a significant interaction between interventions for Group B where intervention B1 is significantly different from B4 (F=3.13, df=3, p=0.0377). There were no significant interactions between interventions, participants or time for Group A.

Conclusions: Due to the preliminary nature of this analysis, sample size is unbalanced between groups. Intervention and group assignments also remain blinded. The significant difference between interventions in Group B indicates that at least two interventions applied within the same group influence corticospinal excitability in different ways. The lack of significant differences found in Group A may change as sample size increases to the predetermined goal of n=20 per group.

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Identifying Predictors of Clinical Response of Medication Refractory Depression with Comorbid Mild Traumatic Brain Injury to Deep Transcranial Magnetic Stimulation

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Background: Traumatic brain injury (TBI) is a common problem with 1.5 million new injuries in the United States each year. In the military, over 25,000 TBIs were reported in 2014 with 84% classified as mild (mTBI). Depression is present in as many as 50% of mTBI cases (Anstey et al., 2004). Unfortunately, those with mTBI that develop psychiatric complications have overall poorer outcomes (Mooney & Speed, 2001). Patients with mTBI and depression typically get management in line with their non-mTBI depressed counterparts. These interventions have varying degrees of success. In the general population, approximately 80% of people treated for depression respond to medications. In mTBI, success rates are much lower (Ashman et al., 2009) with increased side effects. Ultimately, many mTBI patients require psychostimulants to improve mood and cognitive symptoms, and many mTBI depressed patients experience severe medication refractory depression (MRD). Deep Transcranial Magnetic Stimulation (dTMS) has shown tremendous promise in MRD, but it has yet been evaluated in comorbid mTBI and depression. This study will evaluate the safety and efficacy of dTMS for MRD in mTBI and identify potential clinical predictors of response.

Methods: This study is an open-label clinical trial. It will examine the effect of dTMS on MRD in 30 patients with and 30 patients without mTBI. Stimulation will be completed through the use of a Brainsway Deep Transcranial Magnetic Stimulation Device. This device is FDA approved for use in non-psychotic medication refractory depression. The device is labeled for a full course of 20 once per day stimulation sessions (5 days per week for 4 weeks). Each session is 20 minutes in length (18Hz, 2 sec train, 20 sec inter-train, 55 trains, 1980 total pulses). The first stimulation session requires motor response mapping (MAP) and the first stimulation session of each week involves motor threshold determination (MT). Participant’s level of depression will be assessed at the beginning and end of the stimulation course using the The Montgomery-Asberg Depression Rating Scale (MADRS) as the primary measure of intervention efficacy. Follow-up assessments will be conducted at 1, 3, and 6 months post intervention to assess durability of effect.

Results: To date, two patients have received treatment. Both patients tolerated the treatments well and experienced a reduction in symptom severity from severe to mild after 20 treatments.

Conclusions: Initial results are promising with good clinical response. The study is continuing to recruit with a target of 60.

References:

Funding: Defense and Veterans Brain Injury Center
Reducing Impulsivity with Transcranial Direct Current Stimulation (tDCS) and a Cognitive Task

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Background: Impulsivity is a multidimensional construct that includes lack of premeditation, sensation-seeking, and impaired cognitive control. Impulsivity is observed clinically, and can manifest as poor decision-making and excessive risk-taking. Transcranial direct current stimulation (tDCS) applied over dorsolateral prefrontal cortex (DLPFC) has been shown to decrease risk-taking behavior. This study explores the effects of tDCS on risk-taking in participants who exhibit clinically-relevant impulsivity.

Methods: Participants complete two tDCS sessions per day for five days with additional one and two month follow-up sessions. Participants complete questionnaires and behavioral measures of impulsivity and risk-taking (e.g. Cued Reaching Task (CRT), Risk Task) pre- and post-intervention. Participants are randomly assigned to receive either active or sham tDCS during performance of the Balloon Analogue Risk Task (BART) at each of the ten sessions.

Results: Preliminary results on 16 veterans, 8 receiving active tDCS and 8 sham tDCS, suggest that active tDCS (compared to sham) can effectively reduce risk-taking propensity and impulsivity. Results showed a significant increase in 1) choosing the low risk option in the Risk Task and 2) time to move the cursor toward the target in the CRT, both indices of reduced impulsivity, from pre- to post-treatment in the active, but not sham, tDCS group.

Conclusions: This study provides preliminary evidence that tDCS may effectively reduce impulsive and risk-taking behavior in participants who exhibit clinically-relevant impulsivity, extending previous research that has only included healthy participants. Further, this study suggests that tDCS could have potential application as a non-invasive clinical intervention for patients with decreased cognitive control.

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Ultrasound Body Stimulation Activates Auditory Circuits through a Soft Tissue Pathway

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Background: Ultrasound stimulation can activate somatosensory circuits in the brain as measured via EEG [1] or perceptual studies [2]. Recently, we discovered that ultrasound can activate auditory circuits in the inferior colliculus (IC) and primary auditory cortex (A1) when stimulating different body regions. We confirmed that this auditory response was not due to external sound generated by the ultrasound transducer itself. We performed various experiments to determine the pathway of ultrasound activation of the auditory system and hypothesize that the ultrasound wave can travel through the body fluids to activate the cochlea and induce auditory activity.

Methods: A two-shank 32-site array was positioned within the right IC. A four-shank 32-site array was positioned in the right A1 and S1 of ketamine-anesthetized guinea pigs. Ultrasound stimulation (≥0.22 MHz) was presented with varying patterns on different body locations coupled with ultrasound gel. The transducer was placed on the skin surface of the leg/neck, on the side of the leg via an ultrasound gel channel, and above the leg without coupling to the leg with ultrasound gel. Ultrasound stimulation was also performed under several control conditions including, cutting the auditory nerves and breaking the ossicular chain (to rule out a bone conduction pathway [3]).

Results: Ultrasound stimulation of the skin over the leg has lower threshold for activating IC/A1 (200 kPa) than S1 (600 kPa). Ultrasound also evoked more auditory activity with shorter first spike latencies when stimulating the neck region than when stimulating the leg using the same parameters; revealing that the ultrasound induced auditory effects become delayed when stimulating farther away from the head. Breaking the gel channel attached to the body eliminated the auditory response induced by ultrasound stimulation of the gel channel. Disrupting the ossicular chain did not eliminate the ultrasound induced auditory activity but severing the auditory nerves eliminated those responses.

Conclusions: Ultrasound stimulation can activate the receptors on the skin but surprisingly it can also activate the auditory circuits. This auditory activation does not appear to occur solely through a bone conduction pathway involving the ossicular chain in the middle ears. Our findings suggest that the ultrasound energy travels through soft tissue and fluid medium (including the ultrasound gel) in the body to activate the cochlea. It is critical that researchers performing ultrasound experiments in rodents monitor this strong auditory response, which could potentially confound their neural recordings and even deafen the animals.

References:

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Exploring the Auditory Response to Ultrasound Neuromodulation

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Background: Ultrasound stimulation is being developed for use as a focused, noninvasive method of neuromodulation. Using our preliminary data as a foundation, in which ultrasound stimulation massively activates the auditory pathways with much lower intensities (<1 mW/cm²) than reported in literature for direct neural activation, we investigated whether ultrasound may be activating the auditory brain through a cochlear pathway and compared this activation to the motor responses shown in prior work.

Methods: 32-site arrays were positioned within the auditory cortex, visual cortex, or somatosensory cortex of ketamine-anesthetized guinea pigs. Ultrasound stimulation with different frequencies (0.22, 0.52, 0.90, 1.00 MHz) and pulse patterns were presented over those cortical regions, on the skull, or on an exposed nerve of the hind limb while recording from the brain. Auditory Brainstem Responses (ABRs) were also recorded in isoflurane anesthetized mice while ultrasound stimulation was applied above the motor cortex to elicit motor responses. In both animal models the auditory nerves were cut after ultrasound stimulation and several ultrasound stimulation paradigms were repeated.

Results: Ultrasound stimulation of all guinea pig cortical regions, different skull locations, and the exposed leg nerve elicited strong spike activity in the auditory cortex with intensities as low as 1-10 mW/cm². This activity was not present after cutting the auditory nerves bilaterally. Spiking activity after the auditory nerve was cut could be observed with ultrasound stimulation, but only at high intensities exceeding >50 mW/cm² that may be caused by vibration or tactile effects induced by ultrasound on the ascending somatosensory pathways. Ultrasound stimulation of the mouse motor cortex elicited ABRs stereotypical of sound stimulation. Increasing the ultrasound stimulation to levels that elicit a motor response resulted in strikingly large ABRs. Cutting the auditory nerves also eliminated the ABR activity and altered the motor response.

Conclusions: Previous studies report that ultrasound stimulation activates the brain. However, the reported intensities cause extremely strong activity in the auditory cortex in rodents. Given that severing the auditory nerves altered the motor response we could achieve in the mouse, it is possible that the perception of loud sounds induced by ultrasound may elicit startle responses and motor movements in lightly anesthetized animals. Noninvasive measurements of non-auditory regions may be partially masked or influenced by the massive auditory neural response elicited by ultrasound. Further studies are needed to assess how much of an effect the auditory response may have had on the neural and behavioral responses reported in previous studies.

References:

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Measurements and models of electric fields in the \textit{in vivo} human brain during TES

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\textbf{Background}: Transcranial electric stimulation (TES) aims to stimulate the brain by applying weak electrical currents at the scalp (Ruffini et al., 2013). However, the magnitude and spatial distribution of electric fields in the human brain are unknown. Despite increasing sophistication in the computational models for TES, none of them have been directly validated to-date. Here we aim to address this with \textit{in vivo} intracranial recordings in humans by directly measuring field intensities produced by TES at the cortical surface and deeper brain areas.

\textbf{Methods}: Electric potentials during TES were recorded intracranially from ten patients undergoing invasive monitoring for epilepsy surgery, with subdural grids, strips, and depth electrodes. These recordings were then compared to various detailed computational models, including differential conductivity between skull spongiosa and compacta, and white matter anisotropy. Models were also calibrated using the recordings to minimize the difference between measurements and model predictions. In doing so, we obtain calibrated models that conclusively answer outstanding questions about stimulation magnitudes, spatial distribution, and modeling choices.

\textbf{Results}: Conductivities reported in the literature used in existing models tend to overestimate the voltages and electric field magnitudes. After calibrating the models using recorded data, we found that the electric field intensities in the brain reach 0.4 V/m when using 2 mA transcranially. This is approximately half as strong as previous predictions using computational models (Datta et al., 2009). Peak intensities are achieved underneath the stimulation electrodes, but also in deep midline structures such as the anterior cingulate and the peri-ventricular white matter for the specific stimulation configurations tested here (Fpz-Oz). We find that individualized models provide predictions of the spatial distribution of currents with an accuracy of $r=0.89$ for cortical electrodes and $r=0.84$ for depth electrodes when pooling data across all subjects. These models capture individual anatomy for brain, CSF, skull, air cavities and skin at 1 mm$^3$ resolution.

The best fitted conductivity values vary across individuals, and the median values give significantly better prediction of the electric field distribution compared to models using literature conductivities. Including variables such as anisotropic white matter and inhomogeneous bone compartments does not improve prediction performance. But extending the FOV to include the entire head and neck significantly improves prediction accuracy.

\textbf{Conclusions}: This is the first study to validate and calibrate current-flow models with \textit{in vivo} intracranial recordings in humans, providing a solid foundation to target stimulation and interpret clinical trials.

\textbf{References}:


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Evaluation of the cortical silent period in people with spasmodic dysphonia

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Background: Adductor spasmodic dysphonia (AdSD), the primary form of laryngeal dystonia, is characterized by involuntary contractions of the thyroarytenoid muscle. Studies using transcranial magnetic stimulation have reported decreased intracortical inhibition in unaffected muscles in AdSD, such as a hand muscle and the masseter (Samargia et al. 2015). However, it is unknown if there is altered cortical excitability in the laryngeal motor cortex in AdSD. The purpose of this study was to compare the cortical excitability of the laryngeal motor cortex between healthy controls and people with AdSD.

Methods: In 16 healthy controls (age: 52.6±7.6 yr; 5 females) and 19 people with AdSD (age: 63.4±5.5 yr; 11 females), the cortical silent period (cSP) of the hand region was assessed from the right first dorsal interosseous (FDI) muscle. Among these participants, 14 controls (age: 52.6±7.6 yr; 5 females) and 12 people with AdSD (age: 63.5±5.6 yr; 8 females) also participated in laryngeal cSP assessment from bilateral thyroarytenoid (TA) muscles. cSP durations of hand and bilateral laryngeal regions were compared between groups.

Results: For the hand region assessment, the average cSP offset time was 111.2±30.3 ms in the control group and 90.4±21.8 ms in the AdSD group. For laryngeal region assessment in the control group, the average cSP offset time from left hemisphere cortical stimulation was 50.0±11.1 ms in left TA and 48.9±9.9 ms in right TA; average cSP offset time from right hemisphere cortical stimulation was 49.2±11.3 ms in left TA and 49.3±10.7 ms in right TA. In the AdSD group, the average cSP offset time from left hemisphere cortical stimulation was 41.4±9.2 ms in left TA and 39.8±9.6 ms in right TA; average cSP offset time from right hemisphere cortical stimulation was 38.6±7.1 ms in left TA and 40.7±5.8 ms in right TA. T-test showed significantly different cSP duration in hand region between groups (p=0.0364). In laryngeal regions, significant differences in cSP duration were observed in left (p=0.0145) and right (p=0.0231) TA muscles from right hemisphere stimulation and right (p=0.0370) TA from left hemisphere stimulation. A trend of difference was observed in left (p=0.0548) TA from left hemisphere stimulation.

Conclusions: The results indicate significantly shorter cSPs in the AdSD group both for the hand and laryngeal regions, consistent with previously reported results tested in hand and masseter muscles (Samargia et al. 2015). Furthermore, the findings suggest that excitability of the laryngeal motor cortex is different between healthy controls and people with AdSD.

Reference:

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Towards closed-loop tES: a comparison of methods for real time tACS-EEG artifact removal

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Background:

Electroencephalogram (EEG) measures electrical activity reflecting temporal changes in the electrical state of neurons and represents the current flow, which is directly modulated when applying transcranial Alternating Current Stimulation (tACS), making these techniques complement one-another for closed-loop transcranial Electric Stimulation (tES). To date most studies investigating EEG and tACS have been limited to comparing EEG before/after stimulation. Although methods are now available for tACS-artefact removal, to develop closed-loop stimulation protocols these algorithms need to be implemented in real-time. We present here a comparison of performance of existing methods of tACS artifact removal and their suitability for development for closed-loop stimulation.

Methods:

5, 10 and 40 Hz tACS was stimulated, using the Neuroconn DC stimulator Plus, at 250 µA and 500 µA on an Fp2-P3 montage for 1 minute at a time during which the subject was asked to perform an Alpha Task (eyes open and close) or a Face/Non-Face visual task. EEG was recorded using 2 different devices (Enobio, Neuroelectrics and NeuroPrax, Neuroconn) at the P4 with the reference and ground electrodes placed at the Cz. tACS artifact was removed from the recorded EEG data using 3 different methods:

- NeuroPrax, built in tACS artifact removal algorithm
- Superposition using Moving Averages (SMA) [1]
- Adaptive Filter (AF)

Results:

Our results provide an overview of the artifact removal process. Successful reconstruction of EEG data after artifact removal was demonstrated using all 3 methods. Both alpha activity (from alpha test) and N170 ERPs (Face/Non-Face task) were successfully identified after artifact removal.

With regards to compatibility with closed-loop stimulation, SMA was found to have the longest convergence time before valid EEG data is presented. Even though the NeuroPrax has almost no convergence time, it is not suitable for closed-loop stimulation as it requires training prior to recording. This does not suit an experimental design where ongoing EEG activity is used to modulate stimulation parameters. All three methods present an artifact at the end of stimulation.

Conclusions:

Here we compare the performance of all existing methods for real-time tACS artifact removal and find that both SMA and AF are suitable for development of closed-loop stimulation protocols. SMA has higher convergence but AF requires the ’signal output’ from the stimulator which not all existing products offer. Monitoring neural activity during stimulation is a key step towards development of closed-loop stimulation protocols that can allow for systems capable of customized tES therapy.

References:


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Laryngeal vibration as a non-invasive neuromodulation method to improve speech in the voice disorder spasmodic dysphonia

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Background: Spasmodic dysphonia (SD) is a rare voice disorder that develops spontaneously during midlife. Patients with SD typically have a strained or choked speech and report that it takes an exhausting effort to speak. SD does not respond to behavioral speech therapy. It is treated primarily with Botulinum toxin injections, which provides temporary symptom relief to some, but is not well tolerated by all SD patients. At present, there is no cure for SD. We recently confirmed [1] that SD, like other forms of focal dystonia, is associated with proprioceptive dysfunction. This finding opens an avenue for a possible behavioral treatment for SD. Specifically, we suggest that vibrotactile stimulation (VTS) is the suitable tool, given that it is known to alter afferent signals from the vibrated mechanoreceptors in muscles and skin. This study seeks to show that laryngeal VTS represents a non-invasive form of neuromodulation that induces measurable improvements in the speech of SD patients.

Methods: We recorded the acoustic signals during vocalization with and without bilateral laryngeal vibration to determine its effect on voice production in SD patients and healthy controls. In addition, we measured the EEG responses to understand the cortical responses to laryngeal VTS. The SD patients were seen at the end of their Botox cycle when they were symptomatic. Participants received 2 sets of 17 minutes of VTS.

Results: We found that VTS induced a marked desynchronization in somatosensory (Area 1,2,3) and motor cortical areas (Area 4,6). Suppression was most pronounced and consistent in alpha (7-14Hz) and mu (8-13Hz) bands, and more variable across SD participants in the beta (15-30Hz) band (see Fig. 1). Voice analysis showed reduced number of voice breaks and a +3db increase in cepstral peak prominence (CPP). An increase of around 3 dB in CPP is associated with a significant improvement of voice quality in SD [2].

Conclusions: A single, prolonged, 30+ minute application of laryngeal VTS can lead to measurable positive changes in the voice quality of SD patients. These changes in voice and speech coincide with measurable changes in the activity of engaged sensorimotor cortical areas that are expressed as an increase in cortical desynchronization. This motor cortical desynchronization is consistent with research on cervical dystonia showing that effective sensory tricks are associated with pallidal and motor cortical desynchronization at low frequencies (6-8Hz) [3].

References:

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Depicting transcranial magnetic stimulation from a neuronal perspective

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Background: Despite its rapidly expanding application and fast-rising popularity, transcranial magnetic stimulation (TMS) is poorly understood physiologically. The lack of knowledge on TMS physiology, together with the absence of an experimental platform on which various human TMS applications can be studied, developed and refined in vivo at the neuronal level, block the exciting scientific and therapeutic potential of this non-invasive brain stimulation tool.

Methods: We developed a novel experimental method that offers the direct in vivo electrophysiological access to TMS-evoked neuronal activities in the brain. The method, compatible with standard TMS stimulators and coils, attenuates a variety of TMS-induced artifacts in extracellular electrophysiology recordings and allows the recording to resume 0.8 – 1 ms after a variety of Tesla-level strong single or repetitive TMS stimulus. Furthermore, using rodents, a common laboratory animal model, we successfully replicated single-pulse TMS as is routinely used in humans and unveiled TMS-evoked neurons spiking activities in the layer II/III and V of the rodent primary motor cortex.

Results: The suprathreshold monophasic TMS stimulus reliably evoked unilateral activation of the forelimb muscles, evidenced by muscle unit action potentials recorded in the m. biceps brachii (onset latency 11 ms post-TMS). On the neuronal level, the cortical evoked multi-unit activity displayed 5 distinct phases: early excitation (< 6 ms), second excitation (8-26 ms), inhibition (33-172 ms) and rebound excitation (199-238 ms), all of which reveal striking relations to various well-known phenomena in human TMS ranging from intracortical facilitation to late cortical disinhibition.

Conclusions: The data obtained with our method depicted, for the first time, the neuronal response pattern of the classical single-pulse TMS that is widely used in research and clinical works. By bridging the gap between neurons and behaviors, the advance presented here facilitates a new level of insight into the TMS-brain interaction and is vital for developing and utilizing this non-invasive tool to purposefully explore and effectively treat the human brain.

References: N/A

Funding: N/A
How Can Neuromodulation be Tailored to Induce Lasting Behavioral Improvements?: Visual Perceptual Learning in V4

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Background:
Learning a new ability is fundamental to survival and requires a change in the representations present in cerebral cortex. How we might induce the brain to learn, or change in a lasting, favorable way in the cases of dysfunction, is still poorly understood. We need to understand where and how neurons change in their ability to encode stimuli during learning, and how introduced manipulations can control this phenomenon. Visual perceptual training is a useful paradigm, as neurons within the visual system can be quantitatively characterized and learning observed in relation to behavior. V4 is an intermediate visual area with quantifiable receptive fields that integrates low-level visual inputs, and contains neurons sensitive to specific curvatures and shapes, which are the basis for perceiving objects. However, whether learning to detect, and correctly identify, shapes is caused by V4 is unknown. Simple shape learning could be mediated by V4 shape tuned neurons, or may require changes in higher-level object tuned areas. This distinction may affect the efficacy of neuromodulation. However, based on preliminary data, we hypothesize that V4 neurons reflect both the visual stimulus and behavioral choice in a shape detection task, and are sufficient for associated performance improvements.

Methods
We recorded in V4 from a 96-electrode array, while two non-human primates learned a shape detection task1,2. Behavioral reliability (performance) improved during training for both animals, indicating learning. LFP information was computed in varying windows of time, at varying delays since sensory (stimulus appearance) or behavioral choice event. Microstimulation was also paired with visual stimuli.

Results
Specific, small numbers of electrodes do predict behavioral timing and reliability. This suggests that V4 plays a critical role in shape detection and that performance improvements can be explained by changes within local populations. Neuromodulation also induced lasting performance changes, but the sign of the change depends upon small variations in the spatial and temporal distribution of microstimulation.

Conclusions
Preliminary work suggests that V4 is critical to both stimulus detection and decision making during shape learning. We plan to expand on this with two more animals, by comparing shapes with varying training and stimulation histories. We will use fMRI, electrophysiology, and stimulation to determine if V4 is sufficient for shape learning, and how behavioral and stimulation induced changes occur at varying temporal and spatial scales. This will improve our understanding of how neurons change to encode relevant information over time and how neuromodulation can be used to induce lasting changes.

References

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Changes in cortical excitability following a combined transcranial direct current stimulation and rehabilitation intervention in children with unilateral cerebral palsy

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Background: Neuromodulatory interventions such as transcranial direct current stimulation (tDCS) have the potential to improve motor function in adults with stroke and in children with unilateral cerebral palsy (UCP). While neurophysiological changes in the motor cortex following tDCS interventions in adults are well documented1, they are less known in children, resulting in a lack of evidence supporting potential neural mechanisms underlying behavioral changes following tDCS. To address this need, we analyzed changes in cortical excitability in children receiving an active or sham tDCS paired with constraint-induced movement therapy (CIMT), and compared neurophysiologic changes to behavioral changes following the intervention. In addition, we compared outcomes based upon corticospinal tract (CST) organization pattern, a potentially important predictor of response to behavioral and neuromodulatory therapies2.

Methods: Children with UCP were randomized to receive an intervention of tDCS (0.7 mA cathodal M1-SO montage applied to the non-lesioned hemisphere for 20 min) within a 2-hour CIMT session (n =10) or sham tDCS and CIMT (n = 10) as a control3 (clinicaltrials.gov NCT#02250092). Hand function (Assisting Hand Assessment-AHA) was assessed before and after the intervention. Cortical excitability was assessed using single pulse transcranial magnetic stimulation (TMS) of each hemisphere. Cortical excitability measures included resting motor threshold (RMT) and motor evoked potential (MEP) amplitude and latency. CST organization was determined by presence or absence of MEP when stimulating the lesioned hemisphere (contralateral-MEP present; ipsilateral-MEP absent).

Results: In the non-lesioned hemisphere of the intervention group, the RMT increased (active = 2.6±3.5%; sham = -0.17±1.6%) and MEP amplitude decreased (Figure; active = -320±311 µV; sham = 697±693µV), indicating an inhibitory effect of the intervention. No differences in cortical excitability of the non-lesioned hemisphere were noted between children with contralateral or ipsilateral organization. Improvements in hand function were significantly greater in children with contralateral compared to those with ipsilateral organization (F(1,1) = 7.79, p = 0.01). No significant differences in hand function were noted between intervention and control groups (F(1,1) = 1.83, p = 0.20).

Conclusions: Children in the active tDCS had decreased excitability in the non-lesioned hemisphere. CST organization was related to changes in hand function but not cortical excitability. Overall, these data suggest that corticospinal tract organization and tDCS dosing should be explored in future tDCS studies with focus on individualized treatment.

References:

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An Investigation into the Cellular Mechanisms Underlying Ultrasonic Neuromodulation.

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Background: Ultrasound is a promising noninvasive neuromodulation technology with the potential to confer the high spatial resolution of invasive techniques currently utilized to treat a wide range of neurological disorders, including epilepsy and Parkinson’s disease. Although researchers have known for several decades that ultrasound (US) is capable of effecting changes in neural firing rates, in a variety of animal preparations, the underlying cellular mechanisms accounting for such changes have remained elusive.

Methods: To gain a greater understanding of the relative effects of US, we utilized simultaneous ultrasonic stimulation and single-unit electrophysiological recordings in a well-studied invertebrate model, the medicinal leech Hirudo verbana. This preparation provides an especially accessible physiological system in which identified neurons can be studied at the level of their membrane biophysical properties, circuit connections and behavioral roles. One well-studied motoneuron involved in locomotion, the Dorsal Lateral Excitor (DE-3), has one of the largest axons in its nerve root, and thus can be unambiguously detected via extracellular recording.

Results: Using US at a frequency of 960 kHz, we were able to increase or inhibit the firing rate of DE-3 repeatedly and reversibly. Intriguingly, US also induced bursting in the presence of dopamine, a phenomenon that may have resulted from the activation of hyperpolarization-activated ion channels.

Conclusions: We propose that the effects of US that we have repeatedly observed result from US-induced mechanical tension on membrane-bound ion channels resulting in an altered conductance state. Moving forward, we aim to introduce pharmacological agents to determine better the precise channels affected by US stimulation. By gaining a greater understanding of the mechanisms by which US enacts changes in neural activity, we hope to increase its therapeutic potential as a replacement for invasive forms of neuromodulation, including deep brain stimulation.

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A. Focused ultrasound reversibly and repeatedly modulates firing of a motoneuron in the medicinal leech. Multiple trials of sonications (960kHz, 1MPa, pulsed) of same nerve 30 seconds apart; largest unit is identified motoneuron DE-3. Other experiments on same identified neuron produced stimulation (not pictured).

B. Intracellular somatic recording of leech motoneuron during axonal sonication. Modest thickening of baseline is sonication artifact.
Exploring measures of gait variability following neuromodulation: A feasibility study in people with stroke.

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Background: Novel paired associative stimulation (NOVEL-PAS), delivered by pairing movement-related cortical potentials (MRCP’s) with electrical stimulation of somatosensory afferents, is an innovative neuromodulatory intervention. Application of NOVEL-PAS following stroke results in increased corticomotor excitability and improved walking speed, revealing its potential to aid recovery¹. This study investigated the feasibility of delivering 4 weeks of NOVEL-PAS, compared with a CONTROL intervention, in people with stroke. One aim was to explore different outcome measures, including measures of gait variability, which are known to be increased post stroke and are considered to be related to reduced neuromuscular control²,³.

Methods: Four participants with chronic stroke, were randomly allocated to receive NOVEL-PAS (n=2), or a CONTROL intervention (n=2), three times weekly, for four weeks. At the first session each week, participants completed a visually-cued dorsiflexion task with their hemiparetic ankle. Electroencephalography recordings were analyzed to identify the peak negativity of the MRCP. All participants then completed the intervention (Figure 1), performing 50 visually-cued ankle dorsiflexions while the computer delivered either, i) electrical stimulation (NOVEL-PAS), or ii) sham electrical stimulation (CONTROL), to the deep peroneal nerve. The electrical stimulation was timed to coincide with the peak negativity. The intervention was repeated at two further sessions each week.

Results: Interesting changes in gait variability were seen. Post-intervention, the two NOVEL-PAS participants had decreased gait variability (measured by the standard deviation from individual walking trials) in both the ankle dorsiflexion/plantarflexion range during the swing phase, and hemiparetic limb swing time. In contrast, CONTROL participants showed increased variability in these measures. Exploration of the EMG data post-intervention showed one NOVEL-PAS participant had decreased variability in the TA EMG linear envelope (Variation Ratio 0.79 to 0.59), indicating a trend towards a healthy range of variation (0.18-0.38). The other NOVEL-PAS participant had slightly increased variability post-intervention (Variation Ratio 0.18 to 0.30); however, this was accompanied by distinct improvements in the burst characteristics when analyzed visually.

Conclusions: The results from this feasibility study suggest that gait variability measures may change with the NOVEL-PAS intervention, resulting in a more consistent gait pattern. It is therefore important to measure gait variability as an outcome in further studies. This may help to further the understanding of the effects of neuromodulatory interventions on neuromuscular control.

References:

Funding: Neurological Foundation of New Zealand, Physiotherapy New Zealand.
Transcranial Magnetic Stimulation: Quadruple Butterfly Coil with Improved Focality

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Background Transcranial Magnetic Stimulation (TMS) is a non-invasive technique for neuromodulation that can be used for various neurological disorders such as major depressive disorder, traumatic brain injury (TBI), Parkinson’s disease (PD), and post-traumatic stress disorder (PTSD). TMS coil geometry has an important role in determining the region of brain stimulation. Clinicians and basic scientists are enticed in the merits of interest such as focality and maximum electric field, which are responsible for the stimulation.

Methods: In this paper, authors have proposed a novel coil, namely Quadruple Butterfly Coil (QBC) and have further improved the focality of the QBC in a new design by using a high permeability magnetic material [1]. QBC coil configuration stimulates smaller regions of the brain as compared to Figure-8 coil with comparable maximum electric field values. The ferromagnetic material (shield) used for this simulation is Mu-metal which is positioned in between the head model and the QBC coil. Computer modelling has been done using a finite element tool, Sim4life with the help of 50 anatomically realistic MRI derived head models [2-3]. These head models are derived from the healthy individuals with equal number of male and female, in the age range of 22-35 years.

Results: The results have two parts, where in the first part, Figure-8 coil and QBC coil configuration has been placed on the vertex and dorsolateral prefrontal cortex position of all the 50 head models. In the second part, QBC along with the shield has been simulated for all the head models over both of the positions. Parameters such as volume of stimulation, maximum electric field, location of maximum electric field and area of stimulation across all 50 head models have been calculated for both results.

Conclusions: The first part of the result illustrates that volume of stimulation (V-half) was 2.67 cm³ and 3 cm³ for QBC and Figure-8 respectively for all the 50 head models at dorsolateral Prefrontal cortex position, where the electric field was 156 V/m and 230 V/m in the brain. The second part of the results has shown that the maximum electric field in grey matter is relatively unaffected by the shield (130 V/m without and 115 V/m with shielding); however, the volume of stimulation (volume of grey and matter which is above the half of maximum electric field in these regions) has reduced significantly as desired (4.508 cm³ without and 3.020 cm³ with shielding).

References:
[2] Data collection and sharing for this project was provided by the MGH-USC Human Connectome Project. HCP funding was provided by the NIDCR, NIMH, and NINDS.

Fig1. Induced electric field on the grey matter and scalp due to (a) Figure-8 coil on the vertex (b) Quadruple Butterfly Coil on vertex (c) Figure-8 coil on dorsolateral prefrontal cortex (d) Quadruple Butterfly Coil on dorsolateral prefrontal cortex.
Retinal origins of phosphenes induced by occipito-parietal transcranial alternating current stimulation

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Background:
Transcranial alternating current stimulation (tACS) has rapidly gained interest in the visual neuroscience community given that it is able to induce consistent and robust perceptual flickering in the form of phosphenes. Early studies suggested that these phosphenes were due to direct cortical activation in early visual areas as a result of tACS. However, others have pointed to the potential retinal origins of visual phosphenes induced by tACS, particularly during stimulation of prefrontal areas. The goal of this study was to integrate simultaneous EEG/EOG with tACS to delineate current spread associated with standard Oz/Cz tACS.

Methods:
We assessed EEG and EOG activity during the application of tACS at and below phosphene threshold in a group of 18 healthy human subjects. Each subject took part in two experimental sessions that were separated by at least 72 hours. For each experimental session, phosphene thresholds were found using 12 Hz tACS given the lower thresholds associated with alpha-band phosphenes. Sub-phosphene tACS was applied at either 6.66 or 7.5 Hz. 40 seconds of phosphene EEG/EOG data were collected in each session for offline analysis.

Results:
Sub-phosphene threshold tACS targeting Oz/Cz induced an average absolute potential of 2.745 mV in the vEOG channel (SE = 0.611 mV) and an average absolute potential of 2.124 mV in the hEOG channel (SE = 0.595 mV), across 36 experimental sessions for which phosphene data was obtained. For the same set of 36 sessions, the average vEOG potential was 7.993 mV (SE = 0.516 mV) and the average hEOG potential was 7.253 mV (SE = 0.496 mV) during the perception of phosphenes.

Conclusions:
We found widespread shunting of tACS-related current during occipito-parietal tACS, both at and below phosphene threshold. These results suggest that tACS over posterior regions of the cortex can significantly modulate electrical activity at the retinal level, providing evidence for the retinal origins of phosphenes induced by occipito-parietal tACS. Our findings reiterate the challenges of utilizing tACS for studying the visual system and have significant implications for future neuromodulation-based studies of visual perception.

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Montage optimization in targeting the left primary motor cortex and its associated connectivity network

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Background: The traditional montage to target the primary motor cortex in transcranial current stimulation (tCS) employs two electrodes: one over the motor cortex (MC) and one other over the contralateral supra-orbital region. Using resting state functional connectivity MRI it is possible to determine other regions that interact with the MC through networks [1]. Montages to target this network can be obtained using algorithms like the one described in [2]. Here we use finite element (FE) models to compare the electric field (E-field) obtained with a montage optimized (OM) to target the left MC and its associated network, with the traditional bipolar montage (TM) targeting only the left MC.

Methods: The algorithm for montage optimization, [2], outputs the montage that maximizes the component of the E-field normal to the cortical surface ($nF$), in the regions where the t-score of the functional connectivity map is higher. The algorithm provided the following positions and currents for the OM: C1: 872 µA, C2: 888 µA, C3: 1135 µA, C4: 922 µA, Fz: -1843 µA, P3: -1121 µA, P4: -1036 µA and T8: 183 µA. The currents in the TM were set to +/- 2000 µA, for C3/Fp2. Individual FE head models were created from T1 MRIs of 4 of the subjects that participated in this study. The images were segmented into five different tissues (scalp, skull, CSF, GM and WM) using freeware tools available online. Electrodes were modelled as cylinders of conductive gel (radius of 1 cm and a thickness of 3 mm). The generated FE meshes were imported into Comsol (www.comsol.com), where the E-field calculations were performed. The tissues present in the FE model were given conductivity values appropriate to the low frequency range in tCS [3].

Results: For all subjects, the $nF$ distribution is similar within each montage. The field is higher (in absolute value) at the gyri beneath the two electrodes in the TM. In the OM, the distribution is more symmetric, targeting better the distributed motor network. Therefore, the average $nF$ field at a patch of surface on the left MC is higher in the TM (0.14 ± 0.08 V/m average value across subjects) than in the OM (0.08 ± 0.05 V/m).

Conclusions: The observed results were consistent across subjects and independent of individual differences in anatomy. As such, these montages should allow one to investigate group-level differences in tCS induced effects of targeting left M1 versus the distributed motor network.

References:

Funding:
Effect of Transcranial Magnetic Stimulation on Demyelinated Neuron Populations

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Background: Transcranial Magnetic Stimulation (TMS) is a popular means of neuromodulation due to its non-invasive properties and benign side effects, but its effects on neuron activity are not very well-known. In the recent past, studies have shown its effects on brain tissue, but the stimulation of the actual neurons has not been considered.¹ We posit that a deeper understanding of the effects of TMS on neuron populations would be of significant benefit to clinical neuromodulation. In this study we utilize a newly-created model of demyelinated neuron populations. Demyelination of neurons can cause various serious neurological conditions, including Multiple Sclerosis (MS), Guillain-Barré Syndrome (GBS), and possibly depression.² We model populations of healthy neurons as well as those that have undergone varying levels of demyelination, and show the effects of stimulation on each population.

Methods: We use the python-based software package called NEST to model populations of 1000 neurons. To model demyelination, we use steadily increasing values of capacitance (250 to 270 pF), and a Poisson signal generator for normal neuron firing. We also use an AC signal generator to stimulate the neurons. We then calculate the corresponding E-field necessary for each current value using the following values: axon diameter 1 μm, axon length 10 mm, specific membrane capacitance 10 kΩ.³ Next, we use the FEM software package Sim4Life to simulate TMS on a heterogeneous head model and find the nominal E-field induced on the surface of the white matter (the targeted region for MS treatment) under clinical conditions.

Results: We find that relatively low fields are required to stimulate even the most demyelinated neurons to the same synaptic activity as healthy populations. Figure 1 shows the number of impulses recorded in 1 second for all neuron populations. Note that the most demyelinated population (270 pF) is able to reach the same synaptic activity as that of the healthy, unstimulated population (250 pF, 0 pA) with a stimulation of 6000 pA. Using the above-mentioned axon values, this current corresponds to an induced E-field of about 19 V/m. As our Sim4Life model shows, this is far below the E-field induced on the white matter surface during clinical TMS (~79 V/m).

Conclusions: Our calculations reveal that highly demyelinated neurons on the white matter surface can be stimulated successfully using Transcranial Magnetic Stimulation. This model can be further used to study larger and more complex neuron populations, which would be highly beneficial for neuromodulation research.

References:

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Towards Enhancement of Movement Related Cortical Potential via Pavlovian Conditioning Training Paired with Sensory Stimulation

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Background: Movement related cortical potential (MRCP) based Brain-computer Interface (BCI) constitutes an ultra-fast and robust non-invasive brain switch, which detects the user’s intention within few hundred milliseconds and transfers the detected intention into commands to a device [1]. The performance of the BCI system is largely determined by the MRCP waveform induced by the motor imagery (MI) task. Here, we propose a sensory stimulation training method to further improve the MI induced MRCP waveform [2]. By pairing the MI with sensory stimulation, we introduce Pavlovian Conditioning training as a new approach to enhance MRCP signals. This will be a new neuromodulation method to interact with MRCP with the aim to improve BCI detection performance.

Methods: Subjects performed five runs of MI foot dorsiflexion task, with twenty trials in each run. During the first run, no vibration stimulation was applied, and subjects performed MI foot dorsiflexion when a circle moves to the center of the screen. During the second run, when the circle arrives at the center, a vibration stimulus was applied to the skin above the tibialis anterior muscle. During the third and fourth runs, only half of the trials were paired with the stimulus and the other half were not (the delivery of the stimulus were randomized). During the fifth run, there was no stimulus. The structure of each trial was as such: a fixation cross appeared at the centre of the screen; after 2 seconds, a red circle appeared on the left side of the cross, cueing the subject to prepare for the subsequent MI task; over the next 3 seconds, the red circle moved toward the center of the cross; when the circle arrived at the center, it stopped and its color turned green, cueing the subject to perform the MI foot dorsiflexion task immediately. The green circle and the cross was displayed for 2 more seconds and then disappeared. Subjects rested for 2 seconds followed by a 0~2 seconds randomized time interval before the next trial begins. Subjects rested for about 2 minutes between each run.

Results: The signals were filtered between 0.05~3 Hz frequency band using 2nd order Butterworth filter. EEG signal at Cz channel was extracted and averaged across twenty trials. The average MRCP from different runs are shown in Fig. 1. When the MI was paired with sensory stimulation (MI-StimPaired), the corresponding MRCP is larger than that of the first run (MI without stimulation). In the paired Pavlovian Conditioning training, it can be seen that the MI without stimulation during the 3rd and 4th runs resulted in a stronger MRCP compared to the first run. Moreover, in the fifth run, where there was no sensory stimulation, the enhanced MRCP effect from the paired training in the 2nd to 4th runs persisted and the MRCP was stronger compared to that in the first run.

Conclusions: In this pilot study, we proposed a novel method to enhance the MRCP with respect to MI of foot dorsiflexion. Through the 20 minute paired sensory stimulation training, the signal to noise ratio was significantly improved and it will contribute to improve BCI performance.

References:


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Noninvasive Mapping of Brain Activations by Transcranial Focused Ultrasound Targeting in Rodents

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Background: Low-intensity transcranial focused ultrasound (tFUS) has emerged as a noninvasive neuromodulation technique with controllable spatial selectivity [1]. We have demonstrated, in an in vivo rat model, low-intensity tFUS (I_spta < 1 mW/cm², I_poa < 10 mW/cm²) can induce brain responses, and such responses can be monitored using local scalp EEG with outstanding spatial (mm) and temporal (ms) resolutions [2]. However, it is difficult to characterize global brain responses induced by various parameters of tFUS. To address this, we report our pilot experimental study to noninvasively localize brain dynamics after administering different intensities of ultrasound at two different cortical regions.

Methods: A single-element focused ultrasound transducer was used to generate pulsed tFUS with two sonication sequences [2, 3] at the somatosensory or motor cortical regions in an in vivo rat model (N = 4) under ketamine-xylazine anesthesia (I_spta = 0.6, 64 mW/cm², I_poa = 4.2, 228 mW/cm²). A customized 24-channel scalp EEG system was used to measure the tFUS-induced brain activation across the entire rat brain. Current source distributions were estimated using electrophysiological source imaging (ESI) to map spatiotemporal distributions of tFUS-induced brain responses. Meanwhile, sham ultrasound conditions were also introduced for EEG comparisons. 3D printed ultrasound collimators were designed to increase guidance and focus of tFUS to the rat brain. To verify focality of tFUS administered to the animals, ultrasound pressure maps, behind the excised rat skull, were produced using 3D hydrophone scans.

Results: ESI revealed initial focal activations at the tFUS stimulation sites, but along the time, such initial activation propagated to the surrounding cortical areas. When the tFUS stimulation is applied at the different targeted cortical regions, different brain responses can be observed at the respective target sites, demonstrating the specificity of such activations. By comparing brain responses at different tFUS intensities, we found that pulsed tFUS with increased intensity can not only evoke initial brain responses at the targeted stimulation sites, but also activate auxiliary responses, such as those from auditory cortex, in the anesthetized rodent model.

Conclusions: Our results demonstrate the feasibility of noninvasively imaging spatiotemporal distributions of brain activations induced by tFUS in vivo. In addition to the focal activation at the targeted brain area, the global view of the brain responses also enables us to observe different brain activation patterns for the tFUS administered at different stimulation sites and different ultrasound parameters.

References:

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Noninvasive Neuromodulation of the Immune System

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Background: Since its discovery in 2000, the cholinergic anti-inflammatory pathway has been a unique tool to modulate the mammalian immune response. Electrical vagus nerve stimulation (VNS) triggers an inflammatory reflex that dampens the inflammatory response to infection or tissue injury and has been shown to reduce in vivo cytokine production in animals during endotoxemia. Recently, it was discovered that ultrasound energy delivered noninvasively to the spleen of mice diminished inflammation and tissue damage during renal ischemic reperfusion injury (IRI). The authors claim that ultrasound initiates the same cholinergic anti-inflammatory pathway triggered by VNS, but how this pathway is activated remains unclear. Therefore we have spearheaded a multi-faceted investigation to determine how ultrasound stimulation can modulate this cholinergic anti-inflammatory pathway, how the neural activity of the system is altered, and whether or not this treatment can be translated to other diseases.

Methods: For the initial phase of the study we used a mouse model of arthritis to determine if ultrasound-treatment would have any effects on disease severity or cytokine production. The K/BxN transgenic mouse line which is maintained in Dr. Bryce Binstadt’s lab allows consistent transfer of arthritis when serum from host K/BxN animals is injected I.P. into recipient wildtype BL-6 mice. Recipient animals were treated noninvasively with spleen-targeted ultrasound for eight days and serum was collected from a terminal blood draw on day 9 of the experiment, at which point the serum level of cytokines were analyzed. Animals were monitored daily for the extent of arthritis development over the 7 days post injection, including ankle swelling thickness, clinical severity scoring and weight loss.

Results: Preliminary data indicates that disease severity can be noninvasively modulated with splenic ultrasound treatment. In the ultrasound-treated group, average ankle thickness and clinical severity scores were reduced by 43.4% and 28.9%, respectively, from their non-treated cohorts. Serum cytokine analysis has been inconclusive so far. Further work will determine what role cytokines play in the reduction of disease severity through ultrasound treatment.

Conclusions: We have found that noninvasive ultrasound stimulation can alter arthritis severity in a mouse model of the disease and are currently investigating the mechanism by which ultrasound might be modulating the neural-immune interaction in the spleen. This technique could prove to be invaluable to the field of neuromodulation, providing a new means of treating a wide range of immune syndromes.

References:

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Neural plasticity and enhancement of second language learning via adaptive audiovisual speech training

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Background: Adult second language (L2) learners typically encounter tremendous difficulty in perceiving and producing L2 sounds accurately. Neither extended years of naturalistic exposure after immigration nor intensive training with natural or synthetic stimuli targeting the critical acoustic features of the L2 sounds can ensure native-like phonetic mastery. Despite mounting evidence of neurocognitive advantages associated with bilingualism, much remains to be investigated about the scientific theories and development of training methods for optimizing adult L2 learning against the brain mechanism known as Native Language Neural Commitment that constrains and interferes with L2 learning.

Methods: An integrative speech training software program was developed after Zhang et al. (2009) for the current study. The program integrated four levels of spectro-temporal exaggerations of minimal-pair words containing the target sounds, multi-talker variability, audio-visual presentation and adaptive listening in seven sessions (each lasting about 15 minutes). The target sounds were /i/ and /I/ in English, a non-phonemic contrast in Mandarin Chinese. The participants were 20 normal-hearing adult Chinese English-as-a-second-language (ESL) learners who had received at least eight years of ESL education. They were randomly assigned to a training group and a control group. Identical pre- and post-tests were administered one week before and after training. Behavioral measures included discrimination and identification tasks and acoustic analysis of target vowel production. Event Related Potential (ERP) measures were also collected to examine training-induced changes in the mismatch negativity (MMN) responses.

Results: For the training group, the behavioral results showed significant improvement in identification and discrimination scores and a clear shift towards categorical perception of the /i-I/ sound continuum. These behavioral changes were also reflected in the MMN responses as well as in the trial-by-trial neural oscillatory activities for detecting the across- vs. within-category differences at the pre-attentive level. There was also strong evidence for transfer of learning from trained to untrained stimuli as well as from perception to production. By contrast, the control group did not show significant changes in any of the brain or behavioral measures.

Conclusions: The results not only confirm the existence of substantial neural plasticity for speech learning in adulthood but also provide further testimony for the efficacy of the adaptive audiovisual training method for promoting second language phonetic learning within a short period of time, which have important implications for developing cost-effective computer-aided instructional programs for optimizing L2 education.

References:


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NEUROTECHNOLOGIES AND OTHER APPROACHES
Hemodynamic Cortical Response to Pain Stimuli: An fNIRS Study

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**Background:** The definition of pain is a series of processes of sensitization and emotional reaction of an unpleasant sensation to external stimuli or damage. External damage or unpleasant stimulation can be quantitatively applied, however it is difficult to quantitatively measure unpleasant sensory and emotional responses. Pain modulation is to control its intensity to reduce intrinsic pain when unpleasant sensation occurs, and the degree of its function varies from person to person. Therefore, it is difficult to quantitatively measure the degree of pain in the external stimulus. Measuring the response of the cerebrum that sensitizes the pain, rather than the intensity of external stimulation, is considered to be a method to quantitatively measure the pain actually felt by a person.

**Methods:** Functional near infrared spectroscopy (fNIRS) was used to observe pain characteristics in terms of cerebral hemodynamics and to explore the pathways of pain in the cerebral cortex. One healthy volunteer with no history of neurological, physical, or psychiatric illness underwent this study. Cold pressor test (CPT) was performed on the subject for measuring his pain pathway while recording fNIRS [1]. Experiment consisted of a baseline of 30 seconds followed by the immersion of the right hand up to wrist into cold water container at temperature (~4 ºC) for 45 seconds, then 2 min post-rest hand immersion in tepid water at temperature (~25 ºC) for the hemodynamic recovery. NIRS-statistical parametric mapping (NIRS-SPM) built the map of cortical activities with the level of significance at a $p$-value of < 5%.

**Results:** The result showed that a statistically significant increase in $\Delta$oxy levels was mainly observed in the regions corresponding to primary somatosensory cortices (S1), supplementary motor area (SMA), and premotor cortex (PMC). Hemodynamic response disclosed that the pain modulation adjusts to adapt to repetitive pain stimuli.

**Conclusions:** Our results is consistent with other fMRI results for cold-evoked pain sensations [2]. They support the notion that fNIRS is more suitable for pain research because it has less time and space limit than conventional pain analysis using fMRI or PET [3]. Therefore, it is necessary to identify the pain mechanism by analyzing the hemodynamic characteristics of individual signal units beyond the existing functional imaging method, and it is thought that this approach can be a useful tool for the objective diagnosis and the quantitative evaluation of the pain.

![fNIRS cortical activation](image1.png)

![Hemodynamic response](image2.png)

Figure 1. fNIRS cortical activation $t$-map and hemodynamic response for cold-evoked pain stimuli

**References:**

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Renal denervation lowers mean arterial pressure in obese female Schlager mice but adversely affects glucose metabolism.

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Clinical studies have shown that, in addition to lowering arterial pressure (AP), renal denervation (RDNx) improves glucose metabolism in drug-resistant hypertensive obese patients. One-fourth of these patients were females. We have observed a similar arterial pressure response in preliminary studies in obese genetically hypertensive male Schlager mice (BPH/2J). Although sex differences may exist regarding RDNx therapy, the effect of RDNx on AP and glucose metabolism in females specifically has not previously been studied. We hypothesized that, similar to males, RDNx will decrease AP and improve glucose metabolism in high fat fed female Schlager mice. 8-week old mice were fed either a low fat diet (LFD; 10 KCal % from fat) or high fat diet (HFD; 45 KCal% from fat) for 10 weeks. Fasting blood glucose were measured on week 11 of the protocol and radiotelemeters were implanted on week 12 of the protocol for measurement of ambulatory AP. Body weight, food intake, body-composition and glucose metabolism were measured throughout the study. After measuring baseline AP, LFD and HFD groups were then divided into RDNx or Sham treatment and followed for 14 days. After 10 weeks of diet, HFD versus LFD fed mice had increased body weight (30±1 vs. 26±1, g) and fasting blood glucose (83±3 vs. 68±4, mg/dL). HFD increased the baseline AP (124±4 mmHg) compared to LFD mice (112±4 mmHg). RDNx normalized AP in HFD mice (107±3) but had no effect on AP in LFD mice (106±4). Compared to sham treated mice, RDNx had no effect on fasting blood glucose or the glucose tolerance in LFD mice. In contrast to our hypothesis, fasting blood glucose was higher in RDNx-HFD (76±3) compared to Sham-HFD (69±4) mice. Similarly, the area under the curve for the glucose tolerance test was higher in RDNx-HFD (555 ± 51) compared to Sham-HFD (426 ± 24) mice. We conclude that RDNx effectively lowers AP in obese genetically hypertensive female Schlager mice, but also results in adverse effects on glucose metabolism. The mechanisms mediating these responses are currently underway. NHLBI R01 HL116476
Reliability and Biostability Assessment of Neural Interfaces and Electrodes Based on Liquid Crystal Polymer Dielectric

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**Background:** Neural interfaces and electrodes can be fabricated based on flex circuit manufacturing techniques using biocompatible material sets. Liquid crystal polymer (LCP) dielectric has been demonstrated as feasible for producing directly implantable, biocompatible structures without the need for hermetic coatings or housings.[1,2] This approach results in the ability to achieve significantly smaller form factors, as well as to incorporate complex features, channels and routings through the use of photolithography and laser drilling. Due to its very low moisture uptake, LCP is also being evaluated as a means of embedding active and passive components within these implantable structures, further enhancing functionality options.

**Methods:** Electrodes and neural interface structures are fabricated on conventional flex circuit manufacturing equipment combined with thin film vacuum deposition techniques. LCP film is used as the dielectric material with noble metal conductors such as Au, Pt and PtIr. Appropriate cleaning processes can be used to ensure biocompatibility of the final structures.[3] Mock silicon die patterned with Cu are embedded within the LCP to produce test structures for hermeticity studies. Long term biostability evaluations are performed by soak tests in phosphate-buffered saline (PBS) at 77°C, and bend testing at a 0.5 mm radius is conducted for mechanical reliability. Cross-sectional analysis is used to examine regions of failure.

**Results:** Noble metal LCP based neural interface and electrode structures have been successfully fabricated using conventional flex circuit and thin film processing. Structures that have undergone specialized cleaning operations pass the ISO 10993 cytotoxicity test requirements. LCP structures with Au conductors have passed PBS soak testing at 77°C for > 9 months without failure, and LCP with embedded mock silicon die has survived up to 1500 hours. Cross-sections of the embedded mock silicon die failures suggest the moisture ingress occurs along the interface of the LCP dielectric layers. Electrode structures subjected to 0.5 mm radius bend testing have survived up to 100k cycles.

**Conclusions:** Biocompatible neural interfaces and electrode structures can be fabricated from LCP dielectric and noble metal conductors on conventional flex circuit and thin film manufacturing equipment. Passive structures have shown initial feasibility for long term biostability based on PBS soak testing. Structures with embedded die show initial promise for biostability, but further process optimization is needed. These results demonstrate that a new material set comprised of LCP with noble metals is feasible for producing complex implantable structures for neuromodulation applications.

**References:**

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Automated Localization Using Novel Feature Extraction and Clustering in Focal Epilepsy

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Background Epilepsy is a common and debilitating neurologic disease affecting 1% of the population characterized by recurrent seizures. In the United States, approximately 35% of those afflicted cannot achieve reasonable control of their seizures on anti-epileptic medications. The device world has taken notice and in 2014 published results from the Pivotal Trial of a responsive neural-stimulation clinical series. Missing from these devices is information about seizure onset channels or any localization at all. All recording channels are weighted equally in the closed-loop warning system. With this in mind, an automated method for seizure onset detection to be implemented into such devices would be very useful for the epilepsy and medical device communities.

Methods: In a series of patients with temporal lobe focal epilepsy at Mayo Clinic, analysis on 2-hour segments of interictal (between seizure) data was taken in n=7 patients. Data was sampled at 32,000 samples/sec and decimated to 5,000. Anti-aliasing filtering was done at 1,000 Hz. Primary spectral analysis was performed between standard clinical Berger Bands (0-3 Hz = Delta, 3-8 Hz = Theta, 8-13 Hz = Alpha, 13-25Hz = Beta) as well as higher oscillations frequencies [Staba 2004] 25-55Hz = Low Gamma, 65-100Hz = High Gamma, 100-150Hz = epsilon gamma, >150Hz taken as ripple frequency range. After pre-processing using ICA subtraction methods, and accounting for any events (seizures were no closer than 12 hours from any 2-hour segment analyzed) or discontinuities, analysis was performed in both asleep and awake states. Feature extraction was undertaken using methods previously employed [Varatharajah 2016] for the following features: Power-in-Band (PIB) utilizing log-scaled weightings of bands to account for the power law, phase-amplitude coupling [Berry 2016], spectral coherence (SPCO), and time correlation (TMCO). Using this combination of features, coalescent analysis was undertaken on PAC and sequential analysis was undertaken based on a clustering approach. Additionally, a sequential analysis was undertaken based on a Bayesian approach. Gold standard SOZ channels were determined by a trained epileptologist and ROC was utilized to assess the validity of the approach for each patient at different thresholds.

Results: PAC high value epoch analysis resulted in a AUC of 0.79 (range 0.5-0.9). Clustering based approaches resulted in AUC in this series of patients 0.77 with range 0.64-0.92. There were certain patients in this series in whom the approach was highly sensitive and specific and others whose seizure onset localization was barely better than chance. This suggests that future work will need to be tailored to the specific features in that patient which result in optimal localization.

![Analytic Steps and Example on Patient 442](image)

Figure 1. Analytic Steps and example on patient 442. The Approach is seen on the left figure, detailing various aspects of the method where feature extraction is followed by automated clustering and then localization. On the right is an example of the same steps in a patient with focal epilepsy on the right side (RMacro contact 1 and 2).

Conclusions: This work shows that automated localization is possible and may prove useful in devices which track not just electrophysiologic biomarkers of seizure onset but also any neurologic disorder which can be tracked with electrophysiology.

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Investigating the Relationship Between Size of Interface Devices and Peripheral Nerve Damage

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Background: Wire tethers between the nerve implant site and percutaneous connector of nerve interface devices have caused wire breakage and device failure in previous studies in cortex¹ and the periphery²,³. They are also implicated in increasing nerve damage by inducing strain on the electrode-tissue interface through tethering forces. Wireless devices have been developed to eliminate wire tethers by transmitting power and data over a mutual-induction link rather than through a cable. However, this type of interface requires additional components within the on-nerve device package, making it larger and bulkier than that of a comparable wired device. Additionally, it is typically desirable to increase the size of the package to accommodate more complex electronics or larger wireless telemetry coils. This may cause a new mode of failure for peripheral nerve interfaces by inducing additional strain on the target nerve. While the tethering forces have been eliminated, the package attached to the nerve is larger and more cumbersome. The purpose of this study is to investigate the effects of that trade on nerve damage and to identify the maximum size device package that a peripheral nerve can tolerate without significant functional loss.

Methods: Peripheral nerve interface devices are being fabricated and implanted into the sciatic nerve of rats to compare the damage done to the nerve by devices of different physical configuration. All wired and wireless devices are based on floating microelectrode array (FMA & WFMA) technology with penetrating electrodes and feature silicone nerve cuffs. Five different configurations are being used, with six trial groups:

1. a traditional wired FMA
2. a wired FMA with the cable removed
3-5. three sizes of WFMA - 5mm, 7.5mm, and 10mm diameter
6. a control group in which the surgical implantation procedure is performed, but no device is implanted

These groups will allow us to compare the chronic nerve damage and functional losses caused by:

• a standard wired device (group 1)
• a minimum-size device featuring no wired or wireless components (group 2)
• wireless devices with different on-nerve package sizes (groups 3, 4, and 5)
• the implantation procedure alone (group 6)

Each group consists of five animals. Gait pattern will be observed and compared over the length of the implantation, nerve conduction velocity will be measured at the time of explantation, and histological measures will be performed. Functional deficit, axon size and number, mechanical displacement of the device package, and formation of scar tissue around the electrodes will be quantified for each group.

Results: The subjects will be observed over a sixty-day implantation period. The gait, conduction velocity, and histological data will be analyzed to identify the relationship between a device's physical configuration and nerve damage for peripheral nerve interface devices.

Conclusions: These experiments are significant because they will establish a baseline for decisions on the physical configuration of peripheral nerve devices. While it seems logical and is generally accepted that devices that induce greater strain on a nerve will cause greater damage to that nerve, this is the first study that will analyze the effects of device package size and physical configuration on the health of the electrode-nerve interface.

References:
Blunted Responsiveness to DREADD-Mediated Increases in Spontaneous Physical Activity in Aged Mice

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Background: Aging is associated with increased weight gain and decreased physical activity. The neuropeptide orexin influences energy balance and is a promising therapeutic target for achieving and maintaining a healthy body weight. Orexin is produced by neurons located in the lateral hypothalamus (LH), and modulates several physiological processes connected to body weight, notably spontaneous physical activity (SPA), which produces energy expenditure (caloric burning). From infancy to later adulthood, the number of orexin neurons produced within the brain decreases by 23%, which correlates with reduced physical activity during aging. It is unknown to what extent the loss of orexin neurons may be overcome through orexin supplementation to counteract obesity. We hypothesized that activation of the orexin system via Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) would produce reduced increases in SPA in aged mice.

Methods: Five male and 5 female Orexin-Cre mice, aged 18-months, were injected bilaterally with a Cre-dependent AAV vector containing an excitatory DREADD into the caudal lateral hypothalamus (orexin neuronal field). Mice were housed in continuous metabolic phenotyping systems. Following acclimation and several days of saline injections to habituate animals to the injection procedure, 1, 3, or 5 mg/kg clozapine n-oxide (CNO, the designer drug portion of the DREADD) or saline were administered every other day; injection order was counterbalanced using a Latin-Square design. Changes in SPA (e.g., time spent moving) were assessed within 6 hours post-injection.

Results: In contrast to our previous studies, which showed a significant increase in SPA in 4.5-month-old females in the first 4 h following injections of both 1 and 5 mg/kg CNO, there was no significant effect of any CNO dose on SPA in aged female mice. Similarly, whereas our previous studies have shown increases in SPA in 4.5-month-old male mice following injections with 5 mg/kg CNO, the present study failed to find a significant increase in SPA in male mice at any dose. While not significant, the females did show a trend of increased responsiveness to CNO relative to males.

Conclusions: Aged, 18-month old male and female mice failed to show increases in SPA following activation of orexin neurons via DREADDs, suggesting either a decrease in the number of orexin producing neurons in the LH or reduced responsiveness to the orexin released by these neurons. These results indicate there may be a critical period during which orexin neurons may be targeted as a therapeutic approach to obesity.

References:

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Network Analysis of Functional Connectivity using Graph Theory Approach to Study Chronic Pain in Sickle Cell Disease Patients

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\textbf{Background}: Chronic pain affects millions of Americans and is the focus of several neuromodulation therapies including spinal cord stimulation, deep brain stimulation, transcranial magnetic stimulation, and others. However, chronic pain does not have a solitary effect on the brain, but has disease-specific characteristics that make chronic pain unique for different patient populations \cite{1}. In order to improve neuromodulation treatment, chronic pain should be mapped for specific diseases. In order to develop a disease specific model of chronic pain, we recruited sickle cell disease patients to undergo non-invasive imaging. We used functional magnetic resonance imaging (fMRI) to map out sickle pain by comparing their results to healthy controls.

\textbf{Methods}: Resting state fMRI recordings were obtained in 15 sickle cell patients and 15 healthy controls on a 3T scanner. The fMRI sessions lasted for 8 minutes and participants were asked to keep their eyes open during the scan. The CONN toolbox was used to process the data and to compose connectivity matrices for each participant that included 136 anatomical brain regions. The connectivity matrices were used to construct an undirected graph made of nodes and edges. These graphs were analyzed by calculating the characteristic path length, node density, clustering coefficient, global efficiency and small worldness for various sparsity values, ranging from 5\%-60\%, where edges below the cutoff were eliminated.

\textbf{Results}: The patients with clinically higher chronic pain had significantly lower small worldness values compared to controls (p<0.01). Small worldness represents short path lengths and a copious amount of clustering within the graph; a loss of small world characteristics has also been observed in Alzheimer’s disease patients \cite{2}. Small world values of patients was also significantly negatively correlated with the number of hospitalizations in the past 2 years (p<0.001; R\textsuperscript{2}=0.6481). The clustering coefficient (p<0.03) and global efficiency (p<0.01) of patients also showed significantly different values from controls.

\textbf{Conclusions}: These results suggest that graph theory approaches can be used to assess how chronic pain adversely affects the human brain. The small world values reflect the chronic pain severity of patients; and these results can be used to isolate the brain regions most affected by this change of characteristics within the network. These brain regions can be further studied and potentially used as targets for neuromodulation in sickle pain. Graph theory also has the potential detect disease specific effects of chronic pain because migraine patients have been observed to have increased small world values compared to controls \cite{3}.

\textbf{References}:


\cite{3} J. Liu \textit{et al.}, “Gender-Related Differences in the Dysfunctional Resting Networks of Migraine Suffers,” PLOS ONE, vol. 6, no. 11, p. e27049, Nov. 2011.

\textbf{Funding}: NIH U01-HL117664 and NSF IGERT DGE-1069104.
Determining the Effects of Norepinephrine from the Locus Coeruleus by Characterizing Tremor in Harmaline and GABA\textsubscript{A\alpha1}-knockout Essential Tremor Models

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**Background:** Propranolol is a drug that treats essential tremor (ET), although the drug’s location and mechanism of action is unknown. We hypothesize that propranolol acts on the cerebellum and inhibits the actions of norepinephrine (NE) released from the locus coeruleus (LC), and that inhibition of LC input into the cerebellum can inhibit tremors without producing negative effects like immobilization. In order to begin testing this hypothesis, we need to be able to characterize the severity of tremor. A force-plate actometer is an instrument that measures variations in forces, with four force transducers on the corner of a plate. This study will use a custom built force-plate actometer to characterize tremor in two models: the harmaline-induced\textsuperscript{2} and GABA\textsubscript{A\alpha1}-knockout\textsuperscript{1} mouse models. Building a force plate, with generous support from Fowler\textsuperscript{3}, that can reliably detect tremor in both of these models is important for studying how optogenetic stimulation of the LC can effect tremor severity.

**Methods:** To study tremor in ET models and the effect of optogenetic intervention, a force plate actometer was built. The variation in force will be used to detect when tremor is first expressed, and when it is last detected. For the harmaline model, the concentration of power in the frequency domain following an intraperitoneal injection of harmaline will be examined. Additionally, doses of harmaline ranging from 1-20 mg/kg through intraperitoneal injections will be compared. Repeated dosing schedules will also be examined, to see how tolerance to harmaline is built. For the GABA\textsubscript{A\alpha1}-knockout model, the animals will be measured for tremor regularly after P45. An AAV vector for the excitatory opsin Channelrhodopsin (ChR2) will be injected into the LC of these adult mice. The effect on tremor of low and high frequency optical fiber LC stimulation in the GABA\textsubscript{A\alpha1}-knockout model will be studied.

**Results:** With an intraperitoneal injection of 1 mg/kg of harmaline, the animal exhibited tremor between 45 and 80 seconds. At a higher dose of 10 mg/kg, the tremor began at 55 seconds and continued throughout the 20-minute session. The two doses displayed similar power spectra within the 7-16 Hz region, while the control had greater power at low frequencies (0-5 Hz).

**Conclusions:** We can now quantify tremor in harmaline-induced and GABA\textsubscript{A\alpha1}-knockout models with a force plate actometer to examine how optogenetic stimulation of the LC at low and high frequencies will affect the severity of tremor. This enables us to study different therapies for ET, like propranolol.

**References:**

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Dopamine regulates neurotransmission in the nucleus accumbens through activation of astrocytes

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Background: Dopaminergic signaling in the nucleus accumbens (NAc) plays fundamental neuromodulatory roles in neuronal network activity underlying reward and drug-seeking behaviors. Accumulating evidence indicates that astrocytes play key roles in neuromodulation and neural information processing by actively modulating neuronal activity and synaptic function. Astrocytes respond to synaptically-released neurotransmitters with intracellular calcium elevations and the release of signaling molecules, termed gliotransmitters, that modulate synaptic transmission in several brain areas and impact animal behavior. While dopaminergic system has been mainly studied in neurons, the involvement of astrocytes in dopaminergic signaling in this brain area remains unknown. In the present study, we investigated astrocytic responsiveness to dopamine and the consequent effects on glutamatergic synaptic transmission in the NAc core.

Methods: In the present study we used confocal calcium imaging techniques combined with exogenous application of dopamine or selective optogenetic stimulation of dopaminergic axons to investigate astrocytic responsiveness to dopamine. To investigate the consequences of astrocytes activation on synaptic transmission we performed electrophysiological recordings of glutamatergic synaptic transmission and activated astrocytes with exogenous dopamine application, selective optogenetic stimulation of dopaminergic axons, or by activating Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) specifically expressed in astrocytes.

Results: We found that astrocytes responded to exogenous (dopamine application) and endogenous (optogenetic activation of dopaminergic axons) dopamine with intracellular calcium elevations. These dopamine-induced calcium elevations in astrocytes were associated with a depression of excitatory synaptic transmission through activation of adenosine A1 receptors. Furthermore, specific activation of astrocytes with DREADDs resulted in a depression of synaptic transmission that mimicked the dopamine-mediated synaptic depression. These data indicate that astrocytes in the NAc core respond to dopamine and depress excitatory synaptic transmission.

Conclusions: Present results indicate that astrocytes in the NAc core are involved in dopaminergic signaling by responding to dopamine and mediating a dopamine-induced synaptic depression. These results advance our current knowledge of the astrocyte involvement in dopaminergic signaling in the NAc revealing their potential role as targets for treatment of disorders of motivation such as addiction.

References:

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2D Static Magnetic Field Simulator: A Design Tool for MR-Compatible Neural Probes

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Background: Multi-modal magnetic resonance imaging (MRI) studies incorporating electrophysiology are of interest to the functional imaging community, as they correlate the hemodynamic- and metabolic-dependent changes observed in functional-MRI (fMRI) to direct measures of neural activity. One challenge associated with these studies is signal loss in the fMRI data around implanted neural probes due to local magnetic field distortions stemming from the probe. We have implemented a 2D simulator based on previous work [1,2] to estimate magnetic field distortions around neural probes. We will use this tool to evaluate MR-compatible neural probe designs that could be used to study the neural correlates of fMRI in the future.

Methods: A 2D magnetic field simulator was implemented in MATLAB based on the work of others [1,2]. The solver calculates the perturbation to a static magnetic field due to the presence of an arbitrary 2D user-defined object. The simulator solves equation 1, where \( \mu_r \) is the relative permeability and \( \Phi \) is the magnetic scalar potential.

\[
\nabla \cdot (\mu_r \nabla \Phi) = 0
\]

Equation 1 can be solved numerically using the finite-difference method. Whereas previous authors [1,2] utilized a pseudo-time solution, we arranged the problem into a linear system form as presented in equation 2 where \( \Phi \) is a vector of scalar potentials across nodes and \( u \) is a vector containing the boundary conditions. We solved the equation using the reduced row echelon form to avoid taking the inverse of the large, sparse matrix \( A \). The magnetic field is then calculated from \( \Phi \). We validated this approach by comparing simulations with known analytical solutions.

\[
A\Phi + Bu = 0
\]

Results: The simulation results are in good agreement with known analytical solutions for cylindrical geometries. An example is shown in Figure 1 for a hollow cylinder of water (\( r_i = 80\mu m, r_o = 120\mu m \)) in air. The color maps show magnetic field perturbation in ppm (left) and difference between the numerical and analytical solutions (right). The maximum field distortion is approximately 6 ppm and occurs within the cylinder of water, while the maximum error bounds are approximately 0.3 ppm, which is comparable to previous results [1,2]. Further, the error is nearly zero across much of the field-of-view.

Conclusions: We have implemented and validated a 2D numerical tool that will be used to estimate magnetic field perturbations around implanted neural probes. This tool will guide us in the design of an MR-compatible neural probe that will be used in multi-modal fMRI studies to further elucidate the relationship between neural activity and fMRI.

References:

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High fat diet increases cognitive decline and neuroinflammation in a model of orexin loss

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Background: Diets high in saturated fatty acids such as palmitate can increase the propensity for obesity, microglial activation, and central inflammation (neuroinflammation). Cognitive decline is associated with increased neuroinflammation. Moreover, obesity is recognized as a risk factor for neurodegenerative diseases such as Alzheimer’s disease and mild cognitive impairment. A potential mechanism/target of neuronal-glial communication is the neuron-specific chemokine C-X3-C (CX3CL1, fractalkine) and associated microglial receptor (CX3CR1). The CX3CL1-CX3CR1 system, important in modulating hippocampus-specific memory tasks and synaptic plasticity, is perturbed by neuroinflammation and aging. Data suggest that orexins, hypothalamic neuropeptides known to influence cognition, may play an important role in this process. We have shown that orexin A (OXA) treatment improves cognition in a mouse model of orexin degeneration (orexin/ataxin-3; O/A3). Additionally, our lab group has demonstrated that OXA suppresses neuroinflammation and palmitate-induced neuronal damage. As neuronal-glial crosstalk is necessary for maintaining cognition, orexin effects on cognition may occur via modulation of microglia. Our overall hypothesis is that orexin effects on memory depend in part upon immunomodulatory control of microglia. We predict that increased orexin signaling will ameliorate diet-induced hippocampal cognitive decline through a microglial CX3CL1/CX3CR1-mediated pathway.

Methods: This study will be completed in three phases: 1) determine if orexin loss alters neuroinflammation and cognition in response to HFD; 2) determine if exogenous OXA in orexin deficient (O/A3) mice will attenuate neuroinflammation and stabilize cognition in response to HFD; and 3) determine if increasing endogenous OXA signaling via a pharmacogenomics approach will reduce neuroinflammation and improve cognitive function in response to HFD (Fig 1A-C). Phases 1 and 2 have been partially completed. To test the first phase of the study, male O/A3 and wild-type (WT) mice (7-8 mo. of age) underwent training in a two-way active avoidance (TWAA) hippocampus-dependent cognitive task and were retested 24 h later. Body composition was then determined. Mice were randomly divided into 4 groups and were either given HFD (45% total fat, 31.4% saturated fat) or continued receiving normal chow (NC; 4% total fat and 1% saturated fat).

Results: Following 14 and 28 d of diet exposure, mice were retested for TWAA response and body composition. We show that O/A3 mice on NC have increased body fat compared to WT mice on NC on days 1, 14, and 28 (p<0.05). O/A3 and WT mice on HFD have increased body fat compared to WT and O/A3 NC mice on days 14 and 28 (p<0.0001). Additionally, O/A3 mice have significant impairments in the TWAA task (increased latency and reduced avoidances p<0.01). Cognitive impairment was evident at both 2 and 4 weeks in O/A3 mice fed HFD vs. WT mice on normal chow or HFD (increased latency, reduced avoidances p<0.05). Additionally, O/A3 mice had increased gene expression of the microglial activation marker Iba-1 (measured via qRT-PCR, p<0.001). Further characterization of memory tasks and microglial immune response (M1 neurotoxic vs. M2 protective phenotypes) is ongoing.

Conclusions: Collectively, our results indicate that OXA loss impairs short term memory, and that HFD accelerates hippocampus-dependent memory deficits and the onset of neuroinflammation in O/A3 mice. Our study is novel in that we would be the first to pursue a neuromodulatory approach to 1) define a pathway linking orexin to phenotypic changes in hippocampal microglia and 2) directly test if orexin improves cognition through a neuronal-glial mechanism.

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Leveraging anatomical constraints in the decoding of natural motor imagination tasks for intuitive use of EEG-based brain-computer interface

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**Background:** Electroencephalography (EEG)-based brain-computer interfaces (BCIs) using sensorimotor rhythms have allowed users to successfully control various external devices by imagining different kinesthetic movements [1]. However, the low spatial resolution of EEG restricts usable motor imaginations (MI) to those which are often cognitively disconnected from the translated action of the output device. Therefore, in order to drive these systems towards more natural use, we attempted to decode MI EEG of common daily actions, including flexion, extension, supination, and pronation of the right hand. We hypothesize that EEG source imaging (ESI) will increase the discriminability of these signals compared to traditional sensor-based approaches.

**Methods:** Five subjects participated in this study in accordance with a protocol approved by the University of Minnesota IRB. Subjects were instructed to perform 2 Hz self-paced MI of one of the aforementioned tasks in a predefined trial structure while we recorded 64-channel scalp EEG. Initially, data from all tasks were compiled into a single data set. Independent component analysis and ESI mapping were then used to identify a cortical region of interest (ROI) containing the overlapping right-hand task activity. In a parallel analysis, the time course of each individual task EEG was projected onto a cortical model using the weighted minimum-norm estimate [2,3] in order to transform the scalp time series into a whole-brain time series. A time-frequency representation (TFR) was computed for all scalp sensors and dipoles located within the defined ROI using a Morlet wavelet approach and were subsequently split into different frequency bands and time windows for classification.

**Results:** As seen in Fig. 1, the maximum group-level four-class classification accuracy achieved by the sensor-based and source-based method was 69.5% and 82.2%, respectively. Additionally, the proposed source-based method outperformed the sensor-based approach for each of the four individual tasks, with an enhancement ranging between 6.6% and 18.6%. Furthermore, when examining the classifier weights in the spatial source domain, we observed distinct cortical representations of the four right-hand MI tasks that support a functional somatotopic encoding of the primary sensorimotor cortex.

**Conclusions:** The results of this study indicate that MI tasks involving natural hand manipulations can be decoded with high accuracy using ESI techniques. The successful integration of these tasks in an online source-based BCI may help subjects suffering from various neurological disorders perform useful everyday tasks and improve their quality of life.

**References:**


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Multivariate approach to predict the seizure onset zone and improve the outcome of surgery

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Background: The aim of this study was to develop and evaluate a machine learning approach to accurately predict the seizure onset zone (SOZ) in the electrocorticographic (ECoG) recordings.

Method: We retrospectively analyzed 23 seizure episodes in 10 patients (7 males; aged 23.0 ± 9.0 (mean ± SD) years), who underwent a Phase II epilepsy surgery evaluation with intracranial electrodes. Resections were tailored individually based on visual inspection of the ECoG ictal onset in all patients. Patients 1 to 6 were seizure-free after surgery, but not Patients 7 to 10 (although these patients were significantly improved). After preprocessing of ECoG data, phase locking value (PLV) between the phase of low frequency (4-30 Hz) and phase of the Hilbert transform of high frequency (80-150 Hz) was calculated [1]. The following five features were extracted from PLV signal within a 10-30 sec time window before seizure onset in each electrode.

1. PLV positive: This feature was assigned to “1” if the PLV would exceed a threshold of \( \mu_b + 6 \times \sigma_b \), where \( \mu_b \) and \( \sigma_b \) are the mean and standard deviation of PLV in a 60-second baseline, respectively. 2. Duration of PLV positive. 3. Peak 4. Average. 5. Mean of PLV

Finally, the logistic regression (LR) and support vector machine (SVM; with radial basis function kernel) classifiers were trained using the above features in seizure-free patients (Patients 1-6), and tested to predict SOZ electrodes in non-seizure-free patients (Patients 7-10). We also determined the correlation between the number of non-resected SOZ electrodes, identified by LR and SVM, and the seizure frequency output in non-seizure free patients.

Results: Both LR and SVR classification approaches identified SOZ electrodes inside the resection area and some SOZ electrodes beyond that areas in non-seizure free patients. The number of SOZ electrodes, identified by LR and SVM, beyond the resection area had a significant correlation (P<0.001) with seizure frequency outcome in non-seizure free patients.

Conclusions: Using the features extracted form PLV, we identified some SOZ electrodes beyond the resection area in non-seizure free patients, and the number of these electrodes has a significant correlation with the seizure frequency output in these patient.

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References
1. Brain 2013;1236; 3796-3808.

![Figure 1](image-url)

Figure 1: (a), (b) Locations of the resected electrodes: SOZs identified by our algorithm (red) and visually detected by epileptologists (yellow circles); The broken black line shows the resected area. (C) A significant correlation between the numbers of SOZ electrodes, identified by LR and SVM, beyond the resected area and the seizure frequency outcome in four non-seizure free patients was observed (p-value < 0.01).
Integral methods for automatic quantification of electroactive neurotransmitters detected via fast scan cyclic voltammetry

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Background: Recent advances in fast scan cyclic voltammetry (FSCV) utilize oxidation charge measurements, obtained by integrating cyclic voltammograms (Fig 1a), to help estimate basal concentrations of electroactive neurotransmitters in the brain [1-3]. Unfortunately, the selection of integration boundaries (Fig 1a) relies on ad-hoc visual identification of oxidation peaks (i.e., catecholamine “humps”) in each voltammogram, which introduces an additional source of error and precludes the development of automated procedures necessary for analysis and charge quantification in large data sets. To improve charge quantification techniques, we propose novel criteria for automatic selection of integration boundaries. These criteria allow quantification of oxidation reactions and also quantification of reduction reactions. Furthermore, they can be applied to background subtracted as well as non-background subtracted cyclic voltammograms. Here we evaluate these criteria using both in vitro and in vivo experimental data.

Methods: In vitro data collection was performed using a FLA lab 3200 flow injection system (FLA lab Instruments, Seattle, WA) and the WINCS Harmoni device (Mayo Clinic, Rochester, MN). A 110 µm carbon fiber microelectrode (CFM) was placed in a flowing stream of artificial cerebrospinal fluid (aCSF) buffer solution with a pH value of 7.4. Buffered aCSF solutions containing 0.1uM to 5uM of dopamine, adenosine, epinephrine, and norepinephrine were injected for 8 s at 2.25mL/min. In vivo measurements were obtained in a rodent model of medial forebrain bundle stimulation and simultaneous FSCV recording in the dorsal striatum. Both the stimulation electrode and CFM were stereotactically inserted (KOPF instruments, Tujunga, CA). Dopamine release was evoked with a series 2 s stimulations using a range of amplitudes from 0.05-2.0 mA and pulsewidths from 0.8 and 1.8 ms. Analyte measurements were obtained by sweeping the CFM potential from a resting potential of -0.4 V to a switching potential of 1.5 V and back to the resting potential, at a rate of 400 V/s every 100ms. MATLAB was used to filter and smooth recorded voltammograms, as well as to implement automatic integration-boundary detection and selection algorithms.

Results: Our results show that our methods are equally accurate as state-of-the-art methods for quantification of dopamine oxidation charge (Fig. 1b), but are more accurate when applied to other neurochemicals (Fig 1c). Additionally, our methods can be used to quantify reduction reactions, unlike existing charge quantification techniques.

Conclusions: Our results demonstrate the feasibility of developing automated routines for charge quantification of different analytes.

References:

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Towards Developing a Performance Sustaining Decoder for a BCI-controlled neuroprosthetic device

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Background: As part of an ongoing clinical study of a Neural Bypass Technology (NBT) [1], we examined the properties of neural recordings from an intracortically implanted multi-electrode array in a quadriplegic human over an extended period of time. We examined different types of neural features and decoding paradigms to determine which combinations led to optimal performance when retrained regularly as well as demonstrating stability in the signal and our ability to decode it over a period of almost three years. Additionally, we examined which algorithms demonstrated performance sustaining characteristics such that regular retraining could be minimized, which is vital to transitioning this type of BCI technology from the lab to a device that can improve the day to day lives of paralyzed patients [2].

Methods: The NBT has been successfully demonstrated during a Federal Drug Administration (FDA) and Institutional Review Board (IRB)-approved study [1]. The study participant is a 24-year old male who sustained a C5/C6 SCI and was implanted with a 96-channel Utah array in the primary motor cortex. The participant performed tasks to imagine different hand when cued by a virtual hand on a computer. Two experiments were repeated on a regular basis over the course of the study and provide a novel dataset for studying chronic signal stability and performance characteristics of different decoding paradigms.

Results: The neural signals and our ability to decode them has remained steady over the course of the study (Fig 1) after an initial settling period post implantation. The dataset shows promise for building decoders that do not significantly degrade over time which is a significant obstacle to the widespread acceptance of BCI technologies. Intials results can be seen in the right panel of Fig 2 where we compared performance for decoders with and without regularization terms and found that regularization helps when the decoder is used the same day as it was trained but the opposite is true as the decoder ages.

Conclusions: Using a BCI to control a neuroprosthetic device shows great promise for helping paralyzed patients regain some functional movements. In order for this type of technology to gain wide acceptance the recorded signals and the decoding algorithms that ingest them must become more robust to daily variability so that the user is not burdened by having to constantly retraining the system. Our results show promise that such a system can be achieved in humans.

References:

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Figure 1. Left: Neural features and decoding accuracy stability for complex hand movement over 700 days. Right: Changes in decoder performance as the decoder ages.
High-Frequency Oscillations from Different Anatomy of Brain as a Biomarker for Epilepsy

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Background: High-frequency oscillations (HFOs) have been described as interictal, or resting-state intracranial EEG (iEEG) biomarkers for the localization of seizure-generating brain tissue. However, HFOs can also play a role in normal cognitive processing, and accurate identification of seizure onset zone requires differentiation between pathological and physiological HFOs, and characterization of normal or non-pathological HFO activity in different brain regions.

Methods: This study reports HFO rates measured in over 80 patients with intractable epilepsy who underwent wide-bandwidth iEEG as part of clinical presurgical assessment. Discrete HFOs were identified with an automated detector (Cimbalnik, Worrell, & Stead, 2016) in two-hour segments of high quality recordings likely to represent sleep. Electrode locations were determined by coregistering the patient’s pre-operative MRI with an x-ray CT image acquired immediately after electrode implantation. Electrode localization in standard MNI atlas space was performed using EpiSurg (Groppe, et al., 2016), and anatomic locations for each electrode provided by the DK atlas incorporated in FreeSurfer (Fischl, 2012).

Results: HFO rates were measured for seizure onset zones (SOZs) and non-seizure onset zones (non-SOZs) for different anatomical structures of the brain. SOZs and non-SOZs were determined from the patient’s clinical iEEG study by one or more certified epileptologists. HFO rates were significantly higher in SOZ than non-SOZ for all anatomic regions studied (p<0.0001). HFO rates in mesial temporal cortex (hippocampus and amygdala) were significantly higher than neocortex (p<0.003) for SOZ and non-SOZ. HFO rates also differed significantly between hippocampus, amygdala and neocortical regions as shown in Fig 1.

Conclusions: The HFO rates for different anatomy show that the average value of HFO for different anatomy are not same which conclude that different region of brain oscillate differently.

References:


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Fig 1: High Frequency Oscillation rate for different anatomy of brain. The red boxes are for the soz region and blue are for the non-soz regions.
Electrically-Evoked Eye Movements using a Vestibular Prosthesis Designed to Restore Sensation of Gravitoinertial Acceleration

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Background: The vestibular system comprises two classes of end organs: three semicircular canals (SCCs), which sense rotational head velocities, and two otolith end organs (utricle and saccule), which sense gravitoinertial acceleration (GIA, vector summation of linear and gravitational accelerations). Each end organ encodes head motion using frequency modulation of neuronal firing rates to drive ocular and postural reflexes to maintain visual acuity, stable gait, and balance [1]. Research toward a vestibular prosthesis has focused on stimulation of the SCCs [2]; however, with new prosthesis developments, otolith stimulation is feasible to more completely restore vestibular reflexes [3]. The research presented here shows preliminary results of eye movement responses to electrically encoded static head tilts.

Methods: A chinchilla was fit with a head-post and implanted with binocular dual scleral coils used for tracking 3D eye movements. After characterization of normal 3D eye movements, another surgery was completed to implant a polyimide vestibular electrode array with 26 otolith and 24 SCC contacts into the left ear. Bipolar current pulses were delivered while the animal was kept still, in the dark, thus causing sensation of a ‘virtual’ movement and driving purely electrically-evoked eye movements in response to that sensation. Eye movements were recorded during a constant pulse train (a virtual 40 second static tilt) delivered to multiple electrode configurations.

Results: Providing a step change in pulse rate to the SCCs caused an initial change in eye position that decayed back to starting position (consistent with the SCC’s high pass characteristic), while a step change in pulse rate to the otolith end organs caused a prolonged ocular counter-roll for the full 40 seconds (consistent with the otolith end organ’s low pass characteristic). Using a distant reference for otolith stimulation limited the specificity of activation, likely activating the entire end organ and thus eliciting the same directional 3D ocular counter roll from any of the 26 otolith electrodes; however, using a closer reference showed more specificity and control of the direction of ocular counter-roll. The near reference also changed the timing of ocular counter-roll initiation, suggesting less spread to SCCs.

Conclusions: These results are a first step toward restoring the sensation of GIA to drive otolith-ocular reflexes. While preliminary, the results show a promising distinction between stimulation of the SCCs versus otolith end organs. With experiments in subsequent animals, optimal electrode configurations, stimulus parameters, and vestibular prosthesis design can be developed to restore sensation of GIA.

References:

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Spike Decoding without Spike-sorting using Kernel Density Estimation

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Background: Decoding stimuli and intended motor plans from neural spiking activity is crucial for understanding how the brain processes information, and for building neural prosthetics which can restore motor function in individuals with neurological damage. Typically the decoding process involves detecting spikes, sorting the spikes into clusters corresponding to individual neurons, and then decoding information based on the spike rates or times of those individual neurons. Unfortunately manual spike-sorting is not scalable and cannot easily be brought to the clinic, as spike-sorting process requires time and expertise: an experienced spike-sorter must manually group clusters of spikes into putative cells for each electrode. Automated spike-sorting algorithms have been developed, but in practice they perform poorly on average-quality data. A popular alternative is skipping spike-sorting altogether and decoding from population spike rates, but this method throws away valuable information, and decoding performance suffers.

Methods: Building on new ideas from Kloosterman, et al. (2014), we developed a Bayesian decoding method which uses kernel density estimation (KDE) over stimulus (or motor) variables, spike features, and time to decode directly from spike features without assigning the spikes to putative neuron groups. Our method adds KDE over time to avoid assigning spikes into time bins, which has been shown to decrease decoding performance. The algorithm is computationally demanding but highly parallelizable, so we have written a CUDA version of the decoder which runs on a GPU to speed runtime.

Results: We analyze performance and runtimes of the algorithm by decoding rat position on a spatial maze using 96-channel 45-minute-long hippocampal recordings. The Bayesian KDE algorithm yields better decoding accuracy than Bayesian decoding using manually sorted spikes. While manual spike sorting for this dataset took hours for each 45-minute session, the Bayesian KDE decoding algorithm runs faster than real time.

Conclusions: Decoding sensory or motor variables directly from spike features is a faster, more automated, and more accurate alternative to manually sorting spikes or not sorting at all. Increased automation and accuracy of spike-based neural decoding algorithms makes neural interfaces with higher channel counts practical, and prevents the loss of information due to manual sorting, enabling neural interfaces which extract information from the brain with higher fidelity.

References:

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Scratching the surface of elucidating the mechanism and treatment for patients with symptomatic scalp

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Background: Symptomatic scalp patients are difficult to manage. Affected patients present with scalp pain, burning, or pruritus, but usually do not have identifiable abnormalities on clinical or histopathologic examination. The purpose of this study was to assess for abnormalities in the peripheral nervous systems (PNS) by examining epidermal nerve fiber density (ENFd) and neuropeptides (substance P (SP), calcitonin gene-related peptide (CGRP), and vasoactive intestinal polypeptide (VIP) within the subepidermal neural plexus of scalp biopsies from patients with symptomatic scalp and control subjects. Our goal was to uncover abnormalities in the PNS and based on findings, implement targeted treatments.

Methods: Ten patients (9 F, 1 M) between the ages of 30 and 68, with a chief complaint of symptomatic scalp in the parietal scalp region underwent a biopsy for ENF and neuropeptide immunohistochemical localization and measurement. These biopsies were compared to parietal scalp biopsies from 10 healthy, asymptomatic control subjects (6F, 4 M) between the ages of 20 and 33. ENFd was evaluated using confocal microscopy and Neurolucida tracing software. SP, CGRP and VIP density was evaluated quantitatively via epifluorescent microscopy.

Results: The mean ENFd was significantly higher in the parietal scalp biopsies of the control subjects when compared to patients with symptomatic scalp (46.98 fibers/mm vs 31.03 fibers/mm), which was statistically significant (t-test, p=0.046). Further t-tests did not reveal a statistically significant difference in mean expression of SP (p=0.3), CGRP (p=0.80), and VIP (0.80) between symptomatic scalp patients and controls.

Conclusions: While SP, CGRP, and VIP play a crucial role in nerve function and transmission of pain and itch, no statistically significantly difference in neuropeptide immunostaining was observed. The mean ENFd was found to be decreased in patients with symptomatic scalp as compared to control subjects. This suggests that a scalp neuropathy may be present in some patients with symptomatic scalp. For such patients, treatment with either topical or oral gabapentin may aid in management of patients with the diagnosis of symptomatic scalp.

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Component-Based Algorithm to Decode Joint Positions In 3D Using ECoG Recordings in Humans

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Background:
Developing stable and efficient algorithms for decoding arm kinematic parameters from electrocorticography (ECoG) signals is an ongoing challenge for the purpose of establishing a useful brain-machine interface. During motor activity, electrical control signals can be acquired from the contralateral hemisphere and preprocessed into predictive variables decoded by a supervised learning model. A study published recently demonstrated the feasibility of long term decoding of arm kinematics using electrocorticography (ECoG) signals in monkeys (1).

Methods:
1) Behavioral task: The seated subject reached with their right arm toward target circles appearing pseudorandomly in a circular space (8 locations) on a touch screen periphery situated about 80 cm away. The subject performed 5 blocks of reaches; each block consisted of 51±7 trials with a 5 minute rest between blocks.
2) Data acquisition and analysis: Limb trajectory was tracked with 3 degrees of freedom (DOF) motion sensors placed on the shoulder, elbow, wrist, and distal interphalangeal joint. Local field potentials were recorded simultaneously from the contralateral hemisphere. Short-time Fourier transform was used for spectral analysis. A “Features” matrix was assembled by computing the power within 10 log-normalized frequency bands, ranging 1 to 200Hz in 10 time bins, from 1000 to 100 ms before each time-series moment, sampled at 20 Hz, for each of 64 channels. The end result was 6400 features for every moment in the 20 Hz time series (Figure 1).
3) Algorithm: Time-varying spectral components of ECoG from each channel were used as input variables for a partial least squares (PLSR) regression algorithm. The PLS decoder was built using 25% of the data to estimate a set of weights for each of the 6400 features and validated on the remaining 75%. A prediction model was then built.

Results:
Multi-joint 3D arm kinematic parameters were decoded from local field potentials from a human subject during a reach task. Using partial least squares regression, we demonstrated a stable algorithm that achieved continuous kinematic joint predictions up to r=0.74, using only 2 minutes of training.

Conclusion
We have successfully decoded multi-joint 3D positions during a reach task in humans. Even with lower signal fidelity from ECoG compared with single units, information from a wide coverage area was sufficient to generate a robust decoder. With only two minutes of training data, we successfully generated an algorithm that was stable across four 7 minutes blocks. Taken together, ECoG signals could hold promise for brain-machine interface applications.

References

Funding: Internal University of Iowa Department of Neurosurgery Funds were utilized for this project.

Figure 1. Experimental design and assembly of the features matrix. A) Experimental setup showing the subject seated with a touch screen showing a stimulus. A contralateral grid and sensors attached to the left arm are also sketched. B) The subject’s reconstructed brain and the location of the subdural grid. C) ECoG trace and feature extraction method and stacked time frequency plots. D) Sensor kinematics and location during a single block.
Fully Automated Unsupervised Behavioral Stage Classifier Based on a Single Intracranial EEG Electrode

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**Background:** Accurate automated sleep staging from intracranial EEG recording (iEEG) can open new avenues for analysis of the human brain. There has been relatively little exploration of sleep staging from intracranial iEEG recordings (Kremen 2017, Pahwa 2012, Zempel 2012). We developed and tested a robust fully automated unsupervised classifier to differentiate awake, drowsy and REM as one class of behavioral states (AW&N1&REM) from non-rapid eye movement sleep (NON-REM 2 and NON-REM 3 states, aka N2&N3) states using single electrode and single feature extracted from iEEG.

**Methods:** iEEG data recorded from one control dog implanted with Medtronic RC+S device, and six human subjects with drug resistant medial temporal lobe epilepsy. All implanted with intracranial depth electrodes. The human recording had a simultaneous scalp EEG recording over several days and nights. As a gold standard, visual sleep scoring for human data was performed in accordance with standard scalp montage according to American Academy of Sleep Medicine 2007 methods. Data from one control dog were used to test a heuristically developed approach for electrode selection and automated sleep staging. The signals were filtered to Delta frequency band (0.1 – 4Hz) by time domain filters (single pole and Savitzky-Golay). A distribution of automatically detected Delta peaks (DP) was calculated from filtered time domain signal for all electrodes for each 30 second sleep staging epoch. On each electrode of the dog data, a continuous signal with lowest normalized variance of DP was used to calculate an index to select the best suitable electrode for automated sleep scoring. An identical method was applied to human subjects’ data to select an optimal electrode and to perform automated sleep scoring using data from one selected electrode. Prediction accuracy of the classifier was validated using four days and nights of human data, compared to the gold standard sleep scoring.

**Results:** In each patient, only one electrode with lowest variance index in DP was selected and used to calculate a threshold using single extracted feature to differentiate AW&N1&REM from N2&N3. Classification accuracy of classifier was 72.4% with sensitivity 0.74, and specificity 0.75.

**Conclusions:** This fully automated, unsupervised, heuristically developed method differentiated awake/drowsy/REM from consolidated N2&N3 behavioral states human iEEG data. Such iEEG-based behavioral state classifiers could feasibly be incorporated into implantable devices that quantify patient sleep patterns, administer behavioral state-specific therapies, and adjust other iEEG-based classifiers.

**References:**


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Effect of Irreversible Electroporation Probe Orientation on Phrenic Nerve Function Post Therapy

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Background: Phrenic nerve injury can be a serious complication of cardiac ablation procedures used to treat arrhythmias. It is well documented that the pulmonary veins are an area of arrhythmia genesis and thus they are common ablation sites for therapeutic ablations. Recently, irreversible electroporation (IRE) is being considered for such procedures, yet there is little known relative to the energy thresholds of this modality for inducing nerve injury. IRE is a non-thermal ablation method that employs an electric field to elicit localized tissue damage. The objective of this study is to examine the response of the phrenic nerves to IRE utilizing two different probes orientations.

Methods: In an anesthetized swine, phrenic nerves (n=22) were dissected from the pericardial space using direct visualization. Each nerve was placed into a nerve-recording chamber and stimulated proximally with a 1V, 0.1mS square wave pulse. Induced compound action potentials were recorded from three sites on each nerve. The nerve recording chamber was then placed in an ablation apparatus and a single irreversible electroporation therapy ranging from 500V/cm to 2750V/cm was applied to the nerve using the NanoKnife (Angiodynamics, Latham, NY) system. The probes were either placed parallel or perpendicular to the nerve. Following ablation, viability was assessed and between assessments the nerve was submerged in a Krebs buffer and oxygenated. The final action potential waveforms recorded at 2 hours post-ablation, were analyzed to determine the relative effects the ablation.

Results: The average normalized action potential amplitude (to baseline) at the recording site post ablation on the nerve was 0.562 ±0.099 when the probes were placed perpendicular to the nerve compared to 0.62± 0.101 with the probe parallel (p>0.05). This shows that the orientation of the probes did not significantly affect injury formation, thus suggesting that the area of the electric field the nerve is exposed to was not as important as the applied energies of the electric field, when looking at long-term outcome.

Conclusions: The nerve was just as susceptible to damage regardless of probe orientation. This data is helpful for device designers and clinicians as they continue to develop a device that can deliver the IRE ablative therapy, which may or may not alter nerve function. In other words, such data may have important utility when one considers thresholds for minimizing (e.g., during a cardiac ablation procedure) or inducing injury (e.g., in a renal denervation) or comparing IRE to other ablation approaches.

References:

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Noninvasive EEG-Based Control of a Robotic Arm for Reach and Grasp Tasks

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Background: It is of significance to developing brain-computer interface systems controlling external devices or prosthetic limbs [1]. Noninvasive electroencephalography (EEG) based control of a robotic arm for reaching and grasping targets by motor imagination in the real world was explored in this study. Compared with BCI studies in virtual environments [2], interaction with physical device might greatly motivate the subjects to engage in the experiments [3]. We aim to test the hypothesis that human subjects using motor imagination protocol can operate a robotic arm reliably, from sensorimotor rhythms detected from noninvasive scalp EEG.

Methods: EEG data were recorded for 13 subjects by a 64 channel Neuroscan cap, among which EEG channels over left and right motor cortex were utilized to be the online control signals. Each subject performed 8-15 sessions of instructed experiments including virtual cursor control and physical robotic arm control. Each subject first performed one to four sessions of virtual cursor experiments as training and then progressed to two sessions of reaching and grasping with four targets via the robotic arm and three sessions of reaching and grasping with five targets via the robotic arm, all while the moving cursor was displayed on the monitor (Fig. 1a). Finally, they performed two extra sessions of reaching and grasping via the robotic arm and four with five targets in absence of the virtual cursor movement. All of the protocols were approved by the Institutional Review Board of the University of Minnesota. EEG activity from the control channels was spatially filtered and then fed into an autoregressive model to extract the power spectra features. The power activities in the upper mu frequency band over the left and right hemisphere were linearly mapped to the position of the robotic arm. The robotic arm, which is a seven degree of freedoms human-like robotic arm, was mounted on the right side of the subject (Fig. 1a). A two-step task was employed to assist the participants’ ability to reach and grasp an object in 3D space. The robotic arm moved in a horizontal plane in the first step and moved vertically in the second step.

Fig. 1 (a) Experimental paradigm for 5 targets reaching and grasping. (b) Group average PVC of 4 and 5 targets reaching and grasping with and in absence of cursor movement. (c) Group average number of blocks grasped for the same two tasks with and in absence of cursor movement.

Results: Fig. 1b shows the group average percent valid correction (PVC) for the four targets and five targets reaching and grasping tasks on the left side and right side of the plot, respectively. The green bar shows the results of reaching and grasping with the cursor displayed on the monitor and the gray bar shows the same results in absence of cursor movement, in which only designated target to be grasped was shown. The group average PVC for six subjects of reaching and grasping with four targets was about 90%, which was similar to the corresponding results in absence of cursor (~91%). The group average PVC of reaching and grasping with five targets was about 83% and the corresponding results in absence of cursor were about 79%. The group average number of blocks for grasping four targets and five targets in each run are 9.7±2.1 and 9.2±1.4, respectively; 26 trials in each run were completed in about six to nine minutes and each session consisted of four or five runs. The maximum number of blocks (targets) in each run that can be grasped was 13. The group average numbers of blocks for counterparts in absence of cursor in each run are 9.5±1.2 and 9.3±1.4, respectively.

Discussion: With the motivation of controlling a real robotic arm to accomplish a series of reaching and grasping task, the majority of subjects showed high and consistent accuracies in the relatively longitudinal sessions. The comparison of results between the controlling the robotic arm with the virtual cursor and in absence of virtual cursor indicates that there is no significance difference between the two conditions. This implies that controlling a robotic arm by the input of either a remote terminal or subjects’ direct visual input would show similar performance.

Conclusions: We demonstrate the capability for human subjects to control a robotic arm from noninvasive EEG for reaching and grasping tasks in 3D space. Our promising results indicate that noninvasive EEG-based BCI is able to provide high precision and efficiency for controlling a robotic arm to finish complex reaching and grasping tasks in a real world. This promising finding indicates potential in future applications of noninvasive BCI for neuroprosthetics.

References:

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Effects of Soft Drink on Brain Computer Interface

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Background: Studies show that mind-body awareness, motivations, and other factors can perturb brain activity and thus affect online BCI performance [1, 2]. Since caffeine is the most commonly consumed stimulant and soft drinks represent a substantial portion of caffeine intake, this work studied the effects of soft drinks on BCI performance and resting state brain signals [3] used in BCI. Relative to a control soft drink, the sugary soft drink caused a negligible difference in resting-state alpha power and BCI performance. A caffeine soft drink decreased resting-state alpha power, but maintained BCI performance.

Methods: Noninvasive electroencephalography (EEG) data were recorded for 12 healthy subjects via a 64 channel Neuroscan cap. Electrodes over left (C3) and right (C4) motor cortex recorded control signals for online BCI. Each subject came in for three sessions. All sessions started with two runs of left or right (LR) virtual cursor control with 30 trials in each run. Then the subject drank a Coca-Cola variant with either caffeine, sugar, or neither substance (considered control). The drink selected for each session was randomized across subjects to use all six drink order permutations. The subjects were blinded to the Coca-Cola variant and consumed the 12 oz. drink in five minutes. Then 32 minutes of resting-state data were collected by alternating between eyes open and eyes closed for two minutes segments. Finally, subjects performed two more runs of LR cursor control. The power activities in the upper mu frequency band over left and right hemisphere were linearly mapped to the velocity of the virtual cursor. To minimize the residual effects, subjects did not consume sugary nor caffeinated drinks at least four hours before the experiments. We performed most of the experiments between 1:00 PM and 6:00 PM.

Results: The global power of alpha and beta frequency bands for three conditions and channels C3 and C4 throughout resting state is shown in Fig. 1a. For both C3 & C4 and global, note the similarity between control and sugar consumption in the power of alpha and beta band. Caffeine consumption causes alpha power to decrease substantially from control. Group average percent valid correct (PVC) of all subjects is shown before and after each type of drink in Fig. 1b. BCI performance increases slightly after caffeine and control drinks. Sugary drinks cause average PVC to decrease and cause the largest standard deviation of performance. The change of PVC after consumption of each drink is displayed in Fig. 1c. Caffeine consumption shows slightly higher improvement of PVC than the control, while the sugar consumption leads to a decrease of PVC. Caffeine consumption also causes the smallest deviation among drinks, while the sugary drink mostly decreases the PVC.

Discussion: The sugary drink seems to have no significant effect on C3 and C4 alpha power relative to the control. For caffeine, both alpha and beta power decreased in C3 and C4, which is consistent with previous literature and global results, where caffeine caused a decrease in global alpha power [3]. Since the alpha power of C3 and C4 are directly utilized to control virtual cursor movement, this alpha power decrease at rest due to caffeine might lead to a weaker control signal with smaller dynamic range. However, caffeine is also known to increase attention and reduce fatigue [3], which may reduce performance deviation and improve BCI performance. The results show caffeine consumption does not improve BCI performance relative to the control drink. The BCI performance effects due to resting-state alpha power decrease, increased attention, and reduced fatigue seem to cancel out one another. Sugar consumption caused a slight decrease in average BCI performance.

Conclusions: With the prevalence of soft drinks and caffeine, their effects on BCI performance are worthy investigating. Caffeine seems to have negative frequency effects and positive attention effects that combine to cause negligible changes in BCI performance, while sugary drinks might decrease BCI performance relative to the control condition. As researchers push the boundaries of non-invasive BCI systems with quadcopters, robotic arms, and cars, these results shed light on how the world’s most popular stimulant, caffeine, affects BCI performance.

References:

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Paraventricular hypothalamic activation is required for hippocampal stress and glucocorticoid receptor over expression in fear-induced stress

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Abstract

For several decades, the role of corticotrophin and glucocorticoids have been described in the propagation of stress signals in the mammalian nervous system. However, till date the mechanism through which event-dependent corticotrophin-releasing factor receptor (CRF-R) activation, in the paraventricular hypothalamic nuclei (PVN), contribute to hippocampal stress response in predator exposure remains elusive. In this study, we induced stress by exposing naïve mice to a predator (Cat) for two events; 45 minutes each at 10 days’ interval in alternating light and dark cycle. Subsequently, using chemogenetic method, we activated the PVN of a separate set of naïve mice without any predator exposure. In another group, the PVN was inhibited during both predator exposure events. The outcome of this study showed that PVN activation, and predator exposure stress caused an increase in CRF-R expression in the PVN (and brain in general), and was associated with anxiety, then depression-like behavioral changes. For both groups, as an evidence of induced stress, an increase in the expression of hippocampal glucocorticoid receptor (GCR), total brain GCR and heat shock proteins (Hsp70 and Hsp27) were recorded. The effect of predator exposure and PVN activation stress on synaptic dysfunction cannot be overemphasized. As such, downstream kinases (MAPK/ErK and CamKIIα) involved in the regulation of synaptic plasticity in the hippocampus were downregulated. Ultimately, inhibition of the PVN, during a stress event did not prevent hippocampal neuronal activation (c-FOS); although it reduced the threshold of synaptic changes and glucocorticoid receptor expression in the hippocampus. Furthermore, the animals showed an improvement when tested for depression behavior in elevated plus maze (EPM); versus the stress or PVN activation models.

Key words: DREADDs, PVN, Hippocampus, Stress, Synapse
Multiple alpha frequencies comprise the alpha band and are enhanced during binocular rivalry

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Background: Alpha oscillations (5-15 Hz) are a consistent feature of human EEG oscillations that are involved in a multitude of sensory and cognitive tasks, and they are often thought of as reflecting a unitary underlying process. We assessed what types of alpha oscillations are reliably identified during a visual illusion called binocular rivalry, and used ICA (independent components analysis) to find temporally independent alpha oscillations. Modulating the task from spontaneous rivalry alternations to replayed alternations altered the ongoing EEG alpha oscillations showing distinct sub-band peaks and an enhancement of overall power during rivalry.

Methods: We optimized an analysis algorithm to identify and select consistent alpha components across subjects through ICA (Independent Components Analysis). Normal human subjects were asked to respond to gratings presented either in conflict or congruently, and 64 channel EEG (neuroscan) was collected for offline analysis. We filtered ongoing alpha oscillations from 2-30 Hz and manually identified components with physiological properties showing either peaks in alpha (5-15 Hz) or theta (2-6) power spectra.

Results: Alpha oscillations are often grouped into a wide band (5-15 Hz) and thought to comprise a unitary process, however, we find that different sub-bands of alpha oscillations emerge during ongoing rivalry and replay, and are further enhanced during rivalry. We characterize multiple independent components with distinct topographies and spectral distributions and varying levels of involvement in the task, indicating distinct functional subdivisions of the alpha band. We also find temporally independent alpha components which are more likely to be co-identified with the theta band, indicating a possible relationship between the two bands.

Conclusions: Ongoing alpha oscillations during rivalry show distinct topographies and functional divisions during rivalry and replay paradigms. Multiple sub-bands of alpha oscillations can be identified in the ongoing oscillations given sufficient precision of the power spectral density, and seem to change peak frequency over time. Co-derived alpha and theta components can also be observed as independent components.

References:

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ECoG Behavioral Correlates based on Neuromodulation Rates

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Background: Event-related oscillations or induced potentials reflect the synchronous average activity of neural populations over time. In particular, the precise timestamps of such neuromodulations is somehow underestimated when classical decomposition tools are utilized, e.g. Spectrogram or Time-Frequency analysis. In addition, these techniques do not explicitly incorporate the noise component that is pervasive in this type of recordings; hence, they provide a qualitative assessment regarding the structure of the data, however, they fail to quantitatively model the relevant temporal elements of the traces, i.e. neuromodulations. We propose a generative transient-based model that is fully data-driven and is able to preserve the temporal resolution up to the sampling frequency scale. Moreover, neurophysiological priors and robust dependence measures are key factors; in this way, the noise component is processed in a principled manner, thus, guaranteeing that relevant neuromodulations alone are quantitatively modeled.

Methods: Bandpassed single-channel, multi-trial traces are fed to our learning algorithm that resembles the clustering technique, k-means. Singularly, one stage encodes the relevant temporal patterns by assigning them to the closest element in a filter bank, while the second stage updates such filters utilizing low-rank decomposition techniques. In particular, the encoding stage exploits the idea that relevant neuromodulations are only one of the two elements present in a surrogate probability density function; by isolating this mode of the data, the encoding process is not only computationally efficient, but also neurophysiologically sound [1]. The second mode of the data is comprised of inter-phasic events segments that represent unsynchronized neuronal assemblies, ongoing activity or, using a general term, noise. The second stage utilizes correntropy as a robust cost function to update the filters and provide an extra level of insurance against noise [2].

Results: The proposed methods are applied to BCI competition IV dataset 4 [3]. We focus on the low-gamma band (76-100 Hz) of ECoG traces from cued finger flexion tasks. The estimated timestamps of the relevant neuromodulations are then utilized to compute the phasic event rates before and during the motor tasks in a scheme resembling action potential processing. The relative rate difference (Fig. 1) is statistically significant over electrodes for each finger (1-way ANOVA, p < 0.01).

Conclusions: This novel approach to neuromodulations relies on the density or rate of relevant phasic events over time by applying data-driven techniques to ECoG traces. Our analysis goes beyond common amplitude-based paradigms that neither properly consider the noise component nor incorporate fine temporal resolution of event-related oscillations.

References:


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Fig 1. Finger flexion is spatially encoded by the rate difference of neuromodulations. Delta represents the relative rate difference 2 seconds before and 2 seconds during finger flexion tasks for each electrode over the motor cortex. From top to bottom: Finger 1,2,3,4,5.
The analgesic efficacy of MMG22 in targeting a putative MOR/mGluR5 heteromer in a murine model of bone cancer pain

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Background: Pain has been reported to be among the most common symptoms in patients with cancer. It has been reported that 90% of patients with end-stage cancer experience pain. Management of cancer pain with opiates is a challenge due to their side effects and development of tolerance. Studies have shown that co-administration of mu opioid receptor (MOR) agonist and a metabotropic glutamate receptor-5 (mGluR-5) antagonist reduced the tolerance and dependence of morphine as well as augmented its analgesic properties. This finding and reported evidence for MOR-mGluR₅ heteromer in cultured cells led to the development of MMG22, that contains both mu agonist and mGluR-5 antagonist joined by a 22-atom spacer. Intrathecal administration of MMG22 potently reduced mechanical hyperalgesia in a mouse model of bone cancer pain and was ~1000x more efficacious than morphine via i.t. administration. In this study, we determined the efficacy of MMG22 given subcutaneously (s.c), and whether analgesic tolerance developed by this route of administration.

Methods: Adult male C3H/He mice were used. Fibrosarcoma cells were injected into and around the calcaneus bone in one hind paw. Mechanical hyperalgesia was defined as an increase in the frequency of paw withdrawal (PWF) evoked by application of a von Frey monofilament (3.9 mN bending force) applied to the plantar surface of the hind paw. PWF was determined before implantation of cancer cells into the calcaneus bone of the hind paw, and before and at 30, 60 and 120 mins post-injection of either MMG22 or morphine on post- cancer cell injection day (PID) 3, 10, 17 and 24. Compounds were administered s.c. to determine peak time effects and ED₅₀/₈₀s were calculated.

Results: MMG22 produced dose-dependent antihyperalgesia. On PID 3, the ED₅₀ for MMG22 was 0.36mg/kg) and was to be 6.23 times more potent than morphine. The ED₃₀ dose decreased with tumor growth. ED₃₀ doses were 0.15 mg/kg and 0.004 mg/kg on PID 10 and 17; these were 14.9 and 560 times more potent than morphine (ED₃₀: 2.24 mg/kg), respectively. On PID 24 the ED₅₀ dose for MMG22 was 0.002 mg/kg, 1120 times more potent than morphine. The peak time of antihyperalgesia following MCC22 was 60 minutes after injection for all doses. Importantly, unlike morphine MMG22 exhibited no tolerance to its antihyperalgesic effects, and appeared to increase in potency over the time course.

Conclusions: MMG22 potently attenuated hyperalgesia in a murine model of cancer pain when administered s.c. and, unlike morphine, showed potentiation as tumor growth progressed without tolerance. Therefore, MMG22 may be useful for treating cancer pain as well and other pains that are difficult to manage.
MMG22, the Benefits of Combining an mGluR5 Antagonist with a MOR Agonist for Analgesia

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**Background:** Opioids are the most effective pharmacological tools to treat moderate to severe pain; however, the use of opioids for the treatment of chronic non-cancer pain is controversial due to concerns about tolerance, abuse, and addiction. MPEP, an mGluR5 antagonist has been shown to increase the analgesic efficacy of opioids while simultaneously decreasing the development of analgesic tolerance and addiction (1). MMG22 is a novel bivalent ligand made of two pharmacophores: oxymorphone, a MOR agonist, and M-MPEP an allosteric mGluR5 antagonist, linked via a 22-atom spacer (2). Previous studies have shown MMG22 to be an incredibly potent at decreasing inflammatory pain while not producing tolerance or respiratory depression (2). In the present studies, we sought to characterize the ability of MMG22 to modulate neuropathic pain and evaluate its abuse potential.

**Methods:** Using the spared nerve injury of neuropathic pain in mice we assessed the effects of subcutaneous MMG22 on mechanical hyperalgesia by evaluating the frequency paw withdrawal to a tactile stimulus. We also assessed the rewarding properties of MMG22 as compared to morphine in naïve mice using conditioned place preference. Using immunohistochemistry and fluorescence microscopy we evaluated the localization of mGluR5 and MOR in the mouse spinal cord superficial dorsal horn.

**Results:** Preliminary results strongly suggest that while MMG22 is effective in reducing mechanical hyperalgesia, supra-threshold doses do not produce conditioned place preference. Both MOR and mGluR5 are expressed in the superficial dorsal horn.

**Conclusions:** MMG22 has the potential to be an effective therapeutic for the treatment of neuropathic pain that may lack the addictive properties of traditional opioid analgesics.

**References:**


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Model Validation and Stimulus Transduction Properties of Pacinian Corpuscle Vibrotaction

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Background: Utilizing a recently developed multiscale physics model (Quindlen et al 2016) of the Pacinian Corpuscle (PC), a somatosensory afferent responsible for transducing vibrational stimuli, this study aims to explore the psychophysical and neurophysiological properties of vibrotactile stimulation. The ability of human subjects to discriminate a variety of haptic stimuli with multiple spectral components, i.e. chords, is investigated using detection theory, and compared to the ability of the computational model to do the same. This comparison is then used for model validation purposes, and for exploring aspects of PC physiology, in particular the neural signal coding scheme and the effect of noise on information content of spike trains. Deficits in somatosensory perception have been linked to a variety of disease states, such as diabetic peripheral neuropathy, and as a comorbidity with movement disorders, such as Parkinson’s disease or focal dystonia (Patel et al 2014). Parameterizing the physiology of somatosensory afferents in healthy subjects using this approach will provide the groundwork for the design of better clinical testing of somatosensory deficits, as well as provide useful insight into the psychophysics and neural coding properties of PCs for somatosensory neuroprosthetic, and peripheral neuromodulation applications.

Methods: Psychophysical experiments are carried out using the “Same-Difference” method for determining the discriminability of two stimuli (Macmillan and Creelman 2005), using human subjects in accordance with IRB guidelines. Psychophysical experiments are simulated on the PC model using an adapted version of the “Same-Difference” method in conjunction with information theory approaches, specifically mutual information calculations. COMSOL, Neuron, and MATLAB, are used to simulate PC physics, action potential propagation, and signal processing, respectively. Spike trains are processed by a variety of decoding schemes for comparison, such as fire rate, inter-spike interval histogram, and fast-Fourier transform (FFT) of the membrane voltage. Human psychophysical data is then compared to simulated single-cell psychophysics.

Results: Preliminary results indicate that individual, simulated PC axonal firing patterns for chordal stimuli correlate with the discriminabilities of the same stimuli found in human tests in noiseless conditions. Different schemes for decoding the PC firing patterns are effected differently by the addition of noise, for instance FFT and firing rate being more robust than inter-spike interval based codes. Moreover, the addition of some noise to the computational model is able to improve its correlation to real-world, noiseless psychophysical experiments, and, depending on the coding scheme used, the addition of noise can also increase the mutual information of the action potential coding scheme with the stimulus set.

Conclusions: This experiment is still ongoing, however these preliminary results indicate the psychophysics of haptic vibrations can be modeled using single-cell, physics based approaches. In such an approach, noisy signals can better approximate the collective behavior of PC populations underlying human somatosensation. These findings may be useful for the design of clinical tests for somatosensory deficit, or peripheral neuromodulation devices.

References:

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A flexible electrode for investigation of neurotransmission in a freely-moving large animal model

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Introduction: Studies have used fast scan cyclic voltammetry (FSCV) in awake small animal models¹ to measure changes in dopaminergic neurotransmission implicated in many neurologic and psychiatric disorders. Unfortunately, electrode stiffness and wires connecting the electrode to the recording device make existing systems unsuitable for neurochemical monitoring in freely-moving large animals. Here we describe the development, implementation, and preliminary testing of a chronically-implanted flexible electrode for investigation of neurochemical activity in a freely-moving large animal model.

Methods: We developed a custom-built carbon fiber microelectrode (CFM) with a flexible lead system. A T-300 carbon fiber sensing element was mounted onto the front-end of a 50 cm section of 1.27 mm diameter Silastic™ tubing (Figure 1). A ring reference electrode was mounted proximal to the tip of the electrode. Connections to the sensing element and reference electrode were made with stainless steel wire coiled around a tungsten stylet (removed after implantation). The ability of the electrode to measure in vivo neurochemical signals was tested in awake swine by stimulating the substantia nigra pars compacta/ventrotegmental area and recording the neurochemical signals evoked in the striatum using a wireless device, WINCS Harmoni. A six contact 0.6 mm diameter stimulating electrode (NuMed, Hopkinton, NY) was implanted into the substantia nigra pars compacta/ventrotegmental area. Both electrodes were implanted using image-guided stereotactic targeting and externalized at the back of the swine neck. WINCS Harmoni was placed inside a backpack and connected to the externalized electrodes. Stimulation-evoked neurochemical release and associated behavioral responses were recorded in the awake animal 48 hours after implantation and once weekly for five weeks in order to characterize changes in the electrochemical response.

Results: During implantation, stimulation-evoked dopamine release was detected in a large animal model of brain stimulation using the flexible CFM with an integrated reference electrode. Wireless FSCV measurements were successfully performed in the freely moving swine model for more than five weeks post implantation and robust background current was observed, however no stimulation-evoked dopamine release was detected.

Conclusion: The electrode design described herein allows for neurochemical monitoring in large animal models of awake behavior. This represents the first step toward enabling studies aimed at furthering insight into the role neurotransmission during behaviors associated with neurologic health, disease, and response to treatment.

References:


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A Rate-Distortion Analysis of Spike Compression Based On Vector Quantization

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Background: Neuroscience research has benefited tremendously from methods of recordings in awake brains. By introducing microelectrodes into different structures of the brain, scientists have been able to study the response properties of single neurons and the relation between neuronal activities and behaviors. The increasing number of concurrently monitored neurons has introduced new opportunities as well as computational challenges by generating a tremendous amount of data for analysis. To transmit a large amount of data through data links with limited bandwidth, data compression is required to reduce data rate while preserving signal fidelity as much as possible.

Methods: Vector quantization (VQ) is a classic lossy compression algorithm in communication theory and has been widely applied in image/video coding, pattern recognition, etc. Its idea is appealing: in real-world applications, high-dimensional data blocks, or “vectors”, tend to form clusters, occupying small portions of the entire space. By re-quantizing the data using a carefully designed codebook dependent on data distribution and transmitting only the codebook index, significant data compression can be achieved. We notice that spiking activities are sparse in both temporal and spatial domains, which makes them suitable for VQ-based compression. In this work, we design a codebook in two steps, including a fast pairwise nearest neighbor (PNN) algorithm to generate the initial values of codebook and a Linde-Buzo-Gray (LBG) algorithm to fine-tune the codebook through iterative computations. The squared Euclidean distance is chosen as the distortion measurement in our implementation. Inspired from the Shannon’s rate-distortion theory, we further study the relation of compression ratio and spike segmentation by evenly splitting each spike into several pieces.

Results: We prepare 1272 spikes for experiment, each containing 40 data samples previously recorded from an in-vivo preparation. Spikes are digitized in 12-bit. The vector dimension varies from 2 (one spike segmented into 20 pieces) to 40 (no segmentation), and the size of codebook varies from 32 to 512. Compression ratio is calculated as rate = bits × vector dimension / \log_2(\text{size of codebook}). The result, given in Figure 1, shows a clear performance distribution bounded by the rate-distortion theory. VQ-based methods can achieve significantly better results than wavelet, compressive sensing, etc.

Conclusions: We propose an improved spike compression method based on VQ theory and validate its performance using in-vivo data. The method shows great potential in achieving significant data compression compared with previous methods while much preserving signal quality, hence suitable for processing spikes simultaneously recorded from many channels.

![Figure 1](image-url)

Figure 1. Results of compressing 1272 spikes recorded from an in-vivo preparation using VQ with multiple configurations. (a) X-axis is vector dimension, i.e., how many data samples contained in a single vector. Y-axis is the reconstruction accuracy, defined as the ratio of original signal energy over the squared distance between original spikes and reconstructed spikes. The five curves correspond to results obtained with codebooks of different sizes from 32 to 512. (b) Vector dimension versus compression ratios. In general, higher vector dimension and smaller codebook will lead to a higher compression ratio at the cost of poorer reconstruction accuracy, i.e., the “rate-distortion” tradeoff. In the figure, the highest compression ratio is 96× at the upper right corner, when vector dimension is 40 (no segmentation) and reconstruction accuracy is 0.911.
Stimulation and Low-Noise Artifact-Free Recording Chip

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**Background:** It is well known that existing ability to electrically record and stimulate autonomic nerves is limited and that new technologies are required to provide high-fidelity chronic recording and stimulation in animals for basic science studies and eventually for human clinical devices. Several major limitations towards achieving chronically stable neural recording and stimulation include: 1) the poor signal-to-noise ratio of spontaneous neural signals in autonomic nerves, 2) the inability to record microvolt-level nerve activities in the presence of stimulation pulses applied to the same nerve, 3) the inability to extract signals of individual fascicles with current noninvasive electrodes, and 4) the inability to develop chronic stability with current invasive electrodes. In this research, we propose to develop a low-noise recording chip for sensing nerve activities at a sub-10-microvolt range. This low-noise chip will be optimized based on our previous circuits that can support simultaneous recording/stimulation and isolate 20-30µV neural signals from large artifacts.

**Methods:** We propose new circuit techniques to improve neural recorder performance. Specifically, we have optimized the transfer function and increased the loop gain of our frequency shaping amplifier [1] for noise reduction. We have examined and isolated noise injections due to charge transfer from parasitic capacitors and couplings from the environment for reducing stimulation induced artifacts and noise, thus achieving simultaneous recording and stimulation function. We have designed a switched operational amplifier and a gated switching network with adaptive biasing circuits. As a result, the frontend amplifier, main amplifier, buffer, and the built-in low-pass filter share the same operational amplifier, leading to major power saving. To reduce the circuit area, we have used high-density but nonlinear MOS capacitors instead of metal-insulator-metal capacitors. We have carefully designed the operating conditions for each capacitor and successfully avoided nonlinear amplification and signal distortions. Compared with our previous neural recorder [2], the noise, power, and area in the new design have been reduced by 10-fold, 7-fold, and 1.5-fold, respectively.

**Results:** Figure 1 summarizes the measurement data. The input-referred noise of the recorder is 1.71µV at 1-1000Hz, 2.16µV at 300-8000Hz, and 1.0µV at 700-3000Hz. It can accommodate up to 0.4V motion artifacts and stimulation artifacts in experiments. The power consumption is 15µW per channel, and the core area is 0.16mm² per channel. In experiments with microelectrodes, our circuits can isolate 20-30µV neural signals in the presence of stimulation artifacts. To our best knowledge, our chip is the only design that can perform simultaneous recording and stimulation without saturation and without incurring a penalty from stimulation induced noise.

**Conclusions:** A low-noise, low-power neural recording chip has been developed. By using various circuit techniques, we have achieved competitive performance in input impedance (3pF), effective dynamic range, power consumption, and input-referred noise. Our goal is to further improve its noise characteristic and develop electrode noise reduction techniques to resolve sub-10-microvolt neural signals for autonomic recording and neuromodulation.

**References:**


MEG/EEG Source Imaging of Interictal Activity

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Background: Most healthy and pathological processes in the brain involve distributed networks. In order to effectively modulate pathological networks, the underlying dynamics of such networks need to be understood and monitored during the administration of the neuromodulatory therapies [1]. Electromagnetic source imaging (ESI) provides high temporal resolution of underlying brain sources and it is used extensively in monitoring many neurological conditions, including epilepsy [2]. MEG and EEG both record electromagnetic signals with high temporal resolution solutions (~1 ms). ESI can provide estimations of the location of epileptic brain network nodes as well as inter-connections and dynamics of the epileptic network. This information can be used to guide neuromodulation and other therapies for treating epilepsy and other neurological disorders.

Methods: In this study, MEG and EEG were recorded from patients suffering from focal epilepsy. Inter-ictal spikes (IIS) were selected from the recordings of epileptic patients and the underlying epileptic sources were estimated. This was realized through solving the inverse problem, which is the process of estimating underlying brain electrical activity from noninvasive recordings. 148-channel MEG and 64-channel EEG were recorded spontaneously during IIS, as well as subjects’ structure MRI. The patients in this study were considered for surgical resection as these patients were not responding to anticonvulsant medications. The MEG/EEG recordings were monitored for IIS and averaged IIS were input into the ESI algorithms, then results were combined to estimate underlying epileptic nodes. Granger Causality was then applied to analyze network between nodes to determine the onset zone of seizures and epileptic activity. The results were compared to clinical findings such as surgical resection (obtained from post-operational MRI).

Results: The results indicate that source imaging results from MEG/EEG recordings coincide well with the clinical findings. In the example presented in Fig.1, the maximum of localization result fell inside of the resection area and the identified source area was overlapping well (~60%) with the clinically resected zone. In multiple-node case, onset zone determined by network analysis accorded well with resection.

Conclusions: Although, our study was performed in epilepsy only, ESI is a powerful tool that can be used effectively to study and understand the location and inter-dynamics of the nodes of underlying brain networks. Such efficient tools shall provide useful information to guide interventional procedures such as surgery or neurostimulation [3]. ESI methods can be integrated with neuromodulation therapies in a closed-loop fashion to achieve better outcomes.

References:


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MEG Epileptogenic Zone Localization before RNS Implantation in a Mesial Temporal Lobe Epilepsy Patient

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Background: About 30% of epilepsy patients are drug resistant, most of whom have mesial temporal lobe epilepsy. Resective surgery of the anterior temporal lobe including the amygdala and hippocampus has been an effective treatment. However this procedure has the potential to result in memory deficit in some patients and particularly in patients with bitemporal onset. In this population, neuromodulation treatment such as responsive neural stimulation (RNS) may be the treatment of choice. Prior to RNS implantation, identifying epileptogenic zone/s is important for successful treatment. Magnetic source imaging (MSI)/Magnetoencephalography (MEG) has been considered a clinical tool for pre-surgical evaluation in drug-resistant epilepsy patients since 2002. We are reporting a patient with bilateral mesial temporal epilepsy who underwent MSI evaluation before RNS implantation.

Case description: A 63-year-old, right handed female patient has been having seizures since age of 37 due to repeated head trauma. She failed multiple anti-convulsive medications. She averaged one complex partial seizure per month and 4 generalized tonic clonic seizures a year and had a severe short term memory deficit. Her long-term video EEG monitoring revealed independent seizures from left temporal lobe and right frontotemporal lobe. Clinically her seizures presented as automatisms with staring, confusion and unresponsiveness. The MEG/EEG recording was conducted with a 148 magnetometer system simultaneously with 21 channel EEG housed in a magnetically shielded room (MSR). Independent interictal epileptiform discharges from left temporal lobe and right temporal lobe were noted. After averaging the left and right interictal magnetic fields, the dipoles of interictal epileptiform activity were located at left and right mesial temporal lobes. RNS depth electrodes were implanted into left and right hippocampal-amygdala regions and strips on the lateral temporal lobes in August 2016. Independent interictal and ictal discharges were recorded from both depth electrodes. Hippocampal detection prior to therapy revealed prominent and at times nearly continuous independent and synchronous interictal activity. Since RNS therapy initiation using the depth electrodes bilaterally, the patient has had only 1 GTC and the family reports they are not “seeing the staring spells”. The “long episodes” detected with ECoG paradigm have been reduced by 86.4%. Further follow-up is needed to determine the eventual clinical effectiveness of RNS for seizures and possibly improve memory function.

Conclusion: Pre-implantation of RNS, MEG/MSI epileptogenic zone localization/lateralization may be helpful to guide RNS electrodes placement.

Deterministic Compressed Sensing Encoder for On-Chip Neural Data Compression

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Background: Real-world behaviors necessarily involve the simultaneous activation of large populations of selective neurons in patterns that cannot necessarily be characterized by studying neurons one at a time in isolation, as the vast majority of studies have. While recent advances in microelectrode fabrication have dramatically increased the number of individual neurons that can be simultaneously recorded from, further progress requires addressing the capability to transmit and process large-scale neural data in real-time to find causal relationship within the high-dimensional dataset defined by the multi-channel activity and complex behaviors. In this paper, we propose a data compression algorithm and its implementation in microchip for a miniature wireless neural interface. Compressing neural data on-chip allows more channels to be transmitted wirelessly, however, it is constrained by the very limited hardware resources and power budget. Innovating efficient neural data compression algorithms and low-power microchip implementation are the two focuses of this research.

Methods: We propose a novel and efficient compressed sensing (CS) encoder design for spike data compression in resource-limited conditions, such as a high-channel count wireless neural interface. We propose deterministic Quasi-Cyclic Array Code (QCAC) sensing matrix and demonstrate much improved area and power metrics compared with previous designs. We have performed a comprehensive evaluation of different algorithms on a public dataset [1], where we find the proposed QCAC algorithm has maintained a consistent recovery performance using basis pursuit algorithm [2]. In our comparison, all CS encoders are implemented in Verilog HDL with customized near-threshold library (0.5V) in 65nm CMOS standard cell libraries.

Results: Compared to the state-of-the-art CS encoder designs, QCAC-based CS encoder achieves on average (with compression ratio ranging from 0.0625 to 0.25) 42.7% and 49.5% reduction in encoder area and total power consumption, respectively. And the compressed spikes from the QCAC-CS encoder can be recovered with comparable performance toward random matrix based CS encoder designs. Specifically, QCAC-CS encoder leads to better recovery performance at low measurements, which is what we need for the application.

Conclusions: We propose a novel and efficient CS encoder design for on-chip spike compression. It achieves improved reconstruction performance under high compression ratio with reduced hardware resources and power consumption.

Figure 1. (a) Wireless neural recorder employing compressed sensing technique; (b) VLSI architecture for random binary matrix generation and parallel encoder architecture; (c) VLSI architecture for QCAC-CS encoder with efficient matrix generation and parallel-folded architecture; (d) matrix sparsity versus matrix size n, embedded is binary images of random binary matrix (red arrow) and QCAC matrix (blue arrow), black and white squares indicate binary value of “0” and “1”, respectively; (e) Compressed spikes recovery performance: SNDR vs. measurement with an example spike reconstruction illustration of different measurements, m=4, 8, 12, and 16; Signal-to-Noise and Distortion Ratio (SNDR) is defined as SNDR = 20log(||x||^2/||x- x̂||^2); (f) QCAC and RB CS encoder area (synthesized in 65nm CMOS) versus measurement; and (g) QCAC and RB CS encoder power consumption (total, dynamic and leakage in 65nm, 0.5V, 25°C) versus measurement.

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