4th Annual Symposium

October 27, 2014
BioScience Research Collaborative

Organizers:
Behnaam Aazhang, Ph.D., Rice University
Nitin Tandon, M.D., University of Texas Health Science Center at Houston
Dora Angelaki, Ph.D., Baylor College of Medicine
David Dickman, Ph.D., Baylor College of Medicine
Rob Raphael, Ph.D., Rice University
Caleb Kemere, Ph.D., Rice University
Jacob Robinson, Ph.D., Rice University
Melissa S. Thompson, Ph.D., Gulf Coast Consortia

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The Gulf Coast Consortia (GCC), located in Houston, is a dynamic, multi-institution collaboration of basic and translational scientists, researchers, clinicians and students in the quantitative biomedical sciences who participate in joint training programs, utilize shared facilities and equipment, and exchange scientific knowledge. Working together, GCC member institutions provide a cutting edge collaborative training environment and research infrastructure, beyond the capability of any single institution. GCC training programs currently focus on **biomedical informatics, computational cancer biology, molecular biophysics, neuroengineering and pharmacological sciences.** GCC research consortia gather interested faculty around research foci within the quantitative biomedical sciences, and currently include **bioinformatics, chemical genomics, magnetic resonance, protein crystallography, translational pain research, early disease detection, neuroengineering, and translational addiction sciences, in addition to regenerative medicine**. Current members include Baylor College of Medicine, Rice University, University of Houston, The University of Texas Health Science Center at Houston, The University of Texas Medical Branch at Galveston and The University of Texas M. D. Anderson Cancer Center.

Gulf Coast Cluster *for*
NEUROENGINEERING
ReEngineering the Human Nervous System

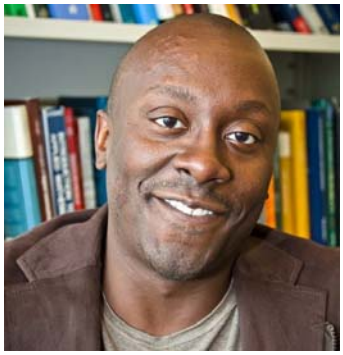
4th Annual NeuroEngineering Symposium

Monday, October 27, 2014
BioScience Research Collaborative (BRC)

Unless otherwise noted, proceedings will take place in the Auditorium.

8:45 AM	**Welcome and Introduction** Behnaam Aazhang, Rice University
8:50 AM	Keynote Address 1 Session Chair: Behnaam Aazhang, Rice University **Towards advancing neuro-engineering with bio-integrated electronics and scalable dynamic analysis methods** Todd Coleman, University of California San Diego
9:50 AM	Break
	Short Talks, Session 1 Session Chair: David Dickman, Rice University and Baylor College of Medicine
10:00 AM	**Engineering better memory** Jack Byrne, University of Texas Health Science Center-Houston
10:35 AM	**The next generation of deep brain stimulation** Ashwin Viswanathan, Baylor College of Medicine
11:10 AM	**On-Chip Electrophysiological Phenotyping in Intact *C. elegans*** Daniel Gonzales, Rice University (Trainee Speaker)
11:25 AM	**Improved Perceptual Performance and Coding Accuracy Following Optimal Stimulation of V1 Populations** Ariana Andrei, University of Texas Health Science Center-Houston (Trainee Speaker)
11:40 AM	**Introduction to IGERT Trainees** Rob Raphael, Rice University
11:50 AM	Poster Session (Event Space)
12:30 PM	Lunch, Poster Session Continued (Event Space)
	Short Talks, Session 2 Session Chair: Anne Sereno, University of Texas Health Science Center-Houston
1:30 PM	**High-Throughput Imaging Systems to Enable Whole Brain Phenotyping** David Mayerich, University of Houston
2:05 PM	**Moving beyond 2D vision: neural computation of 3D object representations** Ari Rosenberg, Baylor College of Medicine
2:40 PM	**The nature of semantic interference across language modalities: behavioral and neuroanatomical evidence** Tatiana Schnur, Rice University
3:15 PM	**An Integrative Bayesian Modeling Approach to Imaging Genetics** Michele Guindani, UT MD Anderson Cancer Center
3:50 PM	Break
4:00 PM	Keynote Address 2 Session Chair: Rob Raphael, Rice University **Stimulating for nothing: filtering peripheral nerve signaling via kHz electrical stimulation** Robert Butera, Jr., Georgia Institute of Technology
5:00 PM	Closing Remarks and Awards
5:15 PM	Reception (Event Space)

Keynote Speaker Biography



Todd Coleman, Ph.D.
Associate Professor of Bioengineering
University of California San Diego

This talk will discuss an inter-disciplinary platform our research group has developed that integrates applied math, neuroscience and bio-integrated flexible electronics. I will discuss the use of applied math and sequential experiment design principles to develop novel brain-computer interface applications. I will then discuss our attempt to address the unmet need for multi-model, wireless monitoring, with the development of "epidermal electronics." I will provide clinical uses of this technology with the context of neonatal neurology and chronic disease monitoring. I will then discuss our research group's development of physiologically-guided analysis methods that track ho behavior and physiology dynamically inter-relate and scale to the cloud. Lastly, I will discuss our ongoing development of implantable systems to monitor and modulate neurological processes inside untethered awake behaving animals, for the purpose of quantifying many aspects of the emerging field of social neuroscience. Throughout the talk, I will emphasize the inter-disciplinary nature of this research, involving research from engineering, statistics, neuroscience and medicine.

Bio: Todd P. Coleman received B.S. degrees in electrical engineering (summa cum laude), as well as computer engineering (summa cum laude) from the University of Michigan. He received M.S. and Ph.D. degrees from MIT in electrical engineering, and did postdoctoral studies at MIT in neuroscience. He is currently an Associate Professor in Bioengineering at UCSD, where he directs the Neural Interaction Laboratory and co-Directs the Center for Perinatal Health. His research is highly inter-disciplinary, lying at the intersection of bio-electronics, medicine and machine learning. HE is conducting research in wearable health by wedding his research group's expertise in large-scale analytics with their recent development of "epidermal electronics," featured in Science in 2011. Current applications of those synergies include perinatal health, chronic disease management, and cognitive monitoring during aging. Dr. Coleman is a science advisor for the Science and Entertainment Exchange (National Academy of Sciences) and his research has been featured on CNN, BCC and the New York Times.

Keynote Speaker Biography

Robert Butera, Jr., Ph.D.
Professor of Bioengineering
Georgia Institute of Technology

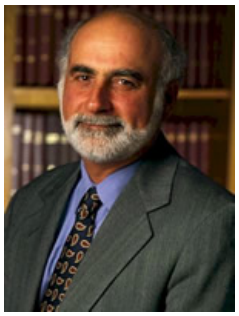
kHz high frequency electrical stimulation by alternating current (KHFAC) has been shown to be a quick and reversible means of blocking all conduction on an identified peripheral nerve. Medical devices using this technique are commercialized and/or undergoing clinical trials for applications varying from stimulators for pain relief of amputees to devices for managing appetite control and restoring bladder control. Recently, our lab has demonstrated that this technique does not have to be all-or-none, but can selectively block nerve conduction on specific nerves while permitting conduction from other nerves within the same fiber bundle. In this talk I will review past and ongoing experiments validating this technique, and discuss recent projects focused on 1) understanding the underlying mechanism via experiments and computational modeling and 2) pursuing clinical applications targeting modulation of internal organ function.

From his webpage:
The research in my lab ranges from neuroengineering to computational neuroscience. We utilize techniques including intracellular electrophysiology, extracellular electrophysiology, computational modeling, and real-time computing applied to conduct many of these experiments. Specific active research areas include:

- Neuromodulation of peripheral nerve activity. We study how kHz electrical AC stimuli block conduction in peripheral nerve, and how in certain circumstances this electrical block can be selective (i.e. only block specific fibers)
- Synchronization properties of neurons. We investigate how the biophysical properties of individual neurons relate to the ability of neurons to synchronize the timing of the firing of their action potentials to other neurons. The synchronization of neuron action potential firing underlies a range of neurological processes from information representation in sensory systems to motor pattern generation underlying repetitive processes such as breathing and walking.
- Real-time computing methods for electrophysiology experiments. Our lab develops open source software (http://www.rtxi.org) that allow real-time computer simulations to interact with ongoing experiments. In general, the system is designed to solve large sets of differential equations in real-time, which maintaining time-locking with external inputs from experiments and generating outputs back to those same experiments. This closed-loop paradigm is called the “dynamic clamp” in neuroscience, but this approach can be applied to many other types of experiments as well.

Other interests include nonlinear dynamical systems and oscillatory electronic circuits inspired by some of our neurobiological research. For much of my career we have also been heavily involved in the study of the neural basis of respiration. We also have a large undergraduate group called Brain Beats that is involved in studying how humans cognitive generate and respond to periodic rhythms (such as music).

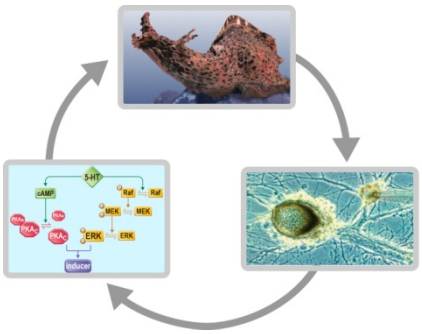
Faculty Speakers



John H. "Jack" Byrne, Ph.D.

June and Virgil Waggoner Chair
Chairman, Department of Neurobiology and Anatomy
University of Texas Health Science Center at Houston

The research interests of this laboratory are the neuronal and molecular mechanisms underlying learning and memory. The marine mollusc *Aplysia californica* is being used as a model system. In *Aplysia* we are studying mechanisms of implicit (nondeclarative) memory associated with simple forms of learning such as habituation, sensitization, classical or Pavlovian conditioning and operant conditioning.



A variety of molecular, biochemical, biophysical, electrophysiological and imaging techniques are used to analyze the properties of the neural circuits and the individual neurons.

The empirical analyses are complemented with realistic mathematical modeling in order to determine the extent to which the observed processes and their interactions are sufficient to explain the behavior of the system.

Ashwin Viswanathan, M.D.

Assistant Professor of Neurosurgery
Baylor College of Medicine

As a physician who is fellowship trained in Stereotactic and Functional Neurosurgery, my clinical practice focuses on deep brain stimulation, trigeminal neuralgia, cancer pain, and chronic pain. My research interests include local field potential analysis to optimize deep brain stimulator implantation, and determining the spinal mechanisms which underlie pain transmission.
Interests: Movement disorders, deep brain stimulation, trigeminal neuralgia, pain management, epilepsy, neuro-oncology, peripheral nerve and general neurosurgery

David Mayerich, Ph.D.

Assistant Professor, Electrical and Computer Engineering
University of Houston

Understanding the structure of tissue is crucial for biomedical research. Our laboratory develops new technologies to collect images of whole organs at subcellular resolution using three-dimensional optical imaging techniques, including: **confocal microscopy**, **knife-edge scanning microscopy (KESM)**, and **two photon tomography**.

Goals: We are particularly interested in three dimensional structure of **tumor biopsies** and **brain tissue**, and hope to develop novel imaging techniques that allow pathologists and researchers to quickly dissect and quantify three dimensional tissue samples in order to further understand the mechanisms of disease progression and tissue development.

Faculty Speakers

Ari Rosenberg, Ph.D.
Assistant Professor, Neuroscience
Baylor College of Medicine

How do we perceive the three-dimensional (3D) structure of the world when our eyes only sense two-dimensional (2D) projections like a movie on a screen? Estimating 3D structure from a pair of 2D images (like those on our retinae) is mathematically an ill-posed inverse problem plagued by ambiguities and noise. Given these complexities, it is surprising how readily our visual system constructs complete 3D representations that enable us to successfully interact with objects in our environment. Indeed, our current understanding of vision remains largely limited to 2D processing. In this talk, I will discuss recent neurophysiological studies and computational modeling which extend our understanding of biological vision beyond 2D spatial processing to the construction of accurate and reliable 3D visual representations.

Tatiana Schnur, Ph.D.

Assistant Professor, Psychology
Rice University

Speech is often effortless and relatively fast. When we talk, we say on average two to three words per second, out of an active vocabulary of tens of thousands of words. There is an infinite number of word combinations, yet we say words in the proper order with the right sounds. How do we successfully select and order words during fluent speech? Why does speech deteriorate because of brain damage? Language is essential to human interaction, yet little is known about how it happens in both the brain and the mind. We use a combination of behavioral, neuropsychological, and neuroscience methods to answer these questions.

Michele Guindani, Ph.D.

Assistant Professor, Biostatistics
University of Texas MD Anderson Cancer Center

In this talk we present a Bayesian hierarchical modeling approach for imaging genetics, where the interest lies in linking brain connectivity across multiple individuals to their genetic information. We have available data from a functional magnetic resonance (fMRI) study on schizophrenia. Our goals are to identify brain regions of interest (ROIs) with discriminating activation patterns between schizophrenic patients and healthy controls, and to relate the ROIs' activations with available genetic information from single nucleotide polymorphisms (SNPs) on the subjects. For this task we develop a hierarchical mixture model that includes several innovative characteristics: it incorporates the selection of ROIs that discriminate the subjects into separate groups; it allows the mixture components to depend on selected covariates; it includes prior models that capture structural dependencies among the ROIs. Applied to the schizophrenia data set, the model leads to the simultaneous selection of a set of discriminatory ROIs and the relevant SNPs, together with the reconstruction of the correlation structure of the selected regions. This is joint work with Francesco C. Stingo (UT MD Anderson Cancer Center), Marina Vannucci (Rice Unversity) and Vince Calhoun (University of New Mexico).

On-Chip Electrophysiological Phenotyping in Intact *C. elegans*

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The nematode *Caenorhabditis elegans* offers a model system in which to carry out large scale studies on the relationship between genetic structure, behavior and electrophysiological activity. Its genetic tractability and fully mapped nervous system consisting of only 302 neurons provide powerful tools to perform critical electrophysiological assays of the genes known to be related to neuro- and muscular degenerative diseases, and also the effects of aging and development on neural activity. Yet, despite great potential, studies such as these are primarily limited by a slow and difficult method of recording electrical activity from muscle cells and neurons. Currently, direct electrophysiological recordings are possible only by performing a precarious dissection protocol followed by pipette-based patch clamping. A novel method that can perform these same measurements in intact animals and in a high-throughput manner has the potential to reshape the status quo for small organism electrophysiology. Here, we show a device that utilizes horizontal nanospear (NS) technology to phenomenally improve on both the invasiveness and throughput of measuring activity from the body wall muscles in *C. elegans* while also being able to distinguish several electrophysiological phenotypes.

Using nano- and microfabrication techniques, a 60 nm high by 4 μm wide horizontal platinum electrode is integrated into an on-chip recording chamber. Interfacing this chip with a conventional PDMS microfluidic device allows for worms to easily be guided into the recording chamber and immobilized against the NS. With sufficient pressure from immobilization, electrical activity at the body-wall muscle neuromuscular junction can be measured through the outer cuticle of these animals without the need for dissection or complete penetration.

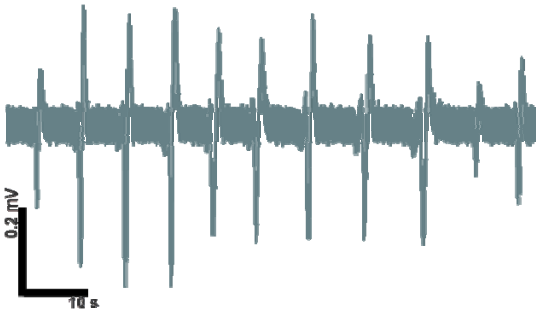

Figure 1 | Actions potentials in the *C. elegans* mutant *shk-1*.

With this method, we have displayed the first ever recordings of actions potentials (APs) in fully intact *C. elegans* (Fig. 1). Additionally, our device has the ability to distinguish several electrophysiological phenotypes based on metrics such as extracellular AP waveforms and the inter-spike interval. Furthermore, NS electrophysiology is highly versatile. Through simple design alterations, we show high-throughput, simultaneous recordings from many worms and also record from several electrodes interfacing with a single worm.

With the success of these experiments, we see NS technology leading the way to never before seen electrophysiological studies of not only *C. elegans*, but also other small organisms such as *Drosophila Melanogaster* embryos

Funding sources
This material is supported by the National Science Foundation Graduate Research Fellowship and the IGERT: *Neuroengineering from Cells to Systems* training grant.

Improved Perceptual Performance and Coding Accuracy Following Optical Stimulation of V1 Populations

Andrei AR, Pojoga S, Janz R, Dragoi V
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The detection of subtle changes in the environment can challenge the limits of the organism's sensory systems. Studying neural activity and behavior at this sensory limit allows us to titrate out the contributions of unique cellular subpopulations to the formation of sensory percepts. In this study, we used optogenetic methods to investigate how the population activity of glutamatergic neurons in primary visual cortex (V1) impacts an animal's ability to detect near-threshold visual stimuli. We delivered the ChR2 gene to multiple sites in V1 using a lentivirus vector with a CaMKII promoter in two monkeys (*macaca mulatta*). Starting 4 weeks after the injection, single and multi-unit activity were recorded using laminar electrodes and a custom built laser positioned 0.5mm from the nearest recording site. Monkeys performed a visual detection task – while maintaining fixation, oriented gratings with differing contrast levels were presented parafoveally over the receptive fields of the neurons of interest for 1300 ms. The monkey signaled the presence or absence of a stimulus by releasing or holding a response bar. Half of the trials were paired with simultaneous optical stimulation (20-50Hz, for ~300ms). We recorded a total of 36 sessions, and a total of 473 light-responsive single and multi-units. 22/36 sessions activated neuronal populations closely tuned to the stimulus orientation, while 14/36 sessions activated distally-tuned populations. We found that optical stimulation of populations of excitatory neurons tuned to the visual stimulus resulted in an 8.0% ± 2.2 SEM improvement in behavioral detection of near-threshold stimuli (P=0.0022, Wilcoxon signed rank test). In contrast, optical stimulation of neurons unresponsive to the visual stimuli resulted in no change in task performance. At the neuronal level, while both session types showed robust firing rate augmentation and increases in signal to noise ratio, pairs of neurons from stimulus tuned sessions also showed a significant decrease in noise correlations (P<0.0001, Wilcoxon signed rank test, n=2436 pairs) and increase in coding accuracy following optical stimulation. These effects are unlikely to be caused by phosphenes elicited by optical stimulation as we did not observe changes in the false alarm rates or the percentage of aborted trials due to broken fixations. Our results suggest that the distinction between relevant and irrelevant information used in behavioral decisions is made at an early stage of visual processing and is reflected in differences in stimulus coding at the local network level.

Supported by NIH EUREKA PROGRAM

Poster Abstracts

(in alphabetical order by presenting author's last name)

Surface Electromyographic Control of the MAHI EXO-II for Spinal Cord Injury Rehabilitation

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Objectives: Every year, approximately 12,000 individuals will suffer a spinal cord injury (SCI) in the U.S. alone. During their subsequent rehabilitation, SCI patients complete highly repetitive movements over long periods of time with the goal of increasing plasticity in the nervous system. This repetition has been shown to increase muscle strength and coordination. Robotic exoskeletons are particularly well suited for this type of training as they do not fatigue, allow isolation of movements, and enable quantitative assessment of movement quality. Studies have shown the efficacy of robotic exoskeletons in rehabilitation roles.

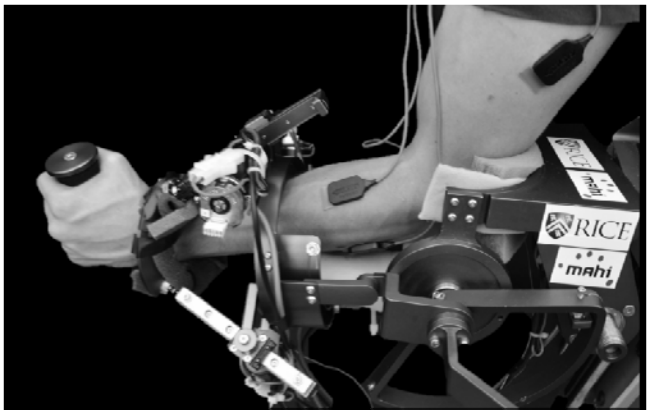

Figure 1. Subject left arm in the MAHI EXO-II with active sEMG electrodes attached

In order to develop an effective exoskeleton control scheme, the user's intent must be accurately discerned; user engagement and participation is critical for effective robotic rehabilitation. Most current state of the art controllers rely on user-initiated movements so that the robot can support or assist appropriately. Use of surface electromyography (sEMG) offers a more sophisticated control architecture that requires proper activation levels of specific muscle groups to control the exoskeleton. The objective of this research is to determine feasibility of sEMG intent detection and control of the MAHI EXO-II, a therapeutic robot exoskeleton.

Methods: Using a combination of custom and commercial hardware, sEMG control schemes were developed and implemented on the MAHI EXO-II. The controllers can be applied independently to each of the MAHI EXO-II's four degrees of freedom: elbow flexion/extension, forearm pronation supination, wrist flexion/extension, and wrist ulnar/radial deviation. Behaviors investigated include continuous versus discrete motion control, triggering, thresholding, and assistive versus resistive modes.

Results: Pilot experiments with two healthy subjects demonstrated the ability to manipulate the MAHI EXO-II position based on recorded sEMG in real time. Parameters including sEMG power, exoskeleton position, velocity, and commanded torque were recorded during these pilot demonstrations.

Conclusions: sEMG is a viable approach to detect user intent during interaction with a robotic exoskeleton. Future work will include validation in the SCI population and incorporation in rehabilitation protocols.

Supported in part by Mission Connect, a project of the TIRR Foundation, and NIH Grant 1R01NS081854

Optimizing Motor Preparation or 'Go' Time Intervals for Detecting Movement Intention during BMI Control of a Therapeutic Exoskeleton

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Recent studies have demonstrated that single-trial movement related cortical potentials (MRCP), recorded via scalp electroencephalography (EEG), can be used for detecting intent of self-paced upper limb movements in stroke and healthy subjects. A Brain-Machine Interface (BMI) based on MRCPs can potentially enhance patient engagement and consequently induce neural plasticity, during robot-assisted stroke therapy. While this is encouraging, we found that during simulated online validation of movement intent classifier on unseen data, a classifier trained using conventional approach of pre-defining 'Go' vs. 'No-go' time intervals did not perform better than random chance.

Moreover, the conventional approach trains a classifier using the same pre-selected time interval (e.g. [-0.7s to -0.1s] before movement onset), for every trial. This approach assumes that the increasing negative potential of single-trial MRCPs is time locked with movement onset, which is separately determined using either movement force, velocity or muscle activity. While the time locking may be true for grand averaged MRCPs across several trials, single-trials often deviate from this norm, giving rise to trial-to-trial variability. This variability partly arises due to differences in movement characteristics such as velocity, subject attention, etc., during repeated trials of a same movement, which is not necessarily accounted for by movement onset calculation. Additionally, single-trial MRCPs are often masked by background neural activity and various non-neural artifacts, and training a classifier with such corrupted MRCP trials further undermines its performance.

In this study, we propose a new technique for classifier training that uses variable but optimized 'Go' time intervals for each trial. Specifically, for every trial we identify the time at which peak of MRCP occurred within an overall interval of [-2s to 0s] with respect to movement onset. Then, a 'Go' interval starting from peak time and up to 600ms (optimally decided) in the past is selected. We also remove trials from training set, when the peak occurred earlier than 1.5s before movement onset, as it is likely corrupted by artifacts. Similar to the conventional approach, 'No-go' interval is taken as 600ms of EEG activity during rest. To compare performance of proposed and conventional techniques, we used EEG data from 3 healthy and 1 stroke subjects, during execution of robot-assisted upper limb movements with the MAHI powered exoskeleton. During online simulations, our proposed technique achieved a median classification accuracy of 75% as compared to 50% obtained using conventional technique.

This work was supported by NIH Grant R01NS081854-02 (National Robotics Initiative).

"The Brain on Art": Assaying the Neuroaesthetics Landscape for Emotional Human Experience

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The study of neuroaesthetics is the characterization of neural mechanisms of the human aesthetic experience in art. In this collaborative study between the University of Houston, conceptual artist Dario Robleto, and the Menil Collection museum, we propose to interrogate the human capacity for creative and aesthetic reflection during a public, *in-natura* viewing of an intellectual installment, *The Boundary of Life is Quietly Crossed* at The Menil Collection. The exhibition is an artistic, philosophical and scientific exploration of the history of registering emotional experiences through physical recording of the human heart and brain, combined with challenges to the historical associations we tie to each them—confirmation of life and death, emotion, authenticity, creativity, spirituality, etc. Specifically, we investigate the dynamic (evolving) patterns of the viewer's whole scalp cortical activity using wearable electroencephalography (EEG) headsets as they move physically and consciously navigate the exhibit. Moreover, we examine how creative and aesthetic reflections experienced by hundreds of viewers across gender and age can lead to common and unique patterns of brain activity. Each participant is encouraged to physically and intellectually explore the exhibition under their emotional disposition; thus, no constraints are placed upon the individual during their exploration of the pieces. In this presentation, early findings from this on-going study (recordings are performed weekly on Saturdays 3-6pm thru December 2014) will be discussed from a pool of ~150 subjects tested at the Menil.

Brain activity is recorded using one of either a 4-, 16-, and 32-channel dry-electrode EEG systems. A custom Bluetooth-based indoor positioning system and radio-frequency identification tags are used to track the trajectories of each participant. These location data are used to correlate epochs of EEG signals to the viewer's visual and emotional engagement in a particular piece within the installment. Sophisticated machine learning algorithms are used to identify patterns of neural activity that statistically differentiate from baseline data recorded during quiet relaxation, prior to entering the exhibit. This study is presented with numerous challenges, including a highly diverse participant population with un-controlled physical and emotional behaviors during viewing. This groundbreaking study opens new horizons for addressing both *empirical problems* (e.g., the acquisition of multimodal *Big data* from freely behaving subjects in a public setting), and *normative problems* (e.g., decoding human intent and emotion from patterns of brain activity) in the field of human neuroscience. This study provides an innovative technological and experimental framework for linking large-scale temporal neural activity maps to quantifiable behavioral paradigms, and enables the curation, sharing, and analysis of multimodal big data from hundreds of subjects.

Acknowledgements: We are glad to acknowledge the support of Michelle White, curator at the Menil Collection, as well as the National Chiao Tung University Brain Research Center, Taiwan, and Brain Vision, LLC (Morrisville, NC) for providing the dry electrode EEG headsets for this study.

Temporal Evolution Of Information In Neural Networks With Feedback

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Recurrent neural networks are pivotal for information processing in the brain. Here we analyze how the information content of a neural population is altered by dynamic feedback of a stimulus estimated from the network activity. We find that the temporal evolution of the Fisher information in the model with feedback is bounded by the Fisher information in a network of pure integrators. The available information in the feedback model saturates with a time constant and to a final level both determined by the match between the estimator weights and the feedback weights. This network then encodes signals specifically from either the beginning or the end of the stimulus presentation, depending on this match. These results are relevant to recent experimental measurements of psychophysical kernels indicating that earlier stimuli have a stronger influence on perceptual discriminations than more recent stimuli. We discuss consequences of this description for choice correlations, a measure of how individual neuronal responses relate to perceptual estimates.

An optogenetic approach to dynamically study the Outer Hair Cell Motor Protein Prestin

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Background: The Organ of Corti contains two types of hair cells, which function synergistically. Outer hair cells (OHCs) work as active signal amplifiers. This active amplification is related to membrane protein Prestin. Prestin, a SLC26A5 family membrane protein, is well considered to be the candidate conferring OHCs with electromotility. However, the role of C-terminal of Prestin, where a STAS domain (sulfate transporters and anti-sigma factor antagonist) located, is still unknown. This work used an optogenetic approach to dynamically study the role of the STAS domain in prestin function and membrane organization.

Methods: First, we designed a Prestin construct with a Tobacco Etch Virus (TEV) protease cleavable linker and tested for membrane expression and prestin function. Prestin function was assayed by electrophysiological measurments of the non-linear capacitance (NLC) Second, we adapted PhyB-PIF6 light-gated dimerization system and split-TEV approach to create a light-gated TEV system. Basically, under 740nm light, the two split parts of TEV is separated to deactivate TEV protease activity, while 650nm light would activate TEV protease by triggering the dimerization of PhyB-PIF6. Thus, we are able to regulate TEV protease activity by exposure to light of different wavelengths.

Results: We tested different sites in the C-terminus of Prestin that will tolerate the 7 amino acid TEV protease recognition linker without disrupting prestin expression and function. We tested different types of linker (flexible, rigid, cleavable) and different lengths. We found that the region between the last trans-membrane domain and STAS domain is highly conserved and sensitive -- even with a small perturbation (7aa insertion) results in complete loss function. The non-funtional Prestin constructs show a significantly decreased Prestin-Prestin interaction by FLIM-FRET experiments. On the other hand, we found that a disordered region in STAS domain, from 563aa to 637aa, can tolerate the TEV protease insertion. We currently have two Prestin constructs with a TEV protease recognition linker inserted between 596/597aa and 620/621aa which still preserve wild type function.

Conclusions: The interface between last trans-membrane domain and cytoplasmic C-terminal is critical to the Prestin-Prestin interaction and the functionality of Prestin. Even a fairly small perturbation in this region would significantly decreases Prestin-Prestin interactions and completely disprupts function. This suggests Prestin self-interaction is important to its functionality. The variable loops between 563aa and 637aa in STAS domain can tolerate insertion without interfering the function. The light activated PhyB-PIF6 system will be a powerful tool for studying the functional consequences of dynamic changes in the C-terminus of Prestin.

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An Integrated Neuro-Robotic Interface for Stroke Rehabilitation using the NASA X1 Powered Lower Limb Exoskeleton

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Stroke induced gait impairment is a large contributor to long-term disability in daily living of patients. Continuously increasing healthcare costs in traditional physical therapy tend to limit supervised therapy times and access to rehabilitation, thereby limiting the functional recovery of patients. Recently, bodyweight supported robot-assisted treadmill training has shown better functional outcomes than before. However, they are less amenable to other functional tasks such as over ground walking and climbing stairs because of their large size. Therefore, newer "wearable" lower-limb robotic devices, namely "exoskeletons," have been developed. Currently, the neurophysiological mechanisms by which these robotic devices interact with the human body are not yet completely understood.

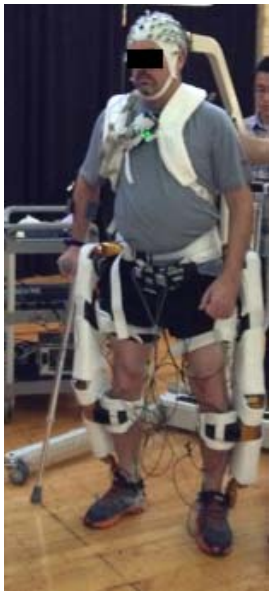

Fig.1. A stroke patient wearing X1 exoskeleton, and fitted with EEG cap, EMG sensors and goniometers

Here, the NASA X1 exoskeleton was used in conjunction with a neural (EEG) and musculoskeletal (goniometry and electromyography (EMG)) interface, in two healthy individuals and an individual with hemiparesis following stroke. EEG, EMG and joint angles were recorded when the subjects walk with the exoskeleton (see Figure 1). The primary objective was twofold: a) to demonstrate feasibility of implementing a multimodal physiological interface with the X1 device, and b) to decode lower limb movement (in terms of kinematics and kinetics) during over ground walking from scalp EEG signals. EEG signals were band-pass filtered at delta band. EMG linear envelope was used to represent muscle activation profile. A 10th order unscented Kalman filter was used to reconstruct aforementioned signals. The decoding accuracy was measured by the correlation coefficient between the measurement and reconstruction of the signals.

Exemplary offline decoding results are shown in Fig. 2. Black lines are the measurement of EMG and goniometer signals, while red lines are reconstruction. In general, we found moderately high decoding accuracy in both healthy and stroke patients, and across all conditions. These results are encouraging because they show the potential of using EEG augmented exoskeletons in stroke rehabilitation. It also serves as good experience in

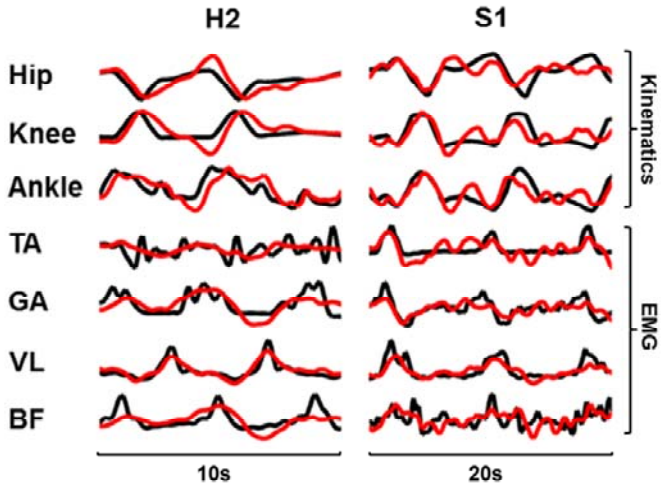

Fig. 2. Exemplary traces of reconstructed joint angular position measured by the X1 and EMG linear envelopes of lower limb muscle activities in the *"Robot On"* condition for one healthy subject (H2) and the affected leg of the stroke survivor (S1). Red traces represent reconstructions (normalized) from the right leg; black traces represent measured data (normalized) from the right leg. TA: Tibialis anterior; GA: Gastrocnemius; VL: Vastus lateralis; BF: Biceps femoris.

the guidance of designing new exoskeletons in the future.

Decoding of Intentional Actions from Scalp Electroencephalography (EEG) in Freely Behaving Infants

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The mirror neuron system (MNS) in humans is thought to enable an individual's understanding of the meaning of actions performed by others and the potential imitation and learning of those actions. In humans, electroencephalographic (EEG) changes in sensorimotor alpha-band at central electrodes, which desynchronizes both during execution and observation of goal-directed actions (i.e., mu suppression), have been considered an electrophysiological correlate of MNS function. However, methodological and developmental issues, as well as the nature of generalized mu suppression to imagined, observed, and performed actions, have yet to provide a mechanistic relationship between EEG mu-rhythm and MNS function, and the extent to which EEG can be used to infer intent during MNS tasks remains unknown.

In this study we present a novel methodology using active EEG and inertial sensors to record brain activity and behavioral actions from freely behaving infants during exploration, imitation, attentive rest, pointing, reaching-to-grasp, and reaching-to-offer an object. We used delta-band (1-4Hz) EEG as input to a dimensionality reduction algorithm (locality-preserving Fisher's discriminant analysis, LFDA) followed by a neural classifier (Gaussian mixture models, GMMs) to decode each MNS task performed by freely behaving 6-24 month old infants during interaction with an adult actor in the context of MNS tasks, including goal-oriented reaching and grasping, imitation, attentive observation, and turn-taking.

Here, we present preliminary results that illustrate our approach and show the feasibility of EEG-based classification of freely occurring MNS behaviors displayed by an infant. These results, which provide an alternative to the mu-rhythm theory of MNS function, indicate the informative nature of EEG in relation to intentionality (goal) for MNS tasks that may support action understanding and thus bear implications for advancing the understanding of MNS function.

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Steerable Microcatheter Using An Electroactive Polymer For Treatment of Stroke.

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There is only a 4-hour window of opportunity to treat cerebral stroke before the patient experiences subsequent brain damage and paralysis. Catheter-based intervention for acute stroke has become a routine part of clinical care, and has distinct advantages over surgical intervention, including reduced complications, morbidity, and mortality. Despite these benefits, current catheter technology requires a high degree of skill due to manual manipulation with fixed shape catheters. Navigation with these catheters during catheterization may result in injury to the cerebral blood vessel walls. As such, there is a need for controllable navigation to allow accurate and safe intervention. In response to this need, we have developed a steerable microcatheter using an electroactive polymer (EAP), which is capable of accurate intracerebral navigation as shown in Figure 1.

In our study, we explored the use of an EAP, ionic polymer-metal composite (IPMC), as a miniaturized actuator. The cylindrical ionic polymer rods were first fabricated in-house. We then inter-digitated the surface electrodes into four sections of the rods and applied combinations of input signals. To test the 2-DOF actuation of the cylindrical IPMC, electrical wires were connected to the four inter-digitated electrodes and desired signals were applied using a customized programmable logic controller module.

We fabricated a cylindrical IPMC with inter-digitated electrodes and demonstrated its two degrees of freedom bending capability as shown in Figure 2. A laser displacement sensor measured the bending deflection and converted bending angle; we achieved bending angles of up to 50° at 4 V.

The use of IPMC as an actuator facilitates the development of a steerable catheter without the use of wires and electrical cables; therefore, IPMC dramatically reduces the size of the catheter, which can then be used for minimally invasive access in a variety of applications, such as cerebral intervention.

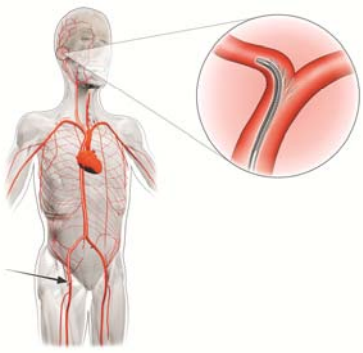

Figure 1. Intracerebral navigation using the steerable microcatheter.

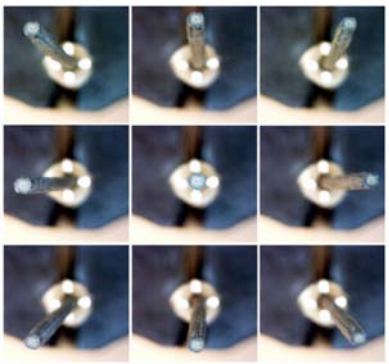

Figure 2. Actuation of the cylindrical IPMC in eight directions.

Inferring Readout Of Distributed Population Codes Without Massively Parallel Recordings

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Abstract
Information about task-relevant variables is often distributed among neurons across multiple cortical areas[1]. Neuronal responses are rarely independent of each other, but are correlated to some degree due to common input as well as recurrent message-passing. Consequently, determining how these neurons collectively drive behavioural changes requires not only examining how individual neurons are correlated with behaviour, but also estimating the correlated variability among neurons[2]. Precisely estimating the structure of correlated variability requires massively parallel recordings, which remains very difficult with current technology. Fortunately, it has recently been shown that the expansion in neural representation from sensory periphery will lead to a predictable pattern of correlations that ultimately limits the information content in brain areas downstream[3]. We examined the implications of these so-called information-limiting correlations for the readout of distributed population codes in a simple discrimination task. Surprisingly we found that both the behavioural precision, as well as the correlation of individual neurons with behavioural choice (*choice correlation*) were determined largely by the relative magnitudes of neuronal weights in the different brain areas and not on their specific pattern. We also found that, in the presence of information-limiting correlations, the choice correlations of neurons within an area should all scale by the same factor following inactivation of other potentially task-relevant brain areas. Together, our results lead to a novel framework for inferring how different brain areas contribute to behavioural response. Specifically we show that the contribution of a brain area can be inferred simply by observing how the magnitude of choice correlations of individual neurons within the area and the behavioural precision are affected by inactivating other areas, thus obviating the need for large-scale recordings.

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Detection of High Frequency Oscillations in Human Intracranial EEG with A Semi-supervised Clustering Method

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Objectives: High frequency oscillations (HFOs) have been considered as a promising clinical biomarker of epileptogenic regions in brain. Due to the low amplitude, short duration, and variability in patterns, the visual identification of ripple (80-250Hz) and fast ripple (250-500Hz) in long-term continuous intracranial EEG (iEEG) is cumbersome. The aim of our study is to improve and automatize the detection of these patterns by developing analysis tools based on a semi-supervised clustering method exploring the time-frequency content of HFO.

Methods: Human iEEG data was recorded with 1024 Hz sampling frequency in two subjects with refractory seizure over 5-6 days using macro-electrodes. We defined baseline data as 10-minute segments in sleep and waking state which are at least 60min away from the onset of the first seizure of each day. The pre-ictal data was defined as 10-minute segments before the seizure onset. An HFO investigation tool integrating initial detection, noise elimination and semi-supervised clustering was developed in Matlab and used to analyze all segments. Following band pass filtering the multichannel iEEG data in 80-500 Hz range, we computed the variance in windows of 100 ms length. To capture high frequency events, we used a median operator as a robust threshold, which was set to 3 times of the median variance. For each detected event, an epoch of 150 ms before and after was extracted and stored as candidate HFO for further analysis. Next, each candidate was investigated in time-frequency plane by using a short time Fourier transform, with a 64 ms sliding window shifted sample by sample. In the following step, distinguishing features were extracted from time and time-frequency domain. A step-wise clustering procedure was implemented where a k-means clustering was executed (k = 2) twice first to eliminate the noise and then isolate HFO events from spike and sharp waves.

Results: Using the baseline and pre-ictal data in both 2 patients, our algorithm successfully localized the seizure onset area, which was consistent with the information provided by neurologists. The second clustering step separated most of the HFOs, whose spatial distribution precisely predicted the electrodes that were placed over the regions where the seizures were thought to originate. Moreover, the time-frequency map of the electrode with maximum number of HFOs during the peri-ictal period showed that the seizure generally started at this particular location.

Conclusions: HFOs are complex dynamic phenomena that are difficult to identify by visual inspection in long-term iEEG data. Our results indicate that semi-supervised methods exploring the time-frequency content of HFOs can be efficiently used to predict the epileptogenic zone before the actual onset of seizure.

Computational Analysis of Cellular Environment During Neural Progenitor Cell Differentiation

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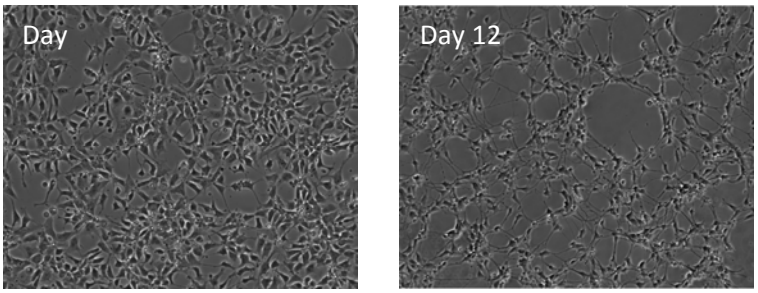
Objectives: Cell fate decisions during neural progenitor cell (NPC) differentiation depend on both cell-autonomous mechanisms and the influence of neighboring cells. Live-cell imaging has proved to be a powerful tool in visualizing dynamic progenitor cell behavior, but the influence of cellular neighborhood on NPC differentiation has been difficult to quantify. The objective of this study is to develop quantitative metrics based on image analysis to help reveal the influence of multi-cellular environment in NPC differentiation.

Methods: Differentiating human NPCs were tracked over 14 days using time-lapse phase contrast microscopy. An intensity-gradient thresholding method was used to extract cell locations and morphological features such as neurite length. A graph theory-based approach was then employed to quantify cellular neighborhood, with vertices defined as cell centroids and spatial proximity between cells used to define edges. Global network properties such as characteristic path length and clustering coefficient were calculated at each time point to quantify the spatial topology of differentiating cells. Parallel assays in patch-clamp electrophysiology were performed to compare functional maturation with network properties.



Phase-contrast images of NPCs at day 0 and day 12 of differentiation

Results: Our image-processing algorithm rapidly and robustly extracts relevant cell morphological features and locations. Time-lapse image sequence analysis showed that cultures at different stages of electrical maturation (assayed through patch clamp electrophysiology) exhibit unique network topology.

Conclusions: We have developed a method to analyze NPC differentiation based on time-lapse microscopy. With this method, we can non-invasively investigate the role of multi-cellular neighborhood at different stages of NPC differentiation. Understanding the interplay between multi-cellular influence and internal cell signaling will lead to a more holistic and predictive model for stem cell differentiation.

This work was supported by NSF CAREER Award 1150645 and an NSF IGERT Training Grant.

Inferring Causal Connectivity In Epileptogenic Zone Using Directed Information

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Abstract:
Directed information, an information theoretic quantity, is developed in this paper to infer the causal connectivity from electrocorticography (ECoG) recordings of an epileptic patient. The causal connectivity can be used to infer the optimal electrodes for electrical stimulation based treatments of epilepsy. A parametric estimator for directed information between two ECoG signals is also proposed. The estimator estimates entropy and causally conditioned entropy and their difference is the estimate of DI. The estimator is then applied to ECoG data recorded from the electrodes in the epileptogenic zone (EZ) in two patients with focal epilepsy to learn the changes in causal connectivity during seizures.

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Design of a Safe, Robust Tendon Actuation System for a New Generation of Wearable Robotic Exoskeletons for Rehabilitation.

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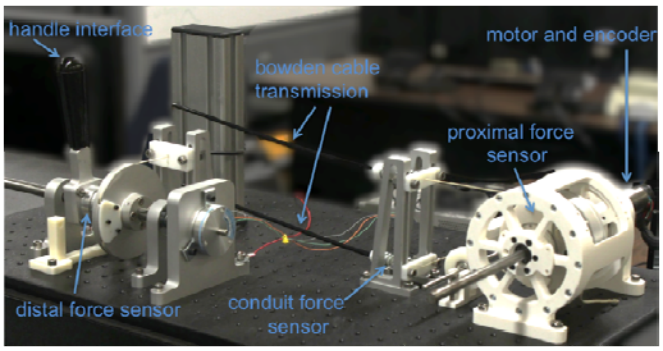

Figure 1: Actuation test bed with Bowden cable transmission and suite of sensors.

The objective of this project is to design a tendon actuation system to robustly control the force interaction between a wearable rehabilitation robot and the user's upper extremity. Patients who have experienced a stroke or a traumatic brain injury (TBI) often suffer damage to the motor cortex, leading to reduced motor function in various parts of the body. A recent development in the rehabilitation of these patients is the introduction of robots designed to help move the patient through repetitive motions that are known to induce neural plasticity, a tedious job generally performed by physical therapists. Typically, robot designs are rigid, with joints driven by electromagnetic motors, often resulting in large, heavy and cumbersome devices. While this approach has worked well for assisting the lower limbs in walking, it has not been as successful when targeting the upper extremities due to the interference of large motors with the complicated workspace of the human arm, limiting range of motion. Furthermore, the weight the actuators add to the robot arm itself provides a significant challenge.

We have taken the approach of moving the actuators and sensors away from the portion of the robot worn by the user to a stationary, well supported location (either a side-bench or a "backpack.") The user is left wearing a comfortable, semi-soft garment that is pulled by biologically-inspired tendons, which are routed to the stationary motors. This style of transmission is known as Bowden cables, and is commonly seen in bicycle braking and gear-shifting systems. Notably, moving the sensors away from the user's arm also makes the device construction more robust and less restrictive to users.

We know that people must be mentally engaged in a therapeutic task to later see improvement in motor function. One known strategy is to apply assistive force to the user only when they fall behind a predefined motion trajectory. This method is appropriately titled assist-as-needed (AAN) control. In order to implement this strategy on our device, we must accurately control the force interaction between the user and the robot. However, complicated force interactions in the Bowden cable transmission can lead to poor force control if not appropriately handled. Without any sensors located directly at the arm, conventional approaches must be adapted. Our proposal is to use a model-based state estimator to implement closed-loop control of the torque and impedance felt at each human joint. In order to experimentally validate our actuation system and controller designs, we have constructed a test bed, **Fig. 1**, with enough modularity to test all potential scenarios. Our current design and experimentation phase is a crucial step toward making a device that can be mechanically transparent (not impede the user), while retaining sufficiently high assistive force capabilities. Ultimately, experiments will inform the electromechanical design of a wearable device prototype, to yield improved performance over traditional approaches.

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neuroPG: Open Source Software Tool for Optogenetics Research

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Patterned illumination using a digital micromirror device (DMD) is a powerful tool for optogenetics. Compared to a scanning laser, DMDs are inexpensive and can easily create complex illumination patterns. Combining these complex spatiotemporal illumination patterns with optogenetics allows DMD-equipped microscopes to probe neural circuits by selectively manipulating the activity of many individual cells or many subcellular regions at the same time. To use DMDs to study neural activity, scientists must develop specialized software to coordinate optical stimulation patterns with the acquisition of electrophysiological and fluorescence data. To meet this growing need we have developed an open source optical pattern generation software for neuroscience - neuroPG - that combines, DMD control, sample visualization, and data acquisition in one application. Built on a MATLAB platform, neuroPG can also process, analyze, and visualize data. The software is designed specifically for the Mightex Polygon400; however, as an open source package, neuroPG can be modified to incorporate any data acquisition, imaging, or illumination equipment that is compatible with MATLAB's Data Acquisition and Image Acquisition toolboxes.

The VEST: A Tactile Sensory Substitution Device for the Deaf and Severely Hearing Impaired

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There are at least 2 million functionally deaf individuals in the United States alone and an estimated 53 million worldwide. The cochlear implant is an effective solution for regaining hearing; however, such implants are expensive, require invasive surgery, and have low efficacy in early-onset deaf adults. Given this, many deaf individuals would benefit from a hearing replacement that is low cost, does not involve an invasive procedure, and may have a higher efficacy for early-onset deaf adults. To this end, we have developed a vibratory wearable—The Versatile Extra-Sensory Transducer (VEST)—by which auditory information is captured, digitally processed, and delivered to the skin of the torso via an array of small vibratory motors. Such sensory substitution approaches have previously been shown to allow congenitally blind individuals to have visual experience through the tongue or skin. We here present the current development status of our device and results of a speech perception experiment involving both hearing and deaf participants. Participants trained on the Vest by engaging in an identification task: on each trial, the participant was presented with a vibration-mapped stimulus of a spoken word from a training set of 50 phonetically balanced words. The participant was then presented with a set of options displayed on a screen from which they selected the word thought to have been felt, and they were given feedback on their choice. After 12 days of training, participants then ran the same procedure on a novel set of 50 words. Our results demonstrate evidence of learning and transfer of knowledge: participants perform better on their first day with the novel test set than their first day on the training set. Further, participants perform at or near chance the first time identifying a word from the training set, and significantly above chance the first time identifying a word from the test set.

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Average Times of Changes in Subthalamic Nucleus Local Field Potentials after Administration of Levodopa in Patients with Parkinson's Disease

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Introduction: Levodopa is the most widely used medication for management of Parkinson's disease (PD), being the primary treatment modality in the majority of Parkinson's patients since its introduction in the 1960s. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective therapy for advanced PD in patients who cannot tolerate medications. Local field potentials (LFP), which represent the summation of the electrical activity of local populations of neurons, have been recorded from implanted DBS electrodes from various nuclei. Previous studies have demonstrated a decline in the beta band power and increase in the gamma band power in the subthalamic nucleus in patients during the medication "on" state. However, to date, no studies have reported on the temporal relationship of levodopa administration to LFP changes. In this study, we report on the timing of onset of changes in LFPs after levodopa administration and the relationship with the clinical "on" state.

Methods: LFP activity was recorded in seven PD subjects who underwent STN DBS placement. LFPs were recorded with 1024 Hz and 16 bit A/D resolution by using the DBS macro electrode (model # 3389, Medtronic) for 36 hours post DBS implantation. Patients were recorded continuously for 30 minutes before medication intake through 30 minutes after they noted the clinical "on" state. Recordings were analyzed using MATLAB R2014a.

Results: Time-frequency analysis of LFPs recorded by macro electrodes revealed a strong baseline beta band (11-30 Hz) activity within the STN in all patients prior to levodopa administration. Following levodopa administration, beta band activity suppressed on average 36.3 minutes (SD=18.6), prior to the clinical "on" state and gamma band (70-90 Hz) activity increased 28.5 minutes (SD = 13.5) prior to the "on" state. Compared to the baseline prior to levodopa administration, relative beta band energy decreased by 47.1% (SD = 34.4) and relative gamma band energy increased by 102.4% (SD = 93.4) during the "on" state. The average time to onset of patient-determined clinical "on" state was 90.4 minutes (SD = 14.6). There was a trend for beta power decline to precede gamma power rise by 15.5 minutes, however, this did not reach statistical significance (p=0.059).

Conclusion: Local field potentials in the subthalamic nucleus undergo reproducible changes following levodopa administration. There is a trend for beta band suppression to precede gamma band power enhancement, and both precede the onset of the clinical "on" state. These preliminary findings suggest the clinical effect of levodopa is temporally related to the electrophysiological changes occurring in the subthalamic nucleus where beta and gamma bands show temporally correlated behavior. These results suggest that not only beta band but also gamma band can be used as a neuromarker for the quantification of the clinical "on" state.

Low Latency Algorithms For Sharp Wave Ripple Detection

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Sharp wave ripples (SWR) are short bursts of co-ordinated oscillatory activity in the CA1 region of the rodent hippocampus. The neural activity during SWRs are believed to play a role in a variety of memory functions ranging from consolidation to recall. Experimental studies that investigate the function of ripples require a signal processing method to detect these events with minimal false-positive rates and low (~10ms) latency. Previous studies have relied on simple thresholding techniques, possibly based on ad-hoc parameters. This study is an investigation into testing and improving the current methods for detection of SWR events during online experiments. Previous methods are profiled and a new method for lower latency in ripple detection is proposed. All algorithms are tested on simulated ripple data. The findings show that simple real-time algorithms can improve upon the elementary power thresholding methods and can detect ripple activity with latencies in the range of 10-20 ms.

Localization of Subthalamic Nucleus Borders Using *Macroelectrode* Local Field Potential Recordings

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Objective: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a highly effective treatment for motor symptoms of Parkinson's disease (PD). However, precise intraoperative localization of STN remains a procedural challenge due to the factors like risk of intracranial hemorrhage, interpretation of single unit neural signal characteristics by the experts which makes the procedure more open to human error with the increased surgical time, especially in the multi-target cases. In this regard, the aim of the present study was to explore the informational content of local field potentials (LFPs) recorded from macro DBS electrodes, in order to identify the anatomical borders of STN. Since LFPs can easily be recorded from macro contacts, their use in the operating room can reduce surgery time and serve as a useful tool for target validation.
Methods: LFP activity was recorded from six PD subjects with 2 kHz sampling frequency and 16 bit A/D resolution from all four contacts of DBS macro electrode (model # 3389, Medtronic). The recordings started generally at 20 mm above the estimated target and continued until the electrode reached -3 mm below microelectrode recording (MER)-determined target through 1mm step size. For the analysis, monopolar LFP signals were converted into bipolar derivation (0-1, 1-2, 2-3) and depth-frequency analysis was performed to explore the energy of LFP sub-bands at each depth. Superior STN border was identified by using the normalized sub-band energy features. Finally**,** in order to compare the borders identified by MER and LFP, the root mean square (RMS) of these differences were calculated.
Results: After the electrode reached the target depth identified by MER, high amplitude LFP activity was observed consistently in all subjects between the superior and inferior border of STN. Surprisingly, excessive LFP activity was not limited to the beta-band (8-30Hz) but was also observed at higher bands, ranging up to 450Hz. The mean value of superior STN border estimated with MERs was 3.61 ±0.92 mm while the mean value of superior border derived from macro electrode LFP recordings was 4.67 ±1.03 mm and 4.08 ±1.56 mm in beta and gamma bands, respectively. The root mean square (RMS) of the difference between MER and LFP was 1.26 mm in beta and 1.06 mm at gamma band.
Conclusion: Previous studies suggested that the excessive beta-band activity of LFP can be used to localize STN. We observed that excessive activity occurs not only in the beta-band, but also in the higher bands, ranging from 40 up to 450 Hz. Subsequent data analysis has shown that the localization error of superior STN border between macro electrode recordings and MER was around 1 mm in both beta and gamma band. These results support the use of intraoperative macro-electrode recordings, in conjunction with preoperative stereotactic imaging for target localization in PD.
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Clearance Mechanisms of Poly-Q Expanded Huntingtin Aggregates

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Huntington's disease (HD) is a fatal brain degenerative disease caused by an abnormal lengthening of a CAG repeat encoding glutamine tract (poly-Q) in the Huntingtin (Htt) gene. The pathological hallmark of HD is characterized by the formation of protein aggregates and the selective degeneration of spiny neurons in the striatum. Importantly, it has been demonstrated that longer polyQ repeats are directly linked with increased formation of aggregates in cell and animal models of HD. We employ *Drosophila melanogaster*, commonly known as the fruit fly, to investigate the dynamics of aggregate formation and clearance of the human exon1-Htt-poly-Q-tagged with eGFP. By generating transgenic flies with variable lengths of polyQ, we have established *Drosophila* HD models where aggregates form robustly in an age- and polyQ-length dependent manner. We determined that clearance of mutant Huntingtin poly-Q aggregates is mediated by macro-autophagy, the catabolic process that signals dysfunctional cellular components for lysosomal degradation. Autophagy is initiated by trafficking of ubiquitinated proteins to the autophagophore by Ref(2)P, the fly homologue of the human P62. We report an alteration in the autophagosome formation mechanisms in a poly-Q length and aggregate size dependent manner. These results suggest a potential role of the autophagic flux in the clearance of polyQ aggregates, and provide potential therapeutic targets for poly-Q diseases. Future work involves testing the function of the autophagosome scaffolding players in regulating the dynamics of mutant Huntingtin poly-Q induced aggregate formation. Based on our results, we expect to observe an aggressive protein aggregation in brains deficient of molecules regulating auto-phagosome initiation.

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E-PhACS: Electrophysiology Assisted Cell Sorting Platform for Protein Engineering

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Current methods for recording and controlling the potential across the cell membrane represent an experimental bottleneck for both characterizing ion channel kinetics, and designing proteins for monitoring and manipulating neural activity. For example, conventional patch clamp electrophysiology relies on highly trained researchers to manually align glass micropipettes to individual cells – a process that typically requires tens of minutes to measure from a single cell. Alternative approaches based on planar patch clamp devices and microfluidic pores help to accelerate the measurement process[2,3], but cells studied with these devices are sealed to the micron-sized pores, preventing subsequent sorting and genetic profiling. To overcome such limitations, we have developed a device to rapidly control or record the transmembrane potential, and subsequently sort cells based on electrophysiological phenotype. This novel electrophysiology-assisted cell sorter incorporates nanowire electrodes into a microfluidic chip. Nanowires can penetrate the cellular membrane and control or record the transmembrane potential[1] and can easily release the cell into the microfluidic channel, allowing for quick cell sorting. Our device represents a major improvement in experimental throughput that will drive the development of new genetic-based approaches to measure and manipulate neural activity, including variants of optically- and chemically-gated ion channels and voltage-sensitive proteins.

Microfluidic devices were fabricated using a combination of photolithography, e-beam lithography, and wet and dry etches. These processes create a suspended platinum nanowire positioned at the center of a microfluidic cell trap fabricated in a biologically friendly photoresist. This cell trap is encapsulated in polydimethylsiloxane (PDMS) and held in place by an acrylic enclosure. To characterize the capabilities of our device we used a line of non-adherent Chinese Hamster Ovary (CHO) cells, transfected as needed with the voltage sensitive protein ArcLight A242 and the light-gated ion channel ChR2.

In addition to performing nanowire electrophysiology, our microfluidic device can also release cells from the trapping chamber and sort these cells into discrete populations. Once the cell populations have been sorted we can collect each population's mRNA from a microfluidic reservoir for transcriptional profiling and genetic analysis.

In conclusion, our electrophysiology-assisted cell sorter represents an innovative platform for rapid and automated cell screening and sorting based on electrophysiological traits. Sorting permits postscreening genetic analysis, so that many mutants may be simultaneously screened, removing several rate limiting steps from the analysis of a library of variants. The device is also easy to use in tests that require photostimulation or rapid cycling of pharmacological agents in the cell's environment. Future work will use these capabilities to develop designer voltage sensitive proteins and ion channels with enhanced or novel properties.

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Robust Nonlinear Neural Codes

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Most interesting natural sensory stimuli are encoded in the brain in a form that can only be decoded nonlinearly. But despite being a core function of the brain, nonlinear population codes are rarely studied and poorly understood. Interestingly, the few existing models of nonlinear codes are inconsistent with known architectural features of the brain. In particular, these codes have information content that scales with the size of the cortical population, even if that violates the data processing inequality by exceeding the amount of information entering the sensory system. Here we provide a valid theory of nonlinear population codes by generalizing recent work on information-limiting correlations in linear population codes. Although these generalized, nonlinear information-limiting correlations bound the performance of any decoder, they also make decoding more robust to suboptimal computation, allowing many suboptimal decoders to achieve nearly the same efficiency as an optimal decoder. Although these correlations are extremely difficult to measure directly, particularly for nonlinear codes, we provide a simple, practical test by which one can use choice-related activity in small populations of neurons to determine whether decoding is suboptimal or optimal and limited by correlated noise. We conclude by describing an example computation in the vestibular system where this theory applies.

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Kernel Methods for Discrete Decoding of EEG Signals for Brain-Machine Interfaces (BMI)

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The restoration and rehabilitation of gait are of great interest to the field of BMIs, i.e. devices that utilize neural activity to control virtual or physical exoskeletons or prostheses. Since gait deficits are commonly associated with spinal cord injury, limb loss, and neurodegenerative diseases, there is a need to investigate innovative therapies to restore gait in such patients. We previously showed decoding of gait kinematics during treadmill walking from EEG of able-bodied subjects with accuracies comparable to that from a similar study in nonhuman primates with electrodes implanted in their brains. Here we extend our results to decoders that can extract and classify (asynchronously) user's internal states (e.g., stop, walk, turn, etc.) from EEG. In this regard, kernel methods have been effectively applied for many machine learning problems, e.g. data regression and classification. Support vector machine (SVM) is a widely used kernel method for pattern recognition, however, it gives little knowledge about the biophysical properties of relevant features. Improved kernel methods can be used to infer information about electrode relevance by identifying which sets of features (EEG channels) are important for classification. To accomplish this, we divided the scalp into regions of interest (ROIs): anterior frontal (AF), left frontal (LF), midline frontal (MF), right frontal (RF), left fronto-central (LFC), midline central (MC), right fronto-central (RFC), left centro-parietal (LCP), middle parietal (MP) and right centro-parietal (RCP).

To test and validate our kernel-based algorithm we decoded EEG data from a tetraplegic subject who had been trained over multiple sessions to control a robotic exoskeleton (Kilicarslan et al, Conf Proc IEEE Eng Med Biol Soc. 2013;2013:5606-9). The robot motions in this study included walking forward, turning right, turning left and stop. The goal is to decode the pattern of these motions and simultaneously learn the relative importance of different scalp areas. By accurately decoding the intended motion of the user, the BMI can then control the robot's lower-body movement. In our experiments, data were acquired (100 Hz; 64 channel electrode cap), and filtered (2^{nd} order Butterworth filter in the 0.1-2 Hz range). After removing the peripheral, eye movement and bad channels, 38 channels were left for analysis and divided into 10 ROIs as described above. The feature matrix was then extracted by applying a 400ms sliding window on each channel with 1 shift (10 ms) each time. We then applied an emerging kernel-based machine learning method, which is based on the automatic optimization of a linear combination of multiple kernels (each dedicated to groups of electrodes corresponding to ROIs, and consequently contributing unique biophysical information). Each “group” of features is assigned a base kernel, and the linear combination of all base kernels is optimized through gradient descent on the support vector machine objective function. This multiple kernel learning (MKL) machine can learn the importance of different groups of features and output the decoding patterns at the same time. We randomly selected half of the total samples for testing, and 500 samples from each class from the remaining samples for training. The weights for different ROIs learned by MKL are shown in Table 1. From the results, it is observed that MF scalp region has the highest weight among all ROIs, which is consistent with the brain regions thought to be involved in the control of lower-limb movements. Moreover, LFC, MC and MP also have relative high weights, while the other ROIs have low weights, which can be explained corresponding to different importance of the brain regions for movement. We are now quantifying electrode relevance across sessions to examine neural signatures that may indicate cortical plasticity triggered by BMI use.

Table 1. Weights learned by MKL for different ROIs

ROI	AF	LF	MF	RF	LFC	MC	RFC	LCP	MP	RCP
Weight	0.0288	0.0553	0.4822	0.0372	0.0996	0.1367	0.0306	0.0324	0.0741	0.0230

Human-Machine System for the H2 Lower Limb Exoskeleton: Neural decoding of robot-assisted walking from scalp EEG for stroke rehabilitation

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Many stroke survivors suffer from gait dysfunction, making gait restoration one of the major goals in post-stroke rehabilitation. Compared to traditional therapy, which involves physically guiding the patient's leg to reinforce normal walking gait, new therapies that employ powered assistance from prosthetic robot devices provide an economical and less labor-demanding solution to deliver consistent and repetitive motor practice to patients. However, neural interfacing of a patient's brain activity to control the robot-assisted gait rehabilitation has not been investigated yet. Enabling direct control of robot-assisted walking through the user's movement intent detected by a neural interface can increase user engagement and motivation, and promote neuroplastic mechanisms of recovery. The goal of this research is therefore to develop and test the feasibility of an EEG-based neural interface for decoding "walking" intent to the H2, a lightweight lower limb powered exoskeleton robot for stroke gait rehabilitation.

Two male participants with post-stroke left hemiparesis were asked to perform an over-ground walking task while wearing the H2 in assist-as needed mode with a pre-selected gait speed along a 100ft circular path. Each session began with a one minute rest, followed by approximately 30 minutes of continuous walking with short rest breaks at the participant's discretion, and ended with a second one minute rest period; participants performed approximately 12 sessions over a period of 5 weeks (for additional details, see companion poster: Venkatakrishnan, et al; Magdo et al and ClinicalTrials.gov, NCT02114450).

64-channel EEG was recorded (BrainProducts, Inc) at a sampling rate of 1000Hz, referenced to FCz. Walking kinematics were sampled at 100Hz by H2. Most frontal and temporal electrodes were removed to avoid contamination by ocular artifacts and muscle artifacts. EEG signals from remaining channels were decimated to 100Hz to align with kinematic data. Walking epochs were truncated and concatenated to build a pseudo-continuous walking dataset. Next, both EEG and kinematics data were band-pass filtered to 0.1-1Hz, which corresponded to over 95% of the kinematics band power, and were subsequently standardized across each channel. After selecting the optimized electrodes set, continuous decoding of walking kinematics was achieved by using a 10th order unscented Kalman filter with a five-fold cross validation.

To evaluate the performance and fluctuation of the algorithm, the grand average of correlation value (CC) between reconstructed kinematics and observed kinematics and CC standard deviation (Std) across the five folds of cross validation were calculated. The results indicate that the Kalman filter can accurately decode the steady speed walking kinematics from scalp EEG waves (average $CC \geq 0.81$, $Std \leq 0.18$). These findings provide initial evidence for the possibility of using brain waves as a control signal for designing a brain-machine interface system for a lower limb exoskeleton in the context of gait rehabilitation in stroke survivors.

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