NeuroFutures 2016

Circuit Structure & Dynamics

June 19-21, 2016

Allen Institute
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Sunday, June 19

5:30-6:30pm

Public lecture
Anne Churchland, *Cold Spring Harbor Laboratory*
"How brains combine multiple pieces of information to guide decision-making"

Humans and animals make better decisions when we combine multiple pieces of information. This is clear intuitively, but how brains achieve this remains mysterious. Recent technologies have enabled us to ask questions like: How do animals combine multiple pieces of information to guide decisions? How are humans different from mice and rats? Or are we different at all?

6:30-7:30pm

Keynote panel and Q&A
NeuroFutures 2026: How will technology transform our ability to understand the 2026 brain?

Large-scale brain research projects around the globe are producing new technologies that allow us to peer inside a working brain, understand the genes of people with neurological disease, reveal the different types of cells in the brain and target those cells with designer drugs, new devices for stimulation and new DNA editing approaches.

The panel of keynote speakers—led by audience questions and interaction—will discuss how this may revolutionize our understanding of the brain and its diseases, ten years from now.

- Linda Buck, Ph.D., *Fred Hutchinson Cancer Research Center, 2004 Nobel Laureate in Physiology or Medicine*
- Anne Churchland, Ph.D., *Cold Spring Harbor Laboratory*
- Jeff Ojemann, M.D., *UW Neurosurgery*
- Afonso Silva, Ph.D., *National Institute of Neurological Disorders & Stroke*

Monday, June 20

7:15-8:00am

Registration and continental breakfast

8:00-8:15am

Welcome and introductory remarks, NeuroFutures committee

- Jane Roskams, Ph.D., *Allen Institute* (chair)
- Kurt Haas, Ph.D., *University of British Columbia*
- Sheri Mizumori, Ph.D., *University of Washington*
- Scott Ransom, Ph.D., *University of Washington*
- Rad Roberts, Ph.D., *University of Washington*
- Bill Rooney, Ph.D., *Oregon Health & Science University*

8:15-9:15am

Opening keynote
Linda Buck, *Fred Hutchinson Cancer Research Center, 2004 Nobel Laureate in Physiology or Medicine*
"Deconstructing smell"

Humans and other mammals detect as many as 10,000 or more chemicals in the external environment – but how do they actually do it? The brain must also translate the detection of those chemicals into different smells, such as rose orgarlic. Finally, pheromones and other social cues elicit hormonal changes and instinctive behaviours in animals. The illumination of the neural circuits underlying these effects may ultimately provide clues to molecular mechanisms that influence basic drives and emotional states in humans.

9:15-9:30am

Morning break

9:30-11:30am

Novel imaging approaches: live awake monitoring of circuits
Moderator: Marcos Frank

Tim Murphy, *University of British Columbia*

"High throughput imaging of mouse mesoscopic activity in health and disease"

Mouse automated home cage cortical mesoscopic imaging supports 5 mice at a time and requires minimal investigator intervention. We monitor cortical functional connectivity up to 24 h/day in >7000 self-initiated and un-supervised imaging sessions up to 90 days. The procedure provides robust assessment of functional cortical maps based on both spontaneous activity and brief sensory stimuli such as light flashes. To identify novel targets for brain stimulation in vivo, simultaneous wide-field of view GCAMP imaging and sub-cortical/ cortical cellular electrophysiology using electrode arrays was used in mice to investigate relationships between spontaneous single neuron spiking and mesoscopic cortical activity. These automated systems have applications for evaluating normal physiological function as well as modeling disease.

Saskia de Vries, *Allen Institute for Brain Science*
"Mapping activity in the visual cortex of the awake mouse"

In order to explore how features of the sensory environment are represented by cortical circuits, the Allen Institute for Brain Science has developed the first survey of neural activity in the living brain, the Allen Brain Observatory, to be announced in July. Using high-throughput 2-photon calcium imaging, we have systematically recorded the visual responses of over 18,000 neurons in the awake mouse cortex, generating a dataset that spans four visual areas, and four distinct Cre lines expressed in multiple cortical layers. This is an extremely rich dataset for exploring cortical computations involved in visual information processing at both the single cell and population level. In this talk, I will present data from this new product and explore early analysis of visual coding in the awake mouse cortex.

Larry Zweifel, *University of Washington*
"Molecular and circuit mechanisms regulating GABAergic control of the ventral midbrain"

Dopamine neurons of the ventral tegmental area play an important role in regulating emotional processing, learning, and memory. I will discuss our recent development of viral-based circuit mapping tools that have allowed us to demonstrate the overwhelming majority of external inputs to the VTA are derived from GABAergic inhibitory projection neurons. In addition to mapping specific inhibitory inputs to the VTA, we have identified the Robo2 signaling pathway as a key regulator of inhibitory synaptic connectivity. Disruption of Robo2 signaling in the adult midbrain potently disrupts inhibitory control of the VTA and generates profound deficits in psychomotor control and learning.

Patricia Kuhl, *University of Washington*
"Imaging the baby brain: imagine a future of improved learning for all children"

New imaging methods allow measures of brain activity while infants are engaged in a task, and these measures are highly predictive of infants' future performance. Baby brain imaging is answering basic science questions about how young children learn, and also providing "biomarkers" of risk for developmental disabilities very early in development, opening an opportunity for creative interventions.

11:30am-12:30pm **Lunch**

12:30-1:30pm **Afternoon keynote**
Liqun Luo, *Stanford University*
"Organization and assembly of neural circuits"

We are interested in how neural circuits are organized in the adult brain, and how they are assembled during development. In this talk, I will summarize our studies on the assembly of complex neural circuits in flies and mice. I will also discuss our recent development of tools to map input-output architectures of neural circuits and their application to the monoamine systems in mice.

1:30-3:30pm **Human and non-human primate circuit function**
Moderator: Sheri Mizumori

Jeff Ojemann, *University of Washington*
"Motor reorganization with brain computer interface use"

New experiences lead to changes in cortical interactions and organization, even in the initial stages of a new task. We use cortical recordings (electrocorticography, or ECoG) in humans obtained as part of the surgical treatment of epilepsy. ECoG can be used as control for brain-computer interface -a completely novel task

which shows changes in the organization of the motor cortex within minutes. With learning, widespread areas become more or less involved. By modulating task requirements, the control area of cortex can be completely repurposed from its original motor role in this short period. This work will explore the ways in which human cortex may rapidly incorporate the experience of models of neuroprosthetics and offer insight into the cognitive neurobiology of this highly novel task.

Beth Buffalo, *University of Washington*
"Using virtual reality in monkeys to probe hippocampal circuitry and the cognitive map"

While it has long been recognized that medial temporal lobe structures are important for memory formation, studies in rodents have also identified exquisite spatial representations in these regions in the form of place cells in the hippocampus and grid cells in the entorhinal cortex. Spatial representations entail neural activity that is observed when the rat is in a given physical location, and these representations are thought to form the basis of navigation via path integration. Recent studies in nonhuman primates have suggested that similar kinds of spatial representations can be identified, even in the absence of physical movement through an environment. I will discuss recent work from my lab that addresses similarities and differences between spatial responses as identified in rodents and primates. I will also discuss areas of opportunity for future research to further our understanding of the function of the hippocampal formation and the nature of the cognitive map.

Verginia Cuzon-Carlson, *Oregon Health & Science University*
"Elucidating brain circuitry underlying behavior in non-human primates using DREADDs"

The ability to reversibly manipulate brain circuitry is important to dissect their role in complex behaviors and disease states. This technology in non-human primates has lagged behind those used in c-elegans, drosophila, and rodents. Here the use of a relatively new chemogenetic technique called designer receptors that are exclusively activated by designer drugs (DREADDs) in non-human primates is explored. The use of DREADDs in non-human primate models acts not only as a tool for analyzing neural function in more sophisticated models of behavior but as a potential use in clinical applications.

Jonathan Ting, *Allen Institute for Brain Science*
"New horizons for the functional analysis of human neocortical cell types and microcircuits"

Human neocortical brain tissue excised during neurosurgeries can be maintained in a vital state in the laboratory and provides a rare opportunity to directly explore the structural and functional architecture of the living human brain. In this talk I will provide an overview or our recently established human ex vivo brain slice platform and describe innovative and forward-thinking research avenues currently under development at the Allen Institute for Brain Science that aim to greatly expand our understanding of human neocortical cell types and circuits.

3:30-3:45pm **Afternoon break**

3:45-5:45pm **Circuits in neurodegeneration**
Moderator: David Newell

Craig Brown, *University of Victoria*
"Chronic optogenetic stimulation of thalamocortical projections enhances sensory circuit rewiring and recovery of sensori-motor function after stroke"

The majority of stroke survivors must cope with chronic disability that often affects the upper limbs. In order to regain sensori-motor functions after stroke, surviving neural circuits must re-organize and make new and stable connections. Axonal projections from the thalamus are the primary source of sensory inputs to the cortex, therefore they are a likely substrate for functional recovery. However, it is unknown how the function and structure of these axonal projections are affected by stroke, and what therapies could specifically optimize the recovery of these circuits. Therefore, we first assessed the response properties of GCaMP6s expressing thalamocortical axons terminating in somatosensory/peri-infarct cortex to assess their response properties after stroke. Our analysis revealed that ~25% of axonal boutons respond to tactile stimuli before stroke, which dropped significantly after stroke and showed partial recovery by 4 weeks. Given this deficit, we hypothesized that chronic optogenetic stimulation of these projections (intermittent 5 Hz stimulation for 1 hour/day from 3-42 days post-stroke) could enhance axonal re-wiring and functional recovery. Using longitudinal 2-photon imaging of thalamocortical projections, we discovered that optogenetic therapy attenuated thalamocortical bouton loss after stroke, stabilized newly formed boutons and increased axon branch growth. Further, chronic optogenetic stimulation accelerated the re-mapping of sensory evoked responses in the peri-infarct cortex

and enhanced recovery of forelimb sensori-motor function in the adhesive tape and horizontal ladder tests. These studies offer encouraging new insights into the application of optogenetic approaches for improving stroke recovery.

Chet Moritz, *University of Washington*
"Neuroprosthetic strategies to improve function after brain and spinal cord injury"

Neuroprosthetic devices that interact with the nervous system by recording and stimulation have tremendous potential to improve quality of life after brain and spinal cord injury. Neuroprostheses have progressed from animal studies to human trials, including ongoing work using brain activity to control Functional Electrical Stimulation (FES) of paralyzed hand muscles. Another promising method for enabling rehabilitation and plasticity is spinal stimulation. Both epidural and intraspinal stimulation can activate neural circuits distal to an injury, leading to either direct muscle contraction or facilitating therapy and enabling volitional movements. Work is underway to merge these techniques and develop a brain controlled spinal stimulation system to restore volitional control of limb movements and perhaps promote directed plasticity and rehabilitation after brain and spinal cord injury.

Julie Harris, *Allen Institute for Brain Science*
"Mapping whole brain connectivity to investigate Alzheimer pathologies in mouse models"

Structural connectivity provides the foundation through which information can travel within the brain. Comprehensive wiring diagrams are therefore fundamental for understanding how circuits control complex behavioral and cognitive processes. Our Allen Mouse Connectivity Atlas is the most comprehensive mesoscale connectome currently available for healthy young adult mouse brain. The Atlas is based on anterograde viral tracing and high-throughput 2-photon imaging methods to visualize inter-areal and cell type-specific projections across the brain. In many neurodegenerative diseases, such as Alzheimer's disease (AD), pathologies appear to spread through selectively vulnerable brain networks in specific patterns that resemble, but do not exactly duplicate, network architecture. How disease state alters connections between regions, and whether current mouse models accurately recapitulate these human features of AD are not known. We hypothesize that specific long range projections will undergo degeneration in AD mouse models, and, furthermore, that anatomical classes of projection neurons exist which preferentially connect to other areas within vulnerable brain networks. We are now testing this second prediction using a combination retrograde and anterograde viral labeling technique. Identifying cell type-specific projection pathways from disease-relevant areas could provide a better structural framework for understanding, predicting, and treating disease progression.

Steve Monteith, *Swedish Medical Center*
"Current and future intracranial applications of MR Guided Focused Ultrasound"

5:45-7:00pm **Poster session and happy hour reception**

Tuesday, June 21

7:30-8:00am **Registration and continental breakfast**

8:00-9:00am **Morning keynote**
Afonso Silva, *National Institute of Neurological Disorders and Stroke*
"Multimodal neuroimaging of brain anatomy and function in awake marmosets"

Our main research goals are to understand the communication between neurons and cerebral blood vessels, and to understand how the cerebral microvasculature reacts, in space and in time, to changes in neuronal activity. In this talk I will summarize the most recent results from our lab in visualizing brain anatomy and function in awake marmosets using a combination of anatomical and functional magnetic resonance imaging, electrophysiological recordings, and two-photon laser scanning microscopy. In addition, I will discuss our experience in generating transgenic marmosets expressing genetically encoded calcium indicators that allow direct visualization of individual neurons and blood vessels.

9:00-11:00am **Imaging and manipulating non-mammalian model circuits**
Moderator: Kurt Haas

Marc Freeman, *Vollum Institute, Oregon Health and Science University*
"Brain circuits—not just for neurons anymore"

Astrocytes associate with synapses throughout the brain and have been proposed to modulate circuit activity, but direct in vivo evidence linking astrocyte signaling to neurotransmission or behavior is limited. Using a combination of opto- and chemogenetics and live imaging of Ca2+ signaling, we found that Drosophila astrocytes exhibit robust somatic Ca2+ increases in response to neural activity. Genetic or acute pharmacological blockade of astrocyte Ca2+ signaling altered the activity of downstream dopaminergic neurons and profoundly affected multiple animal behaviors, including memory performance. We argue astrocytes, beyond their simple support functions, should be considered integral components of neural circuits.

Rachel Wong, *University of Washington*
"Circuit reassembly in the regenerating zebrafish retina"

Recent work has focused on reprogramming resident glial cells to de-differentiate and produce new neurons after damage to the nervous system. Whether or not neurons generated by unconventional progenitors can completely recapture the stereotypic wiring patterns of their cohorts born during development, is not known. Zebrafish retinal Müller glia generate new neurons to replace lost populations. Taking advantage of this regenerative capacity, we ablated specific cell types and mapped the connectivity patterns of the surviving neurons upon regeneration. Our findings iunderscore the potential as well as limitations in recreating the original circuitry even when synaptic partners become available.

Michael Gordon, *University of British Columbia*
"Starvation-dependent depotentiation of bitter taste in *Drosophila*"

Animals display dramatically different responses to food depending on their satiety state. In flies, starvation induces sensitization of sweet taste and desensitization of bitter taste. However, the mechanisms for these effects are unresolved. We have identified a pair of neurons that directly modulates bitter sensory neuron output in response to starvation. The activity of these modulatory neurons decreases upon starvation, reducing the release of a potentiating signal to bitter sensory neuron terminals. Moreover, artificially silencing the modulatory neurons in fed flies phenocopies the sensory and behavioral effects of starvation, suggesting that they underlie a critical step in starvation-induced taste modulation.

Claudio Mello, *Oregon Health & Science University*
"The neural and genetic basis of vocal learning in songbirds"

Vocal learning, a trait essential for human speech and language acquisition, also evolved in songbirds, parrots and hummingbirds. Studies in zebra finches implicate cortical and basal ganglia areas in the acquisition and production of learned vocalizations. Cortical projections onto vocal and respiratory brainstem nuclei allow for refined control of song spectro-temporal features. Evidence from the molecular finch brain atlas (ZEBrA; www.zebrafinchatlas.org) reveals specializations of vocal nuclei, some convergent with human laryngeal and striatal areas (Allen Institute Human Brain database). Differential expression of genes associated with connectivity or excitability (e.g. SLIT1/ROBO1, SCN3B/4B) underscore the uniqueness of circuits for learned vocalizations.

11:00-11:15am **Morning break**

11:15am-12:45pm **Computational modeling of circuits**
Moderator: Scott Ransom

Rajesh Rao, *University of Washington*
"Bayesian brain models: from circuit structure to function"

How can the structure of brain circuits inform large-scale theories of brain function? We explore this question in the context of Bayesian models of perception and action, which prescribe optimal ways of combining sensory information with prior knowledge and rewards to enact behaviors. I will briefly review two Bayesian models, deep predictive coding and partially observable Markov decision processes (POMDPs), and illustrate

how circuit structure can provide important clues to systems-level computation.

Bingni Brunton, *University of Washington*
"Data-intensive approaches to understanding neural computations underlying naturalistic behaviors"

Much of our knowledge about neural computation in humans has been informed by data collected through carefully controlled experiments in laboratory settings; however, understanding the brain in action requires exploration of long-term, naturalistic neural data. I will talk about our recent work using computationally scalable approaches to analyze a large-scale human intracranial brain recording dataset augmented with video and audio, all simultaneously and continuously monitoring a subject for many days. Our unsupervised algorithms discover coherent clusters in the high-dimensional neural recordings that are annotated using automatically extracted behavior labels.

Costas Anastassiou and Stefan Mihalas, *Allen Institute for Brain Science*
"Neuronal modeling and computation at the Allen Institute"

Large-scale, biophysically detailed simulations have the ability to link between different level of granularity (synapses, single neuron-level, brain circuits) and thus bridge the gap between micro-, meso- and macroscopic functioning in the brain in a bottom-up approach. At the Allen Institute we pursue such simulations and I will present how these can be used to provide a holistic understanding of circuit processing as well as insights into pathological functioning in brain disorders such as epilepsy.

12:45-2:00pm **Lunch, posters and informal discussion**

2:00-3:00pm **Afternoon keynote**
David Linde, *Medtronic*
"From observatories to starshots: scientific instrumentation strategies for neuroscience"

This talk will explore strategies for gathering neuroscience data to better inform the basis for neurological disorders and potential strategies for treatment. As one example, I will discuss approaches for using existing medical devices as a scientific payload to gain chronic access to neural networks. Recent instrument designs and data examples from chronic implants will illustrate the general principles and constraints of this payload strategy; these examples will also help motivate several remaining challenges and opportunities.

3:00-3:15pm **Afternoon break**

3:15-5:15pm **Manipulation of circuits in disease**
Moderator: Mona Hicks

Stephanie Borgland, *University of Calgary*
"Projection target defined effects of orexin and dynorphin on VTA dopamine neurons"

Recent evidence has indicated that different subpopulations of VTA dopamine and GABAergic neurons and their projection targets may subserve different functions. However, little is known about the afferent control of VTA dopaminergic neuronal activity and the circuits in which they are embedded. Here, we test they hypothesis that neuromodulatory input to the VTA from lateral hypothalamic orexin neurons can coordinate the activity of VTA dopamine neurons by modulating distinct circuits. Usually neuropeptides can modulate the activity of neurons in either an excitatory or an inhibitory manner. Interestingly, excitatory orexin is coexpressed with the inhibitory kappa receptor agonist, dynorphin (Chou et al., 2001) in the same dense core vesicles (Muschamp et al., 2014), suggesting they may be coreleased. Indeed, receptors for orexin and dynorphin are both expressed in the VTA. Therefore, this unique system presents an exciting opportunity to address the hypothesis that orexin and dynorphin exert their neuromodulatory effects in the VTA via different circuits. We found that BLA projecting and NAc shell projecting dopamine neurons are electrophysiologically distinct and non-overlapping populations. Furthermore, orexin primarily activates VTA dopamine neurons that project to the lateral shell of the nucleus accumbens, where as dynorphin primarily inhibits dopamine neurons projecting to the basolateral amygdala. We propose that through corelease of orexin A and dynorphin, orexin projections coordinate the activity of VTA dopamine neurons to drive motivated reward seeking behaviour.

Jeremy Seamans, *University of British Columbia*
"The dynamic encoding properties of medial frontal cortex neurons and ensembles"

A prevailing view in neuroscience is that cortical neurons have dedicated receptive field properties that are more or less stable through time. Recordings from ensembles of medial frontal cortex neurons suggest a different view. Frontal cortex neurons have varying degrees of responsiveness to all task events and while most neurons do not respond on most trials, the active trials rarely overlap, ensuring temporal uniformity at the ensemble level. A change in the task context causes dramatic re-allocations in neuronal selectivity. However, the re-allocations are so well-balanced across neurons that the ensemble representation exhibits context-invariance. Therefore, individual highly-multimodal frontal cortex neurons may encode 'events in context' yet produce a consistent ensemble representation due to their coordinated interactions.

John Neumaier, *University of Washington*
"DREADDing the lateral habenula"

The Lateral Habenula (LHb) is a tiny bilateral brain region that receives diverse inputs and transmits information about aversive experiences to several brain regions including the dorsal raphe nucleus, rostral medial tegmental nucleus, and the ventral tegmental area. Rather little is known about the chemical anatomy or functions of these neurons. We are using intersectional viral vector strategies in rats to express DREADD receptors and RiboTag to investigate the contribution of specific LHb output pathways to complex behaviors involved in stress reactivity and cocaine seeking behaviors.

Roy Katso, *GlaxoSmithKline*
"Bioelectronics: the journey & opportunity for a transformative treatment paradigm"

GSK's Bioelectronics R&D unit is pursuing the neuromodulation field, because we feel that this could one day result in a new class of medicines for chronic diseases in the peripheral space, with the potential to either sit alongside current treatments or to be standard treatments in their own right. The aspiration is that through these implantable devices, diverse indications across multiple therapeutic areas including respiratory, metabolic and inflammation, will be treated through this paradigm. GSK is a strong advocate of bioelectronics medicines and shares this belief and commitment with an emerging global ecosystem. Our ability to achieve our ambitions in bioelectronics requires access to cutting edge research and technologies so it is imperative that a global open innovation non-competitive framework exists that is coupled to a complementary funding ecosystem, if the neuromodulation field is to be successful. We are at a critical inflection point where the interface between the physical, engineering and life sciences is quite rightly becoming blurred. However, there are some critical outstanding points that this presentation will outline, which needs to be addressed in order for the neuromodulation field to achieve its aims. Why is this worth focusing on? Firstly, the open innovation framework is at the cusp of delivering research platforms that will underpin our ability to decipher neural circuits to a mechanistic understanding that will make neuromodulation a treatment reality. Secondly, there is sufficient reason to believe, as demonstrated by the Initial results from the GSK Exploratory portfolio that is exemplified by the impact for a non-pharmacological intervention in diabetes. Public-Private partnerships lie at the heart of translating the excellent global neuromodulation academic science into tangible treatments to meet unmet patient needs.

5:15-5:30pm **Final wrap-up and poster awards, NeuroFutures committee**

Posters

Monday, June 20

1.1 - Do regions in the mouse default mode network connect via specific cell types?
J. Whitesell, P. Bohn, M. Mortrud, K. Hirokawa, S.W. Oh, S. Mihalas, H. Zeng, J. Harris, Allen Institute for Brain Science

The spread of protein aggregates in neurodegenerative disorders is thought to be driven by templated misfolding transmitted between cells along anatomical connections. In Alzheimer's disease (AD), regions comprising the default mode network (DMN) show early and extensive deposition of amyloid-beta plaques as well as differences in functional connectivity. We hypothesize that brain regions comprising the DMN are preferentially linked by a class of cells selectively vulnerable to neurodegeneration in AD, while a separate group of cells links these regions to non-DMN brain areas. To examine the structural connectivity underlying the functionally-defined rodent DMN, we performed dual stereotaxic injections of retrograde CAV2-Cre virus and anterograde rAAV expressing Cre-dependent fluorescent protein in pairs of connected regions inside and outside the DMN. For a given DMN source, retrograde Cre expression was produced by CAV2-Cre injections into both DMN and non-DMN targets. Whole brain projections from these target-defined neuron populations were labeled by injecting Cre-dependent rAAV-eGFP in the source area. Projections to targets within the DMN were compared with projections to outside-DMN targets and with interareal connectivity datasets obtained as part of the Allen Mouse Brain Connectivity Atlas. Preliminary results show differences in target-defined projections from at least two DMN regions. When completed, this collection of target-defined projection patterns from DMN sources will provide a detailed map of cell type-specific anatomical circuit architecture and also help identify neuron types selectively damaged in AD. Future experiments will test the vulnerability of the DMN to AD pathology in mouse models.

1.2 - SmartScope 2: automated imaging for morphological reconstruction of fluorescently-labeled neurons
B. Long, Z. Zhou, J. Ting, E. Lein, M. Hawrylycz, H. Peng, Allen Institute for Brain Science

Fast and accurate quantification of morphology is a critical challenge in determining neuronal cell types in the brain. To address this challenge, we introduce SmartScope2, the first open source, automated neuron reconstruction machine that integrates automated bioimage analysis and rapid multiphoton imaging. The system integrates a commercially-available microscope with open-source software control for rapid 3D visualization and analysis. We show that SmartScope2 can automatically image and digitally reconstruct neuronal morphology.

1.3 - Ocular Dominance Columns in Rat Primary Visual Cortex: A Quantitative Model to Analyze Deprivation-Induced Cortical Plasticity
B. Lin, A. Andelin, J. Olavarria, Computational Neuroscience Program, University of Washington

What is the effect of sensory deprivation on brain development? Ocular Dominance Columns (ODCs) have been extensively used to study the mechanism of cortical plasticity, although the specific function of ODCs has remained elusive. Using a combination of transneuronal tracing, in situ hybridization for the immediate early gene Zif268 and electrophysiological recordings, our lab recently showed that the primary visual cortex (V1) in pigmented rats has ODCs, and these ODCs correlate with callosal inputs from the opposite hemispheres. Using similar methods, my project aims to understand the effect of monocular deprivation (MD) on the newly discovered system of ODCs in rat visual cortex. I hypothesized that the manipulation of visual input will impact the development and recovery of eye-specific circuitry. Since the distribution of callosal connections is closely associated with ODCs, I am also interested in the effect of monocular deprivation on the callosal pattern. By disrupting the visual input permanently or temporarily in early postnatal life, our lab has been able to measure the deleterious effects on map development, critical periods for these effects and potential for recovery. My project uses monocular eyelid suture and eyeball enucleation to study the effect of monocular deprivation on the organization of ODCs and callosal connections in pigmented rats. By using our experience-dependent model we expect to elucidate the principles and mechanisms underlying the development of cortical modular architecture in mammals. My result showed a clear shift in Hubel-Wiesel ocular dominance scale in central segment and clear desegregation in ODC in MD rats. I also developed computational methods to quantify the anatomical patchiness with a Java-based software and the neuronal activities with a Matlab protocol for our model. As our hypothesis is supported, our novel model may shed new lights on plasticity research, which can guide future clinical studies on the treatment and prognosis of patients suffering eye defects during early development by either innate or incidental pathological causes.

1.4 - Generation of a mesoscale connectome of the mouse visual system using individual functional maps for viral targeting
P. A. Groblewski, A. Bernard, A. Cetin, C. Farrell, D. Feng, M. Garrett, N. Gaudreault, K. E. Hirokawa, A. Ho, T. Keenan, A. Kriedberg, Y. Li, F. Long, V. Maldonado, S. Mihalas, L. Ng, J. Phillips, T. Siuda, C. Thompson, W. Wakeman, C. Koch, H. Zeng, J.A. Harris, Allen Institute for Brain Science

The purpose of the Next Generation Connectivity project is to create a comprehensive mesoscale connectome that maps the inputs to, and outputs from, the mouse visual system with cortical layer and cell type specificity. This project extends the findings of the existing Allen Mouse Brain Connectivity Atlas by adding components that improve precision, increase specificity, and enhance characterization

of mouse visual circuitry. Specifically, the aims of Next Generation Connectivity are to generate 1) an inter-areal retrograde projectome, 2) an inter-areal and cell type-specific projectome using axonal and synaptic labeling, 3) a target-defined inter-areal and cell type-specific anterograde projectome, and 4) an inter-areal and cell type-specific retrograde trans-synaptic connectome. Here we describe the use of intrinsic-signal-imaging (ISI) to obtain retinotopic and sign maps of the visual cortex in individual mice to precisely guide injections of fluorescent anterograde and retrograde viral tracers into specific locations within primary and higher visual areas. Briefly, mice are first implanted with a headframe that allows for through-skull ISI of the visual cortex while mice view a periodic drifting bar stimulus covering the entire field of view -- the resulting maps are then used to guide tracer injections using a custom suite of integrated software and hardware. Using high-throughput 2P serial imaging, coronal sections of the injected brain are generated, viral infection sites are then annotated and all brains are registered to the 3D common coordinate framework (CCF) through our informatics data processing pipeline. Individual ISI maps are then overlaid onto the CCF using surface vasculature patterns. The steps of this workflow, from the initial surgery to final ISI map overlay, require a common registration system that allows for precise alignment of the mouse brain across all experimental and analysis platforms. Lastly, to showcase the results of this project workflow we will present preliminary Next Generation Connectivity datasets that are currently available through our public data portal.

1.5 - High frequency - induced peptide release governs the synchronization of the arcuate kisspeptin neurons

J. Qiu, Oregon Health and Science University; C. Nestor, Department of Physiology and Pharmacology, Oregon Health and Science University; C. Zhang, Department of Physiology and Pharmacology, Oregon Health and Science University; S.L. Padilla, Department of Biochemistry and Howard Hughes Medical Institute, University of Washington; R.D. Palmiter, Department of Biochemistry and Howard Hughes Medical Institute, University of Washington; M.J. Kelly, Department of Physiology and Pharmacology, Oregon Health and Science University, Division of Neuroscience, Oregon National Primate Research Center, Oregon Health and Science University; O.K. Rønnekleiv, Department of Physiology and Pharmacology, Oregon Health and Science University, Division of Neuroscience, Oregon National Primate Research Center, Oregon Health and Science University

Kisspeptin (Kiss1) and neurokinin B (NKB) neurocircuits are essential for pubertal development and fertility. Kisspeptin neurons in the hypothalamic arcuate nucleus (Kiss1ARH) co-express Kiss1, NKB, dynorphin and glutamate and are postulated to provide an episodic, excitatory drive to gonadotropin-releasing hormone (GnRH) neurons, the synaptic mechanisms of which are unknown. We characterized the cellular basis for synchronized Kiss1ARH neuronal activity using optogenetics, whole-cell electrophysiology, molecular pharmacology and single cell RT-PCR. High frequency photo-stimulation of Kiss1ARH neurons evoked local release of excitatory (NKB) and inhibitory (dynorphin) neuropeptides, which were found to synchronize Kiss1ARH neuronal firing. The light-evoked synchronous activity caused robust excitation of GnRH neurons by a synaptic mechanism that also involved glutamatergic input to preoptic Kiss1 neurons from Kiss1ARH neurons. We propose that Kiss1ARH neurons play a dual role of driving episodic secretion of GnRH through differential release of peptide and amino acid neurotransmitters to coordinate reproductive function.

1.6 - Single-cell transcriptomics reveals receptor transformations during olfactory neurogenesis

N. Hanchate, K. Kondoh, Z. Lu, D. Kuang, X. Ye, X. Qiu, L. Pachter, C. Trapnell, L. Buck, Fred Hutchinson Cancer Research Center

The mammalian olfactory system senses and discriminates a myriad of volatile chemicals or odorants, which are perceived as diverse scents. The odorants are primarily detected by odorant receptors (ORs) expressed on the olfactory sensory neurons (OSNs) in the nose. Each mature mouse OSN expresses only one of ~ 1000 OR genes (Olfrs) in the genome. The developmental mechanisms underlying the expression of a single Olfr in each OSN are largely unknown. We used single-neuron RNA sequencing of neurons at different developmental stages from the mouse nasal olfactory epithelium to explore these mechanisms. Our studies revealed that OSNs initially express multiple Olfrs at the early immature stage and then specialize into the expression of a single Olfr at maturation. The multiple Olfrs in the early immature OSNs are expressed at low levels while the single Olfr in mature OSNs is expressed at a high level. Coexpressed Olfrs in immature OSNs localized to overlapping spatial zones of the nasal epithelium, suggesting regional biases in the selection of Olfrs. A single immature neuron could express Olfrs from up to seven different chromosomes, indicating that the expression of multiple Olfrs is not due to chromatin changes at a single genomic locus. The mature state in which expression of Olfr genes is restricted to one per neuron emerges over a developmental progression that appears to be independent of neuronal activity involving sensory transduction molecules.

1.7 - Acquisition of electrophysiological, morphological, and transcriptomic properties from individual cortical neurons in mouse and human.

B. Lee, T.K. Kim, K. Hadley, J. Ting, J. Berg, G. Murphy, E. Lein, B. Tasic, H. Zeng, Allen Institute for Brain Science

The Allen Institute has begun a comprehensive, multi-year endeavor to characterize neuronal diversity and establish hierarchical classification of neuronal cell types. As part of this effort, the Institute has publically released electrophysiological/morphological and transcriptomic data from hundreds of individual neurons of the mouse brain in the Allen Cell Types Database. The existing program utilizes parallel pathways for transcriptomic and electrophysiological/morphological profiling of individual neurons. In order to combine these two approaches, we have implemented a method to obtain transcriptome (RNA-seq) information from human and mouse neurons that were first characterized electrophysiologically via whole-cell patch clamp recordings. For a subset of these cells, we were also able to visualize and reconstruct cells' entire morphology. The multimodal data from a single neuron will facilitate ongoing efforts to derive an integrated taxonomy and the correspondence between different types of properties underlying neuronal diversity in the cortex.

1.8 - Spatiotemporal Localization of Direction-Distinguishing Movement Planning Electrocorticographic Features
J. Wu, B. Brunton, J. Olson, R. Rao, J. Ojemann, University of Washington

The development of human neurorehabilitation via inducing synaptic plasticity, as well as the advancement of effective upper-limb neuroprostheses, may both benefit from the ability to locate and decode goal-oriented pre-movement planning behavior from human cortical signals. Previous work in human electrocorticography (ECoG) has demonstrated the capacity of ECoG signals to detect the existence of premotor responses in finger movement. We further examined ECoG signals during different motor tasks to establish the timing and position of direction-distinguishing, force-predictive, and grasp-onset-predictive premotor planning information preceding motor activity. Subdural cortical surface potential from subjects with intractable epilepsy implanted with ECoG grids for clinical monitoring were sampled using Tucker-Davis Technologies hardware. Patients were cued to apply isometric forces to an affixed AMTI force transducer in one of six directions, or grasp one of six cued objects while wearing a motion-tracking Cyberglove. The signals were filtered for noise and analyzed with a continuous Morlet wavelet transform. Linear discriminant analysis (LDA) or regularized discriminant analysis (RDA) with shrunken centroids regularization was applied to predict movement classes, while Lasso regression was used to predict force. The regularization parameter δ for thresholding the correlation matrix elements was then used to localize in time and space wavelet coefficient features that contain direction-discriminating information, while nonzero β regression coefficients were used to localize force-predictive information. Direction-sensitive LDA prediction features of hand movement occurred in portions of the spectrums different from those predicting movement onset. RDA predicted force application direction significantly above chance (27%, chance 17%). Additional pre-movement information was attributable to direction-discriminatory features found in the ipsilateral premotor cortex up to 400ms before the onset of detected force, which transitions to the contralateral sensorimotor cortex at 250ms before the onset of detected force. Furthermore, these direction-discriminatory timing and features were found to precede force-predictive features, and occur in different locations and in different portions of the spectrum. Early-onset direction-distinguishing motor planning information, including those localized in the ipsilateral dorsal premotor cortex, may offer an insight into motor processes spanning multiple cortical regions. This may hint as to the possible timing of distributed motor planning processes for neuromodulation therapy, as well as maximize extracted information in motor neuroprostheses.

1.9 - Dynamics of excitatory-inhibitory neuronal networks with exponential synaptic weight distributions
R. Iyer, N. Cain, C. Koch, S. Mihalas, Allen Institute for Brain Science

Dynamics of interacting leaky integrate-and-fire (LIF) neuronal networks have been widely studied, both analytically and numerically, with a view to characterizing experimentally observed states of activity in the brain. Analytic approaches typically involve Fokker-Planck methods, based on a continuous stochastic process, that model dynamics of homogeneous neuronal populations with a single partial differential equation. This method abstracts distributions of synaptic weights by their first two moments and works well when higher moments can be neglected. Such an analysis revealed a rich repertoire of states of activity and allowed characterization of phase diagrams of coupled excitatory-inhibitory LIF networks (Brunel 2000). Experiments have observed skewed non-Gaussian synaptic weight distributions with long tails, such as lognormal (Song et al, 2005). A fast, semi-analytic population statistic approach to study stochastic jump processes with arbitrary distributions (Iyer et al, 2013) showed that equilibrium and transient population firing rates vary according to how heavy-tailed the distributions are. mate of the steady state firing rates in an adiabatic approximation, when the synaptic time-scales are much shorter compared to other time-scales in the system. We thus have a tool for rapid exploration of parameter space for large-scale models, with realistic synaptic weight distributions, in which the observables of interest are the mean firing rates of the populations. Parameter-fitting for interesting network behaviors, which is a hard problem for network models, can be simplified with the use of this method.

1.10 - A Dialogue between CRF & IGFBP2 to Enhance Spatial Learning & Memory via neurocircuit development and maturation by both spontaneous and activity dependent mechanism in Intermittent Hypoxia-exposed Neonatal Mice
S. Khan, X. Jiang Liu, J. Weng, Xue-Quen Chen, J-Zeng Du, Zhejiang Universityy

Previous study showed that intermittent hypoxia (IH 16.0% O2, 4 h/day for 4 weeks) enhances learning and memory by improving performance in water maze and 8-arm radial maze1 via SPAR (Rap-specific GTP-ase-Activating Protein)2. However, it remains unclear how IH could accounts for improved information processing for cognition in the neonatal brain.Methods: Mice were placed in a hypobaric chamber and exposed to hypoxia of 2,000 m altitude (79.97 kPa, equivalent to 16.0% O2 at sea level). Acute hippocampal slices (350 μm thick) were prepared from mice aged p14-p17 to record Action Potentials, fEPSP, LTP, m/sEPSC and mIPSC. Western blot, qPCR, hippocampal neuronal culture and water maze task were done. Results: Here we report that, IH enhances the expression of insulin like growth factor binding protein-2 (IGFBP2) in neonatal hippocampus, which is mediated by low dose of CRF. This enhanced expressions of IGFBP2 increased the intrinsic excitability of pyramidal neurons mediated by decreasing the voltage threshold to more hyperpolarized level and thereby primed glutamate synapses in CA1 region by augmenting the frequency and amplitude of AMPA receptor-mediated miniature EPSCs (mEPSCs) via IGF receptor 1 (IGFR1). Thereby, IGFBP2 allow glutamergic synapses in CA1 to undergo a long-term potentiation (LTP) following high frequency stimulation. This long-term potentiation requires an IGFBP2 dependent potentiation of postsynaptic NMDA receptors (NMDARs). Furthermore, microinjection of anti-IGFBP2 antibody prevents memory retention and enhances forgetting without affecting locomotors activity. However, IGFR1 antagonist (JB-1) blocks induction of LTP by both IGFBP2 and low dose CRF indicates both of them share common signalling pathway via IGFR1. Bath application of MAPK-inhibitor (U0126) abolished both IGFBP2- and low dose CRF-LTP. Activation of ERK1/2 is therefore required for both IGFBP2- and low dose CRF-LTP, leading to a dialogue between CRF & IGFBP2 to enhance synaptic plasticity. Conclusions: Intermittent Hypoxia initiate a partial dialogue between CRF and IGFBP2 and in this consequences IGFBP2 accomplishes enhanced synaptic plasticity by both spontaneous and activity dependent mechanisms. Thus, CRF-IGFBP2 signalling may be a new target for cognitive dysfunction.

1.11 - Linking electrophysiology and optophysiology in vivo

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Single-unit recordings remain a core technology for in vivo electrophysiology. Yet, they offer only limited information about the location, morphology, or genotype of the recorded cells. Compared to traditional micro-wire electrodes, high-density silicon `polytrodes' improve single-unit isolation. Nonetheless, accurate, automated spike sorting remains a tremendous challenge, especially for high channel-count, contiguous electrode arrays. Ground truth data that tie in vivo spike signals to the actual spiking neuron, crucial to validating spike sorting algorithms, are extremely difficult to acquire. On the other hand, ground truth data sets have been gathered through simultaneous polytrode recordings and patching of nearby cells in slice [Anastassiou et al, 2015] and in vivo [Henze et al, 2001] yet this approach is impractical for an awake in vivo preparation where many cells contribute to the neural code as well as to the extracellularly recorded signals. In this work, we present viable and scalable alternatives.

1.12 - Effect of distance on the magnitude and timing of Cortico-Cortical Evoked Potentials in oscillation triggered direct electrical stimulation in humans

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Introduction: Cortico-cortical evoked potentials (CCEPs) allow for the study of brain connectivity and short term plasticity changes. The study of the effects of electrical stimulation on short term plasticity assessed through CCEPs could inform the development of devices for neuromodulation and rehabilitation following neurologic injury through diseases such as stroke. Triggering stimulation from endogenous brain activity in the form of beta oscillations may enhance the size of CCEPs following repeated stimulations. Other CCEP characteristics such as the distance from the triggering electrode and latency of the CCEP peak are important in characterizing the effects of stimulation across the brain. Methods: Human subjects were implanted with electrocorticographic (ECoG) grids for the monitoring of intractable epilepsy prior to surgery. Neural signals were acquired, and the band-passed signal (12-20 Hz, representing beta oscillations) at an electrode in somatosensory cortex triggered biphasic, bipolar stimulation across an electrode pair. Neural signals were recorded following stimulation, and subsequently analyzed in MATLAB. CCEPs were converted to z-scored CCEPs relative to a baseline period prior to stimulation, and a peak CCEP value was extracted from the absolute value, baseline subtracted signal following stimulation. Results: Seven subjects were implanted and tested as described above. CCEP latency in general increased with increasing distance from the beta recording electrode across the ECoG grid. Additionally, the magnitude of the CCEP response decreased as the distance from the beta-recording electrode increased. Conclusions: This study indicates that in general as the distance from the beta-oscillation recording channel increases, the magnitude of CCEPs decreases, and the latency of the first CCEP peak increases. Potential physiologic explanations for the decrease in magnitude include decreasing connectivity and oscillation coherence among local electrode regions. Potential physiologic explanations for increased latency include greater distances for neural signals to propagate. Future directions to explore include analyzing the distributions of peak magnitudes, fitting curves to better characterize the distribution of shapes, and comparing these results to theoretical models of brain stimulation.

1.13 - Neuroplasticity & consciousness of neural correlates

M. Owen, University of Birmingham

This work focuses on what neuroplasticity implies about the nature of conscious intentional states that are correlated with neural states. Neuroplasticity has shown that our intentional states can causally affect our neural synapses and neural pathways. This seems to directly imply two things about the nature of such conscious intentional states. First, they're not identical to or reducible to neural states, which they affect. Second, there is causation going from the conscious intentional states to neural states. The first implication entails further implications about the extent of knowledge we can gain about consciousness from knowledge of the brain. The second implication has further methodological implications regarding the priority of conscious intentional states and brain mapping.

1.14 - Mapping cortical mesoscopic networks linked to single cortical and sub-cortical neuron spiking

C. Mitelut, M. Vanni, D. Xiao, A. Chan, Y. Xie, A. Chen, N. Swindale, T. Murphy, University of British Columbia

Understanding the basis of brain function requires knowledge of cortical operations over wide-spatial scales, but also within the context of single neurons. We used in vivo, simultaneous wide-field of view GCAMP imaging and sub-cortical/cortical extracellular electrophysiology in mice to investigate relationships between spontaneous single neuron spiking and mesoscopic cortical activity. The approach involves generating spike-triggered imaging maps and extends spike-triggered averaging methods to wide areas of cortex with the potential for selectivity via genetically targeted indicators of neuronal activity. Spiking thalamic neurons were correlated with complex cortical spatial map features not predicted from consensus intra-cortical networks. Temporally, single thalamic neurons

predicted and reported specific cycles of wide-scale cortical inhibition/excitation. In contrast, spike-triggered maps from single cortical neurons tended to yield spatio-temporal maps expected for regional cortical consensus function. This approach can define network relationships between any point source of neuronal spiking and mesoscale cortical maps and may have use for identifying novel brain stimulation targets to affect connected areas.

1.15 - Hyperactivity in corticostriatal circuits and increased excitability in spiny neurons in Nf1+/- mice
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Deletion of neurofibromin, a Ras inhibitor, results in several cellular and systemic defects. Children suffering from this syndrome, termed neurofibromatosis type 1 (NF1), display a unique profile of attention, memory and various psychomotor impairments that is well replicated in mouse models. NF1-associated increased GABAergic activity and decreased dopaminergic tone have been demonstrated in transgenic NF1 mice. NF1 pediatric patients show increased incidence of autism, and in a subset of autistic individuals dysmorphic striatal regions have been shown. We developed a new approach to study NF1 using intrinsic functional connectivity MRI (fcMRI; also referred to as task-free fMRI) in awake mice. Functional changes in Nf1 heterozygous null mutants (Nf1+/-) as compared to littermate controls (Nf1+/+) were interrogated using a novel structure-function connectivity analysis of high-resolution whole-brain fMRI and electrophysiology. We identified decreased functional connectivity in the motor cortical network that corresponded to increased corticostriatal functional connectivity in the indirect pathway of the basal ganglia, and conversely, increased functional connectivity in the cortical somatosensory network that corresponded to increased corticostriatal functional connectivity in the direct pathway of the basal ganglia. Our results, when considered along with prior evidence, implicate the striatum as a source for altered cortical activity seen in NF1, suggesting that rescue of striatal function may partly alleviate the neurocognitive phenotype in NF1.

1.16 - Mouse Self Directed Home-cage Brain Imaging and Behavioural Apparatus Using the Raspberry Pi
F. Bolanos, J. LeDue, J.D. Boyd, G. Silasi, M. Vanni, D. Haupt, T.H. Murphy, University of British Columbia

Automated assessment of rodent behavior is desired as it reduces experimenter bias, facilitates throughput, avoids disrupting circadian rhythms, and eliminates stress in animals introduced by experimenter handling. We developed an automated self-initiated head-fixation system for mesoscopic functional imaging in mice with extension to 24/7 monitoring. The apparatus consists of a small chamber attached to the outside of the standard 29 by 18 cm mouse home cage that can house up to 5 mice. The chamber contains two mechanical solenoids to head fix the mice by contacting a steel bar glued just posterior of their transcranial window. A raspberry Pi camera was used to acquire brain images under wide-field epifluorescence and an RFID sensor to identify mice allowing aspects of the task to be individualized. To encourage head fixing, mice obtain water by successfully being head-fixed, or smaller amounts of water by just entering the chamber (entrance rewards). To obtain functional brain maps the mice express GCAMP6 calcium indicator using Allen Institute intersectional strategies EMX-cre x Ai94 or Ai93 (Madisen et al. 2015 Neuron). We are able to monitor and assess functional cortical maps in longitudinal studies over 3 months due to their stable chronic window. Individualized performance is logged and imaging parameters are controlled by custom software written in Python running on a Raspberry Pi (Murphy et al. Nature Commun. 2016). Future experiments will introduce a motor and/or cognitive task to quantify brain activity changes as the mice learn the task.

1.17 - Comparing Mesoscopic Functional Organization of Cortico-hippocampal Networks in Mice and Humans using Intrinsic Functional Connectivity
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While the hippocampus has been relatively conserved across mammals, the cerebral cortex underwent massive expansion and elaboration. A central question in brain evolution is how cortical development affected the nature of sensory inputs to the hippocampus. To address this question, we compared cortico-hippocampal connectivity using intrinsic functional connectivity MRI (fcMRI; also referred to as task-free fMRI) in awake mice and humans. Leveraging fcMRI sensitivity to polysynaptic connections, we identified a topographic modality-specific organization of sensory cortices in the mouse parahippocampal region that extends to the dentate gyrus. Examining the topography of sensory cortices connectivity to the mouse hippocampus, we found a gradual increase in overlap of the different modalities, indicating sensory integration. Finally, comparing cortico-hippocampal connectivity across species, we discovered preferential hippocampal connectivity of sensory cortical networks in mice, in contrast to preferential connectivity of association cortical networks in humans. Supporting this observation, in humans but not mice, sensory and association cortical networks are connected to spatially distinct subregions in the parahippocampal region. Collectively, these findings indicate that sensory cortical networks are coupled to the mouse, but not human, hippocampal memory system, suggesting that the emergence of expanded and new association areas in humans resulted in rerouting of cortical information flow and dissociation of primary sensory information from the hippocampus.

1.18 - A role for excitability changes in short-term sequence replay in model neural networks
R. Pang, A. Fairhall, University of Washington Neuroscience Graduate Program

The reactivation of neuronal activity patterns outside the context in which they originally occurred is thought to play an important role

in mediating memory, but the biophysical mechanisms underlying reactivation are not well understood. Especially mysterious is the replay of sequential activity patterns occurring in the recent past, since spike-timing-dependent plasticity, the biophysical mechanism normally invoked to bias model networks towards sequence production, is not thought to have a substantial effect on short time-scales. Here we propose a model in which short-term memory for sequences is maintained in persistent activity triggered by the original sequence activation, and which directly increases the effective excitability of the neural ensembles involved in the sequence, thus leading to an increased probability of replay of sequences involving those ensembles. We show how such a phenomenon can be implemented in a simple dynamical model, and we show that the number of sequences that a randomly connected recurrent network can replay grows polynomially in the number of ensembles in the network with degree equal to sequence length. In a simplified probabilistic model we then show how the decodability of past stimulus sequences from future neural replay sequences increases as the network connectivity becomes reflective of the stimulus transitions. Finally, we discuss the computational principles underlying our model in terms of attractors and the generation of spatiotemporal patterns from spatially defined information. Our model provides a low-complexity, biologically plausible alternative to other sequence reactivation models and makes the prediction that reactivation of arbitrary sequences in biological neural networks will be much less common than reactivation of sequences already preferentially embedded in the network.

1.20 - Systems for analyzing big neuroscience imaging data

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The analysis of image data has been a central part of neuroscience research since its very beginning, but with the more recent accelerated development of methods to image and record the brain at many different scales, large collections of digital image data have become available. The size, diversity and complexity of these data have thrust neuroscience researchers into the era of big data.

1.21 - Comparative analysis of hippocampal brain volume between Thai and Non-Asian volunteers: A case study from Bangkok hospital Phuket

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Several reports have shown a strong relationship between the decrease of hippocampal brain volume and cognitive function. Researchers have demonstrated its clinical application of such a finding as an indicator for early Alzheimer's disease detection. This is the first study to compare hippocampal brain volume in Thai versus Non-Asian healthy populations.

1.22 - Glassy Carbon Based Microelectrode Array Technology for use in Long-Term Neural Recording and Stimulation with Superior Electrical and Electrochemical Properties

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We present our work in the development of a new class of electrodes fabricated from lithographically patterned glassy carbon for electrical and electrochemical neural signal recording and stimulation. As an electrode material glassy carbon has a capacitive behavior that provides superior charge injection capacity (CIC), a wider electrochemical window, and better electrochemical stability as compared to conventional electrode materials, while maintaining a similar conductivity. We demonstrate the ability to fabricate glassy carbon electrodes in a variety of versatile 2D and 3D configurations, and the subsequent ability to integrate the electrodes into a flexible polymeric substrate for the manufacturing of high-resolution, thin-film microelectrode arrays (MEAs). By fabricating the glassy carbon electrodes in different innovative configurations, we are able to create MEAs for both penetrating and surface recording (μECoG) applications. We verified the long-term functionality and stability of the electrodes through in vitro experiments. Exposing the devices to 30mM hydrogen peroxide at body temperature for one week to emulate the acute immune response environment did not result in any significant changes to the electrical properties (impedance) or microstructure of the electrodes. Cyclic voltammetry was then used to study the behavior of glassy carbon electrodes under chronic stimulation, and the results indicate that the electrodes

are able to undergo at least 2500 cycles with no significant change in impedance @ 1kHz and 100 Hz. Additionally, in vitro cell viability tests were performed on both the glassy carbon material and fabricated devices, with both showing no signs of cytotoxicity. Furthermore, chronic ECoG in vivo experiments, in which glassy carbon μECoG MEAs were chronically implanted subdurally in the motor cortex of rat models over a period of six weeks, demonstrated long-term biocompatibility and stability of the devices. Specifically, the devices maintained a low impedance (< 10kΩ) over the course of the experiment, and were able to record high quality sensorimotor evoked potentials. After the conclusion of the six week experiment, histological analysis of the cortical tissue with a depth of 1.3 mm (through the whole sensorimotor cortex) indicated no specific or severe immune response. We submit that this new class of microelectrodes offers a compelling platform for a suite of new applications that require corrosion-resistant, long-term neural implants with not only excellent mechanical and electrical properties, but also superior electrochemical performance.

1.23 - Microfluidic manufacture of RNA-lipid nanoparticles leads to highly efficient delivery of potent nucleic acid therapeutics for controlling gene expression

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Lipid nanoparticles (LNPs) are used to deliver nucleic acids in vitro and in vivo. Here, we describe the robust manufacture and use of clinical-grade lipid-based nanoparticles for nucleic acids delivery at scales suitable for both in vitro screening and in vivo applications. We have conducted studies to evaluate the merits of the technology and further provide insights for delivering short interfering RNA (siRNA) and mRNA. RNA-LNPs were formulated to encapsulate a potent siRNA directed against PTEN. Exceptional cellular uptake (>96%) with minimal toxicity was observed in both primary rat hippocampal and mixed cortical cell cultures. High transfection efficency (>95%) of the encapsulated material resulted in high-level (>85%) PTEN knockdown the first 4 hours of a low dose (100ng/ml) treatment; knockdown was sustained for 21 days. Similarly, RNA-LNPs encapsulating mRNAwere also found to mediate early (75% for 7 days)following a single (500ng/ml) treatment in primary rat mixed cortical cultures. Strategies for locally administering RNA-LNPs into the brain and spinal cord of adult Sprague Dawley rats were also investigated. Localized injections of PTEN-encaspulated siRNA into the motorcortex resulted in significant and sustained (7 days) knockdown. Similarly, local administration at the site of a cervical spinal cord injury significantly reduced target PTEN expression, 10 days later. Collectively, these studies reflect the simplicity and efficacy of this technology in validating new targeted nucleic acid therapies.

1.24 - Mesoscale brain imaging: seed-pixel correlation explorer

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We are developing a cross-platform standalone application for creating and exploring seed-pixel correlation (SPC) maps from mesoscopic brain activity from GCaMP6 transgenic mice and other data sources. The user is able to choose a single pixel called the seed. Pearson correlation zero lag is used to generate a colour map showing how strongly brain activity over time at each pixel correlates with brain activity at the seed (Vanni et al. 2014). The user can also generate standard deviation maps which is a colour map showing how much brain activity varies over time at each pixel. Taken together then, the SPC map reveals brain regions displaying synchronous activity whereas standard deviation maps reveal which regions display the most varying activity. User inputs can specify processing parameters along the processing pipeline, select regions of interest (ROIs) and specify processing parameters specific to those ROIs. The application leverages parallelism and fast fourier transforms to align separate video files to a selected reference frame (Press et al. 2007). Selected video files can be concatenated into one and saved. Regions of interest (ROIs) can be drawn using polygon cropping tool and the subsequent video file consisting of only the ROIs can be saved. The ROI polygons can themselves also be saved. A temporal chebyshev filter can be applied with the user specifying the passband of allowed brain activity signal to increase the signal-to-noise ratio by removing contributing factors to noise such as cardiac and respiratory factors (Vanni et al. 2014). Global signal regression (GSR) can optionally be applied to remove spontaneous fluctuations common to the whole brain using a general linear model. This technique has been shown to facilitate the detection of localized neuronal signals and improve the specificity of functional connectivity analysis (Fox et al, 2009). Finally, SPC maps are generated from the filtered activity be clicking on a position on a canvas to place the seed. Standard deviation maps can likewise also be produced on the filtered activity. Throughout this processing pipeline, a GUI provides a snapshot view of the changes being made to the data. The data can be zoomed in on or translated around for closer inspection against a scale centered on bregma. Bregma's location and the length of a single pixel is user-specified. ROI's can also be used to select a region whose activity will be averaged to generate graphs of activity over time for each ROI. These plots can be placed on the same scale for comparison and dynamically added/removed as the user modifies their ROI's. Of note is that each step of the data processing pipeline can be saved and loaded, with the idea being that the user is given full autonomy over where in the processing pipeline they want to load their data. This is to facilitate rapid post-hoc analysis where parameters can by changed with results viewed quickly. This thereby eliminates the need to ever process the same data twice through an upstream segment of the pipeline after changing parameters further downstream. The application currently works for tif and raw file formats, makes no assumptions as to what brain imaging technique is used (VSD, GCaMP6 etc), is freely available and assumes no programming experience to download and install on Windows or Linux. A demo of the application in its current incarnation, with example data, will be available at the conference. The goal being to receive input from the neuroscience community regarding the application.

1.25 - Fetal diffusion MRI and light microscopy of the rhesus macaque brain: Identifying cellular structural changes that underlie dynamics of water diffusion characteristics in the cerebral cortex

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Diffusion-weighted MRI (dMRI) can be used to study cellular morphological characteristics of biological tissue through biophysical interpretations of quantitative indices of water diffusion within an imaging voxel. In developing cerebral cortical gray matter, water diffusion anisotropy (expressed as fractional anisotropy, FA) decreases throughout the second half of human gestation. Further, deviations from the normal trajectory of FA changes have been associated with pathological processes in contexts of various neurodevelopmental disorders. Thus, fetal dMRI could provide a non-invasive assessment of cerebral cortical development. However, little is known regarding the specific cellular-level changes that underlie changes in cerebral cortical FA. To address this, we quantitatively analyzed 3D confocal data collected on fetal rhesus macaque brain tissue subsequent to acquisition of fetal brain MRI.

1.26 - A potential therapeutic agent for neurodegenerative diseases, NDX-1001, stimulates retention and regrowth of lost circuits

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Loss of normal circuit function in either the central or peripheral nervous system is a common feature of neurodegenerative diseases, and aging populations will face an increasing neurodegenerative disease burden. All neurodegenerative diseases result from a combination of diminished synaptic connectivity and neuron loss and in the case of Alzheimer's disease, losses of neurons and circuitry is related to accumulation of toxic protein plaques. Therefore, an effective treatment would be expected to augment synaptic connectivity, protect neurons from insult, and stimulate the replacement of lost neurons from pools of neural stem cells. These clinical endpoints can all be achieved by therapeutic use of neurotrophic factors, and one particularly attractive neurotrophic factor, hepatocyte growth factor (HGF), has shown promise as a potential treatment of AD and other neurodegenerative diseases. Limitations of stability and CNS bioavailability prevent the direct application of HGF in patients, but M3 Biotechnology, Inc. has developed a novel HGF mimetic (NDX-1001) that is inherently blood-brain barrier permeant and stimulates the HGF signaling cascade at ~< 1nM concentrations in cell culture. The hippocampus is deeply affected by AD neurodegeneration, but NDX-1001 is a potent stimulator of hippocampal synaptogenesis in vitro and in-vivo. Stimulation of synaptogenesis and process formation by NDX-1001 application may promote the reconstitution of lost circuitry within the brain. Furthermore, NDX-1001 is able to reverse cognitive deficits in scopolamine and aging models of dementia in rodent models, and exhibits profound neuroprotective activity. Most relevant, however, is NDX-1001's ability to restore cognitive function in behavioral models of neurodegenerative disease. Additionally, motor neurons of the peripheral nervous system can be protected from degeneration in genetic and chemical models of disease. Current treatment schemes for neurodegenerative diseases like AD focus on symptom amelioration, but NDX-1001 is under development by M3 Biotechnology, Inc. to become the first genuine therapeutic agent of AD that may promote protection of healthy circuitry and restore degenerated neural tissue.

1.27 - MultiScope: Multiplexed Random-Access Scanning for Scalable 3D Imaging of Intact Cortex

D. Tsyboulski, N. Orlova, R. Liu, O. Gliko, P. Saggau, Allen Institute for Brain Science

Two-photon (2P) imaging has become a mainstream tool for imaging neuron's morphology and function in intact cortex. Two-photon scanning microscopy achieves data acquisition rates of ca. 10 megapixels/s and allows observation of fluorescently labeled neurons within limited region of interest at 5 30 frames per second. A complimentary approach for imaging function of "randomly" distributed neurons in a volume termed "random-access" 2P scanning allows switching between points in 3D within time window of 10 - 20 μs and achieves scan rates of 30-50 kilopixels/s. These scan rates allow interrogation of up to 500 neuron cells with temporal resolution of ca. 10 ms in a single experiment. Further increase in scan rates is possible with multiplexed imaging techniques that allow simultaneous fluorescence signal acquisition from multiple points. In this work we present the development of a frequency-multiplexed two photon imaging method that utilizes high-speed amplitude modulation of fs pulses in MHz range to tag each excitation beam and the corresponding fluorescence signals with specific frequencies. Proof of concept work, physics of the effect and imaging experiments will be presented.

1.28 - Controlling Our Brains — On the Implications of Brain Computer Interface-Triggered Deep Brain Stimulation for Essential Tremor

T. Brown, University of Washington Department of Philosophy; M. Thompson, Department of Electrical Engineering, University of Washington; J. Herron, Department of Electrical Engineering, University of Washington; A. Ko, Department of Neurological Surgery, University of Washington; H.J. Chizeck, Department of Electrical Engineering, University of Washington; S. Goering, Department of Philosophy, University of Washington

Deep Brain Stimulators (DBS) are a neurotechnological means of treating a variety of movement disorders, including Essential Tremor (ET). Current stimulation systems apply an electrical current to targets in the brain at a constant rate for as long as they are implanted and activated--treating symptoms but causing uncomfortable side-effects and inefficient power usage. Some users feel of estrangement or isolation. Next-generation DBS systems could sense the user's neural signals and use them to trigger stimulation. Brain Computer Interface-triggered DBS (BCI-DBS) systems would give the user the ability to moderate side-effects and influence battery usage. But

will users want this level of control? It's not yet clear whether such added user control will address or exacerbate psychosocial side effects, and whether the user will feel burdened or freed by it. To explore these questions, we conducted interviews with an ET patient using an experimental BCI-DBS platform. These interviews offer preliminary evidence that if BCI control bolsters his autonomy, but it does not do so directly or without difficulty. While BCI-DBS may facilitate making trade-offs between side-effects and symptom relief, the user will face new trade-offs. BCI-DBS users, we argue, will likely face challenges to their ability to negotiate trade-offs competently.

Tuesday, June 21

2.1 - Generation of transgenic mice with tightly regulated expression for cell type-specific studies
T. Daigle, L. Madisen, U. Knoblich, M. Takeno, B. Lee, H. Gu, M. Mills, L. Gray, J. Ting, N.M. da Costa, B. Tasic, H. Zeng, Allen Institute for Brain Science

Modern genetic approaches have allowed for unprecedented access to diverse types of neurons within the mammalian brain and have greatly facilitated the study of their function. In parallel, the development of highly sensitive molecular sensors and optical tools has enabled the labeling of diverse cell types, the perturbation of neuronal activity with precise temporal control, and the visualization of distinct neural states. Over the last several years, we have developed multiple transgene expression platforms in mice using various molecular genetic approaches that achieve high levels of fluorescent proteins, sensors, and optogenetic tools within selective cell populations, defined largely by unique Cre driver lines. Here we report our newly developed Cre- and tTA-dependent reporter lines that were generated using our previously published strategy (Madisen L et al., Neuron, 2015), in which select transgenes are incorporated into the genomic locus known as TIGRE. We have also developed a new molecular strategy to create the next generation of reporter lines which builds upon the existing approach yet offers several key advantages such as a more simplified breeding strategy, robust transgene expression within different interneuron populations, and potentially greater genetic control. Anatomical and functional data for two of these next generation TIGRE reporter lines will be presented and the lines currently under development will be described. These novel transgenic lines will greatly expand the repertoire of high-precision genetic tools available to effectively identify, monitor, and manipulate distinct cell types within the mammalian brain.

2.2 - Modifying the connectome with genetically engineered synapses
I. Rabinowitch, J. Bai Jihong, Fred Hutchinson Cancer Research Center

One of the big quests of contemporary neuroscience is to chart the elaborate maps of synaptic connectivity (connectomes) of diverse species. This effort was pioneered three decades ago with the complete mapping of the connectome of the microscopic nematode C. elegans. Such descriptive work is invaluable for revealing the organization principles of brain circuits. We propose that in addition to mapping the connectome and recording existing synaptic connections, a method for constructing new synapses and thus modifying the connectome would considerably enhance our ability to link structure to function in neural circuits. As a first step for modifying the connectome, we have recently developed a technique for genetically inserting new electrical synapses into in vivo C. elegans neural circuits. The technique is based on ectopically expressing mouse gap junction protein Cx36 in specific C. elegans neurons to form a new link between them. This has enabled us to probe and alter the function of various circuits, such as flipping olfactory preferences or counteracting the effects of cross-modal plasticity. Such neural circuit engineering should be applicable to other genetically tractable organisms and in the future might enable circuit repair after damage or the design of entire new neural circuits.

2.3 - Developmental plasticity in the effect of visual deprivation on the surface area of visual cortex in animals and humans
A. Andelin, University of Washington; C. Kroenke, Oregon Health and Science University; I. Fine, University of Washington; E. Taber, Oregon Health and Science University; A. Stevens, Oregon Health and Science University; J. Olavarria, University of Washington

Deprivation of visual input early in life induces brain anatomical differences with sighted individuals at maturity. Studies in several species have shown that the primary visual cortex surface area is reduced in the early blind. Here the dependence of the magnitude of visual cortex surface area reduction was characterized as a function of age of deprivation from retinal in put in rats, ferrets, and humans. When post conception ages of each species was translated to a common neurodevelopmental event time scale, a highly consistent inter-species surface area dependence on timing was found. Deprivation of retinal input early in visual system development, beginning prior to the time that retinal axons reach the dorsal lateral geniculate nucleus, produces as much as a 50% reduction in visual cortex surface area. Visual stimulus deprivation at later times result in an exponential approach to visual cortex surface area of sighted individuals, reaching 90% of normal surface area when deprivation begins during the rapid cerebral cortical synaptogenesis phase of visual system development. By implication the surface area effect likely results from attenuated surface area expansion rather than enhanced pruning. A longitudinal follow-up study was performed in developing ferrets to confirm this expectation. This work enables the timing of blindness onset to be estimated from visual cortex surface area at maturity, which potentially relates to an individual's ability to respond to restoration of vision.

2.4 - Neuronal diversity in the dorsal lateral geniculate nucleus of adult mouse

T. Bakken, V. Menon, K. Smith, J. Goldy, D. Bertagnolli, A. Szafer, B. Tasic, T. Dolbeare, M. Hawrylycz, L. Ng, S. Sunkin, J. Philips, A. Bernard, E. Lein, H. Zeng, C. Koch, Allen Institute for Brain Science

Recent advances in RNA-sequencing techniques have led to the identification of transcriptomic cell types in various cortical and subcortical regions of the brain, including components of the mouse visual system: retina (Macosko et al. 2015) and primary visual cortex (Tasic et al. 2016). To broadly capture neuronal diversity in the dorsal lateral geniculate nucleus (dLGN) of the thalamus, we used four transgenic mouse lines to isolate more than 1800 excitatory and inhibitory neurons and profiled their transcriptomes by RNA-sequencing. We profiled cells to a median depth of 2.3 million reads and classified them into putative transcriptomic types using an iterative clustering approach based on principal component analysis (PCA) and gene co-expression methods. Our data and analyses suggest that GABAergic neuronal types in dLGN and in surrounding structures can be subdivided into distinct types with clear on-off gene markers, whereas glutamatergic neurons exhibit gradient variation in gene expression. We also correlated the variation of these transcriptomic types across the anterior-posterior axis and in the "core" and "shell" regions of the dLGN. These transcriptomic data and classification scheme are presented in an interactive web tool for further exploration. Ultimately, the identification of putative transcriptomic cell types in the dLGN, an integral portion of the visual pathway, leads to hypotheses about differing electrophysiological and connectivity relationships among neurons in the early visual system.

2.5 - Logistic Regression for identifying strong expression and structural pattern of gene in Mouse Brain Dataset

R. Shalini, J. Bineeshia, T. Balaji Muthazhagan, PSG College of Technology

Neuroscience data is obtained from Allen institute for Brain Science where it provides gene expression for the developmental stages of mouse brain. This Gene expression data changes throughout the process of development in the mouse brain. So, the challenge is to analyze the gene expression to measure the strong expression and to identify the structural pattern. It is done by comparing expression values across developmental stages with the help of the proposed algorithm. This paper proposes an algorithm (GISP), it compares expression values with common structure IDs across developmental stages and determines the strongly expressed gene between first two embryonic levels. The proposed algorithm identifies the small set of structure in the high expressive gene. Experiment was conducted with approximately 3500 gene characterized by in situ hybridization for two embryonic stages. It is observed that the proposed algorithm has better precision.

2.6 - Hypothalamic AgRP Neurons Link Nutritional State and Fertility

S.L. Padilla, HHMI University of Washington; J. Qiu, Oregon Health and Science University; C.C. Nestor, Oregon Health and Science University; C. Zhang, Oregon Health and Science University; A.W. Smith, Oregon Health and Science University; B.C. Jarvie, HHMI University of Washington; B. Whiddon, HHMI University of Washington; O.K. Rønnekleiv, Oregon Health and Science University; M.J. Kelly, Oregon Health and Science University; R.D. Palmiter, HHMI University of Washington

Women suffering from malnutrition and athletes with low body fat become infertile as a result of low gonadotropin secretion. Leptin, a hormone made in adipose tissue, is required for the central nervous system to drive gonadotropin release, yet the leptin-sensing mechanism responsible for this outcome is unresolved. Leptin-inhibited hypothalamic neurons that make agouti-related protein (AgRP) orchestrate survival during starvation and may relay information to the reproductive axis. To test this idea, we used optogenetics in combination with slice recordings, and found that AgRP neurons directly inhibit two populations of kisspeptin1-expressing neurons the primary drivers of the neuroendocrine reproductive axis. Furthermore, we found that chronic activation of AgRP neurons, using chemogenetics, was sufficient sufficient to delay estrus cycles in female mice -- a prelude of infertility. Thus, activation of AgRP neurons in response to low leptin levels or artificial activation in well-fed mice suppresses fertility by inhibiting the Kiss1 neurons that drive the reproductive axis.

2.7 - Characterization of the spatiotemporal tuning properties of mouse visual cortex

N. Mesa, University of Washington; J. Zhuang, Allen Institute for Brain Science; J. Waters, Allen Institute for Brain Science

Evidence of higher order visual processing in the mouse has gone a long way to establish the mouse as a useful model for visual processing. Differences in the spatial and temporal frequency tuning properties of mouse higher visual areas show evidence of functional specialization akin to that which exists in primates. However, it is unknown whether, within a visual area, there are differences in spatial or temporal frequency tuning. Since each visual area contains a retinotopic map of the visual field, such differences would suggest that parts of the visual field have distinct spatial and temporal frequency preferences. We employed widefield calcium imaging in order to map the spatiotemporal tuning properties of all of the mouse cortex simultaneously. Preliminary evidence suggests that there are indeed differences in spatial and temporal frequency preference within a single visual area, and that these differences may be related to retinotopic location.

2.8 - Functional characterization of activity in the Allen Brain Observatory

G.K. Ocker, M. Garret, A. Henry, A. Kriedberg, A. Jones, A. Doperalski, A. Bernard, A. Sodt, A. Ho, T. Siuda, A. Arkhipov, A.B. Donimirski, B. Rogers, C. Thompson, C. Habel, C. White, L. Kuan, C. Dang, C. Barber, C. Mochizuki, C. Cuhaciyan, C. Koch, C. Hill, C. Lau, R.C. Reid, C. Slaughterbeck, C. Farrell, D. Feng, D. Sullivan, D. Williams, D. Ollerenshaw, E. Lee, E. Mount, F. Lee, F. Griffin, F. Lai, F. Long, H. Zeng, J. Waters, J. Huffman, J. Harrington, J. Perkins, J. Luviano, J. Lecoq, J. Phillips, J.M. Gonzales, J. Larkin, J. Pendergraft, J. Nyhus, J. Johal, K. Roll, K. Godfrey, K. Brouner, L. Pearson, L. Ballsmider, L. Casal, L. Ng, L. Potekhina, M. Garwood, M. Schroedter, M. Sarreal, M. Reding, M. Tieu, M. Chapin, M. Hawrylycz, M.

Stoecklin, M. Robertson, N. Dotson, N. Orlov, N. Wong, N. Gaudreault, N. Sjoquist, N. Mastan, N. Bowles, N. Dee, N. Blesie, N. Hejazinia, P. Hargrave, P. Groblewski, R. Larsen, R. Dietzman, R. Tiburcio, S. Whiteside, S. Olson, S. Caldejon, S. Shi, S. Mihalas, S. Cross, S. Datta, T. Keenan, T. Nguyen, T. Dolbeare, T. Flies, V. Maldonado, V.R. De Guzman Wright, W. Wakeman, Y. Li, Z. Haradon, S. De Vries, M. Buice, Allen Institute for Brain Science

In order to explore how features of the sensory environment are represented by cortical circuits, the Allen Institute for Brain Science will publicly release the first survey of neural activity in the living brain, the Allen Brain Observatory. Using high-throughput 2-photon calcium imaging, we have systematically recorded the visual responses of over 18,000 neurons in the awake mouse cortex, generating a dataset that spans four visual areas, and four distinct Cre lines expressed in multiple cortical layers. This is an extremely rich dataset for exploring cortical computations involved in visual information processing at both the single cell and population level. In this poster, we will present this new data product and explore early analysis of visual coding in the awake mouse cortex.

2.9 - Optogenetic functionally specific modulation in primate visual cortex

M. Chernov, Oregon Health and Science University; R. Friedman, Oregon Health and Science University; G. Chen, Zhejiang University; A. Roe, Oregon Health and Science University and Zhejiang University

The primate visual cortex is organized into functionally specific domains responsible for integrating input from each eye, detecting color, orientation, motion and so on. These domains are approximately 50-500 microns in size and can be detected using intrinsic optical signal imaging as well as electrophysiological mapping. While these domains have been observed in the past, most of the data about the way they are interconnected come from anatomical studies. We hypothesized that we could observe these connections in vivo by targeting specific functional domains using channelrhodopsin-carrying viral vectors in a non-human primate (macaque). After establishing channelrhodopsin vector expression and therefore making domains (specifically, orientation and ocular dominance) sensitive to light, we studied activation patterns observed with intrinsic optical signal imaging in anesthetized subjects by presenting visual or optogenetic stimuli, or a combination of both. We found that optogenetic stimulation of a particular OD column revealed connections to other same eye OD domains up to 3 OD columns away. Stimulation of a particular orientation domain strengthened the optical signal within similar domains in the vicinity of the opsin expression site, while weakening the signal in orthogonal domains. Visual and optogenetic stimuli either suppressed or enhanced each other's effects, as measured using optical imaging and electrophysiological recordings, based on the specific context. We conclude that changes in neural activation as revealed by intrinsic optical signal imaging following optogenetic stimulation are determined in part by the underlying neural architecture (in this case, the OD columns and orientation domains) and in part by the state of the network which, when modified by presentation of a relevant visual stimulus, may facilitate or oppose the influence of the optogenetic stimulus.

2.10 - Within-Day Variation of Electrophyiological Connectivity in the Resting State

K. Casimo, University of Washington Graduate Program in Neuroscience, Center for Sensorimotor Neural Engineering; T. Madhyastha, University of Washington Integrated Brain Imaging Center; J.G. Ojemann, University of Washington Neurological Surgery, University of Washington Graduate Program in Neuroscience, University of Washington Center for Sensorimotor Neural Engineering; K.E. Weaver, University of Washington Integrated Brain Imaging Center, University of Washington Graduate Program in Neuroscience, University of Washington Center for Sensorimotor Neural Engineering

In order to characterize variability in neural network connectivity dynamics generated by an intervention such as learning or BCI use, we must first establish a baseline of spontaneously occurring variability over time. Substantial fMRI literature has examined variability in resting state connectivity. These studies find that connectivity varies both across time scales and between networks, with effects that span multiple sessions on the same day or different days. However, fMRI is limited to the indirect measurement of brain activity that is dependent on a delayed vascular response, and can only access slow time scales of interaction (<2Hz at best). Resting state connectivity patterns, and their variation over time specifically, have been subject to little study in electrophysiology. We examined electrocorticography (ECoG) from epileptic individuals undergoing seizure monitoring. For each patient, we identified two eight-minute resting state sessions during a single day, separated by at least two hours, using clinical video recordings. We then assessed connectivity between ECoG electrodes using several interaction measures. We evaluated significant longitudinal change in connectivity between sessions using a random segment shuffling routine to generate a null distribution of coupled interactions. Each electrode was assigned to a Brodmann area (BA), and we found the mean of all electrode pairs in given pairs of regions. We found that connectivity changes of low magnitude spanned across the cortex. Anticorrelated changes in the frontal and parietal regions indicate that the variability is not merely in magnitude, but involves alterations in the relative connectivity across the cortex. We observed changes across canonical frequencies ranging from delta (0-4Hz) through high gamma (70-200Hz), with the greatest magnitude of change occurring in delta range. The variations were not consistent between bands, with significant heterogeneity across both anatomy and frequency. The presence of these variations is consistent with previous studies conducted using fMRI. Here, we add the novel aspects of direct measurement of neural activity, a broad frequency range including high frequencies, and the use of multiple connectivity measures. These results suggest significant session-to-session variation in electrophysiological coupling occurs in the resting state. Understanding these effects will contribute to future studies aiming to characterize the degree to which changes in connectivity following interventions, such as learning, are above and beyond those caused by natural levels of variation.

2.11 - Neural Coding of Somatosensation in Central Circuits of Drosophila

J. Tuthill, University of Washington; R. Wilson, Harvard Medical School

Somatosensation relies on mechanoreceptor neurons distributed throughout the body, which fire action potentials in response to mechanical forces. A fundamental problem is how the nervous system accurately integrates and transforms signals from diverse

populations of mechanoreceptors. We investigated this question in the central nervous system of the fruit fly, Drosophila. Using pan-neuronal 2-photon calcium imaging and genetically-targeted whole-cell recordings, we identified three classes of central neurons that encode mechanical touch of the fly leg. Optogenetic receptive field mapping revealed that each neuron class performs a sensory comparison: one compares touch signals on different parts of the same limb, one compares touch signals on right and left limbs, and the third compares touch and proprioceptive signals. By recording from pairs of neurons during spontaneous movement, we found that each class encodes distinct features of somatosensory stimuli. Furthermore, the axon of an individual touch receptor can diverge to synapse onto all three classes, meaning these computations occur in parallel, not hierarchically. Representing a stimulus as a set of parallel comparisons represents a fast and efficient way to encode somatosensory information.

2.12 - The effect of electrical synapses on modulation of neural activity

L. Voelker, I. Rabinowitch, J. Bai, Fred Hutchinson Cancer Research Center

An animal must constantly adjust its behavior in order to respond to changing environments and fluctuations in internal states. Animals achieve this by altering neural activity levels through changes known as neural plasticity. While much research has focused on understanding changes that occur at individual synapses or that impact large groups of neurons simultaneously, the effect of plasticity on local circuitry is not well understood. One possible mechanism for coordination of plasticity between neighbors is through electrical synapses, specialized sites of cytoplasmic communication between neurons. While electrical synapses are known to coordinate local electrical activity and to pass the small molecules associated with neural plasticity, a direct role in neural plasticity has not been described. My work looking at modulation of quinine sensitivity in C. elegans suggests that electrical synapses may play an important role in modulating local circuit activity. In C. elegans, the neuron ASH mediates quinine avoidance via a GPCR pathway that is modulated by levels of cGMP. ASH lacks the guanylyl cyclases (GCYs) necessary to produce cGMP, suggesting cell-autonomous modulation, potentially from its neighbor cell ASK via their shared electrical synapse. Genetic disruption of the electrical synapse present between ASK and ASH in hypersensitivity to quinine, a phenotype consistent with reduction in cGMP levels. Restoring this channel rescues sensitivity to wild-type levels, suggesting that the electrical synapse between ASK and ASH functions to modify the quinine sensitivity levels within ASH. Further work will reveal the molecules involved in this modulation.

2.13 - Constructing Precisely Computing Networks with Biophysical Spiking Neurons

M.A. Schwemmer, A.L. Fairhall, S. Denéve, E.T. Shea-Brown, University of Washington

While spike timing has been shown to carry detailed stimulus information at the sensory periphery, its possible role in network computation is less clear. Most models of computation by neural networks are based on population firing rates. In equivalent spiking implementations, firing is assumed to be random such that averaging across populations of neurons recovers the rate-based approach. Recently, however, Denéve and colleagues have suggested that the spiking behavior of neurons may be fundamental to how neuronal networks compute, with precise spike timing determined by each neuron's contribution to producing the desired output (Boerlin and Denéve, 2011; Boerlin et al., 2013). By postulating that each neuron fires to reduce the error in the network's output, it was demonstrated that linear computations can be performed by networks of integrate-and-fire neurons that communicate through instantaneous synapses. This left open, however, the possibility that realistic networks, with conductance-based neurons with subthreshold nonlinearity and the slower timescales of biophysical synapses, may not fit into this framework. Here, we show how the spike-based approach can be extended to biophysically plausible networks. We then show that our network reproduces a number of key features of cortical networks including irregular and Poisson-like spike times and a tight balance between excitation and inhibition. Lastly, we discuss how the behavior of our model scales with network size or with the number of neurons "recorded" from a larger computing network. These results significantly increase the biological plausibility of the spike-based approach to network computation.

2.14 - A role for the lateral habenula in repeated probabilistic reversal learning

P. Baker, K. Kidder, S. Mizumori, University of Washington Psychology

A number of neuropsychiatric disorders including depression, autism spectrum disorder, and Parkinson's disease are characterized by deficits in the ability to rapidly switch behaviors under changing reward contingencies. This ability to change responses when outcomes change is an executive function commonly termed cognitive flexibility. A common task used to test cognitive flexibility across species is known as reversal learning. Previous studies have shown that manipulations of serotonin (5-HT) and dopamine (DA) affect cognitive flexibility in tasks such as reversal learning. Importantly, these two neurotransmitters are known to play a role in a variety of neuropsychiatric conditions, including the ones mentioned, raising the possibility that a common mechanism may play a role across diseases. The lateral habenula (LHb) may be a key structure in mediating reversal learning as it is known to affect transmission of 5-HT and DA. Behaviorally, the LHb is thought to provide an error signal during decision making tasks making it likely that it is critically involved in tasks requiring learning from errors such as reversal learning. To test this hypothesis, a maze based probabilistic reversal learning task (PRL) with male Long-Evans rats was used to examine the role of the LHb via neurotransmitter inactivation with the gamma-aminobutyric acid (GABA) agonists baclofen and muscimol (50ng/0.2 µL).Prior to behavioral testing rats were implanted with guide cannula aimed at the LHb for subsequent injections. The PRL task took place on a t-shaped maze with return arms. The correct arm resulted in reward on 80% of choices while the incorrect arm was never reinforced. Rats ran 200 trials per daily session. If an animal chose the correct arm over 10 consecutive trials, the reward contingences were reversed. Once animals were able to complete at least 3 reversals per session over consecutive days, injections began. Results revealed that inactivation of the LHb led to fewer overall reversals than rats injected with a saline control. Error analysis revealed a slight increase in perseverative errors and a large increase in regressive errors. Additionally deceases in stay/win behavior and increases in shift/loose behavior indicated a generalized reward sensitivity impairment after LHb inactivation. . Overall, these findings suggest that the LHb is important

for learning and/or implementing switches in behavior when reward contingencies change.

2.15 - Investigating a novel mechanism of itch sensation via intensity and population coding
K. Esancy, University of Washington; L. Condon, University of Washington; J. Feng, Washington University; C. Kimball, University of Washington; A. Curtright, University of Washington; H. Hu, Washington University; A. Dhaka, University of Washington

The question of whether lower vertebrates such as fish are capable of experiencing itch is currently unanswered, and addressing it could provide insight into both the evolutionary origins and the neural circuitry underlying this sensation. In mammals, itch is thought to be mediated at the cellular level by the coupling of pruritic G-protein coupled receptors and nociceptive TRP ion channels--the former bind itch-inducing chemicals and then activate the latter, which themselves mediate sensations of pain when activated independently by noxious pain stimuli. At a circuit level, most evidence suggests that itch and pain are conveyed through population coding, which suggests that distinct subpopulations of neurons transduce each sensation through isolated pathways, or "labeled lines". However, some evidence--namely, that a stimulus can produce itch or pain depending upon factors such as concentration--implies a role for intensity coding. We sought to use the zebrafish (Danio rerio) as a model organism in which to investigate further investigate these mechanisms. Here we report a novel form of itch transduction that does not appear to require activation of a pruritic receptor--rather, a previously identified nociceptive ion channel was by itself necessary and sufficient to generate neuronal activity and behavioral responses to a pruritic stimulus. To potentially explain how distinct ligands could provoke a pruritic or nociceptive response via activation of a single ion channel, we determined that a distinct subset of somatosensory neurons with greater sensitivity to noxious stimuli seemed primed to respond to itch stimuli. Our findings were recapitulated through equivalent studies in the mouse, implying conserved mechanisms. Together, these results indicate a means of neural coding through which intensity is mediated via population coding, and suggest that it is evolutionarily conserved between lower and higher order vertebrates.

2.16 - Neural activity in a simultaneous BCI and manual task
B. Lansdell, University of Washington; I. Milovanovic, Rehabilitation Medicine, University of Washington; A. Fairhall, Physiology and Biophysics, University of Washington; E. Fetz, Physiology and Biophysics, University of Washington; C. Moritz, Rehabilitation Medicine, University of Washington

Brain-computer interfaces (BCI) may provide a route to regaining lost motor function after stroke, if a control signal can be identified. Cortical neurons encoding ipsilateral wrist motion are a candidate source. Such interfaces demand that neural activity responsible for control of the unaffected limb be dissociated from activity responsible for BCI control. In this study we designed a dual control (DC) task in which a monkey simultaneously controlled a BCI while performing a motor task with their contralateral hand, and investigated to what extent dissociation between hand movement & neural activity occurs on an individual neuron basis. Previous studies establish there is no relation between performance and control units' tuning in dual control. Here we observe widespread changes in tuning of control and non-control units between both brain control (BC) and dual control tasks, further suggesting that tuning to wrist is not a constraint on dissociation required of the task. Other factors that may constrain control unit activity in dissociation task, such as co-tuning with other units and connectivity, are also shown to not constrain task performance or control unit activity. However, variability of the control units is shown to provide constraints on how the task is performed. This result informs unit selection for such BCIs.

2.17 - Simple method on decoding the stimulus type with neuron activity
C. Wang, A. Fairhall, University of Washington

Finding the important/representative neurons in a group of cells under specific conditions (e.g. different visual stimuli) could be important for designing single-cell optogenetics experiments. In cooperation with Rafael Lab in Columbia University, we hope to provide a baseline model to check the validity of their graphic based model (evaluated by how well this group of cells predicts the visual stimuli). The Allen Brain Observatory is a data resource for understanding sensory processing in the mouse visual cortex. We explored different features on part of these datasets and find out that the neurons may have highly variability under specific stimulus. We tested the very simple naive bayesian algorithm and softmax algorithm on these data. The result turn out to be highly depend on the dataset we use, can vary from 50% to 100% accuracy.

2.18 - Corticosterone dysregulation exacerbates disease progression in the R6/2 transgenic mouse model of Huntington's disease
B. Dufour, Oregon Health and Science University; J. McBride, Division of Neuroscience, Oregon National Primate Research Center

Huntington's disease (HD) is a genetic neurological disorder that causes severe and progressive motor, cognitive, psychiatric, and metabolic symptoms. There is a robust, significant elevation in circulating levels of the stress hormone, cortisol, in HD patients; however the causes and consequences of this elevation are largely uncharacterized. Here, we evaluated whether elevated levels of corticosterone, the rodent homolog of cortisol, contributed to the development of symptomology in transgenic HD mice. Wild-type (WT) and transgenic R6/2 mice were given either: 1) adrenalectomy with WT level corticosterone replacement (10ng/ml), 2) adrenalectomy with high HD-level corticosterone replacement (60ng/ml), or 3) sham surgery without replacement. R6/2 mice on HD-level replacement showed severe and rapid weight loss ($p<.05$) and a shorter latency to death ($p<.01$) relative to the HD mice on WT-level replacement. We further evaluated basal and stress-induced levels of circulating corticosterone in R6/2 mice throughout the course of their life. We found that R6/2 transgenic HD mice display a spontaneous elevation in circulating corticosterone levels that became significant at 10 weeks of age. Furthermore, we identified significant dysregulation of circadian rhythmicity of corticosterone

release measured over a 24 hour period compared to wildtype controls. Unexpectedly, we found that R6/2 transgenic mice show a blunted corticosterone response to restraint stress, compared to wild-type mice. Together, this data provides further evidence that HPA-axis activity is abnormal in R6/2 mice, and highlights the important role that cortisol plays in HD symptom development. Our findings suggest that cortisol-reducing therapeutics may be of value in improving HD patient quality of life. Ongoing experiments are assessing whether high levels of corticosterone replacement exacerbates the progression of other HD symptoms in adrenalectomized R6/2 mice, including metabolism, neuropathology, and muscle physiology.

2.19 - A microLED implant for long-term optogenetic stimulation of the rat spinal cord

S. Mondello, University of Washington; M. Sunshine, Dept. of Rehabilitation Medicine, University of Washington; A. Fischedick, Department of Rehabilitation Medicine, University of Washington; P. Horner, The Institute for Stem Cell and Regenerative Medicine, Department of Neurological Surgery, University of Washington; C. Moritz, Center for Sensorimotor Neural Engineering, Department of Rehabilitation Medicine, University of Washington

Optogenetic stimulation is a novel approach for activating specific neuronal populations in the central and peripheral nervous system. Studies suggest that artificial stimulation may enhance recovery after a variety of nervous system diseases and injuries, and has the potential to increase stem cell transplantation survival and integration. While there has been substantial characterization of optogenetic stimulation in the brain, there has been minimal focus on the spinal cord. Thus, in order to characterize this technology in the rat spinal cord, we mapped forelimb EMG activity in response to optical surface stimulation (OSS) at 8 weeks post AAV1-camkIIa-ChR2-mcherry viral injections into the cervical spinal cord. Most notably, we found that light applied to the surface of the cord was capable of consistently activating neurons located as deep as lamina 7. Strong forelimb movements were only elucidated when there was significant transfection of the superficial laminas 1-3. Building on our success of OSS characterization in the spinal cord, we developed an implantable microLED device to allow for long-term OSS in freely moving rats. We have refined this device and implantation method to produce reliable stimulation of the spinal cord for many weeks. We plan to use this OSS device for testing the effects of long-term optogenetic stimulation on functional recovery post-SCI, as well as on the efficacy and survival of stem cells transplanted in the injured spinal cord.

2.20 - Somatosensory feedback via direct cortical electrical stimulation in humans

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Objective: Somatosensory feedback is essential for efficient and precise motor output. Cortical stimulation through electrocorticographic (ECoG) electrodes is a potential method for providing such feedback, and may offer new avenues for investigating tactile feedback in humans. Previous research has demonstrated that subjects can distinguish between ECoG stimulation of the primary somatosensory cortex (SI) of different frequencies or amplitudes; however, little is understood about how human subjects perceive these novel sensations. Methods: Subjects were hospitalized for clinical monitoring of epilepsy with implanted ECoG grids. We used Tucker-Davis Technologies hardware to deliver constant-current stimulation to the hand area of SI using trains of 200 μs biphasic square pulses. We determined the perceptual threshold for stimulation by incrementally increasing the current amplitude, and examined response times and stimulation waveform parameters. For task-specific sensory feedback, subjects wore a 22 degree-of-freedom dataglove to measure their hand position. Subjects opened and closed their hand while they received state feedback via ECoG stimulation. Three states were encoded: 1) hand too open, no stimulation; 2) within the target position, low intensity stimulation; and, 3) too closed, higher intensity stimulation. Results: Subjects perceived the stimulation on their hands as an abstract sensation, sometimes described as vibration and/or pressure. Perceptual thresholds were in the range of 1.5 to 2.25 mA. On the feedback task, one subject was able to achieve accuracies and R2 values considerably greater than chance level, with performance dropping during a catch trial. Conclusions: These results suggest that subjects can react to cortical sensory stimulation and use it as feedback to modulate motor behavior.

2.21 - Respiratory effects in Human Cerebrospinal Fluid (CSF) Dynamics demonstrated with real-time phase contrast MRI

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Cerebrospinal fluid (CSF) motion undergoes periodic pulsations driven by respiratory and cardiac forces. Early studies have measured the influence of these forces as well as the effects of transient events such as coughing and sneezing in human CSF dynamics using spinal taps. While cardiac modulation of CSF has been investigated using a variety of MRI techniques, the respiratory effects have only recently been studied in a few MRI studies. Hence, the influence of respiratory mechanisms in human CSF dynamics is not well understood. To address this limitation, we have recently employed a real-time phase contrast magnetic resonance (RT-PCMRI) technique to measure various breathing techniques and coughing on CSF flow velocities at the level of Foramen Magnum (FM) in healthy subjects. Observations show that conventional cardiac-gated phase contrast MRI (PCMRI) can only measure the cardiac component and is unable to detect the respiratory effects while RT-PCMRI can non-invasively quantify cardiac and respiratory modulations of CSF velocity in real-time. RT-PCMRI measurements at the FM indicate that there is a comparable contribution of respiration and cardiac pulsations. The study results also suggest that there is an immediate influence of voluntarily controlled breathing on the amplitude

and directionality of CSF velocities, which vary across the subjects.

2.22 - Exploration of perceptual resolution while modulating various stimulation parameters towards development of a low latency artificial sensory feedback system via ICMS

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Current users of brain-computer interface (BCI) technology must rely on visual feedback of cursor or robotic arm movement. The inherent long delays of visual processing likely contribute to relatively slow and unnatural control of BCIs. Despite increasing numbers of electrode sites and ever growing complexity of control algorithms, BCI technology has yet to achieve rapid, dexterous control signals comparable to an intact human system. We believe the lack of tactile and proprioceptive feedback may impose a fundamental limit on speed and accuracy of BCI controlled prostheses or re-animated limbs. By artificially recreating this comparatively low-latency sensory pathway via ICMS, BCI stability and control may be improved. Towards this aim, we are exploring perceptual sensitivity of several stimulation parameters to find a high resolution space in which to provide this feedback. By developing a novel center-out task for rodents, we can use Intra-Cortical Microwire Stimulation (ICMS) to present patterns of artificial stimulation directly to the sensorimotor cortex. By comparing the ability of animals to solve this forelimb spatial exploration task, we can measure comprehension of the encoded stimulation pattern. Rather than cue the subject for a particular target, stimulation will provide proportional feedback of the joystick position, mimicking a real world application of a robotic limb providing real-time ICMS sensory feedback to a human user. Prior to stimulation, neural populations surrounding electrode sites are categorized as responsive to sensory inputs, correlated with features of the behavioral task or novel sites. By constructing these mappings, we can present stimulation both to novel and correlated populations, comparing learning performance in each. After determining the just noticeable difference stimulation parameters, we will present graded stimulation via one or multiple cortical electrodes. Our goal is to formulate a general pattern for providing a high resolution sensory signal which can be mapped to any sensory modality. Through ICMS, we aim to create this low-latency sensory feedback in our BCI control loop for patients with a wide range of impairments including spinal cord injury and stroke.

2.23 - Toward a standardized advanced imaging protocol for multiple sclerosis: inter- and intra-site variability in multiband diffusion measurements acquired by NAIMS

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The North American Imaging in Multiple Sclerosis (NAIMS) Cooperative was formed with the goal of developing sensitive and reliable imaging surrogates for disease progression in MS to accelerate research and treatment trials. A standardized quantitative protocol which is sensitive and tailored for MS pathology will expedite data collection across multiple sites.

2.24 - Neural Security for Brain-Computer Interfaces

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The ability for the brain to communicate with and control the external environment is growing thanks to advances in non-invasive (commercial dry electrode headsets) and invasive (deep brain stimulation, or DBS) technology. While there are many physical and engineering requirements in place, the threat to a user's neural privacy and security has yet to be quantified and evaluated. Our research has already demonstrated that there is a threat to private information via subliminal stimulation in a video game. The current aim is to quantify this threat and develop techniques to protect neural signals from malicious intent.

2.25 - Correlation-based model predicts efficacy of artificially induced plasticity in motor cor- tex by a bilateral Brain-Machine Interface

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Experiments on macaque monkeys reveal that neurons in Motor Cortex (MC) display a variety of activities correlated to their co-activated muscles and the motor task being performed. Generally, MC neurons with overlapping muscle fields are spatially grouped together and may have enhanced synaptic connections as opposed to more distant neurons.

2.26 - Closed-Loop Algorithms and Chronic Brain-Computer Interfacing Using a Deep Brain Stimulator with Electrocorticography

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A platform for closed-loop deep brain stimulation (DBS) and long-term brain-computer interface (BCI) is demonstrated using a deep brain stimulator with implanted electrocorticography (ECoG) electrodes placed on the hand area of the motor cortex. Stable ECoG recordings are shown in a single human subject over a four month period after implantation, which suggest that the platform can be used successfully for long-term BCI experiments. The same subject successfully performed a BCI cursor task with above-chance accuracy using two control schemes: (1) an overt movement control scheme and (2) a motor-imagery control scheme. These initial BCI results demonstrate that users may be able to gain one-dimensional control over a short time period. The demonstrated platform is a promising research tool for conducting chronic BCI learning experiments in addition to potential use for closed-loop DBS.

2.27 - System Identification for Deep Brain Stimulation Control of Parkinsonian Tremor

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Deep brain stimulation (DBS) is a therapeutic approach to treating a variety of neurological disorders, including Parkinson's disease (PD) and essential tremor (ET). Current approaches to control are either open-loop, or employ model-free, threshold-based approaches to closed-loop control, which can be unstable due to delays in transmission from DBS site to measurable therapeutic response. Closed-loop control is desired to eliminate unneeded stimulation (i.e. when symptoms not present), as well as battery power conservation and side effect mitigation. Biophysical models of PD and ET are too complex to be used in an online control application with current hardware and software limitations, which suggests that empirical methods may provide more immediate utility in advancing control methodology for closed-loop applications. Here, we present preliminary experimental results of system identification of the dynamics of PD tremor while switching DBS on and off. We also demonstrate its potential use in online applications both for prediction of future tremor given DBS state, as well as online parameter estimation. Future work will investigate similar methodology in ET patients and deploy identified models in online control applications.