guided by low frequency changes in the nucleus accumbens was previously found to block binge-like eating behavior in mice. Following this preclinical work, in a first-in-human pilot study, we recorded nucleus accumbens electrophysiology during food cravings preceding LOC eating in two patients with BED and severe obesity (trial registration no. NCT03868670). We observed increased bilateral ventral NAc low frequency power and connectivity that appeared selective for states of food craving. We then used the peaks in nucleus accumbens electrophysiological signal that corresponded to increased low-frequency power to guide DBS delivery. Over 6 months, we observed improved self-control of food intake and weight loss in both patients. These findings provide early support for restoring inhibitory control with electrophysiologically-guided NAc DBS in the context of LOC. Further work with increased sample sizes is required to determine the scalability of this approach.
Research Category and Technology and Methods: Translational Research: 1. Deep Brain Stimulation (DBS)

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[PL04]

PAST, PRESENT (AND ?FUTURE) OF TMS

John Rothwell. *University College London, UK*

Of the many methods now available for non-invasive transcranial stimulation of the human brain, we have the clearest understanding of the mechanism of action of TMS. Yet the application of TMS, like high voltage electrical stimulation of the brain that preceded it, was a chance event that had never been predicted, and which might have had a difficult time these days obtaining funding. Similarly, most of the major TMS methods (intracortical inhibition, cortico-cortical and cerebello-cortical connectivity, "virtual lesioning", rTMS and even TMS-EEG) were explored in the 10 years following, a rate of progress that would probably halve in the present regulatory environment. So has TMS reached a plateau of development where it is just one of several tools to probe and interact with brain function, or will developments in TMS-EEG, EEG-TMS or novel designs of stimulator open new and unexpected avenues of research?

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[PL05]

TMS-EEG: A WINDOW ON CORTICAL CIRCUITS IN SEVERE AND FOCAL BRAIN INJURY

Marcello Massimini. *University of Milan, Italy*

TMS in combination with EEG (TMS-EEG) enables a direct assessment of the electrophysiological state of cortical circuits with unprecedented degrees of freedom whereby both primary and associative areas can be directly stimulated with a wide range of stimulation parameters. In this way, TMS-evoked potentials (TEPs) can both inform on the local input-output properties of different neuronal population and assess large-scale remote and re-entrant activations within thalamocortical networks. Furthermore, unlike resting EEG-based measures of connectivity, TMS-EEG measures are causal in nature and unconfounded by common inputs or spurious correlations. In my talk, I will first highlight the principles and caveats of TMS-EEG as well as the tools and procedures that can reliably facilitate the acquisition of high-quality TEPs. Then, I will review a series of recent studies in which TMS-EEG was used to probe the state of cortical circuit after brain injury. I will show how measures derived from TEPs can assist the diagnosis of patients with disorders of consciousness, inform on the state of the perilesional cortex after stroke and bear prognostic value for motor recovery and for the subsequent development of delirium. Finally, I will argue that TMS-EEG data can have a key role in driving a paradigm shift in our understanding of the electrophysiological consequences of brain injury and diaschisis.

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[PL06]

MEASURING INHIBITORY ENGRAMS IN MEMORY STORAGE AND RECALL USING CONCURRENT TDCS-FMRI

Helen Barron. *University of Oxford, UK*

Memories are thought to be represented in the brain by activity in groups of neurons described as memory engrams. Although memory engrams are typically thought to be made up of excitatory neurons, several recent studies suggest that inhibitory neurons also play a critical role. Indeed, by matching their excitatory counterparts, selective inhibitory interneurons may facilitate a stable storage system that allows memories to lie quiescent unless the balance between excitation and inhibition is perturbed. Here I will present a set of studies that show evidence for selective neocortical inhibition in the human brain using ultra-high field 7T MRI and concurrent non-invasive brain stimulation. I will show that matched excitatory-inhibitory engrams provide a stable storage mechanism for neocortical associations, and protect memories from interference. I will then show how neocortical memory engrams interact with brain regions such as the hippocampus during recall, to selectively perturb excitatory-inhibitory balance. To conclude, I will discuss how concurrent MRI and non-invasive brain stimulation can be used as a tool to demonstrate the importance of neural inhibition for computations that underlie higher-order cognition.

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[PL07]

THE ROLE OF CHRONIC BRAIN SENSING TECHNOLOGY FOR INDIVIDUALIZED DEEP BRAIN STIMULATION THERAPY

Andrea Kühn. *Charite University Hospital Berlin, Germany*

Deep brain stimulation is an established therapy for patients with severe movement disorders. Over the last decades invasive recordings from the human basal ganglia were used to characterize disease pattern and symptom specific neuronal signatures as biomarkers for PD and dystonia. This has helped to further elucidate the underlying pathophysiology of these network disorders. Recently, new technological advances in deep brain stimulation devices allow to chronically record neuronal activity from the target structures. Neuronal activity can be used as a feedback signal to inform DBS for closed loop stimulation. I will give an overview on what we have learnt from invasive recordings for movement disorders and how we can use neuronal signatures to inform parameter selection and timing of stimulation in order to better adapt DBS treatment to the individual symptoms in each patient in the future.

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[PL08]

A 12 STEP JOURNEY TO FIND A (TMS) TREATMENT FOR DRUG AND ALCOHOL ADDICTION: FROM DISCOVERY SCIENCE TO CLINICAL TRIALS

Colleen Hanlon. *Wake Forest University School of Medicine, USA; BrainsWay Ltd, USA*

Nearly 3 million people die annually from alcohol abuse. While several pharmaceutical options are available, the side effects are high and medication is not well-tolerated. Through recent innovations in neuroimaging and neuromodulation we, as a scientific community, are now uniquely positioned to evaluate transcranial magnetic stimulation (TMS) as a novel, non-invasive therapeutic tool to help improve the lives of people with alcohol use disorder (AUD).
This talk will cover a series of 12 decision making steps that led from discovery science to clinical trials in AUD. The talk will integrate studies from multiple laboratories and highlight moments that led us to rethink our hypotheses as well as findings that moved us forward. Briefly, our first step was to identify the neural circuits of interest (Target Identification).

This led to a focus on frontal-striatal connectivity to the dorsolateral prefrontal cortex and the medial prefrontal cortex (MPFC). Using interleaved TMS-BOLD imaging, we then determined which target was more uniformly disrupted (Target Selection). Focusing on the MPFC, it became clear that neural architecture would be important to TMS dosing (Methods Refinement). Initial proof of principle data with a single session of TMS (Target Engagement) led to a double-blind sham controlled clinical trial. This created questions regarding the optimal "brain state" or provocation for TMS therapeutic approaches (Methods Refinement). As the field moves forward planning multisite trials, we have begun to appreciate the importance of gender, age, and the overlap between the TMS-induced electric field and the individual's endogenous brain activity as salient factors in treatment response.
This talk is designed to highlight a systematic path for TMS treatment development. This path is not strictly linear, not necessarily optimal, nor exclusive. It is however, an intentional, well-reasoned, and empirically-derived pathway which may serve as scaffolding for translating academic discovery into real-world therapeutic options.

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[PL09]

DIRECTED ACC SIGNALING PATTERNS AS MDD BIOMARKER

Nolan Williams. *Stanford University Medical Center, USA*

Major Depressive Disorder (MDD) is widely hypothesized to result from disordered communication across brain-wide networks. Yet prior resting state fMRI (rs-fMRI) studies of MDD have studied zero-lag temporal synchrony (functional connectivity) in brain activity absent directional information. We utilize the recent discovery of stereotyped brain-wide directed signaling patterns in humans to conduct the first investigation of the relationship between directed rs-fMRI activity, MDD, and treatment response to a novel FDA-approved neurostimulation paradigm termed Stanford Neuromodulation Therapy (SNT). We find that SNT over left dorsolateral prefrontal cortex (DLPFC) induces directed signaling shifts in the left DLPFC and bilateral anterior cingulate cortex (ACC). Directional signaling shifts in the ACC, but not the DLPFC, predict improvement in depression symptoms, and moreover, pre-treatment ACC signaling predicts both depression severity and the likelihood of SNT treatment response. Taken together, our findings suggest that ACC-based directed signaling patterns in rs-fMRI are a potential biomarker of MDD.

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[PL10]

QUADRIPULSE STIMULATION (QPS): APPLICATIONS TO NEUROLOGICAL DISORDERS

Ritsuko Hanajima. *Tottori University, Japan*

Neural plastic changes have been studies in neurological disorders using many kinds of non-invasive brain stimulations (NIBS). Those results were sometimes inconsistent. Our group developed a new NIBS technique named as Quadripulse stimulation (QPS) which consists of bursts of four monophasic transcranial magnetic stimulation (TMS) pulses repeated every five minutes for 30 minutes. Bidirectional plasticity, namely long-term potentiation (LTP) and depression (LTD), can be induced by QPS depending on the interstimulus intervals of the four pulses. Here, I will present several issues about QPS.
Interindividual variability: The interindividual variability is one challenge to all NBS techniques for plasticity induction. We will show a direct comparison between QPS and the most popular NBS [theta burst stimulation (TBS)] in the same individuals. QPS was more robust than QPS.
Age dependency: Comparisons of the degree of plasticity induction and responder rate among the different aged subjects showed that elder subjects had lower degree of plasticity induction than younger ones, as expected.
Anti-parkinsonian drugs on effects of QPS: L-dopa enhanced both LTP/LTD by QPS in normal volunteers, which is consistent with animal experimental knowledge that L-dopa contributes to the bidirectional plasticity. Dopa agonists did not enhance any plasticity in normal volunteers. It may be explained that D1/5 function is requisite for both LTP/LTD, but dopamine agonist has mainly D2/3 function and almost no D1/5 function.
Parkinson's disease (PD), progressive supranuclear palsy (PSP) and others: We applied QPS to several movement disorders. The LTP/LTD were involved in PD, but they were restored by L-dopa. The degree of LTP had a negative correlation with parkinsonian symptoms, especially rigidity and akinesia. The plasticity was also involved and the degree of LTP had a correlation with rigidity and akinesia in PSP. The QPS plasticity may be one of physiological biomarkers of parkinsonian motor symptoms.

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[PL11]

BRAIN STIMULATION LAW: LEGAL ISSUES RAISED BY CURRENT AND EMERGING NEUROMODULATION THERAPIES

Jennifer Chandler. *University of Ottawa, Canada*

This presentation addresses the legal context for neuromodulation therapy. Many of these rules will apply during the research phase and are also useful to have in mind during the development of devices, as the legal context may suggest certain design choices are advisable. Among the rules to be discussed are the laws in various jurisdictions that impose specific eligibility, consent, and oversight procedures for certain forms of neurosurgery for psychiatric disorders, sometimes including deep brain stimulation. Other legal issues to be covered are questions about the collection and use of neurophysiological and other data collected in adaptive DBS, rules regarding telemedicine applicable for remote programming of DBS, and legal arguments regarding rights of access to neuromodulation therapy and discrimination. The applicable laws vary by jurisdiction and so it will be impossible to cover all legal approaches, but the presentation will present each issue with examples of how one or more jurisdictions address it.

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[PL12]

WHAT WOULD EGAS MONIZ THINK OF OUR FIELD NOW?THE CHECKERED PAST, AMAZING PRESENT, AND EXCITING FUTURE OF BRAIN STIMULATION IN NEUROPSYCHIATRY

Mark S. George MD. *Medical University of South Carolina, Charleston, SC USA*

In 1926 Dr. Egas Moniz working here in Portugal injected dye into brain arteries and took x-rays, inventing cerebal angiography. Later, in 1935, reasoning that mental illness originates from abnormal connections within the brain, particularly with the frontal lobes, he teamed with neurosurgeon Almeida Lima to perform prefontal leucotomies on 20 patients with intractable depression or paranoia or hallucinations. This procedure was then widely adopted and eventually overused and even likely misused with repercussions persisting to today. Now, almost 100 years after his first angiogram, what would Dr. Moniz think if he were here sitting at this meeting? What lessons do we need to keep foremost in mind as a field now, with our incredible technologies. This lecture will briefly review Moniz's work and the leucotomy 'lessons', highlighting the aspects of the leucotomy history that we should avoid. I will also present exciting work showing how we can now modify and change brain connections with precision TMS or focused ultrasound, no longer needing Dr. Moniz' procedure to help restore our patients to health.

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