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

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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

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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

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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

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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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