Multimodal connectomics for personalized neurostimulation intervention

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Overview

The last decade has seen a great momentum in connectivity analysis methods for functional and structural neuroimaging, giving rise to the field of connectomics and brain networks. In parallel, physical and physiological knowledge has been gained about methods to stimulate the brain (e.g., TMS, DBS, etc.) thanks to improved technology and modeling, thus increasing their reliability and therapeutic efficacy. In the latter framework, the most recent years have seen the integration of neurostimulation with structural and functional data for neuronavigation and/or electrophysiologically informed stimulation. Nevertheless, the vast majority of these integration approaches are focused at targeting one cortical location at a time, while hardware to simultaneously stimulate multiple brain locations is becoming available to the community. Thus, time is ready for a further step to reconcile neurostimulation with the current view on brain networks, in which integration is achieved at the connectome-level, and, eventually, in real-time. This symposium brings together experts in connectomic and neurostimulation, that are aiming at bridging the gap and getting the best of both worlds.
The symposium will offer the attendees a unique opportunity to learn the most recent developments in the field, as well as to familiarize with the prospects offered by the connectomic-based neuromodulation to address system, cognitive and clinical neuroscience questions. Specifically, the learning objectives of this symposium will cover the understanding of: i) advances in connectomic-based neuromodulation, ii) novel multimodal approaches to real-time neurostimulation; iii) applications to basic and clinical neuroscience.

Lecture 1: *Real-time tractography for structural connectivity guided TMS*
Dogu Baran Aydogan Presenter

We recently developed a real-time tractography-based transcranial magnetic stimulation (TMS) neuronavigation system. Our tool enables the operator to visually observe the structural connections in the brain that might be affected by TMS, in real-time. While conventional TMS neuronavigation, based on T1-weighted magnetic resonance images, only informs about where TMS locally affects the brain, with the addition of real-time tractography, we are also able to provide information about which remote regions could be affected by the stimulation. We believe, the additional real-time information about structural connectivity is highly valuable to determine stimulation targets for manually or automatically controlled TMS applications. In this work, an overview of the system is presented and the challenges of real-time tractography are discussed.

Lecture 2: *EEG connectivity informed TMS: towards real-time application*
Laura Marzetti Presenter

We formulate the hypothesis that single-trial brain functional connectivity prior to a stimulation sets the stage for its impact. To test this hypothesis, we consider the impact of TMS stimulation at the hand cortical area assessed by MEP amplitude after stimulation as a function of EEG functional connectivity state of the motor network before each pulse. Recordings in eight participants were performed at the University of Tübingen (Metsomaa et al. 2021). Single-trial cortical level functional connectivity was estimated, using the imaginary part of the Phase Locking Value, following an individualized seed-based approach to left primary motor area (M1). Group averaged functional connectivity highlighted the presence of a baseline motor network connectivity (lM1 - Supplementary Motor Area, SMA - rM1) at the mu-rhythm frequency. The variability of this connectivity at single-subject and single-trial level is positively related to MEP amplitude. Overall, average peak-to-peak MEP values in trials with high functional connectivity (HFC) were about 4% higher than MEP values in trials with low functional connectivity (LFC). Interestingly, for HFC trials, time lags were robustly estimated from functional connectivity and nicely matched with underlying physiology. This study illustrates that connectivity-targeted neuromodulation can constitute a framework for improving neurostimulation outcome at the individual level and for constructing personalized paradigms in which stimulation is targeted at a circuit other than a single brain area with specific temporization.

Lecture 3: *Personalised brain stimulation – precise targeting of brain circuits to optimize treatment outcomes*
Robin Cash Presenter

Mounting evidence suggests that antidepressant response to TMS depends on functional connectivity with the subgenual cingulate cortex (SGC) at the precise stimulation site. Critically, SGC functional connectivity shows considerable interindividual variation across the spatial extent of the dorsolateral prefrontal cortex, providing a strong rationale for connectivity-based target site personalisation. However, recent research indicated that determination of person-specific connectivity-based TMS targets might not be feasible. To bridge this translational gap, we developed novel methodology that enables personalised connectivity-based cortical stimulation targets to be pinpointed with high (millimetre) accuracy. We validated this methodology in MRI scans acquired across 1000 healthy adults. We further showed that personalised targets were heritable, suggesting that connectivity-guided rTMS personalisation is stable over time and under genetic control. We then demonstrated, via retrospective analysis of a clinical sample, that TMS antidepressant outcomes were better when individuals were serendipitously treated closer in proximity to personalised targets. Our findings have since been independently replicated. Various lines of evidence now suggest that personalised rTMS has the potential to be clinically transformative in the treatment of psychiatric disorders. New evidence will be also presented that brain circuits rather than isolated brain regions are the neurobiological target of TMS.

Lecture 4: *Connectome-targeted neuromodulation across symptoms and modalities*
Shan Siddiqi Presenter

This talk will cover three approaches to circuit-based targeting:
1. Symptom-specific: In two datasets of TMS for depression (n=111), dysphoric symptoms (e.g. sadness) responded best to stimulation of one circuit, while anxious/somatic symptoms responded to a different circuit.

2. Cross-modality: Across 14 datasets, similar “depression circuits” were connected to TMS sites that relieve depression (n=151), DBS sites that modulate depression (n=101), and lesions that cause depression (n=461).
3. Diagnosis-specific: Lesions protective against PTSD (n=189) were connected to a common circuit (split-half cross-validation $p<0.05$). Lesions protective against nicotine use disorder (n=103) and those that reduce alcoholism risk (n=186) were also connected to a common circuit ($p<0.05$).
This illustrates a framework for circuit-targeted neuromodulation studies - neuromodulation can target different circuits for different symptoms; a common circuit can be modulated by TMS, DBS, and lesions; and lesions can reveal targets for other disorders.