Recent advances towards robust and reliable mapping of human cortical connectivity with TMS–EEG

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Overview

By exciting the cortical region of interest with transcranial magnetic stimulation (TMS) and monitoring the spreading of the activity with concurrent electroencephalography (EEG), we can probe effective cortical connectivity with excellent temporal resolution. However, despite its undisputed potential in connectivity mapping, TMS–EEG is a challenging technique. In this symposium, world-leading experts will share their insight into measuring, analyzing, and interpreting TMS–EEG data reliably.

The impact of TMS on the brain depends on several factors that cannot be well-controlled a priori, such as neuronal excitability and the fine cortical anatomy. Dr. Silvia Casarotto will discuss a new method to assess in real-time the early TMS-elicited EEG deflections while minimizing confounding physiological responses. With a novel software tool, the site, orientation, and intensity of TMS-pulses can be optimized to acquire TMS–EEG responses with a high signal-to-noise ratio.

Recent evidence suggests that among the confounding responses, TMS can elicit peripherally evoked potentials (PEP) attributed to multiple sensorial inputs associated with TMS (coil-click and scalp sensations). PEPs can severely hinder the proper interpretation of TMS–EEG data as they are entangled with the direct TMS-triggered cortical activation. Dr. Pedro Gordon will present an optimized sham control procedure that thoroughly pairs its sensory input with that from the real TMS, allowing to reject PEPs from the TMS–EEG signals.

Dr. Tuomas Mutanen will further discuss how to disentangle genuine direct cortical responses to TMS from the confounding signals, focusing on recent advances in TMS–EEG signal processing and providing a critical view on the reproducibility of TMS–EEG signal analysis pipelines.

In the final session, Dr. Domenica Veniero will discuss an innovative experimental design employing TMS–EEG to investigate the role of brain oscillations in long-range connectivity. Dr. Veniero will show how behavioral measures can complement EEG indexes and assist in interpreting the overall results.

Lecture 1: *EEG-guided TMS to obtain a desired cortical activation while minimizing artifacts*

Silvia Casarotto Presenter

The actual impact of TMS on the cortex depends on several factors that cannot be well-controlled a priori, such as neuronal excitability, axonal displacement and mesoscale anatomy. Thus, it is difficult to predict to what extent a certain combination of TMS parameters will activate cortical neurons.
We propose to titrate TMS parameters based on a real-time assessment of the early (8-50 ms) EEG responses elicited under the coil. For this purpose, we have developed a software tool (rt-TEP, real-time TMS-Evoked Potential) that allows (i) to detect – and thus minimize – artifacts on single-trial data and (ii) to measure the amplitude of early EEG responses after averaging a limited number of trials. This real-time readout can be used to optimize TMS parameters (e.g. site, orientation, intensity) before data acquisition in order to ultimately obtain TEPs characterized by high signal-to-noise ratio.

Lecture 2: *Identifying direct cortical EEG responses to TMS via optimized sham procedure*
Pedro Gordon Presenter

The combination of TMS and EEG has been increasingly applied as a tool for investigating human cortical physiology and searching for potential neuropsychiatric diseases biomarkers. However, concerns have been raised regarding the validity of the obtained responses. Specifically, the TMS procedure is known to generate multiple sensorial inputs, including the coil activation click noise, scalp sensation and head muscles contraction around the stimulated area. These sensory inputs also cause cortical activation in the form of peripherally evoked potentials (PEP), which become entangled with the EEG response from TMS direct activation. Consequently, eventual modulation of PEPs can be erroneously interpreted as focal effects elicited by direct cortical activation. By designing an optimized sham procedure that thoroughly pairs its sensory input with that from the real TMS, we reliably identified cortical responses that can only be attributed to direct cortical activation and can thus be safely used as a marker of focal cortical responsivity to TMS. Moreover, we also found responses that indeed correspond to PEPs. Given that some of these responses have been claimed to be TMS-EEG specific markers of focal neuroplastic effects and disease markers by previous reports, it reiterates the importance of the use of proper optimized sham control conditions in future studies.

Lecture 3: *Disentangling genuine direct cortical responses to TMS with source-model-based techniques*
Tuomas Mutanen Presenter

In addition to the brain, the strong electromagnetic pulse of TMS can couple with several other tissues or measurement instrumentations, generating various noise and artifact components in the TMS–EEG signals. However, it is well known that cortical EEG signals arise from post-synaptic currents. Due to the conductive properties of the head and the nature of post-synaptic sources, neuronal activity produces relatively smeared EEG topographies. Here, I will discuss how we can use EEG-forward modeling to separate TMS–EEG data into noise and neuronal components. The recent evidence suggests that among the confounding responses, TMS can activate the cortex indirectly via peripherally evoked potentials (PEP) associated with the click of the TMS coil and the scalp sensations. I will cover potential forward-modeling-based signal-analysis solutions to this problem. Finally, I will address the replicability issues related to complex and variable signal-processing pipelines within the TMS–EEG community and the need for reliable validation of data-processing methods.

Lecture 4: *A multimodal approach to the investigate top-down control in the attentional network*
Domenica Veniero Presenter

Recent developments in neuroscience have emphasised how cognitive functions, from simple perception to complex executive functions, require the integration of information through the coordinated activity of multiple cortical areas. In the present talk, I will provide evidence in support of the role that brain oscillations play in long-range connectivity, in the network involved in visuo-spatial attention. I will describe recent findings showing that frontal areas, known to generate top-down signals, can influence the activity of downstream areas by shifting the phase of their oscillations, thus generating alternating periods of excitation and inhibition. I will discuss data showing that when the Frontal Eye Fields (FEF) are stimulated with Transcranial Magnetic Stimulation (TMS), they induce fluctuation of visual areas excitability corresponding to the canonical beta band, as tested with concurrent EEG recording, phosphenes perception rate and accuracy at a visual task. While this dataset supports the causal involvement of beta oscillations in top-down control, it also provides a different view on how to combine TMS and EEG with behavioural measurement to assist us with the interpretation of the overall results.