Non-invasive neuromodulation of deep brain structures to enhance cognitive functions

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Overview

It is of great interest to modulate key deep brain structures of cognitive functions non-invasively to understand their function and potentially treat their dysfunction. Traditional non-invasive brain stimulation methods such as transcranial magnetic stimulation (TMS) and transcranial direct or alternating current stimulations (tDCS, tACS) cannot target deep brain structures selectively, i.e., without a stronger stimulation of the overlaying cortical layers (depth-focality trade-off).
This symposium will focus on non-invasive neuromodulation of deep brain structures using temporal interference (TI) electrical stimulation (Grossman et al. Cell 2017), a method allowing selective depth stimulation and its application to enhance cognitive functions.
We will introduce the concept of TI-based neuromodulation and show exciting evidence from neuroimaging studies in humans that TI stimulation of the hippocampus can (a) modulate hippocampal activity crucial for memory encoding, (b) modulate spatial navigation and its respective representation in the grid-like areas of the hippocampus entorhinal cortex and (c) that TI stimulation of the striatum can modulate motor learning and the striato-cortical network underlying the learning effects. Furthermore, results from simulation and cadaver studies will be provided.
Given the importance of the hippocampus and striatum in a myriad of brain functions (including learning and memory, spatial navigation, and emotional behavior) and their central role in the most common brain disorders (including Alzheimer's disease, depression, epilepsy, stroke and schizophrenia), the prospective translational impacts of these studies are substantial.
The learning outcome of the symposium will be knowledge about TI stimulation including underlying mechanistic, simulation information, how to apply it in human studies and first results of targeting deep structures like the hippocampus and the striatum by TI evaluated by fMRI and behavioral measures.

Lecture 1: *Non-invasive temporal interference electrical stimulation of the human hippocampus*

Ines Violante Presenter

Temporal interference (TI) is a strategy for non-invasive steerable stimulation of neurons deep in the brain using multiple kHz-range electric fields with a difference frequency within the range of neural activity. Herein we report the validation of the TI stimulation concept in humans. We first use electric field modelling and measurements in a human cadaver to verify that the locus of the transcranial TI stimulation can be steerably focused in the human hippocampus with minimal exposure to the overlying

cortex. We then use functional magnetic resonance imaging (fMRI) to demonstrate the utility of the TI stimulation by noninvasively and focally modulating the human hippocampal activity underpinning the encoding of memories.

Lecture 2: *Modulation of human striatal activity with temporal interference stimulation*
Elena Beanato Presenter

Temporal Interference (TI) stimulation has been recently introduced as a novel non-invasive brain stimulation technique able to overcome the depth-focality trade-off, allowing to reach deep brain structures without engaging overlying cortical areas. Although carrying high potential for future clinical applications, there are currently no studies showing effects of it in humans. To fill this gap, we applied TI stimulation in healthy subjects, targeting the striatum during a well-known motor learning task (e.g., Zimerman et al. 2013; Wessel et al. 2021). The present results demonstrate neuromodulation effects of TI to the striatum on a behavioral level with the respective changes in the underlying striato-cortical network determined by fMRI. This study supports the view of the possibility to neuromodulate the striatum noninvasively in humans, which might pave the way to novel interventions for neurological and psychiatric disorders in which the activity of the striatum plays a critical pathophysiological role.

Lecture 3: *Impact of MTL-targeted TI stimulation on spatial navigation: probing with grid cell-like representation*
Hyukjun Moon Presenter

The hippocampal-entorhinal system is known to play a critical role in spatial processing. In this study, we stimulated the human hippocampal-entorhinal complex non-invasively through the TI stimulation to investigate its causal influence on spatial navigation. In addition, we assessed entorhinal grid cell-like representation based on the fMRI analysis, further probing underlying brain mechanisms.