Title: **NEUROPHYSIOLOGICAL IMPACT OF A FRONTO-TEMPORAL TRANSCRANIAL DIRECT CURRENT STIMULATION IN HEALTHY SUBJECTS: A MULTIMODAL PET-MR IMAGING APPROACH**

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Fronto-temporal transcranial direct current stimulation (tDCS), with anodal stimulation over the left dorsolateral prefrontal cortex and cathodal stimulation over the left temporo-parietal junction, has been reported to reduce treatment-resistant auditory hallucinations, negative symptoms and insight of the illness in schizophrenia. Despite an increasing use in clinical settings, acute and subsequent effects of fronto-temporal tDCS are far from being completely understood. The few imaging and computational reports available suggest that fronto-temporal tDCS effects are not restricted to the brain areas located under the electrodes, but spread through distributed cortical networks functionally connected with the targets and reach subcortical areas, such as dopaminergic areas. Overall, these studies suggest that tDCS modulates functional connectivity within and across resting-state networks and brain activity. However, these effects are currently described at different levels depending on the imaging technique used. Finally, effects of the stimulation applied online are rarely inspected.

**Objectives:** According to the hypothesis that fronto-temporal tDCS modulates brain activity, connectivity and dopaminergic transmission, the aim of this project is to reveal the combined neurobiological impact of an online single session of fronto-temporal tDCS in a unique experiment by developing a simultaneous multimodal imaging approach (PET-MR). The online implementation of the stimulation will allow deciphering changes induced during and after stimulation compared to baseline levels.
**Methods:** As a first step, before investigating patients with schizophrenia, 30 healthy subjects will be randomly assigned in two groups (active, n=15 vs sham, n=15) and will receive a single-session of either active or sham fronto-temporal tDCS during a simultaneous PET and MR scan of 110-minutes duration. The stimulation will start 40 minutes after the injection of the tracer, last 30 minutes and be set at 1 mA in active mode.
The distributed changes will be explored at rest through:
• Specific and localized dopaminergic transmission evaluated by PET using dopaminergic D2 subtype receptor availability via [$^{11}$C]raclopride binding. The tracer will be administered intravenous, using a bolus-plus-continuous-infusion method. A simple pseudo-equilibrium 5-min ratio of region of interest (right and left nucleus accumbens, caudate nucleus, putamen) to cerebellum activities provided an assessment of extracellular dopamine concentration before, during and after tDCS.
• Spontaneous functional connectivity assessed by resting state functional MRI (rs-fMRI, three 13 min scans before, during and after tDCS).
• Brain activity assessed by cerebral blood flow quantitatively and directly measured by pseudo-continuous arterial spin labelling (pCASL, three 6 min scans before, during and after tDCS).

• Connectivity assessed by diffusion tensor imaging (DTI, two 10 min scans before and after tDCS).
**Results:** With the first subjects included in the study, image analysis protocols are being developed independently for each modality in order to establish correlations. Also, the combination of these modalities is being considered.
**Conclusion:** Our unique approach will create a coherent ensemble, which is a mandatory and critical step to understand the mechanisms of action of tDCS. Moreover, in the long run, we expect that it will provide an imaging biomarker essential to improve our understanding of the "normal brain" and deficient mechanisms underlying schizophrenia as well as neurological disorders.