REMOPD Scientific Abstract:

Deep Brain Stimulation (DBS) with electrode implants has been a success story in the treatment of Parkinson's Disease (PD). This project will develop and apply noninvasive stand-alone and hybrid neuromodulation technology targeting basal ganglia to restore motor functions in PD with interference electrical fields and ultrasound (US).

Two groups (Partners 2-3) will focus on patients, while the rest will pursue basic research and technology development. Non-invasive electrical stimulation: Partner 2 will apply electric temporal interference fields (TIF) induced by two high-frequency transcranial Alternating Current Stimulators (tACS) with shifted frequencies to activate the internal globus pallidus (GPi) by the resultant TIFs of lower (130 Hz) frequencies. The stimulation intensity will be optimized with modeling (Partner 5) and validated based on invasive recordings in patients during pre-surgical epilepsy evaluation, and in experimental rats (Coordinator-Partner 1 and 2). Clinical efficacy of TIF stimulation will be verified using Unified PD Rating Scale (UPDRS) scores and by recording well-defined excitability parameters of the motor cortex, via transcranial magnetic stimulation (TMS) (Motor Evoked Potentials, i.e. MEP, silent period, Short- Interval Intracortical Inhibition (SICI)) and others in PD patients and controls (Partner 2). Non-invasive high-precision US stimulation of basal ganglia using low-intensity focused US (LIFUS) will be investigated with a new, multichannel stimulator developed by Partner 4.

The effects of LIFUS will be verified using UPDRS scores and by recording local field potentials from PD patients, targeting the subthalamic nucleus (STN) or GPi. Stimulation parameters will be optimized based on the clinical response, pathological β oscillations, and connectivity studies using fMRI (Partner3). The focus of Partner 2 will be primarily on pathophysiology in PD, while Partner 3 will conduct clinical efficacy studies. In exploratory, high-risk high-gain experiments, hybrid tACS and LIFUS will be applied by Partner 2, for testing synergistic effects. For this, the US frequencies will be reduced to ~150 kHz while the frequency of electrical stimulation will be increased to ~ 150 kHz to achieve an electroacoustic effect. Partner 5 will explore additive effects using a combination of various stimulation modalities (electric, magnetic, and LIFUS) along with realistic numerical models and tests in head phantoms, while the focus of Partner 6 is hardware development and adaptation of new hybrid systems for experimental use.

The possible utility of an alternative neuro-stimulation based on Lorentz fields caused by interactions of LIFUS and magnetic fields will be also explored by Partner 5. The main focus of Partner 1 will be the mechanistic analysis of non-invasive neuro-modulation in rat brain and neurons in vitro, to define underlying electrochemical processes and circuit mechanisms. Safety margins and optimal operational range will be also defined by Partner 1, using functional and histochemical tests. By targeted activation of selected neurons with LIFUS, thermo and mechanosensitive effects will be dissected and assigned to specific channels expressed in neurons.

Through an ingenious blend of innovative technologies and synergy of expertise, thus, for the first time, the most promising standalone and hybrid neuro-stimulation methods will be put to a rigorous trial, from cultured neurons in vitro, through animal experiments and clinical tests in PD patients. The non-invasive technologies described are expected to facilitate not only better management and restoration of motor functions in PD but to improve the understanding of underlying mechanisms and safety, for optimization and expatiated translation into routine medical practice.