NEURIPIDES

Structural connectivity of the basal ganglia from patient-individual tractography for predicting therapeutic effects of deep brain stimulation in Parkinson's Disease

Poster number 14
Poster presenter: Ricardo Loução

Aims, research questions and working hypothesis
Motor control is achieved through the interplay of multiple nodes of the cortico-basal ganglia-thalamocortical loop. Therapeutic approaches for PD patients include deep brain stimulation (DBS) of the subthalamic nucleus (STN). However, the mechanisms underlying the therapeutic effects of STN-DBS are not completely understood. In this work, we investigate the patient-specific structural connectivity associated with DBS and its links to therapeutic effects. We hypothesise that DBS reduces hyperactivity of the STN-related networks , which consequently leads to a clinical improvement.

Methods implemented by the consortium
Two centres from the consortium were involved in this project: Cologne (Germany), responsible for the development of the imaging analysis methods; and Prague (Czech Republic), responsible for validation and development of advanced statistical analysis methods. To examine the structural connectivity of the network in question, we applied tractography, a technique based on diffusion-weighted magnetic resonance imaging (dMRI) used to reconstruct the white matter pathways of the brain in each individual patient. Imaging data were acquired from PD patients scheduled for STN-DBS at the two centres ($N_{Cologne}$ = 69, N_{Prague} = 55, N_{total} = 125). In addition to the dMRI data, clinical assessments including motor and non-motor assessments (e.g. parts III and I of the UPDRS questionnaire, respectively), were acquired before and after DBS surgery to determine clinical outcome. Imaging analysis methods focused on optimising fibre tracking in the basal ganglia, which included exploration of dMRI distortion correction methods, signal modelling approaches, and tractography settings. Once the imaging pipeline was established, we investigated the connectivity of the volume of tissue activated (VTA) from the active DBS electrode to the cortex in general and correlated the derived connectivity with the clinical outcomes. Then, we specifically targeted the connectivity within the cortico-basal ganglia-thalamocortical loop for tractography. Degree of dysconnectivity was determined by the ratio of node-to-node connections affected by the VTA and these ratios were correlated with clinical outcome. Finally, a prediction model of clinical outcome will be developed using the Cologne dataset, and validation of this model will be performed on the Prague data. Additionally, single-item response analysis will be carried out by the Prague team to identify specific relations between UPDRS questionnaire items and (dys-)connectivity patterns.

What are the outcomes of the project?
Initial analysis correlating VTA connectivity to the cortex revealed that VTA's primarily connect to the SMA. Correlation analysis revealed a positive correlation between motor clinical outcome and VTA connection to the SMA, pre-motor, and motor cortices. Other expected outcomes include identification of connectivity patterns for non-motor scores and predictive models of the clinical outcome based on (dys-)connectivity patterns.

Significance and impact of the work on the field
This is, to the best of our knowledge, the largest study including patient-specific tractography of PD patients that underwent DBS to date. The collaborative nature of the project ensures that the results obtained by one group can be validated by another, increasing applicability to other centres. These results demonstrate the project's fit with the call's mission of harnessing imaging to improve brain stimulation. Taken together, the VTA (dys-)connectivity profiles and the clinical outcome predictive model have the potential to advance the understanding of DBS on PD. Additionally, such models could be used in a clinical context as a tool to guide therapy.

Next steps and future challenges
The next steps will focus on incorporating non-motor symptoms into the analysis, along with the development of symptom-specific predictive models.

Funding statement
Funds have been provided by the European Joint Programme Neurodegenerative Disease Research (JPND) 2020 call “Novel imaging and brain stimulation methods and technologies related to Neurodegenerative Diseases” for the Neuripides project ‘Neurofeedback for self-stImulation of the brain as therapy for ParkInson Disease’. The Neuripides project has received funding from the following funding organizations under the aegis of JPND: The Netherlands, The Netherlands Organization for Health Research and Development (ZonMw); Germany, Federal Ministry of Education and Research (BMBF); Czech Republic, Ministry of Education, Youth and Sports (MEYS); France, French National Research Agency (ANR); Canada, Canadian Institutes of Health Research (CIHR); Turkey, Scientific and Technological Research Council of Turkey (TUBITAK).