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Main supervisor at home institution:

Dr. Vadim Nikulin nikulin@cbs.mpg.de
Max Planck Institute for Human Cognitive and Brain Sciences, Department of Neurology, Leipzig, Germany

Supervisor at host institution:

Dr. Ashwini Oswal ashwini.oswal@ndcn.ox.ac.uk
University of Oxford, Nuffield Department of Clinical Neurosciences, Oxford, United Kingdom

Description of learned methods and knowledge

In the past, clinical neuroscience has focused on pathological brain *areas*, for example, the loss of dopaminergic neurons in the substantia nigra in Parkinson's disease patients. Over the last decade, the focus has shifted toward the analysis of pathological brain *networks*. As a result, many diseases are now regarded as network diseases.

Local changes in brain dynamics, such as the application of deep brain stimulation (DBS) in the subthalamic nucleus (STN), can profoundly change global network dynamics. However, the relationship between brain *area* activity and brain *network* activity is still poorly understood. Investigating the interplay of local and global neuronal dynamics, essential for treating pathological brain networks, is the core of my Ph.D.

My supervisors Vadim Nikulin and Gabriel Curio have tremendous experience in the quantification of local brain area dynamics, for example, neural oscillations, aperiodic activity, phase-amplitude coupling, or long-range-temporal correlations. In addition, they taught me how to reveal functional brain networks using magnitude coherence or imaginary coherency. However, electrode placement varies across subjects. Therefore, subject-specific *functional* connectivity should be complemented with subject-specific *structural* connectivity.

Therefore, we sought out Dr. Ashwini Oswal from the University of Oxford who can complement my supervisor's expertise with his proficiency in tractography. Tractography is a powerful method to estimate the trajectory of bundles of axons based on diffusion magnetic resonance imaging (dMRI), thereby revealing structural connectivity. Moreover, he is also an expert on functional network dynamics and he has successfully linked structural and functional connectivity previously (Oswal *et al.*, 2021a; b).

During my research visit to Oxford, we examined the structural connections of the deep brain stimulation electrodes for all subjects in my dataset. We used a normative dMRI connectome from the Parkinson's Progression Markers Initiative (PPMI) project and applied it to the electrode locations of all 13 subjects, which were localized on their MRI scans. The preliminary result is shown in Figure 1. We used the DBS electrode voxels as seeds to

visualize all tracts passing them in black. It becomes apparent, that many fibers lead to the contralateral hemisphere even though this is anatomically false (Coudé *et al.*, 2018). Therefore, it is crucial to pinpoint the limitations of tractography.

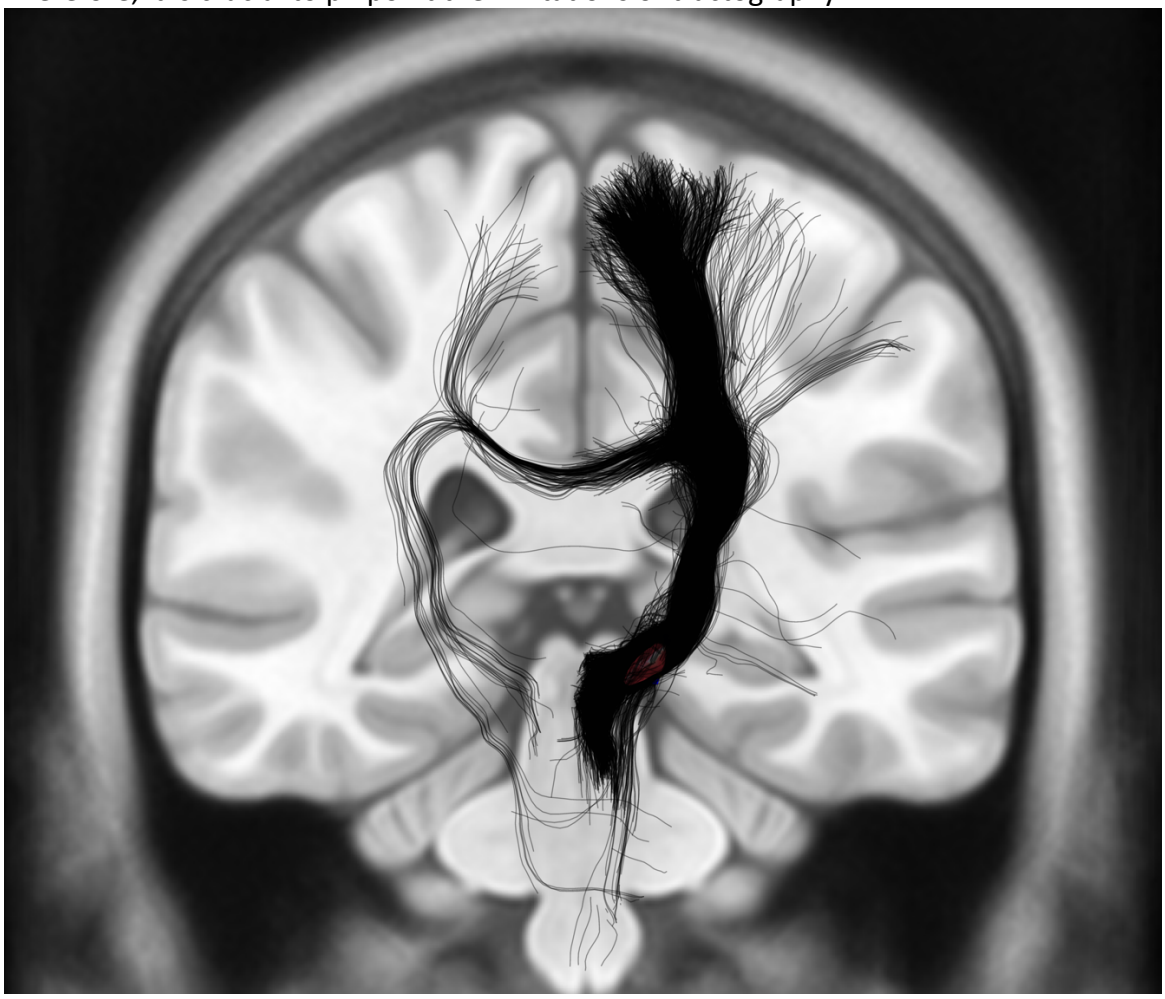

Figure 1 dMRI cannot handle fiber crossings well. All fibers in this figure pass the DBS electrodes in the right STN within a radius of 1 mm. While many of these fibers correctly project from the unilateral motor cortex to the STN via the hyperdirect pathway, many fibers in this figure connect the right STN with the left hemisphere which is anatomically incorrect.

Phantom dMRI experiments showed that for every true streamline, four invalid false-positive streamlines were found (Maier-Hein *et al.*, 2017). dMRI primarily detects long and myelinated fibers and underestimates the presence of short or thin bundles (Alho *et al.*, 2020; Horn *et al.*, 2019; Zhang *et al.*, 2010). For the found fibers, dMRI cannot indicate the direction or connectivity strength (Jones *et al.*, 2013). Its estimates are based on the fractional anisotropy of water molecules. In neuronal axons, the diffusion is limited along one axis (**an**isotropic diffusion). When fibers are crossing in the brain, however, diffusion becomes more **iso**tropic. dMRI therefore cannot distinguish crossing fibers very well (Dhollander and Yang, 2022). This is highlighted by the PPMI connectome in Figure 1, where left STN fibers “take a wrong turn” and enter the right hemisphere. This figure, therefore, highlights the limitations of dMRI.

In general, dMRI should be combined with a priori anatomy knowledge (Schiavi *et al.*, 2020) as summarized in the paper “Brain connections derived from diffusion MRI tractography can be highly anatomically accurate—if we know where white matter pathways start, where they end, and where they do not go” (Schilling *et al.*, 2020). Following this rule requires

anatomical expert knowledge though and it is therefore not feasible for neuroscientists working in other fields. However, recently Petersen et al. created a new holographic atlas based on dMRI, histology, and previous literature (Petersen *et al.*, 2019). Using virtual reality, the structural connectivity was visualized in 3D, manually corrected by anatomy experts, and made publicly available. During my research visit, we decided to take advantage of this recent development.

Figure 2 A shows all fibers passing through a seed region around the DBS electrodes of one exemplary subject. Note, that compared to the PPMI connectome in Figure 1, the holographic fibers do not cross the other hemisphere. The STN is shown in red, the DBS electrodes are in blue, and the local field potential (LFP) regions of interest (ROI) are in yellow. The primary motor cortex (M1) is indicated green. In addition to DBS electrodes, the subjects in this dataset also have electrocorticography (ECoG) electrodes on the motor cortex. They are shown as blue discs in their original size. The yellow ECoG ROI is shown for the two most frontal (bipolar) electrodes. The hyperdirect pathway fibers passing through the STN ROIs projecting to the cortex are shown in black. Of those, some project to the cortical ROI and are indicated in yellow.

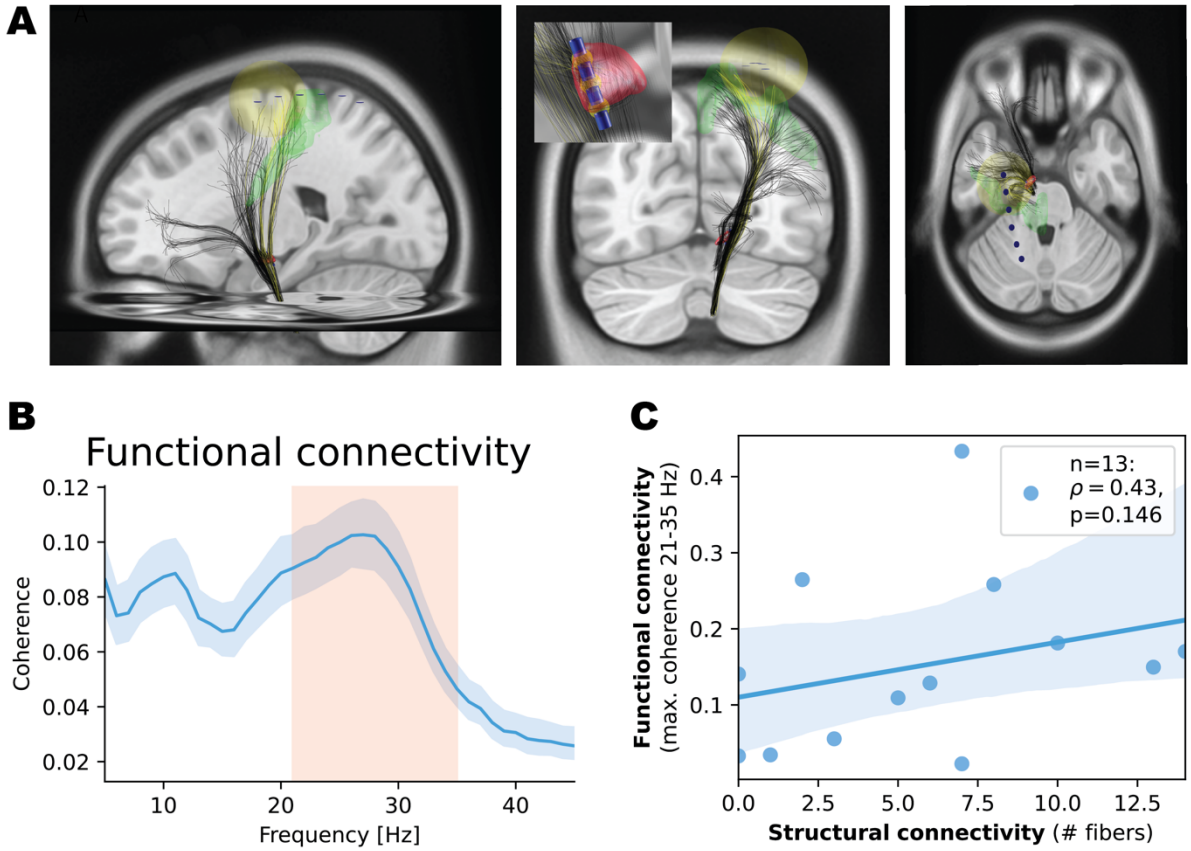

Figure 2 ***A****: Sagittal, coronal, and axial view on a normative MRI with the primary motor cortex (M1) indicated in green and the STN in red. The plotted fibers are from the normative holographic atlas. However, the DBS electrodes (blue cylinders) are shown for one exemplary subject and only those fibers are plotted, which traverse the DBS ROIs (yellow) within a radius of 1 mm. The ECoG electrode positions (blue) are specific to this subject as well. Of all black hyperdirect pathway fibers, only a few project to the most frontal ECoG ROI (large yellow sphere). These fibers are shown in yellow.* ***B*** *Magnitude coherence across subjects for the bipolar DBS channel closest to the M1 terminals and strongest connected bipolar ECoG channel.* ***C*** *The number of fibers connecting the bipolar DBS channel with the bipolar ECoG channel from B is shown on the x-axis. Their maximum high beta coherence is plotted on the y-axis.*

The LFP in the STN is generated by the synaptic transmembrane currents (Buzsáki *et al.*, 2012). Since we are interested in the electrophysiological hyperdirect pathway input, we pick for each subject only the DBS ROI which is closest to the M1 synapses terminating in the STN. The synapse locations were obtained from the holographic atlas (c.f. Figure 4 of Petersen *et al.*, 2019). Of those fibers passing this specific ROI, we next pick the structurally strongest connected ECoG pair, estimated by the maximum number of fibers connecting both ROIs.

For this single DBS-ECoG pair, we show the subject-averaged magnitude coherence in Figure 2 B. Note the distinct alpha and beta peaks. In Figure 2 C we show that there is indeed a trend for structurally stronger connected pairs to be also functionally stronger connected in the beta range. We focus on high beta coherence (21-35 Hz) because Parkinson's disease symptoms are hypothesized to result from exaggerated cortical high beta input to the STN (Oswal *et al.*, 2021a). Note that this relationship does not reach significance in this small sample size. However, more subjects will be added to the analysis in the future.

The trend between functional and structural connectivity highlights the importance of complementing functional analyses with patient-specific structural ones. For my further Ph.D. research on global brain networks, I can now specifically investigate those channels, which record neuronal activity relating to the hyperdirect pathway.

To our knowledge, a relationship between structural and functional connectivity using DBS and ECoG has never been shown before. Furthermore, previous analyses have not utilized the recently developed holographic atlas which is considered superior.

How to implement learning in the home lab

For most Parkinson's patients treated with DBS, MRIs are available. Apart from those, tractography does not require special equipment or expensive software. The essential data, such as normative human connectomes, and analysis software, such as LeadDBS or Python, are freely available. The critical bottleneck for applying this method is a proper understanding. With my gained experience, I will be able to introduce other colleagues to this exciting field. While I have not become an expert during such a short stay, I do understand the basics and I know the relevant resources and scientists for further inquiries. If someone in my lab would like to get started, I feel capable of pointing them in the right direction.

Picture of me with the lab

Figure 3 From left to right: Dr. Ashwini Oswal (host), Moritz Gerster (NENS visiting student), Bahman Abdi (Postdoc).

Contribution to professional and personal development

Living in the UK is very expensive. Therefore, this research visit would not have been possible without financial help through the NENS exchange grant. This visit has tremendously benefitted my career through the important scientific results I obtained in this short time. Tractography is an important method I might use many times in my future career. In addition, I gave talks and advertised my research in the labs of Prof. Huiling Tan and Prof. Mark Woolrich. Furthermore, I met many very friendly, smart, and interesting lab members with whom I will stay in contact.

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