Altered resting state functional connectivity in a subthalamic nucleus - motor cortex - cerebellar network in Parkinson's Disease

S. Baudrexel[1,2], T. Witte[1], C. Seifried[1], F. von Wegner[1], J. C. Klein[1], H. Steinmetz[1], R. Deichmann[2], and R. Hilker[1]
[1]Department of Neurology, University Hospital, Goethe University Frankfurt, Frankfurt am Main, Germany, Germany, [2]Brain Imaging Center, Goethe University Frankfurt, Frankfurt am Main, Germany

Introduction Parkinson's disease (PD) is characterized by a loss of dopaminergic projections from the substantia nigra to the basal ganglia, resulting in altered metabolic and electrophysiological functional connectivity (FC) of large scale motor, cognitive and limbic networks [1,2]. Using PET, increased metabolic activity is typically found in the basal ganglia, primary motor cortex and cerebellum, whereas metabolic decreases are usually found in premotor, frontal and parietal areas [1]. However, multiple cell recordings from the human subthalamic nucleus (STN), generally considered as a key player in PD-pathophysiology, and electrophysiological studies from other species suggest that it is not necessarily the mean firing rate but, above all, the temporal pattern of neurologic activity that is altered in PD [3]. Specifically, an increased STN-oscillatory activity in the EEG beta-frequency band and in the cortical EEG is characteristically found in PD-patients and probably relates to PD-motor symptoms [4,5]. Here we investigate, whether an altered STN-FC pattern may also be observed non-invasively in PD on the basis of very low frequency BOLD fluctuations, using resting state fMRI and a common seed-voxel approach.

Methods 31 patients with early PD (H&Y stage I and II, mean age 59.4 +/-10.7 y) and 43 age and gender matched healthy controls underwent resting state fMRI using a gradient echo EPI sequence on a 3 T Siemens Trio system with the following parameters: TR = 3s, TE = 30 ms, matrix size = 64x64, FoV = 192x192 mm^2, 45 slices, slice thickness 2 mm, scan duration 13 min. PD patients were scanned 12 h after cessation of all antiparkinsonian medication. After discarding the first 9 scans, 251 data points were left for subsequent FC-analysis. In addition to the functional scans, high resolution quantitative T1-maps were acquired using an RF-spoiled gradient echo sequence as described in [6]. Data analysis was performed with SPM8 and custom built programs, consisting of the following steps: 1. Spatial realignment 2. Physiological noise regression on the basis of the acquired cardiac and respiratory signal (modified according to RETROICOR [7]). 3. Coregistration of functional data sets onto the individual high resolution T1-map. 4. Normalization to MNI-space with spatial resampling to 2x2x2 mm^3 resolution. 5. Smoothing by convolution with a 5 mm isotropic Gaussian kernel. 6. Nuisance regression, using 6 movement parameters (and their first derivatives) obtained from spatial realignment and the mean white matter and cerebrospinal fluid signal. 7. Temporal band pass filtering with cut off frequencies $0.008<f<0.01$ Hz. 8. Seed-region specification and FC-analysis: The STN was delineated manually on the basis of the mean EPI-image over all subjects. For each individual, the mean STN time-series was calculated and correlated with the time series of all other brain voxels. After Fisher's r-to-z transformation, a second-level random effects analysis was performed using SPM8.

Results Thresholded t-maps ($p < 0.005$, uncorrected) for the group statistic $FC_{STN\ left}(PD) > FC_{STN\ left}(Control)$ are displayed in Fig. 1. Data reveal a huge cluster of 1403 voxels of increased subthalamic FC to the bilateral primary and supplementary motor cortex ($p < 0.001$, corrected for multiple comparisons at cluster level, peak level T = 4.73 at MNI -38,-36,58 (right hand areal)). A similar pattern was observed for the right STN. Contrarily, the opposite contrast $FC_{STN}(PD) < FC_{STN}(Control)$ did not reveal significant results, neither for the left nor the right STN. In a consecutive analysis, a spherical ROI of 5 mm radius centred around the peak coordinates in Fig.1 was used as seed-region to investigate changes in FC of the primary motor cortex. The results for the contrast $FC_{left\ motor\ cortex}(PD) > FC_{left\ motor\ cortex}$ (Controls) are depicted in Fig. 2. The most significantly increased FC-values were found bilaterally in the cerebellum (cluster size 6810, $p < 0.001$, cluster level corrected, peak level T = 5.86 at MNI 6,-74,-22 (right cerebellum)) and, in addition to the left STN, bilaterally in frontal areas. Significant FC-reductions were found in the contralateral motor cortex and bilaterally in BA 37 (data not shown).

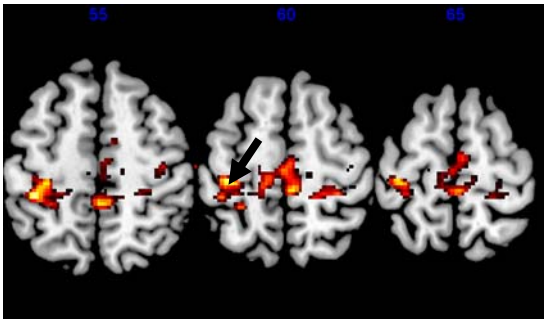

Fig 1: Thresholded t-maps of increased (left-) STN FC in patients as compared to healthy controls ($p < 0.005$, uncorrected). The arrow indicates peak coordinates at MNI (-38,-36,58) used for the seed-voxel analysis in Fig. 2. The left side corresponds to the left hemisphere.

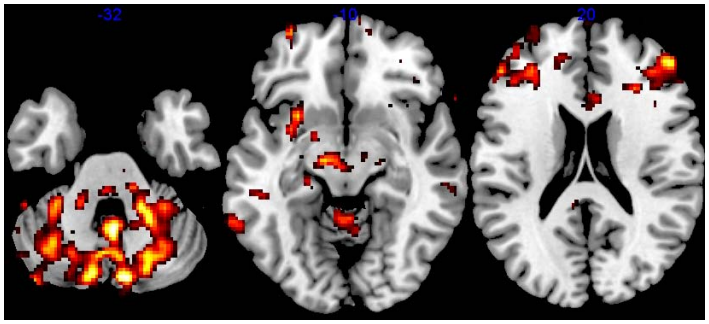

Fig 2: Thresholded t-maps of increased (left-) primary motor cortex FC in patients as compared to healthy controls ($p < 0.005$, uncorrected). In this analysis, a spherical ROI of 5 mm radius centred around the peak coordinates from Fig. 1 (arrow) was used as seed region. The left side corresponds to the left hemisphere.

Discussion Using resting state FC fMRI we provide evidence of wide-spread alterations in network coupling related to PD. Most strikingly, we found increased FC values within a large subthalamic-motor cortex-cerebellar network, which, speculatively, may partly result from pathological oscillatory activity aliased from higher frequency bands (e.g. from the beta-band). However, the physiological relevance and the exact electrophysiological origin of this finding remain further to be determined.

References

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