

Resting State Functional Connectivity of the Subthalamic Nucleus in Parkinson's Disease Assessed using Arterial Spin Labeling

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Target audience: MRI scientists and neuroscientists interested in the use of functional connectivity (FC) MRI in the resting state.

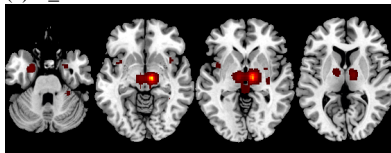
Introduction: Parkinson's disease (PD) is a common neurodegenerative disease whose pathophysiological mechanisms are still unclear. The disease is characterized by a degeneration of dopaminergic neurons in the substantia nigra that results in a loss of brain dopamine, most prominently in the striatum. The study of pathological brain activity both in PD animal models and in PD patients has revealed that dopaminergic depletion leads to an increase in oscillatory activity in several basal ganglia structures, but most dramatically in the neurons of the subthalamic nucleus (STN). Indeed the STN has become a primary target in deep brain stimulation treatment of PD patients. A recent functional connectivity (FC) fMRI study has shown abnormal resting state FC of the STN in PD, evaluating the synchrony of low frequency spontaneous fluctuations in the BOLD signal (1). Arterial spin labeled (ASL) perfusion MRI offers the possibility of measuring cerebral blood flow (CBF) and assessing FC by means of evaluating the fluctuations in the CBF time series. Recent work has shown that ASL FC has statistical power comparable to that of BOLD FC (2) and could provide a better characterization of low frequency fluctuations than BOLD (3).

Purpose: In this work, ASL FC has been used to study FC connectivity of the STN in healthy controls and to evaluate STN FC alterations in PD.

Methods: Studies were performed on a 3T Siemens Trio using a 12-channel head array. Twenty-four PD patients (7F, age=63.4±6.7 years, UPDRS ON=12.4±5.4, 14 / 10 with predominant right / left side affection, respectively) and 34 age-matched healthy volunteers (12F, age=63.5±6.6 years) participated in the study after signing informed consent. Patients were examined at their clinical ON state. During the scanning session resting perfusion was measured using a pseudo-continuous arterial spin labeling (PCASL) technique (4) with a background-suppressed 3D GRASE readout (5) (TE_{eff}=56ms, TR=3.5 sec, resolution=4x4x7 mm³, FOV=250x188x112 mm³, 16 nominal partitions with 13% oversampling, slice 5/8 partial Fourier, matrix size=64x49, BW=2790 Hz/pixel, BS T11=1800 ms, T12= 500 ms). The labeling time was 1.6 sec and post-labeling delay was 1.5 sec. 50 label/control pairs were acquired in a scan time of 6 min, followed by a short scan of 5 label/control pairs acquired without background suppression to obtain control images needed for the CBF calculation. Each subject's images were realigned and co-registered to the anatomical dataset, acquired using a T₁-MPRAGE sequence, before subtraction of label and control. 49 perfusion images were obtained, after discarding the first label/control pair. CBF maps were computed from the perfusion weighted images using the one-compartment model, normalized to a standard brain template and smoothed with a 6 mm isotropic Gaussian kernel. Seed-to-voxel resting state FC analysis was carried out to examine correlations in slow spontaneous fluctuations in the CBF time series, using the Functional Connectivity toolbox (<http://web.mit.edu/swg/software.htm>). Two seeds were evaluated, located in the right (R) and left (L) STN, respectively, comprising the full extent of each structure, in each hemisphere, as defined by the masks in the WFU PickAtlas toolbox. Several sources of spurious variance were removed from the data by linear regression: realignment parameters and averaged CBF signal in four ventricular and two white matter ROIs. The CBF time series was filtered with a low-pass filter ($f < 0.08$ Hz). Seed to voxel connectivity was estimated by calculation of Pearson's correlation coefficient. The r-values were converted to z-scores using Fisher's z transform. Maps of the STN FC in healthy controls were obtained by one sample t-tests and thresholded at $p < 0.05$, FWE corrected at the voxel level. Differences in FC between patients and controls were assessed by two sample t-tests and thresholded at $p < 0.05$, FWE corrected at the cluster level.

Results and Discussion: FC maps of the R and L STN in healthy controls are shown in Fig. 1. Strong positive correlations were found with other basal ganglia nuclei, including contralateral STN, ipsilateral putamen, globus pallidus, and substantia nigra. Connectivity was also found with the thalamus, insula, hippocampus and amygdala. Comparisons between PD patients and healthy controls showed increased FC of the STN in the PD group (Fig. 2). The R_{STN} showed increased FC within the sensorimotor cortico-basal ganglia circuit, including primary sensorimotor, premotor, SMA and motor cingulate cortices and subcortically the putamen and globus pallidus. Other cortical areas primarily affected by the R_{STN} connectivity alterations were precuneus (a node of the cortico-basal ganglia spatial network), orbitofrontal cortex, hippocampus and amygdala (nodes of the cortico-basal ganglia limbic network). The L_{STN} also showed increased FC in the PD patients with cortical areas of the sensorimotor network but not at the subcortical level. Alterations of the left STN connectivity were also found in precuneus, dorsolateral prefrontal cortex, inferior parietal areas and occipital areas. These results are partially in agreement with the study of Baudrexel et al., who were the first to use BOLD FC to study FC changes of the STN in PD patients (1). Their results showed increased FC between the STN and cortical motor areas, however they did not observe altered FC of the STN with other basal ganglia nuclei, most likely due to sensitivity limitations in their study. In addition, our results show that alterations of the STN FC in PD affect other circuits beside the motor network, in which the STN occupies a central position, such as the limbic and associative circuits.

(a) R_{STN}



(b) L_{STN}

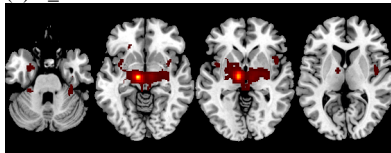
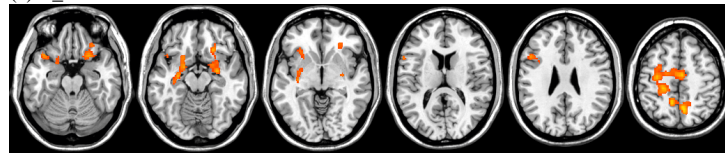


Figure 1. ASL FC maps of the STN, R (a) and L (b), in healthy controls, overlaid on anatomical T₁-weighted axial sections ($p < 0.05$, FWE corrected at the voxel level).

(a) R_{STN}



(b) L_{STN}

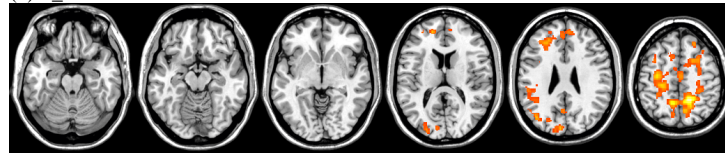


Figure 2. Areas of increased FC with the STN in PD patients compared with controls, R (a) and L (b) overlaid on anatomical T₁-weighted axial sections ($p < 0.05$, FWE corrected at the cluster level).

Conclusions: Resting state functional connectivity of the STN is abnormally increased in PD, in sensorimotor, limbic and associative areas. Our results show that FC ASL has enough sensitivity to assess functional connectivity in the healthy brain and also to detect pathological changes in the diseased brain.

References : 1. Baudrexel et al, Neuroimage 2011; 55:1728-38. 2. Vidorreta et al, ISMRM Workshop on Perfusion MRI 2012; Amsterdam. 3. Dai et al, ISMRM Workshop on Perfusion MRI 2012; Amsterdam. 4. Dai et al. Magn Reson Med 2008; 60:1488-97. 5. Fernández-Seara et al. Magn Reson Med 2008; 59:1467-71.

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