Altered Cerebral Perfusion and Functional Connectivity in a Response-control Network in Parkinson's Disease Measured by ASL

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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. Studies of metabolism and perfusion using PET and SPECT have revealed abnormalities in the resting state. PD patients present hyperperfusion in regions of the basal ganglia, thalamus and cerebellum and hypoperfusion in certain cortical areas although the sites of cortical decrease vary among studies (1). In addition, recent functional connectivity (FC) fMRI studies have shown abnormal resting state FC in PD (2-4). Arterial spin labeling (ASL) perfusion MRI offers the unique possibility of measuring both cerebral blood flow (CBF) and FC using data acquired in a single scan. In this work, ASL perfusion MRI has been used to study CBF and FC abnormalities in PD.

Materials and Methods

Studies were performed on a 3T Siemens Trio using a 12-channel head array. Twenty-four PD patients (5F, age=63.2±7.9 years, UPDRS=14±5, 15 / 9 with predominant right / left side affectation, respectively) and 26 age-matched healthy volunteers (9F, age=61.8±6.3 years) participated in the study after signing informed consent. Patients were studied at their clinical ON state. During the scanning session resting perfusion was measured using a pseudo-continuous arterial spin labeling (PCASL) technique (5) with a background-suppressed 3D GRASE readout (6) (TEeff=56ms, TR=3.5 sec, resolution=4x4x7 mm^3, FOV=250x188x112 mm^3, 16 nominal partitions with 13% oversampling, slice 5/8 partial Fourier, matrix size=64x49, BW=2790 Hz/pixel, BS TI1=1800 ms, TI2= 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 T_1-MPRAGE sequence, before subtraction of label and control. 49 perfusion images were obtained, after discarding the first label/control pair. A cerebral blood flow (CBF) map was computed from the mean perfusion image using the one-compartment model (7), normalized to a standard brain template and smoothed with an 8 mm Gaussian kernel. Voxel-wise statistical comparisons of the CBF data without prior normalization by the global mean and after global mean normalization were performed with SPM5, using a two-sample t-test to compare the patient and control groups. 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), with seeds in the supplementary motor area (SMA) and pre-SMA, regions of maximum hypoperfusion in the PD patients. Several sources of spurious variance were removed from the data by linear regression: realignment parameters and averaged CBF signal in the ventricular ROIs. The CBF time series was filtered with a band-pass filter (0.004 < 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. Differences in FC between patients and controls were assessed by two sample t-tests.

Results and Discussion

Whole brain voxel-wise statistical analysis on the absolute CBF data showed hypoperfusion in PD patients compared with controls in a large cluster (k=4721) that included parietal, motor, premotor and supplementary motor areas (p<0.005, corrected at the cluster level) (Fig. 1) with no regions of hyperperfusion. Comparison of relative CBF maps yielded similar areas of hypoperfusion, additionally revealing hyperperfusion in the middle and superior temporal lobes, reaching the left posterior putamen (data not shown). More interestingly however increases in FC with pre-SMA were found in the PD patients in the subthalamic nucleus (STN), thalamus, sensorimotor cortex and frontal cortex in inferior (BA 46), middle (BA 10) and superior (BA9) frontal gyri (p<0.01, uncorrected for multiple comparisons, k>40). Strong functional connections between STN and the supplementary motor area have been observed in PD patients using EEG and the coherence between STN and cortex has been related to parkinsonian rest tremor (8). Increased FC between the STN and the bilateral primary and supplementary motor cortex in PD has also been previously reported using BOLD fMRI (2). Pre_SMA, STN and inferior frontal cortex are part of a frontal-subcortical network for response control (i.e. a neural breaking system) as shown by DWI tractography and fMRI (9). Alterations in the connectivity within this network are likely to be related to parkinsonian symptoms. Our results also showed FC decreases in the middle temporal gyrus (data not shown). The FC analysis with seed in SMA yielded FC increases in PD in frontal areas of the right hemisphere and FC decreases in parietal and occipital areas (data not shown).
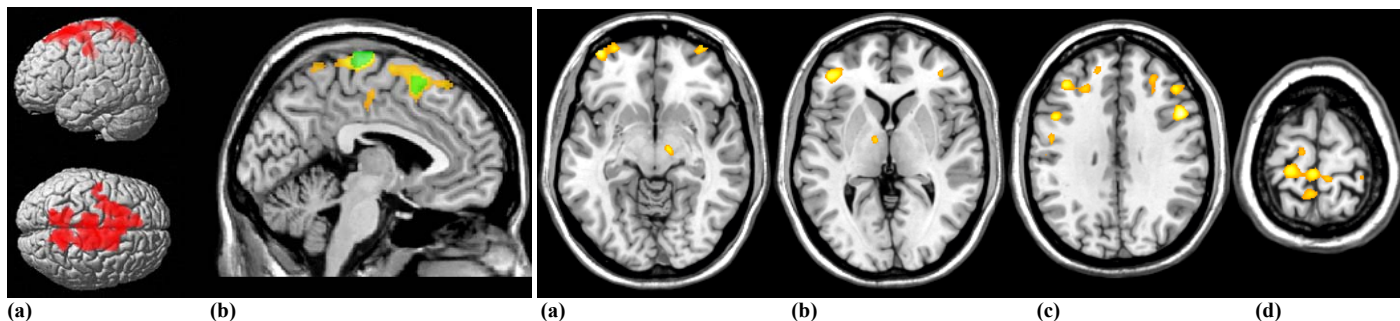

(a) **(b)** **(a)** **(b)** **(c)** **(d)**

Figure 1. (a) Hypoperfusion map in PD patients overlaid on a 3D-rendered brain (p cluster < 0.005, corrected). (b) Hypoperfusion overlaid on an anatomical T_1-weigthed sagittal section, showing the seeds in SMA and pre-SMA selected for the FC analysis (in green).

Figure 2. Areas of increased FC with pre-SMA in PD patients compared with controls overlaid anatomical T_1-weigthed axial sections (p<0.01, uncorrected, k>40): (a) STN, (b) thalamus, (c) frontal cortex, (d) motor cortex.

Conclusions

Resting state perfusion and functional connectivity are abnormal in PD. Our results showed hypoperfusion in parietal and sensori-motor cortical areas. In addition, increased functional connectivity was found in a network responsible for response control, with a key node in the STN.

Bibliography

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