Effects of Levodopa Therapy on Resting Brain Perfusion and Functional Connectivity in Parkinson's Disease Patients Measured by ASL Perfusion MRI

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Introduction

Parkinson's disease (PD) is a neurodegenerative process characterized by the degeneration of dopaminergic neurons in the substantia nigra, resulting in a reduction of dopamine concentration in the striatum, which regulates execution of planned motor responses. The consequences are the slowness of voluntary movements (bradykinesia), dysfunction of learned movement, absence of automatic movements (akinesia) and presence of involuntary movements (tremor). Thus, antiparkinsonian therapies most commonly involve dopaminergic medication, such as oral levodopa and dopamine agonists. It is known that medication can influence brain metabolism in cortical and subcortical regions, as well as some cognitive functions. However, studies assessing the differences between the medicated (*"on"*) and unmedicated (*"off"*) states on PD patients during rest are scarce and have led to divergent results (1-4). Hence, here we have evaluated the influence of levodopa therapy on resting perfusion and functional connectivity in PD patients using a novel non-invasive technique, arterial spin labeling (ASL) perfusion MRI.

Materials and Methods

Five male PD patients without dementia and with predominant right side affectation, of age 58 ± 14 years, participated in the study after signing informed consent. Disease duration was 7 ± 5 years, motor UPDRS during *on* was 8 ± 8 and mean levodopa dose was 430 ± 300 mg/day. Studies were performed on a 3T Siemens Trio using an 8-channel head array in two sessions: the *off* session ~12h after medication withdrawal, and the *on* session under normal medicated condition (~2h after medication intake). During each scanning session resting perfusion was measured using an optimized ASL technique that combined pseudo-continuous labeling (PCASL) (6) with a background-suppressed (BS) single shot 3D GRASE sequence for readout (7), with imaging parameters: resolution=4×4×6 mm^3, FOV=250×187×96 mm^3, TE=52 ms and TR=3.5 s. The labeling time was 1.6 sec and post-labeling delay was 1.5 sec. 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 pairs. 49 perfusion images were obtained in a scan time of 6 min, after discarding the first pair. A cerebral blood flow (CBF) map was computed from the mean perfusion image using the one-compartment model (8), normalized to the standard template and smoothed with an 8 mm Gaussian kernel. Normalization by the global mean was conducted on the CBF maps to minimize inter-subject variability. Voxel-wise statistical analysis of the CBF data was performed using SPM8. Finally, a functional connectivity analysis was conducted using the Functional Connectivity toolbox (http://web.mit.edu/swg/software.htm), with a spherical seed on the left posterior putamen, (r = 4mm, center MNI coordinates [-29 -10 10]), chosen based on the previous analysis (see Results). Sources of spurious variance were removed from the data by linear regression: realignment parameters and averaged CBF signal in the ventricular ROI. CBF time series were 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. In both analyses, differences between *on* and *off* conditions were assessed using paired t-tests.

Results and Discussion

Whole-brain mean CBF differences were not significant between conditions (p > 0.3). However, the voxel-wise comparison of the relative CBF maps in the *off* versus *on* states granted several statistically significant regions. The administration of levodopa lowered the perfusion levels of the following areas (listed in order of significance): parietal lobe (left temporal gyrus, left precuneus and bilateral superior parietal lobule), left insula, left posterior putamen, frontal lobe (Supplementary Motor Area (SMA) and right superior frontal gyrus; right middle/inferior frontal gyrus), parietal lobe (left angular gyrus and left inferior parietal lobule) and right medial thalamus (Fig.1, cold scale). Several cortical areas showed increased perfusion after medication intake (Fig. 1, hot scale). Previous studies that have assessed perfusion changes between patients in *off* state and healthy controls have reported hyper-perfusion in basal ganglia nuclei and thalamus (for a review, see (10)). This suggests that levodopa is responsible for normalizing the perfusion abnormalities caused by dopamine depletion.

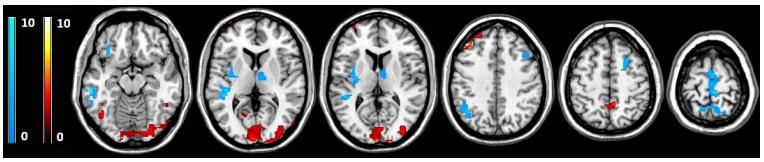

Figure 1. Changes in brain perfusion of PD patients in the *on* state compared to their *off* state during rest (paired t-test, p < 0.05, k > 140). Areas depicted in hot/cold color-scale indicate regions exhibiting significantly higher/lower perfusion during the *on* state.

The connectivity analysis conducted placing the "seed-voxel" at the left posterior putamen (Fig. 2) revealed that connectivity levels significantly increased in multiple cortical-sensorimotor and striatal areas after levodopa administration: middle cingulate cortex, left postcentral gyrus, right superior temporal gyrus, rolandic operculum (bilateral), insula (bilateral), right thalamus, left anterior putamen, left fusiform gyrus and precentral gyrus (bilateral). Recent work (11) has found similar couplings with the posterior putamen when comparing healthy controls to PD patients in the *off* state. Cingulate cortex, putamen, SMA, superior temporal and middle frontal gyri also gained regional homogeneity in (4). Thus, we interpret that levodopa therapy restores normal connectivity activity in the posterior putamen. Main connectivity decreases were found in rostral SMA (pre-SMA), superior frontal gyrus (bilateral), caudate, right cuneus, right calcarine sulcus and right occipital gyrus.

Inter-regional connectivity patterns appear to be altered in PD (11). Here we see how oral levodopa therapy restores connectivity levels back to a relatively normal state. Interestingly, the contralateral putamen shows abnormally high perfusion levels in the unmedicated state, and presents an increased connectivity with caudate nuclei and pre-SMA region, which is known to be involved in motor preparation. This alteration may underlie the motor clinical manifestations of akinesia and bradykinesia.

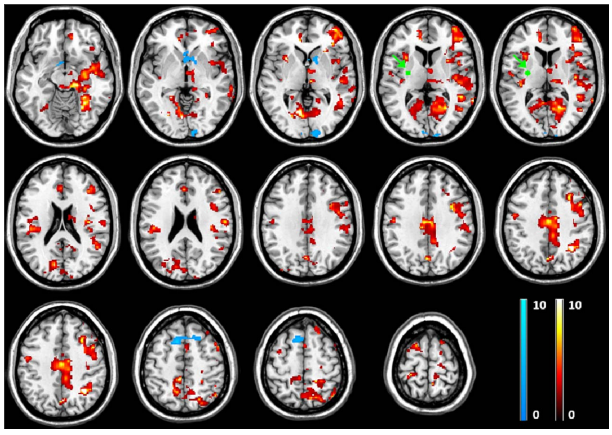

Figure 2. Brain regions showing either increased (hot) or decreased (cold) connectivity with left posterior putamen ROI (green) in PD patients in the *on* state compared to *off* state during rest (paired t-test, p < 0.05, k > 140).

Conclusions

ASL has provided a quantifiable measure of the effect of levodopa therapy in PD patients. Medication is responsible for normalizing increased perfusion levels found while in *off* state in SMA and the posterior putamen contralateral to the affected body side, among other areas, compared to the *on* state. Also, abnormal connectivity patterns related to the disease are shown to be balanced by the medication.

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