Cortical hypoperfusion in Parkinson's disease assessed with arterial spin labeling MRI

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Purpose

Cerebral perfusion disturbances have been observed in various neurodegenerative and psychiatric disorders. Cerebral blood flow (CBF), considered one of the most relevant functional parameters, has been assessed mainly using single-photon emission computed tomography (SPECT). CBF can be directly related to neural activity and regional metabolism, due to the phenomenon of neurovascular coupling.

Parkinson disease (PD) is the second most frequent neurodegenerative disorder after Alzheimer disease [1]. It is clinically characterized by a complex motor disorder known as parkinsonism, which is manifested principally by resting tremor, slowness of initial movement, rigidity, and general postural instability. Generally, routine MRI examinations of patients with PD are normal. In PD, the most useful neuroradiologic diagnostic feature has been occipital hypoperfusion [2] and hypometabolism [3]. Occipital hypoperfusion and hypometabolism are thought to be associated with visuoperceptual dysfunction in Parkinson's disease and can be evaluated by using single photon emission computed tomography (SPECT) or positron emission tomography (PET).

Arterial spin labeling (ASL) is a method of measuring the cerebral blood flow (CBF) noninvasively; because it uses arterial blood as an autogenous tracer, no exogenous contrast agents or radioactive tracers are needed. ASL perfusion MRI has been recently introduced as a non-invasive alternative for perfusion measurements in PD. Using quantitative ASL methods, we also previously reported that absolute perfusion decreases in PD in occipital and parietal cortical areas [4].

However, investigations by SPECT and PET have shown that the cerebral hypoperfusion and hypometabolism are not restricted to the occipital and parietal lobes but are found also in the frontal lobes [5], the temporal lobes, and the basal ganglia [5].

In the present study, Quantitative STAR labeling of Arterial Regions (QUASAR) method, a pulsed ASL method developed by Petersen et al[6] has been used to quantify absolute CBF in PD patients and age-matched healthy controls. We hypothesized that perfusion alterations in PD would consist in cortical decreases and that those alterations could be detected using statistical parametric mapping analysis with this technique.

Methods and Materials

Subjects

This study was approved by the institutional review board, and informed consent was obtained from all participants before evaluation. Twenty-eight PD without dementia
patients and 28 normal controls were scanned by using a quantitative ASL method with a 3T magnetic resonance imaging (MRI) unit.

All PD patients were diagnosed by neurologists and fulfilled the United Kingdom Parkinson's Disease Society Brain Bank criteria. All PD patients were taking levodopa at the time of the MRI and clinical examination. Twenty eight normal control subjects were recruited from the general population as control subjects and they were carefully matched in age to the patients. Individuals with any history of hypertension, diabetes mellitus, cardiovascular diseases, stroke, brain tumor, epilepsy, Parkinson's disease, dementia, depression, drug abuse, or head trauma were excluded.

**MR Imaging**

The brains of all patients were examined using a 3T MRI unit (Achieva Quasar Dual; Philips Medical Systems, Best, the Netherlands) and an eight-channel array receiving head coil for sensitivity encoding (SENSE) parallel imaging. ASL was performed by using QUASAR, which combines pulsed STAR labeling of arterial regions (PULSAR) [7] with a Look-Locker strategy for sampling at multiple time points and a repetitive Q2-TIPS-like bolus saturation scheme for clear definition of the arterial blood bolus[8]. The general scan parameters were repetition time (TR) = 4000 ms/echo time (TE) = 22 ms/D inversion time (TI) = 300 ms/TI1 = 40 ms, 13 inversion times (40-3640 ms), matrix size = 64 × 64, slice thickness = 6 mm, gap = 2 mm, 7 slices, field of view (FOV) = 240 × 240 mm, flip angle = 35/11.7, SENSE = 2.5, imaging time = 5 min 52 s. Forty-two pairs of labeled and nonlabeled images were acquired, of which 24 pairs were obtained with crusher gradients (velocity encoding = 4 cm/s) and 12 pairs were obtained without crushers. These 36 pairs were obtained at a flip angle of 35. The other six pairs were acquired at a lower flip angle (11.7) without crushers.

Together with ASL images, high-resolution three-dimensional (3D) T1-weighted whole brain images were obtained using the magnetization-prepared rapid angle gradient echo (MPRAGE) sequence. The imaging parameters were as follows: TR = 8.3 ms, TE = 3.8 ms, TI = 240 ms, flip angle = 8°, SENSE factor = 2, NSA = 1, FOV = 240 mm, matrix size = 240×240, slice thickness = 1 mm, imaging time = 5 min 20 s.

**Image analysis**

The ASL data were extracted and transferred to a personal computer, which was used to map absolute rCBF for each subject. This was done using a dedicated software package[8] developed and provided by Petersen et al. (National Neuroscience Institute, Singapore). Calculated rCBF map were spatially preprocessed using statistical parametric mapping 8 (SPM8) software (Welcome Trust Center for Neuroimaging, London, UK).
First, the rCBF maps were coregistered to the corresponding T1- weighted structural images using mutual information. Further, a unified segmentation method was applied to the 3D T1-weighted images to produce the normalized deformation parameters, and spatial normalization was performed on the coregistered CBF map images using these parameters, thus allowing voxelwise analysis of the rCBF maps in a common stereotaxic space (Fig. 1). The alignment of normalized images was checked by visual inspection. Finally, the spatially normalized rCBF maps were smoothed using an isotropic Gaussian kernel with a 10-mm full width at half-maximum to reduce the noise and residual anatomical differences among the brains.

**Statistical analyses**

The mean values of subject’s ages were compared between the control and PD groups by using t test at a significance level of p<0.05. In order to determine the area of hypoperfusion due to PD, both the rCBF maps were statistically compared between PD and control groups by using SPM by means of the two-sample t test at a voxel level significance threshold of p<0.05 corrected for multiple comparisons.

**Images for this section:**

<table>
<thead>
<tr>
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<th>Control (n=28)</th>
<th>PD (n=28)</th>
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<tr>
<td><strong>Table 1</strong>: Table 1. Demographic characteristics of subjects. Note: PD, Parkinson disease; SD, standard deviation.</td>
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**Fig. 1:** Overview of data processing steps used for the voxel based analysis of the rCBF map. First, the rCBF maps were coregistered to the corresponding T1-weighted structural images using mutual information. Further, a unified segmentation method was applied to the 3D T1-weighted images to produce the normalized deformation parameters, and spatial normalization was performed on the coregistered CBF map images using these parameters, thus allowing voxel-based analysis of the rCBF maps in a common stereotaxic space (Fig. 1). The alignment of normalized images was checked by visual inspection. Finally, the spatially normalized rCBF maps were smoothed using an isotropic Gaussian kernel with a 10-mm full width at half-maximum to reduce the noise and residual anatomical differences among the brains.
Results

No significant age difference was seen between the control (mean ± SD = 66.1 ± 6.7 years) and AD (mean ± SD = 73.5 ± 9.6 years) groups (p>0.05).

SPM analyses revealed focal hypoperfusion in areas over the bilateral precuneus in PD patients in comparison with control subjects (p<0.05, corrected) (Fig. 2, Table 1).

Images for this section:

Fig. 2: Fig. 1. Maximum intensity projection (MIP) of SPM results (P

<table>
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<tr>
<th>Comparison</th>
<th>Brain region</th>
<th>Broadman area</th>
<th>Talairach coordinates *</th>
<th>t-value</th>
<th>P&lt;0.05 corrected</th>
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Table 2: Table 2. Regions of PD-related hypoperfusion defined by statistical parametric mapping (SPM) analysis. Peak locations are reported in the Talairach coordinates (x, y, z) Talairach coordinates *: Lancaster JL, et al. Human Brain Mapping 2000.
Conclusion

discussion

The major finding of this study is that ASL can be used to detect regional hypoperfusion in the posterior cortex in patients with PD. The areas of cerebral hypoperfusion agreed satisfactorily with the results of our previous ASL study using the ROI method [4 on page ] as well as past reports of SPECT [2 on page ] and PET on page on page .

The underlying mechanism of the regional hypoperfusion in the posterior cortex of PD remains controversial. The occipital cortices in PD generally have few neuropathological lesions such as neuronal loss or presence of Lewy bodies [9 on page ]; in contrast, the amygdala contains significant Lewy body pathologies and neuronal loss, which are related to visual hallucinations [9 on page , 10 on page ]. Because the amygdala has reciprocal connections with the primary visual and visual association cortices through other vision-related cortical regions on page , occipital hypoperfusion in PD could be attributed to diaschisis of the amygdala. It is also possible that posterior hypoperfusion causes visuoperceptual dysfunction in PD. This notion is supported by a previous study showing that the rCBF in the right visual association area of PD patients, evaluated by SPECT, was positively correlated with the Raven's Coloured Progressive Matrices (RCPM) score, suggesting impaired cortical visual processing [2 on page ]. In a previous report, the pattern electroretinogram showed a reduction in amplitude for the occipital lobe in PD patients on page . The abnormal pattern electroretinogram is thought to be attributable to a reduced number of dopaminergic neurons in the retina, which in turn is thought to be responsible for the occipital hypoperfusion in PD.

ASL has several benefits compared with SPECT and PET, which are commonly used for clinical and research imaging studies of neurodegenerative diseases. ASL is completely noninvasive and free from exposure to ionizing radiation, contrast agents, or radioactive isotopes. Therefore, ASL is a very useful method for studying perfusion in healthy individuals or in patients who require repetitive follow-up studies. The QUASAR technique that we used is attractive for longitudinal studies of CBF in healthy and diseased individuals, or as a surrogate marker of metabolism [8 on page ]. Longitudinal repetitive QUASAR might also be useful to monitor the effect of levodopa, a complex therapy. Xe-enhanced CT showed increased rCBF in the striatum after L-dopa treatment on page . L-dopa also reduced rCBF in the striatum contralateral to the symptomatic limbs, but rCBF increased in the same regions when patients had adverse reactions such as hyperkinesias and on/off symptoms on page . QUASAR might, therefore, also be used to predict the emergence of side effects in PD.

conclusion
It is possible to confirm the areas of cerebral hypoperfusion in PD patients with the ASL method using a whole brain voxel based analysis. This method can be used as a non-invasive tool for assessing treatment effects and monitoring disease progression in PD.

**References**


**Personal Information**