# Abnormal Iron Content and Distribution in the Basal Ganglia in Parkinson's Disease: A Susceptibility-Weighted Imaging Study

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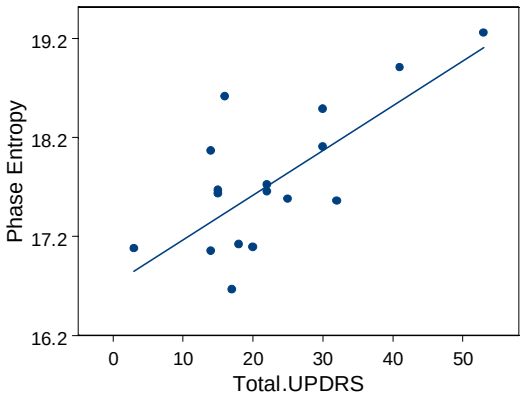
**Background**: Finding a robust MRI marker for Parkinson's disease (PD) is extremely important because of the difficulty of correctly diagnosing PD, especially at an early stage. Several MRI relaxation studies reported abnormal R2 and R2* values in PD in agreement with histopathological findings of increased iron deposition in the brain's nigrostriatal system. However, substantial problems remain to consistently and accurately quantify brain iron using MRI. An alternative MRI technique to measure brain iron is susceptibility-weighted imaging (SWI), which exploits the effect that subtle magnetic susceptibility differences alter the phase of the MRI signal. One advantage of SWI is that the phase should decrease linearly with brain iron concentration in contrast to R2 and R2* which show nonlinear changes (1). Moreover, since the phase is independent of the signal magnitude, phase is also more robust in the presence of noise (1). The aim of this study was to explore if SWI could be a useful marker for PD that also tightly correlates with severity of the clinical symptoms. Specifically, we hypothesized that PD is associated with decreasing SWI phase in the movement controlling network, including the substantia nigra (SN), subthalamic nucleus (STN), globus pallidus (GP), putamen (PUT), and caudate nucleus (CAU), and furthermore that phase correlates with disease severity.

**Methods:** Eighteen male patients diagnosed with mild to moderate PD as measured using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III motor score in the off-medication state (mean age 65 ± 6 years, UPDRS range from 3 to 52) and 23 male healthy controls of comparable age volunteered for this MRI study at 4 Tesla. All subjects received a comprehensive neurological evaluation to establish presence or absence of PD. The scan protocol included 1 $mm^3$ T1 MPRAGE and FLAIR as well as 0.5 x 0.6 x 1.2 mm SWI (TR/TE=32/25 ms, courtesy of Dr. E.M. Haacke). The structural MRIs were co-registered to each other. The regions of SN, STN, GP, PUT, and CAU were identified by a combination of automated labeling using nonlinear warping of the images to a brain atlas with Freesurfer software (http://surfer.nmr.mgh.harvard.edu/) and manual refinement by experienced readers blinded to all clinical information. The phase images of SWI were high-pass-filtered to remove low-spatial-frequency components. The final phase images appear on a scale from 0 to 4096, corresponding to $-\pi$ to $+\pi$. To evaluate the regional dispersion of the phase, we evaluated the 2nd order coincidences (co-occurrences) between pairs of phase values within the traced anatomical regions. For a region with a uniform phase distribution, the co-occurrences lie close to the diagonal of the co-occurrence matrix, whereas they appear off-diagonal for a heterogeneous distribution. We quantified co-occurrences by computing the entropy of the co-occurrence matrix (2), where greater entropy reflects increasing numbers of off-diagonal occurrences, equivalent to greater regional phase dispersion. The effect of PD on phase and phase entropy was statistically evaluated using ANOVA with age as co-factor. Correlations between UPDRS motor scores and phase or entropy were evaluated using Spearman Rank tests ($\alpha$=0.05).

| | Mean Phase | | |
|---|---|---|---|
| **Region** | **PD** | **Control** | **p- value** |
| Substantia Nigra | | | |
| Right | 2056 ± 139 | 2122 ± 184 | n.s. |
| Left | 2076 ± 135 | 2144 ± 219 | n.s. |
| Subthalamic Nucleus | | | |
| Right | 2077 ± 87 | 2108 ± 64 | n.s. |
| Left | 2056 ± 139 | 2173 ± 116 | 0.01 |
| Globus Pallidus | | | |
| Right | 2072 ± 28 | 2084 ± 39 | n.s. |
| Left | 2065 ± 26 | 2087 ± 48 | n.s. |
| Putamen | | | |
| Right | 2065 ± 18 | 2084 ± 27 | 0.01 |
| Left | 2056 ± 25 | 2100 ± 35 | n.s. |
| Caudate Nucleus | | | |
| Right | 2087 ± 21 | 2103 ± 25 | 0.02 |
| Left | 2093 ± 20 | 2113 ± 33 | 0.03 |

**Results**: SWI phase values (+/- SD) in PD and controls are listed in the table by regions. The most significant phase reductions, implying increased iron, occurred in the left STN (p = 0.01), right PUT (p = 0.01), and bilaterally in the CAU (p = 0.03), whereas differences in the SN and GP were not significant after accounting for age. The phase in the PUT significantly correlated with PD severity (left: p = 0.002; right: p = 0.01), whereas for STN and CAU these correlations were only a trend. Phase entropy was not significantly associated with PD in any region. However, phase entropy increased with increasing PD severity (higher UPDRS motor scores) in the CAU (p = 0.01), PUT (p = 0.007), and STN (p = 0.003), as depicted in the figure for the STN.

**PD Severity in Terms of UPDRS and SWI Phase Entropy of Subthalamic Nucleus**




**Conclusions:** The findings support our a-priori hypotheses. The findings taken together suggest that SWI phase and entropy have potential value as markers for an objective diagnosis of PD, assessment of disease severity, as well as for response to disease-modifying interventions.

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**References:** (1) Haacke E.M. et al. Magnetic resonance imaging: Physical principles and sequence design. John Wiley & Sons, 1999; (2) Hadjidemetriou S. et al. Restoration of MRI data for field nonuniformities using high order neighborhood statistics. SPIE conference on medical imaging, San Diego, 2007.