Voxel-Based DTI Analysis of White Matter Alterations in Parkinson's Disease

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Introduction

As new potentially disease-modifying drugs for Parkinson's disease (PD) are being developed, there is increasing need for imaging markers to accurately diagnose PD and monitor progression. MRI-based techniques could play a particular role for drug studies of PD, because MRI measures do not rely on receptor binding, unlike radiotracer imaging with PET and SPECT [1-3]. In the present study, diffusion tensor imaging (DTI) [4] was applied to assess microscopic alterations of white matter (WM) tracts in PD. Specifically, we hypothesized that PD would be associated with fractional anisotropy (FA) reductions in brain regions known to be associated with PD, such as the substantia nigra (SN). Furthermore, we predicted that greater FA reductions in these regions would correlate with increased severity of PD symptoms.

Methods

Fourteen patients diagnosed with mild-moderate PD as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) [5] (all males, age=68±8 yrs, UPDRS off-medication motor score=26.3±12.2), and 20 healthy male controls matched for age and education volunteered for this MRI study on a 4T scanner (Siemens). The scan protocol included DTI (EPI: TR/TE= 6s/77ms, voxel=2x2x3mm, GRAPPA=2, direction=6 at b=800s/mm^2, 4 repetitions), FLAIR (TR/TE/TI= 5000/355/2030ms), and T1 MPRAGE (TR/TE/TI= 2300/3.5/950 ms) images. Susceptibility-weighted images (SWI) were also collected to measure brain iron deposition [6]. All subjects received a comprehensive neurological evaluation to establish presence or absence of PD. Severity of PD was tested "off medication." Subjects were excluded if they had pathological diagnosis of any other neurological disorder, history of central nervous system infection, seizures, significant cognitive impairment (defined as MMSE < 26), or history of alcohol and/or drug abuse. MRI data showing strong motion artifact or WM lesions in raw images were also excluded from analysis. FSL (http://www.fmrib.ox.ac.uk/fsl/) was used for eddy current correction and DTI preprocessing offline. The tract-based spatial statistics (TBSS) technique [7] was implemented for DTI processing. One normal subject (age=65 yrs) was chosen as the "target" on which the FA maps of all subjects were nonlinearly co-registered, and non-FA DTI data were transformed by following the same pipeline. Aligned DTI data were then interpolated to 1x1x1mm resolution and spatially normalized into a T1 template in the Talairach space. A non-parametric permutation t-test was performed to provide the group comparisons with interpretable p values. An orthogonal linear regression algorithm was applied to estimate and remove age-related effects on a voxelwise basis. Pearson's cross-correlation coefficients between the DTI and UPDRS measurements were estimated for each voxel. No smoothing or clustering techniques were applied.

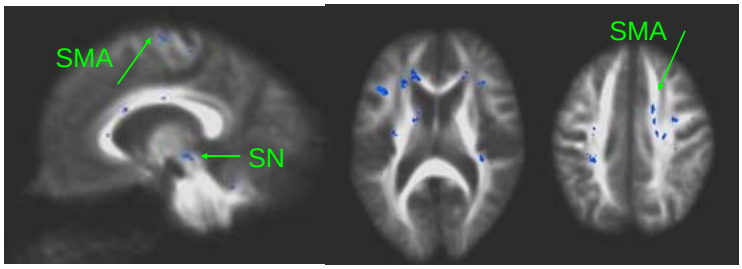

Fig 1: Abnormal DTI in PD compared to Controls

Results

Group comparisons: In Fig.1, reduced FA ($p<0.01$) in PD compared to normal controls is illustrated as blue clusters, superimposed on the mean FA map in normalized space. The DTI abnormalities in PD were primarily seen in proximity to the substantia nigra (SN), posterior striatum, as well as in frontal white matter and along projection fibers to the supplementary motor areas (SMA).

Correlation results: In the PD patient group, negative correlations ($p<0.01$) between the FA and UPDRS scores were found close to the SN as shown in Fig.2 (a). Moreover, the phase values of SWI in SN, presumably reflecting the regional iron levels, also correlated ($p<0.01$) with the FA in the WM tracts and projections to the SMA as illustrated in Fig.2 (b).

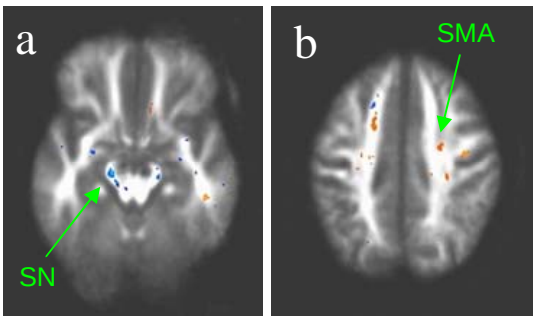

Fig.2: Correlations results in the PD patients

Discussions

Voxel-based DTI analysis revealed widespread decrease of FA in PD, primarily seen in WM close to the SN, as hypothesized, as well as in the posterior striatum, frontal lobe, and projections to the SMA, potentially indicating axonal degradation of neuronal pathways that play a role in movement planning and initiation [8]. Further support for an association between DTI alterations and PD comes from correlation analyses showing that the DTI abnormities in SN increased with the PD severity, and that the WM integrity in SMA is associated with changes of the iron level in SN. Taken together, these results suggest that DTI may help improve diagnosis and staging of PD.

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