Detecting Alterations in Substantia Nigra in Parkinson's Disease

Xiangchuan Chen[1], Daniel Huddleston[2,3], Jason Langley[1], and Xiaoping Hu[1]

[1]*Biomedical Imaging Technology Center, Emory University, Atlanta, GA, United States,* [2]*Kaiser Permanente Center for Health Research Southeast, Atlanta, GA, United States,* [3]*Department of Neurology, Emory University, Atlanta, GA, United States*

Introduction

Magnetic resonance imaging (MRI) has been used to detect the alterations in the substantia nigra (SN) in Parkinson's disease (PD). For quantitative analysis of the effects of PD, the SN was usually segmented manually in previous studies. However, possible inaccuracy and inconsistency in delineating the SN may confound the results from the manual approach, leading to negative reports [1]. In this study, a semi-automated method was applied to investigate changes in signal intensity and volume of the SN associated with PD. Contributions of changes in these MRI measures to the behavioral outcomes of PD were also examined.

Methods

Eighteen subjects (including 8 controls and 10 PD patients) participated in this study. MRI data were obtained on a 3.0 Tesla Siemens Magnetom TRIO scanner (Siemens Medical Solutions, Malvern, PA) using a 2D gradient echo sequence with magnetization transfer contrast (MTC) preparation pulse. The sequence parameters were as follows: TR = 335 ms, TE = 2.68 ms, 15 slices, slice thickness = 3.0 mm, FOV = 200 mm, matrix size = 512 × 416, 1 average, 7 measurements, flip angle = 40º, and bandwidth = 470 Hz/Px. Imaging data were analyzed with AFNI [2]. First, all images from the 7 measurements were registered to the first one, and then averaged. In the averaged images, ROI for the SN was defined by following these steps: (1) Reference ROIs (circles with diameter in 6 mm) were placed in the tissues surrounding the SN for 4 consecutive slices, starting from the bottom one which barely showed the SN. Each slice had 2 ROIs, flanking both the left and right SNs (Fig. 1B-1). (2) Voxel intensities of these ROIs were verified as approximately normally distributed (Fig. 1B-2). After that, mean (I_{mean}) and standard deviation (I_{sd}) of signal intensity were calculated for the reference ROIs. (3) After calculating $I_{diff} = I_{voxel} - I_{mean} - 3 \times I_{sd}$ for each voxel, a binary map (Fig. 1B-3) was generated in this way: if $I_{diff} > 0$, then $I_{voxel} = 1$; otherwise, $I_{voxel} = 0$. (4) ROIs for the SN were defined on the binary map, which did not require an accurate delineation of the SN (Fig. 1B-4). (5) The contrast to noise ratio (CNR) was calculated as: $CNR = (I_{voxel} - I_{mean}) / I_{sd}$. Mean CNR and number of voxels (volume) were then obtained for the SN. Further statistical analysis was performed with SPSS.

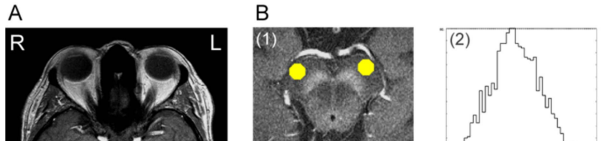

Fig. 1. **A**. Image from a control subject showing the SN. R: right hemisphere, L: left hemisphere. **B**. Procedure for defining ROI for the SN.

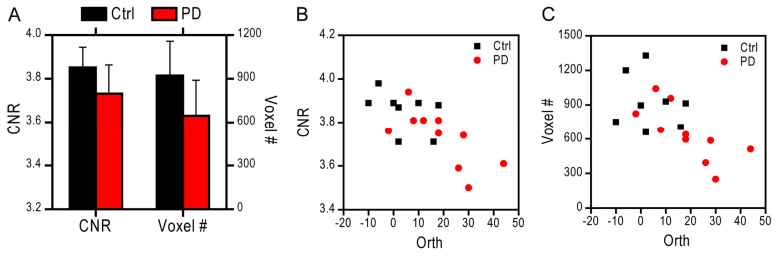

Fig. 2. **A**. Group differences in CNR and number of voxels in the SN. Ctrl: control group. Error bar: 1 SD. **B**. Correlation between CNR and Orth. **C**. Correlation between number of voxels and Orth.

Results

Multivariate analysis showed that both CNR and volume of the SN were significantly different between the control and PD groups (Fig. 2A. CNR: $F_{1,16} = 4.795$, $p = 0.044$; volume: $F_{1,16} = 5.855$, $p = 0.028$). The two MRI measures were significantly correlated with the orthostatic blood pressure drop (Orth), a phenotypic measure relevant to PD (Fig. 2, B and C. Pearson's correlation, CNR: $r = -0.725$, $p = 0.001$; volume: $r = -0.661$, $p = 0.003$). When controlling the group factor with partial correlation, the MRI-Orth correlations were still significant (CNR: $r' = -0.631$, $p = 0.007$; volume: $r' = -0.529$, $p = 0.029$). In addition, univariate analysis showed that the Orth was significantly different between the control and PD groups ($F_{1,16} = 6.618$, $p = 0.020$). To examine the role of SN in PD related changes in Orth, the two MRI measures were set as covariates in the univariate analysis. The result showed that the group difference in Orth was not significant ($F_{1,16} = 1.410$, $p = 0.255$).

Discussion and Conclusion

Brain tissues with neuromelanin (e.g., the SN) are sensitive to the MTC effect (Fig. 1A). As the reference ROIs were placed in the tissues surrounding the SN and their intensity distribution was approximately normal, we assumed that these ROIs represented the background tissues not showing neuromelanin related signal. Voxels whose intensities are above the $I_{mean} + 3 \times I_{sd}$ are significantly different from the surrounding voxels, and based on this intensity difference are assumed to arise from neuronal tissue containing neuromelanin. This assumption is supported by the binary map shown in Fig. 1B-3 where voxels in the SN are highlighted, but the surrounding tissues of the brain stem are not. In this case, the mean CNR and number of voxels may correspond to the amount of neuromelanin present and number of neurons which contain neuromelanin. As predicted, these two MRI measures showed significant differences between the PD and control groups (Fig. 2A), supporting the idea that loss of neuromelanin containing neurons, as occurs in PD, can be measured with this MRI approach. The pathophysiology of orthostatic hypotension (OH) in PD is not fully understood. The negative correlation between the SN integrity as assessed by our MRI measures with degree of orthostatic hypotension (Fig. 2, B and C) is an interesting finding warranting further investigation, as it implicates the role of SN in the pathophysiology of OH in PD.

Acknowledgements This work was supported by The William N. and Bernice E. Bumpus Foundation Innovation Award (Huddleston, BFIA 2011.3), the Emory Udall Center for Excellence in Parkinson's Disease Research Pilot Award (P50-NS071669), and the Biomedical Imaging Technology Center of Emory University.

References

1. Lehericy S, et al. Magnetic Resonance Imaging of the Substantia Nigra in Parkinson's Disease. Movement disorders. 2012, 27 (7): 822-830.
2. http://afni.nimh.nih.gov/afni/