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Subthalamic and red nucleus volumes in patients with Parkinson's disease: Do they change with disease progression?☆

Mustafa Efkan Colpan [a,b], Konstantin V. Slavin [b,*]

[a] Department of Neurosurgery, University of Minnesota, Minneapolis, MN 55455, USA
[b] Department of Neurosurgery, University of Illinois at Chicago, 912 South Wood Street, M/C 799, Chicago, IL 60612, USA

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ABSTRACT

Objective: To examine a possible correlation between disease progression and the volumes of the subthalamic nucleus (STN) and red nucleus (RN) in patients with Parkinson disease (PD).
Methods: Twelve patients with PD (mean time since diagnosis 10.8 ± 2.9 years) and age-matched 12 normal control subjects were enrolled. The volumes of the STN and RN were measured using 3-dimensional volume reconstructions of stereotactic magnetic resonance images.
Results: The PD and control groups were similar with regard to age and gender. The STN volume was 0.13 ± 0.01 cm^3 (mean ± SD) in PD patients and 0.27 ± 0.01 cm^3 in controls ($P < .001$). The RN volume was 0.31 ± 0.02 cm^3 in PD patients and 0.21 ± 0.02 cm^3 in controls ($P = .002$). Positive correlations of RN volume with time since diagnosis ($P = .004$) and disease stage ($P = .01$) were observed. On average, the STN volumes were 48% smaller and RN volumes 32% larger in PD patients than in control subjects; the volumes of the two nuclei were negatively correlated ($r = -0.46$; $P = .03$).
Conclusions: Our results suggest that advanced disease stage and longer disease duration are associated with increased RN volume. STN volume was significantly smaller in Parkinson group. These findings may be useful in estimating disease status and rate of progression, and may also have implications for surgical treatment. Larger studies are needed to validate these results and determine their usefulness.

1. Introduction

Parkinson disease (PD) is a neurodegenerative disease that usually occurs late in life, affecting 1.5–2% of the population older than 60 years [1,2]. The etiology of PD is still not completely understood, but it appears to be associated with several factors such as age, genetics, and environment [1,2]. Age-related attrition and death of dopamine-producing neurons in the substantia nigra (SN) has been suggested as a major etiopathological cause of PD; studies show that neuronal loss is approximately 50–60% at the time of symptom onset [1,3]; The progressive worsening of symptoms is believed to be the result of degeneration of dopaminergic neurons in the SN [3–7]. Early detection and monitoring of the neurodegenerative changes in PD can help clarify the disease and its progress. Objective radiological measurements that can aid in assessing prognosis and the effects of treatment would also be valuable.

Currently, various imaging techniques such as single photon emission computerized tomography and positron emission tomography [3] are used to detect neurodegenerative changes in PD. These two techniques, however, have some drawbacks: both of them can detect the striatal dopamine changes, but other subthalamic structures that may also have important roles in PD are not visualized at all. In addition, although both techniques are sensitive and useful for PD staging and follow-up, they are relatively expensive.

Magnetic resonance imaging (MRI) technology provides a widely available and relatively inexpensive means of visualizing the key neuroanatomic structures in patients with PD, allowing evaluation of some of the neurodegenerative and morphological changes in PD [4,6,8–11]. Such changes detected by MRI are considered by some to be important in evaluating the disease stage [4,5,8,9]. Conventional MRI techniques are limited in their ability to show microstructural changes in patients with PD, but high-resolution 3 Tesla (3 T) MRI may provide detailed information about structural changes [12]. Increasingly, 3 T voxel-based volumetric techniques that can detect subtle structural changes are being used in diagnosing PD and estimating disease severity. Only a limited number of MRI-based volumetric studies of morphometric changes in the brain in cases of PD have been reported in the literature [4–8,10,11,13–17]. Most of these focused on dopamine-related anatomical structures such as the SN, putamen,

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* Corresponding author. Tel.: +1 312 996 4842; fax: +1 312 996 9018.
E-mail address: kslavin@uic.edu (K.V. Slavin).

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caudate nucleus (CN), and striatum. However, there are few reports evaluating other possible structural changes in the brain. Because the subthalamic nucleus (STN) is deeply involved in PD, it is a target of various stereotactic surgical interventions, primarily deep brain stimulation. The red nucleus (RN) is one of the landmarks used for surgical targeting and may also be involved in the pathogenesis of PD. To date, the volumes of the STN and RN in PD have not been systematically assessed. In this study, we used stereotactic 3T MRI images to compare volume changes in the STN and RN in patients diagnosed with PD. Age and gender matched normal control subjects were used to rule out STN and RN nucleus volumes changes in PD patients.

2. Material and methods

This retrospective study was conducted at University of Illinois at Chicago-Medical Center. PD diagnose was made based on presence of clinical signs; bradykinesia, rigidity, resting tremor, and postural instability. Patients involved in this study were followed by the Neurology service and dopamine response was recorded. Medication resistant PD patients were referred to Neurosurgery service for deep brain stimulation treatment. Routine CT scan and MRI scan was performed to rule out other pathological processes. Twelve patients (7 of them male) who received stereotactic deep brain stimulation for PD and 12 age-matched normal control subjects (7 of them male) were involved in this study. The mean age was 61.5 ± 12.9 years (mean ± SD). Pre-procedural MRI images were obtained and used in this research for PD patients. The Leksell stereotactic frame type G (Elekta Instruments, Atlanta, GA) was applied to each patient in Parkinson group immediately before MRI with the frame balanced using the ear bars. The MRI localizer was attached to the frame for coordinate calculation. Scanning was performed using a 3 T Signa MR scanner (Signa 3T94 VHi; GE Healthcare, Milwaukee, WI) according to the following protocol for Parkinson patients and normal subjects: A rapid 3D image localizer covering the entire brain was used to prescribe volumes of high-resolution, contiguous, T2-weighted, fast spin-echo imaging (section thickness, 1.5 mm; matrix size, 512 × 512; field of view, 676 cm^2 (26 cm × 26 cm); TR, 4600–6200 milliseconds; TE, 95–108 milliseconds; acquisition time, <5 min). TR values varied for different patients and for each of 3 planes, but all other imaging parameters remained constant throughout the studies. The images were acquired in axial, sagittal, and coronal planes through the region of the midbrain and basal ganglia. Special attention was paid to the SN and RN. The MRI data were then transferred into a computer (Dell XPS M1710 2.0 GHz, Round Rock, TX) for 3D image reconstruction and volume measurement of the STN and RN. Right and left nucleus volumes were measured separately. Data including patient's age, gender, time since diagnosis (disease duration), Hoehn–Yahr stage, and STN and RN volumes were collected and statistically evaluated. The dorsal–ventral diameter of the STN in each individual in the PD group was measured using 2 methods: (1) microelectrode recording data obtained during electrode placement for deep brain stimulation, and (2) MRI data analyses. Measurements from the microelectrode data were compared with the radiological measurements to check the accuracy of the radiological measurements.

2.1. Image analysis and volume reconstruction

Complete sets of images were obtained for all 24 cases. The imaging window's intensity was adjusted to allow maximum visualization of the STN and RN, and voxel-based hand tracing was used to determine their boundaries. Image processing was performed using 3-D Slicer software, v. 2.6 (Brigham and Women's Hospital, Inc., Boston, MA), which permits the user to view images in the axial, sagittal, and coronal planes. The software magnifies the region of interest, allowing the user to precisely define the boundary of an anatomical structure based on the voxel change. The entire boundary of the structure is chosen in each slice using voxel-based hand tracing; the software can then calculate the structure's volume. This approach was used to determine the volume of the STN and RN in each patient (Fig. 1) and then to calculate the volume of each nucleus after 3D reconstruction (Fig. 2).

The validity and variability of volume measurements were tested by repeated measurements of the STN and RN in each subject to reduce variability and maximize the accuracy of interpretation for this single study. Observers had no information about the patients during image analysis. A total of 192 measurements of the STN and RN were done. To reduce inter-observer variability, 2 different trained observers individually determined the shape of the STN and RN using 3T MR images and achieved consensus. The volume measurements were repeated twice by each observer to maximize accuracy of interpretation. There was no statistical difference between inter-observer measurements of STN and RN volumes ($p = .09$). Reproducibility was excellent for both STN and RN volume measurements.

2.2. Statistical analysis

Student's t test was used to compare STN and RN volumes of the PD and control subjects. Right and left nucleus volumes were compared using paired t tests. Correlation between the two groups was assessed using the Pearson correlation test. Nonparametric data analysis was performed using Mann–Whitney U test. Tests were performed using JMP, The Statistical Discovery Software (SAS Institute, Inc). Significance was set at $P < .05$.

3. Results

There were no statistically significant differences between PD and control subjects based on age or gender ($P = 1$). The mean time since the Parkinson's disease diagnosis (disease duration) was 10.8 ± 2.9 years (mean ± SD). There was no correlation between age and disease duration ($r = 0.03$, $P = .8$), or between age and Hoehn–Yahr stage ($P = .3$); there was, however, a statistically significant correlation between disease duration and Hoehn–Yahr stage ($P = .002$).

The STN volume was 0.13 ± 0.01 cm^3 (mean ± SD) in patients with PD and 0.27 ± 0.01 cm^3 in control subjects; the difference between the two groups was statistically significant ($P < .001$; Fig. 3). The volume of the STN was 48% smaller on average in the patients with PD compared with the control patients. There was no statistically significant difference between disease duration and STN volume ($r = -0.17$, $P = .5$). Correlation between STN volume and Hoehn–Yahr stage was not statistically significant ($P = .7$)

Microelectrode recordings were used to validate radiographic size of the STN in at least one direction in PD group, allowing us to directly compare radiological and electrophysiological measurements of the STN.

The dorsal–ventral diameter of the STN was 6.6 ± 1.6 mm (mean ± SD) based on microrecording data and 6.5 ± 1.7 mm according to radiological data; this difference was not statistically significant ($P = .6$). Microelectrode data was not obtained and analyzed in non-PD group because these patients did not have DBS electrode placement.

The volume of the RN was 0.31 ± 0.02 cm^3 (mean ± SD) in patients with PD and 0.21 ± 0.02 cm^3 in control subjects. This difference was statistically significant ($P = .008$; Fig. 4). The RN volume in the control patients was 32% larger on average than that in the PD group. Also, a significant positive correlation was noted between PD duration and RN volume ($r = 0.7$, $P = .004$) and between RN volume and Hoehn–Yahr stage ($P = .01$).

The volumes of the STN and RN themselves were negatively correlated ($r = -0.46$, $P = .03$). Neither correlated with patients' age ($r = 0.00$, $P = .9$ for STN volume; $r = 0.04$, $P = .8$ for RN volume). The difference in STN and RN volumes on the right and left sides was analyzed using paired t tests, which showed no significant difference ($P = .8$ for STN volume; $P = .7$ for RN volume), indicating that there was no correlation between nuclear volumes and the side of tremor dominance. The combined volumes of the STN and RN in PD and control patients were also compared, but showed no statistically significant difference ($P = .2$; Fig. 5).

When TR and TE value variability was tested between PD and non-PD subjects, there was no statistical difference between PD and non-PD patient group ($p = .07$). TR and TE value variability did not correlate with measured volumes of STN and RN, as well as the stage of the PD and disease duration, which confirmed that the TR and TE values did not affect data collection and analysis ($r = 0.01$, $P = .8$ for STN volume; $r = 0.03$, $P = .7$ for RN, $r = 0.02$, $P = .6$ for stage of the PD, $r = 0.04$, $P = .7$ for disease duration).

4. Discussion

Parkinson disease is a neurodegenerative condition associated with the death of neurons and neuroglial cells in the brain [1]. It is thought that the death of dopamine-producing neurons is primarily responsible for the neurotransmitter imbalance seen in