SHORT REPORT

Parkinson's disease: a novel MRI method for determining structural changes in the substantia nigra

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Abstract

Objectives—To use MRI in a novel way to image and quantify the changes occurring in the substantia nigra in Parkinson's disease.

Methods—Six patients with idiopathic Parkinson's disease were compared with six age matched control subjects. The subjects were imaged using a combination of pulse sequences hypothesised to be sensitive to cell loss.

Results—The images showed patterns of change in patients with Parkinson's disease. Highly significant differences between the patients and control population were found ($p < 0.001$).

Conclusions—This methodology suggests the possibility of detecting presymptomatic disease in those judged to be at risk, and also in confirming the diagnosis in patients with early disease. Furthermore, the technique seems to hold promise as a means for staging the disease, and possibly differentiating other forms of parkinsonism.

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Parkinson's disease involves the degeneration of neurons in the substantia nigra (mainly in the pars compacta). About 5% to 10% of all cases may be familial and inherited in an autosomal dominant pattern.¹ In the era of potential neuroprotective therapies for this disorder, the earliest diagnosis and perhaps even the detection of presymptomatic disease is highly desirable. Moreover, a simple non-invasive method for staging the disease is of importance in evaluating the results of neuroprotective interventions.

The possibility of detecting structural changes in the substantia nigra pars compacta (SN_c) using conventional MRI has the advantage of a simple and readily available, relatively inexpensive modality for diagnosing and studying the disease. Several previous publications have employed various MRI strategies to demonstrate nigral changes using MRI. These fall essentially into two categories.

The first involves using pulse sequences sensitive to the increased iron deposition in the substantia nigra that is seen in Parkinson's disease.^{2–4} Iron is deposited in the nigra in normal aging, however, which may create difficulties in separating patients from controls, particularly in the elderly population.⁴ The second approach involves measurement of the width of the pars compacta of the substantia nigra^{5–7} using T2 weighted images. Although thinning of this structure does occur in Parkinson's disease, there may be considerable variation of the thickness of this structure in patients and even in normal subjects. Moreover, the width itself may be difficult to define with precision.

At the present time, the most sensitive imaging techniques for the detection of Parkinson's disease are positron emission tomography (PET)^{8–11} and single photon emission computed tomography (SPECT).¹² Both techniques measure changes in the striatum but not in the substantia nigra itself. PET has traditionally used a label of striatal uptake of DOPA, whereas SPECT utilises a tracer (β -CIT), which is a label for dopamine transporters in the striatum.

We present here a novel MRI technique for imaging the structural changes in the substantia nigra itself, using a combination of two pulse sequences, and taking advantage of the known geometric variation in the degeneration of this nucleus (from lateral to medial and rostral to caudal).¹³ The sequences are both of the inversion recovery type, one designed to suppress white matter and the other to suppress grey matter. By combining these pulse sequences we have been able to demonstrate changes in the substantia nigra in even the earliest cases of symptomatic disease, demonstrating that these cases are quite distinct from normal subjects. This suggests the possibility of detecting presymptomatic disease. Furthermore, our results also suggest the possibility of staging the disease.

Patients and methods

SUBJECTS

Six patients in various stages of the disease (Hoehn and Yahr stages I to III, ages 38 to 70, mean age 58) were scanned. All patients were taking their usual antiParkinson medication at

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(A) The upper row shows upper and lower ratio images of a normal subject. Note that the substantia nigra pars compacta (SN_C) reaches the edge of the peduncle in the upper slice and becomes smaller in the lower slice. The substantia nigra pars reticulata (SN_R) is also seen in the upper slice, extending into the corticospinal tracts anteriorly. The colour bar shows the pseudocolour used for display and ranges from 0 to 255 (bottom to top). The ratio image of an early case shows, in the upper slice, thinning and loss of signal in the lateral part of the SN_C . Note that the lower slice shows islands of destruction. The ratio images of an advanced stage show considerable signal loss in the SN_C in both upper and lower slices. In addition, the SN_C is essentially reduced to two rings of preservation in the lower slice. (B) The graph is a plot of DU and DL (see text) for patients and controls. Note that the controls (green dots) cluster at the origin and that the patients (red dots) are distributed along a diagonal path in correspondence with Hoehn and Yahr disease stage (indicated by a Roman numeral next to each dot).

the time of the scan. Six normal subjects (ages 37 to 72, mean age 56) were also scanned using the same pulse sequences. None of the control subjects had any known relatives with Parkin-

son's disease, and all were examined and questioned by an experienced neurologist to rule out signs and symptoms suggestive of early Parkinson's disease.

METHODS

Scanning was performed using a Siemens 1.5 T Vision system. To avoid head motion artefacts, all subjects were immobilised using a chinstrap, which had proved invaluable in a prior functional MRI study,¹⁴ where head immobilisation was perhaps even more crucial. White matter suppressed (WMS) images were obtained with the following pulse sequence: inversion recovery (modulus), TE=20 ms, TI=250 ms, and TR=1450 ms. Grey matter suppressed (GMS) images were obtained with a similar inversion recovery sequence but with the following parameters: TE=20 ms, TI=420 ms, and TR=2000 ms. The field of view was 200 mm and the image matrix was 256×256 (NEX=2). Slice thickness was 3 mm and the gap was 0.2 mm. Four axial slices were obtained in each case, with slice selection being obtained from a sagittal scout image of the brain stem. Slices were chosen perpendicular to the longitudinal axis of the midbrain. Using the WMS image it was ascertained that the substantia nigra was visualised in each of the four slices. By selecting the middle two slices for analysis we thereby ensured that there was no contamination by volume averaging.

Changes in signal were seen in both WMS and GMS images, the GMS signal increasing in areas of degeneration, whereas the WMS signal decreased in the same areas. Therefore, for each of the selected slices, a ratio of WMS to GMS images was generated, this ratio image providing increased sensitivity compared with either the WMS or GMS alone. Nevertheless changes in the WMS images were less substantial than those seen in the GMS images, so that the WMS image served to define the boundaries of the substantia nigra, whereas the GMS image (in patients) did not. A blinded observer then performed a region of interest (ROI) analysis, with regions of about 200 pixels being placed within the boundaries of the substantia nigra defined in both lateral and medial segments of the WMS image. These same regions were then placed on the ratio images and average pixel values for the lateral and medial segments computed. Because of uncertainties in absolute signal levels it is common practice in quantifying MRI to take ratios within each subject to make valid a comparison between subjects. Therefore, for each subject the ratio *R* of lateral to medial values was defined, both for the upper slice (*RU*) and for the lower slice (*RL*). Furthermore, these values were divided into a ratio for the left *SN_C*, denoted by subscript "l", and the right *SN_C*, denoted by subscript "r". Therefore each subject in the study was represented by two pairs of values (*RU_l*, *RU_r*) and (*RL_l*, *RL_r*), the first pair representing the upper slice and the second the lower. The centroid (the mean value of the ratio) of these values for normal subjects was defined as *RU* and *RL*. These values were also defined for both left and right *SN_C*. For each subject (both patients and normal controls) the distance from this centroid was defined as the pair of values (*DU*, *DL*), where:

$$DU = \sqrt{(\overline{RU_l} - \overline{RU})^2 + (\overline{RU_r} - \overline{RU})^2}$$

$$DL = \sqrt{(\overline{RL_l} - \overline{RL})^2 + (\overline{RL_r} - \overline{RL})^2}$$

For all 12 subjects, these (euclidean) distances (*DU* and *DL*) are presented in figure B.

Results

Figure A shows the ratio images of the upper and lower slices for a typical normal subject, an early case (Hoehn and Yahr stage I), and a more advanced case (Hoehn and Yahr stage III) respectively. These are displayed in pseudocolour to enhance the visual representation. In normal subjects it is seen that the substantia nigra extends to the lateral borders of the peduncle in the upper but not in the lower slice. This is demonstrated in the WMS image (not shown). In the graph, each subject is represented by a pair of values *DU* and *DL*, as defined in the Methods section. Normal subject values are represented as green solid circles while the patients' values are displayed as red solid circles. Next to each patient symbol is a Roman numeral denoting the Hoehn and Yahr stage of the patient (as judged off medication). A two tailed *t* test separated normal subjects from patients (*p*<0.001).

Discussion

The neuroimaging of the substantia nigra in Parkinson's disease, by means of conventional MRI techniques, has been a desirable but elusive goal. Potential benefits include the detection of presymptomatic disease and the staging of the disease. Detection of presymptomatic disease, especially in the inherited disorder, could allow the early introduction of neuroprotective treatments in those determined to be at risk. Furthermore the potential for staging the disease would allow for evaluation of neuroprotective interventions in the symptomatic patient. Techniques of this kind may also serve to differentiate idiopathic Parkinson's disease from other forms of parkinsonism.

Two inversion recovery sequences were used and a ratio image defined from them. We note that the ratio image depends (for TR much greater than TE) only on T1, so that the signal values in the ratio image could be recast in the form of a T1 map. To define a numerical measure of degeneration (*DU* and *DL*) which could be used to make a comparison between subjects, intersubject variability in absolute signal was eliminated by making each subject his own control and defining a lateral to medial ratio of signal intensity within this ratio image. We note that the numerical measure is therefore defined in terms of a ratio of ratios.

Visual inspection of the images confirms that the substantia nigra degenerates from lateral to medial and in a rostral to caudal direction. There is also thinning, and the structure takes on a mottled appearance compared with the normal subjects. In particular, we noted that in all six patients, in the lower slice there were zones of cell loss surrounded by rings of relative preservation. These were not seen in any of the normal subjects. The significance of this pattern of cell loss has yet to be ascertained. However, the sharp delineation of these structures serves to demonstrate that the overall changes seen in the patient group were not the result of motion

artefact. Artefacts of this kind tend to blur and degrade small structural changes.

The graph shows that the normal subjects are clustered close to the origin of the plot. The least symptomatic patient, a 38 year old woman with a 1 year history of the disease is seen in the top left hand corner. The clear separation of this patient from the group of normal subjects suggests the possibility of detecting presymptomatic disease. Moreover, the graph also suggests the possibility of staging the progression of the disease, as there seems to be a correlation between severity of disease and the distance from the top left hand corner. Note that DU tends to normalise as the disease progresses. This reflects the fact that the lateral segment reaches an asymptotic signal value first, and the medial segment finally approaches the same asymptote, so that lateral and medial segments finally tend to the same value.

What is demonstrated here for the first time is the potential efficacy of inversion recovery sequences in imaging the substantia nigra in both health and disease. It is likely that different pulse sequence parameters can be found that will yield further improvements in image quality. Moreover, further work will be needed to refine the technique, particularly in the use of thinner slices, faster sequences, and the use of automated image segmentation techniques.

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