The Substantia Nigra in Parkinson Disease: Proton Density-Weighted Spin-Echo and Fast Short Inversion Time Inversion-Recovery MR Findings

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BACKGROUND AND PURPOSE: A reduction in the area of the substantia nigra (SN) has been shown in patients with Parkinson disease. The substantia nigra is anteroinferolateral to the red nucleus, and it is important to precisely locate its true anatomic location to accurately measure SN area. Our purpose was to determine the exact location of the substantia nigra by correlating imaging and anatomic findings. We also attempted to quantitate SN area in patients with Parkinson disease compared with that in healthy control subjects on the basis of proton density–weighted spin-echo (SE) and fast short inversion time inversion-recovery (STIR) MR imaging findings.

METHODS: In four healthy volunteers, dual-echo SE and fast STIR MR images were obtained in three orthogonal planes and an oblique coronal plane. These images were correlated with anatomic specimens to determine the location of the SN. The area of the SN was also measured on oblique coronal fast STIR images obtained at a plane perpendicular to the SN in 22 patients with Parkinson disease and in 22 age- and sex-matched healthy volunteers.

RESULTS: The true anatomic location of the SN, anteroinferolateral to the red nucleus, was accurately identified, not on T2-weighted images, but on proton density–weighted SE images and fast STIR images as an area of hyperintense gray matter. The hypointense area seen on T2-weighted images corresponded to the anterosuperior aspect of the SN and to the adjacent crus cerebri. No statistically significant differences were noted in the size of the SN when the oblique coronal images of patients with Parkinson disease were compared with those of the control groups.

CONCLUSION: The SN is located mainly beneath the red nucleus. Its location cannot be determined on the basis of T2-weighted imaging results but rather on the basis of proton density–weighted SE or fast STIR findings. SN volume loss is not found in Parkinson disease, and this finding is compatible with that of recent pathology reports in the literature.

The signal intensity of iron-containing deep nuclei, such as the globus pallidus and red nucleus, is decreased on T2-weighted MR images (1, 2). The substantia nigra (SN), which also contains iron, can be distinguished as a two-layered structure on axial T2-weighted images at the level of the upper midbrain. A hypointense area in the posterior region of the crus cerebri is considered to be the pars reticulata (SNr), and a relatively hyperintense area between the SNr and red nucleus is the pars compacta (SNc). This knowledge has been applied in the evaluation of patients with Parkinson disease, and narrowing of the SNc area or restoration of the SNr signal intensity is present in patients with Parkinson disease (2–4). However, several neuroimaging articles have described that the SN is visible on proton density–weighted or short inversion time inversion-recovery (STIR) images, although the SNr and SNc cannot be distinguished (5–9). In these articles and in neuroanatomic atlases, the described location of the SN, which is anteroinferolateral to the red nucleus (Fig 1), does not match that of the two-layered structure depicted.
on T2-weighted images (10–12). The purpose of this study was to investigate the MR characteristics of the SN area in healthy subjects compared with those in patients with Parkinson disease on the basis of proton density-weighted and fast STIR imaging findings.

Methods

Subjects

Initial MR imaging studies of the SN were prospectively performed in healthy volunteers and in consecutive patients with a clinically established diagnosis of Parkinson disease between August 1999 and September 2000.

To explore the MR imaging anatomy of the SN, four volunteers (one male and three female; age range, 54–60 years; mean age ± SD, 57.3 years ± 2.2) were examined. Twenty-two patients with Parkinson disease (nine male and 13 female; age range, 43–72 years; mean age ± SD, 59.8 years ± 9.2) and 22 healthy volunteers (10 male and 12 female; age range, 43–74 years; mean age ± SD, 58 years ± 8.8) underwent MR imaging. Patients were evaluated for the severity of the disease by using the Hoehn-Yahr scale. Eleven patients were classified as having mild disease (stage 1 or 2), and 11 had moderate disease (stage 3). The duration of the disease was 0.5–11.9 years (mean ± SD, 2.7 years ± 2.6). All subjects provided written informed consent before participating in this study.

MR Imaging

A 1.5-T superconductive system (Signa Lx; GE Medical Systems, Milwaukee, WI) was used for MR imaging. The fol-
The following pulse sequences were used: conventional dual-echo spin-echo (SE) sequence (TR/TE/NEX, 2500/34 and 100/1), fast STIR sequence (TR/TI/TEeff/NEX, 4000/120/363; echo train length, 12, echo spacing, 12 ms; tailored radio frequencies). We used a relatively short inversion time to improve the signal-to-noise ratio and to enhance gray matter–white matter contrast.

SE imaging and fast STIR imaging were performed with 4-mm-thick sections, a 1.5-mm intersection gap, and a 22-cm field of view (FOV) in three orthogonal and oblique coronal directions. The matrix size was 256 \times 1100 \times 192 on the SE images and 256 \times 256 on the fast STIR images. Axial images were oriented parallel to the anterior commissure–posterior commissure (AC-PC) line and they were carefully positioned to include sections through the upper midbrain (red nucleus and superior colliculus) and the lower midbrain (decussation of superior cerebellar peduncle and inferior colliculus). Coronal images were oriented perpendicular to the AC-PC line. Sagittal images were also obtained. Oblique coronal images were set at 45° to the AC-PC line, because this orientation is almost perpendicular to the SN, according to the atlas of Talairach (13). The sections were carefully positioned to include the planes through the posterior commissure and the superior colliculus, which were used to measure the area of the SN. These oblique coronal images enabled us to avoid partial-volume effects and to measure of the SN.

We also obtained 3D T1-weighted images with a 3D Fourier transform fast spoiled gradient-recalled acquisition in the steady state (FSPGR) sequence, (TR/TE, 11.7/2.4; flip angle, 20°). FSPGR sections were 1.3 mm thick, with a 22-cm FOV and a 256 \times 224 \times 128 matrix size. Images obtained in four directions corresponding with the SE and fast STIR images were reconstructed from the 3D datasets.

**Anatomic Analysis**

To clarify the location of the SN on the MR images, we compared the anatomic appearances of the cadaveric specimens with the MR images obtained in four directions. After 10% formaldehyde fixation and paraffin embedding, axial sections through the upper and lower midbrain and oblique coronal sections through the red nucleus of human brains were obtained from three cadavers (59-year-old man, 52-year-old man) without Parkinson disease or other CNS diseases. The section thickness was 26 μm, and a combination of the Weigert myelin stain and the Nissl stain was used. One of the authors (K.T.) prepared the specimens. We also used coronal and sagittal gross specimens through the red nucleus from two
cadavers (71-year-old man, 61-year-old woman) without Parkinson disease or other CNS diseases. Two radiologists (H.O., M.S.) reviewed the anatomic specimens and the MR images to estimate the location of the SN on the MR images.

**Analysis in Parkinson Disease**

One of the authors (H.O.) measured the area of the SN in a blinded fashion. The measurements were performed on the oblique coronal fast STIR images perpendicular to the SN and on the axial T2-weighted images through the upper midbrain. A workstation (Advantage Windows; GE Medical Systems) was used. After carefully setting the window level, window width, and magnification, regions of interest were manually traced with a mouse-driven cursor on a monitor. On the oblique coronal fast STIR images, we measured the area of the SN and the midbrain on two contiguous sections through the posterior commissure and the superior colliculus. We also measured the thickness of the SN on the oblique coronal fast STIR images through the posterior commissure. We normalized the area of the SN by using the area of the midbrain to adjust for age-related changes (14). On the axial T2-weighted images, we measured the width of the relatively hyperintense band between two hypointense areas, as described in previous reports (3). The measurements were performed at the same levels in all of the patients.

Statistical comparisons were based on results of the Student and Welch t tests. P values less than .05 were considered to indicate a significant difference.

**Results**

**Normal MR Findings**

On the proton density–weighted and fast STIR images, an area of gray matter signal intensity that suggested the SN was depicted in the axial planes at the level of the upper and lower midbrain (Figs 2 and 3). On the coronal and sagittal images through the red nucleus, a tilted band with gray matter signal intensity was found inferolateral and anteroinferior to the red nucleus, respectively (Figs 4 and 5). These findings corresponded well to those of the specimens and were not visible on the T2-weighted images (Figs 2–5).

On T2-weighted images, the area of low signal intensity corresponding to the SNr and the area of relatively high signal intensity corresponding to the SNe were depicted, as reported in previous articles.
The locations of the hypointense areas were minimally correlated to those on the specimens and those on proton density–weighted and STIR images. On axial images, the hypointense area extended anterior to the anteromedial end of the crus cerebri; this finding suggested that the area included medial parts of the crural fibers (Figs 2 and 3). Moreover, the hypointense area seemed not to exclude the area of gray matter seen on the proton density–weighted or STIR images at the lower midbrain. Coronal and sagittal images showed low signal intensity at only the upper end of gray matter (Figs 4 and 5).

On the oblique coronal proton density–weighted and fast STIR images perpendicular to the SN, the SN was depicted as a well-marginated area of gray matter signal intensity (Fig 6); the SN was not evident on the T2-weighted images (Fig 6). These findings suggested that the SN did not show low signal intensity except at its superoanteromedial part (Fig 7, Table 1).

**Measurement of the Substantia Nigra**

To avoid intrarater variability, every measurement was performed three times, and the measurements were averaged. The intraclass correlation coefficients (Ri) for these measurements were 0.87–0.99 for areas of the SN and midbrain and 0.68–0.90 for the width of the hyperintense band on T2-weighted images.

The area of the SN was 42.4–59.2 mm² in patients with Parkinson disease (mean ± SD, 51.2 mm² ± 5.1), and it was 44.3–63.2 mm² (mean ± SD, 53.1 mm² ± 6.2) in the control group (P > .05). The area of the SN normalized with that of the midbrain was 9.3 mm² in Parkinson disease and 9.1 mm² in the control group (P > .05). The thickness of the SN was 3.6–4.8 mm in the patients with Parkinson disease (mean ± SD, 4.3 mm ± 0.4) and 3.5–5.1 mm (mean ± SD, 4.4 mm ± 0.4) in the control group (P > .05). Atrophy of the midbrain was not identified in patients with Parkinson disease. On the other hand, the width of the hyperintense band on the T2-weighted images was 1.3–2.3 mm (mean ± SD, 1.6 mm ± 0.2) in the Parkinson disease group and 1.3–2.3 mm (mean ± SD, 1.7 mm ± 0.3) in the control group (P > .05). The results did not reveal a statistically significant difference between the patients with Parkinson disease and the control group in any parameter (Figs 8 and 9;...
Table 2). No signal intensity changes were noted in the SN in either the Parkinson disease or control group.

**Discussion**

The SN is a pair of tilted platelike structures that lie within the midbrain. It is located between the crusal fibers and the red nucleus. The SN runs in the anterosuperolateral aspect to the posteroinferomedial aspect through the entire midbrain, and it is located mainly beneath the red nucleus (11). The SN is divided into two parts: a dorsal cell-dense part, the SNc, and a ventral cell-sparse part, the SNr. Neurons pigmented by neuromelanin in the SNc contain high concentrations of dopamine and are known as a principal source of striatal dopamine. On the other hand, neurons in SNr involve γ-aminobutyric acid (GABA) (ie, they are GABA-ergic), and they project to the thalamus and the pedunculopontine tegmental nucleus (11).

Drayer et al (1) originally introduced the MR anatomy of the SN on axial T2-weighted SE images through the upper midbrain. The hypointense areas represent the SNr and the red nucleus because of their high iron concentration. A band of relative hypointensity between the hypointense SNr and red nucleus represents the SNc, which contains half the iron of the SNr (1, 15). This finding has been supported by that of other investigators who used gradient-echo, fast SE, and diffusion-weighted echo-planar imaging techniques (3, 4, 16–20). The hypointense area, considered to be the SNr, is not evident at the level of lower midbrain in which the SNr does exist in anatomic specimens; to our knowledge, this discrepancy has not been described.

In MR textbooks, the SN is described as structures of hyperintense gray matter that are anteroinferolateral to the crusal fibers on proton density–weighted or STIR images (5–7). Its configuration and location agree well with those in the corresponding anatomic specimens (5–12). On axial images, hyperintense gray matter suggestive of the SN is evident at the level of lower midbrain in which the SNr does exist in anatomic specimens; to our knowledge, this discrepancy has not been described.

In MR textbooks, the SN is described as structures of hyperintense gray matter that are anteroinferolateral to the red nucleus on proton density–weighted or STIR images (5–7). Its configuration and location agree well with those in the corresponding anatomic specimens (5–12). On axial images, hyperintense gray matter suggestive of the SN is evident at the level of the lower as well as in the upper midbrain. MR microscopic findings in fixed brain specimens are the same (8, 9). In this study, the SN was depicted as a tilted bandlike structure with hyperintense gray matter on proton density–weighted and fast STIR images, as previously reported. The location of this structure was exactly the same as that seen in brain specimens and anatomic textbooks. Moreover, the corresponding structure was not visible on T2-weighted images.
Recently, abnormal signal intensity in the SN has been reported in cases of St Louis encephalitis and nigral degeneration secondary to striatal infarction (21, 22). In these cases, lesions with abnormal signal intensity were observed mainly beneath the red nucleus; the location and configuration were the same as our findings. These previous reports also support our results. Proton density–weighted and STIR images, and not T2-weighted images, seem to enable the direct visualization of the SN as a gray matter structure, although they cannot be used to distinguish the SNr from the SNc.

A short T2 relaxation time in the deep nuclei is reported to be largely dependent on the iron concentration (1). However, some investigators have shown that T2 values in brain structures are poorly associated with iron concentration. The signal intensity of iron-containing structures depends not only on the amount of iron but also on its physical state, its microscopic distribution, and its diffusion in the surrounding tissue (23, 24). We revealed that the hypointense area in the upper midbrain does not correspond to the distribution of the SNr, but it includes medial parts of the crural fibers, although the iron concentration in the SNr is higher than that in the crus cerebri (25). We do not have good explanation for why the crural fibers partly show strong signal-intensity attenuation.

Changes in the SN in Parkinson disease and secondary parkinsonism have been reported previously (2–4, 14, 16–20, 26–29). Several investigators have noted signal-intensity attenuation in the hypointense area on T2-weighted images (17, 18, 26). Others describe a reduction in the width of the hyperintense band on T2-weighted images and suggest that it may represent volume loss in the SNc or increased iron accumulation in the SNr (2–4, 14, 17, 19, 26, 27). Restoration of the low signal intensity on T2-weighted images is also reported (2) and is explained by...
by iron depletion due to increased metabolic activity or by neuronal death with expansion of the extracellular space. However, many reports contradict the aforementioned results. Large overlaps or no significant difference is observed in the hyperintense band width or signal-intensity restoration in patients with Parkinson disease compared with control subjects (14, 19, 20, 26, 27). Moreover, all of these studies involved the use of axial images that were not perpendicular to the SN; with these, partial-volume effects cannot be avoided. In addition, only T2-weighted or T2*-weighted images were evaluated.

Despite recent advances in MR technology, the SN has never been evaluated directly. To our knowledge, this is the first report to measure the visible SN with in vivo MR imaging. Instead of T2-weighted SE images, we used proton density-weighted and fast STIR images to eliminate iron-related magnetic susceptibility effects and to enhance gray matter–white matter contrast. We did not use axial images but instead used oblique coronal images perpendicular to SN to avoid partial-volume effects, which are notable on axial images. However, we did not find any significant differences in the size of the SN between patients with Parkinson disease and control subjects. Parkinson dis-

### Figures

**FIG 8.** On fast STIR images, volume loss in the SN was not evident in patients with Parkinson disease. On T2-weighted images, thinning of the relatively hyperintense structure (arrow in C) was not evident in patients with Parkinson disease.

A–C, Images in a patient with Parkinson disease, a 52-year-old woman. Oblique coronal fast STIR images through the level of the posterior commissure (A) and superior colliculus (B) and axial T2-weighted image (C).

D–F, Corresponding images in a control subject, a 55-year-old woman.

**FIG 9.** Area of the SN in Parkinson disease.

<table>
<thead>
<tr>
<th>Change</th>
<th>Parkinson Disease Group (n = 22)</th>
<th>Control Group (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area of the SN, mm²</td>
<td>$51.2 \pm 5.1^*$</td>
<td>$53.1 \pm 6.2$</td>
</tr>
<tr>
<td>Area of the midbrain, mm²</td>
<td>$553 \pm 40^*$</td>
<td>$587 \pm 58$</td>
</tr>
<tr>
<td>SN/midbrain, %</td>
<td>$9.3 \pm 0.1^*$</td>
<td>$9.1 \pm 0.1$</td>
</tr>
<tr>
<td>Thickness of SN, mm</td>
<td>$4.3 \pm 0.4^*$</td>
<td>$4.4 \pm 0.4$</td>
</tr>
<tr>
<td>Width of hyperintense band on T2 Weighted images, mm</td>
<td>$1.6 \pm 0.2^*$</td>
<td>$1.7 \pm 0.3$</td>
</tr>
</tbody>
</table>

* $P > .05$, compared with value in control subjects.

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TABLE 2: Changes of the SN in patients with Parkinson disease
ease is pathologically characterized by the loss of pigmented neurons and by the presence of Lewy bodies in the SN (30–33). However, recent pathologic studies reveal that the size of the SNCs is not significantly decreased in patients with Parkinson disease, despite remarkable neuronal cell loss (30, 31). Our results support these reports.

We used fast STIR images to investigate the SN because of its excellent gray matter–white matter and brain-CSF contrast. On STIR images, spin attenuation, and T1 and T2 relaxations synergistically affect image contrast, improving the gray matter–white matter and brain-CSF contrast (34). Although proton density–weighted images have excellent gray matter–white matter contrast, their brain-CSF contrast is much lower than that of STIR images, and this is a disadvantage of proton density–weighted imaging in measuring the area of the SN. Compared with conventional STIR sequences, fast STIR sequences have an improved overall image quality and a shorter imaging time (35, 36). Blurring artifacts are observed with fast imaging because of T2 decay during k-space sampling. However, blurring can be minimized with short echo intervals, tailored radio frequencies, and k-space scrolling (37).

One of the limitations of this study was the relatively mild Parkinson disease in the patient group compared with the disease in previous reports (2–4). Some have reported that the clinical severity of Parkinson disease is strongly correlated with the width of the hyperintense band on T2-weighted images (27). The lack of thinning of the hyperintense band on T2-weighted images in this study may have been due to the mildness of the disease in the Parkinson disease group. Another limitation of this study is the relatively low spatial resolution. We used conventional SE images because the iron-related signal-intensity attenuation was better detected on conventional SE images than on fast SE images. To improve the spatial resolution by reducing the FOV or section thickness in the conventional SE technique is different because of its long acquisition time. A positive correlation exists between the field strength and signal-to-noise ratio or iron-dependent transverse relaxation rate (23). By using a high-field-strength machine, high-resolution SE images can be obtained with an excellent signal-to-noise ratio and with strong iron-related signal-intensity attenuation. We are now examining the SN by using a system equipped with a 3-T magnet. Another limitation of this study is that the SNr and SNC cannot be discriminated on proton density–weighted or fast STIR images, although the entire SN was visualized as a structure with gray matter signal intensity. Further investigation is needed to determine the substructures of the SN on MR images.

Conclusion

The SN is located beneath the red nucleus, and it can be directly identified as a hyperintense gray matter structure on proton density–weighted and fast STIR images. Axial T2-weighted images are not suitable for identifying the SN. We did not find significant differences in the size of the SN between patients with Parkinson disease and volunteers in the healthy control group in the quantitative evaluation of oblique coronal fast STIR images perpendicular to SN.

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References


