Neuromelanin-Sensitive MRI

Basics, Technique, and Clinical Applications

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Abstract
The basics and the technique of magnetic resonance imaging (MRI) for visualizing the neuromelanin present in dopaminergic and noradrenergic nuclei in the substantia nigra pars compacta (SNc) and locus caeruleus (LC) are introduced. Neuromelanin, a black pigment produced during catecholamine synthesis, has paramagnetic T1-shortening effects. Conventional MRI techniques fail to depict the contrast generated by neuromelanin, but neuromelanin-sensitive T1-weighted fast spin echo technique at 3 T allows the direct visualization of the SNc and LC as hyperintense areas. In Parkinson's disease, neuromelanin-related signals from the SNc and LC are diminished, suggesting neuronal degeneration in both the nuclei. In depression and schizophrenia, signals from the LC are reduced while those from the SNc are augmented, suggesting monoamine and dopamine hypotheses, respectively. Neuromelanin-sensitive MRI is a promising technique to elucidate the pathologic or functional changes in the catecholamine neurons of the brain stem that occur in degenerative and psychiatric diseases.

Key Words: Neuromelanin · Magnetic resonance imaging · Substantia nigra · Locus caeruleus

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Neuromelaninsensitive MRT. Grundlagen, Technik und klinische Einsatzmöglichkeiten

Zusammenfassung
Die Grundlagen und die Technik der Kernspintomographie (MRT) zur Visualisierung des in den dopaminergen und noradrenergen Nuklei in der Pars compacta der Substantia nigra (SNc) und im Locus caeruleus (LC) vorhandenen Neuromelanins werden vorgestellt. Neuromelanin, ein schwarzes Pigment, welches durch die Katecholaminsynthese entsteht, hat eine paramagnetische, T1-verkürzende Wirkung. Konventionelle MRT-Techniken sind nicht in der Lage, den durch das Neuromelanin generierten Kontrast darzustellen. Eine neuromelaninsensitive, T1-gewichtete, schnelle Spinechotechnik bei 3 T hingegen erlaubt eine unmittelbare Visualisierung der SNc und des LC als hyperintense Areale. Bei der Parkinson-Krankheit sind die neuromelaninbedingten Signale aus der SNc und dem LC vermindert und lassen auf eine neuronale Degeneration in beiden Nuklei schließen. Bei Depressionen und Schizophrenie sind die Signale aus dem LC vermindert, während die Signale aus der SNc erhöht sind und auf eine monoamine bzw. dopamine Hypothese hindeuten. Die neuromelaninsensitive MRT ist eine vielversprechende Technik zur Klärung der bei degenerativen und psychiatrischen Krankheiten vorkommenden pathologischen oder funktionellen Veränderungen der katecholaminen Neuronen des Hirnstamms.

Schlüsselwörter: Neuromelanin · Kernspintomographie · Substantia nigra · Locus caeruleus

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Introduction

It is widely known that some catecholamine neurons in the human brain stem, such as those of the substantia nigra pars compacta (SNc) and locus caeruleus (LC), contain a black pigment called neuromelanin [1]. These neuromelanin-containing nuclei can be easily identified as black areas in gross specimens. However, these nuclei have remained invisible on magnetic resonance imaging (MRI), and the neuromelanin-generated contrast has hardly been studied. Recently, we proposed a new MRI technique that can depict the neuromelanin-related contrast generated by these nuclei and demonstrate pathologic changes occurring in some degenerative and psychiatric diseases [2–5]. In this review, we introduce the basics, the imaging technique, and clinical applications of neuromelanin-sensitive MRI.

What Is Neuromelanin?

Neuromelanin is a dark polymer pigment measuring 0.5–2.5 μm that exists within certain catecholamine neurons of the human brain, such as the dopaminergic neurons of the SNc and the noradrenergic neurons of the LC [6]. Neuromelanin is structurally similar but not identical to peripheral melanins (i.e., eumelanin and pheomelanin): it is a polymer of eumelanin, pheomelanin, and cysteinyl-dopa with lipid/protein components [6, 7]. It is considered to form as a by-product of the catecholamine metabolism cascade by enzymatic and/or oxidative polymerization. Its formation is proportional to the activities of catecholamine synthesis (Figure 1) [6, 7].

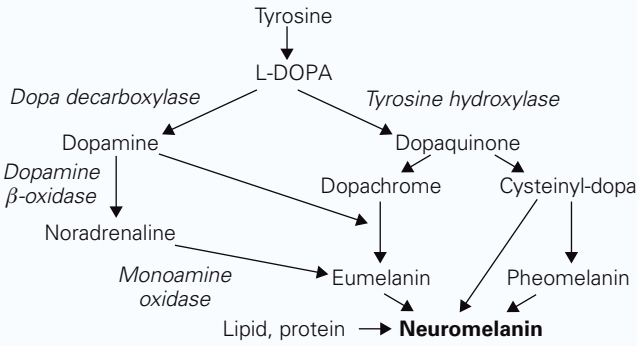
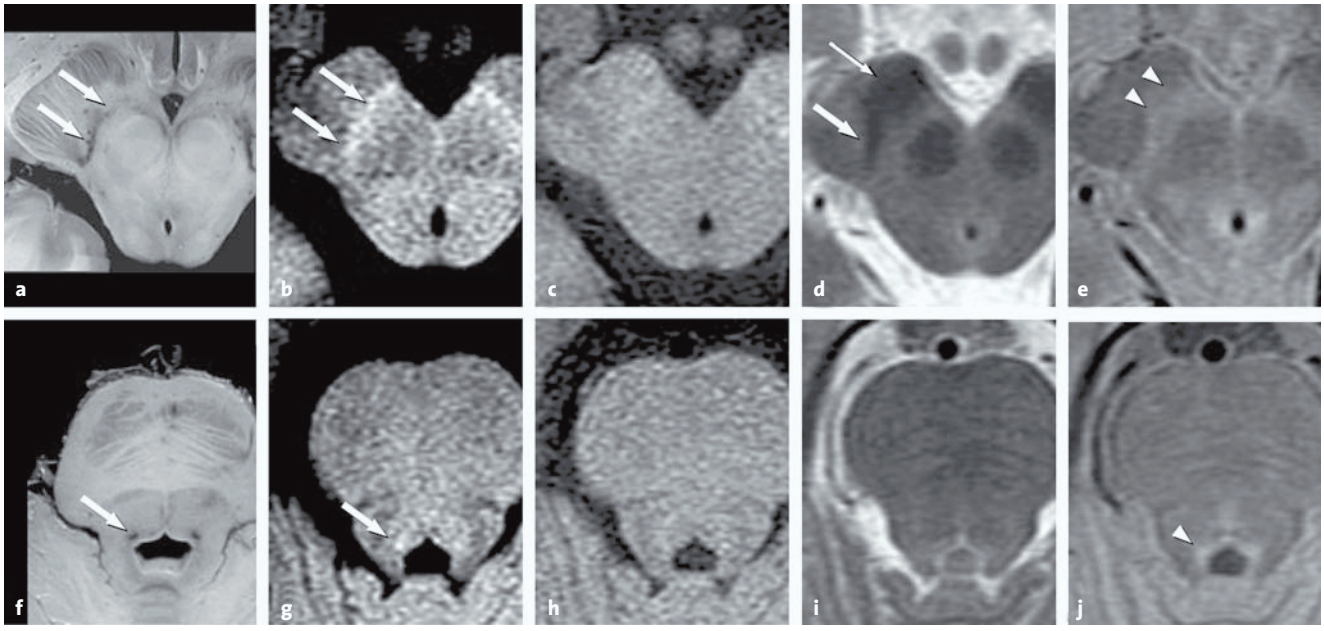


Figure 1. Suggested pathways for the synthesis of neuromelanin.

Neuromelanin plays protective roles against the accumulation of toxic catecholamine derivatives and



Figures 2a to 2j. Neuromelanin-sensitive and conventional magnetic resonance (MR) images of the substantia nigra and locus caeruleus. a–e) Axial sections at the level of the midbrain; f–j) axial sections at the level of the upper pons; a, f) macroscopic specimens; b–e, g–j) MR images of a 42-year-old healthy woman obtained at 3 T; b, g) neuromelanin-sensitive images; c, h) T1-weighted images; d, i) T2-weighted images; e, j) proton density-weighted images. Neuromelanin-sensitive images clearly depict the hyperintense areas at locations corresponding to the locations of the substantia nigra pars compacta and locus caeruleus in the macroscopic specimens (a, b, f, g; arrows). T1-weighted images cannot delineate a similar contrast (c, h). On T2-weighted images, the substantia nigra (d; large arrow) as well as the peduncular fibers (d; small arrow) appear as low signal intensity areas. On proton density-weighted images, areas including the substantia nigra and locus caeruleus (e, j; arrowheads) appear as gray-matter signal intensity areas.

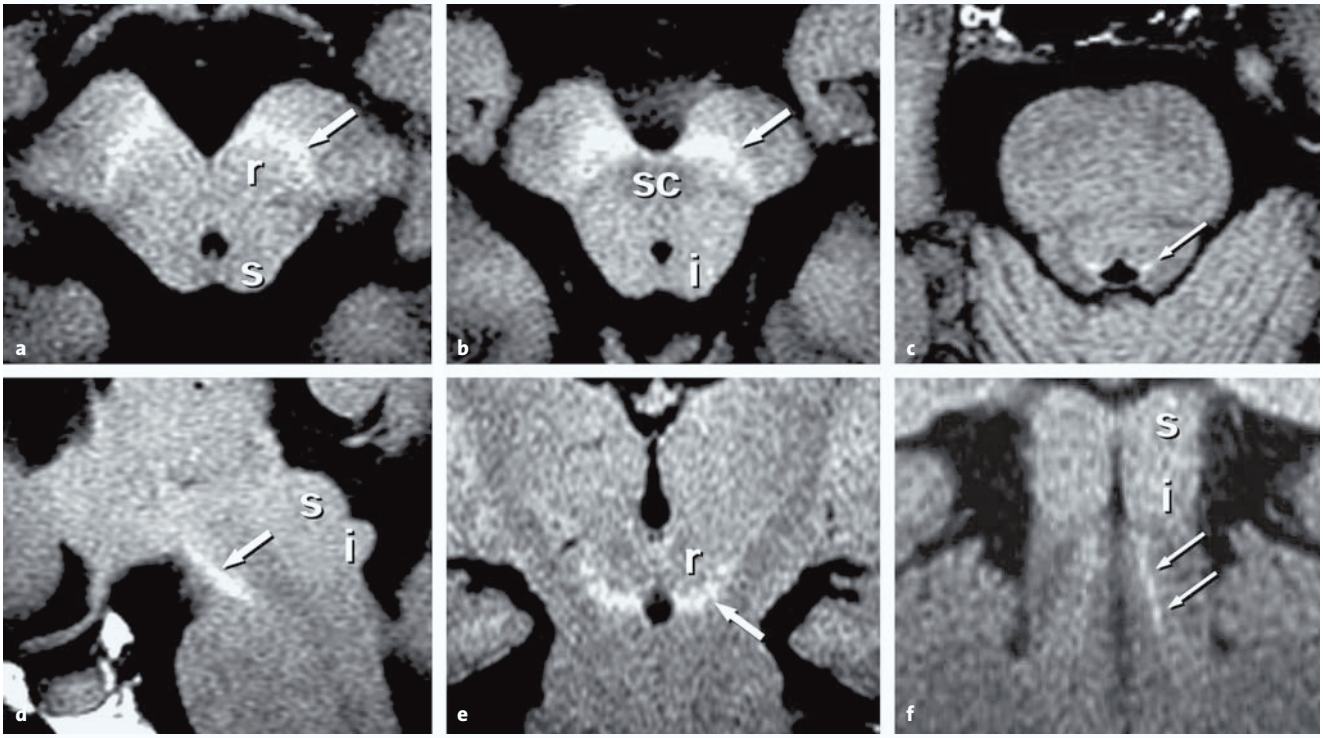
against oxidative stress induced by toxic metals or hydroxyl radicals by binding with metals such as iron, zinc, copper, and manganese [8–10]. It also interacts with proteins, including α-synuclein, which is a precursor of Lewy bodies that binds with neuromelanin during the early stage of Parkinson's disease (PD) [11].

Neuromelanin can function as a paramagnetic agent on combining with metals such as iron and copper [12]. In vitro experiments have revealed the concentration-dependent T1-shortening effects of the melanin pigment on T1-weighted images (T1WI); its longitudinal and transverse relaxivities, i.e., R1 and R2, have been reported to be 1.02 $mM^{-1}s^{-1}$ and 1.32 $mM^{-1}s^{-1}$, respectively, at 0.47 T under the condition of 10% iron [13].

How Does MRI Enable the Visualization of Neuromelanin?

Conventional MRI techniques have failed to depict neuromelanin-containing nuclei such as the SNc and LC. We have recently proposed that high-resolution fast spin echo (FSE) T1WI images obtained at 3 T can capture the neuromelanin-generated signals from these nuclei [2] by virtue of the synergic effects of high signal-to-noise ratio, high spatial resolution, signal suppression of the surrounding brain tissue by T1 prolongation at a high magnetic field [14], and magnetization transfer effect during multislice FSE acquisition [15]. We used the following conditions for the neuromelanin-sensitive MRI: 3-T MRI scanner (Signa Excite HD; GE Healthcare, Milwaukee, WI, USA); FSE (repetition time/effective echo time, 600/14) with tailored radiofrequencies; slice thickness, 2.5 mm with 1-mm gaps; field of view, 22 cm; matrix size, 512 × 320; echo trains, two; number of excitations, eight; and acquisition time, 12 min.

On axial neuromelanin-sensitive MR images, band-like high-signal areas in the posteromedial portion of the cerebral peduncle are distinctly visualized at the level of the midbrain (Figure 2) [2]. Their distribution corresponds well to that of the neuromelanin pigment in the gross specimens, suggesting that the high-



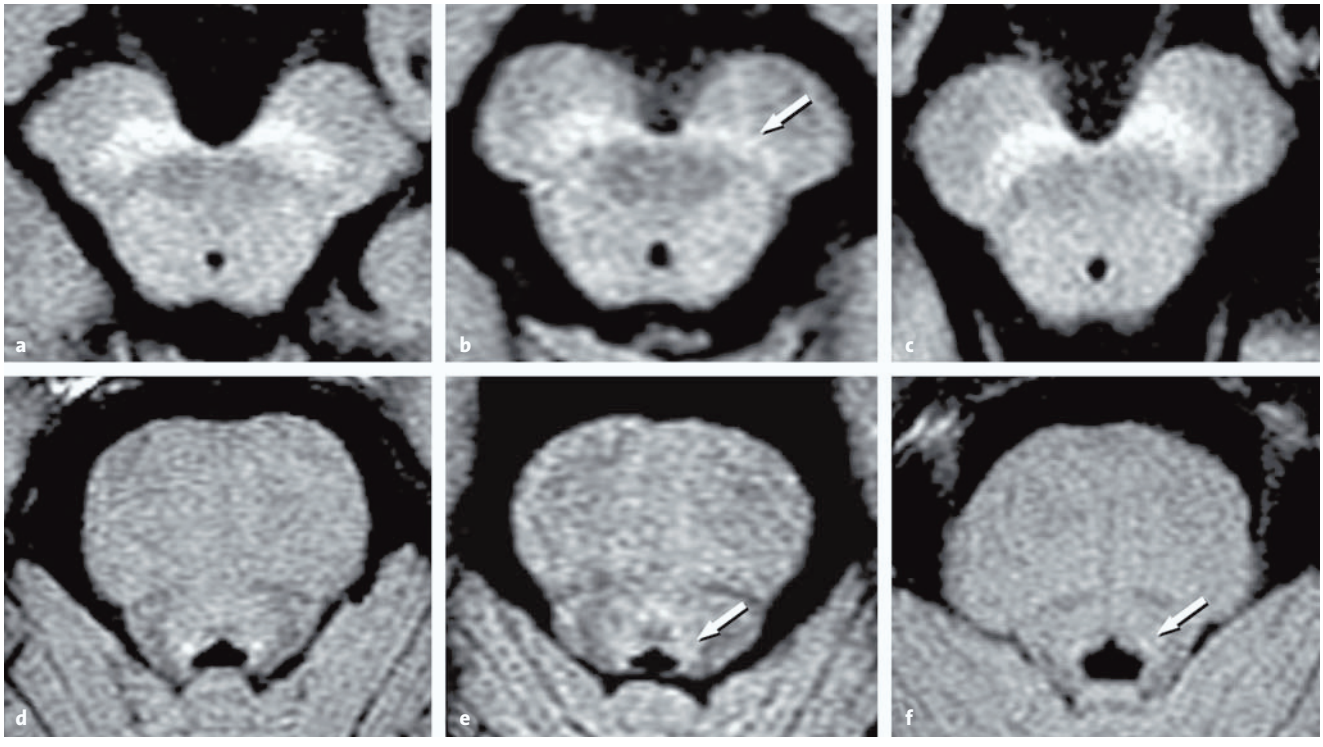
Figures 3a to 3f. Multidirectional neuromelanin-sensitive images of the substantia nigra and locus caeruleus. Images of a 48-year-old healthy woman. a–c) Axial images at the level of the upper midbrain (a), lower midbrain (b), and upper pons (c); d) sagittal image; e, f) coronal images. High signal intensity area reflecting the neuromelanin-containing neurons of the substantia nigra pars compacta is distributed in the posterior part of the cerebral peduncle and is located anteroinferolateral to the red nucleus (large arrows). The locus caeruleus is identified as a pair of rod-shaped hyperintense areas near the lateral edge of the fourth ventricle floor (small arrows). i: inferior colliculus; r: red nucleus; s: superior colliculus; sc: decussation of the superior cerebellar peduncle.

signal areas reflect the neuromelanin-containing dopaminergic neurons in the SNc. However, the conventional spin echo (SE) T1WI hardly shows the aforementioned contrast in these areas. On a T2-weighted image (T2WI), not only the substantia nigra (SN) but also the medial parts of peduncular fibers show low signal intensity due to physiological iron deposition [16]. On a proton density-weighted image (PDWI), the SN can be identified as a gray-matter signal area, but the SNc cannot be discriminated from the SN pars reticularis (SNr; Figure 2) [16]. Hence, neuromelanin-sensitive MRI is considered to be a unique technique for the direct visualization of SNc by using neuromelanin as an intrinsic molecular probe. By using multidirectional images, we could visualize the three-dimensional distributions of the SNc, and observed distributions were closely correlated with those described in neuroanatomic textbooks (Figure 3).

Neuromelanin-sensitive MRI also visualizes bilateral areas of rod-shaped high signal intensity within the pontine tegmentum, immediately anterolateral to the fourth ventricle floor at the level of the upper pons (Figures 2 and 3) [2, 3]. The location was identical to that of the LC in the gross specimen, suggesting that the high-signal spots reflect the neuromelanin in the noradrenergic neurons of the LC. T1WI, T2WI, and PDWI obtained at an identical section could not reveal any contrasts originating from the LC, although relatively bright areas on PDWI indirectly and roughly indicated the myelin-sparse zones containing the LC (Figure 3).

What Are Clinical Applications of Neuromelanin-Sensitive MRI?

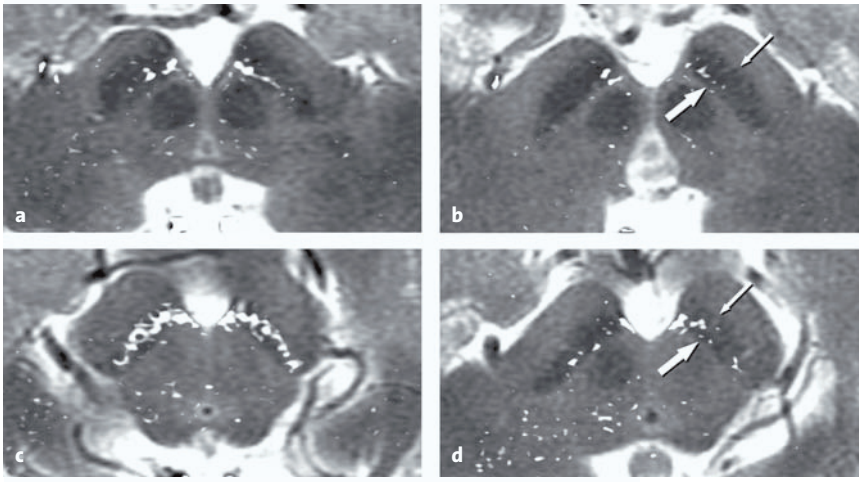
Neuromelanin-sensitive MRI can be used for the assessment of pathologic changes in the SNc or LC in certain degenerative diseases. The pathology of PD is mainly characterized by neuronal depletion and a decrease in the intraneuronal neuromelanin content with deposition of Lewy bodies in both the SNc and LC [17, 18]. Although narrowing of the relatively hyperintense "SNc area" and restoration of the hypointense "SNr area" on T2WI have been reported [19, 20], these findings are currently controversial because of their extensive overlap between PD patients and healthy subjects [21, 22]



Figures 4a to 4f. Neuromelanin-sensitive images of patients with degenerative diseases. a–c) Axial images at the level of the lower midbrain; d–f) axial images at the level of the upper pons; a, d): images of a 68-year-old healthy woman; b, e) images of a 70-year-old man with Parkinson's disease; c, f) images of a 72-year-old woman with Alzheimer's disease. Signal intensities of the substantia nigra pars compacta and locus caeruleus are evidently diminished in the patient with Parkinson's disease (b, e; arrows), while the signal intensity of the locus caeruleus is selectively reduced in the patient with Alzheimer's disease (f; arrow) as compared to that in the healthy subject (a, d).

and substantial discrepancies in the distribution of the SNc and SNr areas between T2WI and macroscopic and histological specimens [16]. Further, PDWI and short inversion-time inversion-recovery images fail to detect significant changes in PD, although these images can identify the SN as a gray-matter signal area [16]. By contrast, neuromelanin-sensitive MRI could depict significant signal reduction in both the SNc and LC in PD patients, reflecting a decrease in the neuronal number and intracellular neuromelanin in these nuclei (Figures 4 and 5) [2]. We speculate that neuromelanin-sensitive MRI can depict the pathologic changes in the neuromelanin-containing nuclei in other degenerative disorders; for instance, we could observe selective signal reduction in the LC in Alzheimer's disease (Figure 4), which is characterized by marked neuronal loss in the LC [23].

We recently discovered that neuromelanin-sensitive MRI can also assess functional changes in the SNc or LC in patients with psychiatric disorders such as depression and schizophrenia, in which the neuronal number is maintained [4, 5]. The principal mechanism that produces symptoms in depression and schizophrenia is believed to be a dysfunction in the monoamine and dopamine systems, respectively, known as monoamine and dopamine hypotheses [24, 25]. According to the monoamine hypothesis, dysfunction of the noradrenergic, dopaminergic, and serotoninergic systems plays an important role in depression, while according to the dopamine hypothesis, hyperactivity of the mesolimbic/cortical dopaminergic system contributes to schizophrenic symptoms. Neuromelanin-sensitive MRI shows that the signal intensity of the LC, particularly of its rostral two thirds, is significantly lower in depressive patients than in healthy controls and schizophrenic patients, suggesting a decreased intracellular neuromelanin content in the noradrenergic neurons that belong to the ascending noradrenergic system (Figure 6) [4, 5]. Further, the signal intensity of the SNc tends to be significantly higher in schizophrenic patients than in healthy controls and depressive patients, suggesting an increase in the dopamine activities in schizophrenia (Figure 6) [5].

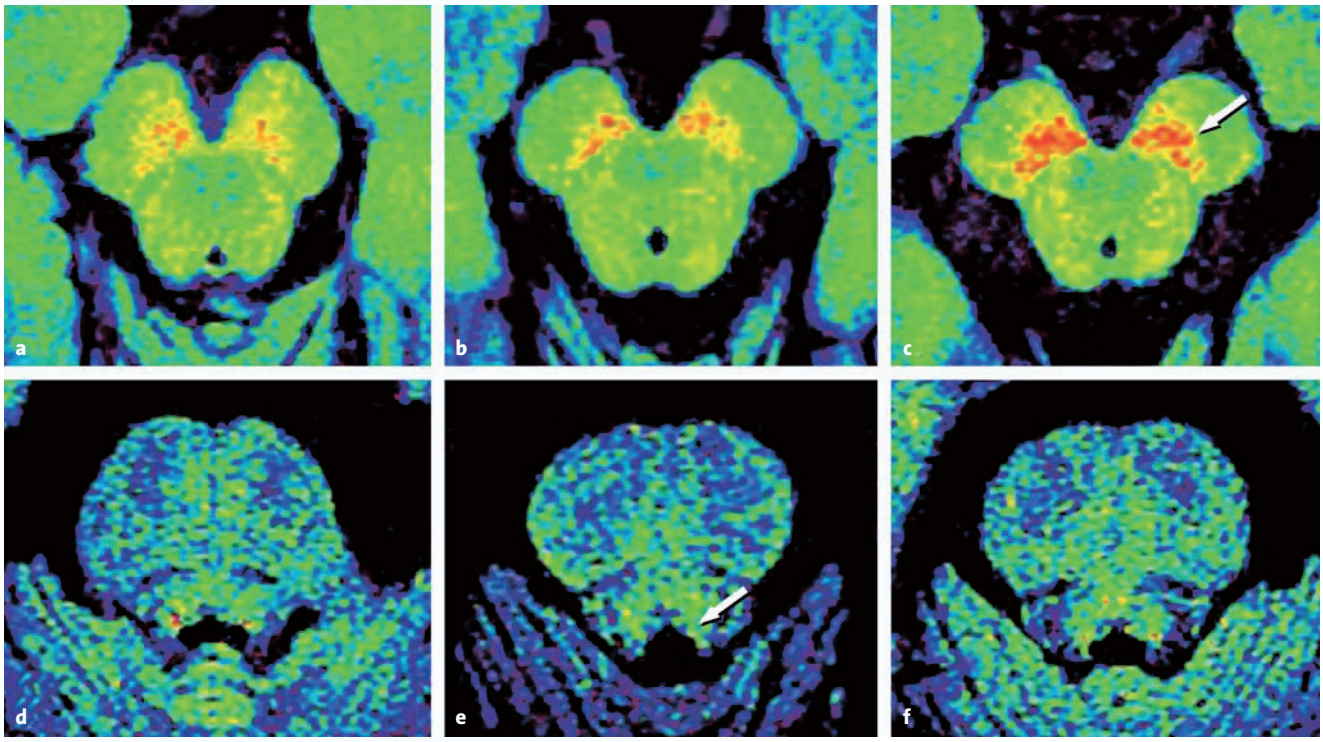


Figures 5a to 5d. Neuromelanin-sensitive images superimposed on the T2-weighted images of a patient with Parkinson's disease. Oblique axial images perpendicular to the craniocaudal axis of the substantia nigra (anteverted at 45° toward the anterior commissural-posterior commissural [AC-PC] line) at the level of the posterior commissure (a, b) and superior colliculus (c, d) [16]. a, c) Images of a 66-year-old healthy man; b, d) images of a 64-year-old man with Parkinson's disease. Neuromelanin-sensitive images are superimposed on the corresponding T2-weighted images after thresholding. Hyperintense areas indicating neuromelanin-containing neurons are remarkably diminished in the patient with Parkinson's disease (b, d; large arrows), while hypointense areas reflecting iron deposition appear unchanged (b, d; small arrows) as compared with the corresponding areas in the healthy subject (c, d).

What Are the Limitations and Future Prospects of Neuromelanin Imaging?

The suggested technical limitations of neuromelanin-sensitive MRI include a relatively low spatial resolution (0.4 × 0.7-mm pixels and 2.5-mm thickness) as compared to the size of the LC, long acquisition time (12 min for obtaining ten sections), and signal nonuniformity in a given plane due to the heterogeneity of the radiofrequency magnetic field generated by reduced radiofrequency penetrations and increased dielectric effects at 3 T [26]. These technical issues may cause substantial errors in the quantitative analysis of signal alteration, particularly in the LC. We need a sophisticated three-dimensional gradient echo technique that is sensitive to neuromelanin-related contrast in order to overcome these limitations and to improve the reproducibility and feasibility of neuromelanin-sensitive MRI.

Some factors potentially modulate the signal intensity of the SNc and LC on neuromelanin-sensitive MRI. The neuronal number and intraneuronal neuromelanin content of the SNc and LC change substantially with age [27, 28]. Our preliminary study showed a significant age-dependent variance in the signal intensity of the LC [3]; this



Figures 6a to 6f. Neuromelanin-sensitive images of patients with psychiatric disorders. Color-coded axial images obtained with the same window width at the level of the lower midbrain (a–c) and upper pons (d–f). a, d) Images of a 42-year-old healthy woman; b, e) images of a 39-year-old woman with depression; c, f) images of a 37-year-old woman with schizophrenia. The signal intensity of the locus caeruleus is lower in the patient with depression (e; arrow) than in the healthy subject and the patient with schizophrenia; however, the signal intensity of the substantia nigra is augmented in the patient with schizophrenia (c; arrow) as compared with other individuals.

variance should be considered while evaluating signal alteration. The iron concentration in the SNc neurons, which strongly influences the T1-shortening effects of neuromelanin [13], is increased in normal subjects with aging and in PD patients [28, 29]. The enhancement of the SNc signal by abundant iron in PD may lead to the underestimation of the neuronal degeneration-induced signal alteration; this underestimation should be corrected by some compensation techniques. Smoking may enhance the signal intensity of the LC because nicotine can induce the activation of the noradrenergic neurons of the LC [30]; this nicotine effect should also be adjusted to improve the precision of quantitative assessment by MRI. All the aforementioned issues will be the targets of future investigations.

Future applications of neuromelanin-sensitive MRI to degenerative diseases may include early and differential diagnoses of parkinsonism and dementias, assessment of coexisting psychiatric symptoms, and prediction of vulnerability of the SNc during the preclinical stage of PD. Its application in psychiatric disorders may include differential diagnosis, drug selection, prediction of suicidal tendency, assessment of clinical severity and drug response, and prediction of the onset or recurrence of affective disorders and schizophrenia.

Conclusion

Neuromelanin-sensitive MRI at 3 T is a novel technique that can be used for the direct visualization of the neuromelanin-containing dopaminergic neurons in the SNc and the noradrenergic neurons in the LC. This technique will facilitate the assessment of these nuclei for pathologic changes in degenerative diseases such as PD and for functional changes in psychiatric disorders such as depression and schizophrenia.

Acknowledgments

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Conflict of Interest Statement

We certify that there is no actual or potential conflict of interest in relation to this article.

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