Use of Neuromelanin-Sensitive MRI to Distinguish Schizophrenic and Depressive Patients and Healthy Individuals Based on Signal Alterations in the Substantia Nigra and Locus Ceruleus

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Background: We investigated alterations in the substantia nigra pars compacta (SNc) and locus ceruleus (LC) in schizophrenic and depressive patients by using a neuromelanin-sensitive magnetic resonance imaging (MRI) technique that enables direct visualization of these nuclei and examined whether this technique could distinguish between these disorders and healthy subjects.

Methods: Using a neuromelanin-sensitive T1-weighted MRI technique, we examined 20 schizophrenia patients, 18 depressive patients, and 34 healthy control subjects. The signal intensities of the areas corresponding to the SNc and LC were measured, and the contrast ratios (CR) to the adjacent white matter were calculated.

Results: The CR of the SNc was significantly higher in schizophrenic patients (22.6 $\pm$ 5.6) than in depressive patients (19.2 $\pm$ 4.7) and healthy control subjects (19.6 $\pm$ 3.8), whereas the CR of the LC in depressive patients (7.7 $\pm$ 2.4) was significantly lower than that in healthy control subjects (11.0 $\pm$ 3.9) and schizophrenic patients (10.0 $\pm$ 3.1). Further, the difference in the CR between the SNc and LC was significantly greater in schizophrenic patients (12.6 $\pm$ 6.7) than in control subjects (8.6 $\pm$ 4.1).

Conclusions: Neuromelanin-sensitive MRI enables visualization of alterations in the SNc and LC that are observed in schizophrenia and depression.

Key Words: Depression, locus ceruleus, magnetic resonance imaging, neuromelanin, schizophrenia, substantia nigra

The dopamine and monoamine hypotheses are widely used to explain the etiologies of schizophrenia and depression, respectively, although controversies remain. The dopamine hypothesis states that excessive dopamine release in the dopaminergic projection systems causes schizophrenic symptoms such as hallucination and delusions, whereas the monoamine hypothesis states that dysfunction in the dopaminergic, noradrenergic, or serotoninergic systems (or a combination of these) results in symptoms observed in the affective disorders (1–4). Various imaging techniques including magnetic resonance imaging (MRI) and positron emission tomography (PET) have been used to determine the morphologic and functional changes that occur in these disorders. However, these techniques have not been used to visualize monoamine nuclei in the brain stem or to provide evidence to support the dopamine/monoamine hypotheses (5–8).

Neuromelanin is known to be a by-product of dopamine and noradrenaline metabolism (9) and is found predominantly in the dopaminergic neurons of the substantia nigra pars compacta (SNc) and the noradrenergic neurons of the locus ceruleus (LC) in the human brain. We recently developed a novel imaging technique to visualize neuromelanin using 3-Tesla (3T) fast spin-echo (FSE) T1-weighted MRI and demonstrated neuromelanin-related signal changes in the SNc and LC (10). Using this technique, we found a reduction in neuromelanin-generated signal in the SNc and LC in patients with Parkinson's disease (10) and in the LC in patients with depression (11). However, signal changes in schizophrenic patients and signal-related differences among schizophrenic and depressive patients and healthy subjects remain to be elucidated. This study therefore aimed to demonstrate the changes in the dopaminergic and noradrenergic nuclei in patients with schizophrenia and depression and to determine whether the neuromelanin-sensitive MRI technique can be used to distinguish between schizophrenic and depressive patients and healthy subjects.

Methods and Materials

Patients

From February to April 2006, we prospectively examined 20 consecutive inpatients (13 men and 7 women) who met DSM-IV-TR diagnostic criteria (category 295.xx), were aged less than 65 years, and were free of any other organic disorders. In addition, we examined 18 age-matched patients with major depression (10 men and 8 women) who met DSM-IV-TR category 296.xx criteria as disease control subjects and 34 healthy age-matched subjects (17 men and 17 women) as normal control subjects. The ages of the schizophrenic and depressive patients and the healthy control subjects ranged from 27 to 64 years (mean: 44.6 years), 22 to 64 years (mean: 44.6 years), and 23 to 64 years (mean: 43.8 years), respectively. History of cigarette smoking was noted for 65%, 14%, and 21% of the subjects, respectively. Age at the onset of disorder in the schizophrenic and depressive patients ranged from 16 to 40 years (mean: 26.5 years) and 21 to 63 years (mean: 40.3 years), respectively; duration of illness ranged from 3 to 39 years (mean: 18.3 years) and 0 to 21 years (mean: 4.1 years), respectively. All of the schizophrenic patients were being administered neuroleptics (chlorpromazine-equivalent dose: 150 to 2250 mg [mean: 671

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mg]), and all depressive patients were being administered antidepressants (selective serotonin reuptake inhibitors [SSRI]: 13/18; selective serotonin and noradrenaline reuptake inhibitors [SNRI]: 3/18; tricyclic antidepressants [TCA]: 5/18; benzodiazepine [BZD]: 16/18; and/or others: 3/18). The scores of the Oxford version of the Brief Psychiatric Rating Scale (BPRS), the global rating scores (the sum of four global ratings) of the Scale for the Assessment of Positive Symptoms (SAPS), the global rating scores (the sum of five global ratings) of the Scale for the Assessment of Negative Symptoms (SANS), and Global Assessment of Functioning (GAF) in schizophrenic patients ranged from 8 to 66 (median: 26), 2 to 69 (median: 14), 1 to 67 (median: 14), and 10 to 78 (median: 48.5), respectively. The scores of BPRS, GAF, and the Hamilton Depression Scale (HDS) of the depressive patients ranged from 10 to 32 (median: 18), 29 to 70 (median: 55), and 11 to 36 (median: 24.5), respectively. There were no significant differences among groups in the aforementioned clinical characteristics, except for the age at onset and duration of illness (Table 1). All examinations were carried out after obtaining institutional review board approval. Written informed consent was obtained from all patients and control subjects.

Imaging Protocol

We used a 3T superconductive MRI scanner (Signa Excite HD, GE Healthcare, Milwaukee, Wisconsin). The following pulse sequence was used as described previously (10): T1-weighted FSE: repetition time/effective echo time, 600/14; echo train length, 2; number of slices, 10; slice thickness, 2.5 mm; intersection gaps, 1 mm; matrix size, 512 × 320; field of view, 220 mm (pixel size: .42 × .68 mm); and acquisition time, 12 min. The sections were carefully set in the oblique axial plane perpendicular to the fourth ventricle floor with coverage from the posterior commissure to the inferior border of the pons, and one section was located at the inferior edge of the inferior colliculus. We also acquired axial T1- and T2-weighted images of the entire brain to exclude coexisting disorders and confirmed the absence of abnormalities other than changes in the SNc and LC or age-related changes in all patients and control subjects. Gray-scale and color-coded images were obtained for visual assessment.

Table 1. Clinical Characteristics of the Patients with Schizophrenia, Patients with Depression, and Healthy Control Subjects

	Schizophrenia (n = 20)	Depression (n = 18)	Control (n = 34)	p Values[b]
Age, Mean (SD)	44.6 (12.4)	44.6 (15.2)	43.8 (11.2)	.97
Gender (Male) (%)	13/20 (65.0)	10/18 (55.6)	17/34 (50.0)	.40
Smoking (%)	13/20 (65.0)	3/18 (14.3)	7/34 (20.6)	.16
Age of Onset, Mean (SD)	26.5 (6.9)	40.3 (14.4)	—	<.001[a]
Duration (years), Mean (SD)	18.3 (11.7)	4.1 (5.4)	—	<.001[a]
Medication				
CP-E, Mean (SD)	671 (572)	—	—	—
SSRI (%)	—	13/18 (72.2)	—	—
SNRI (%)	—	3/18 (16.7)	—	—
TCA (%)	—	5/18 (27.8)	—	—
BZD (%)	—	16/18 (88.9)	—	—
Others (%)	—	3/18 (16.7)	—	—
BPRS, Median (QD)	26 (34)	18 (6.5)	—	.10
GAF, Median (QD)	48.5 (11.5)	55 (12.5)	—	.16
SAPS, Median (QD)	14 (16)	—	—	—
SANS, Median (QD)	14 (10.5)	—	—	—
HDS, Median (QD)	—	24.5 (6)	—	—

BPRS, Brief Psychiatric Rating Scale; BZD, benzodiazepines; CP-E, chlorpromazine equivalents; GAF, Global Assessment of Functioning; HDS, Hamilton Depression Scale; QD, quartile deviation; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SSRI, selective serotonin reuptake inhibitor; SNRI, selective serotonin and noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant.

[a]Statistically significant.

[b]One-way analysis of variance, Fisher Exact Test, or Mann-Whitney *U* Test.

Data Analysis

For quantitative evaluation, we measured the signal intensities of the SNc and the adjacent decussation of the superior cerebellar peduncle (SCP) as well as those of the LC and the adjacent pontine tegmentum. Regions of interest were measured on a liquid crystal display using circular cursors of the same shape and size. The SNc and SCP decussation signals were measured at the slice through the lower midbrain, whereas those of the LC and pontine tegmentum were measured at the slice 7 mm below the inferior edge of the inferior colliculus. Blinded measurements were performed three times by one of the authors, and the intensity values obtained were then averaged. We calculated the contrast ratio (CR) of the SNc (CR_{SN}) and CR of the LC (CR_{LC}) by using the following equations: $CR_{SN} = (S_{SN} - S_{DS})/S_{DP}$, $CR_{LC} = (S_{LC} - S_{PT})/S_{PT,}$ where S_{SN} and S_{DS} are the signal intensities of the SNc and SCP decussation, respectively, and S_{LC} and S_{PT} are the signal intensities of the LC and pontine tegmentum, respectively.

Statistical Analysis

Statistical analysis was performed to determine the differences in the CR_{SN}, CR_{LC}, and $CR_{SN} - CR_{LC}$ values among schizophrenic and depressive patients and healthy control subjects by using one-way analysis of variance (ANOVA), followed by the post hoc Tukey and the least significant difference (LSD) tests. In addition, we examined whether any correlations exist between the CR_{SN}, CR_{LC}, or $CR_{SN} - CR_{LC}$ values and clinical features or medications in the group of all subjects and between the contrast ratios and psychiatric rating scales in patients with schizophrenia or those with depression by multiple regression analysis. An alpha level of .05 was used for all statistical tests.

Results

In all patients and healthy control subjects, the SNc and LC were readily identified as high signal intensity areas in the posterior part of the cerebral peduncle and at the upper pontine tegmentum (Figure 1). The signal intensity in the SNc was stronger in schizophrenic patients than in depressive patients and healthy control subjects. In contrast, the signal intensity in the LC was remarkably attenuated in depressive patients compared with that in the schizophrenic patients and healthy control subjects (Figure 1).

Quantitative analysis demonstrated that the CR_{SN} values in schizophrenic patients were higher (n = 20; 22.6% ± 5.6%) than those in depressive patients (n = 18; 19.2% ± 4.7%) and healthy control subjects (n = 34; 19.6% ± 3.8%; one-way ANOVA, p = .037; post hoc LSD test, p = .025 and p = .023, respectively), although the post hoc Tukey test did not demonstrate a significant difference among these patients and healthy control subjects (Figure 2, Table 2). No difference was observed in the CR_{LC} values between schizophrenic patients (10.0% ± 3.1%) and healthy control subjects (11.0% ± 3.9%); however, the CR_{LC} values in depressive patients (7.7% ± 2.4%) were significantly lower than those in healthy control subjects (one-way ANOVA,

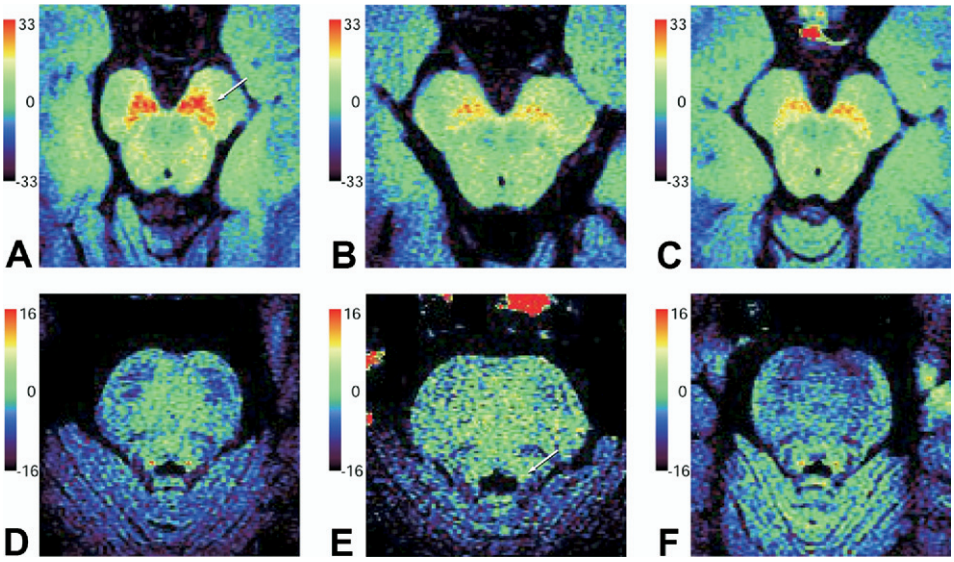

Figure 1. Neuromelanin-sensitive magnetic resonance imaging (MRI) of the substantia nigra and locus ceruleus in schizophrenic and depressive patients and healthy control subjects. **(A–C)** substantia nigra; **(D–F)** locus ceruleus; **(A, D)** schizophrenic patient (37-year-old woman); **(B, E)** depressive patient (43-year-old man); **(C, F)** healthy subject (38-year-old woman); color scale: contrast ratio (CR). Color-coded images illustrate that the signal intensity of the substantia nigra in the schizophrenic patient (CR: 27.9) (A, arrow) is substantially higher than that in the depressive patient (CR: 18.2) and healthy subject (CR: 20.0). The signal intensity of the locus ceruleus in the depressive patient (CR: 4.3) (E, arrow) is apparently diminished as compared with that in the schizophrenic patient (CR: 9.5) and healthy subject (CR: 12.4).

p = .004; post hoc Tukey test, p = .003) and schizophrenic patients (LSD test, p = .035). In addition, the difference between the CR_{SN} and CR_{LC} values was significantly larger in schizophrenic patients (12.6% ± 6.7%) than in healthy control subjects (8.6% ± 4.1%; one-way ANOVA, p = .019; post hoc Tukey test, p = .024), whereas the difference between these values in depressive patients (11.5% ± 5.5%) tended to be higher than that in healthy control subjects, although not to a significant extent.

Between CR_{SN}, CR_{LC}, and $CR_{SN} - CR_{LC}$ on the one hand and presence of the diseases, clinical background factors (age, sex, cigarette smoking, or duration of illness) and use of medication (chlorpromazine, SSRI, SNRI, TCA, BZD, or other drugs) on the other, no significant correlations were found on multiple regression analysis, except for a positive correlation between CR_{SN} and schizophrenia (p = .023), negative correlation between CR_{LC} and depression (p = .001), positive correlation between CR_{LC} and smoking (p = .025), and positive correlation between $CR_{SN} - CR_{LC}$ and schizophrenia (p = .009; Table 3). We detected no significant correlation between any of contrast ratios and psychiatric rating scales in patients with schizophrenia or patient with depression (Table 4).

Discussion

We investigated the differences in neuromelanin-generated signals from the SNc and LC in schizophrenic and depressive patients and found a significant increase in the signal intensity of the SNc in schizophrenic patients compared with that in depressive patients and healthy control subjects. In addition, we demonstrated a significant decrease in the signal intensity of the LC in depressive patients compared with those in schizophrenic patients and healthy control subjects. In this study, the increase

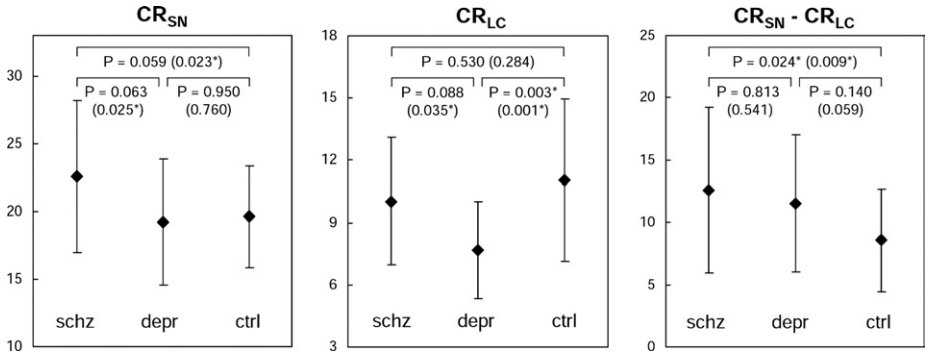

Figure 2. Contrast ratios (CR) of the substantia nigra and locus ceruleus in schizophrenic and depressive patients and healthy control subjects. CR_{SN} and CR_{LC} represent the contrast ratios of the substantia nigra and locus ceruleus, respectively, and "schz," "depr," and "ctrl" indicate schizophrenic patients, depressive patients, and control individuals, respectively. CR_{SN} in schizophrenic patients was significantly higher than that in depressive patients and healthy control subjects. CR_{LC} in depressive patients was significantly lower than that in healthy control subjects and schizophrenic patients. $CR_{SN} - CR_{LC}$ in schizophrenic patients was also significantly greater than that in healthy control subjects. p values without parentheses and those enclosed in parentheses represent results obtained by post hoc Tukey test and the least significant difference test, respectively, and asterisks represent statistically significant differences.

Table 2. Contrast Ratios of the Substantia Nigra and Locus Ceruleus in Patients with Schizophrenia, Those with Depression, and Healthy Control Subjects

	Schizophrenia ($n = 20$)	Depression ($n = 18$)	Control ($n = 34$)	p Values[b]
CR_{SN}, Mean (SD)	22.6 (5.6)	19.2 (4.7)	19.6 (3.8)	.037[a]
CR_{LC}, Mean (SD)	10.0 (3.1)	7.7 (2.4)	11.0 (3.9)	.004[a]
CR_{SN}-CR_{LC}, Mean (SD)	12.6 (6.7)	11.5 (5.5)	8.6 (4.1)	.019[a]

CR_{LC}, contrast ratio of the locus ceruleus; CR_{SN}, contrast ratio of the substantia nigra.
[a]Statistically significant.
[b]One-way analysis of variance.

in the SNc signal in schizophrenic patients and the reduction in the LC signal in depressive patients corresponded well with the dopamine and monoamine hypotheses, respectively. To the best of our knowledge, this is the first study in which changes in both the dopaminergic and noradrenergic systems of the brain stem were detected with neuroimaging techniques in patients with schizophrenia and depression.

Neuromelanin is a black pigment located in the human brain and is particularly abundant in the dopaminergic neurons of the SNc and the noradrenergic neurons of the LC (9,12). Neuromelanin is considered a by-product of dopamine and noradrenaline metabolism (9,12) and is thought to protect neurons from oxidative stress mediated by free metals or free radicals. Although no studies have revealed a relationship between neuromelanin and the pathophysiology of schizophrenia or depression, alterations in the neuromelanin content of the SNc or LC neurons may indirectly reflect dopaminergic or noradrenergic activities, respectively.

We recently proposed the use of a novel imaging technique to visualize neuromelanin-generated contrast directly in the SNc and LC of the human brain with the use of 3T MRI (10). Neuromelanin is structurally similar to peripheral melanin (13) and exhibits paramagnetic properties when bound with iron that result in acceleration of T1 relaxation (14,15). However, conventional MRI cannot detect neuromelanin-generated contrast. Using our novel technique, however, neuromelanin can be successfully visualized because of the synergistic effects of high signal-to-noise ratio at 3T, background signal suppression due to prolongation of T1 values of the brain tissue at 3T (16), and FSE-related magnetization transfer effect (17). Our previous studies revealed reduction in SNc and LC signals in patients with Parkinson's disease in whom these nuclei have undergone degeneration, reduction in LC signal in depressive patients in whom neuronal numbers has been preserved, and an age-related signal alteration corresponding to histologically proved changes in neuromelanin concentration (10,11,18). On the basis of these findings, it can be concluded that neuromelanin-sensitive MRI is capable of providing information on the number of neuromelanin-containing neurons or the neuromelanin content within these neurons (or both).

Table 3. Correlation Between Clinical Characteristics and Contrast Ratios of the Substantia Nigra and Locus Ceruleus in All Subjects ($N = 72$)

	p Values[b]		
	CR_{SN}	CR_{LC}	$CR_{SN} - CR_{LC}$
Schizophrenia	.023[a]	.284	.009[a]
Depression	.755	.001[a]	.059
Age	.261	.085	.917
Gender	.957	.093	.317
Smoking	.960	.025[a]	.174
Duration of illness	.174	.746	.161
Medication			
CP-E	.685	.992	.726
SSRI	.371	.077	.055
SNRI	.562	.739	.768
TCA	.740	.883	.699
BZD	.319	.762	.495
Others	.938	.801	.925

BZD, benzodiazepines; CP-E, chlorpromazine equivalents; CR_{LC}, contrast ratio of the locus ceruleus; CR_{SN}, contrast ratio of the substantia nigra; SSRI, selective serotonin reuptake inhibitor; SNRI, selective serotonin and noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant.
[a]Statistically significant.
[b]Multiple regression analysis.

Table 4. Correlations Between Psychiatric Rating Scales and Contrast Ratios of the Substantia Nigra and Locus Ceruleus in Schizophrenia and Depression

	p Values[a]					
	Schizophrenia ($n = 20$)			Depression ($n = 18$)		
	CR_{SN}	CR_{LC}	$CR_{SN} - CR_{LC}$	CR_{SN}	CR_{LC}	CR_{SN}-CR_{LC}
BPRS	.241	.233	.729	.589	.638	.504
GAF	.066	.747	.196	.555	.762	.525
SAPS	.866	.719	.769	—	—	—
SANS	.639	.942	.747	—	—	—
HDS	—	—	—	.255	.762	.270

BPRS, Brief Psychiatric Rating Scale; CR_{LC}, contrast ratio of the locus ceruleus; CR_{SN}, contrast ratio of the substantia nigra; GAF, Global Assessment of Functioning; HDS, Hamilton Depression Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.
[a]Multiple regression analysis.

In this study, the signal intensity in the SNc was higher in the schizophrenic group than in the other groups, although a previous pathologic study did not reveal a significant increase in neuromelanin content of the SNc in schizophrenic patients (19). In addition, in our study, the signal intensity of the LC in schizophrenic patients tended to be attenuated compared with that in age-matched control subjects, although the difference between these groups was not significant because of a large overlap in findings; this suggests impaired noradrenaline activity in schizophrenia, which has also been detected in previous postmortem studies (20,21). We speculate that the discrepancy in neuromelanin-generated signal between the SNc and LC, that is, the increase in $CR_{SN}-CR_{LC}$ values, may be a characteristic of schizophrenia.

The dopaminergic system originating in the midbrain consists of nigrostriatal and mesolimbic/mesocortical projections. Of these, hyperactivity in the mesolimbic/mesocortical system, in which the dopaminergic neurons in the ventral tegmental area (VTA) project to the nucleus accumbens or prefrontal cortex, is believed to play an important role in the genesis of schizophrenic symptoms (22). We assessed the SNc, which is a part of the nigrostriatal system and not of the mesolimbic/mesocortical system, because the VTA cannot be identified by the technique used in this study. However, signal augmentation in the SNc may indirectly reflect increase in dopamine in the mesolimbic/mesocortical system. We are currently examining the mesolimbic system directly with a new imaging technique that can be used to identify the VTA.

In depressive patients, decreased activity in the ascending noradrenergic system in the LC is believed to be one of the prerequisites for the manifestation of symptoms (23). Consistent with this, we previously reported signal attenuation in depressive patients only in the rostral two thirds of the LC, which projects mainly onto the cerebral cortex and hypothalamus (11). In addition, this study revealed that LC signal is attenuated in depressive patients compared with that in normal subjects and schizophrenic patients. However, the CR_{SN} value in depressive patients was almost identical to that in healthy control subjects. This suggests that a dysfunction in the nigrostriatal dopaminergic system may not accompany depression, although disturbance of neuronal activity in the mesolimbic dopaminergic system has been suggested to cause depressive symptoms (24).

One of the limitations of this study is that because all patients were under medication and had a relatively long duration of illness, we could not rule out bias in our findings because of the effects of drug use. The multivariate analysis we performed revealed no significant correlation between CR_{SN} or CR_{LC} and the amount of chlorpromazine-equivalent dose or usage of other drugs, suggesting that use of medications minimally affected neuromelanin-related signal alterations. However, tendencies toward negative or positive correlation were observed between CR_{LC} or $CR_{SN} - CR_{LC}$ and SSRI administration, although these were not significant ($p = .077$ and .055, respectively). Although it is likely that CR_{LC} would be reduced particularly in patients taking SSRIs, we cannot exclude the possibility that SSRIs affect signal alteration in the LC to some extent. In addition, we found a positive correlation between CR_{LC} value and history of smoking ($p = .025$), suggesting that nicotine might enhance neuromelanin-related contrast by inducing activation of LC neurons (25), although the negative correlation between CR_{LC} and depression was much more significant ($p = .001$). To establish diagnostic significance of this technique for distinguishing among schizophrenia, depression, and healthy subjects, further investigations with larger numbers of patients including drug-free or drug-naive individuals with normalization of smoking-related signal modulation appears to be needed.

The second limitation is that the imaging technique used in this study has certain disadvantages, including a long acquisition time of 12 min, relatively low spatial resolution compared with the size of the LC, and the existence of in-plane signal inhomogeneity produced by reduced penetration of radiofrequency pulses into brain tissue (10). In addition, interindividual differences in the concentration of iron molecules coupled with neuromelanin in dopaminergic neurons can cause variations in the neuromelanin-related signal of the SNc (26), although the iron content in the SNc has been reported to remain unchanged in schizophrenic patients (27). In this study, a significant difference in CR_{SN} was observed between schizophrenic and depressive patients or healthy control subjects with the post hoc LSD test but not the post hoc Tukey test, which is considered to be more reliable; this was presumably because signal intensity of the SNc fluctuated mainly as a result of interindividual differences in iron concentration in this nucleus. These imaging-related issues can be overcome by a novel gradient echo-based three-dimensional imaging technique with correction for iron concentration, which is currently under development.

In this study, no correlation was found between CR_{SN} or CR_{LC} values and psychiatric rating scale scores in either schizophrenic or depressive patients. This finding suggests that alterations of SNc or LC signals in neuromelanin-sensitive MRI are general findings observed in schizophrenia and depression. However, GAF scores tended to correlate with CR_{SN} in schizophrenic patients, although not to a significant extent ($p = .066$). Hence, further investigations of a large number of patients and more sophisticated imaging and postprocessing techniques are required to determine whether neuromelanin-related signal alterations reflect the severities, subtypes, or other pathophysiologic features of these illnesses.

In conclusion, we used a new application of the neuromelanin-sensitive MRI technique to evaluate functional changes in the catecholamine neurons of schizophrenic and depressive patients and demonstrated a significant increase in SNc signal in schizophrenic patients and a significant decrease in LC signal in depressive patients. These results suggest dopaminergic hyperactivity in the former and noradrenergic hypoactivity in the latter.

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