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Original Article

Efficacy and safety of rotigotine in Japanese patients with restless legs syndrome: a phase 3, multicenter, randomized, placebo-controlled, double-blind, parallel-group study

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ABSTRACT

Objective: We aimed to ascertain the efficacy and safety of transdermal rotigotine (2 and 3 mg/24 h) in Japanese patients with restless legs syndrome (RLS).
Methods: In our double-blind placebo-controlled study, 284 Japanese patients with idiopathic RLS were randomly assigned to receive rotigotine 2 mg/24 h or 3 mg/24 h, or placebo, for 13 weeks. The primary endpoint was the change in International Restless Legs Syndrome Study Group rating scale (IRLS) total score.
Results: The placebo-subtracted decreases in IRLS total score for rotigotine 2 mg/24 h and 3 mg/24 h were −2.8 ± 1.3 and −3.1 ± 1.3, respectively, which were significant ($P < 0.05$). The interaction between baseline Pittsburgh Sleep Quality Index (PSQI) and treatment group for the change in IRLS total score was significant, indicating greater improvements in IRLS total score in patients with severe insomnia. Overall, 80.0%, 86.2%, and 51.6% of patients in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively, experienced adverse events (AEs) including application site reactions in 42.1%, 50.0%, and 7.4% of patients, respectively. None of the AEs were severe.
Conclusions: Our results showed that rotigotine was effective without major safety concerns at doses of up to 3 mg/24 h in Japanese patients with RLS.

1. Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder associated with abnormal sensations, particularly in the legs [1,2]. Patients often have a strong desire to move the affected extremities and these sensations are either completely or partially relieved by voluntary movements such as walking. These symptoms are aggravated at rest during the night and often lead to insomnia [3]. Serious RLS can result in daytime sleepiness or malaise associated with nocturnal sleep deprivation, resulting in deteriorated quality of life, depression, and anxiety disorders [4–6]. RLS is also known to be a risk factor for the development of cardiovascular disease [7,8]. Several epidemiologic surveys have been conducted using the International Restless Legs Syndrome Study Group (IRLSSG) and the National Institutes of Health (NIH) criteria [9] and revealed that the morbidity of RLS ranges from 5% to 10% in Western countries [4,10,11] and from 2% to 4% in Japan [12,13].

The four essential criteria for RLS established by the IRLSSG/NIH [9] are as follows: (1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) an urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; (3) an urge to move or unpleasant sensations are partially or totally relieved by movements, such as walking or stretching, at least as long as the activity continues; and (4) an urge to move or

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unpleasant sensations that become clearly worse in the evening or at night than during the day or only occur during these periods.

For pharmacotherapy, dopamine receptor agonists are regarded as the first-line treatment of moderate to severe RLS [14–17]. Rotigotine is a non-ergot-derived dopamine agonist for all dopamine receptors (D1–D5), with highest affinity for the D3 dopamine receptor [18,19]. When formulated as a patch, stable plasma concentrations of the drug can be maintained over a 24-h period by continuous delivery [20], allowing control of RLS symptoms during both the daytime and the nighttime [21,22]. To date several clinical trials have been conducted in the United States and Europe to confirm the superiority of the treatment response with rotigotine to that with placebo [21,22]. However, such studies have not yet been conducted in Asian patients. Moreover, the effects of rotigotine on subjective insomnia associated with RLS have not been confirmed. For these reasons, we investigated the efficacy of rotigotine (2 mg/24 h and 3 mg/24 h) on RLS symptoms, the RLS-associated subjective sleep disturbances using an authorized sleep disturbance questionnaire, and the safety of rotigotine (2 mg/24h and 3 mg/24 h) in Japanese patients with idiopathic RLS.

2. Methods

2.1. Patients

Our phase 3, multicenter (44 institutions in Japan), randomized, double-blind, placebo-controlled, parallel-group study of Japanese patients with idiopathic RLS was conducted between February 2010 and December 2010. Patients who fulfilled the following inclusion criteria were enrolled: (1) ages 20 to <80 years at the time of providing informed consent, (2) diagnosis of RLS fulfilling all four items of the IRLSSG/NIH criteria, (3) responsive to prior dopaminergic therapy or no prior treatment for RLS, (4) baseline International Restless Legs Syndrome Study Group rating scale (IRLS) total score $\geqslant$15, and (5) RLS symptoms on $\geqslant$2 days per week for two consecutive weeks before entering the study.

Patients with any of the following criteria were excluded: (1) coexisting sleep disorders other than RLS; (2) somatic conditions that can cause secondary RLS, such as end-stage renal disease or iron deficiency (based on reference values; serum ferritin <18.6 ng/mL [reference range, 18.6–261 ng/mL] in males or <4.0 ng/mL [reference range, 4.0–64.2 ng/mL] in females); (3) concurrent neurologic disease (e.g., polyneuropathy, Parkinson disease, dementia); (4) psychiatric symptoms (e.g., hallucinations, delusions); and (5) symptoms of orthostatic hypertension. The concomitant use of drugs that could possibly affect RLS symptoms, including antiparkinsonian agents, psychoneurotropic agents, hypnotic sedatives, anxiolytic agents, antiepileptic drugs, opioid drugs, gastrointestinal agents with antagonistic effects on dopamine receptors, iron preparations, antihistamines, other central nervous system agents, drugs with opioid-like effects, clonidine, triptans for the treatment of migraine, and magnesium preparations, was prohibited [21,22]. Drugs that could cause QT prolongation (e.g., quinidine, procainamide, amiodarone, sotalol) were also prohibited. Patients were withdrawn from the study if they used any prohibited drugs for any length of time from 14 days before the start of study drug administration to the end of the treatment period. The use of less sedating antihistamines (fexofenadine and loratadine), vitamin B12, and folic acid was permitted during the study, but their dosing regimen was required to remain unchanged from 14 days before starting treatment to the end of the study period.

All patients were provided with an explanation of the study, including its purpose, procedures, and possible risk for adverse reactions or discontinuation, and they gave written informed consent to take part in the study before enrollment. Our study was conducted in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was reviewed and approved by an institutional review board at each study site. The study was registered with Clinicaltrials.gov (identifier: NCT01084551) and the Japan Pharmaceutical Information Center (identifier, Japic CTI-101053).

2.2. Treatments

The patients were randomly assigned (1:1:1) to receive rotigotine 2 mg/24 h, rotigotine 3 mg/24 h, or placebo. The doses of 2 and 3 mg/24 h were chosen for our study, as a previous dose-finding study in Japan found no significant difference in the efficacy between 1 mg/24 h and placebo (unpublished data; clinicaltrials.gov trial identifier NCT00666965). The study treatment period consisted of a 5-week dose titration period and an 8-week dose-maintenance period, followed by a dose-tapering period at a daily dose of 1 mg/24 h for up to 1 week. We used a fixed-dose titration method [21], in which the rotigotine dose was started at 1 mg/24 h and increased to 2 mg/24 h after 1 week; then the dose was increased to 3 mg/24 h after 2 weeks. After reaching the assigned dose in each group, sham titration was performed. After reaching a dose of 2 mg/24 h or higher, down titration to the previous dose level was permitted only once during the titration period if an intolerable adverse event (AE) occurred.

2.3. Endpoints

The primary endpoint was the change in the IRLS total score (Japanese Version 2.2) [23,24] from baseline to the end of treatment (EOT) at week 13. The proportion of IRLS responders was defined as patients with a $\geqslant$50% improvement in IRLS total score at the EOT compared with the score at baseline as a secondary end point [22]. Other secondary endpoints included improvements in Clinician Global Impression Improvement (CGI-I) and Patient Global Impression Improvement (PGI-I) scores [25], and the total score on the Japanese version of the Pittsburgh Sleep Quality Index (PSQI) manifested the severity of subjective sleep disturbance, mainly insomnia [26,27]. Patients with a CGI-I or PGI-I rating of very much improved or much improved were defined as responders. A PSQI total score $\geqslant$5.5 was defined as pathologic sleep disturbance.

Safety assessments included AEs, and changes in laboratory tests, vital signs, 12-leads electrocardiography, skin irritation assessment [28], the Japanese version of the Epworth Sleepiness Scale completed by the patients to assess safety of sleepiness [29,30], physical and neurologic examinations, and the Japanese version of the modified Minnesota Impulsive Disorders Interview [31] to assess obsessive–compulsive disorders or impulse control disorders. Skin irritation was assessed based on the following six criteria [28]: (1) no reaction; (2) mild erythema; (3) erythema; (4) erythema and edema; (5) erythema plus edema plus papules, seropapules, or small vesicles; and (6) large vesicles.

2.4. Statistical analysis

Based on the results of a previous dose-finding trial of rotigotine in Japanese patients with RLS (unpublished data; clinicaltrials.gov trial identifier NCT00666965), the difference between the rotigotine and placebo groups in the change in IRLS total score from baseline to the EOT was assumed to be 4.5 with a standard deviation (SD) of 9.0 for the change in each group. Under these assumptions, we estimated that we would need a sample size of 80 patients per group to provide an overall power of at least 80% with

the closed testing procedure. Efficacy analyses were conducted on the full analysis set (FAS), which was defined as all patients who received at least one dose of study drug and underwent efficacy assessments at least once after starting treatment. The safety analysis set (SAS) consisted of all patients who received the study drug at least once. For efficacy analysis, the last observation carried forward approach was applied with the last observed value being entered as the missing value. For the primary endpoint, the closed testing procedure was used to maintain the overall significance level at 5% (two-tailed). Superiority was accepted if the upper limit of the 95% confidence interval [CI] was <0. Superiority of rotigotine 3 mg/24 h to placebo and that of rotigotine 2 mg/24 h to placebo were verified by *t*-tests. For the proportion of patients with a reduction of ⩾50% in IRLS total score from baseline, the difference between each rotigotine group and the placebo group was calculated using χ^2 tests. For secondary endpoints, the improvements in CGI-I and PGI-I were evaluated by calculating the numbers and proportions of patients defined as responders (very much improved or much improved). The improvement in PSQI total score was also evaluated by calculating the mean ± SD score and the proportion of patients with a score of <5.5 at the EOT. For secondary endpoints, the groups were compared using the Kruskal–Wallis test for continuous variables or χ^2 tests for categorical variables to provide further insight into the effects of rotigotine. Two-sided 95% CIs for the difference of groups were also calculated.

Possible interactions between the changes in IRLS total score or PSQI total score within each treatment group and baseline variables (sex, age, disease duration, baseline IRLS total score, and baseline PSQI total score) were evaluated using analysis of variance. The median IRLS total score at baseline (<23 vs ⩾23) or the median PSQI total score (<8 vs ⩾8) at baseline was used in our analysis. Subgroup analyses were conducted using factors that interacted with the treatment group.

Baseline characteristics were presented descriptively as mean ± SD or as frequencies. Safety endpoints were summarized using descriptive statistics. AEs were coded in accordance with the Medical Dictionary for Regulatory Activities (Japanese Version 13.1).

3. Results

3.1. Patient characteristics

Of the 480 enrolled patients, 196 were withdrawn before randomization. Therefore, 284 were randomized with 95, 94, and 95 patients assigned to the rotigotine 2 mg/24 h, 3 mg/24 h, and the placebo groups, respectively (Fig. 1). All of these patients were included in the FAS and SAS. Down-titration was performed in five patients (5%) in the rotigotine 2 mg/24 h group and 10 patients (11%) in the 3 mg/24 h group. Treatment was discontinued in 31 patients (14, 8, and 9 patients in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively). The most common reason for discontinuation was AEs. Six patients ($n = 4$, rotigotine 2 mg/24 h; $n = 2$, placebo group) were withdrawn from the study because they used prohibited drugs during the treatment period. A total of 81 (85%), 86 (91%), and 86 (91%) patients completed the study in the rotigotine 2 mg/24 h, rotigotine 3 mg/24 h, and placebo groups, respectively (Fig. 1).

The characteristics of the patients included in the FAS are shown in Table 1. The general characteristics of all three groups were similar except for age, as there tended to be more patients aged ⩾65 years in the placebo group than in both rotigotine groups. Most patients had de novo RLS, and <15% of patients in any group previously received any treatment for RLS, including dopamine receptor agonists, L-DOPA (Levodopa), or benzodiazepines (Table 1).

3.2. Efficacy

3.2.1. Primary endpoint

Fig. 2 shows the time course of changes in IRLS total score from baseline to the EOT. There were decreases in IRLS total scores in both rotigotine groups as early as week 1 in the titration phase, and the scores continued to decline until the EOT. The mean ± SD changes in IRLS total score from baseline to the EOT were −14.3 ± 8.9, −14.6 ± 9.0, and −11.6 ± 8.2 in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively.

The mean differences in the change in IRLS total score from baseline to the EOT between the rotigotine 2 mg/24 h group and

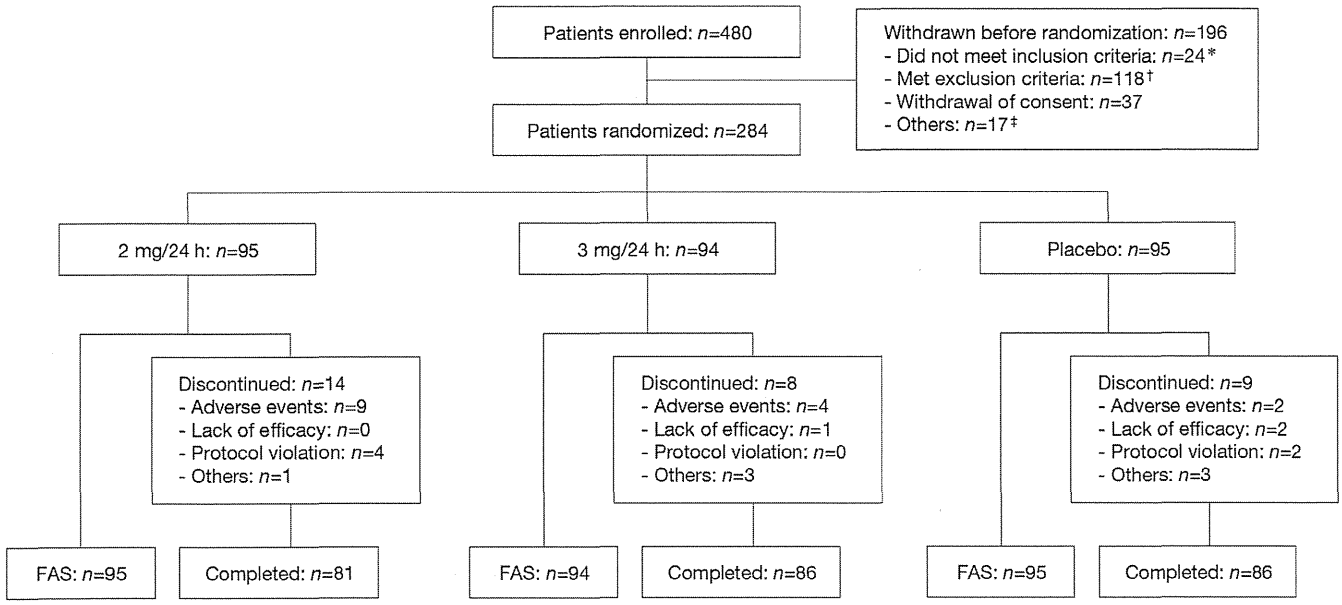

Fig. 1. Patient disposition. *Abbreviation:* FAS, full analysis set. *Mild/infrequent ($n = 22$) or doubtful ($n = 2$) RLS symptoms. †Includes iron deficiency ($n = 87$), echocardiogram parameters beyond the recommended range ($n = 11$), coexisting sleep disorders ($n = 7$), concurrent disease that can affect RLS symptoms ($n = 5$), or another exclusion criterion ($n = 5$). ‡Includes harmful events before starting drug administration ($n = 17$), the investigator's discretion ($n = 8$), or loss to follow-up ($n = 2$).

Table 1
Baseline characteristics of the patients in each treatment group (full analysis set).

	Rotigotine 2 mg/24 h (n = 95)	Rotigotine 3 mg/24 h (n = 94)	Placebo (n = 95)	P value
Sex				
Male	41 (43.2)	48 (51.1)	41 (43.2)	0.453[a]
Female	54 (56.8)	46 (48.9)	54 (56.8)	
Age, years	50.7 ± 13.3	50.9 ± 13.7	53.4 ± 15.3	0.254[b]
<65 years	77 (81.1)	77 (81.9)	65 (68.4)	0.047[a]
⩾65 years	18 (18.9)	17 (18.1)	30 (31.6)	
Duration of disease morbidity, years	13.4 ± 13.1	12.5 ± 12.3	15.7 ± 14.4	0.185[b]
Time since diagnosis, years	0.6 ± 1.1	0.6 ± 1.2	0.7 ± 1.7	0.978[b]
IRLS total score	23.4 ± 5.3	22.7 ± 5.1	23.1 ± 4.9	0.664[b]
Moderate RLS (11–20)	30 (31.6)	36 (38.3)	31 (32.6)	0.676[a]
Severe RLS (21–30)	57 (60.0)	54 (57.4)	56 (58.9)	
Very severe RLS (31–40)	8 (8.4)	4 (4.3)	8 (8.4)	
PSQI total score	7.6 ± 3.0	7.6 ± 3.3	7.9 ± 3.0	
<5.5	23 (24.2)	22 (23.4)	21 (22.1)	0.942[a]
⩾5.5	72 (75.8)	72 (76.6)	74 (77.9)	
De novo RLS[c]	82 (86.3)	80 (85.1)	87 (91.6)	0.921[a]
Prior treatment for RLS	13 (13.7)	14 (14.9)	8 (8.4)	0.354[a]
Dopamine receptor agonists	7 (7.4)	11 (11.7)	7 (7.4)	0.479[a]
L-dopa	1 (1.1)	0	0	0.369[a]
Benzodiazepines	4 (4.2)	3 (3.2)	1 (1.1)	0.406[a]
Other drugs	4 (4.2)	2 (2.1)	1 (1.1)	0.361[a]

Abbreviations: IRLS, International Restless Legs Syndrome Study Group rating scale; RLS, restless legs syndrome; PSQI, Pittsburgh Sleep Quality Index; L-dopa, Levodopa. Values are expressed as mean ± standard deviation for continuous variables or n (%) for categorical variables.
[a] χ^2 test.
[b] Kruskal–Wallis test.
[c] Patients not previously treated for RLS.

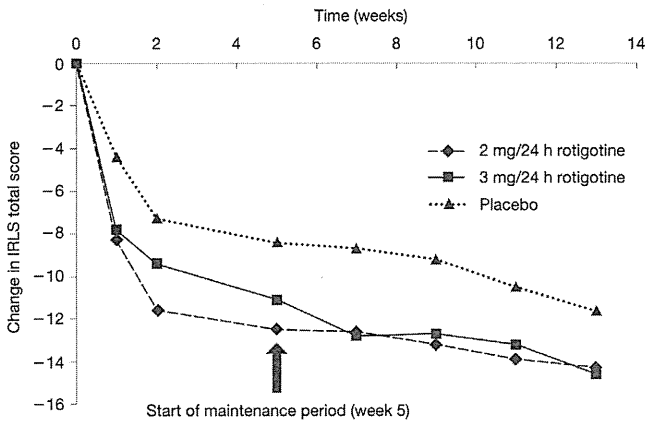

Fig. 2. Changes in IRLS rating scale total scores during the dose maintenance period (full analysis set, last observation carried forward). The analysis of the primary endpoint was performed using the scores recorded at week 13.

the placebo group and between the rotigotine 3 mg/24 h group and the placebo group were −2.8 ± 1.3 (95% CI, −5.3 to −0.3) and −3.1 ± 1.3 (95% CI, −5.6 to −0.6), respectively (Table 2). The upper limit of the 95% CI was below 0, demonstrating the superiority of both rotigotine doses to placebo. The proportions of IRLS responders were 60.2%, 66.0%, and 47.4% in the rotigotine 2 mg/24 h, rotigotine 3 mg/24 h, and placebo groups, respectively.

3.2.2. Secondary endpoints

The mean changes in PSQI total score from baseline to the EOT in the rotigotine 2 mg/24 h and 3 mg/24 h groups were −3.1 ± 3.2 and −3.2 ± 3.3, respectively, which were not significantly different from the change in the placebo group (−2.5 ± 2.4). However, the proportions of patients with a PSQI total score of <5.5 at the EOT were 77.4% (72/93 patients), 74.4% (67/90 patients), and 56.4% (53/94 patients) in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively. The proportions of patients with a PSQI total score of <5.5 at the EOT were significantly greater in both rotigotine groups than in the placebo group (Table 2). The proportions of patients with CGI-I or PGI-I rated as much improved or very much improved (CGI-responders and PGI-I responders, respectively) in the rotigotine 2 mg/24 h group were not significantly different from those in the placebo group. On the other hand, the proportions of CGI-I and PGI-I responders were significantly greater in the rotigotine 3 mg/24 h group than in the placebo group.

3.2.3. Factors interacting with the primary endpoint

In interaction analyses, the interaction between the baseline IRLS total score and treatment group was not statistically significant for the change in IRLS total score (Table 3). However, the interaction between the baseline PSQI total score and treatment group was statistically significant for the change in IRLS total score (P < 0.01). The changes in IRLS total scores in patients with less severe insomnia (i.e., baseline PSQI total score <8) were −12.9 (95% CI, −15.1 to −10.7), −11.7 (95% CI, −13.9 to −9.5), and −12.3 (95% CI, −14.7 to −9.9) in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively. In patients with more severe insomnia (i.e., baseline PSQI total score ⩾8), the changes were −16.0 (95% CI, −18.8 to −13.3), −18.3 (95% CI, −21.1 to −15.6), and −11.0 (95% CI, −13.4 to −8.5) in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively. The changes in IRLS total scores in both rotigotine groups were greater than those in the placebo group in patients with more severe insomnia.

The interaction between the baseline PSQI total score and treatment group was also statistically significant for the change in PSQI total score (P < 0.01). The changes in PSQI total scores in patients with less severe insomnia were −1.5 (95% CI, −2.1 to −0.9), −1.4 (95% CI, −1.9 to −0.8), and −1.8 (95% CI, −2.4 to −1.2) in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively. In patients with more severe insomnia, the changes were −5.0 (95% CI, −5.9 to −4.1), −5.4 (95% CI, −6.3 to −4.5), and −3.2 (95% CI, −4.0 to −2.3) in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively. The changes in PSQI total scores in both rotigotine groups were also greater than those in the placebo group in patients with more severe insomnia.

3.3. Safety

Overall, 80.0% (76/95) of patients in the rotigotine 2 mg/24 h group, 86.2% (81/94) of patients in the rotigotine 3 mg/24 h group, and 51.6% (49/95) of patients in the placebo group experienced AEs (Table 4).

AEs occurring with an incidence of ⩾5% in any group are listed in Table 4. The most common AE was application site reaction, which was more frequent in both rotigotine groups compared with the placebo group. Other AEs, including nausea, vomiting, and somnolence, were also frequent in both rotigotine groups. Nine patients (9.5%) in the rotigotine 2 mg/24 h group, four patients (4.3%) in the rotigotine 3 mg/24 h group, and two patients (2.1%) in the placebo group discontinued treatment due to AEs. Application site reactions were the most common AEs responsible for treatment discontinuation and were responsible for discontinuation in four patients in the rotigotine 2 mg/24 h group and one patient in the rotigotine 3 mg/24 h group. Other events leading to discontinuation included nausea, gastritis, insomnia, sudden onset of sleep, and worsening of RLS symptoms in one patient each in the

Table 2
IRLS response rate and improvements in IRLS score according to the severity of RLS or sleep disturbances.

	Change from baseline (mean ± SD or%)[a]			Rotigotine vs placebo (LS mean or %)[b]			
	Rotigotine 2 mg/24 h (n = 95)	Rotigotine 3 mg/24 h (n = 94)	Placebo (n = 95)	Rotigotine 2 mg/24 h		Rotigotine 3 mg/24 h	
				Difference (95% CI)	P value	Difference (95% CI)	P value
IRLS total score	−14.3 ± 8.9	−14.6 ± 9.0	−11.6 ± 8.2	−2.8 (−5.3 to −0.3)	0.030	−3.1 (−5.6 to −0.6)	0.016
PSQI total score	−3.1 ± 3.2	−3.2 ± 3.3	−2.5 ± 2.4	−0.6 (−1.4 to 0.3)	0.188	−0.7 (−1.6 to 0.2)	0.112
IRLS responders[c]	60.2	66.0	47.4	12.8 (−1.3 to 27.0)	0.077	18.6 (4.7 to 32.5)	0.010
PSQI total score <5.5 (%) at the EOT	77.4	74.4	56.4	21.0 (7.9 to 34.2)	0.002	18.1 (4.6 to 31.5)	0.010
CGI-I responders (%)[d]	67.7	74.2	57.9	9.8 (−3.9 to 23.6)	0.163	16.3 (3.0 to 29.6)	0.018
PGI-I responders (%)[d]	73.1	80.6	62.1	11.0 (−2.3 to 24.3)	0.107	18.5 (5.9 to 31.2)	0.005

Abbreviations: SD, standard deviation; LS, least squares; CI, confidence interval; IRLS, International Restless Legs Syndrome Study Group rating scale; PSQI, Pittsburgh Sleep Quality Index; EOT, end of treatment; CGI-I, Clinician Global Impression improvement; PGI-I, Patient Global Impression improvement.
[a] Values are expressed as mean ± standard deviation for continuous variables or % of patients for categorical variables.
[b] Values are least-squares means for continuous variables or % of patients for categorical variables.
[c] % of patients with a ⩾50% improvement in IRLS total score at the EOT compared with baseline.
[d] % of patients with CGI-I or PGI-I rated as very much improved or much improved.

Table 3
Interaction between treatment group and baseline variables for the improvements of IRLS total score or PSQI total score.

Interaction	Change in IRLS total score P value[a]	Change in PSQI total score P value[a]
Sex (male vs female) × treatment group	0.629	0.807
Age (<65 years vs ⩾65 years) × treatment group	0.664	0.596
Time since diagnosis (<1 year vs ⩾1 year) × treatment group	0.503	0.700
Baseline IRLS total score (as a continuous variable) × treatment group	0.090	0.228
Baseline IRLS total score (median, <23 vs ⩾23) × treatment group	0.117	0.429
Baseline PSQI total score (as a continuous variable) × treatment group	0.001	<0.001
Baseline PSQI total score (median, <8 vs ⩾8) × treatment group	0.006	0.001

Abbreviations: IRLS, International Restless Legs Syndrome Study Group rating scale; PSQI, Pittsburgh Sleep Quality Index.
[a] Analysis of variance.

Table 4
Adverse events occurring with an incidence of ⩾5% in at least one group.

	Rotigotine 2 mg/c24 h (n = 95)	Rotigotine 3 mg/24 h (n = 94)	Placebo (n = 95)
Any adverse event	76 (80.0)	81 (86.2)	49 (51.6)
Application site reaction[a]	40 (42.1)	47 (50.0)	7 (7.4)
Nausea	32 (33.7)	41 (43.6)	9 (9.5)
Nasopharyngitis	12 (12.6)	16 (17.0)	12 (12.6)
Somnolence	10 (10.5)	14 (14.9)	2 (2.1)
Vomiting	4 (4.2)	10 (10.6)	1 (1.1)
Headache	5 (5.3)	2 (2.1)	0

Values are expressed in n (%).
[a] Corresponds to the Medical Dictionary for Regulatory Activities term, application and instillation site reactions.

rotigotine 2 mg/24 h group; somnolence, palpitation, increased blood creatine phosphokinase, and cold sweats in one patient each in the rotigotine 3 mg/24 h group; and lacunar infarction and agitation in one patient each in the placebo group.

Serious AEs included two events (road traffic accident and contusion due to accumulated nocturnal sleep loss) in one patient in the rotigotine 3 mg/24 h group and lacunar infarction and facial nerve paralysis, most likely due to viral infection, in one patient each in the placebo group. A possible relationship to the study drug was ruled out for all of these events, except the lacunar infarction in one patient in the placebo group. There were no deaths in our study.

For skin irritation, large vesicles were not observed in any group. One patient assigned to rotigotine 2 mg/24 h group exhibited erythema, edema, papules, seropapules, and small vesicles at week 5 of treatment. However, these signs had reverted to mild erythema at the following visit without requiring a reduction in rotigotine dose. Skin irritation did not exceed erythema in the majority of patients.

4. Discussion

Our study was conducted to confirm the superiority of rotigotine at doses of 2 mg/24 h and 3 mg/24 h to placebo; both doses were found to be superior to placebo in the improvement in IRLS total score from baseline to the EOT. Notably a larger proportion of patients experienced a ⩾50% improvement in IRLS total score in both rotigotine groups compared with the placebo group. The mean changes in IRLS total scores in our study were −14.3 and −14.6 for the rotigotine 2 mg/24 h and the 3 mg/24 h groups, respectively. These results are consistent with those reported in a similarly designed study conducted in European patients, in which the corresponding values were −16.2 and −16.8 [22]. Overall 60.2% and 66.0% of patients in the rotigotine 2 mg/24 h and the 3 mg/24 h groups, respectively, were defined as IRLS responders in our study, compared with 57.8% and 55.4% in the European study. The proportions of patients with a PSQI total score within normal range (i.e., PSQI <5.5) at the EOT were higher in both rotigotine groups compared with the placebo group, supporting the finding that the effectiveness of rotigotine yielded a certain improvement of insomnia at the EOT. However, it must be noted that the placebo group in our study showed a relatively large effect, as reported elsewhere [32]. In our study, the mean change in IRLS total score and the proportion of IRLS responders were −11.6% and 47.4%, respectively, in the placebo group, both of which were larger than the values of −8.6% and 25.4% in the European study [22]. One possible explanation for this finding is that we included a larger proportion of patients with de novo RLS [32], unlike the earlier studies.

The PSQI is a scale used to evaluate insomnia symptoms and shows high sensitivity [26,27]. In our study, we evaluated insomnia symptoms using the PSQI; however, other scales including the RLS-6 (single item) and Medical Outcomes Study Sleep Scale were used in previous rotigotine studies [21,22]. Using this scale, we conducted interaction analyses to identify the factors that could influence the changes in IRLS and PSQI total scores. In these analyses, the baseline PSQI total score and treatment group were significantly associated with the improvements in PSQI and IRLS total scores. In other words, the improvements in IRLS among patients with more severe insomnia (i.e., PSQI $\geqslant$8) were greater in both rotigotine groups than in the placebo group. Patients with more severe insomnia also showed a greater improvement in insomnia symptoms following treatment with rotigotine. These findings indicate that the PSQI scale may be relatively important for predicting the outcomes of rotigotine treatment for RLS.

In our study, AEs were observed in 80.0% of patients in the rotigotine 2 mg/24 h group, 86.2% of patients in the rotigotine 3 mg/24 h group, and 51.6% of patients in the placebo group. The incidence rates of nausea, vomiting, somnolence, and application site reaction were higher than the placebo group in both of the rotigotine groups, and the rates seemed to be higher in the 3 mg/24 h group than in the 2 mg/24 h group. Nausea, vomiting, and somnolence are known to be associated with the pharmacological action of dopaminergic drugs. Meanwhile application site reactions are specific to the patch formulation. In our study, application site reactions occurred in 42.1% and 50.0% of patients in the rotigotine 2 mg/24 h and 3 mg/24 h groups, respectively, and these rates are similar to those obtained in the European study [22]. Overall, the AE profiles of rotigotine in our study generally were comparable with those reported in other studies of rotigotine in the United States and Europe [21,22]. Thus rotigotine generally appears to be well-tolerated in Japanese patients with RLS.

There is one limitation of our study that warrants mention, namely, the assessment of sleep disturbances using the PSQI. In our study, the patients were asked to subjectively evaluate their sleep disturbances over the preceding 2 weeks, even though evaluation over a 1-month period was originally proposed by Buysse et al. [26].

Our study confirmed that rotigotine at 2 mg/24 h and 3 mg/24 h was superior to placebo in improving IRLS total score in Japanese patients with RLS. The reduction of RLS disease severity was associated with concomitant improvements in sleep disturbances. Both doses of rotigotine generally were well-tolerated and no serious AEs were observed with either dose.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.07.007.

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References

[1] Ekbom KA. Restless legs syndrome. Neurology 1960;10:868–73.
[2] Ondo W, Jankovic J. Restless legs syndrome: clinicoetiologic correlates. Neurology 1996;47:1435–41.
[3] Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. Mov Disord 1995;10:634–42.
[4] Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 2005;165:1286–92.
[5] Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. Sleep Med 2006;7:545–52.
[6] Hening WA, Allen RP, Chaudhuri KR, Hornyak M, Lee HB, Winkelman J, et al. Clinical significance of RLS. Mov Disord 2007;22(Suppl. 18):S395–400.
[7] Batool-Anwar S, Malhotra A, Forman J, Winkelman J, Li Y, Gao X. Restless legs syndrome and hypertension in middle-aged women. Hypertension 2011;58:791–6.
[8] Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. Neurology 2008;70:35–42.
[9] Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4:101–19.
[10] Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. Arch Intern Med 2004;164:196–202.
[11] Bjorvatn B, Leissner L, Ulfberg J, Gyring J, Karlsborg M, Regeur L, et al. Prevalence, severity and risk factors of restless legs syndrome in the general adult population in two Scandinavian countries. Sleep Med 2005;6:307–12.
[12] Nomura T, Inoue Y, Kusumi M, Oka Y, Nakashima K. Email-based epidemiological surveys on restless legs syndrome in Japan. Sleep Biol Rhythms 2008;6:139–45.
[13] Nomura T, Inoue Y, Kusumi M, Uemura Y, Nakashima K. Prevalence of restless legs syndrome in a rural community in Japan. Mov Disord 2008;23:2363–9.
[14] Garcia-Borreguero D, Stillman P, Benes H, Buschmann H, Chaudhuri KR, Gonzalez Rodriguez VM, et al. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. BMC Neurol 2011;11:28.
[15] Chesson Jr AL, Wise M, Davila D, Johnson S, Littner M, Anderson WM, et al. Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep 1999;22:961–8.
[16] Hening WA, Allen RP, Earley CJ, Picchietti DL, Silber MH. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004;27:560–83.
[17] Silber MH, Ehrenberg BL, Allen RP, Buchfuhrer MJ, Earley CJ, Hening WA, et al. An algorithm for the management of restless legs syndrome. Mayo Clin Proc 2004;79:916–22.
[18] Scheller D, Ullmer C, Berkels R, Gwarek M, Lübbert H. The in vitro receptor profile of rotigotine: a new agent for the treatment of Parkinson's disease. Naunyn-Schmiedeberg's Arch Pharmacol 2009;379:73–86.
[19] Jenner P. A novel dopamine agonist for the transdermal treatment of Parkinson's disease. Neurology 2005;65(2 Suppl. 1):S3–5.
[20] Elshoff JP, Braun M, Andreas JO, Middle M, Cawello W. Steady-state plasma concentration profile of transdermal rotigotine: an integrated analysis of three, open-label, randomized, phase I multiple dose studies. Clin Ther 2012;34:966–78.
[21] Hening WA, Allen RP, Ondo WG, Walters AS, Winkelman JW, Becker P, et al. Rotigotine improves restless legs syndrome: a 6-month randomized, double-blind, placebo-controlled trial in the United States. Mov Disord 2010;25:1675–83.
[22] Trenkwalder C, Benes H, Poewe W, Oertel WH, Garcia-Borreguero D, de Weerd AW, et al. Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2008;7:595–604.
[23] Hening WA, Allen RP. Restless legs syndrome (RLS): the continuing development of diagnostic standards and severity measures. Sleep Med 2003;4:95–7.
[24] Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003;4:121–32.
[25] Clinical Global Impressions. In: Guy W, editor. ECDEU assessment manual for psychopharmacology. Rockville (MD): National Institute of Mental Health; 1976. p. 217–22.

[26] Buysse DJ, Reynolds 3rd CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
[27] Doi Y, Minowa M, Uchiyama M, Okawa M, Kim K, Shibui K, et al. Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. Psychiatry Res 2000;97:165–72.
[28] Kawamura T, Sasagawa S, Masuda T, Honda S, Kinoshita M, Harada S, et al. Basic studies on the standardization of a skin patch test. Jpn J Dermatol 1970;80:301–14 [In Japanese].
[29] Takegami M, Suzukamo Y, Wakita T, Noguchi H, Chin K, Kadotani H, et al. Development of a Japanese version of the Epworth Sleepiness Scale (JESS) based on item response theory. Sleep Med 2009;10:556–65.
[30] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–5.
[31] Christenson GA, Faber RJ, de Zwaan M, Raymond NC, Specker SM, Ekern MD, et al. Compulsive buying: descriptive characteristics and psychiatric comorbidity. J Clin Psychiatry 1994;55:5–11.
[32] de la Fuente-Fernandez R. The powerful pre-treatment effect: placebo responses in restless legs syndrome trials. Eur J Neurol 2012;19:1305–10.

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Letter to the Editors

Clozapine-induced cardiomyopathy: A first case in Japan

Dear Editors,

Clozapine, with proven efficacy for treatment-resistant schizophrenia, was first introduced in Japan in 2009. However, clozapine has serious adverse effects, including agranulocytosis and cardiovascular events. There is a need to determine the predictive factors of adverse effects for Japanese patients and establish safe treatment. Herein, we report the first case of clozapine-induced cardiomyopathy in Japan.

Four years ago, a 20-year-old man was diagnosed with schizophrenia and started risperidone at 7 mg/day in our hospital. Risperidone was changed to olanzapine at 20 mg/day because of ineffectiveness. Olanzapine was also inefficacious. The patient was diagnosed as treatment-resistant schizophrenia and admitted to our hospital for clozapine therapy. His Brief Psychiatric Rating Scale score was 45 points. Electrocardiogram (ECG) and general laboratory test results indicated no abnormal findings. His only medical history was cerebral palsy. After admission, he was gradually switched from olanzapine to 100 mg/day of clozapine for 9 days. He developed a fever with a body temperature of 37.5 °C 8 days after clozapine initiation. Physical and laboratory examinations indicated no abnormalities. Acetaminophen improved the fever, so the clozapine dose was gradually increased to 150 mg/day 13 days after the initiation of clozapine; however, hyperthermia continued (maximum body temperature, 39.6 °C). The clozapine dose was decreased to 50 mg/day, improving the fever. We diagnosed the fever as clozapine-induced benign fever. Eighteen days after clozapine was started, the patient complained of dyspnea, accompanied with sinus tachycardia (heart rate, 100 beats/min) and hypotension (blood pressure, 72/52 mmHg). A chest radiograph indicated cardiac outline enlargement and bilateral lung hyperlucency. An ultrasound cardiogram (UCG) showed diffuse global left ventricular hypokinesia with an ejection fraction (EF) of 25% and a 20-mm inferior vena cava dimension. No pericardial effusions were noted. There was mild tricuspid regurgitation as valvular abnormalities. The C-reactive protein level (23 mg/L) was elevated. White blood cell count, cardiac enzymes, and other laboratory test results were within normal limits. Consulted cardiovascular specialists diagnosed clozapine-induced cardiomyopathy. Clozapine was discontinued, and intravenous steroid injection was initiated. Four days after clozapine was discontinued, a UCG indicated improvement of the left ventricular EF of 38%, and administration of olanzapine at 20 mg/day was restarted. Thirteen days after discontinuation, a UCG indicated an improvement of left ventricular EF of 75%. Twenty days after discontinuation of clozapine, the patient was discharged from the hospital with preadmission-equivalent symptoms. During the subsequent 1-year follow-up, neither fever nor cardiac function depression was observed.

Prescription of clozapine has increased because of efficacy and fewer extrapyramidal adverse effects, hyperprolactinemia, and tardive dyskinesia. However, clozapine is notorious for adverse effects such as agranulocytosis and cardiovascular adverse effects. Clozapine-induced fever is also an adverse effect. In this case, fever developed 8 days after clozapine initiation. Physical and laboratory examination results indicated no abnormal findings. The decreased clozapine dose improved the fever (duration, 9 days). Lowe et al. (2007) reported that the rate of clozapine-induced fever varies from 0.5% to 55%. Fever usually develops within 10–15 days after treatment initiation and lasts 2–4 days. The mechanism of clozapine-induced fever is not clearly understood. One theory suggests a relationship with clozapine immunomodulating effects (Lowe et al., 2007). If findings rule out neuroleptic malignant syndrome, infection secondary to agranulocytosis, and other medical serious conditions, clozapine-induced fever is considered a benign fever.

Cardiomyopathy associated with clozapine was first reported in 1996 (Leo et al., 1996). The reported incidence has varied from 0.02% in the United Kingdom to 0.1% in Australia (Layland et al., 2009). To the best of our knowledge, this is the first report of clozapine-induced cardiomyopathy in Japan. Myocarditis seemed to occur within 3 weeks after starting clozapine, and cardiomyopathy may occur within 2–36 months (Kilian et al., 1999; La Grenade et al., 2001). Cardiomyopathy likely generally presents later than myocarditis. One-third of patients develop nondilated cardiomyopathy (Wooltorton, 2002). In our case, cardiomyopathy occurred 18 days after starting clozapine (dose, 50 mg/day). The mechanisms of cardiomyopathy associated with clozapine are not clearly understood. Merrill et al. (2005) reported that anthracycline induces cardiomyopathy with direct cardiotoxic effects. Devarajan et al. (2000) reported increased clozapine concentrations because of deficiencies in cytochrome P450-1A2 and P450-1A3. Another theory is that nondelayed cardiomyopathy is related to an IgE-mediated hypersensitivity reaction (type 1 allergic reaction; Kilian et al., 1999). If cardiomyopathy is suspected, general laboratory tests, chest radiograph, ECG, and UCG are necessary. In Japan, however, a number of hospitals where clozapine treatment is possible are single-psychiatry department hospitals. At these institutions, specialized examinations such as UCG and consultation with necessary specialists without delay are difficult. Layland et al. (2009) reported the utility of B-type natriuretic protein for the screening of left ventricular dysfunction among patients receiving clozapine. Although it is imperative that physicians warn of general condition changes and patients must undergo periodic cardiovascular monitoring, given the clozapine accumulation-induced cardiomyopathy cases, establishing simple screening tests is necessary.

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Conflict of interest

All the authors have no conflicts of interest to declare. This manuscript has not been published previously and is not under consideration for publication elsewhere.

Contributors

Dr. Kikuchi performed treatment in this case and wrote the manuscript. Drs. Ataka, Yagisawa, and Omori also administered treatment. Ms. Shimizu provided the symptom assessment. Dr. Kanbayashi provided the overall treatment management of this case. Dr. Shimizu supervised the writing of the manuscript. All the authors contributed to and approved the final manuscript.

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References

Devarajan, S., Kutcher, S.P., Dursun, S.M., 2000. Clozapine and sudden death. Lancet 355 (9206), 841.
Kilian, J.G., Kerr, K., Lawrence, C., Celermajer, D.S., 1999. Myocarditis and cardiomyopathy associated with clozapine. Lancet 354 (9193), 1841–1845.
La Grenade, L., Graham, D., Trontell, A., 2001. Myocarditis and cardiomyopathy associated with clozapine use in the United States. N. Engl. J. Med. 345 (3), 224–225.
Layland, J.J., Liew, D., Prior, D.L., 2009. Clozapine-induced cardiotoxicity: a clinical update. Med. J. Aust. 190 (4), 190–192.
Leo, R.J., Kreeger, J.L., Kim, K.Y., 1996. Cardiomyopathy associated with clozapine. Ann. Pharmacother. 30 (6), 603–605.
Lowe, C.M., Grube, R.R., Scates, A.C., 2007. Characterization and clinical management of clozapine-induced fever. Ann. Pharmacother. 41 (10), 1700–1704.
Merrill, D.B., Dec, G.W., Goff, D.C., 2005. Adverse cardiac effects associated with clozapine. J. Clin. Psychopharmacol. 25 (1), 32–41.
Wooltorton, E., 2002. Antipsychotic clozapine (Clozaril): myocarditis and cardiovascular toxicity. CMAJ 166 (9), 1185–1186.

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Neuroanatomic Pathways Associated with Poststroke Affective and Apathetic Depression

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Objectives: *Our goal was to localize lesions in poststroke depression patients using magnetic resonance imaging, based on the statistical parametric maps image analysis technique that can be used to combine image data from multiple participants and correlate these images with other data sets.* **Methods:** *Magnetic resonance imaging acquisitions were obtained from 149 poststroke patients, who were assessed for affective and apathetic symptoms using the Hospital Anxiety and Depression Scale and the Apathy Scale, respectively. We created a statistical parametric map that displayed an association between lesion location and affective and apathetic symptoms.* **Results:** *Among the patients with higher depressive scores, the lesion overlap centered on the brainstem, left basal ganglia, and left frontal cortex. Among the patients with higher apathy scores, the lesion overlap centered on the brainstem and bilateral striatum. The overlap lesion for both affective and apathetic depression centered mainly on the brainstem; however, the two types of depression often did not overlap.* **Conclusions:** *Two core symptoms that can occur after stroke, affective and apathetic symptoms, appear to be associated with different monoaminergic neuroanatomic pathways (serotonergic and dopaminergic).* (Am J Geriatr Psychiatry 2013; 21:840–847)

Key Words: Apathy, depression, magnetic resonance imaging, monoamine pathway, statistical parametric map, stroke

Depression and apathy are common neuropsychiatric consequences of stroke, ones that have been reported to negatively affect functional and cognitive recovery.[1–8] Previously, we examined the relationships between poststroke depression (PSD), functional recovery, and lesion location (using computed tomography images), after separating PSD into two core symptom dimensions: affective

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(depressive) and apathetic (loss of interest).[1–3] These two core symptom dimensions appear to have different underlying neuroanatomic mechanisms, and appear to exert different effects on functional recovery: apathy was a better predictor of poor functional recovery after a stroke than depression.[1–3] It is therefore important that studies of PSD consider the two symptom dimensions separately.

Many previous studies of depression in stroke patients have demonstrated several morphologic changes (e.g., in the left frontal lobe and left basal ganglia), although such findings remain controversial.[1,9–12] One methodologic problem in many prior studies has been an inability to localize lesions to specific brain regions across a number of participants. Most studies have only been able to identify lesions in general regions, such as the aforementioned left frontal lobe or basal ganglia. Statistical parametric mapping (SPM) is an image analysis technique that can be used to combine image data from multiple participants and correlate such information with other sources of data.[12–14] Using this technique, automatic three-dimensional rendering of the patients' magnetic resonance imaging (MRI) lesion data derived from the transverse slices is available, such that correlations between this and other data can be calculated. Using this technique, previous reports have clarified the critical brain regions associated with several neurologic or psychological symptoms (e.g., spatial neglect).[12–14] However, this technique has yet to be applied to a lesion location analysis of PSD.

Conflicting evidence on whether the risk of depression after a stroke is influenced by the location of the brain lesion could have arisen because vascular lesions may confer vulnerability to depression through a mechanism that acts alone or in synergy.[6,7] In the latter case, accumulation of lesions exceeding a threshold may create a predisposition to depression.[7] We hypothesized that the specific brain structure abnormalities in the predisposition to PSD resulting in affective or apathetic symptoms would be different, and that the point of damage to the brain structure involve different parts of the structure. Thus, to clarify the structural abnormalities related to the two types of symptoms, we used the SPM technique that combines MRI data from multiple stroke patients and separately correlated them with affective or apathetic symptoms.

METHODS

Patients

The approval of our institutional ethics committee was obtained for this prospective study. Written informed consent was obtained from all patients. The patients were selected from a consecutive series of 149 poststroke individuals who were admitted to the Hibino Hospital less than 3 months after suffering a hemorrhagic or occlusive stroke. They presented for rehabilitation therapy and were diagnosed using magnetic resonance images. Exclusion criteria were the same as those described in our previous report.[2]

Psychological Assessment

We used the Hospital Anxiety and Depression Scale (HADS; cut-off point: 8) to examine subjective severity of affective symptoms of depression,[1,15,16] and a Japanese version of the Apathy Scale (AS; cut-off point: 16) to quantify apathetic symptoms.[2,3,8,17,18]

Lesion Analysis

We obtained brain images including a T2-weighted sequence using a 1.5-T MRI scanner (Signa EXCITE XL, version 11.0; GE Healthcare, Milwaukee, WI), within 1 month after admission (around the same time as the psychological assessment). The magnetic resonance protocol included a fast spin–echo pulse sequence. Imaging was performed at 1.5 T on a commercial MRI system (GE Signa, GE Medical Systems, Milwaukee, WI) using the standard quadrature head coil.

Brain lesions were identified using T2-weighted MRI scans of each patient. First, images were converted from dicom to analyze format and were then spatially normalized to the Montreal Neurological Institute brain template. At that time, the image was re-sliced with a voxel size of 2 × 2 × 2 mm. These conversions and normalizations were performed using statistical parametric mapping 8 (SPM8; Wellcome Department of Cognitive Neurology, London).[19,20] The normalized T2 image of each patient was mapped using MRIcron software (http://www.cabiatl.com/mricro/mricron/index.html), and the lesions were drawn manually. Two brain surgeons took part in this estimation

process, and the interrater reliability for the individual amount of lesion volume was assessed using the κ coefficient, showing 0.944. The voxels judged as lesions were assigned to 1, and all others to 0. The lesion images were saved in the MRIcron volume-of-interest format. The volume-of-interest images of the patients were used in the group analysis.

During the last step, whole-brain multiple regression analysis was performed using SPM8. Poststroke depression has previously been reported to be related to lesion volume.[7] Therefore, the independent variables were the HADS and AS scores, with other factors such as age, sex, stroke type, the time lag between MRI and clinical assessment, and lesion volume being regressed out as nuisance covariates. Because affective and apathetic symptoms were thought to partially overlap, we also examined overlap voxel of whole-brain multiple regression results for both types of symptoms. To estimate cluster level, we use T-contrast using a one-tailed test. The statistical criteria were set at $p < 0.05$ for voxel levels and a cluster size of >20.

RESULTS

Baseline Structures and Frequency of Poststroke Affective and Apathetic Symptoms Across All Patients

The participants included 97 men and 52 women. The mean age of these patients was 66.8 ± 10.3 years (range: 37–86). Forty-three patients had experienced intracerebral hemorrhage and 106 patients had experienced cerebral infarction. The mean time lag between MRI and clinical assessment was 18.2 ± 17.3 days (range: 0–90; median: 14). The mean HADS score for all patients was 5.9 ± 3.8 (range: 0–17; median score: 5), and the mean AS score was 14.1 ± 7.1 (range: 0–34; median score: 15), suggesting that affective and apathetic symptoms were relatively mild. The mean lesion location volume (mL) was 18.7 ± 27.3 (range: 0.2–212; median: 8.8). Depression score of HADS and AS scores over the clinical cut-offs occurred for 46 (30.9%) and 66 (44.3%) patients, respectively. Of these, 29 patients (19.5%) showed an elevation of both depression and AS scores; therefore, 83 patients (55.7%) were found to have affective and/or apathetic PSD. The tendency (degree and frequency) of affective and apathetic symptoms after a stroke was nearly identical to that reported in our previous study.[2,3]

Effects of Lesion Location on Affective and/or Apathetic PSD

Figures 1 and 2 (see also Tables 1 and 2) show the overlay plots of each affective or apathetic symptom of poststroke patients. The number of overlapping lesions is illustrated by color coding, with frequency increasing from red to yellow. Among the patients with higher depression scores, the lesion overlap centered on the brainstem, left basal ganglia, and left frontal cortex (Figure 1). Among the patients with higher apathy scores, the lesion overlap centered on the brainstem and bilateral basal ganglia (especially the striatum: Figure 2).

There was a partial overlap of both affective and apathetic symptoms. Therefore, we also examined whether there were overlap lesions related to both affective and apathetic symptoms using SPM8. Figure 3 shows the overlap lesions related to affective and apathetic symptoms. Overlap voxel was 581 voxels, which was 21.0% that of affective (2765 voxels) and 11.7% that of apathetic (4986 voxels) symptoms. The overlap lesions of both affective and apathetic depression were mainly centered on the brainstem. These results suggest that lesions related to affective and apathetic symptoms often did not overlap.

CONCLUSIONS

We used SPM to examine the separate neuroanatomic correlates of affective and apathetic PSD. Higher depression scores as measured using the HADS were related to lesions of the brainstem, subthalamic region, and left frontal cortex, whereas higher apathy scores as measured using the AS were related to lesions of the brainstem and bilateral striatum. Most lesions related to affective and apathetic symptoms did not overlap. This result is consistent with our previous study in suggesting that there are two separate core symptoms of PSD (affective or depressive) and (apathetic), with different underlying neuroanatomic mechanisms.[1–3]

FIGURE 1. **Overlay lesion plots of the poststroke patients as concerned with depression score on the HADS. [A] SPM results for lesion areas correlated with depression score (for exact coordinates, see Table 1). [B] The number of overlapping lesions is illustrated by different colors that code increasing frequencies from red to yellow. Colored regions were significant even after controlling for age, sex, stroke type, lesion volume, and the time lag between MRI and clinical assessment. df = 142.**

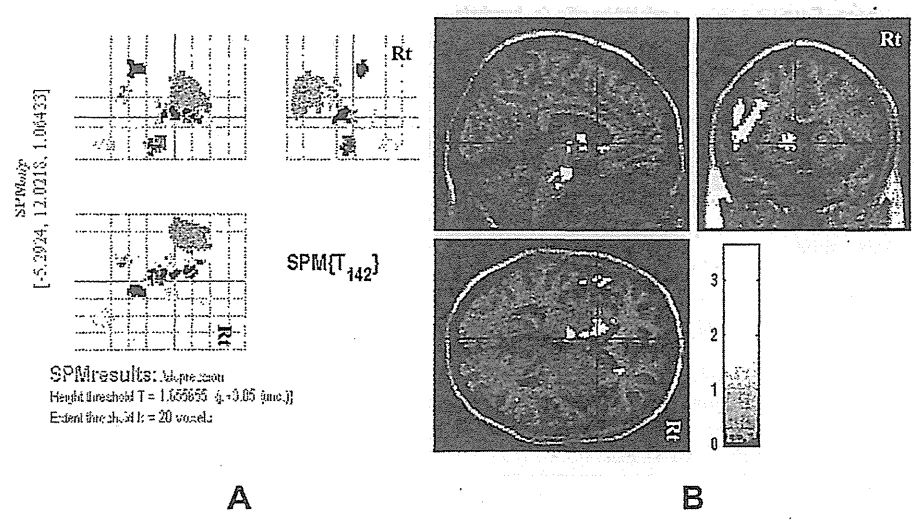
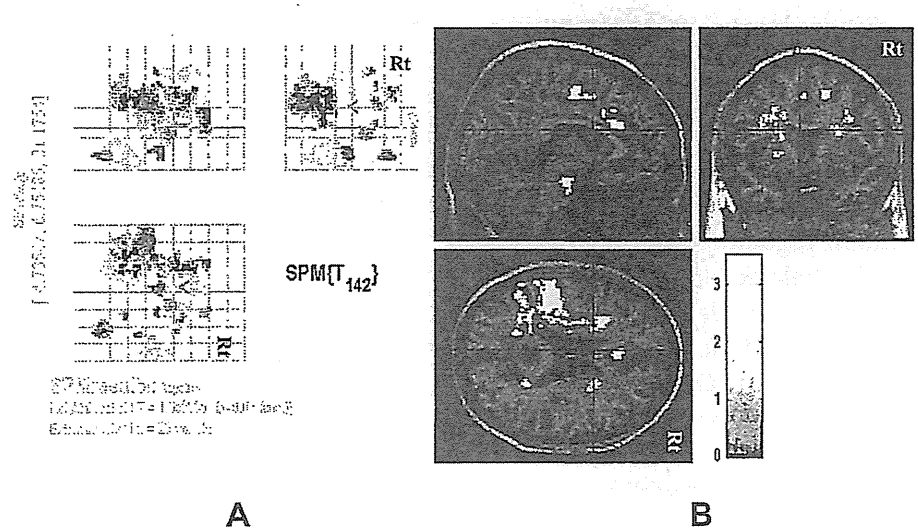


FIGURE 2. **Overlay lesion plots of the poststroke patients as concerned with apathy scores (AS). [A] SPM results for lesion areas correlated with apathy score (for exact coordinates, see Table 2). [B] The number of overlapping lesions is illustrated by different colors coding for increasing frequencies from red to yellow. Colored regions were significant even after controlling for age, sex, stroke type, lesion volume, and the time lag between MRI and clinical assessment. df = 142.**



The results of this study also indicated that the lesions related to affective and apathetic symptoms mainly overlapped on the brainstem, whereas other lesions, including those of the striatum and cerebral cortex, did not overlap.

Neuronal Network of the Affective Dimension of PSD

Since the unexpected discovery of the monoamine oxidase inhibitors and tricyclic antidepressants, depression has been thought to result from failures

TABLE 1. Statistical Parametric Mapping Results for Lesion Areas Correlate With Depression Score

	Cluster Level		Voxel Level				
Area	p	*k*	p	*Z*	*x*	*y*	*z*
Left cerebrum, sublobar, thalamus	<0.001	74	<0.001	3.55	−12	−12	1
Left cerebrum, sublobar, caudate, caudate head	<0.001	113	0.001	3.20	−8	12	5
Left cerebrum, sublobar, caudate, caudate head	<0.001	53	0.001	3.20	−8	4	3
Left brainstem, pons	<0.001	189	0.001	3.07	−4	−24	−22
Left cerebrum, frontal lobe, subgyral	0.007	22	0.001	3.00	−20	25	−6
Right cerebrum, limbic lobe, cingulate gyrus, Brodmann area 31	<0.001	140	0.001	3.00	8	−41	39
Left cerebrum, sublobar, extranuclear	<0.001	67	0.003	2.71	−18	−49	21
Left cerebrum, frontal lobe, inferior frontal gyrus	<0.001	1,598	0.005	2.57	−34	7	27
Left cerebrum, sublobar, lentiform nucleus, putamen	0.001	33	0.009	2.35	−24	−7	10
Left cerebrum, frontal lobe, subgyral	0.008	21	0.010	2.34	−18	−2	33
Right cerebellum, posterior lobe, tuber	<0.001	156	0.026	1.94	43	−67	−24
Right cerebrum, sublobar, extranuclear	<0.001	59	0.026	1.94	14	−4	−10
Right cerebrum, frontal lobe, subgyral	0.004	26	0.026	1.94	20	33	−7
Right cerebrum, temporal lobe, middle temporal gyrus	<0.001	214	0.042	1.73	57	−45	−10

Notes: Statistical parametric mapping whole-brain multiple regression analysis; the name of the areas described above points to the peak of activation with each cluster. p-corrected p value for spatial extent (cluster p value) and peak height (voxel level p value) of the activation: all areas exceeding the corrected cluster level threshold of 0.05 are displayed; *k*: number of voxels in cluster; Z: z score; *x*, *y*, *z*: location according to the standard Talairach coordinates (in mm); df = 142.

of the serotonin/noradrenaline pathway (the monoamine hypothesis).[21,22] However, the monoamine hypothesis in itself could not explain the entire mechanism of action of antidepressants, nor could it provide a comprehensive understanding of the pathophysiology of depression.[21]

Serotonergic cell bodies are located in the midbrain raphe nucleus, and their axons project to the frontal cortex, hypothalamus, and basal ganglia.[21,23,24] Some noradrenaline pathways project to the same areas of the brain as the serotonergic neurons. Among these, the axons projecting to the frontal cortex are thought to be important for mood regulation, the failure of which is thought to be related to the affective dimension of PSD.[24] Moreover, left frontal lobe theory posits that damage or dysfunction to this area is associated with depression.[1–3,5,9] Our present data can be thought to bridge the monoamine hypothesis and left frontal lobe theory, such that the affective dimension of PSD might be associated with failure of the serotonergic/noradrenergic pathway projecting to the left frontal lobe.

Neuronal Network of the Apathetic Dimension of PSD

Apathy is defined as reduced motivation to engage in activities or lack of initiative.[1–3,8] Apathy is commonly thought to be associated with neurologic disorders such as Parkinson disease.[1,25–30] However, apathy is also thought to be a symptom of depression (i.e., loss of interest)[1–3] and is reportedly more prominent in vascular depression, which typically occurs later in life and is characterized by changes that result from cerebral vascular disease.[6,9] We previously reported that patients with vascular depression (or depressed patients with silent cerebral infarction) have a relatively poor prognosis.[31] In addition, apathetic symptoms appear to be associated with a worse functional prognosis than depression after stroke.[2] The poor prognosis of PSD may be primarily due to apathetic symptoms.

Apathy was commonly thought to be associated with prefrontal lesions or lesions of the basal ganglia,[3,4,8,17,18,25] with the symptom profile of conditions such as Parkinson disease being evoked to support this notion. Parkinson disease is thought to develop when dopamine is depleted, and apathy among patients with Parkinson disease can be improved using dopamine therapy.[26–28] Apathy is, therefore, thought to be related to the intracranial dopamine pathway, including projections from the substantia nigra and ventral tegmental nucleus (midbrain) to the ventral striatum.[23,24] Our present data implicating brainstem and basal ganglia lesions (mainly striatum) might embody this association between poststroke apathetic symptom and dopaminergic pathway projections to the bilateral striatum.

TABLE 2. Statistical Parametric Mapping Results for Lesion Areas Correlate With Apathy Scale

Area	Cluster Level		Voxel Level				
	p	*k*	p	*Z*	*x*	*y*	*z*
Left cerebrum, frontal lobe, subgyral	<0.001	2,317	<0.001	3.43	−26	15	23
Right cerebrum, frontal lobe, inferior frontal gyrus	0.001	42	0.002	2.82	40	4	33
Right cerebrum, frontal lobe, subgyral	<0.001	43	0.003	2.73	28	9	22
Right cerebrum, frontal lobe, subgyral	<0.001	156	0.003	2.72	38	−69	−23
Right cerebrum, parietal lobe, inferior parietal lobule	0.001	42	0.004	2.69	44	−34	26
Left cerebrum, frontal lobe, subgyral	<0.001	133	0.004	2.67	−28	33	−2
Right cerebrum, frontal lobe, subgyral	0.009	21	0.004	2.65	24	−12	41
Right cerebrum, parietal lobe, subgyral	0.002	31	0.005	2.57	26	−45	23
Left brainstem, pons	<0.001	103	0.005	2.56	−6	−17	−21
Right cerebrum, frontal lobe, medial frontal gyrus	0.010	20	0.006	2.53	16	−13	49
Right cerebrum, sublobar, extranuclear	<0.001	70	0.011	2.30	14	−4	−10
Right cerebrum, frontal lobe, subgyral	0.003	29	0.011	2.30	20	33	−7
Left cerebrum, sublobar, lentiform nucleus, putamen	<0.001	77	0.012	2.27	−28	2	4
Left cerebrum, limbic lobe, cingulate gyrus	<0.001	160	0.016	2.14	−2	21	28
Left cerebrum, parietal lobe, subgyral	0.009	21	0.022	2.01	−20	−48	41
Right cerebrum, temporal lobe, inferior temporal gyrus, Brodmann area 21	0.002	32	0.026	1.95	61	−7	−15
Right cerebrum, temporal lobe, middle temporal gyrus, Brodmann area 21	<0.001	59	0.026	1.95	60	−26	−7
Right cerebrum, temporal lobe, superior temporal gyrus, Brodmann area 22	0.001	37	0.026	1.95	63	−8	2
Left brainstem, pons	<0.001	1,200	0.027	1.93	−8	−40	−30
Right cerebrum, limbic lobe, cingulate gyrus	<0.001	58	0.027	1.93	14	12	42
Left cerebrum, frontal lobe, superior frontal gyrus	0.001	34	0.027	1.93	−12	24	43
Left cerebrum, limbic lobe, cingulate gyrus, Brodmann area 24	<0.001	81	0.035	1.82	−2	−4	44
Left cerebrum, temporal lobe, middle temporal gyrus	0.005	25	0.046	1.68	−50	−48	4
Right cerebrum, temporal lobe, inferior temporal gyrus	<0.001	195	0.048	1.67	55	−49	−13

Notes: Statistical parametric mapping whole-brain multiple regression analysis; the name of the areas described above points to the peak of activation with each cluster. p-corrected p value for spatial extent (cluster p value) and peak height (voxel level p value) of the activation: all areas exceeding the corrected cluster level threshold of 0.05 are displayed; *k*: number of voxels in cluster; Z: z score; *x*, *y*, *z*: location according to the standard Talairach coordinates (in mm); df = 142.

PSD and Monoaminergic Theory

Although there is much popular and professional literature attesting to the veracity of the link between depression onset and monoaminergic dysfunction, direct evidence of such a link has been lacking.[21–24] In explaining the role of neuroanatomic lesions in affective and apathetic dimensions of PSD, the neuroanatomic system might be regarded as a projection system with the brainstem being the nuclei of origin of both affective and apathetic symptoms of depression, as confirmed in this study, and the striatum and cortex being projection areas. Such an explanation may account for the differences between affective and apathetic symptoms. Therefore, this study provides some evidence for an association between two separate monoaminergic pathways and the two separate symptom dimensions in poststroke depression: an affective dimension, correlated with the serotonergic pathway functioning, and an apathetic dimension, related to dopaminergic function. Theories of poststroke depression etiology must account for these two separate underlying neuroanatomic and neurobiologic mechanisms.

Study Limitations

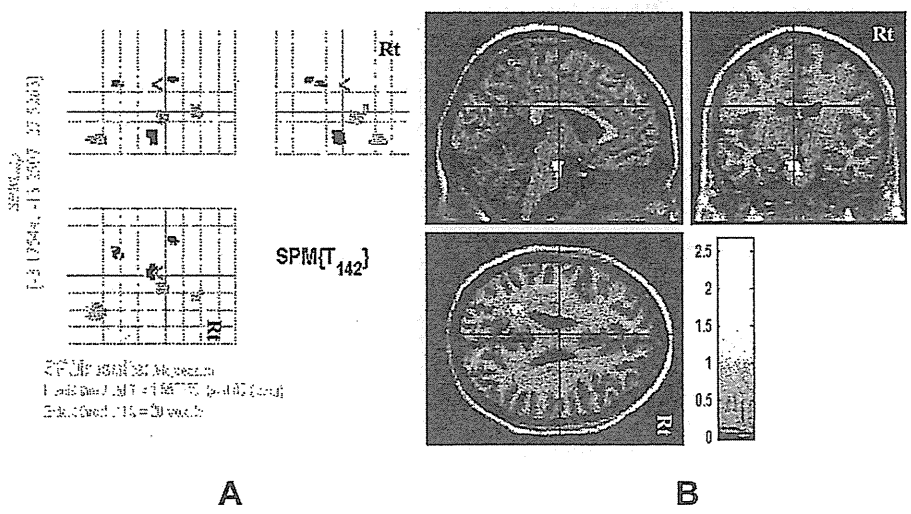
Several methodologic limitations of this study should be acknowledged. Because patients with severe comprehension deficits were excluded from the study, these results may not be applicable to all stroke patients. We did not examine monoamine status directly, an approach that contemporary medicine does not permit. Moreover, the degree of affective and apathetic symptoms of depression observed in this study was relatively mild compared with that usually observed in patients with major depression. The degree of affective and apathetic symptoms was also mild in our previous study; however, the previous study demonstrated that the two core dimensions (affective and apathetic) were related to different underlying neuroanatomic regions and that they exerted different effects on functional recovery. Therefore, it is suggested that not only severe depressive symptoms but also

TABLE 3. Statistical Parametric Mapping Results for Lesion Areas Correlate With Overlap Lesion

	Cluster Level		Voxel Level				
Area	p	*k*	p	*Z*	*x*	*y*	*z*
Left cerebrum, limbic lobe, cingulate gyrus	0.002	30	0.004	2.63	−18	−47	26
Left cerebrum, frontal lobe, inferior frontal gyrus	0.009	20	0.005	2.57	−34	7	27
Left brainstem, pons	<0.001	95	0.006	2.50	−4	−15	−26
Right cerebellum, posterior lobe, tuber	<0.001	156	0.026	1.94	44	−67	−24
Right cerebrum, sublobar, extranuclear	<0.001	59	0.026	1.94	14	−4	−10
Right cerebrum, frontal lobe, subgyral	0.004	26	0.026	1.94	20	33	−7
Right cerebrum, temporal lobe, inferior temporal gyrus	<0.001	195	0.045	1.69	55	−49	−13

Notes: Statistical parametric mapping whole-brain multiple regression analysis; the name of the areas described above points to the peak of activation with each cluster. p-corrected p value for spatial extent (cluster p value) and peak height (voxel level p value) of the activation: all areas exceeding the corrected cluster level threshold of 0.05 are displayed; *k*: number of voxels in cluster; Z: z score; *x*, *y*, *z*: location according to the standard Talairach coordinates (in mm); df = 142.

FIGURE 3. Overlay lesion plots of the poststroke patients as concerned with overlapped with affective and apathetic symptoms. [A] SPM results for lesion areas correlated with overlap between both HADS depression score and apathy score (for exact coordinates, see Table 3). [B] The number of overlapping lesions is illustrated by different colors between red and yellow for increasing frequencies. Colored regions were significant even after controlling for age, sex, stroke type, lesion volume, and the time lag between MRI and clinical assessment. df = 142.



mild ones should be taken seriously and treated after a stroke. We explored the T-contrast using a one-tailed test. We also explored the F-contrast using a two-tailed test, which showed almost the same trend as T-contrast test in this study (see Figures S1–S3, Supplemental Digital Content; available online). We could not estimate cluster level using the F-contrast test; thus, we chose T-contrast as many prior studies using the SPM statistical program.

In conclusion, the combination of image segmentation, spatial normalization, and statistical parametric map creation permits the identification of probable areas where lesions may directly relate to depression or apathy. Two core symptoms of poststroke depression, depressed mood and apathy, appear to have different neuroanatomic and neurobiologic mechanisms.

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References

1. Hama S, Yamashita H, Yamawaki S, et al: Post-stroke depression and apathy: interactions between functional recovery, lesion location, and emotional response. Psychogeriatrics 2011; 11:68–76
2. Hama S, Yamashita H, Shigenobu M, et al: Depression or apathy and functional recovery after stroke. Int J Geriatr Psychiatry 2007; 22:1046–1051
3. Hama S, Yamashita H, Shigenobu M, et al: Post-stroke affective or apathetic depression and lesion location: left frontal lobe and bilateral basal ganglia. Eur Arch Psychiatry Clin Neurosci 2007; 257:149–152
4. Onoda K, Kuroda Y, Yamamoto Y, et al: Post-stroke apathy and hypoperfusion in basal ganglia: SPECT study. Cerebrovasc Dis 2011; 31:6–11
5. Robinson RG: Poststroke depression: prevalence, diagnosis, treatment, and disease progression. Biol Psychiatry 2003; 54:376–387
6. Krishnan KR, Hays JC, Blazer DG: MRI-defined vascular depression. Am J Psychiatry 2007; 154:497–501
7. Alexopoulos GS, Meyers BS, Young RC, et al: "Vascular depression" hypothesis. Arch Gen Psychiatry 1997; 54:915–922
8. Starkstein SE, Fedoroff JP, Price TR, et al: Apathy following cerebrovascular lesions. Stroke 1993; 24:1625–1630
9. Robinson RG, Kubos KL, Starr LB, et al: Mood disorders in stroke patients. Importance of location of lesion. Brain 1984; 107:81–93
10. Lee SH, Payne ME, Steffens DC, et al: Subcortical lesion severity and orbitofrontal cortex volume in geriatric depression. Biol Psychiatry 2003; 54:529–533
11. Shimoda K, Robinson RG: The relationship between poststroke depression and lesion location in long-term follow-up. Biol Psychiatry 1999; 45:187–192
12. MacFall JR, Payne ME, Provenzale JE, et al: Medial orbital frontal lesions in late-onset depression. Biol Psychiatry 2001; 49:803–806
13. Karnath HO, Ferber S, Himmelbach M: Spatial awareness is a function of the temporal not the posterior parietal lobe. Nature 2001; 411:950–953
14. Karnath HO, Fruhmann Berger M, Zopf R, et al: Using SPM normalization for lesion analysis in spatial neglect. Brain 2004; 127:E10
15. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67:361–370
16. Matsudaira T, Igarashi H, Kikuchi H, et al: Factor structure of the Hospital Anxiety and Depression Scale in Japanese psychiatric outpatient and student populations. Health Qual Life Outcomes 2009; 7:42
17. Yamaguchi S, Kobayashi S, Koide H, et al: Longitudinal study of regional cerebral blood flow changes in depression after stroke. Stroke 1992; 23:1716–1722
18. Yamagata S, Yamaguchi S, Kobayashi S: Impaired novelty processing in apathy after subcortical stroke. Stroke 2004; 35: 1935–1940
19. Wright IC, McGuire PK, Poline JB, et al: A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia. Neuroimage 1995; 2:244–252
20. Ashburner J, Friston K: Spatial normalization using basis functions, in Human Brain Function. Edited by Frackowiak RSJ, Friston Kj, Frith CD, Dolan RJ, Price CJ, Zeki S, Ashburner J, Penny W. 2nd ed. London, Elsevier Science, 2004, pp 655–672
21. Hindmarch I: Beyond the monoamine hypothesis: mechanisms, molecules and methods. Eur Psychiatry 2002; 17(Suppl 3): 294–299
22. Willeit M, Praschak-Rieder N: Imaging the effects of genetic polymorphisms on radioligand binding in the living human brain: a review on genetic neuroreceptor imaging of monoaminergic systems in psychiatry. Neuroimage 2010; 53: 878–892
23. Walter H, Abler B, Ciaramidaro A, et al: Motivating forces of human actions. Neuroimaging reward and social interaction. Brain Res Bull 2005; 67:368–381
24. Stahl S, Briley M: Understanding pain in depression. Hum Psychopharmacol 2004; 19(Suppl 1):S9–S13
25. Levy R, Dubois B: Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb Cortex 2006; 16: 916–928
26. Czernecki V, Pillon B, Houeto JL, et al: Motivation, reward, and Parkinson's disease: influence of dopatherapy. Neuropsychologia 2002; 40:2257–2267
27. Czernecki V, Pillon B, Houeto JL, et al: Does bilateral stimulation of the subthalamic nucleus aggravate apathy in Parkinson's disease? J Neurol Neurosurg Psychiatry 2005; 76:775–779
28. Pluck GC, Brown RG: Apathy in Parkinson's disease. J Neurol Neurosurg Psychiatry 2002; 73:636–642
29. Dobkin RD, Menza M, Bienfait KL, et al: Depression in Parkinson's disease: symptom improvement and residual symptoms after acute pharmacologic management. Am J Geriatr Psychiatry 2011; 19:222–229
30. Berman K, Brodaty H, Withall A, et al: Pharmacologic treatment of apathy in dementia. Am J Geriatr Psychiatry 2012; 20: 104–122
31. Yamashita H, Fujikawa T, Takami H, et al: Long-term prognosis of patients with major depression and silent cerebral infarction. Neuropsychobiology 2010; 62:177–181

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Distinctive neural responses to pain stimuli during induced sadness in patients with somatoform pain disorder: An fMRI study ☆

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ABSTRACT

Pain is a multidimensional phenomenon. Patients with somatoform pain disorder suffer from long-lasting pain, with the pathology being closely associated with cognitive–emotional components. Differences between these patients and controls in cerebral responses to pain stimuli have been reported. However, to our knowledge, no studies of somatoform pain disorder have evaluated altered pain-related brain activation as modulated by emotional dysregulation. We examined the distinct neural mechanism that is engaged in response to two different pain intensities in a sad emotional condition, performing functional magnetic resonance imaging (fMRI) on a group of 11 somatoform pain patients and an age-matched control group. Our results showed that the ratio for low-pain intensity ratings between the sad and neutral conditions in patients was higher than in controls. They also showed significant increased activation in the anterior/posterior insula in the low pain sadness condition. Furthermore, there was specific functional connectivity between the anterior insula and the parahippocampus in patients during presentation of low-pain stimuli in the sad context. These findings suggest that a negative emotional context such as sadness contributes to dysfunctional pain processing in somatoform pain disorder. Greater sensitivity to low levels of pain in an emotional context of sadness might be an important aspect of the psychopathology of somatoform pain disorder.

1. Introduction

Pain has many physiological as well as psychological aspects. Clinical and experimental studies have elucidated the sensory-discriminative and the emotional–affective dimensions of pain (Price, 2002), and have revealed that both dimensions are influenced by various emotional elements aroused by psychological stimuli, including such states as fear, anxiety, and sadness. For example, greater subjective pain intensities have been reported during a state of sadness (Lehoux and Abbott, 2011; Loggia et al., 2008). Various studies have explored brain mechanisms underlying emotional modulation of pain in healthy subjects (Apkarian et al., 2005; Berna et al., 2010; Peyron et al., 2000). We have used functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) to show that sadness can enhance subjective pain perception and pain-related brain activity, including that of the anterior cingulate cortex (ACC), during pain processing in healthy volunteers (Yoshino et al., 2010; Yoshino et al., 2012).

Somatoform pain disorder is defined as the occurrence of one or more physical complaints for which appropriate medical evaluation reveals no explanatory physical pathology or pathophysiologic mechanism, or when such a pathology is present, the physical complaints or resulting impairment are grossly in excess of what would be expected from the physical findings, according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (APA, 1994). This disorder diminishes quality of life and is associated with increased depression and anxiety (Williams et al., 2012). Various studies have examined the mechanisms underlying chronic pain states from the brain structural, neuroplastic, neurochemical, electrophysiological, hormonal, and cognitive–emotional abnormality viewpoints (Apkarian et al., 2005; de Greck et al., 2011; Fayed et al., 2012; May, 2008; McEwen and Kalia, 2010; Noll-Hussong et al., 2013; Otti et al., 2013; Seifert and Maihöfner, 2011). fMRI studies of somatoform pain disorder patients report differences between patients and controls in cerebral responses to pain stimuli (Gündel et al., 2008; Stoeter et al., 2007). For example, Gündel et al. (2008) investigated cerebral processing of noxious heat stimuli, and found pain-related hypoactivation of the ventromedial prefrontal/orbitofrontal cortex, along with hyperactivation of the parahippocampus, amygdala and anterior insula in the patient group. Stoeter et al. (2007) investigated

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cerebral activation induced by pin prick pain stimuli, and found greater activation of brain regions such as the thalamus, anterior insula, hippocampus, and prefrontal cortex in the patient group.

Emotion plays an important modulatory role in pain perception of somatoform pain disorder patients (Dimsdale and Dantzer, 2007), and it is well established that negative emotions increase pain sensitivity in patients with chronic pain disorders as compared to controls (Burns, 2006; Zautra et al., 2005). However, to our knowledge, there are no other fMRI studies on negative emotion-induced brain activity changes in response to pain stimuli in somatoform pain disorder. Pain sensitivity in such patients is significantly affected by negative emotion (Burns, 2006; Zautra et al., 2005), and elucidating the mechanisms underlying this relationship is of both theoretical and clinical importance. Our previous studies examined sadness in this context (Yoshino et al., 2010, 2012). Sadness is one of the basic human emotions and it is generally accepted that sadness occurs in response to an aversive experience (Ellsworth and Smith, 1988).

We used fMRI to investigate how sadness affects subjective pain and associated brain mechanisms in patients with somatoform pain disorder, who responded to both moderate and low pain intensities. We hypothesized that both subjective pain intensities and pain-related brain activations (as modulated by sadness) would be greater in patients with somatoform pain disorder as compared to healthy subjects. Considering the relationship between somatoform pain disorder and cognitive–emotional abnormalities, the expected altered brain processing should involve mainly the brain structures mediating the emotional–affective dimensions of pain, including the ACC, insula, amygdala, and hippocampus.

2. Methods

2.1. Participants

The participants were eleven patients with somatoform pain disorders (6 women, mean age = 40.9 ± 6.5 years), diagnosed according to the DSM-IV criteria, and eleven gender- and age-matched control subjects (6 women, mean age = 40.6 ± 6.1 years). All participants were right-handed Japanese. Patients were recruited from outpatient sources at the Hiroshima University Hospital. The Structured Clinical Interview for DSM-IV (SCID) (Spitzer et al., 1992) was used to confirm participants' diagnostic status. Any analgesic that would be expected to alter pain perception was discontinued 24 h prior to fMRI scanning. Control participants were recruited from non-clinical populations and were matched to patients according to age and gender. The control participants endorsed no chronic pain problems and had no history of psychiatric disorders. All participants gave their written informed consent before participation, according to a protocol approved by the ethics committee of Hiroshima University.

2.2. Clinical assessments

2.2.1. Pain characteristics

The Short-Form McGill Pain Questionnaire (SF-MPQ) was used to assess pain characteristics (Melzack, 1987). The SF-MPQ consists of 15 descriptors (11 sensory, 4 affective) which are rated on an intensity scale as follows: 0 = none, 1 = mild, 2 = moderate or 3 = severe. The SF-MPQ is based on the full-length version and has a high degree of internal consistency. The SF-MPQ also includes the Present Pain Intensity (PPI) index and a visual analog scale (VAS). The Pain Catastrophizing Scale (PCS) was also used (Sullivan et al., 1995). The PCS is a 13-item self-report inventory designed to assess the extent to which a person uses a catastrophic thinking approach in response to pain stimuli. Patients are instructed to reflect on a painful experience and to indicate the extent to which they thought about each statement using a 5-point Likert scale ranging from 0 ("not at all") to 4 ("all the time"). Total catastrophizing scores range from 0 to 52. The PCS has demonstrated high internal consistency (Cronbach's $\alpha = 0.91$) and high test-retest reliability over a 6-week period ($r = 0.75$).

2.2.2. Psychometric evaluation

The Beck Depression Inventory (BDI) was used to measure depression symptoms (Beck et al., 1961). The BDI, a widely used 21-item self-report measure of depressive symptom severity, has acceptable psychometric properties that have been reviewed elsewhere (Rabkin and Klein, 1987). The State-Trait-Anxiety Inventory (STAI) was also administered (Spielberger, 1983). This inventory includes two scales to differentiate anxiety related to a transitory or situational state (STAI-S), and trait anxiety (STAI-T) that is a more consistently stable characteristic of the individual, resembling a personality trait. The Short Form Health Survey (SF-36) is a 36-item questionnaire that assesses functional status and well-being. The SF-36 is comprised of the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The PCS has four subscales: (1) physical functioning, (2) role-physical factors in functioning, (3) bodily pain, and (4) general health. The MCS has an additional four subscales: (5) vitality, (6) social functioning, (7) role-emotional factors in functioning and (8) mental health. Each scale score ranges from 0 to 100, with 0 representing the poorest functioning and 100 representing optimal health. The Cronbach's alpha reliability estimates for the Japanese SF-36 range from 0.71 to 0.87 for the subscales, indicating good test–retest reliability (Fukuhara et al., 1998). The Japanese version of the National Adult Reading Test (NART), a reading test of 50 irregularly spelled Japanese words, was used as an assessment of intellectual functioning (Matsuoka et al., 2006; Nelson, 1982).

2.2.3. Experimental paradigm and stimuli

The experiment was a simple 2 × 2 block within-subject design with the variables of pain stimulation (moderate or low) and emotional context (sad or neutral). A schematic representation of the experimental design is shown in Fig. 1. Facial expressions were presented for 4 s. The same emotion was represented four times sequentially *via* different randomly selected faces. Pain stimuli were delivered while the facial stimuli were presented. The interval between the pain stimuli was randomized, with an average duration of 1 s between stimuli (0.8–1.2 s). The present experimental design was a simplification and modification of the design used in our previous studies (Yoshino et al., 2010, 2012). We used two emotional conditions (sad or neutral) instead of three and a block design instead of an event-related task design. Each block was composed of four facial pictures with the same emotional valence (sad or neutral), sixteen pain stimuli of the same intensity (moderate or low), a rating activity, and a rest period. Each block was 32 or 36 s in duration. The participants rated the average intensity of the pain stimuli at the end of each block using a Numerical Rating Scale (NRS) projected onto the same screen for 8 s. The whole paradigm comprised a sequence of 16 randomized blocks (four blocks for each condition), and the total experimental duration was about 9 min. The order of the experimental conditions was counterbalanced across participants to mitigate order effects.

An intraepidermal stimulation method (Inui and Kakigi, 2012; Inui et al., 2002) was used to induce minor pain at the superficial skin level. The original method was slightly modified to provide a higher selectivity for the activation of nociceptors. We used a stainless steel concentric bipolar needle electrode (Nihon Kohden, Tokyo, Japan) for intraepidermal stimulation. The anode was an outer ring 1.2 mm in diameter, and the cathode was an inner needle that protruded 0.1 mm from the outer ring. This needle electrode permitted the selective stimulation of cutaneous A-delta fibers. The electrical stimuli used were 50 Hz current constant double pulses of 0.5 ms in duration. The electrical stimuli were intended to evoke the feeling of receiving an injection. The needle electrode was exchanged for each participant. The constant current stimulator (SEN-2201; Nihon Kohden, Tokyo, Japan) was located outside the MRI

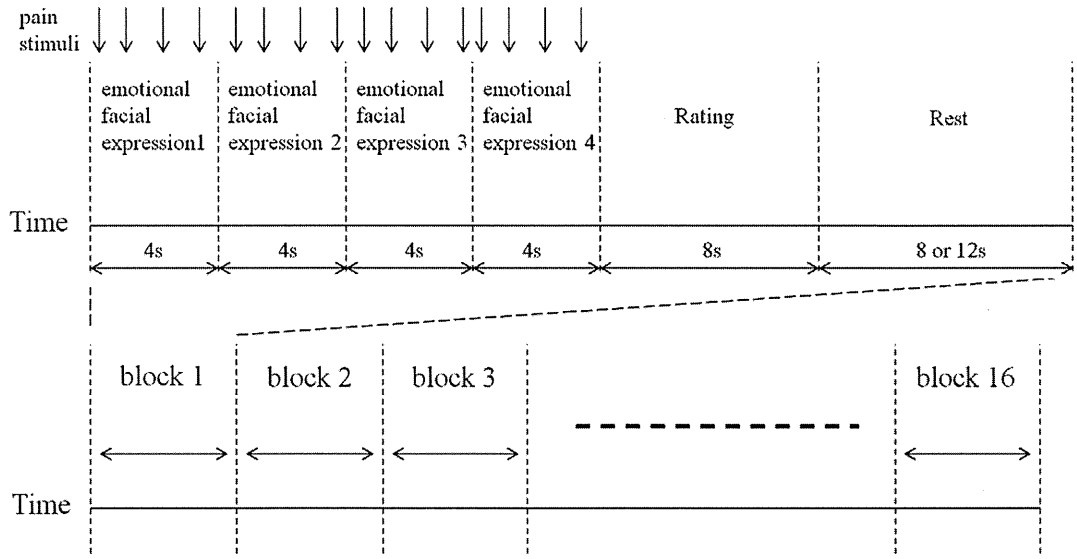

Fig. 1. Schematic representation of the experimental design. Facial expressions were presented for 4 s. The same emotion was represented 4 times sequentially in different faces randomly selected. Pain stimuli were delivered while the facial stimuli were presented. The interval between the pain stimuli was randomized, with an average of 1 s. Immediately after the pain stimuli, participants were instructed to rate their average level of pain across the 8 s using a numeric rating scale (NRS) ranging from 0 (no pain at all) to 10 (worst imaginable pain). They pushed the button to stop the bar moving between 0 and 10 to rate the intensity of their pain perception.

room, and the electrode was connected to the stimulator *via* a magnet-compatible extension cable. We established the stimulus current intensities for moderate pain (1.3 mA) and low pain (0.35 mA) based on our previous studies (Yoshino et al., 2010, 2012) and a preliminary experiment conducted before the present study. We stimulated the left forearm of each participant. The insertion of the needle electrode caused no bleeding or visible damage to the skin of any participant.

We used pictures of faces as emotional stimuli of the type that have been employed in previous functional neuroimaging studies that examined neural responses to emotional stimuli (Doallo et al., 2012; Groenewold et al., 2012; Whalen et al., 2013). We used sad and neutral facial expressions to induce different emotional contexts while the participants were exposed to the pain-inducing stimuli. Eight sad or eight neutral facial expressions displayed by eight different Japanese individuals (4 females and 4 males) were taken from a standardized series of stimuli (Kamachi et al., 2001) and were presented for 4 s each per facial image. During fMRI recording, participants were instructed to imagine how the person depicted in each image felt when the image appeared on the screen. An MR-compatible back projection screen (Silent Vision SV-6011; Avotec, USA) was used to present the facial stimuli.

2.2.4. Behavioral data analysis

Subjective pain intensity ratings were analyzed using 3-way repeated measures ANOVAs performed using SPSS version 16.0, with group (patients or controls) as a between-subjects factor, and pain (moderate or low) and emotional context (sad or neutral) as within-subjects factors. We examined the pain intensity rating ratios between the sad and neutral contexts in order to contrast the strength of pain perception in the sad emotional context condition with the neutral condition, based on a previous study (Murray and Arnott, 1993). The ratio was analyzed using 2-way repeated measures ANOVAs, with group (patients or controls) as a between-subjects factor and pain (moderate or low) as a within-subjects factor. These data were also examined using post-hoc tests performed using SPSS version 16.0.

2.2.5. fMRI acquisition

The fMRI procedure was performed using a Magnex Eclipse 1.5 T Power Drive 250 (Siemens, Munich, Germany). A time course series of 366 scans was acquired using T2*-weighted, gradient echo, echo planar imaging (EPI) sequences. Each volume consisted of 28 slices, with a slice thickness of 4 mm with no gap, and covered the entire cerebral and cerebellar cortices. The time interval between two successive acquisitions of the same image (TR) was 3000 ms, the echo time (TE) was 46 ms, and the flip angle was 90°. The field of view (FOV) was 256 mm, and the matrix size was 64 × 64, giving voxel dimensions of 4 mm × 4 mm × 4 mm. Scan acquisition was synchronized to the onset of each trial. After functional scanning, structural scans were acquired using a T1-weighted gradient echo pulse sequence (TR =2160 ms; TE = 3.93 ms; flip angle = 15°; FOV = 256 mm; voxel dimensions of 1 mm × 1 mm × 1 mm) to facilitate localization.

2.2.6. fMRI analysis

Image processing and statistical analyses were carried out using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, London, UK). The first three volumes of each fMRI run were discarded because the MRI signal was unsteady. Each set of functional volumes was realigned to the first volume. A slice timing correction was performed on the model slice to correct for the sequential sampling of the brain in the slice direction. Volumes were spatially normalized to a standard template based upon the Montreal Neurological Institute (MNI) reference brain, and finally smoothed using an 8-mm FWHM Gaussian kernel.

For the statistical analysis, subject-specific t-contrast images were calculated for the pain effects using the general linear model (first level analysis). For each participant the preprocessed data were assigned to the following four conditions in the model specification: High pain during sad facial images, low pain during sad facial images, high pain during neutral facial images, and low pain during neutral facial images. These contrasts were entered into the second level analysis. Using group analysis according to a random effects model, we conducted repeated measures 3-way ANOVAs as implemented in SPM8 with group (patients or controls) as a between-subjects factor and pain (moderate or low) and emotional context (sad or neutral) as within-subjects factors. BDI, STAI-S, and STAI-T scores were used as covariates to control for individual differences in depressive and anxiety states, in consideration of the modulatory effects of depression and anxiety on pain sensitivity. The spatial coordinates provided by SPM8, which are in MNI brain space, were converted to