flammation than is fracture callus formation. In fact, our further quantitative analysis of the osteophyte area according to the OARSI Histopathology Initiative recommendations (18,19) confirmed a lack of effect of celecoxib treatment, genetic deficiency of COX enzymes, or proinflammatory cytokines (data available from the corresponding author upon request).

In contrast to COX-2 and mPGES-1, levels of the constitutive enzymes COX-1, cPGES, and mPGES-2 were markedly decreased in the OA cartilage (Figure 1A), suggesting that these enzymes may maintain the physiologic homeostasis of joint cartilage, similar to their function in gastric mucosal defense and renal homeostasis (2). However, OA development was not enhanced in *Ptgs1*$^{-/-}$ mice (Figures 2A–C). This is in accordance with previous reports of normal gastrointestinal and renal phenotypes in these mice (2). Since expression of cPGES and mPGES-2 was not upregulated in *Ptgs1*$^{-/-}$ mouse cartilage, some mechanism other than PGE_2 synthetic enzymes might possibly compensate for the physiologic homeostasis of joint cartilage.

The present results support the findings of previous preclinical and clinical studies showing the lack of a chondroprotective effect of celecoxib (7,8). However, we cannot completely rule out the possibility of a direct protective effect of COX-2 inhibition on joint cartilage, because a beneficial effect might possibly have been counteracted by increased loading of the affected joint due to the drug's antiinflammatory or analgesic effects, with associated progression of OA. Although we sought to examine changes in synovial inflammation in the present model according to the OARSI Histopathology Initiative recommendations, the synovitis was too minimal to be evaluated even in untreated or wild-type mouse knee joints, again providing evidence against the involvement of inflammation in OA progression. In contrast, celecoxib and rofecoxib are reported to improve gait parameters, with alleviating effects on mechanical allodynia, in rat OA models (20,21). Clinical evidence has also shown an acceleration of OA development with conventional NSAIDs, probably due to increased daily activity (3). Although our preliminary gait analysis, measured by stride time, failed to reveal any changes related to OA induction or celecoxib treatment, more sensitive study methods for use in this mouse OA model are needed in order to clarify the effect of COX-2 inhibition on activity and pain control.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kawaguchi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Prevalence of Malignant Hyperthermia and Relationship with Anesthetics in Japan

Data from the Diagnosis Procedure Combination Database

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ABSTRACT

Background: Malignant hyperthermia (MH) is a rare but life-threatening disease that occurs during general anesthesia. The actual prevalence of MH remains unclear, and the association between MH and various anesthetic drugs remains controversial because of a lack of universal reporting.

Methods: Using the Japanese Diagnosis Procedure Combination database, we collected data of inpatients who had general anesthesia between July and December 2006–2008. Patients' age, gender, diagnoses, procedures, and the use of drugs during anesthesia, including volatile agents, muscle relaxants, and propofol, were investigated. Univariate comparisons were made to examine the relationship of each anesthetic drug or demographic factor with the occurrence of MH.

Results: Of 1,238,171 surgical patients undergoing general anesthesia, we identified 17 MH patients (odds ratio: 13.7, 95% CI 7.2–20.3 per million). Only one in-hospital death was identified. Men were significantly more likely to contract MH (odds ratio: 3.49; 95% CI 1.14–10.7; $P = 0.029$). No MH patient was found among 19,871 suxamethonium users. The prevalence of MH was relatively high in users of sevoflurane (odds ratio: 15.0; 95% CI 7.1–22.9 per million) and rocuronium (odds ratio: 24.3; 95% CI 4.9–43.8 per million) compared with nonusers but was not statistically significant.

Conclusions: No single drug was significantly associated with the occurrence of MH. Data should be continuously compiled, and further analyses with larger numbers of cases are necessary to identify possible causative agents.

What We Already Know about This Topic

- In Japan, the prevalence of malignant hyperthermia was estimated to be 1:60,000

What This Article Tells Us That Is New

- Using a national database of more than 1.2 million inpatients, maligant hyperthermia was diagnosed in 17 (rate, 1:73,000), and males were three times more likely to be diagnosed

MALIGNANT hyperthermia (MH) is a potentially life-threatening pharmacogenetic disease associated with abnormal intracellular calcium regulation that occurs during general anesthesia.[1] The essential biochemical abnormality of MH is characterized by an increase in the release of calcium ions in skeletal muscle cells caused by genetic mutations mainly in two genes: ryanodine receptor type 1 (RYR1) and CACNA1S.[2] In addition to these genes, more than one MH-susceptible allele has been identified.[3]

In previous Western studies, the estimated prevalence of MH ranged widely from 1:10,000 to 1:220,000.[4,5] In Japan, the prevalence of MH was presumed to be approximately 1:60,000.[6] In New York State, the prevalence of MH was confirmed to be 9.6 per million surgical discharges using a macroscale database.[7] However, these figures were based on rough estimates or data from limited geographical areas. A national prevalence of MH remains unclear because of a paucity of universal reporting in any country.

Investigations on the drugs that might trigger MH have still not reached any conclusions. A well-known potential risk factor for MH is the use of depolarizing muscle relaxants (suxamethonium) or volatile anesthetic agents (sevoflurane, isoflurane, halothane, and enflurane).[1,8–10] However, the association between other anesthetic agents and MH occur-

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rence remains unclear. Nondepolarizing muscle relaxants (vecuronium, pancuronium, and rocuronium) are considered to be safer than suxamethonium, but this still has not been fully evaluated. It is controversial whether propofol can induce MH.[11–13]

In this report, we verified the prevalence of MH in Japan and analyzed the relationship between the use of several drugs administered during general anesthesia and the occurrence of MH, using a nationally representative inpatient database, the Japanese Diagnosis Procedure Combination (DPC) database.

Materials and Methods

DPC Database

The DPC is a case-mix system, which is similar to the diagnosis-related groups in Medicare in the United States. This patient classification system was launched in 2002 by the Ministry of Health, Labor, and Welfare of Japan and linked with a lump-sum payment system. Key objectives of the DPC system are to implement a standardized electronic claims system and to provide transparency of hospital performance.[14] All 82 university teaching hospitals are obliged to adopt the DPC system, but adoption by community hospitals is voluntary. The survey of the DPC hospitals is conducted between July 1 and December 31 each year by the DPC Research Group, in collaboration with the Ministry of Health, Labor, and Welfare.[15–17] Not only administrative claims data, but also detailed patient data, are collected for all inpatients discharged from the participating hospitals between July 1 and December 31. Data are used mainly for profiling practice patterns, refinement of case-mix classification, and health policy planning, such as resource allocation. The survey started in 2003 with 82 teaching hospitals, and the number of participating hospitals steadily has increased: 262 in 2006, 926 in 2007, and 855 in 2008. Today, DPC hospitals are distributed throughout Japan. Data on all the acute-care patient admissions in the participating hospitals were compiled, and the capture rate of patient admissions was 100%. The numbers of patients included were 1.08, 2.99, and 2.86 million in 2006, 2007, and 2008, respectively. The number in 2008 (2.86 million) represented approximately 40% of all inpatient admissions to acute-care hospitals in Japan. All of the data for each patient were recorded at discharge. Hospitals sent all of the anonymous data for each month between July and December to the research group, and data were compiled in the database server in the Department of Health Management and Policy at the University of Tokyo.

The database includes the following data: location of hospitals; patients' age and gender; diagnoses and comorbidities at admission and complications after admission recorded with text data in the Japanese language and the International Classification of Diseases, 10th Revision codes; procedures coded with Japanese original codes; drugs and devices used; lengths of stay; and discharge status.

The DPC database partially corresponds to the Nationwide Inpatient Sample in the United States[18] but has several unique advantages. In the DPC database, complications that occurred after admission are clearly differentiated from comorbidities that were already present at admission. To optimize the accuracy of the recorded diagnoses, physicians in charge are obliged to record the diagnoses with reference to medical charts. At discharge, the diagnoses and comorbidities were registered to the DPC database once per admission. Medical clerks and licensed medical information managers accurately record the dates of all major and minor procedures and of drug administration and device use. Physicians and hospitals have a strong incentive for data compliance because it is mandatory to obtain the DPC-based reimbursement of medical fees.

Data Extraction

From the DPC database, we identified records of all patients who underwent surgical procedures with general anesthesia in 2006–2008. We extracted information on patients' age and gender and the use of several potentially causative drugs, including volatile anesthetic agents (sevoflurane, isoflurane, enflurane, and halothane), muscle relaxants (suxamethonium, vecuronium, pancuronium, and rocuronium), and propofol.

For the identification of MH patients from the database, we performed a free text search with the term *malignant hyperthermia* (*akusei-konetsu* in Japanese), using Microsoft SQL Server 2008 software (Microsoft Corp., Redmond, WA). With regard to identification of MH patients, a simple search using the specific International Classification of Diseases code for MH (T883) was considered unreliable. Because T883 was rarely used and physicians and medical information managers in Japan were unfamiliar with the choice of T883 code, miscoding, such as a coding of R509 (fever, unspecified), could occur. For this reason, we performed a text-based search to accurately capture all of the patients with a diagnosis of MH. To ensure the reliability of the search results, two authors (Yasunaga and Horiguchi) independently performed these procedures.

Detailed profiles of the MH patients were collected, including age, gender, comorbid diagnoses, surgical procedures, use of causative agents, and use of dantrolene.

This study was based on a secondary analysis of the administrative claims data. Given the anonymous nature of the data, the requirement for informed consent was waived. Study approval was obtained from the Institutional Review Board in University of Occupational and Environmental Health (Kitakyushu, Fukuoka, Japan).

Statistics

Univariate logistic regression analyses were performed to examine the relationship of each anesthetic drug or demographic factor with the occurrence of MH. The threshold for

Table 1. Patients' Backgrounds and Use of Potentially Problematic Anesthetic Agents (N = 1,238,171)

Patient Characteristics and Anesthetic Agents	N	%
Patient gender		
Male	597,148	48.2%
Female	641,023	51.8%
Patient age (yrs)		
0–29	222,104	18.0%
30–69	650,571	52.6%
≥70	365,496	29.4%
Volatile anesthetic agents		
Sevoflurane	932,771	75.3%
Isoflurane	33,231	2.7%
Halothane	682	0.1%
Enflurane	35	0.0%
Muscle relaxants		
Suxamethonium	19,871	1.6%
Vecuronium	782,899	63.2%
Pancuronium	11,286	0.9%
Rocuronium	246,572	19.9%
Propofol	949,694	76.7%

significance was set at $P < 0.05$. All statistical analyses were conducted using the software Statistical Package for Social Sciences version 17.0 (Statistical Package for Social Sciences Inc., Chicago, IL).

Results

Of 6.9 million inpatients in the DPC database, a total of 1,238,171 surgical patients, who underwent general anesthesia, were identified during the survey period, including 344,224 (27.8%) in teaching hospitals and 893,947 (72.2%) in community hospitals. Table 1 shows the surgical patients' backgrounds and the use of potentially causative anesthetic agents. Overall, 48% of patients were men, and 18% were at least 29 yr of age. Sevoflurane was applied in approximately 75% of patients, whereas isoflurane, halothane, and enflurane were rarely used. Suxamethonium was infused in only 1.6% (19,871) of patients. Approximately 63% were given vecuronium, 20% were given rocuronium, and pancuronium was rarely used. Propofol was administered to 77% of patients.

We identified 17 patients with a diagnosis of MH during the study period. The two authors who independently per-

Table 2. Details of Cases with Malignant Hyperthermia

No.	Gender	Age	Diagnosis	Surgery	Dead or Alive	Sev	Iso, Hal, Enf	Sux	Vec	Pan	Roc	Pro	Dan
1	M	49	Acute epidural hematoma	Open craniotomy	Dead	+	−	−	+	−	−	−	+
2	M	12	Acute appendicitis	Appendectomy	Alive	+	−	−	+	−	−	+	+
3	M	28	Acute appendicitis	Appendectomy	Alive	+	−	−	+	−	−	+	+
4	M	59	Rectal carcinoma	Low anterior resection	Alive	+	−	−	+	−	−	+	+
5	M	60	Lung carcinoma	Thoracoscopic lobectomy	Alive	+	−	−	+	−	−	+	+
6	M	64	Metastatic chest wall tumor	Tumor resection	Alive	+	−	−	+	−	−	+	+
7	M	71	Volvulus of sigmoid colon	Hemicolectomy	Alive	+	−	−	+	−	−	+	−
8	M	77	Rectal carcinoma	Low anterior resection	Alive	+	−	−	+	−	−	+	+
9	F	61	Pancreatic head carcinoma	Pancreaticoduodenectomy	Alive	+	−	−	+	−	−	+	+
10	F	80	Thoracic aortic aneurysm	Aortic arch replacement	Alive	+	−	−	+	−	−	+	+
11	M	1	Undescended testicle, bilateral	Orchiopexy	Alive	+	−	−	−	−	−	−	−
12	M	30	Repeated shoulder abarticulation	Shoulder synovectomy	Alive	+	−	−	−	−	+	−	+
13	M	69	Lung carcinoma	Thoracoscopic lobectomy	Alive	+	−	−	−	−	+	+	+
14	F	62	Descending colon carcinoma	Colectomy	Alive	+	−	−	−	−	+	−	−
15	M	19	Auditory ossicle malformation	Tympanoplasty	Alive	−	−	−	−	−	+	+	−
16	M	41	Distal clavicle fracture	Open reduction and internal fixation	Alive	−	−	−	−	−	+	+	−
17	F	2	Severe respiratory depression	Tracheostomy	Alive	−	−	−	−	−	−	+	−

Dan = dantrolene; Enf = enflurane; Hal = halothane; Iso = isoflurane; Pan = pancuronium; Pro = propofol; Roc = rocuronium; Sev = sevoflurane; Sux = suxamethonium; Vec = vecuronium.

Table 3. Incidence of Malignant Hyperthermia and the Odds Ratio in Each Subgroup

Characteristics and Anesthetic Agents	Gender and Age	*N*	MH	Incidence [95% CI] (per 1 Million)	Odds Ratio [95% CI]	*P* Value
Gender	Females	641,023	4	6.2 [0.12–12.4]	Reference	
	Males	597,148	13	21.8 [9.9–33.6]	3.49 [1.14–10.7]	0.029
Age	≥ 30 yr	1,016,067	12	11.8 [5.1–18.5]	Reference	
	0–29 yr	222,104	5	22.5 [2.8–42.2]	1.91 [0.67–5.41]	0.226
Sevoflurane		932,771	14	15.0 [7.1–22.9]	1.53 [0.44–5.32]	0.505
Vecuronium		782,899	10	12.8 [4.9–20.7]	0.83 [0.32–2.18]	0.831
Rocuronium		246,572	6	24.3 [4.9–43.8]	2.19 [0.81–5.93]	0.122
Propofol		949,694	12	12.6 [5.9–19.9]	0.73 [0.26–2.07]	0.729

CI = confidence interval; MH = malignant hyperthermia.

formed the text-based search obtained the same results. The prevalence was calculated to be approximately 13.7 per million patients (or 1:73,000), and the 95% CI was 7.2–20.3 per million. None of the 1,238,171 patients had a preoperative diagnosis of MH. None of the 17 MH patients had a comorbid disease that was likely to constitute a risk factor for MH (*e.g.*, Duchenne muscular dystrophy).

Table 2 shows the details of the 17 patients with MH. Only one in-hospital death was identified (patient no.1), a 49-yr-old man, who underwent open craniotomy for acute epidural hematoma, and was given sevoflurane and vecuronium. Of the 17 MH patients, 14 were given sevoflurane, 10 vecuronium, 6 rocuronium, and 12 propofol, whereas no MH patient was found in patients who received isoflurane, halothane, enflurane, suxamethonium, or pancuronium. All 10 patients who were given vecuronium also received sevoflurane. Of the three patients without sevoflurane (patients no. 15, 16, and 17), all received rocuronium and two received propofol. Dantrolene was administered to 11 of 17 MH patients.

Table 3 shows the prevalence of MH in each subcategory, and the results of the univariate logistic regression analyses. Men were approximately 3.5 times more likely to have MH (odds ratio: 3.49; 95% CI 1.14–10.7; $P = 0.029$). The prevalence of MH in patients at least 29 yr of age was relatively high compared with those older than 30 yr (22.5; 95% CI 2.8–42.2 *vs.* 11.8; 95% CI 5.1–18.5 per million), but the difference was not significant. The rate of MH was relatively high in sevoflurane users (15.0; 95% CI 7.1–22.9 per million) or rocuronium users (24.3; 95% CI 4.9–43.8 per million), but no statistical significance was found for any drug.

Discussion

Diagnosis of MH

There are no validated gold-standard MH diagnostic criteria globally. The diagnosis of MH is based on clinical presentation with or without laboratory testing (*e.g.*, caffeine halothane contracture test). In the Clinical Grading Scale developed by Larach *et al.*,[19] differential weighting is given to each of the manifestations of MH, but not all the tests can be performed in an individual MH episode. In Japan, the original MH criteria established by the Japan Society of Anesthesiologists are widely used and consist of two elements: body temperature increase (more than 40°C or more than 38°C with a markedly increasing rate [*i.e.*, > 0.5°C per 15 min]) and other clinical presentations of MH (*e.g.*, tachycardia, arrhythmia, metabolic acidosis, muscle rigidity, and myoglobinuria).

Our study identified 17 patients diagnosed as MH during the study period in Japan, based on the designation as MH by the physicians in charge. The anesthesiologists in charge were responsible for diagnosing MH. However, we could not confirm whether the patients definitely fulfilled the MH criteria because we could not obtain information on the detailed clinical features or laboratory data through the DPC database.

Prevalence and Patient Fatality Rate in MH

A marked advantage of the DPC database is its population representativeness. According to the Survey of Medical Institutions 2008 in Japan,** the number of surgeries under general anesthesia performed throughout Japan was 187,097 per month. Our survey included 1,238,171 patients during a total of 18 months, which represented approximately 36.8% (1,238,171/18/187,097) of all surgeries under general anesthesia in Japan. Our results showed the actual prevalence of MH (13.7 per 1 million) in the Japanese population between 2006 and 2008, which was similar to the roughly estimated figure (16.7 per 1 million) presented in a previous Japanese report.[6] Our study was the first to confirm the actual nationwide prevalence of MH, based on large-scale cross-sectional data.

According to the reported evidence, the genetic background related to MH seems to be different between Japanese and Western patients. For example, recent progress in screening for causative MH mutations of the RYR1 gene has shown a genetic diagnosis in 30–50% of Swiss MH families, whereas only one Japanese family was reported to have the MH mutation.[20,21] The detection rate of RYR1 mutations in Japanese MH patients was lower than that in North Ameri-

** Survey of Medical Institutions 2008. Vital and Health Statistics Division, Ministry of Health, Labour and Welfare, Japan. http://www.mhlw.go.jp/toukei/saikin/hw/iryosd/08/index.html. Accessed August 13, 2010.

can MH patients.[22] Nevertheless, the prevalence of MH in the Japanese population (13.7 per million) was comparable with that in New York State (9.6 per million).[7] Although several genes related to MH have been identified,[2,3] there still may be unknown genetic factors both in Japanese and Western populations. The database may be useful not only for determining MH prevalence in Japanese but also for suggesting the existence of other undetected MH mechanisms. Further studies should be conducted to elucidate other etiologies of MH in any population.

Our results also showed that men were three times more likely to contract MH than women. The prevalence of MH was relatively high in patients aged younger than 30 yr compared with those older than 30 yr. These results coincide with recent Japanese and American reports.[23,24]

In the current study, the patient fatality rate was 5.9% (1 of 17 patients). The patient fatality rate in MH in the 1970s was approximately 70%,[8] whereas a recent North American study reported that of 291 events from 1987 to 2006, 8 (2.7%) resulted in cardiac arrest and 4 (1.4%) resulted in death.[25] In Japan, the patient fatality rate decreased over time, from 42.3% during 1961–1984 to 15.0% during 1985–2004.[23] A possible explanation for the recent decrease in the death rate after MH is the improved system of monitoring and treatment. Widespread use of end-tidal carbon dioxide monitors and continuous body temperature measurement, with improved availability of dantrolene, could have resulted in early detection and improved clinical consequences of MH.[6] In the current study, dantrolene was given to only 11 of 17 MH patients. One possible reason is the availability of dantrolene in Japanese facilities. A previous Japanese study reported that 22.5% of hospitals had no stock of dantrolene in their operating rooms and 3.0% of hospitals had no stock on their premises.[6] Another reason may be that six patients might have responded to other therapies (*e.g.*, active cooling of the body), resulting in successful improvement without dantrolene use. That there were no in-hospital deaths in the six MH patients treated without dantrolene might support this possibility.

MH Risk of Anesthetic Agents

In contrast to the New York database[7] and others,[18] the unique advantage of the DPC database is that it can provide comprehensive information on all drugs given to all inpatients. We could identify the drugs given during anesthesia not only in MH patients but also in all patients undergoing general anesthesia. Therefore, the database enabled us to make a statistical comparison of the rates of MH between users and nonusers of problematic anesthetic agents.

Suxamethonium is a well-known triggering agent of MH. After exposure to this agent, deterioration of calcium homeostasis in the skeletal muscle cells may lead to muscle contracture, metabolic failure, lactic acidosis, and heat production.[1,8] Suxamethonium had commonly been used in anesthetic induction for decades; however, use of this drug has gradually decreased, and use of vecuronium and rocuronium has gradually increased. Our results showed that suxamethonium was used in only 1.6% of all patients who underwent general anesthesia, and the association between suxamethonium and MH could not be assessed because no MH patient was found among suxamethonium users.

As well as suxamethonium, volatile anesthetics also are considered triggering agents of MH. *In vitro* experiments, animal models, and human case series reports showed the potential risk of sevoflurane for MH.[9,10] Our data showed that sevoflurane was widely used and other volatile agents were rarely used in Japan. Our epidemiologic study indicated a relatively but not significantly high prevalence of MH in sevoflurane users. There was no MH case with volatile anesthetics other than sevoflurane.

Nondepolarizing muscle relaxants are now considered to be much safer than suxamethonium. However, limited evidence suggested a possible MH risk with nondepolarizing muscle relaxants. Several case reports suggested that severe masseter muscle rigidity might have been occasionally induced by administration of a nondepolarizing muscle relaxant.[26,27] Severe masseter muscle rigidity was identified as an early sign of generalized muscle rigidity and one of the signs for evaluating the likelihood of MH.[28] In practice, 32.7% of Japanese MH patients showed severe masseter muscle rigidity,[29] and 50% of Western patients with severe masseter spasms were subsequently confirmed to be MH-susceptible from muscle biopsies and contracture testing.[30–32] Based on these limited data, in the current study, we hypothesized a relationship between nondepolarizing muscle relaxants and MH. The prevalence of MH in vecuronium users was relatively low, and no MH patient was found among the pancuronium users. Furthermore, use of rocuronium also was not statistically or significantly associated with MH. Our results thus supported the conventional consideration that nondepolarizing muscle relaxants are safe; however, the current study did not definitely eliminate a possible association of increased MH occurrence with rocuronium because of a relatively increased risk of MH. Our data might be useful in suggesting to anesthesiologists the possibility of MH when using rocuronium. We should continuously gather follow-up data on the relationship among nondepolarizing muscle relaxants and MH. Furthermore, future studies will be necessary to investigate the direct relationship by means of MH-susceptible muscle biopsy and contracture testing.

Whether propofol can induce MH or not remains controversial.[11–13] Our epidemiologic data showed a relatively low prevalence of MH in propofol users and did not support an association between propofol and MH.

We should consider the possible effect of inhalation of residual volatile agents in the anesthetic circuits. Technical recommendations for the management of patients known to be MH-susceptible include: having clean anesthesia equipment and delivery of 10 l/min oxygen flow through the

equipment for more than 5 min preoperatively; removal of volatile agents from the equipment; and having a fresh carbon dioxide absorbent in the canister or nonrebreathing system.[33] We found three MH patients without exposure to suxamethonium and any volatile anesthetics. It is possible that they might have been accidentally exposed to residual volatile agents in the anesthesia equipment.

Limitations

Several limitations should be acknowledged. The first limitation is related to the use of an administrative claims database. Generally, the recorded diagnoses in such databases are less well validated than those in planned prospective surveys. However, several advantages of the data submission processes in the DPC database, such as physician-dependent diagnosis reporting, requirement of data entry *via* a strict data format, and mandatory submission linked with reimbursement, maximized the accuracy and consistency of reporting. Second, given the anonymous nature of the database, it is not possible to determine whether the same individual has been noted to have MH more than once during multiple admissions. Third, the database does not include information on patients' signs and symptoms or laboratory data; thus, we could not evaluate the validity of MH diagnosis and the severity of each individual MH episode. Underreporting or biased reporting (withholding sensitive cases) could lead to underestimation of MH events. Fourth, although the database included 40% of acute-care inpatients in Japan, participation in the DPC system was voluntary for each hospital, and patient selection was not based on a random sampling method. The database only included data between July and December, and such a time restriction will cause inaccurate estimation of the incidence of several diseases that show seasonal variation. However, to our knowledge, the occurrence of MH is unlikely to show seasonal variation, and this time restriction should have little affect. Finally, it was not possible to perform a multivariate analysis to examine the concurrent effect of multiple factors, including patient characteristics and drugs used, because of the extreme rarity of MH occurrence. Data should be continuously compiled, and further analysis with larger numbers of cases is necessary.

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Case Report

Complex Regional Pain Syndrome Revived by Epileptic Seizure Then Disappeared Soon during Treatment with Regional Intravenous Nerve Blockade: A Case Report

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We present a case of complex regional pain syndrome (CRPS), in which symptoms, including burning pain and severe allodynia, were alleviated by using a regional intravenous nerve blockade (Bier block) combined with physiotherapy, but reappeared following an epileptic seizure. Symptoms disappeared again following control of epileptic discharges, as revealed by single-photon emission computed tomography (SPECT) and electroencephalography (EEG) results. Although systemic toxicity of a local anesthetic applied by Bier block was suspected as a cause of the first seizure, the patient did not present any other toxic symptoms, and seizures repeatedly occurred after Bier block cessation; the patient was then diagnosed as having temporal symptomatic epilepsy. This case suggests that symptoms of CRPS may be sustained by abnormal brain conditions, and our findings contribute to the understanding of how the central nervous system participates in maintaining pain and allodynia associated with CRPS.

1. Introduction

Complex regional pain syndrome (CRPS) causes extreme pain. Dysfunctions of the peripheral nervous system, including the sensory and sympathetic nervous systems, are typically considered to sustain CRPS. The central nervous system (CNS) has also been reported to play an important role in CRPS emergence and maintenance [1]. Although many clinical studies on CRPS and studies using animal models have been conducted, the pathophysiological mechanism of CRPS is not yet clear [2–5]. Here, we report a case of a CRPS patient whose pain was improved by a regional intravenous nerve blockade combined with physiotherapy; however, CRPS relapsed into intolerable pain and severe allodynia following an epileptic seizure. Recurrent CRPS then rapidly improved through the control of epileptic discharges. During epileptic episodes, we investigated the CRPS patient using single-photon emission computed tomography (SPECT) and electroencephalography (EEG). Our findings may contribute to the understanding of how the CNS participates in maintaining CRPS-related pain and allodynia.

2. Case Report

A 65-year-old woman with aortic regurgitation following infectious endocarditis had undergone twice aortic valve replacement procedures within 2 months. After the second operation, more than 3 weeks were required before she could be weaned from intensive treatment, including artificial ventilation and sedative drug administration. Following recovery from heart failure, sedative drug administration was discontinued. The patient's clouded consciousness persisted for several days, but she did not show signs of epilepsy. At that time, a computed tomography (CT) scan of the brain showed a diffuse lacunar infarction but no distinct lesion. As the patient's consciousness increased, she complained of intense pain and allodynia originating from the neck and radiating to

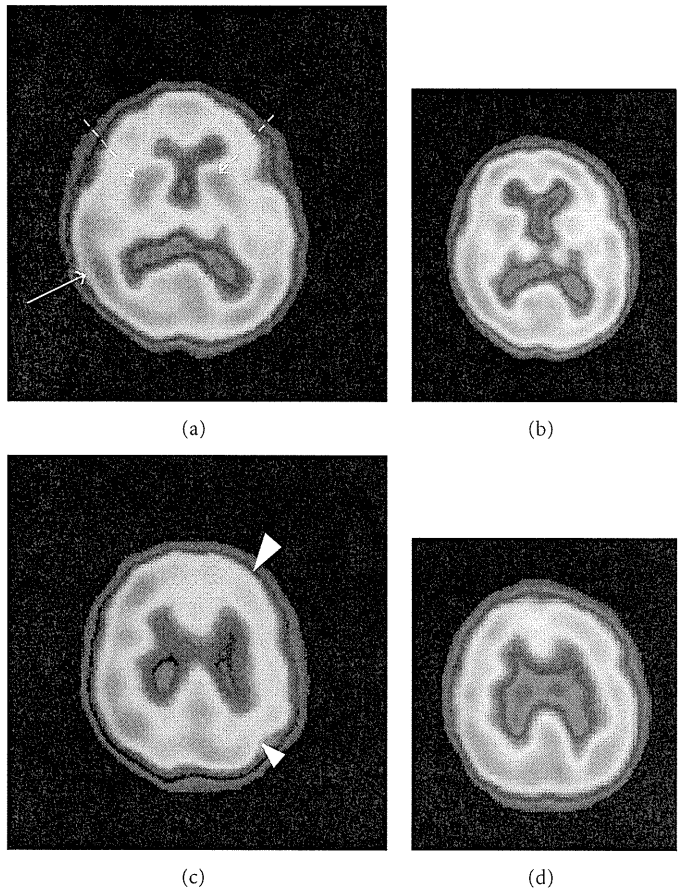

FIGURE 1: 99^{m}-HMPAO-SPECT images acquired during a seizure and 10 days later. (a) and (c) show relative hyperperfusion in the right parietal lobe (arrow) and both thalami (dotted arrows) and relative hypoperfusion in the left prefrontal and parietal lobes (arrow heads) during a seizure. (b) and (d) are the same axial slices as (a) and (c), respectively, obtained 10 days after the final seizure. In (b) and (d), relative hyperperfusion and hypoperfusion are not noted, as bilateral symmetrical cerebral perfusion has been normalized.

her left hand. The patient was treated with oral nonsteroidal anti-inflammatory drugs, but no favorable effects were observed. Her pain worsened, and she consulted our pain clinic 3 months after the second operation. She showed no signs and symptoms of neurological complications, except for pain and allodynia, before and after the cardiovascular surgeries.

During the first examination at our pain clinic, she complained of spontaneous burning pain and severe allodynia from her neck to her hand; her left hand was swollen, pale, and hot. We diagnosed her condition as complex regional pain syndrome (CRPS) [6] and began treatment, although the initiating injury was unknown. Because she was being administered anticoagulant therapy, many of the available neural blockades could not be used, except for a regional intravenous nerve blockade (Bier block, with 20 mL of 0.5% lidocaine). This neural blockade was performed 4 times per week concurrently with oral administration of a tricyclic antidepressant, nortriptyline (20 mg); this treatment resulted in the gradual reduction of pain and allodynia, which allowed the patient to receive physiotherapy. One month after treatment, pain and allodynia symptoms were nearly eliminated and swelling had also diminished. Additionally, her upper limb motor disturbance was significantly improved.

One hour after the 18th Bier block, the patient suddenly experienced a major epileptic seizure and lost consciousness during physiotherapy. This was the first time in the patient's life that a seizure episode had occurred. Intravenous administration of diazepam followed by thiamylal was used to control the seizure. An emergency CT scan of the brain showed no distinct lesions, which was confirmed by magnetic resonance imaging (MRI). The following day, the patient regained consciousness and complained of burning pain and severe allodynia localized in her left upper limb; subsequently, there was a recurrence of other CRPS symptoms (swelling, skin temperature escalation, and paleness). Despite regular intravenous administration of phenytoin, seizures occurred several times over the following 3 days, which occasionally required additional administrations of intravenous diazepam or thiamylal, and consciousness was again lost. When the patient was partially asleep due to intravenous anticonvulsants, she executed escaping movements for noxious stimulations on various healthy body parts but did not respond to noxious and tactile stimulations

on the left upper limb, suggesting an absence of hyperalgesia and allodynia. After 3 days, her consciousness was fully recovered and no seizure episodes occurred. The patient had no further complaints of burning pain or allodynia. SPECT examinations, using 99^m-Tc-hexamethyl-propylene amine oxime (HMPAO), were performed during the seizure period and 10 days later (Figure 1). The first image, obtained during a seizure, showed relative hyperperfusion in the right parietal lobe and both thalami and relative hypoperfusion in the left frontal and parietal lobes (Figures 1(a) and 1(c)), which improved after 10 days (Figures 1(b) and 1(d)). Electroencephalography (EEG) examinations were also carried out immediately following a seizure and 2 weeks later. EEG readings immediately following a seizure showed irregular and sporadic spiked waves in the left temporal lobe, followed by spikes in both the temporal lobes. Clinically, the patient showed an intermittent left upper limb spasm, although obvious epileptic discharges were not noted on EEG readings after the 3-day seizure episodes. Although postictal EEG readings occasionally displayed irregular spiked waves in the left posterior parietal and temporal lobes, the patient did not show epileptic symptoms. Clinical symptoms suggested that spiked waves were not related to the intermittent left upper limb spasm. On the basis of the SPECT and EEG findings, our neurologist diagnosed the patient as having temporal symptomatic epilepsy focused in the right parietal lobe. Her recovery was uneventful, and pain and allodynia nearly disappeared, although her skin color remained pale and her hand remained hot.

We obtained her consent to report her progress in accordance with the Declaration of Helsinki.

3. Discussion

The initiating injury causing CRPS symptoms in our patient was unknown. We speculated that an unconfirmed brachial plexus injury induced by a median sternotomy [7] and/or prolonged immobilization by sedative drug administration [8, 9] may have been a trigger. Furthermore, pain and allodynia may have been derived from disturbed cerebral function, possibly related to the use of heart-lung machines on 2 occasions and for many hours, and infectious endocarditis, which can induce epileptic seizures. Ictal pain related to an epileptic seizure has been noted in approximately 3% of reported epilepsy cases, typically involving an entire limb, a part of a limb, or hemibody [10–12]. Ictal allodynia-related epileptic seizures have been reported in only 2 cases, and both were in children [13, 14].

This is the first known case of successfully treated CRPS revived by an epileptic seizure. Following the first seizure, we suspected systemic toxicity of the local anesthetic (lidocaine, 100 mg) applied by Bier block. However, the anesthetic may not have been responsible for the seizures because the first seizure occurred one hour after Bier block, and the patient did not present symptoms of systemic toxicity to local anesthetics (e.g., change in speech pattern, lightheadedness, dizziness, or agitation) before the seizure, and seizures recurred several times for 3 days following Bier block cessation. The patient's SPECT and EEG abnormal findings were primarily concentrated to the temporal and parietal lobes, whereas epileptic discharges induced by systemic toxicity of local anesthetics are known to generally originate from nonspecific regions of the brain. The patient was therefore diagnosed with temporal symptomatic epilepsy.

A previous report of a brain tumor case suggested that epileptic discharges involved in the main pain pathways (i.e., primary and secondary somatosensory cortices (SI, SII), insula, and amygdale) can cause ictal pain and allodynia [13]. A congenital epilepsy case report suggested that deregulation of pain control established by relative hypoperfusion in the thalamus may play an important role in causing ictal pain and allodynia [14]. Furthermore, acute CRPS is reported to be related to hyperperfusion in the thalamus [15]. On the basis of these findings, we considered that the epileptic discharges noted on the EEG readings and subsequent hyper- and hypoperfusion in the specific brain regions, as revealed by 99^m-HMPAO SPECT, originated from the right parietal lobe, which includes the two main pain pathway regions (i.e., SI and SII); hyperfusion and hypofusion then spread over the entire brain, including other regions in the pain pathways (i.e., thalamus, anterior cingulate cortex, insula, and amygdala), during the seizure. This abnormal brain condition likely resulted in pain and allodynia. Further, recent advancements in functional brain imaging revealed that the anterior insula, which is strongly associated with autonomic nervous function, is reorganized in CRPS patients [16]. For our patient, abnormal autonomic-like symptoms (i.e., edema, skin discoloration, and skin temperature asymmetry) were revived by epileptic seizures. This may be related to reorganization of autonomic cerebral regions. In the present case, the second episode of CRPS symptoms occurred immediately after the first epileptic seizure episode and then rapidly disappeared with the control of epileptic discharges, although we administered antiepileptic medications, which has little potential to improve neuropathic pain. We therefore concluded that epileptic discharges relapsed into CRPS. Alternatively, we speculate that repeated seizures contributed to improvement of the second bout of CRPS symptoms. For epileptic seizure and pain relief, it has been reported that electroconvulsive therapy (ECT) can be used as an alternative treatment for chronic neuropathic pain [17]. In ECT, epileptic seizures are necessary for pain relief, as fewer seizures are related to a reduced analgesic effect. A possible mechanism of ECT for pain relief may involve alteration of neurotransmitter levels in cerebrospinal fluid, resulting in pain perception modulation. Therefore, we cannot completely rule out the possibility that repeated seizure episodes may have improved the second occurrence of CRPS symptoms.

In conclusion, the present case suggests that a pathophysiological condition(s), such as epileptic discharge and/or abnormal brain perfusion, can repeatedly trigger ictal pain, allodynia, and other signs and symptoms of CRPS when brain regions participating in pain perception have been sensitized. However, why abnormal autonomic-like symptoms of CRPS remain after controlling epileptic discharges and improvement of pain and allodynia is unclear.

4. Conclusion

We present a case of CRPS in which the symptoms of burning pain and severe allodynia were once resolved but returned following an epileptic seizure. These symptoms disappeared following the control of epileptic discharges. This suggests that CRPS symptoms may be sustained by abnormall brain conditions, and our results contribute to the understanding of how the CNS participates in maintaining pain and allodynia associated with CRPS.

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ORIGINAL ARTICLE

Human brain activity associated with painful mechanical stimulation to muscle and bone

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Abstract
Purpose The purpose of this study was to elucidate the central processing of painful mechanical stimulation to muscle and bone by measuring blood oxygen level-dependent signal changes using functional magnetic resonance imaging (fMRI).
Methods Twelve healthy volunteers were enrolled. Mechanical pressure on muscle and bone were applied at the right lower leg by an algometer. Intensities were adjusted to cause weak and strong pain sensation at either target site in preliminary testing. Brain activation in response to mechanical nociceptive stimulation targeting muscle and bone were measured by fMRI and analyzed.
Results Painful mechanical stimulation targeting muscle and bone activated the common areas including bilateral insula, anterior cingulate cortex, posterior cingulate cortex, secondary somatosensory cortex (S2), inferior parietal lobe, and basal ganglia. The contralateral S2 was more activated by strong stimulation than by weak stimulation. Some areas in the basal ganglia (bilateral putamen and caudate nucleus) were more activated by muscle stimulation than by bone stimulation.
Conclusions The putamen and caudate nucleus may have a more significant role in brain processing of muscle pain compared with bone pain.

Keywords Pain · Muscle · Bone · Neuroimaging · fMRI

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Introduction

Physical pain originating from deep tissues—including sprains, fibromyalgia, rheumatic polymyalgia, and other muscle-derived pain, and bone-derived pain such as fractures, spondylosis, and bone tumors—is very commonly encountered. Consequently, understanding how these conditions come to be painful through brain processing is clinically important. Recent imaging research using the blood oxygen level-dependent-based (BOLD) functional magnetic resonance imaging (fMRI) method successfully revealed cognitive mechanisms in response to painful stimulation.

In the field of anesthesiology, fMRI has been on trial as a tool for investigating cerebral pain processing [1–5]. Previous reports, however, have mainly been studies of

heat stimulation to skin [6, 7]. More recently, studies targeting brain activation when muscle pain is caused using electric stimulation or hypertonic saline have successfully demonstrated that some areas are differently activated, including the contralateral primary somatosensory cortex (S1), the ipsilateral anterior insula, the contralateral motor cortex, the cingulate motor area, and the perigenual cingulate [8–10]. However, there are few studies of the brain processing activated by mechanical stimulation to deep tissues [11]. To elucidate the central processing of painful mechanical stimulation to deep tissues (muscle and bone), we compared the brain activation induced by two different intensities of stimulation (strong and weak) at two different targets (muscle and bone), using fMRI.

Materials and methods

Subjects

All the procedures were approved by the Osaka University Hospital Institutional Review Board. Twelve healthy volunteers (7 men, 5 women; aged 24–56 years) agreed to receive painful stimulation while their brain activation was evaluated. They had no neurological disorders or detectable MRI abnormalities in the brain and were free from any medication within 24 h before the study. In written informed consent, each acknowledged that they were willing to receive experimental painful stimulation. Before the protocols were carried out, each volunteer was familiarized with the experimental protocol, the types of stimulation, and the tasks performed.

Painful stimulation

To determine suitable stimulation intensities for each subject, a preliminary testing was performed immediately before the fMRI study. Perpendicularly applying a round 10-mm solid tip of an algometer probe (Pressure Algometer NPA-1, Shinko, Japan) on the surface (skin) at the medial point of the right tibia (Fig. 1), the experimenter gradually increased the pressure until the subject verbally indicated that the stimulation was painful. At that point, the pain intensity was taken to be '3' on a subjective 10-point numerical rating scale (NRS). The three median values of five trials were averaged to determine the weak stimulation to be applied to the tibia of particular volunteers. Similarly, the subject was asked to verbally indicate when the pain was such that it would probably be intolerable for more than 20 s without withdrawal movement. At this point, pain intensity was scored as '8' on the volunteer's subjective 10-point NRS. Similar grading of muscle pain was also carried out [12]. Here the tip of the probe was applied to the skin on the gastrocnemius muscle at a medial point 3–5 cm from the stimulation point of the tibia (Fig. 1). For each volunteer, as in the bone protocol, subjective NRS pain scores of '3' and '8' were obtained. These procedures were conducted by one experimenter (M.S.) who, in each instance and so far as possible, endeavored to consistently apply the required level of pressure perpendicularly.

Protocol

Each subject participated in a trial comprising 12 fMRI task sessions. At each right-leg site that was evaluated in the preliminary testing, three trials of 20 s of strong or weak stimulation were applied in each session. The site and strength of stimulation were pseudo random for each series. After each series of three stimulations (in a session lasting 3 min; Fig. 2), there was a pause of 1 min before the next session. MRI scans were acquired throughout the 36-min period. The subjects were asked to rate, using NRS, the overall pain at the end of each series of three stimulations (mean of three periods of 20-s stimulation). Before the

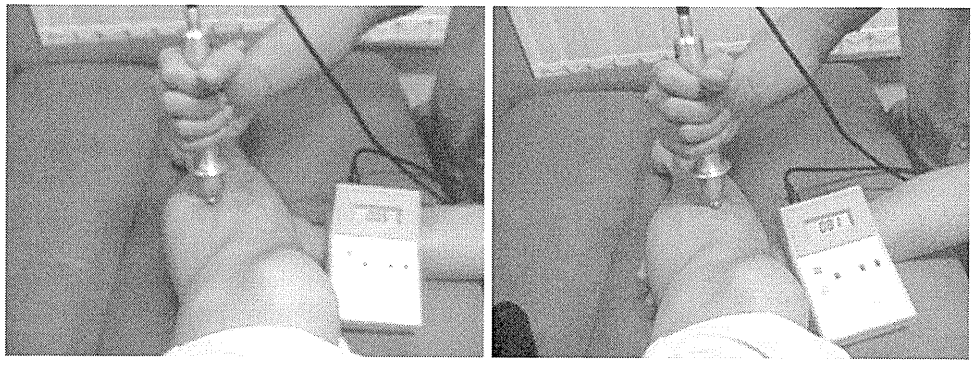

Fig. 1 Photograph showing how a digital algometer was used to apply stimulation to muscle (*left*) and bone (*right*). Bone stimulation was applied to the surface (skin) at the midpoint of tibia. Muscle stimulation was applied to the surface of gastrocnemius 3–5 cm posterior from bone stimulation point. Intensities of stimulation (muscle vs. bone, strong vs. weak) were decided for each subject by averaging the values of the median of three of five trials

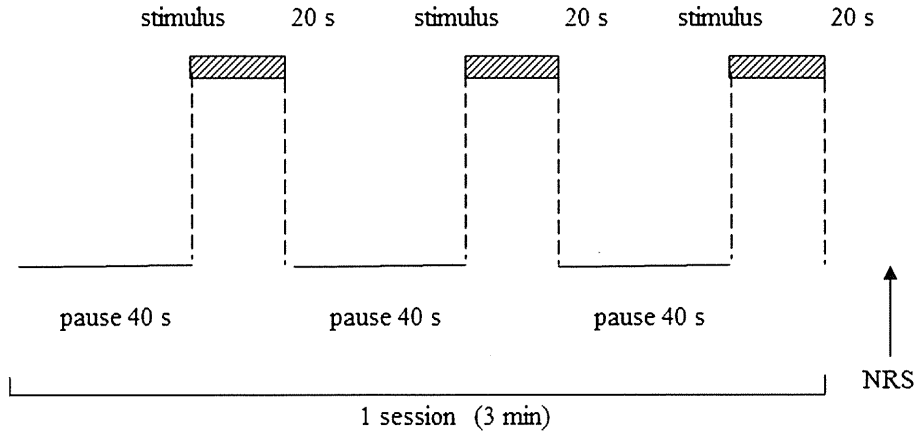

Fig. 2 Schematic representation of the experiment. Each subject underwent one trial comprising 12 sessions with a 1-min interval between sessions. Each session, lasting a total of 3 min, started with 40-s pause, and then a 20-s strong or weak stimulation to either muscle or bone. Weak and strong stimulations for each volunteer were decided in the preliminary testing. The order of stimulation was pseudo randomized. After each session, volunteers were asked to score the perceived pain. *NRS* numerical rating scale

commencement of the protocol, each volunteer was informed that the site (muscle or bone) and intensity (weak or strong) of the forthcoming series of stimulation would be random.

MRI

Imaging was performed with a 1.5-T MRI scanner (Signa EXCITE Xl 11.0; GE Healthcare, Milwaukee, WI, USA). Functional MR images were obtained using a multislice echo planar imaging technique (EPI) based on 30 oblique slices (repetition time, 3,000 ms; time to echo, 60 ms; flip angle, 90°; slice thickness, 5 mm; gap, 0 mm; field of view, 300 mm × 300 mm; in-plane resolution, 4.69 mm × 4.69 mm). All the subjects were positioned in the scanner with a foam rubber pad to minimize head movement and instructed simply to lie with their eyes closed without moving or speaking. Their heads were placed so that the uppermost superior aspect of brain was within the field of view. High-resolution T_1-weighted anatomic images with the same orientation as the EPI slices were collected from each subject. In the subsequent analysis, these images were used for coregistration of functional and anatomic data.

Data analysis

Psychophysics

Using paired *t* testing, we compared the stimulation intensity and the average subjective NRS scores for muscle (weak and strong) and bone (weak and strong), respectively. Effects of order of stimulus application on NRS were evaluated with two-way analysis of variance (ANOVA); $P < 0.05$ was regarded as significant. Values are given as mean ± SD.

fMRI data analysis

The fMRI data were analyzed with Statistical Parametric Mapping software (SPM99; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 6.1 (Mathworks, Sherborn, MA, USA). The functional images were realigned to correct for head movements, coregistered with each subject's anatomic MRI, and transformed to the format of the standard brain according to Talairach coordinates [13]. The functional images were spatially smoothed with an 8-mm full-width half-maximum Gaussian kernel. We fitted a linear regression model (fixed effects within subjects). Each condition was modeled with a boxcar function and convolved with a hemodynamic response function. Temporally, the voxel time series were high-pass filtered (124-s cutoff periods) to remove slow trends in the data, and low-pass filtered with a hemodynamic response filter.

We compared image data for each group—weak muscle stimulation, strong muscle stimulation; weak bone stimulation, strong bone stimulation—against the data from each resting condition, respectively. All the data were pooled for group statistical comparisons. Across the subjects, random effect analysis was performed to determine the significant activation associated with different sites and intensities of stimulation ($P < 0.001$ uncorrected; minimum cluster size, 20 voxels). To investigate the brain network related to painful stimulation intensity, we calculated the difference in the areas activated by strong stimulation minus weak stimulation (paired *t* test; $P < 0.005$ uncorrected; minimum cluster size, 20 voxels). To identify the brain areas that are differently activated by muscle and bone stimulation, we also analyzed the data separately (strong muscle minus strong bone; weak muscle minus weak bone; and all

together) (paired t test; $P < 0.005$ uncorrected; minimum cluster size, 20 voxels).

Results

Stimulation and pain intensity

The mean intensity of muscle stimulation was 21.1 ± 8.4 N for weak stimulation and 40.7 ± 7.8 N for strong stimulation; the mean intensity of bone stimulation was 14.2 ± 5.7 N for weak stimulation and 30.1 ± 7.9 N for strong stimulation. The NRS scores with strong muscle and strong bone stimulation were significantly higher than those with weak muscle and weak bone stimulation, respectively ($P < 0.05$ for both) (Table 1). All the volunteers clearly distinguished the two intensities of stimulation because the weaker stimulation was always scored lower. Although the volunteers found weak muscle stimulation trials more painful ($P < 0.05$) than weak bone stimulation, no similar difference was found for strong stimulations. Comparing the data among the three trials of the same intensity at the same site, no differences in NRS scores were found; this indicates that repeated mechanical stimulation did not sensitize or desensitize the volunteers ($P > 0.05$).

fMRI

In response to painful muscle stimulation, brain activation was apparent within the bilateral anterior cingulate cortex (ACC), insula cortex, the secondary somatosensory cortex (S2), the inferior parietal lobule (IPL), the posterior cingulate cortex (PCC), putamen, the ipsilateral dorsolateral prefrontal cortex (DLPFC), thalamus, caudate, and the contralateral claustrum (Fig. 3a,b; Table 2). In response to painful bone stimulation, brain activation was also apparent within the bilateral ACC, the IPL, the S2, the PCC, the ipsilateral DLPFC, and the contralateral claustrum (Fig. 4a,b; Table 2). Peak coordinates (x, y, z) in Montreal Neurological Institute (MNI) space and Z-scores (>6.00) for the activated brain regions by muscle and bone pain are shown in Table 2. Differences in the areas activated by strong versus weak muscle stimulation were mainly found in the contralateral S2 and the bilateral thalamus (Fig. 3c). For strong versus weak bone stimulation, the difference was found in the contralateral S2 (Fig. 4c). With weak stimulations, the activation differences between muscle and bone stimulation were apparent in the bilateral caudate nucleus and contralateral Brodmann areas 22 and 45 (Fig. 5a). With strong stimulations, the activation differences were apparent in the bilateral putamen, the ipsilateral ACC, and the contralateral claustrum (Fig. 5b). Analyzing the sum of the differences between muscle- and bone-related pain revealed that activation was different in the bilateral caudate and contralateral putamen (Fig. 5c; Table 3).

Discussion

In this study, as an initial step toward elucidating the brain activation associated with mechanically induced deep tissue pain, we found that the contralateral S2 was more activated by stronger stimulations to muscle or bone. We also found that parts of the basal ganglia (putamen and caudate nucleus) were more activated by muscle stimulation than by bone stimulation.

Psychophysics

The NRS scores measured during fMRI were higher than those determined in the preliminary testing. Although the reason is not clear, the difference of the rate of pressure increase between preliminary testing and the fMRI session may be a cause.

On the other hand, the NRS scores for the two sets of three stimulations at each site did not change during the protocol (see Table 1), suggesting that no further change in sensitivity occurred. Nie et al. [14] have reported that after

Table 1 Numerical rating scale (0–10 NRS) by mechanical stimulation

	1st stimulation	2nd stimulation	3rd stimulation	mean
weak muscle stimulation	4.83±1.99	4.67±1.88	4.5±1.98	4.67±1.90
strong muscle stimulation	8.17±1.34	8.5±1.17	8.25±1.42	8.31±1.28
weak bone stimulation	4.25 ±2.14	3.25 ±1.14	3.92 ±1.78	3.81±1.74
strong bone stimulation	8.83 ±1.03	8.25 ±1.36	8.17 ±1.70	8.42 ±1.38

NRS with strong muscle and strong bone stimulation were significantly higher than those with weak muscle and weak bone stimulation (*$P < 0.05$). In weak stimulations, NRS with muscle stimulation was higher than with bone stimulation (**$P < 0.05$). There were no differences between strong muscle and bone stimulations among NRS with 1st, 2nd, and 3rd stimulation in the same study groups

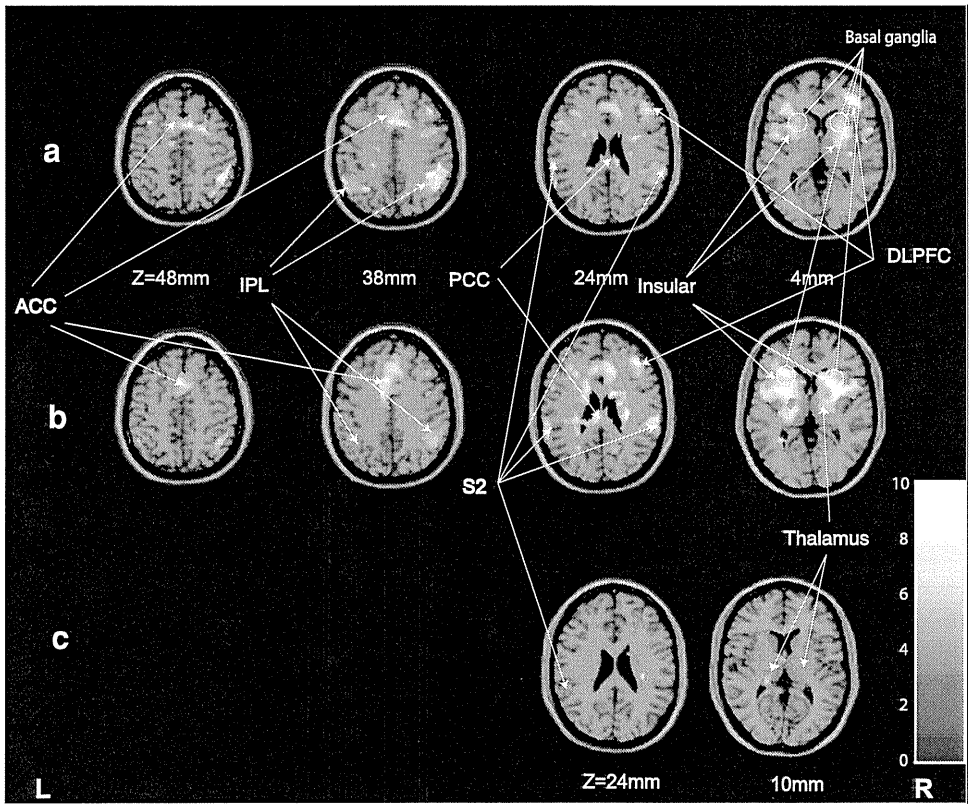

Fig. 3 Brain activation induced by muscle stimulation: weak stimulation (**a**), strong stimulation (**b**), and contrast of strong and weak stimulation (**c**). In millimeter elevations relative to a line through the anterior–posterior commissure (AC–PC line), brain slices are shown in superior–inferior sequence. The axial slices are arranged from dorsal (*left*) to ventral (*right*). Statistical map thresholds are $P < 0.001$ (**a**, **b**, uncorrected), and $P < 0.005$ (**c**, uncorrected, paired test). Minimum cluster size is 20 voxels. Right (*R*) and left (*L*) sides are indicated. *ACC* anterior cingulate cortex; *IPL* inferior parietal lobule; *S2* secondary sensory cortex; *DLPFC* dorsolateral prefrontal cortex; *PCC* posterior cingulate cortex

ten stimulations with 30-s intervals between stimulations, subjects gave higher VAS scores, increasing to 192% ± 71% for stimulation of the tibia and to 117% ± 42% for stimulation of the tibia anterior muscle. In the present study, the protocol specified a 60-s interval during all the sessions. This interval was apparently long enough to prevent temporal sensitization. To evoke equivalent pain in muscle and bone, greater stimulation had to be applied largely to the muscle; this may be because nociceptive nerve density is greater in the periosteum than in muscle [15].

Imaging

A previous positron emission tomography (PET) study and event-related fMRI study using noxious electronic stimulation of muscle showed activation in the ACC, S2, and anterior insula [8, 10]. Also, PET and fMRI study using injection of hypertonic saline into muscle evoked the activation in contralateral insula and putamen [9, 16]. In our study, the results for mechanical stimulation are consistent with the previous muscle pain studies, which have shown that the different types of stimulation (hypertonic saline, electrical stimulation, and mechanical stimulation) applied to muscle induce equivalent activation patterns [8, 10, 16]. We found that stronger muscle stimulation resulted in greater activation in the contralateral S2, the bilateral thalamus (contralateral > ipsilateral), and that stronger bone stimulation caused greater activation in the contralateral S2. In each case, the contralateral S2 was more activated by strong stimulation. However, caution is needed in interpreting these results because greater application of the force to skin is also involved during strong stimulation. The activation of the contralateral S2 may also come from greater cutaneous stimulation. In a PET study investigating thermal stimulation to skin, Coghill et al. [17] have shown that the ipsilateral cerebellum, the contralateral S1, the supplementary motor area, the bilateral S2, the lentiform nucleus, the insular cortex, and the thalamus and ACC are more activated depending on perceived pain intensity. In an fMRI study, using mechanical phasic stimulation on the skin, Ringler et al. [18] have shown that the contralateral S2 is more activated by stronger stimulation. The contralateral S2 may take part in processing pain intensity derived from both skin and deep tissues.

Comparison of the activation associated with muscle and bone stimulation revealed that caudate nucleus and putamen were more activated by muscle than by bone stimulation. No activation existed that was evoked by (bone > muscle) stimulation (data not shown). The activation in these areas is supposed to be related to stimulated sites (muscle or bone), not to stimulation or pain intensity, because these areas were not included as a contrast when we stimulated the single target (muscle or bone) with the

Table 2 Peak coordinates (*x*, *y*, *z*) in Montreal Neurological Institute (MNI) space and *Z*-scores (>6.00) for the activated brain regions by muscle and bone pain

Region	BA	Muscle pain				BA	Bone pain			
		Peak voxel coordinate			*Z*-score		Peak voxel coordinate			*Z*-score
		x	*y*	*z*			*x*	*y*	*z*	
ACC	32	−8	12	44	7.07					
	32	−6	18	32	6.42					
	32	−12	26	30	6.42					
Insula right	13	28	26	2	6.33					
		34	4	8	6.09					
Insula left		−34	6	8	6.25	44	−48	10	6	6.27
	47	−28	24	−8	6.05					
S2 right	40	62	−32	30	6.32					
S2 left	40	−60	−32	28	6.39					
IPL left						40	−48	−52	40	6.57
	40	−48	−58	42	6.33	40	−48	−40	28	6.48
	40	−44	−48	42	6.13	40	−62	−36	32	6.27
Thalamus right		20	−18	10	6.04					
Putamen right		26	2	6	6.16					
		20	−4	8	6.10					
Putamen left		−32	6	6	6.54					
Claustrum left		−26	12	10	6.39		−30	10	6	6.18
Caudate right		16	12	8	6.13					

Brodmann areas are given where available

BA Broadmann area, *ACC* anterior cingulate cortex, *S2* secondary sensory cortex, *IPL* inferior parietal lobule

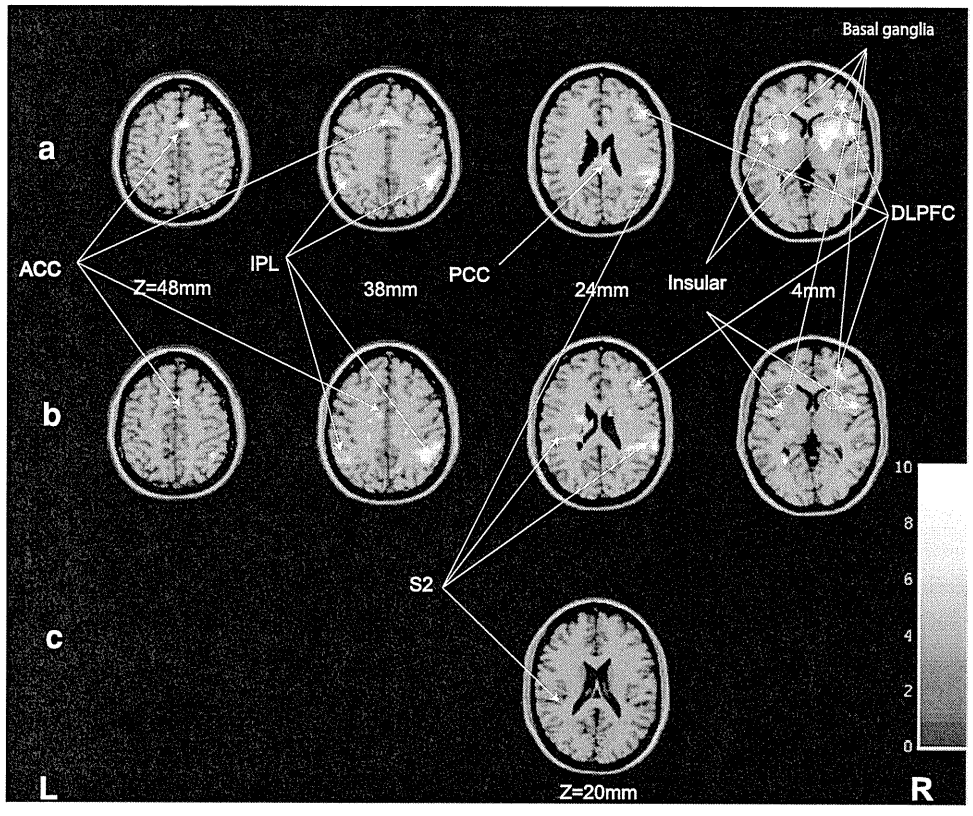

Fig. 4 Brain activation induced by bone stimulation: weak stimulation (**a**), strong stimulation (**b**), and contrast of strong and weak stimulation (**c**). In millimeter elevations relative to a line through the anterior–posterior commissure (AC–PC line), brain slices are shown in superior–inferior sequence. The axial slices are arranged from dorsal (*left*) to ventral (*right*). Statistical map thresholds are $P < 0.001$ (**a**, **b**, uncorrected), and $P < 0.005$ (**c**, uncorrected, paired test). Minimum cluster size is 20 voxels. Right (*R*) and left (*L*) sides are indicated. *ACC* anterior cingulate cortex; *IPL* inferior parietal lobule; *S2* secondary sensory cortex; *DLPFC* dorsolateral prefrontal cortex; *PCC* posterior cingulate cortex

different intensities. Additionally, pain intensities were identical between strong muscle and strong bone pain. Reports of the previous pain imaging studies have suggested that the putamen is activated by nociceptive stimulation [17, 19], including muscle pain with hypertonic saline [16]. Basal ganglia are reported to have a role in

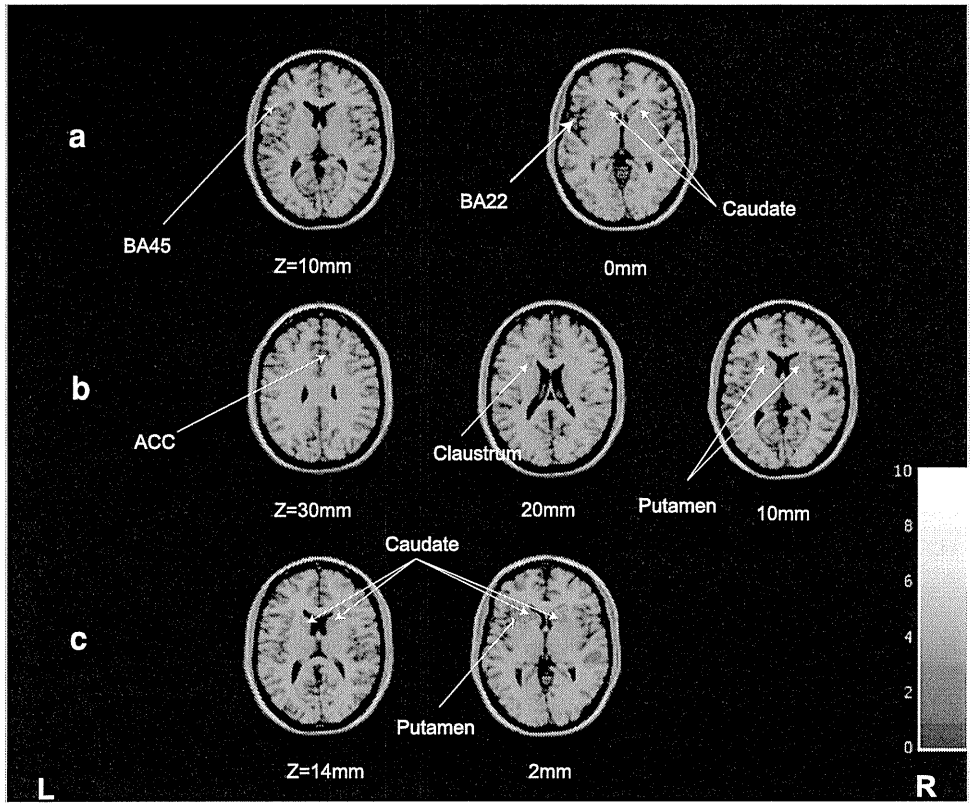

Fig. 5 Contrast of brain activation induced by muscle and bone stimulation: contrast of weak stimulation to muscle and bone (**a**), contrast of strong stimulation to muscle and bone (**b**), and contrast of all the stimulations to muscle and bone (**c**). In millimeter elevations relative to a line through the anterior–posterior commissure (AC–PC line), brain slices are shown in superior–inferior sequence. The axial slices are arranged from dorsal (*left*) to ventral (*right*). Statistical map thresholds are $P < 0.005$ (uncorrected, paired test). Minimum cluster size is 20 voxels. Right (*R*) and left (*L*) sides are indicated. *BA* Brodmann area; *ACC* anterior cingulate cortex

Table 3 Peak coordinates (x, y, z) in Montreal Neurological Institute (MNI) space and *Z*-scores for activated brain regions by muscle–bone pain

Region	(Muscle–bone) pain			
	Peak voxel coordinate			*Z*-score
	x	y	z	
Putamen left	−24	12	24	4.12
Caudate left	−18	16	8	4.01
Caudate right	16	22	0	3.95

motor preparation, movement control, and emotional, motivational, and cognitive function [20–22]. Processing in the putamen and caudate nucleus is also reported to be related to pain-avoidance behavior [23]. Our results suggest that the putamen and caudate nucleus may have a more significant role in the brain processing of muscle pain compared with bone pain.

Conclusion

In conclusion, the putamen and caudate nucleus may have a more significant role in the brain processing of muscle pain compared to bone pain.

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Conflict of interest None.

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