the phantom limb must be stimulated [16]. In addition to MCS, electrical spinal cord stimulation (SCS) has been used to treat phantom limb pain, but the analgesic mechanism of this treatment has not yet been shown in detail. In functional brain imaging studies, various brain regions are activated during SCS. In a majority of these studies, M1 activation was specifically observed [17, 18]. One proposal is that SCS stimulates the dorsal column of the spinal cord and its electric impulses ascend through the dorsal column–medial lemniscal pathway to the brain. In physiological conditions, the dorsal column–medial lemniscal pathway conveys proprioception, vibratory sense, and discriminative touch sense, and these types of somatosensory information are thought to terminate at S1. However, recent studies clearly show that proprioceptive information is directly transmitted to both S1 and M1 [19], and proprioceptive information is mainly perceived at M1 [20]. On the basis of these notions, electric impulses generated by SCS would ascend the dorsal column–medial lemniscal pathway and terminate in M1, and the impulses may then be perceived at M1. Finally, SCS may produce an analgesic effect through the stimulation of M1. Interestingly, no analgesic effect is observed when patients treated with SCS cannot perceive the electrically stimulated sense in their phantom limb, suggesting that SCS must stimulate the phantom limb's somatotopic area in M1 in order to be effective. Although the somatotopic area of the phantom limb is invaded and submerged after amputation by the reorganization of M1 (i.e., expansion of mouth/facial surface area), electrical impulses by SCS (or MCS) toward the somatotopic area of the phantom limb may induce further reorganization of M1 (i.e., expansion of the phantom limb area and shrinkage of the mouth/facial surface area). This could theoretically result in the alleviation of phantom limb pain, but future studies would be needed to confirm such a viewpoint.

Reconstruction of the somatotopic map of phantom limbs: future perspectives on neuropathic pain therapy

In order to improve activities of daily living, patients with an upper limb amputation sometimes wear an electrical hand prosthesis connected to the stump of the amputated limb. Hand movements are produced by the contraction and relaxation of muscles at the stump. The prosthesis can become functional through training, and this training can also be useful for treating phantom limb pain [21]. Since the somatotopic map in S1/M1 corresponding to the prosthesis forms after motor learning of the functional limb [22, 23], it seems likely that the acquisition and expansion of the somatotopic area in S1/M1 that corresponds to the residual limb and phantom limb is linked to the analgesic effects of the prosthesis training. In fact, the somatotopic area in S1/M1 is reported to expand through the training of repeated somatosensory stimulations, and this seems to alleviate neuropathic pain in the affected limb [24, 25]. There are many reports on neurorehabilitation for neuropathic pain using visuomotor feedback of the affected limb. Following visuomotor feedback, the generation of voluntary movement perceptions of the affected limb can induce expansion of the somatotopic area in S1/M1 and then alleviate neuropathic pain, such as phantom limb pain [26–28], post-spinal cord injury pain [29], post-brachial plexus injury pain [30], and complex regional pain syndrome (CRPS) [31].

We have conducted neurorehabilitation using visuomotor feedback treatments (namely, mirror visual feedback and prism adaptation to optical deviation [32, 33]), but the treatments are still not effective for alleviating pain in many patients. We believe that, in addition to visuomotor feedback from the affected limb, a more powerful neurorehabilitation strategy using motor control of and somatosensory feedback from the affected limb should be developed. To accomplish this, we are now cooperatively developing a rehabilitation robot suit system (Fig. 1) [34, 35]. The system detects movements from a sensor attached to the healthy limb (for example, elbow joint flexion), and then artificial muscles and wires of the actuator (attached to the affected limb) create passive movements of the affected limb resembling those of the healthy limb. Thus, the affected limb, which may have been paralyzed following nerve injury, can be exercised voluntarily when patients intend to exercise the affected and healthy limbs simultaneously in similar manners.

Under the condition in which motor commands to the limb are successively generated from motor intention and then somatosensory feedback of the limb movement reaches S1, the activation of S1 is stronger than the condition in which the limb is exercised passively without any motor intentions or commands [36]. Furthermore, M1 activation is observed much more strongly when exercising the limb voluntarily than during passive movements of the limb. In particular, activation of the somatotopic area of the limb was observed in M1. By intending to command and actually commanding the affected and healthy limbs to exercise simultaneously, therefore, the rehabilitation system enables voluntary movements of the affected limb, and then (1) visuomotor feedback regarding the affected limb movements is acquired, as in a mirror visual feedback treatment, (2) somatosensory feedback of the affected limb movements are derived through the residual limb, and finally (3) the somatotopic area corresponding to the affected limb would expand, and this would result in alleviating neuropathic pain. With this rehabilitation system, the coordinative linkage of visuomotor and

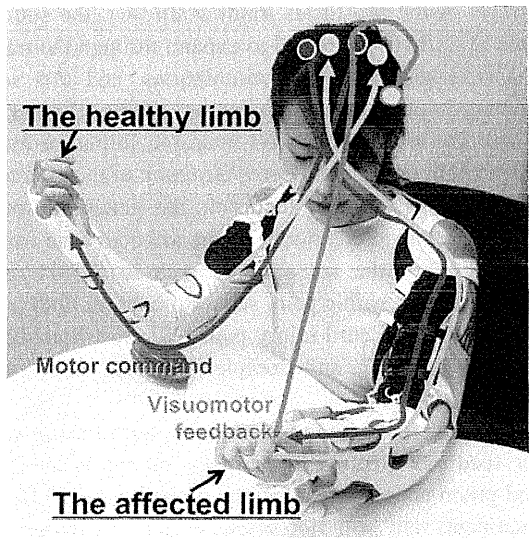

Fig. 1 Rehabilitation robot suit system for an upper limb with motor paralysis and neuropathic pain. A sensor suit is worn on the *right* upper limb (the healthy limb). On the *left* upper limb (the affected limb), an actuator consisting of artificial muscles and wires is fitted. Intending and forwarding the same motor commands from bilateral motor cortices toward both upper limbs (*red circles* and *arrows*), the sensor suit detects movements of the right limb, and the actuator carries out movements of the left limb resembling the movements of the healthy right limb. Thus, using this system, patients can passively but voluntarily exercise their affected limb, even in cases of motor paralysis and neuropathic pain resulting from nerve injury. Even though voluntary-like movements of the left limb are performed passively, patients perceive visuomotor (*green circle* and *arrow*) and somatosensory (*blue circle* and *arrow*) feedback in accord with their motor intention and commands of the left limb. Thus, the system can help a patient reconcile the coordinative sensorimotor integration of the left limb, secondarily expand the somatotopic area in the primary motor and somatosensory cortices, and finally provide relief from neuropathic pain (Co-development with Active-link Inc)

somatosensory feedback in accordance with motor intentions and commands of the affected limb could become a more effective strategy than current conventional neurorehabilitation treatments. In fact, in a psychophysical study involving healthy individuals, performance of the discriminant somatosensory function of the limb improved after exposure to the rehabilitation system (personal communications and unpublished data). In addition to determining the future clinical utility of the rehabilitation system for motor paralysis and neuropathic pain, we aim to gain supporting evidence through functional brain imaging studies.

Conclusion

Phantom limb sensation and phantom limb pain are often discussed as one phenomenon, but some patients who have a phantom limb do not perceive pain. The neuromatrix theory (i.e., a hypothesis that neural substrates for recognizing one's own body in the central nervous system underlie phantom limb sensation and phantom limb pain) [37] is a convenient and attractive thesis for explaining phantom limb phenomena, but it does not provide a satisfactory explanation for why phantom limbs are accompanied by pathologic pain.

Since pathological pain and coordinative linkage of sensorimotor integration are intimately related [32, 33], we anticipate that therapeutic mechanisms which affect the reorganization in M1/S1 may lead to a clarification of the underlying mechanisms of phantom limb sensations as well as of phantom limb pain.

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References

1. Jensen TS, Krebs B, Nielsen J, Rasmussen P. Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to pre-amputation pain. Pain. 1985;21:267–78.
2. Flor H, Nikolajsen L, Jensen TS. Phantom limb pain: a case of maladaptive CNS plasticity? Nat Rev Neurosci. 2006;7:873–81.
3. Wringley PJ, Press SR, Gustin SM, Macefield VG, Gandevia SC, Cousins MJ, Middleton JW, Henderson LA, Siddall PJ. Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. Pain. 2009;141:52–9.
4. Maihofner C, Handwerker HO, Neundorfer B, Birklein F. Patterns of cortical reorganization in complex regional pain syndrome. Neurology. 2003;61:1707–15.
5. Karkin-Tais A, Muftic M, Suljevic S, Hadziahmetovic N, Miladinovic K, Alajbegovic A. 13-year study of pain in phantom limbs of amputees-victims of war in Sarajevo (period 1992–2005). In: Proc Pain Europe V: Congress European Federation of IASP. Istanbul.
6. Roux FE, Ibarrola D, Lazorthes Y, Berry I. Virtual movements activate primary sensorimotor areas in amputees: report of three cases. Neurosurgery. 2001;49:736–42.
7. Willoch F, Rosen G, Tolle TR, Oye I, Wester HJ, Berner N, Schwaiger M, Bartenstein P. Phantom limb pain in the human brain: unraveling neural circuitries of phantom limb sensations using positron emission tomography. Ann Neurol. 2000;48:842–9.
8. Paus T. Primate anterior cingulated cortex: where motor control, drive and cognition interface. Nat Rev Neurosci. 2001;2:417–24.
9. Petrovic P, Ingvar M. Imaging cognitive modulation of pain processing. Pain. 2002;95:1–5.
10. Mercier C, Reilly KT, Vargas CD, Aballea A, Sirigu A. Mapping phantom movement representations in the motor cortex of amputees. Brain. 2006;129:2202–10.
11. Reilly KT, Mercier C, Schieber MH, Sirigu A. Persistent hand motor commands in the amputee's brain. Brain. 2006;129:2211–23.

12. Sumitani M, Yozu A, Tomioka T, Yamada Y, Miyauchi S. Using the intact hand for objective assessment of phantom hand-perception. Eur J Pain. 2010;14:261–5.
13. Karl A, Birbaumer N, Lutzenberger W, Cohen LG, Flor H. Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. J Neurosci. 2001;21:3609–18.
14. Saitoh Y, Shibata M, Sanada Y, Mashimo T. Motor cortex stimulation for phantom limb pain. Lancet. 1999;353:212.
15. Hirayama A, Saitoh Y, Kishima H, Shimokawa T, Oshino S, Hirata M, Kato A, Yoshimine T. Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. Pain. 2006; 122:22–7.
16. Roux FE, Ibarrola D, Lazorthes Y, Berry I. Chronic motor cortex stimulation for phantom limb pain: a functional magnetic resonance imaging study. Neurosurgery. 2008;62:S978–85.
17. Stancak A, Kozak J, Vrba I, Tintera J, Vrana J, Polacek H, Stancak M. Functional magnetic resonance imaging of cerebral activation during spinal cord stimulation in failed back surgery syndrome patients. Eur J Pain. 2008;12:137–48.
18. Kishima H, Saitoh Y, Oshino S, Hosomi K, Mohamed A, Hirata M, Goto T, Maruo T, Yanagisawa T, Sumitani M, Osaki Y, Hatazawa J, Yoshimine T. Modulation of neuronal activity after spinal cord stimulation for neuropathic pain. NeuroImage. 2010; 49:2564–9.
19. Kleinfeld D, Waters J. Wilder Penfiel in the Age of YouTube: visualizing the sequential activation of sensorimotor areas across neocortex. Neuron. 2007;56:760–2.
20. Naito E, Ehrsson HH, Geyer S, Zilles K, Roland PE. Illusory arm movements activate cortical motor area: a positron emission tomography study. J Neurosci. 1999;19:6134–44.
21. Weiss T, Miltner WHR, Adler T, Bruckner L, Taub E. Decrease in phantom limb pain associated with prosthesis-induced increased use of an amputation stump in humans. Neurosci Lett. 1998;27:131–4.
22. Giraux P, Sirigu A, Schneider F, Dubernard JM. Cortical reorganization in motor cortex after graft of both hands. Nature Neurosci. 2001;4:691–2.
23. Paz D, Campos JA, Willadino BL. Brain activation in a myoelectric prosthetic hand: the role of the brain in the rehabilitation of amputees. J Pediatr Orthop. 2007;27:947–51.
24. Flor H, Denke C, Schaefer M, Grusser S. Effect of sensory discrimination training on cortical reorganization and phantom limb pain. Lancet. 2001;357:1763–4.
25. Maihofner C, Handwerker HO, Neundorfer B, Birklein F. Cortical reorganization during recovery from complex regional pain syndrome. Neurology. 2004;63:693–701.
26. Chan BL, Witt R, Charrow AP, Magee A, Howard R, Pasquina PF, Heilman KM, Tsao JW. Mirror therapy for phantom limb pain. N Engl J Med. 2007;357:2206–7.
27. Sumitani M, Miyauchi S, McCabe CS, Shibata M, Maeda L, Saitoh Y, Tashiro T, Mashimo T. Mirror visual feedback alleviates deafferentation pain, depending on qualitative aspects of the pain: a preliminary report. Rheumatology. 2008;47:1038–43.
28. MacIver K, Lloyd DM, Kelly S, Roberts N, Nurmikko T. Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. Brain. 2008;131:2181–91.
29. Moseley GL. Using visual illusion to reduce at-level neuropathic pain in paraplegia. Pain. 2007;130:294–8.
30. Moseley GL. Graded motor imagery for pathologic pain. Neurology. 2006;67:2129–34.
31. McCabe CS, Haigh RC, Ring EFJ, Halligan PW, Wall PD, Blake DR. A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). Rheumatology. 2003;42:97–101.
32. Sumitani M, Rossetti Y, Shibata M, Matsuda Y, Sakaue G, Inoue T, Mashimo T, Miyauchi S. Prism adaptation to optical deviation alleviates pathologic pain. Neurology. 2007;68:128–33.
33. Sumitani M, Shibata M, Iwakura T, Matsuda Y, Sakaue G, Inoue T, Mashimo T, Miyauchi S. Pathologic pain distorts visuospatial perception. Neurology. 2007;68:152–4.
34. Ueda N. Development of an upper limb training support robot for hemiplegic cerebral stroke patients applying power assistance technology. In: Proc JSME Symp Welfare Engineering; 2006, p. 250–253.
35. Fujimoto H. Upper limb training support suit for teaching the paralyzed side the direction of motion of the healthy limb (in Japanese). Ronen Igaku (Jpn J Geriatric Psychiatry). 2008; 19:300–5.
36. Christensen MS, Lundbye-Jensen J, Geertsen SS, Petersen TH, Paulson OB, Nielsen JB. Premotor cortex modulates somatosensory cortex during voluntary movements without proprioceptive feedback. Nat Neurosci. 2007;10:417–9.
37. Melzack R. Phantom limbs and the concept of a neuromatrix. Trends Neurosci. 1990;13:88–92.

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Development of comprehensive diagnostic criteria for complex regional pain syndrome in the Japanese population

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ABSTRACT

Complex regional pain syndrome (CRPS) is a syndrome that describes a broad spectrum of sensory, motor and autonomic-like features with unproven etiology. The International Association for the Study of Pain (IASP) diagnostic criteria of CRPS shows high sensitivity but poor specificity. Using statistical-pattern-recognition methods, American researchers have suggested a new set of criteria offering acceptable sensitivity and high specificity. However, non-American CRPS patients present distinct subsets of CRPS-related signs/symptoms from those of American patients. Here, we followed a series of American studies to develop a set of CRPS diagnostic criteria that would be most suitable for the Japanese population. A standardized sign/symptom checklist was used in patient evaluations to obtain data on CRPS-related signs/symptoms in 195 participants meeting the IASP criteria. Using factor analysis, we grouped CRPS-related signs/symptoms into five distinct subgroups (trophic change, motor dysfunction, abnormal pain processing, asymmetric sudomotor activity and asymmetric edema). Discriminant function analysis of these subgroups, regarding their ability to discrim2;inate between CRPS and non-CRPS etiology, indicated that modifying the IASP criteria could increase clinical diagnostic accuracy in the Japanese population. Our diagnostic criteria are not exactly the same as the American criteria, indicating a need for more regionally based CRPS diagnostic criteria. Different sets of CRPS diagnostic criteria could lead to dissimilar patients being diagnosed as CRPS, however, presenting problems for translation of therapeutic effects found in various studies. Therefore, we further recognize a need for a global set of common CRPS diagnostic criteria.

1. Introduction

Complex regional pain syndrome (CRPS) is a syndrome that describes a broad spectrum of sensory, motor and autonomic-like features, predominantly present in the extremities. CRPS is encountered in patients recovering from limb trauma, who complain of persistent pain long after most patients with a similar injury would be symptom free, and/or patients with an immobilized limb. Consequently, activities of daily living are significantly impaired in many CRPS patients [9].

In 1994, the international association for study of pain (IASP) introduced the terms CRPS type 1 and 2, which were meant to substitute for reflex sympathetic dystrophy and causalgia, respectively, and simultaneously proposed a set of consensus-based diagnostic criteria [17,23]. Because office, laboratory and radiographic tests add little to the overall accuracy of diagnosing CRPS [1,2,19], the IASP criteria are based largely on history and self-reported subjective symptoms rather than on physician-examined objective signs, and no special equipment or testing is required. Developing these standardized diagnostic criteria was an appropriate first step toward an improved understanding of CRPS. The accuracy of these consensus-based criteria should be refined over time, through controlled validation studies using the best means available. However, IASP has not yet optimized the criteria. One study clearly revealed that the IASP criteria lack specificity (0.36) while being very sensitive (0.98) [8]. Researchers have not yet reached general consensus on the best method of diagnosis.

A series of reports using statistical-pattern-recognition methods had a clear application to the issue of CRPS diagnostic internal and external validities [3,10]. These statistically derived criteria from Bruehl et al. increased diagnostic accuracy (specificity 0.60; sensitivity 0.85) [3] and provided an objective determination of

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distinct subsets of CRPS-related signs/symptoms. Meanwhile, two studies [20,25] from different Dutch groups who directly investigated the inter-observer reliabilities of three sets of CRPS diagnostic criteria suggest that both the IASP and Bruehl's criteria appear unreliable, but empirical criteria from Veldman et al. (Dutch researchers) [26] achieve good reliability. Patient profiles (duration of complaints, pain location, a combination of clinical manifestations) of Dutch CRPS patients meeting Veldman's criteria appear to be different from those reported in the American study [10]. Concerning different patients' profiles, the perception of pain is sensitive to various biological constraints, mental processes and psychosocial functions (e.g., cognition, belief, culture, past experiences) and is also influenced by macro-level general factors (e.g., environment, the health insurance system). In fact, a genetic contribution to pain perception in CRPS has been reported from patients across the world [6]. Furthermore, supporting evidence may come from population-based studies in which the CRPS incidence rate of 0.026% in the Netherlands [5] is more than four times higher than in the USA (0.0055%) [22], although the diagnostic criteria are not exactly the same. We therefore considered that CRPS could manifest differently in different populations, and we designed the present study to develop CRPS diagnostic criteria that would be more specific and appropriate to the Japanese population. We based our studies on the statistical-pattern-recognition approach of preceding studies [3,10] because of their robustness and objectivity.

2. Methods

2.1. Design

The present study is a multisite, between-subjects design comparing patients with CRPS to those with non-CRPS persistent pain disorders. We started to design this study in August 2004 and finished all of the analyses in May 2007.

2.2. Subjects

Over 20 months (from April 2005 to November 2006), our study physicians consecutively invited patients to take part in this study. The following inclusion criteria applied: patients with upper or lower limb pain of at least 3 months in duration (i.e., chronic pain), at least 18 years old and able to provide informed consent to the survey. Exclusion criteria were as follows: inability to understand the questions in Japanese without any help, inability to give informed consent, inability to clearly differentiate between the affected and unaffected limbs in severity of the disease, and altered level of consciousness.

Subjects included 195 participants (34.9% men; mean age: 47.8 ± 16.0 years) meeting the IASP criteria for CRPS [17] who came for evaluation and treatment at the data collection sites. Data collection sites included 14 university hospitals (76.4% of CRPS patients), one medical center (4.1%), and six district hospitals (19.5%). Data collection was performed in departments of anesthesiology (75.9% of the sample) and orthopedics (24.1%). All study physicians across sites received standardized instructions on how to assess CRPS signs and symptoms on the basis of the IASP criteria as published [17]. Using abnormal electromyography/nerve conduction velocity test results and evident history of nerve injury as a conservative diagnostic criterion for CRPS type 2, 21.5% of the participants were diagnosed with CRPS type 2 [17]. In addition to CRPS participants, 146 non-CRPS participants (48.6% men; mean age: 56.8 ± 16.6 years) with chronic (>3 months) pain in one limb and who came to the data collection site for evaluation and treatment also participated in the study. In contrast to the Bruehl et al. study [3], we included not only participants with neuropathic pain (e.g., painful diabetic neuropathy, post-herpetic neuralgia, radiculopathy, post-brachial plexus avulsion pain) (56.2%) but also those with pain accompanied by inflammatory disease (e.g., rheumatoid arthritis, osteoarthritis) (11.1%), post-traumatic pain syndrome with unproven etiologies (28.1%) and others (e.g., fibromyalgia, erythromyalgia, peripheral vascular disease) (4.8%), because CRPS is often developed after trivial trauma and its etiology is unproven. Non-blinded study physicians applied the IASP diagnostic criteria, except the exclusion criterion for CRPS, to the non-CRPS participants. Some did not meet any conditional statements of the IASP criteria for CRPS at all. Others met the first three conditional statements of the IASP criteria (the presence of an initiation noxious event or a cause of immobilization; continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event; and evidence at some time of edema, changes in skin blood flow or abnormal sudomotor activity in the region of pain) but did not meet the last conditional statement about the exclusion criterion (in other words, the participants had a somewhat evident condition(s) which could account for the pain and dysfunction). All participants gave their informed consent to participate. Formal Institutional Ethical Review Board approvals were not required for this study-type in Japan, according to the "Private Information Protection Guideline for Healthcare Professionals" of the Japan Ministry of Health, Labour and Welfare (24, December, 2004).

2.3. CRPS database checklist

We received a copy of the CRPS database checklist and instructions from Dr. Norman R. Harden (Center for Pain Studies, Rehabilitation Institute of Chicago, USA), and we translated it into Japanese. To ensure standardized collection of signs and symptoms data across sites, we used the database checklist, which involved obtaining a participant history to assess subjective symptoms, as well as a physical examination conducted by a study physician to assess objective signs. To avoid potential inter-observer reliability problems, we used dichotomous measures (i.e., presence or absence) to assess signs and symptoms, instead of an interval rating scale [12]. To maximize uniform assessment across sites, we standardized the method for collecting the signs and symptoms with the checklist before data collection began. Subsequently, for CRPS and non-CRPS participants, an evaluation of signs and symptoms was conducted using the checklist at each site. We gathered a total of 352 checklists, but 11 of them (3 CRPS, 8 non-CRPS) were excluded because they showed symmetrical suffering in their upper or lower limbs, which would block our ability to make a comparison between the affected vs. unaffected limb (i.e., the participation rate was 96.9%).

2.4. Statistical analysis

We used statistical-pattern-recognition methods (factor analysis and discriminant function analysis) to test the validity of internal and external CRPS diagnostic criteria. These statistical methods have been used for validation of diagnostic criteria of disorders such as headaches and psychiatric diseases whose underlying pathophysiological mechanisms are unclear [15,16]. Factor analysis (FA) was used for the primary analysis. FA results in factor loadings that indicate the degree of correlation between each variable (i.e., signs and symptoms of CRPS), and it shows how various factors group together. Variables are highly correlated with one another within a factor, and relatively uncorrelated with variables in other factors. Thus, FA identifies coherent and presumably conceptually linked subsets of variables within a dataset and each factor is relatively independent from others. For the purpose of this

Table 1
Demographic and pain characteristics across diagnostic groups.

Variables	CRPS (n = 195)	Non-CRPS pain (n = 146)	p value
Gender	65.1% female	51.4% female	<0.02
Age	47.8 ± 16.0 (male: 47.6 ± 17.0) (female: 48.0 ± 15.6)	56.8 ± 16.6 (male: 59.0 ± 16.0) (female: 54.9 ± 17.0)	<0.001
Pain duration (month)	29.8 ± 42.3	37.4 ± 55.7	0.19
Pain location	65.6% Upper limb	58.2% Upper limb	0.05
VAS (right now)	5.5 ± 2.4	5.1 ± 2.7	0.14
VAS (worst in the last week)	7.4 ± 2.3	6.9 ± 2.5	0.06

CRPS, complex regional pain syndrome; VAS, visual analogue scale (0 = no pain; 10 = pain as bad as it can be).

study, a factor loading of 0.50 or greater was required for a variable to be assigned to a given factor [18]. Varimax rotation was used in all analyses. The number of factors was determined on the basis of both examination of screen plots and theoretical and clinical consistency. Coherent subsets of variables identified by FA could provide an empirical basis for determining the proper decision rules of CRPS diagnostic criteria, but did not permit determination of the optimal decision rules.

Discriminant function analysis (DFA) was used for the secondary analysis. DFA determines a discriminant score for each case, and then applies Bayes' theorem to derive a general rule for classifying cases into one of two groups. In this study, in addition to Bruehl's criteria, results of DFA were used to develop optimal decision rules of the empirical subsets derived from FA in order to discriminate between CRPS and non-CRPS participants, on the basis of the following three indicators: sensitivity (i.e., being able to detect CRPS when it is present), specificity (i.e., minimizing false-positive diagnosis of CRPS) and discriminant accuracy (i.e., efficiency of discrimination between CRPS and non-CRPS participants). In addition to these three indicators, we evaluated positive predictive power (PPP; the probability that a diagnosis of CRPS is accurate) and negative predictive power (NPP; the probability that a diagnosis of non-CRPS is accurate), because PPP and NPP measures could be used to maximize the probability of correct diagnosis when the actual disease status is unknown [14]. PPP was defined as: (CRPS base rate * true positive rate)/[(CRPS base rate true positive rate) + (1 − CRPS base rate * false positive rate)]. NPP was defined as: [(1 − CRPS base rate) * true negative rate]/[(1 − CRPS base rate * true negative rate) + (CRPS base rate * false negative rate)]. These five indicators of diagnostic efficiency were contrasted to determine the adequate accuracy and likely diagnostic utility of each. All probability values are two-tailed. Demographic data were compared between CRPS and non-CRPS participants by the Mann–Whitney test. All statistical analyses were performed using SAS 8.0.2. software, and a p value of less than 0.05 was considered to be significant.

3. Results

3.1. Demographics and pain characteristics

The demographics of CRPS and non-CRPS groups differed significantly in age and gender (Table 1). CRPS-related signs/symptoms, resulting from the checklist among CRPS and non-CRPS participants, are summarized in Table 2.

3.2. Factor analysis

The resulting five factors appeared generally consistent with what might be clinically expected in the Japanese population (Table 3). The first subset consisted of signs and symptoms of trophic changes including hair, skin, nail and/or bone atrophy. The second factor identified was motor dysfunction in which decreased range of motion, muscle weakness, tremor and/or dystonia were involved. The third subset was a sensory factor, which involved hyperalgesic signs, allodynic signs and symptoms of hyperesthesia. "Burning pain", a symptom reported frequently by CRPS patients, did not reach the factor loading criterion of 0.50 for inclusion in this factor. The fourth subset was an abnormal sudomotor factor, consisting of the signs and symptoms of asymmetric sweating. In

Table 2
Frequency of CRPS-related signs/symptoms among CRPS patients and non-CRPS patients.

Variable	CRPS patients (n = 195)		Non-CRPS patients (n = 146)	
	Signs (%)	Symptoms (%)	Signs (%)	Symptoms (%)
Burning pain	NA	64.6	NA	39.0
Hyperesthesia	NA	45.6	NA	21.9
Temperature asymmetry	36.4	73.8	18.5	32.2
Color changes	60.5	74.4	10.3	22.6
Sweating changes	36.4	48.7	5.5	13.7
Edema	47.7	84.1	9.6	39.7
Trophic changes				
Nail	25.6	26.2	4.1	5.5
Hair	13.3	17.4	0.0	1.4
Skin	39.0	42.1	13.0	15.1
Muscle weakness	81.0	83.1	54.8	56.2
Tremor	21.5	30.3	11.6	16.4
Dystonia	16.9	21.0	4.8	8.2
Decreased range of motion	75.4	75.4	31.5	46.6
Hyperalgesia	60.0	NA	23.3	NA
Allodynia	62.6	NA	21.2	NA

NA = not applicable. Items were assessed as objective sign or subjective symptom only.

Table 3
Factors (and factor loadings) resulting from factor analysis of CRPS-related signs/symptoms.

Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Trophic sign (0.72)	Decreased range of motion symptom (0.83)	Hyperesthesia symptom (0.74)	Sweating asymmetry symptom (0.74)	Edema sign (0.60)
Trophic symptom (0.66)	Decreased range of motion sign (0.79)	Allodynia sign (0.60)	Sweating asymmetry sign (0.71)	Edema symptom (0.50)
		Hyperalgesia sign (0.54)		

CRPS, complex regional pain syndrome.

the final subset, the signs and symptoms of asymmetric edema met the inclusion criteria of factor loading. The latter three factors are currently included in the IASP criteria. On the other hand, the former two factors are listed in associated signs and symptoms of CRPS but not used for diagnosis of CRPS in the IASP criteria [17]. We conducted FA separately on 153 CRPS type 1 participants alone and 42 CRPS type 2 participants alone. FA results of CRPS type 1 participants alone were consistent with the results from both CRPS type 1 and type 2, although the first and second factors were interchanged. When the results from CRPS type 2 participants alone were analyzed by FA, two factors—sensory disturbance and motor dysfunction—were extracted, and three factors of 'absence' of abnormal sudomotor activity, trophic changes and skin color changes were characterized.

Thus, there are substantial similarities between the FA results combining CRPS type 1 and type 2 participants or using CRPS type 1 participants alone, whereas using FA results of CRPS type 2 participants alone were quite different. However, the sample size of CRPS type 2 participants alone was limited and hence the statistical results were undoubtedly underpowered; a larger independent data set would be required.

3.3. Discriminant function analysis

Five factors derived from FA were tested using 16 types of decision rules for determining the threshold for diagnosis of CRPS. The 16 decision rules ranged from a requirement that at least two of five sign factors and at least two of five symptom factors be positive, to a more stringent rule that all five sign factors and all five symptom factors must be positive. Adding the rules from Bruehl's criteria for clinical and research purposes to the 16 rules, all rules discriminated significantly between CRPS and non-CRPS participants (chi2, $p < 0.05$) (see Table 4 for a complete list of the 18 decision rules tested).

3.4. Diagnostic efficiency

Since all 18 decision rules significantly discriminated between the two patient groups, we further examined the decision rules regarding diagnostic efficiency (Table 4). Among the 18 decision rules, we examined four decision rules more carefully (5-1, 5-2, 5-5 and 5-6), as their diagnostic accuracy was greater than 70%. On the basis of combination of an acceptable sensitivity (0.83) and moderately high specificity (0.79), we adopted the 5-1 decision rule (chi2 = 59.8, $p < 0.001$) for clinical diagnostic criteria of CRPS in Japan. Furthermore, we adopted the 5-6 decision rule (chi2 = 37.0, $p < 0.001$) for research diagnostic criteria of CRPS in Japan, with the highest specificity (0.92) at the expense of relatively low sensitivity (0.59). Following Bruehl's study, we displayed PPP in combination with NPP for all possible CRPS prevalence rates. However, displays of PPP and NPP were comparable among the four types of decision rules (data not shown), and hence PPP and NPP were not relevant in our study.

4. Discussion

We used statistical-pattern-recognition methods to develop a specific set of CRPS diagnostic criteria for Japan, simulating preceding studies by American CRPS experts [3,10]. Five subsets of signs and symptoms were clustered: (1) trophic changes; (2) motor dysfunction; (3) abnormal pain processing; (4) asymmetric sudomotor activity; and (5) asymmetric signs and symptoms of edema. On the basis of these subsets, we proposed two kinds of decision rules to diagnose CRPS for clinical and research purposes (Appendixes A

Table 4
Sensitivity, specificity and diagnostic accuracy of diagnostic criteria/decision rules to discriminate CRPS from non-CRPS conditions. Numbers listed in the decision rules refer to number of sign and symptom categories (out of five possible categories for each) required to be present for the syndrome to be considered CRPS.

Criteria/decision rule			Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)
5-1	⩾2 sign categories and ⩾2 symptom categories	*	82.6	78.8	80.9
5-2	⩾2 sign categories and ⩾3 symptom categories	*	70.8	85.6	77.1
5-3	⩾2 sign categories and ⩾4 symptom categories	*	44.6	91.8	64.8
5-4	⩾2 sign categories and ⩾5 symptom categories	*	16.9	95.9	50.7
5-5	⩾3 sign categories and ⩾2 symptom categories	*	61.0	90.4	73.6
5-6	⩾3 sign categories and ⩾3 symptom categories	*	59.0	91.8	73.0
5-7	⩾3 sign categories and ⩾4 symptom categories	*	40.0	93.2	62.8
5-8	⩾3 sign categories and ⩾5 symptom categories	*	16.4	96.6	50.7
5-9	⩾4 sign categories and ⩾2 symptom categories	*	29.2	95.2	57.5
5-10	⩾4 sign categories and ⩾3 symptom categories	*	28.2	95.9	57.2
5-11	⩾4 sign categories and ⩾4 symptom categories	*	24.1	95.9	54.8
5-12	⩾4 sign categories and ⩾5 symptom categories	*	11.8	98.6	49.0
5-13	⩾5 sign categories and ⩾2 symptom categories	*	6.2	100.0	46.3
5-14	⩾5 sign categories and ⩾3 symptom categories	+	6.2	100.0	46.3
5-15	⩾5 sign categories and ⩾4 symptom categories	+	5.1	100.0	45.8
5-16	⩾5 sign categories and ⩾5 symptom categories	#	3.6	100.0	44.9
B-1	Bruehl's criteria for clinical purpose	+	45.4	84.8	62.2
B-2	Bruehl's criteria for research purpose	#	20.9	95.9	52.8

* $p < 0.001$.
\+ $p < 0.01$.
\# $p < 0.05$.

and B). These Japan-specific diagnostic criteria are different from Bruehl et al.'s criteria [3]. Applying Bruehl's clinical criteria on our Japanese CRPS and non-CRPS participants gave a sensitivity of 0.45, specificity of 0.85 and diagnostic accuracy of 62.2%. Thus, Bruehl's diagnostic criteria seem to be less effective for the Japanese population than for the American population (sensitivity 0.85; specificity 0.69; diagnostic accuracy 85.6%). Using our new Japan-specific diagnostic criteria, however, the diagnostic efficiency markedly improves (specificity 0.79; sensitivity 0.83; diagnostic accuracy 80.9%). Our criteria can thus be considered more clinically valid for Japanese patients than the IASP or Bruehl's criteria.

What are the essential differences between Bruehl's criteria and our Japan-specific criteria? Although we standardized our method to assess CRPS participants before data collection, our multiperspective and multisite assessment probably reached a wide variety of CRPS participants. Factor analysis clearly confirmed the existence of the five-factor solution, but the five-factor solution accounted for only 40.8% of the total variance (i.e., signs and symptoms). Harden et al. did not show their cumulative contribution rate by factor analysis [10], and therefore we cannot make any judgments about the relative diversity of our participants compared with theirs. CRPS is undoubtedly composed of "complex" signs and symptoms, as its name suggests. CRPS would be etiologically too heterogeneous to present particular combinations of signs and symptoms that are associated with specific etiologies. Therefore, the relatively low cumulative contribution rate of our CRPS participants' signs and symptoms is to be expected. We must develop more objective criteria by statistically correct methodological approaches. Future studies will be necessary to test the applicability of our criteria to other populations. Furthermore, underlying mechanisms of different clinical manifestations of CRPS in diverse countries should be investigated.

The perception of pain is sensitive to various biological constraints, mental processes (e.g., cognition, emotion), and, sometimes more strongly, psychosocial functions (e.g., culture, religion) and macro-level general factors (e.g., environment, health insurance system). In the present study, we developed independent CRPS diagnostic criteria for Japanese populations. Our results strongly suggest the necessity of regionally based CRPS diagnostic criteria. Interestingly, since the introduction of the term CRPS and its diagnostic criteria in 1994, the applied diagnostic criteria have frequently been determined by the country or institute in which the study was performed. Studies using the criteria created by a Dutch author were performed in the Netherlands; studies designed by a British author were performed in the United Kingdom, and studies designed by a French author were performed in either France or Switzerland [24]. Differences among varied sets of diagnostic criteria led to different patient profiles [20,25], and these facts probably indicate that each nation's diagnostic criteria would have more potency in distinguishing CRPS from other clinical entities of pathologic pain. Therefore, in the absence of clear evidence supporting one set of criteria, different populations with different psychosocial backgrounds would need individual nation-based CRPS diagnostic criteria.

However, if the IASP authorizes individual nation-based CRPS diagnostic criteria, there could be some negative consequences. Different sets of CRPS diagnostic criteria would lead to dissimilar patients being diagnosed as CRPS and potential problems with translation of therapeutic effects found in various studies using different diagnostic criteria. In particular, these adverse effects have been observed substantially in several meta-analyses [13,21] and systematic reviews [4,7,11] on CRPS. Therefore, clinical physicians, basic investigators and also patients around the world probably need one set of common global diagnostic criteria of CRPS. Our results further suggest that the IASP should unify the diagnosis process and validate one set of the scientifically authorized CRPS diagnostic criteria.

Here we propose a set of CRPS diagnostic criteria for Japan (see Appendixes A and B, with explanatory footnotes). These criteria will be refined over time through repeated and controlled validation studies. At present, these criteria suggest that the diagnostic accuracy of CRPS meeting the IASP criteria can be enhanced and that general physicians can diagnose CRPS as accurately as Japanese CRPS experts. In fact, no special equipment or testing and simple dichotomous measurements are required for our Japanese diagnosis criteria of CRPS, suggesting that general physicians and perhaps non-healthcare professionals may diagnose CRPS. Our criteria are not completely perfect (i.e., sensitivity 1.0, specificity 1.0), and therefore we sincerely hope that our criteria will not be used in court to replace healthcare professionals in determining whether CRPS is present or not. Therefore, we footnote that these criteria should not be used in situations (e.g., lawsuit, indemnity) in which patients recovering from limb trauma but complaining of persistent pain are judged to suffer from CRPS or not, and also we footnote that these criteria cannot be used for assessing impairment of a person's activity of daily living (ADL). Using these new CRPS diagnostic criteria in Japan could mitigate the clinical flaws caused by the IASP criteria (i.e., high sensitivity at the expense of specificity), such as over-diagnosis and ultimately unnecessary and potentially invasive treatments. Furthermore, our diagnostic criteria, developed by our objective methodological approach, may help debunk the myth that CRPS is not a "real" disorder because of its variability across patients.

In the absence of defined pathophysiological mechanisms underlying CRPS, the choice for a set of diagnostic criteria remains arbitrary, leading to arbitrary differences in CRPS patients' profiles. If this trend continues, problems with translation of therapeutic effects found in various studies using different diagnostic criteria should remain. Large prospective studies that evaluate all features of world-wide CRPS would contribute to a better understanding of this syndrome and subsequently aid in the development of new scientifically based universal criteria.

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Conflicts of interest

None.

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An overview of Japanese CRPS diagnostic criteria has now been published in the Japanese literature (Mashimo T. Annual report on Health Labour Sciences Research Grant "H17-kokoro-022" to Japan Ministry of Health, Labour and Welfare) for the Japanese public benefits. This paper is submitted with permission from the Japan Ministry of Health, Labour and Welfare.

Appendix A. Japanese CRPS diagnostic criteria for clinical purposes[2]

A.1. Must report at least one symptom in two or more of the following five categories, at some time

1. *Trophic changes:* reports of trophic changes of hair and/or skin and/or nail and/or bone.
2. *Motor dysfunctions:* reports of decreased range of motion and/or motor dysfunction (muscle weakness, tremor, dystonia).
3. *Abnormal sensory processing:* reports of pain disproportionate to the inciting event and/or burning pain and/or hyperesthesia.
4. *Asymmetric sudomotor activity:* reports of sweating changes and/or sweating asymmetry.
5. *Asymmetric edema:* reports of edema.

A.2. Must display at least one sign in two or more of the five following categories, at the physical examination

1. *Trophic changes:* evidence of trophic changes of hair and/or skin and/or nail and/or bone.
2. *Motor dysfunctions:* evidence of decreased range of motion and/or motor dysfunction (muscle weakness, tremor, dystonia).
3. *Abnormal sensory processing:* evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch).
4. *Asymmetric sudomotor activity:* evidence of sweating changes and/or sweating asymmetry.
5. *Asymmetric edema:* evidence of edema.

[2] Japanese CRPS diagnostic criteria were developed for discriminating between patients who meet the IASP criteria of CRPS and are reasonably diagnosed as CRPS by Japanese CRPS experts and patients with pain in any extremities due to non-CRPS etiologies. Using the Japanese diagnostic criteria for clinical purposes, acceptable diagnostic efficiency (specificity 0.79; sensitivity 0.83) are warranted. Japanese diagnostic criteria for research purposes lacks high sensitivity (0.59) but increases specificity (0.92).

Appendix B. Japanese CRPS diagnostic criteria for research purposes[3]

B.1. Must report at least one symptoms in three or more of the five following categories, at some time

1. *Trophic changes:* reports of trophic changes of hair and/or skin and/or nail and/or bone.
2. *Motor dysfunctions:* reports of decreased range of motion and/or motor dysfunction (muscle weakness, tremor, dystonia).
3. *Abnormal sensory processing:* reports of pain disproportionate to the inciting event and/or burning pain and/or hyperesthesia.
4. *Asymmetric sudomotor activity:* reports of sweating changes and/or sweating asymmetry.
5. *Asymmetric edema:* reports of edema.

B.2. Must display at least one sign in three or more of the five following categories, at the physical examination

1. *Trophic changes:* evidence of trophic changes of hair and/or skin and/or nail and/or bone.
2. *Motor dysfunctions:* evidence of decreased range of motion and/or motor dysfunction (muscle weakness, tremor, dystonia).
3. *Abnormal sensory processing:* evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch).
4. *Asymmetric sudomotor activity:* evidence of sweating changes and/or sweating asymmetry.
5. *Asymmetric edema:* evidence of edema.

References

[1] Baron R, Janig W. Complex regional pain syndromes—how do we escape the diagnostic trap? Lancet 2004;364:739–41.
[2] Baron R, Blumberg H, Janig W. Clinical characteristics of patients with complex regional pain syndrome in Germany with special emphasis on vasomotor function. In: Janig W, Stanton-Hicks M, editors. Reflex sympathetic dystrophy: a reappraisal. Seattle: IASP Press; 1996. p. 25–48.
[3] Bruehl S, Harden RN, Galer BS, Saltz S, Bertram M, Backonja M, Gayles R, Rudin N, Bhugra MK, Stanton-Hicks M. External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. Pain 1999;81:147–54.
[4] Cepeda MS, Lau J, Carr DB. Defining the therapeutic role of local anesthetic sympathetic blockade in complex regional pain syndrome: a narrative and systematic review. Clin J Pain 2002;18:216–33.
[5] de Mos M, de Bruijn AGJ, Huygen FJPM, Dieleman JP, Stricker BHCh, Sturkenboom MCJM. The incidence of complex regional pain syndrome: a population-based study. Pain 2007;129:12–20.
[6] Edwards RR. Individual differences in endogenous pain modulation as a risk factor for chronic pain. Neurology 2005;65:437–43.
[7] Forouzanfar T, Koke AJ, van Kleef M, Weber WE. Treatment of complex regional pain syndrome type 1. Eur J Pain 2002;6:105–22.
[8] Galer BS, Bruehl S, Harden RN. IASP diagnostic criteria for complex regional pain syndrome: a preliminary empirical validation study. Clin J Pain 1998;14:48–54.
[9] Geertzen JH, Dijkstra PU, van Sonderen EL, Groothoff JW, ten Duis HJ, Eisma WH. Relationship between impairments, disability and handicap in reflex sympathetic dystrophy patients: a long-term follow up study. Clin Rehabil 1998;12:404–12.
[10] Harden RN, Bruehl S, Galer BS, Saltz S, Bertram M, Backonja M, Gayles R, Rudin N, Bhugra MK, Stanton-Hicks M. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? Pain 1999;83:211–9.
[11] Jaded AR, Carroll D, Glynn CJ, McQuay HJ. Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study. J Pain Symptom Manage 1995;10:13–20.

[3] Japanese CRPS diagnostic criteria for clinical purposes would help determine the management of patients and take patients to leading medical agencies. Japanese CRPS diagnostic criteria for research purposes should be used when conducting clinical research on CRPS patients. Japanese CRPS diagnostic criteria should not be used in any situation (e.g., lawsuit, indemnity) in which patients recovering from trauma but complaining of persistent pain are judged to suffer from CRPS or not. Japanese CRPS diagnostic criteria can not assess impairment of activity of daily living or severity of suffering.

[12] Janig W. Experimental approaches to reflex sympathetic dystrophy and related syndromes. Pain 1991;46:241–5.
[13] Kingrey WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. Pain 1997;73:123–39.
[14] Landau S, Milich R, Widiger TA. Predictive power methods may be more helpful for making a diagnosis than sensitivity and specificity. J Child Adolesc Psychopharmacol 1991;1:343–51.
[15] Merikangas KR, Dartigues JF, Whitaker A, Angst J. Diagnostic criteria for migraine: a validity study. Neurology 1994;44:S11–6.
[16] Merikangas KR, Frances A. Development of diagnostic criteria for headache syndromes: lessons from psychiatry. Cephalalgia 1993;13:S34–8.
[17] Merskey H, Bogduk N. Descriptions of chronic pain syndromes and definition. In: Merskey H, Bogduk N, editors. Classification of chronic pain. Seattle: IASP Press; 1994. p. 209–14.
[18] Norman GR, Streiner DL. Principal components and factor analysis. In: Biostatistics: the bare essentials. 3rd ed. Ontario: BC Decker Inc.; 1994. p. 194–209.
[19] Oerlemans HM, Oostendorp RA, de Boo T, Perez RS, Goris RJ. Signs and symptoms in complex regional pain syndrome type 1/reflex sympathetic dystrophy: judgment of the physician versus objective measurement. Clin J Pain 1999;15:224–32.
[20] Perez RS, Burm PE, Zuurmond WW, Giezeman MJ, van Dasselar NT, Vranken J, de Lange JJ. Interrater reliability of diagnosing complex regional pain syndrome type 1. Acta Anesthesiol Scand 2002;46:447–50.
[21] Perez RS, Kwakkel G, Zuurmond WW, de Lange JJ. Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials. J Pain Symptom Manage 2001;21:511–26.
[22] Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type 1: incidence and prevalence in Olmsted County, a population-based study. Pain 2003;103:199–207.
[23] Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. Pain 1995;63:127–33.
[24] van de Beek WJT, Schwartzman RJ, van Nes SI, Delhaas EM, van Hilten JJ. Diagnostic criteria used in studies of reflex sympathetic dystrophy. Neurology 2002;58:522–6.
[25] van de Vusse AC, Stomp-van den Berg SG, de Vet HC, Weber WE. Interobserver reliability of diagnosis in patients with complex regional pain syndrome. Eur J Pain 2003;7:259–65.
[26] Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;342:1012–6.

Q&A

〈質問〉幻肢痛に対するミラー療法について

幻肢痛に有効な治療法として，ミラー療法について，その機序と今後の発展について教えてください．（東京，A.M.生）

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四肢の運動では，体性感覚情報や視覚情報を基にして四肢の位置や関節角度を認識し，次いで運動企図から運動指令の出力に続き，四肢運動が実行されます．そして，運動が実行されると，再び四肢の感覚情報が脳へとフィードバックされます．このような感覚系と運動系におけるループ状の情報伝達の繰り返しを知覚－運動協応と呼び，身体認知の基本的な神経基盤になります．幻肢痛をはじめとする病的疼痛の発症機序として，この知覚－運動協応の破綻が生じた際に病的疼痛が惹起されるという仮説があります[1]．この考えを仮説と記載したのは，現状では脳機能画像などの研究手法を用いてもこの理論を証明する方法がないからです．疼痛は身体の異常を知らせるための警告系として生体に備えられたシステムであることを考えると，通常であれば統合されているべき感覚－運動ループが，神経損傷や四肢切断などによって破綻した際に四肢の異常を知らせるアラームとして疼痛（幻肢痛）が起きるのは当然のことのように思います．

健常ヒトにおいて，感覚系と運動系が協応関係にあることは，感覚系の関門的役割を果たす脳領域である一次体性感覚野の体部位再現地図と，同様に運動系の関門的役割を果たす脳領域である一次運動野の体部位再現地図がほぼ相同であることからも理解されます．幻肢痛などの神経障害性疼痛では，神経損傷に伴う感覚入力の遮断が，S1とM1の体部位再現地図の縮小として脳内では表現されており，罹患部位の体部位再現地図が縮小すればするほど幻肢痛が強くなることが明らかにされています．一方，神経損傷や四肢切断があってもこの体部位再現地図が縮小していない患者では幻肢痛が発生していないことも知られています．したがって，幻肢痛患者では幻肢の知覚－運動ループの協応関係を再統合することによって体部位再現地図の書き換え（罹患部位の地図を拡大）させることが治療的意義を持つと考えられます．

四肢の位置や関節角度を認識するための感覚情報として，ヒトは体性感覚と視覚を用いると上述しましたが，実は視覚情報が最も重要であることが知られています（2番目に体性感覚が重要）．したがって，知覚－運動協応が破綻した四肢についての感覚情報を脳へとフィードバックする際には，その四肢に関する正しい視覚情報（映像）を入力することが知覚－運動ループの協応関係を再統合するために最も効率的な方法になります．このような理論背景からわれわれは幻肢痛の治療としてミラー療法を行っています．左右四肢からの感覚情報は脳内で統合されて一つの感覚表象を形成し，運動系へと情報伝達が行われる[3]ので，鏡を用いることによって左右四肢が同時に全く同一の運動を行っている視覚情報が入力できることは，幻肢の知覚－運動協応の再統合にとっても好都合であると考えています．

【方法】身体正中矢状断面に鏡を置き，健肢を鏡に映します（鏡の中に患肢が存在しているような視覚像が見えます）．そして，健肢の手指を自由に運動させ，あたかも患肢が動いているような鏡像を観察させます．同時に，患肢が鏡像肢と同様の運動をしているようなイメージ

〈Q & A〉
Mirror treatment for phantom limb pain
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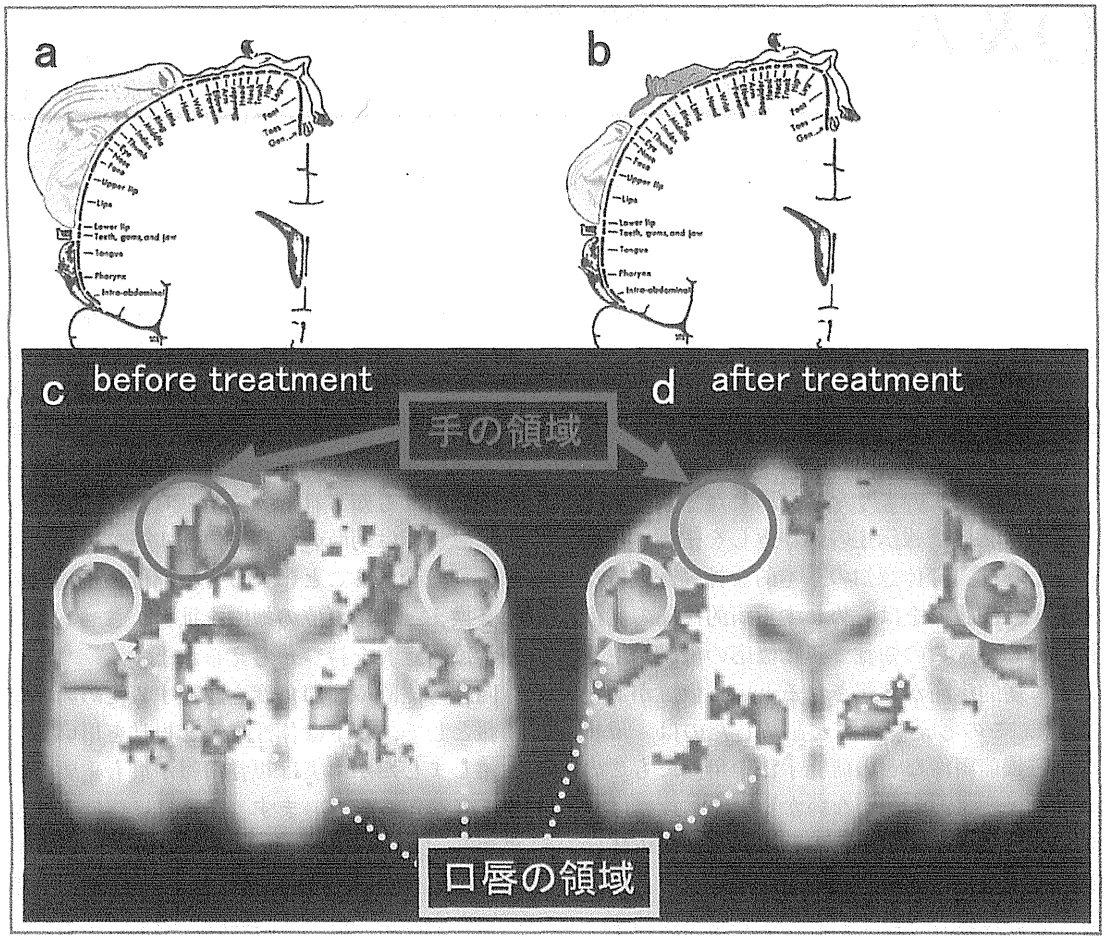

図1　幻肢痛に対する鏡療法施行前後の口唇運動時の脳活性化の違い
（文献4，5より改変引用した図を文献6より転載）
下段は口唇運動時の感覚運動皮質冠状断面の活性化を示す．鏡療法による幻肢の随意運動感覚の獲得前（c）には口唇の運動によって感覚運動皮質の外側部（白円）だけでなく頭頂付近にも活性化が認められるが，鏡療法後には大脳外側部だけに限局している（d）．これは，感覚運動皮質における体部位再現地図における手の領域（濃灰円）が回復したことを示す．上段は鏡療法前（a）と後（b）の体部位再現地図の模式図を示す．

を想像させます（患肢に運動指令を出す）．これを1日1回約10分間行い，患者の希望によって数週間継続します．

この治療法によって，従来から行われている治療法に抵抗性を示した患者のうち2/3で神経障害性疼痛の軽減が得られました[2]．

ミラー療法の鎮痛機序は，知覚－運動協応の再統合によるものと考えられています．この知覚－運動協応の再統合が得られていることは，ミラー療法の治療前にはS1/M1での体部位再現地図が縮小していたものが，ミラー療法後に拡大していることからも示唆されています（**図1**）．

ただし，われわれの幻肢痛患者のうち，1/3に対してはミラー療法は全く無効でした．したがって，さらに強力な鎮痛治療法の開発が求められます．われわれは，体性感覚情報フィードバックとして最も重要な視覚情報だけでなく，2番目に重要な体性感覚も利用して，知覚－運動協応を再統合するリハビリ・ロボットスーツの開発をアクティブリンク社と共同で行っています（**図2**：NEDO若手グラント08C46216）．残存四肢からの体性感覚情報が幻肢の体部位再

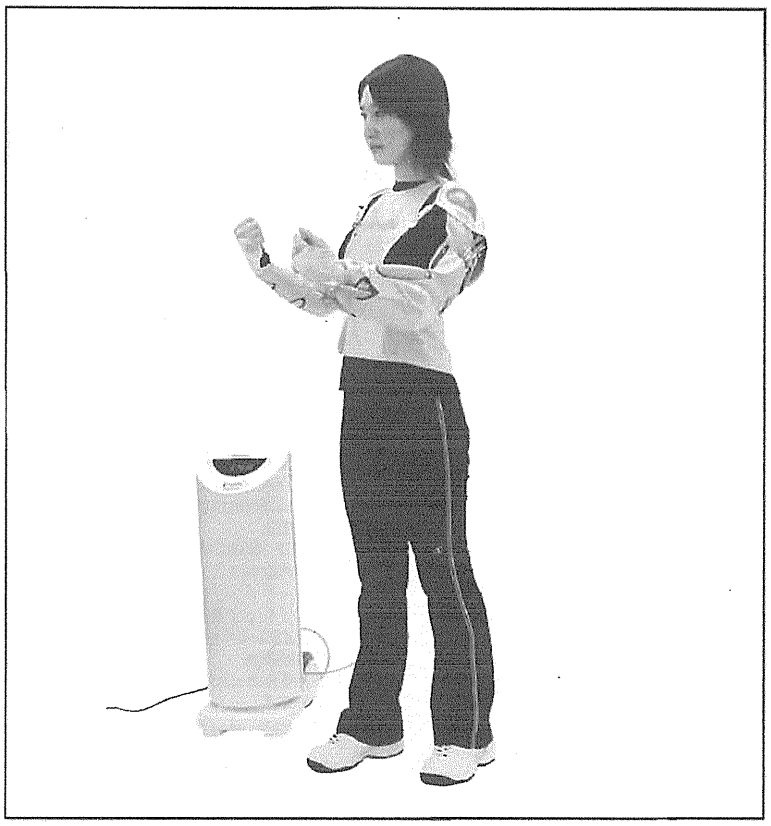

図2　視覚入力と体性感覚入力を用いた上肢リハビリテーション支援ロボットスーツ（文献7より掲載）
右上肢（健肢）にセンサースーツを着用し，左上肢（患肢）に人工筋肉とワイヤーで構成される駆動スーツを装着する．左下は人工筋肉を駆動させるための空気圧調整器．右上肢を運動すると，受動的に左上肢も右上肢の運動を遂行する．（アクティブリンク社との共同開発）

現地図形成に役立つ可能性が示されていることから，われわれのロボットスーツは神経障害性疼痛の治療に新たな可能性を提案できるかもしれません．

文　献

1) Harris AJ: Cortical origin of pathological pain. Lancet 354：1464-1466, 1999
2) Sumitani M, Miyauchi S, McCabe CS, et al: Mirror visual feedback alleviates deafferentation pain, depending on qualitative aspects of the pain: A preliminary report. Rheumatology 47：1038-1043, 2008
3) Sumitani M, Yozu A, Tomioka T, et al: Using the intact hand for objective assessment of phantom hand-perception. Eur J Pain (in press)
4) Farne A, Roy AC, Giraux P, et al: Face or hand, not both: Perceptual correlates of reafferentation in a former amputee. Curr Biol 12：1342-1346, 2002
5) MacIver K, Lloyd DM, Kelly S, et al: Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. Brain 131：2181-2191, 2008
6) 住谷昌彦，宮内　哲，山田芳嗣：神経障害性疼痛と鏡療法－脳内機序解明に向けて－．臨床麻酔 32：1623-1629, 2008
7) 住谷昌彦，宮内　哲，四津有人，他：高次神経機能に視点をおいた難治性疼痛に対する神経リハビリテーション．理学療法 26：649-654, 2009

◆総　説

幻肢痛の脳内メカニズム

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要旨　四肢切断後に現れる幻肢痛をはじめとする神経障害性疼痛の発症には末梢神経系と脊髄での神経系の異常興奮とその可塑性に加え，大脳を中心とした中枢神経系の可塑性が関与していることが，最近の脳機能画像研究から確立しつつある．本稿では，幻肢痛を含む病的疼痛全般は脊髄よりも上位の中枢神経系に由来するというわれわれの持論から，まず幻肢の感覚表象について概説し，続いて幻肢の随意運動の中枢神経系における制御機構から「幻肢が中枢神経系にとって健常肢として存在すれば幻肢痛が寛解する」という仮説を提案する．この仮説を，われわれが行っている鏡を用いて幻肢の随意運動を獲得させることによる臨床治療（鏡療法）から検証し，鏡療法の有効性と限界，そして今後の幻肢痛および神経障害性疼痛に対する新規神経リハビリテーション治療の可能性について概説する．

キーワード　幻肢痛，鏡療法，知覚－運動ループ

（日本ペインクリニック学会誌　Vol.17 No.1, 1～10, 2010）

I　はじめに：幻肢と幻肢痛とは？

四肢切断後の患者の80％以上は，失った四肢が存在するような錯覚（phantom limb awareness）や失った四肢が存在していた空間に温冷感やしびれ感などの感覚（phantom sensation）を知覚し，これらの感覚経験を幻肢と総称する．幻肢は四肢切断でなくても，脳卒中，脊髄損傷や末梢神経損傷などの運動麻痺や感覚遮断によっても発症し，これらは余剰幻肢と呼ばれる．また，乳房や陰茎，眼球などの切除後にも幻身体（phantom body）は現れる．幻肢に合併する病的痛み（幻肢痛：phantom limb pain）の発症頻度は四肢切断患者の50－80％とされ，その長期予後は報告によって異なるものの大部分の患者では数年を経ても幻肢痛を伴っている[1]．

幻肢痛の発症機序としては，末梢神経の損傷によってできた神経腫由来の異常インパルスや脊髄レベルでの神経細胞の易興奮性，脊髄よりも上位中枢神経系レベルでの易興奮性がさまざまな要因によって誘発されることが動物実験から示されてきていたが，ヒト幻肢痛患者を対象とした脳機能画像研究からは大脳などの脊髄よりも上位の中枢神経系レベルでの機能再構築（reorganization）が幻肢痛の発症基盤として中心的な役割をしていると考えられている．一次体性感覚野（S1）には身体部位に応じた脳領域が存在することが知られ，これらを体部位再現地図（somatotopy）と呼ぶ（**図1上右**）．上肢切断後患者では患側上肢に相当する脳領域が縮小し，上肢の隣に位置する口/顔面の領域が拡大してくる機能再構築がS1で認められる（**図1上左**）[2]．このような四肢切断後幻肢痛患者でのS1の機能再構築では，断端部の触覚弁別を訓練することによって上肢の領域が拡大（口/顔面の領域が縮小）する機能再構築が再び起こり，それと同時に幻肢痛が軽減することが報告されている[2]．さらに，一次運

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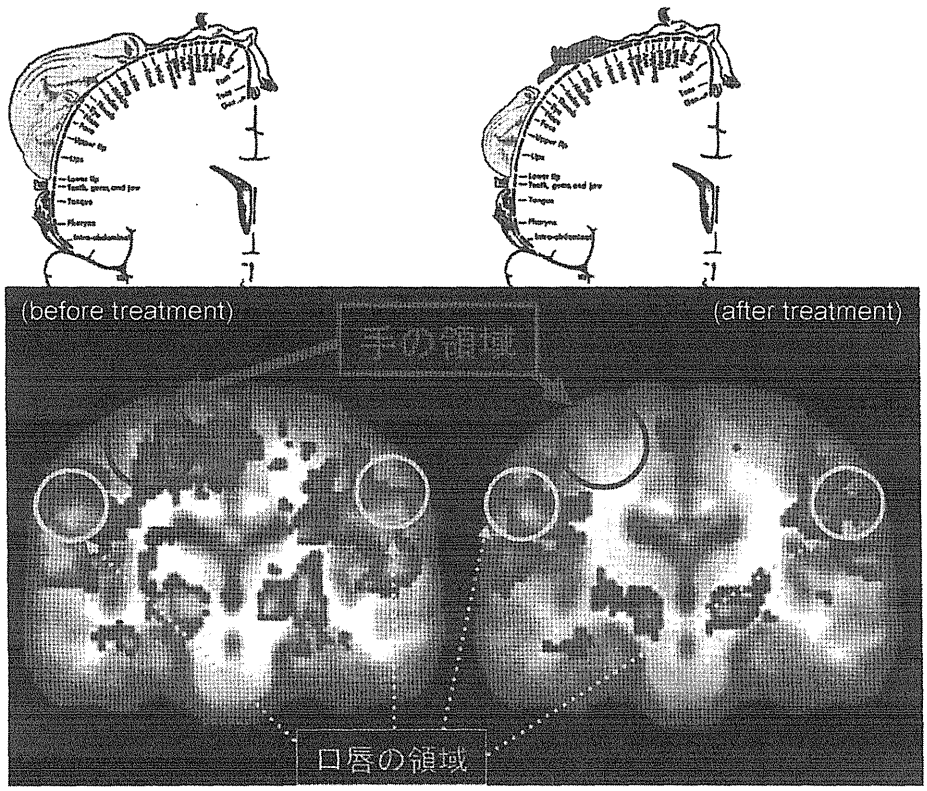

図 1　幻肢の随意運動感覚獲得前後の口唇運動時の脳活性化の違い

（文献 21, 24 から改変して使用）

下段は口唇運動時の一次運動野（M1）冠状断面の活性化を示す．幻肢の随意運動感覚の獲得前（左下図）には口唇の運動によって M1 の外側部（白円）だけでなく頭頂付近にも活性化が認められるが，幻肢随意運動感覚の獲得後（右下図）には口唇運動に伴う M1 活性化部位は外側部だけに限局している．このことは M1 の体部位再現地図における手の領域（濃灰円）が回復したことを示す．上段に，幻肢の随意運動感覚獲得前（左上図）と獲得後（右上図）の体部位再現地図の模式図を示す．

動野（M1）にも体部位再現地図があり，上肢切断後幻肢痛患者では上肢領域の縮小と口/顔面領域の拡大が認められ上肢領域に存在する神経細胞の興奮性が高まっている．このような S1/M1 の機能再構築は，上肢切断後に幻肢を知覚するが疼痛（幻肢痛）を伴わない患者には観察されず[3]，M1 への磁気刺激や電気刺激が幻肢痛をはじめとする難治性疼痛に有用なことも報告[4-5]されていることから，M1 と幻肢痛は密接に関連している．S1/M1 以外では視床にも体部位再現地図が観察されるが，神経損傷による求心路遮断によって視床体部位再現地図の再構築が起こる[6]．この視床体部位再現地図の再構築は視床電気刺激による治療で正常地図へと再び再構築が起こる[7]ので，視床も幻肢痛の発症と密接に関連していると考えられる．

II　幻肢を科学的に扱う：幻肢の準客観的な評価方法の開発

幻肢は常に一定に知覚されるわけではなく，幻肢を正常な長さの肢のように感じたり，断端部に手が埋まっているような非常に短い肢に感じたりと，幻肢の大きさ知覚はさまざまに変化する．このような幻肢の大きさが変化する現象をテレスコーピング現象と呼ぶ．S1/M1 体部位再現地図の手の領域が縮小して体幹の領域に近付く度合いとテレスコーピングを知覚する度合い（どの程度，幻肢を短く感じるか？）が相関することが明らかになっており，幻肢の大きさ知覚も S1/M1 の体部位再現地図と密接に関連している．幻肢の大きさや姿勢・運動については多くの脳機能画像研究が報告されているが，これらのいずれもが幻肢患者の主観的な報告に依存しており，幻肢を客観的に評価することはできない．幻肢痛の診療

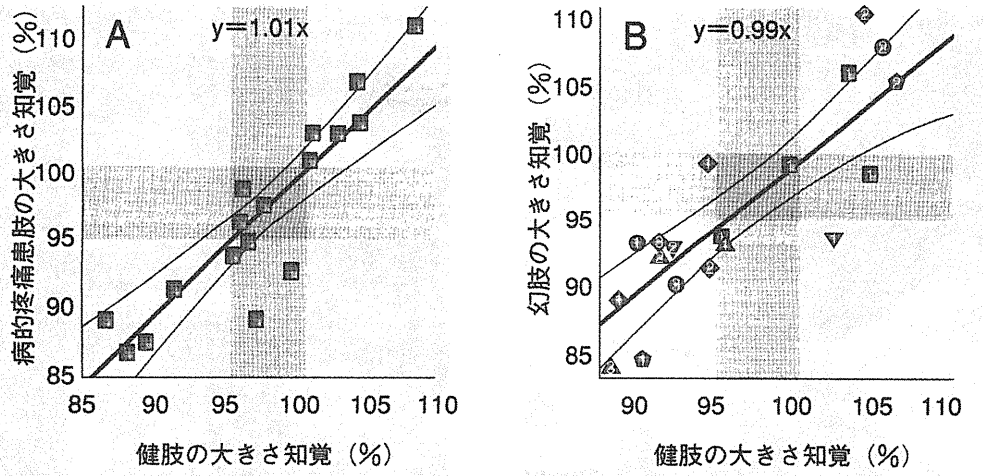

図2　病的疼痛患肢と幻肢の大きさ知覚の変化は健肢の大きさ知覚に反映される

（文献9より改変して使用）

A：上肢病的疼痛（CRPS type 1）患者の患肢の大きさ知覚（y軸）と健肢の手の大きさ知覚（x軸）の散布図とその相関．■は個々のCRPS患者の患肢と健肢の手の大きさ知覚の結果をプロットしている．患肢と健肢の手大きさ知覚は1.1の関係性（y=1.01x）である（Spearman test. $P<0.0001$, $R^2=0.82$）．

B：上肢幻肢患者の幻肢の大きさ知覚（y軸）と健肢の手の大きさ知覚（x軸）の散布図とその回帰．個々の幻肢患者の幻肢と健肢の大きさ知覚をシンボルで示す．シンボル内の数字は両手の大きさ知覚を評価した回数を示し，共通のシンボルは同一患者の結果を示す．健肢の大きさ知覚は幻肢の大きさ知覚に1.1の関係性（y=0.99x）で回帰する（重み付け回帰分析．$P<0.0001$, 調節 $R^2=0.73$）．

A, Bともにx, y軸の100%は健肢の実際の大きさと被験者が答えた手の大きさが一致することを意味し，灰色の領域は健常者10人（のべ20手）の大きさ知覚の10–90パーセンタイルを示す．

では，患者が具体的に幻肢について口述するが，それを医師が共有することはできず，患者との相互理解の障壁となりうる．このような問題意識からわれわれは幻肢を患者の口述以外で評価する方法の開発を行った．

ヒトは局所麻酔を受けた身体部位を腫れているように感じ，また侵害刺激（侵害受容性疼痛）を受けた身体部位も腫れているように感じる[8]．そこで，われわれはまずはじめに，神経損傷のない病的疼痛（CRPS type 1）も侵害受容性疼痛と同様に罹患部位を大きく感じるかを検証した．その結果，CRPS患肢は一概に大きく感じられるわけではなく，極端に小さく感じている患者もいた（**図2A**）．そして，患肢の大きさ知覚が変化している患者は反対側の健肢の大きさ知覚も患肢と同様に変化（患肢を通常よりも大きく感じていると健肢も大きく感じ，患肢を小さく感じていると健肢も同様に小さく感じる）していることを発見した（**図2A**）．このように患肢の大きさと健肢の大きさ知覚は1：1の対応が認められることを利用して，幻肢患者でも健肢の大きさ知覚を評価することによって準客観的に幻肢の大きさを評価できるかを検証した．すると，幻肢患者でもCRPS患者と同様に幻肢と健肢の大きさ知覚が1：1の関係性になっていることが明らかになった（**図2B**）．幻肢の大きさ知覚はその時々によって変化するが，このような幻肢と健肢の1：1の関係性はテレスコーピング現象の出現と消退時に幻肢の手の大きさが変化した場合においても維持されていた（**図2B**）[9]．運動系の観点からは両側上肢は1つの手運動表象として扱われ，運動プログラムが生成される最も初期の段階では一方の上肢に対する運動であっても両側上肢に対する共通の運動プログラム（generalized motor program）が生成されると考えられている．感覚系を運動系への情報伝達機構と考えると，1つの手運動表象の形成のためには，左右手からの感覚情報をそれぞれの手へと独立して情報伝達した後に1つの手運動表象が形成されるよりも，左右手からの感覚情報を統合して1つの手感覚表象を形成した後に1つの手運動表象へと情報伝達したほうが効率的である．このことから，感覚表象としての幻肢と健肢は1つの手表象に収束するので1：1の大きさ知覚の関係性が示されたと，われわれは考えている．

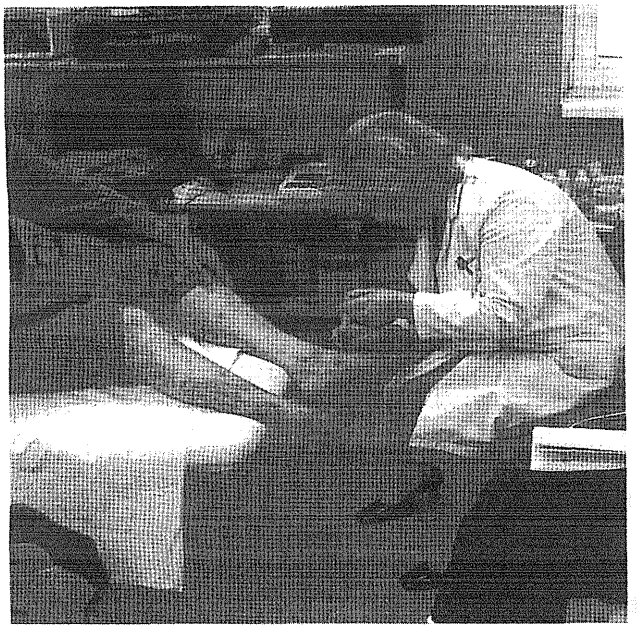

図３　幻肢痛の反対側健肢に対する神経ブロック治療
（2006 年大阪大学医学部附属病院疼痛医療センター前田　倫 *医師 & JICA expert*）
神経ブロック手技の充分な普及がなされていないボスニア・ヘルツェゴビナでは，幻肢痛患者の反対側健肢へのトリガーポイントブロックが行われており，ある程度の有効性を認める．

左右の身体部位情報が統合されて１つの身体部位感覚表象が形成されていることは，幻肢痛患者の治療として健肢に対して神経ブロックを行う（**図 3**）[10] ことの治療メカニズムと関連しているかもしれない．

III　幻肢の運動制御：幻肢の不随意運動と随意運動

幻肢痛患者はさまざまな性質の疼痛を訴える．ボスニア・ヘルツェゴビナでの内戦によって四肢を失った幻肢痛患者 1,250 人を対象とした調査では，刃物で裂かれるような，電気が走るような，しみるような，など皮膚表在感覚に関連した疼痛を約 58％の患者が訴える一方で，幻肢がけいれんするような，こむら返りするような，幻肢がねじれるような，など運動感覚（自己受容感覚）に関連した疼痛を約 42％の患者が訴えている[11]．このように幻肢痛患者の半数近くの者が幻肢の不快な不随意運動を知覚している．では，幻肢の運動感覚はどのような神経基盤によってもたらされているのであろうか？　幻肢患者の中には幻肢を随意に運動することができる（幻肢が運動しているように鮮明に知覚できる）者がおり，その際には健常な四肢随意運動に類似した一次運動野（M1）/感覚野（S1），補足運動野（SMA）の賦活化が脳機能画像研究によって観察される（**図 4**）[12]．幻肢に不快

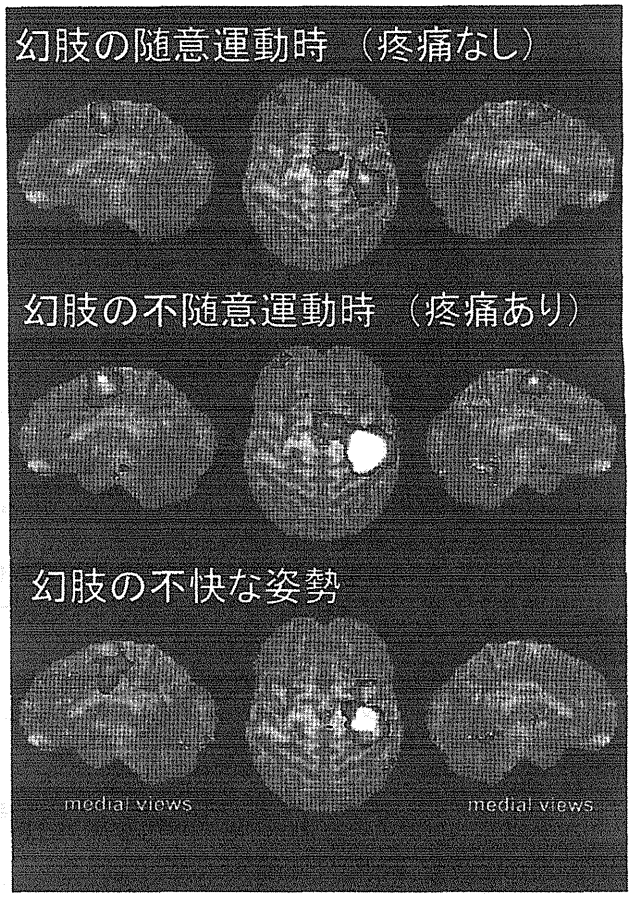

図４　幻肢の異なる感覚経験によって活性化される脳領域
（文献 12 より改変して使用）
幻肢は常に一定に知覚されるわけではなく，その時々によって幻肢患者は異なる感覚経験を知覚する．このような異なる感覚経験時には異なる脳領域の活性化が観察されるが，感覚運動皮質（一次体性感覚野と一次運動野）の活性化は共通している．

感を伴う不随意運動時には，S1/M1, SMA に加えて，小脳，前帯状回（ACC），後部帯状回（PCC）の賦活化が観察される[13]．ACC と PCC はともに四肢運動の制御と認知にも関連する脳領域[14] であるが，この研究では ACC/PCC の賦活化が幻肢不随意運動によって惹起される疼痛や不快感の程度と相関していたことから，ACC/PCC は不随意運動の制御に関連しているというよりは不快な情動の生成[15] と関連していると理解するほうが妥当である．これらの不快情動生成領域以外の幻肢運動に伴う脳賦活化パターンは随意運動であろうと不随意運動であろうとよく似ており，さらには健常肢運動時の脳賦活化パターンともほぼ相同であることから，脳内での四肢運動の実行・認知に関しては幻肢と健常肢には区別がないように推察できる．さらに，中枢神経系における幻肢と健常肢の区別の有無については，次のような興味深い研究が報告されて

いる．両側上肢を同時に運動する際には両側上肢に対して共通の運動プログラムが出力されていることから一側上肢の運動パターンがもう一方の上肢の運動パターンに影響を与え両側上肢の運動が1つの運動パターンに収束する（例：右手で三角形を描きながら左手で円を描くと，右手の三角形が円形に近づいていく）[16]．このような両上肢協調運動の影響は幻上肢随意運動ともう一方の健常上肢の運動パターンにも観察され，幻肢を随意に運動することができない患者では観察されない[17]．このような行動学的評価でも，中枢神経系での四肢運動制御機構では幻肢と健常肢をほぼ相同のものとして扱っているような知見が得られている．ただし，手を脳内で無意識的に運動することを評価する mental hand rotation task と呼ばれる心理課題では幻肢の認知（運動イメージ）が健常肢に比べて低下している[18]ことから，運動実行の準備段階である運動企図（運動イメージ）レベルでは幻肢と健常肢は異なる神経基盤によって制御されていることが示唆され，今後の研究が期待される．

IV　幻肢痛の脳内メカニズム

1．知覚：運動ループの破綻と病的疼痛の発症

四肢運動の際には，運動の指令に続いて運動後に知覚される感覚情報フィードバック（腕の肢位など）の予測（efference copy という）と実際の運動（execution）が起こり，続いて実際の運動によってフィードバックされた感覚情報が運動予測（efference copy）と比較されることによって，さらに新たな運動指令が準備される．この運動に伴う一連の運動系と感覚系の情報伝達は常に中枢神経系でモニターされ知覚–運動ループと呼ばれる．自己身体部位のそれぞれについて知覚–運動ループが整合されている状態では，ヒトはその身体部位を自分の体の一部と認知できる．言い換えると，ある身体部位に関して知覚–運動ループの整合性が破綻した際には，ヒトはその身体部位を自己身体の一部であると認知できない[19]．このような自己身体認知にかかわる知覚 – 運動ループは体性感覚だけでなく多感覚情報を統合して制御されており，中でも視覚情報が最も重要である[19]．例えば，自分の上肢を隠し，その上肢の横に目視できるゴム手を置き，隠された上肢とゴム手に対して触覚刺激を同時に与えるとゴム手を自分の手と認知してしまうこと[20, 21]や自身の身体と連続性があるようにみえる上肢，言い換えると視覚的に正しい肢位の上肢は他人の上肢であっても自分の上肢と認知してしまうこと[19]などが挙げられる．このように手の位置を正しく認識するためには体性感覚情報だけでは不十分で視覚的に認識しなければならず，視覚的情報の修飾によって自己身体部位の認知は容易に攪乱される[19]．このような身体部位認知における視覚情報の優位性を利用して，健常者上肢の視覚的な運動感覚と体性感覚的な運動感覚を解離させて上肢の知覚 – 運動ループを破綻させると，病的疼痛や手の喪失感をはじめとする異常感覚が生じることが報告されている[22]．この現象は，“痛み”とはそもそも身体の異常を知らせるための警告信号であるという観点から，生理的には知覚–運動ループの整合性が保たれるべき状態で，それが破綻するとその異常（破綻）に対する警告として“痛み”が中枢神経系で起こる（認知される），というように解釈されている[23–24]．

さらに，身体部位の運動感覚の出現にも視覚入力は重要な役割を示し，サルが餌を掴んで食べる動作をするときに活動する神経核群は，ヒト（あるいは別のサル）が食物を掴んで食べる動作をサルが観察するだけでも神経発火が認められる．このような神経核群は mirror neuron system と呼ばれ，視覚的に動作を観察することによって自己身体にもその動作を模倣するような運動プログラムを準備すると同時にその動作の理解・認知を行っていると考えられており[25]，mirror neuron system は他人の動作を自己身体部位の運動感覚として認知するような機能を持っている．このような mirror neuron system は単一の脳領域だけに存在するのではなく複数の脳領域で観察され，それぞれの mirror neuron system が連携して身体部位認知を行っていることから body parts coding network として注目されている[26]．四肢を運動した経験のない先天性四肢欠損患者にも幻肢感覚が現れることは古くから知られているが，このような患者が訴える幻肢は随意運動感覚を伴っていることが多く，先天性四肢欠損患者の幻肢随意運動時には body parts coding network の中で中心的な役割を果たしている運動前野の脳賦活化が観察される[27]．この脳賦活化パターンは，後天性の四肢切断後患者の幻肢随意運動時の脳賦活化パターン[12]とは明らかに異なり，運動前野には mirror neuron system が含まれていることから，先天性四肢欠損患者の幻肢と幻肢の運動感覚は他人の四肢運動の視覚情報から形成されていることが示唆される．

2．幻肢痛に対する visuomotor training

Ramachandran らが鏡を用いたリハビリテーション（以下，鏡療法）（**図 5**）によって幻肢の随意運動の獲得とそれに伴う幻肢痛の緩和を報告[28]して以来，幻肢痛に対す

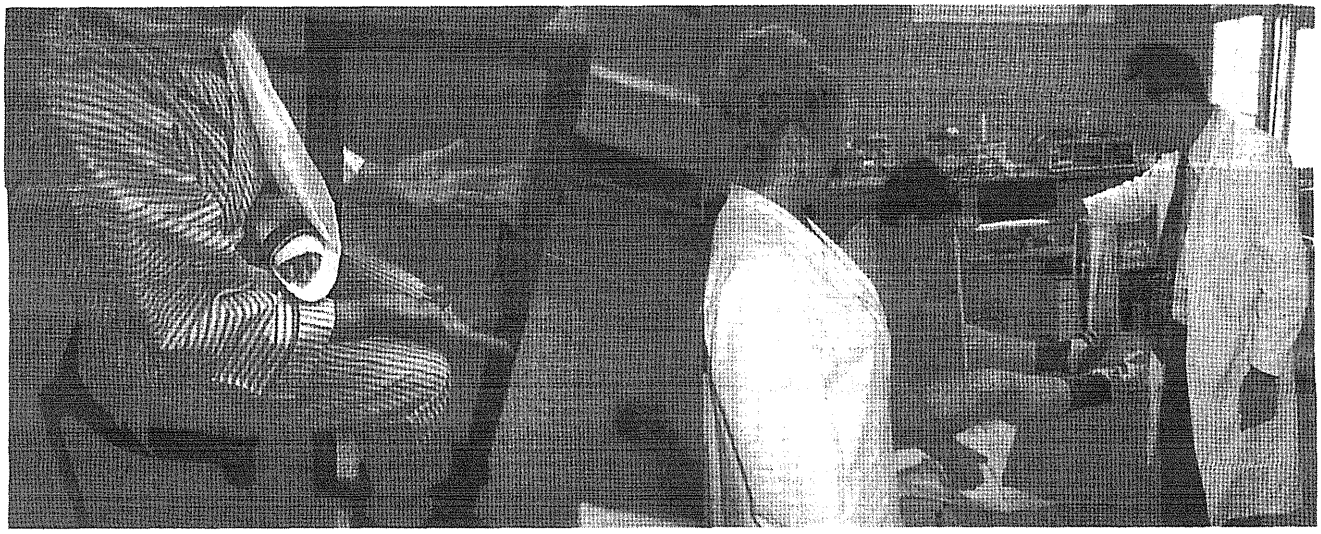

図5　鏡療法の診療風景
(2006年大阪大学医学部附属病院疼痛医療センター前田　倫医師& JICA expert).（文献49より許可を得て掲載）
患者の身体正中矢状断面に鏡を置き，鏡の中に患肢が存在しているような視覚像が得られるように健肢を鏡に映す．健肢の手指を自由に運動させ，あたかも患肢が動いているような鏡像を観察させる．同時に，患肢が鏡像肢と同様の運動をしているようなイメージを想像させる（実際に患肢に対する運動指令を行わせる）．これを1日1回約10分間行い，患者の希望によって数週間継続する．左：左腕神経叢引き抜き損傷後余剰幻肢痛患者．肘より末梢側に，体幹に対して垂直方向に幻肢を知覚している，右：戦争後遺症による左下肢切断後幻肢痛患者．われわれの診療グループはボスニア・ヘルツェゴビナでも鏡療法を指導している

る鏡療法の有用性はさまざまに検証されてきた[29-32]．これらの研究を通じて鏡療法の鎮痛機序についていくつかの知見が蓄積されてきたところであり，われわれは知覚−運動ループの破綻と幻肢痛の関連を示唆する研究結果を得ているので概説する．

われわれの鏡療法の方法と結果

身体正中矢状断面に鏡を置き，健肢を鏡に映す（鏡の中に患肢が存在しているような視覚像が見える）（**図5**）．そして，健肢の手指を自由に運動させ，あたかも患肢が動いているような鏡像を観察する．同時に，患肢が鏡像肢と同様の運動をしているようなイメージを想像する（患肢に運動指令を出す）．これを1日1回約10分間行い，患者の希望によって数週間継続する．

この方法を用いて，神経障害性疼痛患者22例（四肢切断後幻肢痛11例，腕神経叢損傷後疼痛7例，胸部脊髄部分損傷後疼痛2例，末梢神経損傷後疼痛2例）に対して鏡療法を行い，10例で50％以上の疼痛緩和，5例で30–50％の疼痛緩和を得た一方，7例では無効であった[32]．さらにわれわれは，鏡療法の前後に患者が自発的に述べる痛みの性質を記録し，その性質を皮膚受容感覚（表在感覚）と自己受容感覚（深部感覚）[26]に関連した性質に分類した．その結果，鏡療法によって自己受容感覚に関連した性質の痛み（例：ねじれるような）は有意に減少したが，皮膚受容感覚に関連した性質の痛み（ナイフで刺されたような）にはあまり効果がなかった[32]．加えて，鏡療法前後での幻肢の随意運動の可否についても評価した．有効例の患者では，鏡療法によって幻肢の随意運動を獲得し，運動感覚を伴う不快な幻肢感覚・幻肢痛（例：幻肢の“こむら返り”など）が不随意に出現した際にそのような幻肢の不随意運動に拮抗するような幻肢の随意運動（例：こむら返りに対して腓腹筋を伸展する）を行うことにより，幻肢の不快感・疼痛を自己管理できるようになった患者が多かった（**図6**）．また，幻肢の随意運動を行うことによって，運動感覚を伴わないような持続痛も軽減した．今回示したわれわれの結果は単回の鏡療法前後の評価であるが，幻肢の随意運動の獲得と随意運動による幻肢痛の自己管理を繰り返すことによって，幻肢痛の軽減効果が長期的に持続するだけでなく，幻肢そのものが消失した患者も経験している．ただし，Ramachandranの報告[28]とは異なり，鏡療法が著効した患者でも初回の鏡療法施行直後および数回の鏡療法施行だけでは明らかな変化を自覚する患者はほとんどおらず，鏡療法を継続（最低でも2〜3週間，最長例は9カ月）することによって幻肢の随意運動を行うことができるようになった患者がほとんどである．

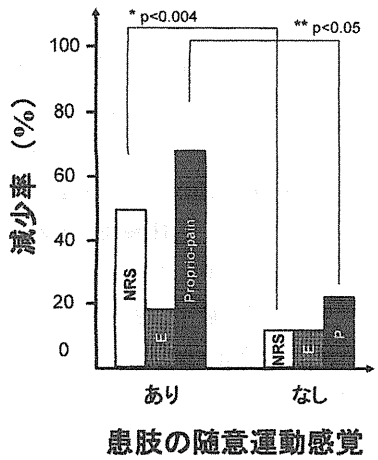

図6　幻肢の随意運動の出現による鏡療法の有効性の差異

（文献32より改変して使用）

縦軸は治療前後の疼痛強度（0～10までの11段階で評価したNRS＝numerical rating scale）と皮膚表在感覚に関連した性質の疼痛（E＝exteroception associated pain）の訴え，および自己受容感覚に関連した性質の疼痛（Proprio-pain, P＝proprioception associated pain）の訴え，それぞれの減少率を示す．横軸は，鏡療法施行前後による患肢随意運動の出現の有無によって患者群を2群（あり：n＝15，なし：n＝7）に分けている．

*：P＜0.004，**：P＜0.05.Mann-Whitney test

3．幻肢痛の発症機序：鏡療法からの考察

四肢切断とそれに続く幻肢を知覚-運動ループの観点から評価すると，「脳からは切断肢を運動する指令（例：姿勢調節など）が常に発動されているが，実際には切断肢の運動が起こらないために感覚情報のフィードバックが欠損し，運動指令に続く運動予測（efference copy）との間に解離が起き，知覚－運動ループの整合性が得られていない」状況と考えることができる．上述したように四肢認知についての視覚情報の影響はきわめて強いため，単独では自己身体を認知するには不十分な体性感覚情報を代償する能力がある[19]．このことから鏡療法の治療機序は，「切断肢（あるいは神経損傷肢）が運動しているかのような鏡からの視覚情報は，四肢切断（あるいは神経損傷）に起因する自己受容感覚の欠損を代償して中枢神経系に運動感覚をフィードバックし，その結果，切断肢（神経損傷肢）の知覚－運動ループが再統合され病的痛みが緩和する」と考えられる．健常者を対象とした電気生理学的研究では四肢の皮膚受容感覚は知覚-運動ループにはあまり関与していない一方，自己受容感覚は四肢の運動感覚や運動制御に強く関与していることが示されており，自己受容感覚は皮膚受容感覚よりも知覚－運動ループと密接に関与している[33-35]．このことが自己受容感覚に関連した性質の幻肢痛に対して鏡療法がきわめて効果的であったことの理由であると考えている．逆に言うと，われわれの無効例では鏡療法を継続しても幻肢の運動感覚は出現せず，皮膚受容感覚に関連した痛みを主に訴えていたことが鏡療法が無効であったことの理由として考えられる．また，われわれのこのような考察は，合目的な運動が知覚－運動ループの統合によってなされていることから，電動義手を用いて患肢を合目的な機能肢として運動学習をすることによって幻肢痛が寛解するという研究[36]と矛盾しない．

患肢の随意運動の獲得時には，感覚運動皮質における患肢の体部位再現地図が拡大する[37,38]ことも明らかになっており（**図2**），感覚運動皮質の体部位再現地図の機能再構築（患肢領域の縮小）が疼痛強度と相関しているという知見からも，鏡療法による鎮痛機序は患肢の体部位再現地図の拡大によると考えられる．

4．幻肢痛（神経障害性疼痛）に対する視覚入力だけでなく体性感覚入力も利用した神経リハビリテーションの開発

これまでわれわれは，知覚-運動協応の再統合を目的に視覚入力（鏡）を用いた神経リハビリテーションを行ってきたが，われわれの鏡療法に対して抵抗性を示す難治性疼痛患者も少なくはない．そこでわれわれは，視覚情報に加えて，神経障害による運動不全を呈する患肢を受動的に運動させることによって体性感覚情報も同時に入力するリハビリロボットスーツ（**図7**）を共同開発中である（四肢切断後患者の場合は義肢も併用する）[39,40]．このスーツは健肢に装着したセンサーの情報（例：肘関節を屈曲）を検知し，患肢に装着した人工筋とワイヤーが作動し，鏡の中に存在するような患肢の映像（健肢が鏡に映った映像）を運動させる時と同じように患肢の受動的運動が実行される．運動企図から運動指令が形成されその運動に応じた体性感覚情報の入力がある状態では，単に受動的に運動が行われた条件よりもより強いS1の活性化が観察され[4]，さらには，単なる受動運動ではM1の活性化はあまり観察されないが，能動運動時には運動しようとする身体部位に応じたM1体部位領域が強く活性化することから，われわれが共同開発中のロボットスーツを使用する際に患者が健側肢と同様の運動を患肢でも実行しようと意図することにより，①鏡療法のように健側上肢を運動した際に患側上肢が同様の運動を行うため，身体運動に関する視覚情報が入力されること，②断端肢に幻肢の感覚表象が形成され，断端肢からの体性感覚情