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

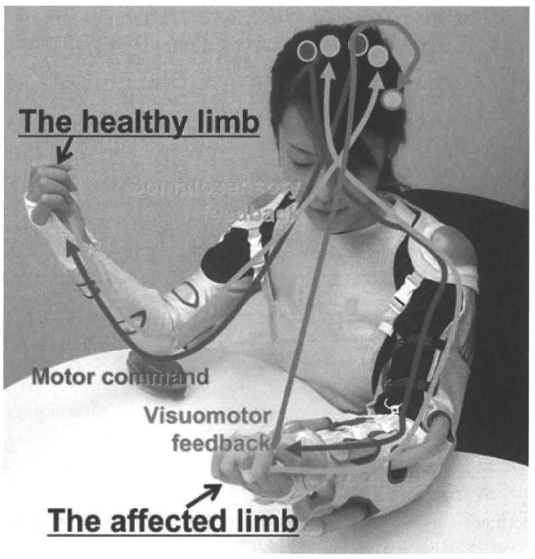

Fig. 1 Rehabilitation robot suit system for an upper limb with motor paralysis and neuropathic pain. A sensor suit is worn on the *right* upper limb (the healthy limb). On the *left* upper limb (the affected limb), an actuator consisting of artificial muscles and wires is fitted. Intending and forwarding 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.

Acknowledgments This study was funded by the New Energy and Industrial Technology Development Organization (no. 08C46216) and the Ministry of Education, Science, Sports and Culture [(c) no. 18591702].

Conflict of interest statement No conflict of interest has been declared by the authors.

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.