CASE REPORT

Relief of neuropathic pain after spinal cord injury by brain–computer interface training

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OBJECTIVES: The aim of this study was to report the effects of brain–computer interface (BCI) training, a neurofeedback rehabilitation technique, on persistent neuropathic pain (NP) after cervical spinal cord injury (SCI).
SUBJECTS AND METHODS: We present the case of a 71-year-old woman with NP in her left upper extremity after SCI (C8). She underwent BCI training as outpatient rehabilitation for 4 months to enhance event-related desynchronization (ERD), which is triggered by the patient's motor intuition. Scalp electroencephalography was recorded to observe the ERD during every BCI training session. The patient's pain was evaluated with the McGill Pain Questionnaire (MPQ) and a visual analog scale (VAS). The MPQ was performed after every BCI training session, and the patient assessed the VAS score on her own, once every few days during the BCI training period.
RESULTS: After the BCI training started, the patient's ERD during the BCI training period increased significantly, from 15.6–30.3%. Moreover, her VAS score decreased gradually, from 8 to 5, after the BCI training started, although the MPQ did not change significantly.
CONCLUSION: BCI training has the potential to provide relief for patients with persistent NP via brain plasticity, and to improve their activities of daily living and quality of life.

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INTRODUCTION

Neuropathic pain (NP), which is caused by disease of or injury to the nervous system, includes various chronic conditions that affect up to ~ 10% of adults who have severe chronic pain.[1] Chronic pain is often associated with spontaneous pain, as well as with changes in sensitivity to several somatosensory stimuli.

More than two-thirds of individuals with spinal cord injury (SCI) experience persistent pain.[2] Several types of pain may occur after SCI, including musculoskeletal pain, visceral pain and two different types of NP that manifest at or below the level of the SCI. A cohort study[3] reported the presence of below-level NP in 34% of the subjects evaluated. Of all possible pain types, below-level NP is the type of SCI pain most likely to be described as severe or persistent. NP has an adverse effect on activities of daily living and rehabilitation, and it frequently leads to depression and even suicide. It has also been reported that 5–45% of subjects with noxious pain after SCI suffered greatly from interference of activities or from poor quality of life.[4]

Treatment is seldom successful, and moderate relief may be achieved only after undergoing a combination of interventions over the long term. Available treatments, which include non-pharmacological, pharmacological and interventional therapies, provide only symptomatic relief. The present prevailing pharmacological and recommended first-line treatments are antidepressants (tricyclic agents and serotonin–norepinephrine reuptake inhibitors) and anticonvulsants (gabapentin and pregabalin).[5]

Brain regions involved in persistent pain are thought to display the cortical adaptive processes related to chronic pain.[1] Thus, any treatment that approaches pain-related brain activity has the potential to have an effect on NP, including functional magnetic resonance imaging or electroencephalogram (EEG) feedback, transcranial direct current stimulation and repetitive transcranial magnetic stimulation. In the area of neuro/psychostimulation, transcranial direct current stimulation has led to a temporary reduction in pain, with minimal side effects and good tolerability.[6] NP was further decreased by integrated transcranial direct current stimulation with virtual gait self-perception.[7] The effective use of visual illusion of walking after sensory system injury (including cauda equina) was first achieved by Moseley on the basis of NP as a cause of changed cortical body representation and disrupted sensory afferents.[8] Some theories, including correction of sensory–motor mismatch, were guesses regarding the mechanism of the effect.[9]

Brain–computer interface (BCI) technology is a newly developed technique that has generated a great deal of interest. Recent studies have indicated that brain activities measured by EEG or magnetoencephalography provide information for the presumption of motor intention.[7] Using BCI technology, real-time feedback involving cortical activity can be provided to the patient through visual and somatosensory information. BCI was shown to monitor motor-related cortical activity in an EEG recorded over the sensorimotor area in the affected hemisphere of a chronic stroke patient.[10] Sensorimotor rhythm (SMR) that is observed over the sensorimotor cortex indicates the subject's motor intention. SMR has the arch-shaped mu rhythm (8–13 Hz) and the central beta rhythm.[11] Two types of SMR pattern variation are shown in the sensorimotor process: event-related desynchronization (ERD), which is characterized by SMR amplitude decline, and event-
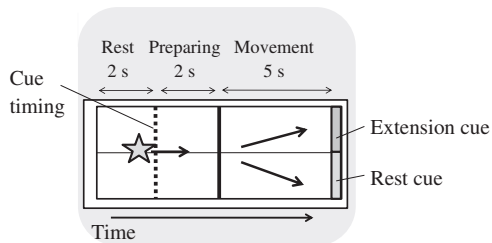
Figure 1. Either the extension or rest cue is presented at the right side of the screen 2 s after the star appears. If the EEG catches the ERD pattern for the movement phase, the star moves upward on the screen to provide visual feedback based on SMR classification. EEG, electroencephalography; ERD, event-related desynchronization; SMR, sensorimotor rhythm.

related synchronization, which is characterized by SMR amplitude enhancement.

Although it has been reported that neurofeedback training with SMR activity is effective in alleviating the symptoms and signs of fibromyalgia syndrome,[12] in the present study we specifically used ERD feedback in a BCI system for relief of severe NP after cervical SCI.

SUBJECTS AND METHODS

The patient in this case report was a 71-year-old female who incurred a fracture and dislocation of the fifth cervical vertebra and SCI following a traffic accident. She underwent orthopedic stabilization of the vertebral column 3 days after the injury at a general hospital. The patient received inpatient rehabilitation for about 7 months at a rehabilitation hospital after the surgery, and at the time of discharge she was able to walk with the aid of a T-cane. About 12 years later, she began outpatient rehabilitation at a rehabilitation hospital after suffering noxious NP referred to as above level and at level in the left arm caused by the SCI. Although she was taking some medication (non-steroidal anti-inflammatory drugs, vitamin B and pregabalin) for the pain, those treatments had an insufficient effect on the persistent NP. About 5 years after beginning the outpatient rehabilitation, we were consulted regarding the NP by the patient. The initial physical examination at our hospital revealed that the neurologic status was C8 incomplete tetraplegia (ASIA impairment D). Superficial sensory deficit was found in the left T1 and T2, and from the L1 to L5 dermatomes. Deep sensation of the left extremity was intact. Range of motion was restricted in plantar flexion of the left wrist and extension of the left second and third proximal interphalangeal joints. No remarkable deficits or pathological signs were apparent in the trunk or in the other limbs. The pain, which often forced the patient to restrict activities of daily living, had distressed her for a long time. Because she required a great deal of pain reduction, we used BCI training to alleviate her suffering.

During the BCI training, the patient was seated in a chair and relaxed, with her arms on the armrests in pronation in front of the monitor. To obtain the SMR component in the EEG, the electrodes were placed at C3, C4, FC3, FC4, C5, C1, C2, C6, CP3 and CP4 (10 channels), according to the International 10/10 system.[13] The ground and reference electrodes were located on the forehead and the left ear lobe, respectively. The EEGs were then converted to a reference-free form by a Laplacian algorithm[14] that used the set of the four neighbor electrodes. For electrode C3 (C4), these were anterior, posterior, left and right to C3 (C4). The two Laplacian EEGs are called the left EEG (C3) and the right EEG (C4) in this study.

During the BCI training, a visual feedback monitor displayed a star moving upward or downward, depending on the EEG features, at an update rate of 16 Hz. A similar visual feedback

method was used in a previous study.[15] The star moved from left to right over nine seconds on the screen, and either the task or rest cue was presented 2 s after the star appeared (Figure 1). Two seconds after the task cue sign, the patient was directed to perform self-paced wrist-extension movements with the affected hand for 5 s. The star fluctuated around the baseline if a decrease in SMR was not clearly seen. The star moved upward if a decrease in SMR was continuously seen, which means ERD appeared. We checked the EEG before, during and after every BCI training session. In particular, we paid attention to the variety of ERD values. ERD value was defined by the equation described in the published paper,[15] and approximately means the occurrence frequency of ERD. The BCI training was finished for the day when the patient indicated that she was fatigued.

The patient gave written informed consent for this study and for the publication of individual data. The study was approved by the local ethics committee of Asahikawa Medical University Hospital and was conducted in accordance with the Declaration of Helsinki. The patient participated in the experiment twice a month for 4 months, for a total of 7 days. Every training session was completed within 2 h to avoid fatigue. In addition to the BCI training at our hospital, the patient continued outpatient rehabilitation at the rehabilitation hospital and used the same medication as in previous years.

We examined the patient's pain status with the McGill Pain Questionnaire (MPQ). The evaluation was performed by a physician and an occupational therapist at the beginning and end of each BCI training session. The MPQ is composed of a pain rating index and a present pain intensity score. The pain rating index is scored as the sum of the rank values of words chosen in each of 20 categories that are divided into four subscales (A = affective, E = evaluative, M = miscellaneous, S = sensory). The patient self-reported daily pain intensity on a visual analog scale (VAS) in a daily notebook using the unrestricted right hand.

RESULTS

During the pre-training assessments, the patient's VAS score was 7–8. During the BCI training period, the VAS scores varied gradually (Figure 2a). This intervention led to moderate relief of the pain in the left arm, with a VAS score of ~ 5. The patient came to be able to perform activities of daily living with either mild or moderate pain. Although we were unable to achieve a remarkable decrease in MPQ score, the score did show a downward tendency (Figure 2b).

The average ERD value in the pre-training and post-training conditions, which was recorded in the right hemisphere on each training day, gradually increased from 15.6 to 30.3% (Figure 3).

DISCUSSION

In this pilot study, we applied SMR-based BCI training to ease persistent NP that was refractory to some treatments, including medications and rehabilitation at other hospitals. We succeeded in showing that a BCI system that provides SMR feedback can reduce VAS scores and enhance ERD values to provide some relief of persistent NP in one patient in this pilot study.

We thought our BCI training might facilitate motorically relevant regions of the sensorimotor system in our patient with NP. Although the primary motor cortex (M1) is not part of the pain matrix, it is thought to play an important role in the modulation of pain in different chronic pain syndromes.[16] Maladaptive plasticity of M1 is a common change in patients with chronic pain, and many studies in animal models and human subjects have shown that modulation of the activity of this cortical area causes important analgesic effects.[17] Because M1 has extensive connections to brain areas linked to modulation and perception of pain, facilitation of this loop by training is a potentially beneficial
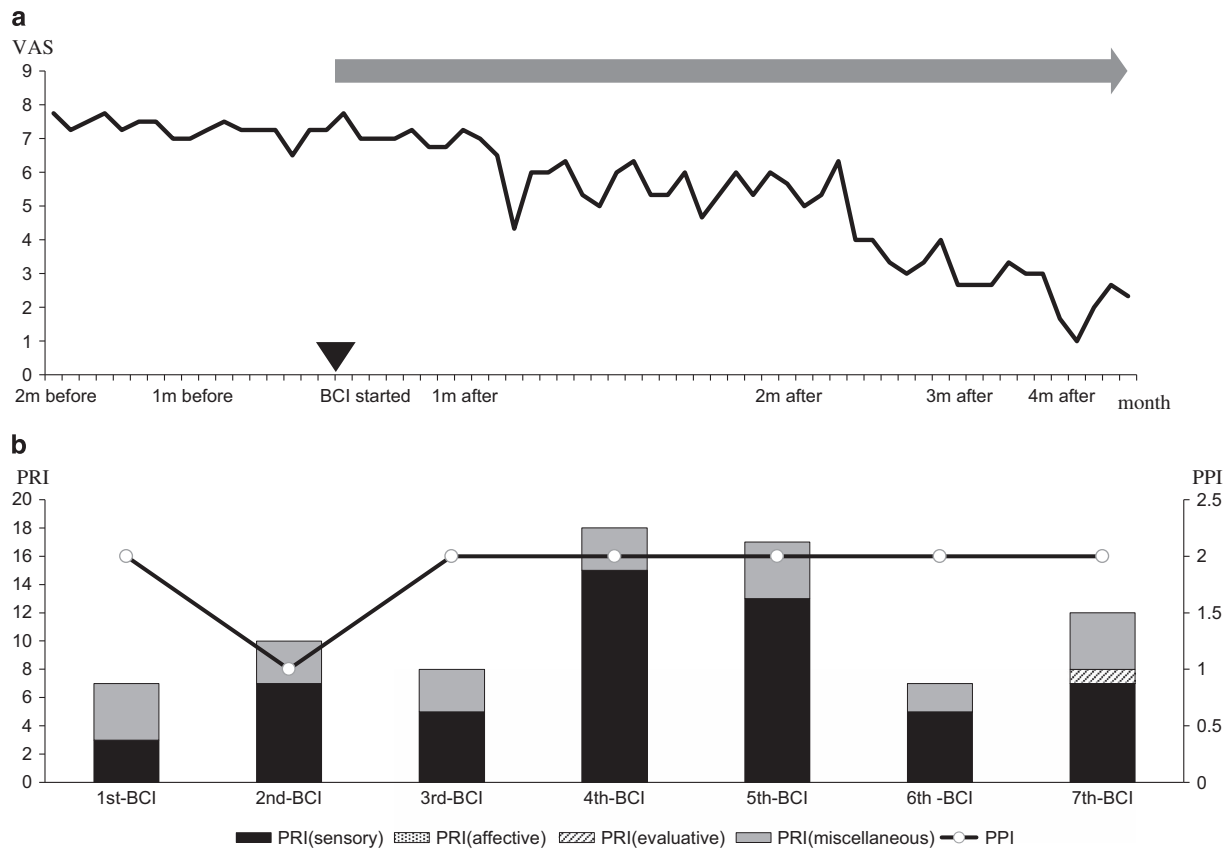
Figure 2. The patient self-reported VAS scores. The gray arrow indicates the period of BCI training (**a**). The MPQ score, composed of pain rating index (columns) and resent pain intensity (line with circles), was recorded after every BCI training session (**b**). BCI, brain–computer interface; MPQ, McGill Pain Questionnaire; PRI, pain rating index; PPI, present pain intensity; VAS, visual analog scale.
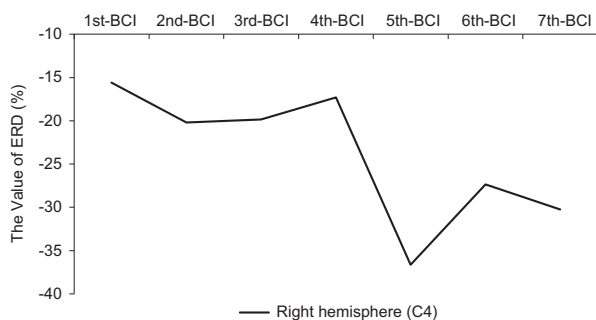

Figure 3. Averages of ERD value were recorded over the right hemisphere (C4) in a selected period and frequency bands (1–3 s, 18–28 Hz). The average ERD value gradually increased after the brain–computer interface training started.

treatment for NP.[16] ERD magnitude during motor imaging is associated with an increase in contralateral M1 excitability.[18] We observed that BCI training increased ERD value, which means that M1 excitability was raised. These results indicate that BCI training has the potential to reduce NP by modulating the sensorimotor system, including the M1 area.

SMR training seems to facilitate thalamic inhibitory networks. SMR, including ERD and event-related synchronization patterns, is normally related with a quiet body and active mind, and is considered to be generated through thalamocortical interactions during burst firing activity in ventrobasal thalamic relay nuclei associated with the suppression of somatosensory afferent gating.[13] The P300 amplitude on an EEG indicates the degree of

central nervous system inhibition; the larger the amplitude, the greater the inhibition.[19] SMR training increases the P300 amplitude, supporting the observation that SMR training promotes thalamocortical inhibitory mechanisms.[13] Furthermore, we observed that EEG variation of brain activity in the relative power of beta frequencies (18–28 Hz) increased. Beta activity is rather related with increased alertness in thalamocortical systems.[20] Parietal and sensorimotor areas combine somatosensory signals with learning and memory and are at the origin of a pathway that converges on the same cortical and subcortical limbic structures (the anterior cingulate cortex, insular cortex and amygdala) that receive direct signals from spinal pain pathways.[21] We suggest that the BCI training may have changed several networks in the brain, including the thalamocortical inhibitory mechanism, which led to pain relief.

Another theory is that a mirror neuron had an effect on pain relief. The mu rhythm (SMR) has been thought to reflect the downstream modulation of primary sensorimotor neurons by visuomotor mirror neurons in the premotor cortex.[12] It was reported in a previous study that a patient with phantom limb pain could feel the same sensation or emotion of the normal body part by observing the mirror image, thus activating a mirror neuron.[22]

Although there are several neurofeedback studies using scalp EEG in pain patients, the key difference between these traditional studies and our study is the use of the SMR-extraction method based on the machine-learning technique. For example, the quantitative EEG method[23] uses three different neurofeedback protocols depending on the EEG frequency bands and the position of electrodes. There is no evidence that the EEG signal is truly SMR or a motor-related response to cortical activity.

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To extract SMR appropriately, the electrode distance needs to be closer. Then, measurement of ERD/event-related synchronization occurring via movement is necessary before training to check for the existence of SMR. As neurofeedback in our study, we employed only SMR, which represents the exaggerated excitability of the sensorimotor cortex during hand movements to accurately provide neurofeedback derived from EEG-related voluntary

movements. The question of whether or not to use only SMR is very important in the physiological context and for its expected effect on patients.

Several limitations of this research should be noted. First, it is important to recognize that a single patient case cannot establish cause-and-effect relationships between the intervention provided and the outcomes observed. Because experimental proof that validates our beliefs is lacking, the evidence level in this study may be low. These results are not generalizable to all patients with NP after SCI. Second, the measurements of NP were indicated by a VAS in this study, although a numerical rating scale has previously been recommended to measure chronic/idiopathic pain in clinical trials.[24] We used a daily notebook that was printed with a vertical line, and the patient was required to make a record of her state of pain. This method made it easy for the patient to record her pain level using her unrestricted hand. In a future study, we will carefully consider how numerical rating scale may be employed to evaluate daily pain. Third, the possibility of the placebo effect should also be considered, given the patient's high expectations of a novel treatment. Positive expectations can strongly ease the subjective experience of pain evoked by a consistently noxious stimulus, whereas negative expectations can lead to the amplification of pain.[25] We need to undertake a larger number of cases and carry out more controlled investigations to determine the efficacy and mechanism of NP relief, define the optimal amount and frequency of BCI training, expand clinical indications, and demonstrate a long-term effect.

In conclusion, the findings of this case report may suggest that the BCI training was associated with the relief of persistent NP and plasticity of the sensorimotor cortex in this patient. Although there are many limitations, these results may lead to the feasibility of using BCI technology as one of the treatments for persistent NP, and potentially it may even be able to have a beneficial effect on the activities of daily living and quality of life in patients with noxious NP. These results therefore encourage further research with controlled studies of BCI training.

COMPETING INTERESTS

The authors declare no conflict of interest.

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