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Nonimmersive Virtual Reality Mirror Visual Feedback Therapy and Its Application for the Treatment of Complex Regional Pain Syndrome: An Open-Label Pilot Study

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Abstract

Objective. **Chronic pain conditions such as phantom limb pain and complex regional pain syndrome are difficult to treat, and traditional pharmacological treatment and invasive neural block are not always effective. Plasticity in the central nervous system occurs in these conditions and may be associated with pain. Mirror visual feedback therapy aims to restore normal cortical organization and is applied in the treatment of chronic pain conditions. However, not all patients benefit from this treatment. Virtual reality technology is increasingly attracting attention for medical application, including as an analgesic modality. An advanced mirror visual feedback system with virtual reality technology may have increased analgesic efficacy and benefit a wider patient population. In this preliminary work, we developed a virtual reality mirror visual feedback system and applied it to the treatment of complex regional pain syndrome.**

Design. **A small open-label case series. Five patients with complex regional pain syndrome received virtual reality mirror visual feedback therapy once a week for five to eight sessions on an outpatient basis. Patients were monitored for continued medication use and pain intensity.**

Results. **Four of the five patients showed >50% reduction in pain intensity. Two of these patients ended their visits to our pain clinic after five sessions.**

Conclusion. **Our results indicate that virtual reality mirror visual feedback therapy is a promising alternative treatment for complex regional pain syndrome. Further studies are necessary before concluding that analgesia provided from virtual reality mirror visual feedback therapy is the result of reversing maladaptive changes in pain perception.**

Key Words. **Complex Regional Pain Syndrome; Pain; Virtual Reality; Neuronal Plasticity**

Introduction

Chronic pain conditions such as phantom limb pain and complex regional pain syndrome (CRPS) are difficult to treat [1] because they are resistant to traditional pharmacologic treatment and invasive nerve block. Moreover, the side-effects of these treatments are of concern. CRPS includes a variety of pain conditions with both motor and autonomic symptoms [2]. The underlying pathogenesis has not been fully understood, which makes it difficult to establish effective treatments. Alternative analgesic modalities have been actively sought for the treatment of CRPS. Meanwhile, recent advances in functional imaging technology have revealed that chronic pain conditions are a consequence of neuronal plasticity in the central nervous system (CNS) [3]. Modalities that rectify such maladaptive changes would constitute novel treatment candidates.

Ramachandran and Roger–Ramachandran introduced mirror visual feedback (MVF) therapy with a virtual mirror box for the treatment of phantom limb pain and reported its promising analgesic efficacy [4]. CRPS type 1 shares many strikingly similar characteristics with phantom limb pain; therefore, McCabe expanded MVF therapy to patients with CRPS type 1 [5] in order to achieve a similar analgesic effect. However, not all patients benefit from this therapy. Because similar neuronal plasticity exists in the CNS of patients with CRPS and phantom limb pain as in that of stroke patients [6–8], stroke rehabilitation therapy intended to restore normal cortical activity can be applied for the treatment of CRPS and phantom limb pain [9].

During stroke rehabilitation, it is essential to repeat task-oriented training with intensity in order to reverse cerebral neuronal plasticity [10]. This technique may also be applicable to MVF therapy for the treatment of CRPS.

The advancing MVF system with virtual reality technology (VRMVF) contains very specific target-oriented motor control tasks and enables subjects to feel engaged and rewarded, thus encouraging them to repeat the exercise with intensity. In this regard, VRMVF has tremendous potential as a noninvasive alternative analgesic modality for CRPS.

The VRMVF system not only reconciles the incongruence between motor intention and proprioceptive feedback in the same way as the original MVF system, but may also engage different brain regions. The VRMVF system consists of target-oriented motor tasks that require planning and coordination of movements that activate the parietal, premotor, and primary motor cortices, where adaptive changes are known to occur in patients with CRPS [11–13]. Distraction [14] and anxiety reduction [15] are also potential candidates for the underlying mechanism of the analgesia provided with our VRMVF system.

In this preliminary work, we have applied our VRMVF system to the treatment of patients with various pain conditions of the upper limb and hand such as phantom limb pain, avulsion injury of the brachial plexus, and CRPS. In the present article, we present its promising analgesic efficacy for CRPS.

Methods

Virtual Reality Mirror Visual Feedback System

A personal computer-based desktop virtual reality system was developed for MVF therapy. The system contains a personal computer (operating system: Windows XP Professional SP2; central processing unit: Intel Core2 Duo 3.16 GHz; graphics: Radeon HD 4679), CyberGlove (Immersion Co., San Jose, CA) as a hand input device, FASTRAK (Polhems Co., Colchester, VT) as a real-time position and motion tracker, and a 20-inch desktop monitor (EIZO FlexScan SX2761W, EIZO Nanao MS Corp., Japan). A virtual environment (VE) was developed using commercially available software, Autodesk 3DS Max (San Rafael, CA). The original system of the present study, including the VE, was produced by a virtual reality specialty company (Asahi Electronics Corp., Japan) and named the Okayama University Simulator for chronic pain treatment. The system is shown in Figure 1. In the VE, three objects of different sizes and shapes (a large orange, a medium green lime, and a small cherry) are initially located on the table with a back shelf. The level of difficulty grasping increases as the size of the target decreases. The affected side of the forearm and hand appears on VE and every movement or any laterality of the real arm can be precisely reproduced. The movement of the fingers and wrist of the virtual hand is simulated by the CyberGlove, which is attached on the nonaffected side because pain is induced if the affected hand is used. The CyberGlove is a stretchable data glove with 18 embedded bend sensors that measure the metacarpo–phalangeal and proximal interphalangeal joint angles of the thumb and fingers as well as finger abduction and wrist flexion. The Fastrak, a position tracker that determines the position and orientation of the virtual arm, is mounted on the affected side. The Fastrak is a magnetic sensor that employs alternating low-frequency fields generated by a transmitter. In the VRMVF system, a virtual forearm moves in the same manner as the affected side, but the hand and finger motions are simulated by the nonaffected side. This is the biggest difference between MVF therapy with a mirror box and VRMVF therapy.

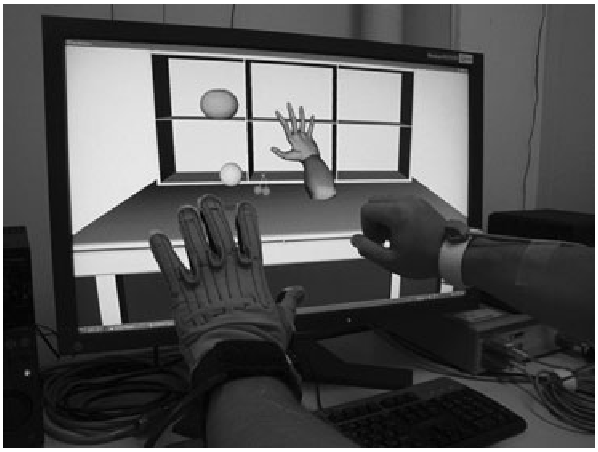

Figure 1 A personal-computer-based desktop virtual reality system for mirror visual feedback therapy. The arm on the affected side (right) and the targets appear in the virtual environment. Finger motion is simulated by the CyberGlove on the non-affected side (left) and arm motion is simulated by FASTRAK on the affected side.

Virtual Reality Mirror Visual Feedback Exercises

The exercises are target-oriented motor control tasks. The sequences of hand exercises consisted of the movements of reaching out, grasping, transferring, and placing. Subjects are instructed to focus on the motion of the virtual hand (affected side) on the PC monitor. When subjects intend to reach the target in VE, they extend their FASTRAK-mounted forearm (affected side) into the appropriate position. In grasping the target with the virtual hand, patients intentionally close their virtual fingers around the target and subsequently get visual feedback of the affected hand as if it grasped the target. The motion of the virtual hand is manipulated by the nonaffected hand and the affected hand is not allowed to move. Motor commands to close the fingers are made on both hands synchronously but only the proprioception of the nonaffected side returns. This is the exactly the same mechanism underlying the original mirror box therapy for phantom limb pain in which patients plan hand movement synchronously and no proprioception returns to their phantom limb, but visual feedback comes from the reflected image in the mirror.

After successfully grasping the target, subjects move it a distance and then open their fingers to release it. Subjects may repeat the exercise with the same target or another target. Because the VE in the present system was constructed in three dimensions, targets may be stacked one by one or lined up from the front to the back. Thus, subjects can create their own way to practice. The system allows subjects to perform repetitive and intensive exercises and receive visual feedback about their ongoing performance.

Application for Patients with Complex Regional Pain Syndrome

Study procedures were approved by the University of Okayama Institutional Review Board and informed written consent was obtained from all participants. Five patients with CRPS of the hand attended VRMVF therapy. Patient characteristics are presented on Table 1. All five patients fulfilled the accepted diagnostic criteria for CRPS of the International Association for the Study of Pain [16]. The therapy is given once a week at an outpatient pain clinic in Okayama University Medical Center, where the VRMVF system was set up.

In each session of therapy, no time limit was set. Analgesic medications were continued at the same regimens as before the therapy. If patients reported an increase in pain intensity or related side-effects of VRMVF therapy, treatment was immediately cancelled and additional drugs or treatment were administered. However, if patients reported decreased pain intensity, medication was adjusted or stopped as directed by the patient. Subjective pain was evaluated according to a visual analog scale (VAS: 0 = no pain, 100 = worst pain) before and after each treatment session.

Results

All patients reported spontaneous pain in the affected limb that increased with movement. The pre-treatment value of the VAS (64 ± 14) (mean ± SD) decreased to 31 ± 26 after consecutive treatment sessions. Four of the five patients (80%) showed 50% reduction of the

Table 1 Characteristics of patients with complex regional pain syndrome

Subjects	Affected Limb	Age (Years)	Sex	CRPS Duration (Years)	Cause	Dominant Hand	Prescribed Medications
Case 1	Left hand	46	Female	2	Radius & finger fracture	Right	Amytriptyline 20 mg, Carbamazepine 300 mg
Case 2	Both hands	65	Female	2	Bil distal radius fracture	Right	Amytriptyline 20 mg
Case 3	Left hand	46	Male	3	Hand fracture	Right	Amytriptyline 25 mg, Gabapentin 600 mg, Neurotropin* 16 unit
Case 4	Right hand	48	Female	3	Post excision of tendon sheath	Right	Amytriptyline 20 mg, Gabapentin 1200 mg
Case 5	Right hand	74	Female	1	Distal radius fracture	Right	Amytriptyline 10 mg

* An extract from inflammatory rabbit skin inoculated with vaccinia virus.

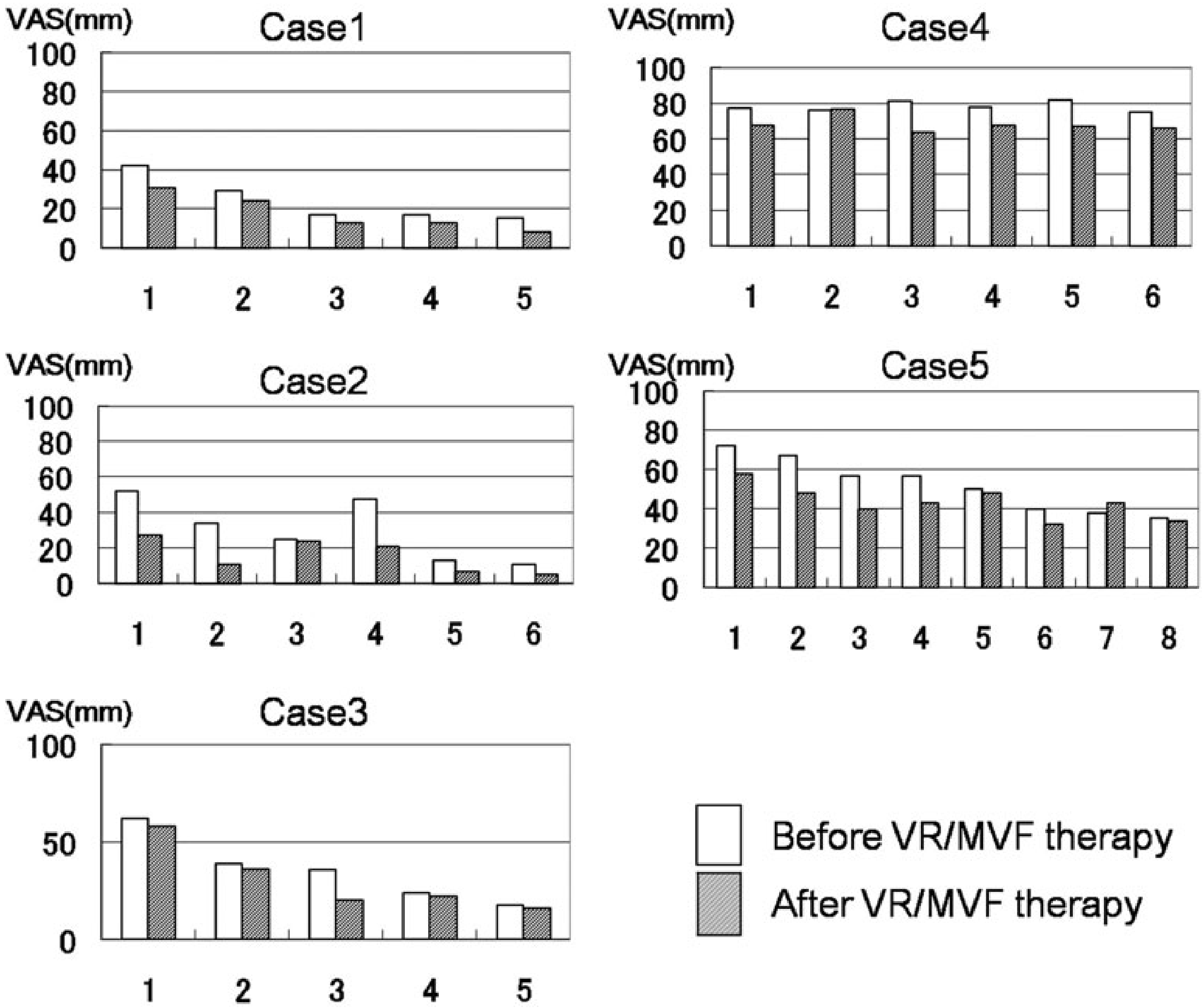

Figure 2 Analgesic effect provided by virtual reality-based mirror visual feedback therapy in five cases of complex regional pain syndrome. All cases showed a short-term reduction in pain intensity (before-and-after comparison of the visual analogue score in each session) and four of the five cases showed consecutive decrease of visual analogue score, which lead to a 50% reduction of the pre-treatment value after respective treatment sessions. VAS = visual analog scale; MVF = mirror visual feedback.

pre-treatment VAS value. Effective pain reduction (50% reduction) was accomplished after the third treatment session in Cases 1 and 2, the fourth session in Case 3, and the eighth session in Case 5 (Figure 2).

In Case 1, CRPS developed after a distal radius fracture and open fracture of the third to fifth digits. Light touch induced severe pain accompanied by numbness. Skin and bone atrophy were significant on the patient's affected fingers, especially on the fourth finger where contracture was pronounced.

As VRMVF treatment proceeded and the intensity of pain decreased, the patient in Case 1 commented that her affected hand returned to belonging to her again. This was also associated with improvement in wrist and finger ranges of motion (ROM). After five consecutive treatment sessions, prescriptions for amitriptyline and carbamazepine were terminated. The patient ended her visits to our pain clinic. Telephone communication 1 year after the cessation of VRMVF therapy revealed that she was still able to cope with the CRPS without medication. In Case 2, sudomotor abnormality including edema and a tremor-like movement abnormality were pronounced. Hand coordination when reaching and grasping for targets was very poor because the patient's ability to recognize the positional relationship between targets and the virtual arm was limited. The tremor was resolved immediately after each treatment session but her coordinating ability did not improve. In Case 3, CRPS developed after a hand fracture. Pain was induced by hand movement and was localized in the thumb but referred to the third to fifth digits. ROM of the interphalangeal joint of thumb was full but bone atrophy was visible. The coordinating ability of this patient was also limited at the very beginning of the therapy, but as the therapy proceeded, performing speed increased and accuracy improved dramatically. After five consecutive treatment sessions, amitriptyline was not required and the treatment was ended. This man did not visit our pain clinic again for the recurrence of pain. In Case 4, stenosing tendovaginitis (De Quervain's disease) was diagnosed and treated with excision of the tendon sheath. After the operation, pain intensity increased. Neurolysis of the superficial branch of the radial nerve was undertaken. However, pain in the wrist and finger remained. The patient's performance ability was quite high and well coordinated from the beginning of therapy. She reported that pain was temporarily induced in the affected side by arm motion but it did not result in an increase in baseline pain intensity. This patient discontinued VRMVF therapy because no pain reduction was provided by the therapy. The degree of the engagement in VRMVF of Case 4 was no different from those of the other cases. In Case 5, fracture of the distal radius was immobilized in a cast. After casting, severe pain, heat sensation, and stiffness emerged in the upper arm and hand. The patient reported spontaneous pain and mechanical hyperalgesia. Thermography detected higher skin temperature in the affected hand. Although edema was not visible, hyperhidrosis was observed. Motor weakness, joint stiffness, and soft tissue changes were pronounced. As therapy proceeded, finger pain decreased but arm pain persisted. Swelling before VRMVF initiation was only seen in one subject (Case 2) out of the four responders and improvement in swelling was associated with pain relief. In all responders, improvement in dexterity in managing the task-oriented motor training in MVF and also improvement in allodynia were associated with pain relief. Patients did not engage in any particular form of self exercise but all responders started to use their affected fingers and hands because severe pain or abnormal sensation such as allodynia or hyperalgesia were no longer induced by movement. Three out of four responders were able to reduce their medication and this reduction was sustained over the course of the treatment program.

No patient reported feeling any therapy-related side-effects such as motion sickness or fatigue. Neither increasing pain intensity nor worsening symptoms, including edema or tremor, was recognized.

Discussion

In this preliminary work, our VRMVF therapy was able to provide successful analgesic efficacy: 80% of patients showed more than a 50% reduction of pain intensity after three to eight consecutive treatment sessions. It is worth noting that all five patients were in a chronic state of CRPS, which is known to be difficult to treat by original MVF therapy with a mirror box. In two patients, the analgesic effect continued even after cessation of the therapy. Moreover, none of the five patients in the present study reported experiencing any related side-effects. Our result showed that VRMVF therapy is a promising alternative treatment for CRPS.

Virtual reality technology is used in a variety of fields and possible medical application attracts keen interest. Potential benefits have been reported in applications such as treatment of post-traumatic stress disorder following the terrorist attack on the World Trade Center [17], rehabilitation following a stroke [18], and disability management following accidents or surgery [19]. Application as an analgesic modality attracts special attention. Hoffman et al. developed an immersive virtual reality system for the wound care of burned patients [20]. A computer-generated VE is interactive and it holds the attention of a patient even during painful wound care. Virtual reality technology holds the promise as an analgesic modality in diverse ways.

CRPS includes a variety of pain conditions with both motor and autonomic symptoms [2] and is resistant to traditional treatment [1]. Commonality in clinical symptoms and similar neuronal plasticity in the CNS exist among patients with CRPS, phantom limb pain, and stroke [6–8,21]. Complex regional pain syndrome is known to occur in patients after a stroke [22,23].

It is also revealed that chronic pain conditions are a consequence of neuronal plasticity in the CNS [3,24] and its relevance with treatment resistance seen in these pain conditions has been speculated [25]. Flor et al. demonstrated the correlation between the extent of reorganization in the primary somatosensory cortex (S1) and phantom limb pain [26]. Discriminative therapy could reverse this reorganization and was associated with pain reduction [27]. A modality that could reverse these changes would be a candidate for a new treatment. McCabe et al. first introduced MVF for the treatment of CRPS but only a limited patient group in the early stage of the disease received the benefit [5]. Moseley advanced MVF and developed a motor imagery program [28]. Although the motor imagery program provided a beneficial, pain-relieving effect for patients, even those with chronic CRPS, it required patients to repeat three stages of training tasks several times a day and took several weeks before therapeutic effect was seen. An alternative treatment that was less burdensome with a shortened treatment period was sought.

Enhancing MVF therapy with VR technology can add a unique dimension to MVF therapy and provide one solution. Virtual reality technology is excellent for immersion. In addition, its property of interaction with the VE allows subjects to feel engaged and rewarded, which helps them to repeat the exercise with intensity. Repeating task-oriented training with intensity is important for restoring normal organization in the CNS within a patient after a stroke [10]. Because similar neuronal plasticity is known to exist in patients with phantom limb pain and CRPS is present after a stroke [6–8], this technique may be applicable to the treatment of CRPS. This might explain why the VRMVF system that we developed can provide analgesic effects in such a short period of time, and even after a 1-week interval.

The present study conducted the first application of VRMVF therapy for the treatment of patients with CRPS and demonstrated its promising analgesic effect for the chronic state of CRPS.

Similar virtual reality technology was utilized for both Hoffman's immersive virtual reality system [14,20] and our system. In Hoffman's system, most of the analgesia is derived from distraction [14,20]. Distraction is one possible underlying mechanism of the analgesia provided by our VRMVF system. Distraction can reduce pain intensity and its associated effects, usually only during the intervention. Two types of decreased pain intensity were derived from our results: immediate pain reduction after each session and long-lasting reduction of pain intensity between consecutive sessions with a 1-week interval. In the case of immediate pain reduction, there was a possibility that the analgesic effect mainly originated from distraction.

Although the mechanism behind MVF-induced pain relief is not fully understood, it is speculated that analgesia is provided by reconciliation between motor output and visual feedback [4]. However, questions remain regarding whether the visual feedback is indeed an important part of mirror therapy [29]. If so, the natural appearance of the virtual hand should be crucial. Although the realism of the depicted hand in our system is obviously inferior to that of the reflected image in the mirror, VRMVF therapy provides promising analgesic efficacy. It does not seem likely that analgesia provided by VRMVF therapy depends upon whether subjects recognize the virtual arm as their own.

In initial brain imaging studies for pain, the association of reorganization in S1 with chronic pain conditions drew special attention [8,26]. However, similar neuroplastic changes had been revealed in motor-related regions. Chronic pain conditions have been associated with adaptive changes in the motor-related neural network, such as the primary motor, premotor, and posterior parietal cortices [11–13]. These changes are strongly correlated with motor dysfunction in patients with CRPS [11–13]. VRMVF not only reconciles the incongruence between motor intention and visual feedback in the same way as the original MVF, but also engages different brain regions. Virtual reality MVF consists of target-oriented motor tasks that require patients to move the limb to the target and to coordinate the positional relationship between the target and hand for grasping, which activates the parietal cortex, premotor cortex, and primary motor cortex. These regions are where adaptive changes are known to occur in patients with CRPS [11–13]. Distraction is one possible analgesic mechanism and reduced anxiety is also a potential candidate for the underlying mechanism for analgesia provided with our VRMVF system [15]. Virtual reality technology has been successfully applied to the treatment of post-traumatic stress disorder [17] and phobias [30].

Watching the movement of another person's limb or just imagery of hand movement increases the activity in motor-related regions such as the motor cortex or premotor cortex [31,32]. Because deep stimulation of the motor cortex provides analgesia [33,34], it is expected that activation of the motor-related cortex by watching or imagining movement of the affected limb would also provide analgesia. However, contrary to our expectations, movement imagery alone exacerbated pain in patients following complete thoracic spinal cord injury [35] and in patients with CRPS [36]. One possible explanation for the failure of mental imagery to reduce pain is that indirect activation of the motor-related cortex by this method is weaker than direct stimulation. However, the question arises as to whether our system could produce strong enough activation of the motor-related cortex to provide an analgesic effect. In both the mirror box system and our system, the patient watches moving images of the hand on the affected side, which reasonably activates the motor-related area of the affected side. In addition to this activation, our system forces subjects to exercise a target-oriented motor control task. Planning the movement of reaching out and grasping targets magnified the activation in the motor-related area. It is appropriate to say that the activation in the motor-related area by our system is stronger than that by the mirror box system. This might be an explanation for the analgesia provided by the VRMVF therapy in patients with chronic CRPS and the lack of analgesia provided by the MVF therapy with the mirror box.

One patient could not get pain relief from the VRMVF therapy. One possible explanation of this failure was that she was treated by neurolysis of the radial nerve. Her sustained pain may have been caused by consequential nerve injuries, which suggests a diagnosis of type 2 CRPS. The remaining four patients were given a diagnosis of type 1 CRPS.

Because this was a pilot study to evaluate the analgesic efficacy of VRMVF therapy for patients with CRPS type 1, the effective time course, frequency, and duration of the therapy remains to be established. In contrast to original MVF therapy, which can be provided at home and at the patient's convenience, our VRMVF system has to be set up at a facility like a university hospital. This is one of the drawbacks of our system. When the VRMVF therapy was applied to the first patient, social factors did not allow her to come to our pain clinic more than once a week. According to the studies of McCabe [5] and Moseley [27], it is reasonable to assume that therapy needs repeating on consecutive days to reverse the maladaptive organization in patients with CRPS. However, our first case showed a striking reduction of pain intensity and an increase in motor function even with therapy once a week. Thus, for the following sessions of VRMVF therapy, the frequency was set at once a week; however, the duration of each session was set without a time limitation. The design of the present study is an open-label case series with no control conditions. This is a major limitation of the present study. Further study must be conducted with and without VRMVF for patients with CRPS and it is also necessary to determine the optimal time course of our VRMVF therapy.

We did not evaluate the changes in the neuronal network caused by CRPS with brain imaging technology such as functional magnetic resonance imaging. This is one limitation of the present study. However, the extent of neuroplastic change is known to be correlated with the duration of pain symptoms [37] and pain intensity [8]. It is appropriate to consider that neuroplasticity may exist in the participants in the present study because all of the subjects experienced pain for more than 1 year. Further studies are necessary before concluding that analgesia provided from VRMVF therapy is acquired as a result of the modulation of the underlying changes in the neural network in the CNS.

Conclusion

Our preliminary results indicate that VRMVF therapy is a promising alternative treatment for CRPS. In addition to the lack of side-effects, an attractive feature of VRMVF therapy is that it enables subjects to perform repetitive training with intensity, which is fundamental to restoring neuronal plasticity and leads to a virtuous circle of therapeutic action.

The cortical network of pain perception changes in CRPS. Further studies are necessary before concluding that the analgesia provided by VRMVF therapy is acquired as a result of the modulation of the underlying changes in pain perception.

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