Case Report

Deactivation of Distant Pain-Related Regions Induced by 20-day rTMS: A Case Study of One-week Pain Relief for Long-Term Intractable Deafferentation Pain

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Background: Deafferentation pain secondary to brachial plexus avulsion, spinal cord injury, and other peripheral nerve injuries is often refractory to conventional treatments. Stimulation of the primary motor cortex (M1) has been proven to be an effective treatment for intractable deafferentation pain. The mechanisms underlying the attenuation of deafferentation pain by motor cortex stimulation remain hypothetical.

Objectives: The purpose of this case report is to: (1) summarize a case in which a patient suffering chronic intractable deafferentation pain for 25 years underwent rTMS treatment over M1, (2) describe the evidence from PET imaging, and (3) reveal a possible relief mechanism with cortical plasticity.

Study design: Case report.

Setting: University hospital.

Results: This patient had successful pain control with no transient or lasting side effects. The pain relief remained stable for at least one week. At the end of the 20-day procedure, pain relief was obtained according to the Visual Analog Scale (VAS) (-34.6%) and the McGill Pain Questionnaire (MPQ) (-31.6%). In the PET/CT scans, the glucose metabolism was significantly reduced contralaterally to the pain side in the anterior cingulate cortex (ACC), insula, and caudate nucleus. There was no statistically significant difference in any other cortical area.

Limitations: Single case of a patient with long-term intractable deafferentation pain having a PET study.

Conclusion: This study implies that a single session of 20 Hz rTMS over the motor cortex could reduce the pain level in patients suffering from long-term, intractable deafferentation pain. The stimulation of the M1 induces deactivation in the ACC, insula, and caudate nucleus. The changes in these pain-related regions may mirror an adaptive mechanism to pain relief after rTMS treatment.

Key words: Neuropathic pain management, deafferentation pain, transcranial magnetic stimulation, motor cortex stimulation, cortical plasticity, positron emission tomography

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Brachial plexus avulsion is a devastating injury that is followed by chronic pain in the deafferented area in 30% to 90% of patients (1). This pain is characterized as constantly unbearable and is resistant to most effective treatments for neuropathic pain, as well as to anticonvulsants and antidepressants (2). In the last 2 decades, epidural electrical motor cortex stimulation (MCS)

has frequently been applied as a clinical method for alleviating drug-resistant neuropathic pain. Stimulation of the primary motor cortex (M1) has been proven to be an effective treatment for intractable deafferentation pain (3). It is thought that the stimulation of M1 affects pain perception through indirect effects via neuronal networks synapsing on pain-modulating areas. However, the mechanisms underlying the attenuation of deafferentation pain by MCS remain hypothetical (4).

Several novel noninvasive cortical stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), have been used in experimental and clinical neuroscience for manipulating brain function (5-7). These new methods facilitate the clinical application of MCS for the treatment of intractable deafferentation pain. However, the exact role of brain plasticity in the rTMS-treatment of chronic pain has still not been clarified. Positron emission tomography (PET) scans have been successfully used to visualize areas of excessive asymmetric cortical activity in the left or right cortex in several studies (8,9). Changes in neural activity and differences in activity between regions can be observed by PET because they are tightly coupled to associated changes in both regional brain blood flow (rBBF) and glucose metabolism. Hence, PET is the ideal choice for providing functional evidence of neuroplasticity.

In this study, we report the results obtained by performing rTMS over M1 in a single subject with long-term intractable deafferentation pain. Additionally, we investigate the exact role of cortical plasticity by searching for in vivo evidence with PET.

Case Report

Patient

A 51-year-old, right-handed farmer, "WG," was involved in a traffic accident 25 years ago (1986). He sustained a complete injury to the right brachial plexus without fracture. On physical examination, the patient had a flail limb with a Horner's sign. The trapezius was functioning, but there was no muscle activity below this level. Sensation was absent from below the shoulder laterally. Sensation in the axilla was present but altered. Pain commenced instantly on injury; it was constant and burning, felt mostly in the forearm and hand. This pain was severe and made sleep very difficult.

The brachial plexus was explored 3 months after the injury. The nerves from C5 to T1 were all avulsed. WG received procedures that included nerve transfer from the intercostal nerve to the musculocutaneous nerve and from the spinal accessory nerve to the suprascapular nerve. He was monitored every 3 – 6 months. At 9 months, there was recovery of function into the supraspinatus and the biceps brachii. At 24 months, he had a 60-degree range of active shoulder abduction, and the muscle power was Medical Research Council (MRC) scale grade 4. At 24 months, he had a 90-degree range of active elbow flexion, with muscle power of MRC grade 4. At 5 years, he had motor power of MRC grade 4+ in the muscles of the supraspinatus and the biceps brachii and grade 3 (S3) sensation recovery in the lateral upper arm. However, sensation remained absent in the forearm and hand. The pain decreased to a certain extent immediately after the surgery; however, it returned to the baseline one year later and remained at that level. In 1994, WG underwent the procedure of dorsal root entry zone (DREZ) lesioning. The surgery was successful, but the pain did not decrease. By the 25-year follow-up, multiple pharmacological treatments (such as nonsteroidal anti-inflammatory drugs, opioids, and antidepressants) and alternative approaches (such as acupuncture and electroacupuncture) for pain relief had been unsuccessful (Table 1). At his next visit recently, he had not taken any pharmacotherapy for 4 years. He was advised to take the Visual Analog Scale (VAS), on which he scored 7.8/10. After a description of the study to the patient, written informed consent was obtained through a protocol approved by the ethics committee of Fudan University. The patient had no family history of seizure.

Methods

The rTMS procedure was performed with a MagPro (MagVenture A/S, Denmark). A circular coil was applied tangentially on the scalp to stimulate the corresponding hand and forearm area. By following the guidelines from the International Federation of Clinical Neurophysiology (10,11), the rest motor threshold (RMT) of the pain region was defined as the lowest intensity required to elicit motor evoked potentials (MEPs) of more than 50 μV peak-to-peak amplitude in at least 50% of 10 successive trials on resting target muscles. Because the patient had a devastating injury of the right upper extremity, the RMT was determined at the contralateral side, starting with 40% of maximum stimulator output and increasing stepwise in 5% intervals. Once MEPs could be evoked, the stimulus intensity was reduced in steps of 1% until the RMT could be identified. The stimulation site was the motor cortex contralateral

Table 1. *The summary of pharmacotherapy, surgery, and rTMS treatments.*

Treatment	Route	Date	Interval (months)	Doses
Amitriptyline	Oral	12/1987 – 12/1993	72	Stared at 10 mg per day, with 10 mg upward for every 3 days. Finally the dose is 30 mg per day.
		5/1994 – 8/2000	76	
		1/2001 – 11/2006	71	
Gabapentin	Oral	1/2005 – 11/2006	23	2400 mg per day
Tramadol	Oral	6/2001 – 12/2002	pro re nata	100 mg each time and no more than 400 mg per day
Celecoxib	Oral	12/2006 – 8/2007	pro re nata	200 mg each time and no more than 800 mg per day
Acupuncture	acupuncture	12/1987 – 6/1988	6	3 – 4 times per week
Dorsal root entry zone (DREZ) lesioning	Surgery	2/1994	-	-
rTMS	noninvasive magnetic stimulation	6/2011	0.5	20 days of daily TMS treatment, including twenty 5-second, 20-Hz stimulations with 120% of the RMT intensity over 20 min (2000 pulses per session) as an active treatment once daily

*TMS = transcranial magnetic stimulation; rTMS = repetitive transcranial magnetic stimulation; RMT = rest motor threshold.

to the pain site. TMS sessions were scheduled daily in a 20-day sequence, including twenty 5-second, 20-Hz stimulations with 120% of the RMT intensity over 20 minutes (2000 pulses per session) as an active treatment once daily. No other treatment was performed.

Because the McGill Pain Questionnaire (MPQ) and VAS have become the most frequently used tools for monitoring pain (12), the patient was required to take both of these tests before and after active rTMS treatment.

Both a baseline Positron emission tomography with 2-deoxy-2-fluoro- D-glucose integrated with computed tomography (FDG PET/CT) scan and a post-rTMS treatment FDG-PET scan were performed using an ECAT EXACT HR+ tomography unit (Control Technology, Inc.) with the interslice septa retracted. The cerebral glucose metabolism data were analyzed with commercially available mapping software (SPM8, Wellcome Department of Cognitive Neurology) implemented in Matlab 7.10 (Mathworks, Inc.). This system expresses activity within predefined regions of the patient's brain image as standard deviations of the mean activity, in the same predefined regions, obtained from a normal PET brain database.

Results

Clinical Effects

The patient participated in all of the planned sessions of rTMS, and no transient or lasting side effects, including seizures, were observed. During the 20-day-period following the operative procedure, pain relief was obtained according to VAS (-34.6%) and MPQ (-31.6%) (Table 2). During the follow-up, the pain relief remained stable for at least one week.

Table 2. *Pain score monitoring of patient WG (VAS & MPQ).*

	Pre-rTMS scores	Post-rTMS scores
VAS	7.8	5.1
MPQ	57	39

Effects on Cortical Excitability

Significant differences in glucose metabolism were observed between the pre- and post-treatment PET scans. At the end of the 20-day procedure, the glucose metabolism was significantly reduced contralaterally to the pain side in the anterior cingulate cortex (ACC), insula, and caudate nucleus. There was no statistically significant difference in any other cortical area (Fig. 1).

Discussion

In this study, we performed high frequency rTMS on a brachial plexus avulsion injury patient for the treatment of long-term (more than 20 years) intractable deafferentation pain. A significant pain relief effect was observed, and the neuroimaging results suggested that the deactivation of the ACC, insula, and caudate nucleus may synergistically contribute to the relief of long-term intractable deafferentation.

It is known that cortical stimulation can alter the regional neural synaptic activity in the brain and lead to specific neuroplasticity procedures (13). This induced plasticity laid the foundations for novel pain

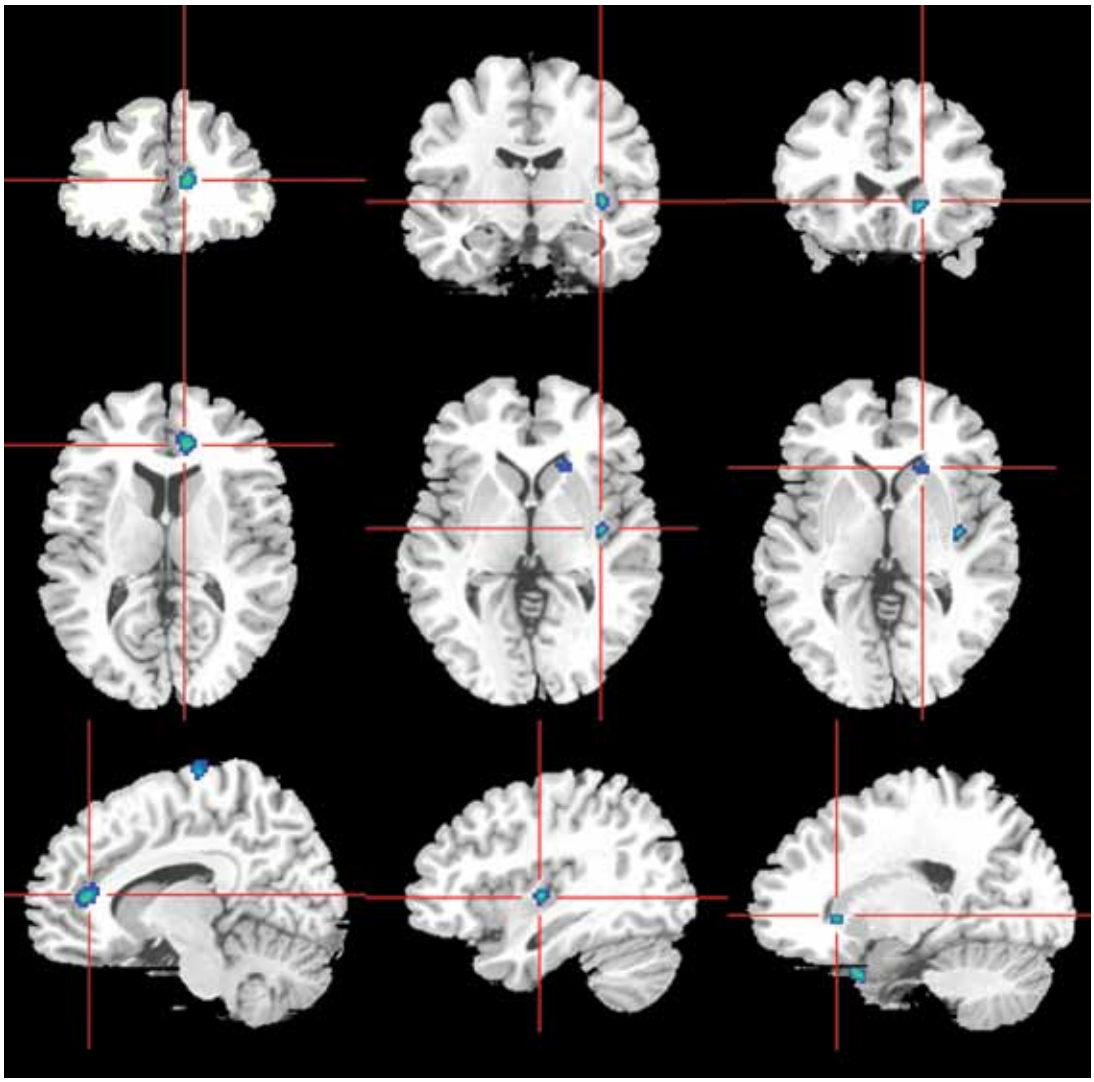

Fig. 1. *PET sections normalized according to the Talairach space, showing regions with significant (z > 3.5) reductions in glucose metabolism post-rTMS, including the anterior cingulate cortex (A), insula (B), and caudate nucleus (C) ipsilateral to the stimulation. No significant glucose metabolism change was observed in any other cortical area.*

relief treatments, such as repetitive magnetic stimulation. However, direct MCS does not result in significant changes within the primary motor or the sensory cortex. Rather, significant changes could be observed in structures distant from the motor cortex. The phenomena address an interesting point for the investigation of neuropathic pain.

Deafferentation pain resulting from brachial plexus avulsion is a specific subtype of neuropathic pain. As many as 90% of patients with predominantly preganglionic lesions may experience long-term, drug-resistant and refractory pain (14). Most of these patients may be referred for neurosurgery, including nerve grafting, repair, or neurotization. Timely surgical treatment can partially prevent the onset of pain (15,16). Subsequently, only various destructive operations, such as DREZ lesioning, deep brain stimulation, and epidural MCS, may have some effects (17- 19).

Treatment with rTMS over M1 was reported to efficiently decrease pain in patients with chronic pain

in the past 2 decades (20-22). However, few studies have reported the effect on long-term intractable deafferentation pain. In our study, a circular coil was used to provide the stimuli, and significant pain relief was finally achieved after the procedure, as demonstrated by the VAS and MPQ results and supported by the PET image. We carefully compared our study with the literature and found several interesting factors. In the literature (23), stimulations with 80% of RMT intensity as active treatment were performed, failing to produce significant analgesia, whereas 120% of RMT (12,24) was used in our study. Stimulation at intensities below the relaxed motor threshold usually requires longer trains before any lasting effect is observed (25). Larger coils are more efficient than small or 8-shaped ones, but what they gain in efficacy is lost in spatial resolution. Maximal electric currents are induced near the outer edge of circular coils, thus being able to activate excitable structures all around the coil (26). With 8-shaped coils, for moderate intensities, the maximal electric current is induced at the intersection of the loops, focalizing the stimulation on given cortical regions. However, spatial resolution tends to decrease if strong stimuli are used (4). Therefore, when the stimulus intensity increases, it will meet the shortfall of spatial resolution and take effect. However, it is reported that each subject had a different pattern of frequency tuning curve and that the interindividual variability of the modulatory effects was high (27). Further research is required to confirm the effectiveness of the rTMS parameters.

It is likely that there is no single mechanism for the pain relief after rTMS treatment. Instead, a number of interacting mechanisms may co-exist, reflecting the multifaceted aspects of pain and the variety of central nervous system (CNS) structures. Many of the papers reporting rTMS results associate its mechanism with the most widely studied phenomena of plasticity induction, long-term potentiation (LTP) or depression (LTD). "LTP-like" or "LTD-like" are commonly found descriptors of the action of rTMS (4). In addition, the modulation of neurotransmitter levels and gene induction appear to be contributing factors (28). It is well accepted that several neurotransmitters and neuromodulators, such as dopamine (29,30), glutamate (31,32), and brain-derived neurotrophic factor (BDNF) (33,34), play important roles at central synapses in pain pathways at both the spinal and the supraspinal levels. However, compelling evidence for these relationships is still lacking (4). Neuroimaging offers a valuable means of exploring how rTMS affects the human brain, providing new insights into the changeability of functional brain networks (35).

In our study, we found that the deactivation of the ACC, insula, and caudate nucleus may synergistically contribute to the relief. It is known that the ACC, an important component of the limbic system, contributes to the development of pain-related emotion under the condition of chronic pain (36-38). Neuroimaging studies show that the ACC, together with other cortical structures, is activated by acute noxious stimuli, psychological pain, and social pain. The ACC synapses on the neurons in the thalamus and other cortical neurons, and sends descending projecting systems to affect the spinal cord sensory transmission. Furthermore, injury triggers long-term plastic changes in the ACC and related cortical areas, and these plastic changes subsequently contribute to enhanced behavioral responses to sensory stimuli and possibly to chronic pain. Treatment with rTMS induced potent functional changes in ACC blood flow that may play an important role in the motivational–affective aspect of pain (38,39). The insular cortex and caudate nucleus are also crucial for pain processing in the brain. A previous study suggested that noxious electronic stimulation of muscles may active the ACC, S2, and anterior insular cortex (33,40), whereas others confirmed that painful mechanical stimulation targeting muscle and bone activated cortical areas including the bilateral insula, ACC, and caudate nucleus (41,42). Furthermore, the caudate nucleus is considered to play a vital role in processing acupuncture analgesia for acute and chronic pain (43). On the molecular level, several lines of evidence have shown the relationship between BDNF and LTP in the insular cortex, acting in long-lasting increases in pain synaptic transmission (34,44). Several other studies have revealed a positive relationship between the amount of dopamine released in response to pain and the patients' perceived pain intensity throughout the caudate nucleus (29,30). As noted above, it may be that activity in the networks among the medial thalamic cortex, the limbic areas, and the motor and premotor cortices is modulated by rTMS, entailing a cascade of synaptic events in pain-related structures receiving afferents from these nuclei, including the ACC, insula, and caudate nucleus. It was interesting that the simple stimulation of the motor cortex could result in the deactivation of these pain-related cortical regions, which were distant from the original stimulation point (45). The neural connectivity between these regions may contribute to these specific synergetic changes.

Conclusion

This study implies that a single session of 20 Hz rTMS over the motor cortex could reduce the pain level in patients suffering from long-term, intractable deafferentation pain. The stimulation of the motor cortex induces deactivation in the ACC, insula, and caudate nucleus. The changes in these pain-related regions may mirror an adaptive mechanism to pain relief after rTMS treatment.

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Disclaimer

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Conflict of interest

Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

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