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Effects of Repetitive Transcranial Magnetic Stimulation on Psychological Aspects of Patients with Chronic Lower Back Pain

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To investigate the effects of repetitive transcranial magnetic stimulation (rTMS) to the anterior cingulate cortex (ACC) area on changes in psychological aspects in chronic lower back pain patients. Twenty-one subjects were randomly assigned to control group (n=10, both general physiotherapy and sham rTMS) and experimental group (n=11, both general physiotherapy and rTMS). Each group received treatment (physiotherapy : 20 minutes, 10 Hz rTMS : 10 minutes) five days per week for 4 weeks. Assessment of psychological aspects was measured pre, post, and 2 week follow up after treatment. The comparison results with regard to heart rate variability (HRV), EEG (α wave), Beck Depression Inventory version (K-BDI), Fear of Daily Activities Questionnaire (FDAQ), and Fear-Avoidance Belief Questionnaire (FABQ) confirmed that experimental group had a greater recovery to positive levels in comparison to control group. As a results, the application of rTMS to the ACC together with physiotherapy can have a positive effect on pain-related psychological aspects.

Keywords : repetitive transcranial magnetic stimulation, psychological aspects, anterior cingulate cortex, chronic lower back pain

1. Introduction

Pain is the most universal problem faced by patients undergoing rehabilitation, and is accompanied by physical, physiological, and psychological impairment [1]. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage" [2].

In patients with chronic low back pain (LBP), pain sensitization occurs, marked by hyperalgesia and allodynia in response to even subthreshold pain stimuli, as a result of increased expression of the peripheral receptors and increased sensitivity of the skin and joints to mechanical stimulation [3, 4]. Persistent pain causes stress, activating the sympathetic autonomic nervous system (ANS), which leads to hypertension, tachycardia, anxiety, increased perspiration, and muscle tension [5].

In addition, sensitization becomes more severe as it progresses to a chronic disease, resulting in physical dysfunction and emotional issues, such as depression, avoidance behavior, and fear, further worsening the pain [6, 7]. Pain is both a physiological and emotional phenomenon, and the psychological factors are of a particular importance in chronic LBP [8]. A multifaceted approach is essential for the understanding and treatment of the psychological aspects related to chronic pain, such as depression, anxiety, and fear [9].

However, in most treatment approaches, pain is viewed simply as the result of an organic problem due to tissue damage [10], and general pain treatments to control the pain [11] or reduce muscle tension [12] are applied.

Transcranial magnetic stimulation (TMS), a non-invasive cerebral stimulation method that does not control pain through a peripheral stimulus, induces depolarization of neurons using magnetic field waves from electromagnetic coils [13] and maintains excitatory changes and effects in the cerebral circuitry for a long time. It is widely used as a treatment tool for neuropsychiatric disorders, including chronic pain, tinnitus, obsessive-compulsive disorder, and movement disorders among others [14, 15].

Electroencephalography (EEG) could offer precise know-

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ledge of cortical information concerning activity of brain nerve cells [16]. EEG is divided into four common brain wave ranges, these being delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta waves (> 13 Hz) [17]. In particular, alpha wave has associated with memory recall, lessened discomfort and pain, and reductions in stress and anxiety [18].

Most previous studies have tested its therapeutic effects by evaluating the physical pain due to tissue damage. Conversely, in this study, we aimed to examine the effects of TMS treatment based on the relationship of physiological and psychogenic variables. For this purpose, we used repetitive TMS (rTMS), which has been shown to be effective in cognitive neuroscience based on neurophysiological mechanisms, and examined its effects on the ANS and psychogenic symptoms.

2. Material and Methods

2.1. Study participation

The participants consisted of patients with chronic LBP persisting for at least 6 months, with a Fear-Avoidance Beliefs Questionnaire (FABQ) score ≥ 30, Fear of Daily Activities Questionnaire (FDAQ) score ≥ 40, no other pain-inducing factors, such as scalp disease, wounds, or burns, and no previous experience of TMS. Those who understood the intention of this study and gave voluntary consent to participate were enrolled as subjects. The study adhered to the claims of the Declaration of Helsinki and the protocol was approved by the local ethics committee (Institutional Review Board of the Dongshin University).

2.2. Intervention

The 21 patients with chronic LBP were divided into control group (n=10) and experimental group (n=11) by random sampling. Those in control group underwent general physical therapy, consisting of 10 min of hot pack application, 10 min of transcutaneous electrical nerve stimulation, 5 min of ultrasound, and lumbar extensor strengthening exercises (3 sets of 10 repetitions). Sham rTMS stimulation was administered at the same parameters as experimental group. The patients in experimental group underwent the same general physical therapy, followed by high-frequency (10 Hz) rTMS for 10 min, once per day, 5 days per week, for 4 weeks, making a total of 20 treatment sessions. Data were collected pre-intervention, post-intervention, and at follow-up.

2.2.1. Repetitive transcranial magnetic stimulation (rTMS)

For rTMS, we used an STM9000 device (Standard, EB-Neuro Inc., Florence, Italy) (Fig. 1). Before the stimulation, using a cotton cap with a grid (1 × 1 cm^2) from the nasion to the inion, TMS stimuli were applied and motor evoked potentials were measured. At the point with the highest amplitude among the electromyography signals from the left 1st abductor pollicis brevis, the stimulation intensity was gradually increased in 1-2 % intervals, and the intensity that induced an amplitude ≥ 50 μV in 4 out of 10 stimuli was set as the motor threshold [19]. In order to target the ACC, stimulation was applied to the Fz point of the International 10-20 system [20]. The stimulation coil was placed against the scalp at a 45º angle to the mid-sagittal plane, and the magnetic current was made to flow vertically. Using a stimulation intensity of 80 % of the motor threshold and a stimulation frequency of 10 Hz, 50 stimuli were applied for 5 s, followed by 55 s of rest, and this was repeated 20 times in 10 min, making a total of 1,000 stimuli [21].

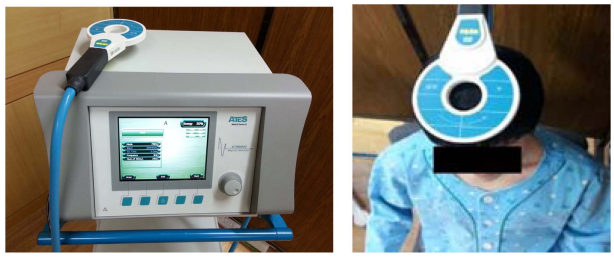

Fig. 1. (Color online) STM 9000, EB-Neuro Inc., Florence, Italy.

2.3. Measurement methods

2.3.1. Heart rate variability (HRV)

Heart rate variability (HRV) was measured for quantitative evaluation of the autonomic nervous system. We measured the heart rate variability in both biceps brachii at the same time as electroencephalography (EEG) using poly G-I (LATHA Inc., Daejeon, Korea). The rate of change

Fig. 2. (Color online) Poly G-I, LATHA Inc., Daejeon, Korea.

in the heart rate was calculated from the LF (low frequency)/HF (high frequency) values using the Telescan™ program (ver. 3.03, LATHA Inc., Daejeon, Korea) [22] (Fig. 2).

2.3.2. EEG (α wave)

Poly G-I (Poly G-I, LATHA Inc., Daejeon, Korea) was used to record the brainwaves. Using the International 10-20 system, electrodes were placed at Fp1, Fp2, F3, F4, Fz, and Cz; the reference electrode was placed on the right mastoid process and the ground electrode was placed on the left mastoid process. The raw data was used to inspect for artifacts, and the first and last 30 s of the recording were excluded. Fast Fourier transform algorithm was applied to inspect the α waves (8-13 Hz). Relative power analysis was used to derive the results for the calculated frequency. The participants were in a sitting position with their eyes open, looking at a plain wall during the recording. They were asked to minimize eye movements to reduce artifacts. while To obtain the relative power, background brainwaves were measured for a total of 5 min; the first and last 1 min of the recording were excluded, and the middle 3 min were used in the analysis.

2.3.3. Psychogenic symptom indicates

To examine the changes in depression, we used the Korean Version of Beck Depression Inventory (K-BDI), which consists of 21 questions; a score of 0-16 points is categorized as normal, 17-20 points as depressive tendency, 21-24 points as depression, and ≥ 25 points as severe depression [23]. To evaluate the changes in fear of daily activities, we used the FDAQ; 10 daily activities related to fear were each scored from 0 to 100 points, and the score for the questionnaire was calculated as the total sum, *n*, divided by 10 [24]. To evaluate the psychological factors related to fear and avoidance, we used the FABQ which consists of 16 items; the minimum score is 0 points and the maximum score is 66 points, with a higher score indicating higher levels of fear and avoidance [25].

2.4. Statistical analysis

We calculated the means and standard deviations (SDs) from the data using SPSS 20.0 version. The homogeneity of the participants' general characteristics was tested using the Fisher's exact test and independent t-tests. To compare the differences between the three time points within each experimental group, we performed repeated measures ANOVA and post-hoc analyses. To compare the differences between the experimental groups at each time point, we performed independent t-tests. All tests used a statistical significance level of $p = .05$.

3. Results

3.1. General characteristics of subjects

The general characteristics of the study participants are shown in Table 1.

3.2. Changes of heart rate variability (HRV) after treatment

There were no significant changes in the HRV over time in the patients in control group. Those in experimental group exhibited significant changes in the LFs and LF/HF between pre- and post-intervention and between pre-intervention and follow-up ($p < .05$). In the between-group comparison, there were significant differences

Table 1. Characteristics of the study participants.

Characteristics	Control group (n=10)	Experimental group (n=11)
Age (years)	46.14±7.76	48.99±8.16
Height (cm)	161±5.25	157±9.11
Weight (kg)	60.17±9.15	58.81±6.53
Duration of pain (months)	10.12±7.15	13.15±9.57
FABQ (score)	36.7±3.40	35.4±3.27
FDAQ (score)	47.8±7.13	46.7±5.52

All values are presented as mean ± SD. Control group: general physical therapy (non-rTMS); Experimental group: rTMS application after general physical therapy; FDAQ: Fear of Daily Activities Questionnaire, FABQ: Fear-Avoidance Beliefs Questionnaire

Table 2. Comparison of the heart rate variability with and without the application of rTMS.

	Control group (n=10)			Experimental group (n=11)		
	Pre	Post	F/u	Pre	Post	F/u
LF (log)	4.78±0.78	4.62±1.18	4.57±2.45	4.87±0.94	$8.43\pm0.78^{1)**,\#}$	$7.98\pm1.562^{2)*,\#}$
HF (log)	5.41±0.65	4.89±1.01	5.13±2.82	5.61±0.74	4.15±0.75	$3.85\pm1.86^{2)*}$
LF/HF (ratio)	0.83±0.48	0.99±1.09	0.89±1.10	0.89±0.81	$2.01\pm1.82^{1)***,\#\#}$	$2.14\pm1.81^{2)**,\#}$

All values are presented as mean ± SD. Control group: general physical therapy (non-rTMS); Experimental group: rTMS application after general physical therapy; LF: low frequency; HF: high frequency; Pre: pre-intervention; Post: post-intervention; F/u: follow-up. Significance tested using repeated measure ANOVA, Post-hoc contrast test: $^{1)}$pre-post ($^{**}p < .01$; $^{***}p < .001$), $^{2)}$pre-f/u ($^{*}p < .05$; $^{**}p < .01$). Significance tested using independent t-test: ($^{\#}p < .05$; $^{\#\#}p < .01$).

Table 3. Comparison of alpha wave activity with and without the application of rTMS.

Parameters	Control group (n=10)			Experimental group (n=11)		
	Pre	Post	f/u	Pre	Post	f/u
Fp1	0.19±0.15	0.25±0.12	0.22±0.20	0.20±0.11	0.47±0.17$^{1)**}$	0.45±0.14$^{2)**}$
Fp2	0.22±0.12	0.23±0.12	0.21±0.21	0.19±0.14	0.39±0.20	0.45±0.99$^{2)**}$
F3	0.18±0.09	0.16±0.59	0.26±0.20	0.23±0.22	0.37±0.14	0.42±0.13$^{2)*}$
F4	0.22±0.09	0.23±0.14	0.23±0.14	0.21±0.15	0.38±0.17	0.48±0.14$^{2)**}$
Fz	0.18±0.16	0.16±0.11	0.21±0.14	0.17±0.11	0.34±0.12$^{1)*}$	0.40±0.15$^{2)*}$
Cz	0.27±0.17	0.43±0.18	0.37±0.17	0.33±0.24	0.39±0.15	0.32±0.15

All values are presented as mean ± SD. Control group: general physical therapy (non-rTMS); Experimental group: rTMS application after general physical therapy; Pre: pre-intervention; Post: post-intervention; F/u: follow-up. Significance was tested using repeated measure ANOVA, Post-hoc contrast test: $^{1)}$ pre-post ($^{**}p < .01$); $^{2)}$pre-f/u ($^{*}p < .05$; $^{**}p < .01$).

Table 4. Comparison of the psychological aspect scales with and without the application of rTMS.

Scale	Control group (n=10)			Experimental group (n=11)		
	Pre	Post	F/u	Pre	Post	F/u
K-BDI	26.5±2.95	24.7±1.95	24.6±1.96	25.5±1.78	17.6±1.65$^{1)***,\#\#\#}$	17.4±1.26$^{2)***,\#\#\#}$
FDAQ	47.8±7.13	46.1±5.64$^{1)**}$	44.9±6.77$^{2)**}$	46.7±5.52	31.7±6.18$^{1)***,\#\#\#}$	30.9±9.39$^{2)***,\#\#\#}$
FABQ	36.7±3.40	34.4±4.60$^{1)*}$	32.9±3.38$^{2)****}$	35.4±3.27	25.4±3.98$^{1)***,\#\#\#}$	26.1±2.38$^{2)***,\#\#\#}$

All values are presented as mean ± SD. Control group: general physical therapy (non-rTMS); Experimental group: rTMS application after general physical therapy; K-BDI: Korean Version of Beck Depression Inventory; FDAQ: Fear of Daily Activities Questionnaire; FABQ: Fear-Avoidance Beliefs Questionnaire; Pre: pre-intervention; Post: post-intervention; F/u: follow-up. Significance tested using repeated measure ANOVA, Post-hoc contrast test: $^{1)}$pre-post ($^{**}p < .01$; $^{***}p < .001$), $^{2)}$pre-f/u ($^{**}p < .01$; $^{***}p < .001$). Significance tested using the independent t-test: ($^{\#}p < .05$; $^{\#\#}p < .01$; $^{\#\#\#}p < .001$).

between the two groups in the LFs and LF/HF post-intervention and at follow-up ($p < .05$) (Table 2).

3.3. Changes of EEG (α wave) after treatment

The patients in control group exhibited no significant changes in α wave activity over time. Those in experimental group exhibited significant differences in Fp1 between pre- and post-intervention and between pre-intervention and follow-up ($p < .01$), significant differences in Fp2 ($p < .01$), F3 ($p < .05$), and F4 ($p < .01$) between pre-intervention and follow-up, and significant differences in Fz between pre-intervention and post-intervention ($p < .05$) and between pre-intervention and follow-up ($p < .01$) (Table 3).

3.4. Changes of psychogenic syndrome indicators after treatment

The patients in control group exhibited significant decreases in the FDAQ and FABQ scores over time, as compared between pre- and post-intervention, and between pre-intervention and follow-up ($p < .05$). Those in experimental group exhibited significant decreases in the K-BDI, FDAQ, and FABQ scores over time, as compared between pre- and post-intervention, and between pre-intervention and follow-up ($p < .001$). In the between-group comparison, there were significant differences in all indices post-intervention and at follow-up ($p < .001$) (Table 4).

4. Discussion

LBP is one of the most common pain disorders. It has a considerable effect on the functional activities and is difficult to treat, often showing chronicity or recurrence [26]. The pathogenesis of LBP is closely related to areas of the cerebral cortex, such as the somatosensory cortex, motor cortex, prefrontal lobe, parietal lobe, ACC, thalamus, and hypothalamus [27]. In particular, the ACC modulates pain cognition and is known to be responsible for the psychological aspects of pain, such as pain cognition and emotion, showing increased activity during pain and responding directly to harmful stimuli [28, 29]. In addition, the ACC is involved in avoidance behavior, emotional behavior, and memory of pain. Controlling the excitability of the ACC is of great importance for alleviating chronic pain [30, 31].

TMS involves repeated, non-invasive stimulation of the motor area cortex. It alters the excitability of brain circuits and has relatively long-lasting effects. It is frequently used as a therapeutic tool for psychiatric disorders [14, 15], and has also been reported to be effective in changing cognitive and motor functions [32]. High-frequency

stimulation increases the excitability, whereas low-frequency stimulation reduces it; the target site, stimulation intensity, frequency, total number of stimuli, and the stimulation schedule are important factors in this treatment [33, 34].

In this study, we administered 10 Hz rTMS to the ACC in patients with chronic LBP and examined its effects on the ANS and psychogenic symptoms.

In the HRV, which is used to measure the ANS function, the LF component reflects the sympathetic nerve activity, the HF component reflects the parasympathetic nerve activity, and the LF/HF ratio reflects the balance between these two [35]. This variable is used to assess the presence or absence of current stress [36].

In this study, we used the HRV to measure the ANS activity. The patients with chronic LBP exhibited lower LF values than the mean LF values of healthy Koreans in their 40 s (5.93); those in control group exhibited an increase in the LF values over time, indicating reduced pain intensity, and an increase in the LF/HF values, indicating restoration of the sympathetic/parasympathetic balance. It is thought that rTMS stabilizes the ANS activity by activating the inhibitory neurons and blocking the ascending pain pathways [37].

We performed brainwave analysis to measure the electrical activity associated with stress (psychological, physical, and emotional) due to chronic pain [38, 39]. α waves are closely related with stress and are reduced by negative stimuli, such as persistent pain [40]. In our study as well, the patients with chronic LBP exhibited low pre-intervention. However, 2 weeks after rTMS, they exhibited significant increases in the α-wave activity in Fp1, Fp2, F3, F4, and Fz, corresponding to the frontal lobe, which is responsible for cognitive and emotional function. This is thought to be the result of a significant effect on the ACC, which controls the excitability and cognitive processing of pain [28, 29].

Chronic progression of pain leads to abnormal cognition and behavior, inducing psychological changes [41]. In particular, patients with depression due to chronic pain exhibit reduced cell count and volume in the ACC, resulting in impairment of the executive function and emotional control [42, 43, 44]. In this study, we assessed the psychogenic symptoms using the K-BDI, FDAQ, and FABQ to examine the therapeutic effects of rTMS. Post-intervention and at follow-up, we observed significant changes in all indices of psychogenic symptoms, demonstrating that rTMS was effective. rTMS seems to have an antidepressant action, induced by adjustment of the inhibition and excitability in the cortex through altering the synaptic release and neurotransmitter mechanisms [45, 46]. The reduction of pain in peripheral areas and the enhanced function in the ACC are thought to be responsible for the positive effect on psychological improvement.

The mechanism of the effects of rTMS has been explained by various theories, such as increasing the beta-endorphin levels, modulating the opioid receptors, and inhibiting the transmission of pain information to the thalamus via the spinothalamic tract, and the effects of rTMS have been reported to be long-lasting [47, 48]. In this study, we administered high-frequency rTMS to the ACC, which is responsible for modulating the cognitive processing of pain as well as the psychological aspects of pain, and we demonstrated that this intervention had positive effects on pain-related psychogenic symptoms. In the future, a more comprehensive and systematic approach is required in the assessment and treatment of patients with chronic LBP; such that addresses not only the organic problems, but the psychological and emotional aspects as well [49].

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