Verification of the Therapeutic Pain Inhibition and Neurophysiological Response by Combined Vibration and Thermal Stimulation to the Abdomen

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Abstract: This study investigated the pain inhibition and neurophysiological responses elicited by combined vibration and thermal stimulation applied to the abdomen. Eighteen healthy male volunteers participated in a crossover study comparing vibratory stimulation to the abdomen alone with combined vibratory and thermal stimulation. The primary outcomes measured were the pressure pain threshold (PPT), autonomic nervous function (using heart rate variability), and brain wave activity (using EEG). The results showed no significant differences between the conditions in PPT, comfort levels, autonomic nervous, or brain wave activities. However, significant correlations were observed between PPT and autonomic nervous activities and between brain waves and autonomic nervous activities in the combined condition, suggesting a neurophysiological interaction. Specifically, increased parasympathetic activity was associated with reduced pain perception, indicating potential vagus nerve involvement. This study suggests that while combined stimulation does not enhance pain inhibition more than vibration alone, it does indicate complex neurophysiological interactions. Further studies should explore these mechanisms and the clinical potential of combined stimulation for pain relief, particularly in cases where direct stimulation is challenging.

Keywords: vibration; thermal; neurophysiological

1. Introduction

Various physical agents that are widely used in physical therapy, such as vibratory stimulation, transcutaneous electrical nerve stimulation (TENS), cryotherapy, and thermotherapy, have been demonstrated to possess analgesic effects [1]. The efficacy of these physical agents in pain inhibition has been demonstrated through improvements in subjective pain assessment scales [2] and increases in local pressure pain thresholds [3]. While the analgesic effects of these physical agents are primarily local, recent studies have reported remote analgesic effects as well [4,5].

The pain inhibition mechanisms attributed to physical agents include the gate control theory, endogenous opioid system, and descending pain inhibition [6]. The mechanism of remote analgesia is thought to involve descending pain inhibition, which entails the inhibition of spinal dorsal horn cell activity, thereby inhibiting the transmission of pain information to the brain. Recent attention has also been given to vagus nerve stimulation because of its potential to reduce pain, depression, anxiety, migraines, and refractory epilepsy [7]. Previous studies suggest that afferent vagus nerve stimulation may induce an anti-inflammatory response by activating the cholinergic anti-inflammatory pathway, thereby inhibiting pain signaling [8]. In recent years, a treatment concept has been developed using the possibility that vibratory stimulation of the abdomen stimulates the vagus...
nerve [9], and its application as an analgesic in chronic musculoskeletal pain has been verified [10]. The effect of abdominal vibration stimulation on pain suppression at remote sites has attracted considerable attention.

The analgesic effects of combining various physical agents, such as TENS with vibratory or thermal stimulation, have been recently reported [5,11]. However, the mechanisms underlying the analgesic effects of these combined stimulation physical agents, particularly at remote sites, need to be elucidated. If combined stimulation is proven to be more effective than individual stimulation physical agents, it could provide enhanced pain relief for patients with hyperalgesia or allodynia, in whom direct physical stimulation of painful areas is challenging. This study focused on the combined effects of vibratory and thermal stimulation on the abdomen, investigated whether they offer superior remote analgesic effects compared to individual vibration stimulation, and explored the underlying neurophysiological mechanisms.

2. Materials and Methods

2.1. Participants

Eighteen healthy young male volunteers (age $21.0 \pm 1.0$ years) participated. The exclusion criteria included current pain and a history of neurological disorders. This study was approved by the Ethics Committee of Kyoto Tachibana University (approval number: 24-10), and written informed consent was obtained from the patients.

2.2. Study Protocol

A crossover design with two conditions was conducted: vibratory stimulation alone (vibration condition) and combined vibratory and thermal stimulation (combination condition). A washout period of 24 h was maintained. Participants were randomly assigned to either the vibration or combined condition, with nine participants in each condition (Figure 1). The abdominal temperature was measured before and after stimulation (average temperatures: combination condition pre $33.7 ^\circ C$, post $36.4 ^\circ C$; vibration condition pre $33.8 ^\circ C$, post $35.0 ^\circ C$), and the participants rated their comfort and discomfort on a questionnaire after stimulation. Brain waves and photoplethysmography were recorded during stimulation to assess temporal changes (Figure 2).
2.3. Vibratory and Thermal Stimulation

The participants received vibratory stimulation, with or without additional thermal stimulation, using a device capable of simultaneously delivering both modalities (Steady Corporation). The vibratory stimulation parameters followed the manufacturer’s settings, with a frequency of 50 Hz and an amplitude of 8 mm. The temperature during thermal stimulation was set to 38 °C. Participants were seated with their arms resting on armrests and instructed to hold the device with their left hand. Before starting, the participants were informed that they could adjust the stimulation area on their abdomen if they felt any discomfort. The stimulation lasted for 20 min and the superficial abdominal temperature was measured before and after stimulation using a surface thermometer (Testo 905-T2, Testo SE & Co. KGaA, Titize-Neustadt, Germany). After vibration stimulation, we checked participants for the appearance of symptoms derived from vibration stimulation, such as discomfort symptoms related to the abdomen and internal organs. Still, none of the subjects complained of discomfort symptoms.

2.4. Evaluation of Comfort/Discomfort in Response to Stimulation

Changes in comfort/discomfort resulting from the vibratory and combined stimulations were assessed using a 100 mm visual analog scale (VAS), where the left end represented “feeling very bad” (0 mm) and the right end represented “feeling very good” (100 mm). Measurements were performed immediately after each stimulation session [12].

2.5. Electroencephalography (EEG)

In this study, the EEG was measured as an indicator of the effects of relaxation. A biosignalsplux device (Biosignalsplux, Plux, Inc., Lisbon, Portugal) was used with electrodes placed at the Fp1 and Fp2 areas based on the international 10–20 system, with the reference electrode attached to the right earlobe. The Fp1 and Fp2 areas were explicitly chosen for measurement, corresponding to the prefrontal cortex and involved in emotional stress [13]. The sampling frequency was set to 1000 Hz. The electrode attachment sites were cleansed prior to sensor placement, according to the Biosignalsplux manual. Additionally, to minimize arousal’s impact on EEG, the participants were instructed to get enough sleep the night before the measurement and avoid consuming alcohol and caffeine. The measurements were conducted in a quiet environment to minimize their impact on the EEG.

The analysis of the EEG data included segments during both vibration stimulation and combined stimulation periods. The EEG data underwent a rigorous preprocessing and artifact correction process to ensure the integrity and quality of the signals. Initially, the raw EEG data were visually inspected to identify and document any observable artifacts such as eye blinks, muscle movements, and electrical noise. Following this, the data were filtered using a 1–30 Hz band-pass filter to remove low-frequency drifts and high-frequency noise, which are typically irrelevant for EEG analysis. Channels exhibiting excessive noise or poor connectivity were either interpolated based on neighboring channels or removed from the analysis. To further reduce noise and artifacts, Independent Component Analysis (ICA) was employed using the Extended Infomax algorithm implemented in the EEGLAB toolbox. This algorithm was chosen for its robustness and effectiveness in separating independent
sources of brain activity from artifacts. Each independent component was then examined for characteristics indicative of artifacts. Automated classification tools like ICLabel were used to assist in this process, identifying components likely representing artifacts such as eye movements, muscle activity, heartbeats, or line noise based on their spatial and temporal properties. Components identified as noise were selected for removal.

Wavelet analysis (Figure 3) was applied to compute the power values in the theta (4–7 Hz), alpha (8–12 Hz), and beta (13–30 Hz) frequency bands, which were transformed using the natural logarithm. As an index of EEG activity, the $\alpha/\beta$ ratio was calculated to optimize the index for each individual by dividing the alpha wave’s power value by the beta wave’s power value, which indicates activity in the cerebral cortex. As indices of EEG activity for statistical analysis, the $\alpha/\beta$ ratio of the prefrontal (Fp) and the left–right ratio of the $\alpha/\beta$ ratio of Fp1 and Fp2 (Fp1/Fp2) were calculated as the mean values of Fp1 and Fp2, and the mean value indexed each index during the stimulation period. The analysis verified that fatigue and concentration during stimulation did not affect the theta wave measurements, confirming minimal measurement impact.

![Figure 3. Example of scalogram of EEG wavelet analysis. EEG, electroencephalography.](image)

### 2.6. Photoplethysmography

Photoplethysmography autonomic nervous activity was also assessed using photoplethysmography sensors (BioSignalplux, Plux, Inc., Lisbon, Portugal). Photoplethysmography measures heart rate based on the volume of blood passing through tissues with each heartbeat. The sampling frequency was set to 1000 Hz, and the measurements were taken from the tip of the right index finger.

Heart rate variability analysis was applied to the photoplethysmography data during the vibration and combined stimulation periods. Using wavelet analysis (Figure 4), we extracted power values for the high-frequency (HF: 0.15–0.40 Hz) and low-frequency (LF: 0.05–0.15 Hz) domains and log-transformed them to calculate the LF, HF, and LF/HF ratios. HF indicates parasympathetic nervous activity, LF reflects both sympathetic and parasympathetic activities, and the LF/HF ratio indicates the balance between sympathetic and parasympathetic activities [14]. These indicators represent the average values during the stimulation period.

### 2.7. Pressure Pain Threshold (PPT)

The effectiveness of the stimuli for pain inhibition was assessed by measuring the PPT. A pressure algometer (model RZ-10, Aikoh Engineering, Osaka, Japan) was used. PPT was measured before and after the intervention stimulus in both conditions (combination and vibration conditions). The upper trapezius muscle fibers were selected to verify the pain inhibition effect on remote sites of the abdomen, which is the intervention area of this study. The upper trapezius muscle is based on its anatomical location at the midpoint between the seventh cervical vertebra and the acromion on each side [15]. Measurements were conducted in a seated position, with the participants keeping their backs straight.
and looking forward to minimize body movement. A pressure algometer was applied perpendicularly to the skin surface of the shoulder at a rate of 5 N/s. The pressure was discontinued when the participant reported pain, and the value at that point was recorded. Three measurements were obtained, and the average of these three trials was calculated for each side, with the mean of the left and right values used as the PPT. The PPT measurements were performed before and after the vibratory stimulation. The intraclass correlation coefficient (ICC) for the PPT measurements was 0.97.

Figure 4. Example of scalogram of Photoplethysmography wavelet analysis.

2.7. Pressure Pain Threshold (PPT)

Figure 4. Example of scalogram of Photoplethysmography wavelet analysis.
Table 1. Cont.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Combination Condition (n = 18)</th>
<th>Vibration Condition (n = 18)</th>
<th>BF_{10}</th>
<th>95% CI [Lower, Upper]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fp α/β ratio</td>
<td>1.5 (1.3)</td>
<td>0.6 (0.5)</td>
<td>11.7</td>
<td>0.2, 1.2</td>
</tr>
<tr>
<td>Fp1/Fp2 α/β ratio</td>
<td>1.0 (1.8)</td>
<td>1.0 (1.2)</td>
<td>0.2</td>
<td>−0.4, 0.4</td>
</tr>
</tbody>
</table>

Median (interquartile range). PPT, pressure pain threshold; VAS, visual analog scale; LF, low frequency; HF, high frequency; BF, Bayesian factors; CI, credible interval.

3.2. Correlation Analysis within Each Condition

Figure 5 shows the correlation matrices for the vibration and combined stimulus conditions. In the rate of change in PPT, the combined stimulus condition showed a positive correlation with HF (Kendall’s τ = 0.35, 95%CI = 0.006, 0.58). In the vibration condition, there was a moderately positive correlation with the VAS score (Kendall’s τ = 0.35, 95%CI = 0.014, 0.59).

![Figure 5](image_url)

Figure 5. Correlation matrices under combination (A) and vibration conditions (B) * the 95% CI did not include zero. PPT, pressure pain threshold; VAS, visual analog scale; LF, low frequency; HF, high frequency.
In the correlation analysis of autonomic nerve activity and EEG activity, a moderate negative correlation was found between the LF/HF ratio and the left–right ratio of the \( \alpha/\beta \) ratio (Kendall’s tau B = −0.35, 95%CI = −0.58, −0.007) in the compound stimulation condition, and no significant correlation was found between the other autonomic nerve activity indices and EEG activity indices. No significant correlations were found between any autonomic and EEG activity indices in the vibration stimulation condition.

4. Discussion

This study investigated whether adding thermal stimulation to vibratory stimulation could enhance pain inhibition at remote sites compared with vibratory stimulation alone. Neurophysiological responses focusing on the autonomic nervous system and brain wave activities were also examined. Only EEG activity in the frontal region showed significant differences between conditions. However, correlations were observed between PPT and autonomic nervous activities and between brain waves and autonomic nervous activities in the combined condition, suggesting a neurophysiological interaction.

A comparison of the variables between the combination and vibration conditions revealed no significant differences across all the measures. Both conditions employed low-frequency vibratory stimulation as a standard parameter, and previous studies have suggested that low-frequency vibratory massage (15–50 Hz) can increase local tissue temperature, relax fascial tissues, decrease emotional tension, and produce an overall analgesic effect [16]. Although both conditions showed increased PPT post-stimulation, the combined stimulation did not yield higher analgesic effects than the vibration-only stimulation. Previous studies have shown that combined stimulation with TENS and thermal stimulation achieved better analgesic effects than individual stimulations [11]. However, in our study, the addition of thermal stimulation to vibratory stimulation did not enhance the analgesic effects. This poor analgesic effect suggests that the additional effects of thermal stimulation in a combined setting must be sufficiently achieved. Deep thermal therapy has been suggested to enhance pain suppression more effectively than superficial thermal therapy [17,18]. However, in our study, the thermal stimulation method did not increase pain suppression beyond that achieved using vibration alone. Furthermore, reports indicate that thermal therapy did not alter the PPT in healthy subjects [19], suggesting that sufficient analgesic effects were not achieved in healthy individuals in this study either.

Regarding autonomic nervous activity, physical and thermal stimuli to the abdomen have been reported to increase parasympathetic activity and suppress sympathetic activity [20,21]. A combination of vibratory and thermal stimulation was hypothesized to enhance parasympathetic activity beyond individual stimulations; however, no differences were observed. Previous studies have indicated that positive emotions, such as joy, are associated with increased parasympathetic activity [22]. Brainwave activity measured in the prefrontal cortex, which is indicative of emotional activity, showed differences between the two conditions, but there were differences observed in the degree of pleasant emotions, suggesting that differences in unconscious emotional response were evident between the combination and vibration conditions.

A significant positive correlation was observed between the PPT and VAS scores for comfort/discomfort under the vibration condition. Previous research has shown that interventions that evoke positive emotions can effectively reduce pain sensitivity [23], and that stimuli perceived as pleasant decrease overall pain perception. In contrast, stimuli perceived as unpleasant do not cause pain, but can increase overall pain [24]. Thus, the increase in PPT, indicative of pain suppression, was likely due to the pleasant emotions evoked by the stimulation. Regarding the pain-relieving mechanism associated with pleasant emotions, it has been reported that pleasant emotions activate the network between the prefrontal cortex and the nucleus accumbens, releasing dopamine, which in turn produces endogenous opioids [25,26]. In the present study, pleasant emotions elicited by vibratory stimulation were possibly linked to the release of endogenous opioids, which contributed to their analgesic effects.
In the combination condition, a significant positive correlation was found between the PPT and HF (indicative of parasympathetic activity). Increased parasympathetic activity is associated with reduced pain perception [27], suggesting that increased parasympathetic activity induced by stimulation may have contributed to the analgesic effects. Regarding the brain waves and autonomic nervous activity, a negative correlation was observed between the LF/HF ratio and the α-wave activity left/right ratio (Fp1/Fp2). As positive emotions are associated with increased parasympathetic activity [22], vibratory and thermal stimulations are likely to induce positive emotions, enhance parasympathetic activity, and suppress sympathetic activity. However, no correlation was found between the PPT and VAS in the combination condition, suggesting that while the combined stimulation did not evoke subjective pleasant emotions, it might have elicited ‘physiologically pleasant emotions’ associated with brain waves and autonomic nervous activity. Previous research has suggested that subjective emotions and the physiological responses driven by emotions do not always align [28]. Regarding the pain-relieving mechanism of the combined stimulation, it is possible that vagus nerve stimulation associated with vibratory stimulation played a role, as in the vibration-only condition. The effects specific to the thermal stimulation added to the abdominal region in the combined condition are suggested to have contributed. Previous studies have shown that thermal therapy increases parasympathetic activity and suppresses sympathetic activity [21]. In addition, it has been reported that the combination of music and vibration that is used in vibro-acoustic therapy evokes changes in pain perception, heart rate variability, respiration rate, endocrine function, and low-frequency sound and music [29]. Therefore, the significant positive correlation observed between the PPT and HF in the combined stimulation condition may indicate that the addition of thermal stimulation enhanced the link between PPT changes and vagus nerve stimulation.

A distinctive aspect of this study is its focus on abdominal vibratory stimulation, which is anticipated to elicit effects mediated by vagus nerve stimulation, along with its examination of the analgesic effects and neurophysiological responses at remote sites when combined with thermal stimulation. Previous research has suggested that thermal stimulation enhances autonomic and brainwave activities. We hypothesized that combined vibratory and thermal stimulation would produce more excellent pain inhibition and relaxation than vibratory stimulation alone. However, the study did not observe enhanced pain inhibition effects with the combined stimulation compared with vibration alone, suggesting that the additional effects of thermal stimulation need to be sufficiently realized. Additionally, factors related to the effectiveness of pain inhibition, including neurophysiological responses, were examined. In the vibration-only condition, an increase in PPT was correlated with pleasant emotions, which are known to be associated with the production of endogenous opioids [25,26], suggesting that the pain inhibition effects in the vibration condition were related to the elicited pleasant emotions.

In contrast, in the combined stimulation condition, although no correlation was observed between PPT increase and pleasant emotions, a correlation was noted with parasympathetic activity. Similar to previous findings, increased parasympathetic activity was associated with reduced pain perception [27], indicating that adding thermal stimulation to vibratory stimulation might strengthen the relationship between pain inhibition effects and vagus nerve stimulation. Furthermore, a relationship was observed between the balance of autonomic nervous system activity (LF/HF ratio) and brainwave activity in the prefrontal cortex. The neurovisceral integration model, proposed for controlling autonomic nervous activity by the central nervous system [30], suggests that the prefrontal cortex forms a pathway with the amygdala. In this pathway, inhibition from the prefrontal cortex to the amygdala is essential for controlling heart rate variability [31]. Therefore, this study suggests that the combined stimulation applied to the abdomen alters brain activity related to emotions in the prefrontal cortex, which modifies autonomic nervous activity via the prefrontal cortex–amygdala pathway.

This study indicates that the combination and vibration conditions resulted in pain suppression effects at remote sites, suggesting that abdominal vibratory stimulation could
be a feasible option for pain suppression in cases where direct stimulation of painful areas, such as hypersensitivity and allodynia, is challenging. However, because better analgesic effects were not observed at remote sites with the combined stimulation used in this study, future research should explore the adaptation of various physical stimulations in combination to enhance clinical outcomes.

This study has several limitations. First, the participants were limited to young males. Differences in autonomic nervous activity due to age and sex have been reported [32], with studies noting sex differences in pain threshold responses to vibratory stimulation [33]. Second, the relatively small sample size may have influenced the results, thereby limiting the generalizability of the findings. Third, although the study aimed to verify the pain inhibition effects of vibratory and combined stimulations, it focused on changes in the PPT of healthy individuals. If pain inhibition effects were evaluated in subjects experiencing pain, changes in subjective pain intensity, rather than PPT, might have been observed. Fourth, the focus was on pain inhibition effects at remote sites; while no differences were observed in pain inhibition at these sites, differences at the stimulation sites might have occurred. As peripheral sites were not assessed for pain inhibition, this study’s interpretations might apply primarily to central nervous system-mediated pain inhibition mechanisms. Finally, the study did not compare resting (setting of baseline and placebo control) and stimulation-induced activity for the autonomic nervous system and brain wave indices during pain stimulation, suggesting the need for further research to explore various combinations of physical therapies to enhance pain inhibition in clinical settings.

5. Conclusions

This study demonstrated that combined vibratory and thermal stimulation did not inhibit pain at remote sites better than vibration stimulation alone. However, it did indicate neurophysiological interactions related to prefrontal cortex relaxation activity. Because this study did not have an adequate study setting, including control of factors that could lead to a placebo effect, further research is required to explore the potential clinical applications of such combined stimulation in pain treatment, especially in cases where direct physical stimulation is not feasible.


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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Kyoto Tachibana University (approval no. 24-10, 10 May 2024).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent was obtained from the patients to publish this paper.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Conflicts of Interest: The authors declare no conflicts of interest.
References


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