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# Enhancing pain modulation: the efficacy of synchronous combination of virtual reality and transcutaneous electrical nerve stimulation

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## ABSTRACT

**Introduction** Virtual reality (VR) and transcutaneous electrical nerve stimulation (TENS) have emerged as effective interventions for pain reduction. However, their standalone applications often yield limited analgesic effects, particularly in certain painful conditions.

**Aims** Our hypothesis was that the combination of VR with TENS in a synchronous manner could produce the best analgesic effect among the four experimental conditions.

**Methods** To address this challenge, we proposed a novel pain modulation strategy that synchronously combines VR and TENS, aiming to capitalise on both techniques' complementary pain modulation mechanisms. Thirty-two healthy subjects participated in the study and underwent three types of interventions: VR alone, a combination of VR with conventional TENS, and a combination of VR with synchronous TENS. Additionally, a control condition with no intervention was included. Perceived pain intensity, pain unpleasantness, positive and negative affect scores, and electroencephalographic (EEG) data were collected before and after the interventions. To delve into the potential moderating role of pain intensity on the analgesic efficacy of VR combined with synchronous TENS, we incorporated two distinct levels of painful stimuli: one representing mild to moderate pain (ie, low pain) and the other representing moderate to severe pain (ie, high pain).

**Results** Our findings revealed that both combination interventions exhibited superior analgesic effects compared with the VR-alone intervention when exposed to low and high pain stimuli. Notably, the combination of VR with synchronous TENS demonstrated greater analgesic efficacy than the combination of VR with conventional TENS. EEG data further supported these results, indicating that both combination interventions elicited a greater reduction in event-related potential magnitude compared with the VR-alone intervention during exposure to low and high pain stimuli. Moreover, the synchronous combination intervention induced a more significant reduction in N2 amplitude than the VR-alone intervention during exposure to low pain stimuli. No significant differences in EEG response changes were detected between the two combination interventions. Both combination interventions resulted in a greater reduction in negative affect compared with the VR-alone intervention.

**Conclusions** Altogether, our study highlights the effectiveness of the synchronous combination of VR and TENS in enhancing pain modulation. These findings offer valuable insights for developing innovative pain treatments, emphasising the importance of tailored and multifaceted therapeutic approaches for various painful conditions.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Virtual reality (VR) and transcutaneous electrical nerve stimulation (TENS) have been widely applied in pain management. However, the limited analgesic effect of single intervention due to each technique's isolated pain modulation mechanisms has been recognised.

### WHAT THIS STUDY ADDS

⇒ This study demonstrated that the combined interventions of VR and TENS produced superior analgesic effects compared with VR alone. Importantly, the combination of VR with synchronous TENS exhibited even greater analgesic efficacy than the combination of VR with conventional TENS.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study offer valuable insights into developing more effective pain treatments. By highlighting the benefits of synchronising VR and TENS, this research emphasises the importance of adopting multifaceted therapeutic approaches to address the needs of patients with different painful conditions. These findings can potentially influence future research directions, guide clinical practice and shape policies related to pain management by encouraging the implementation of combined interventions for improving pain relief and enhancing patient outcomes.

## INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[1] Millions of patients suffer from acute or chronic pain worldwide. However,

inadequate pain management is a significant healthcare concern. Commonly used analgesics do not always provide sufficient pain relief and are often associated with undesirable side effects, such as dependence or addiction.[2] In light of this, non-invasive cognitive modulation and neuromodulation techniques have emerged as potential alternatives for pain management.[3–8] Given that pain experience is a complex phenomenon influenced by many physical and psychological factors and that non-invasive therapies target specific pain modulation mechanisms,[9 10] combining different treatments can potentially enhance the analgesic effects by capitalising on their complementary pain modulation mechanisms.

Virtual reality (VR) and transcutaneous electrical nerve stimulation (TENS) have emerged as promising non-pharmacological interventions for acute and chronic pain management, with the potential to reduce reliance on opioid medications.[3–6 11–13] Both techniques have distinct mechanisms of action.[3 6] TENS mainly reduces pain by affecting peripheral and central nervous systems through the gate control theory (ie, high-frequency conventional TENS) and endogenous opioid release.[3] On the other hand, VR provides an immersive, multisensory, and three-dimensional environment that reduces pain by distracting attention away from noxious stimuli or regulating emotions.[6] Given the complementary pain modulation mechanisms of TENS and VR (eg, one therapy might focus on reducing nociceptive signalling, while another therapy could aim to modulate the emotional and cognitive aspects of pain), combining these interventions may achieve a better analgesic effect than any single intervention. Moreover, synchronously combining VR and TENS stimuli can lead to more natural and realistic multiple sensations; that is, visual and auditory cues in VR could be accomplished by tactile feedback provided by TENS.[14] Synchronising these sensory inputs can create a multisensory integration that enhances the perception of the virtual environment and induces a more immersive experience. This synchronisation can lead to a more realistic perception of multiple sensations, potentially resulting in additional analgesic benefits.

Here, we proposed a novel pain modulation strategy that synchronously combined VR and TENS, that is, modulating the intensity of TENS by the loudness of the sound in the VR environment. To investigate the effectiveness of this combination and explore the associated neural mechanisms, we recruited 32 healthy subjects receiving three types of interventions: VR alone, a combination of VR with conventional TENS, and a combination of VR with synchronous TENS. A control condition with no intervention was also included. We measured perceived pain intensity, pain unpleasantness, and positive and negative affect and collected electroencephalographic (EEG) data before and after the interventions. We hypothesised that the combination of TENS with VR in a synchronous manner could produce the best analgesic effect among the four experimental conditions.

## METHODS

### Subjects

Thirty-four right-handed, healthy and pain-free adults (16 men and 18 women; mean (standard deviation, SD) age 24.50 (2.85) years; age range 20–30 years) who had never had TENS before were recruited through local advertisement (figure 1). Exclusion criteria were (1) peripheral or central nervous system diseases, (2) chronic pain and concomitant analgesic treatments, (3) history of dizziness when watching 3D videos, and (4) ingestion of pain medication or substances (eg, alcohol and coffee) within 24 hours of engaging in the experiment.

### Sensory stimulation

Nociceptive somatosensory stimuli were pulses of radian heat generated by an infrared neodymium yttrium aluminumite laser with a wavelength of 1.34 µm and a pulse duration of 4 ms (Electronical Engineering, Italy). The laser beam was transmitted via an optic fibre and focused by lenses to a spot with a diameter of ~7 mm (~38 $mm^2$).

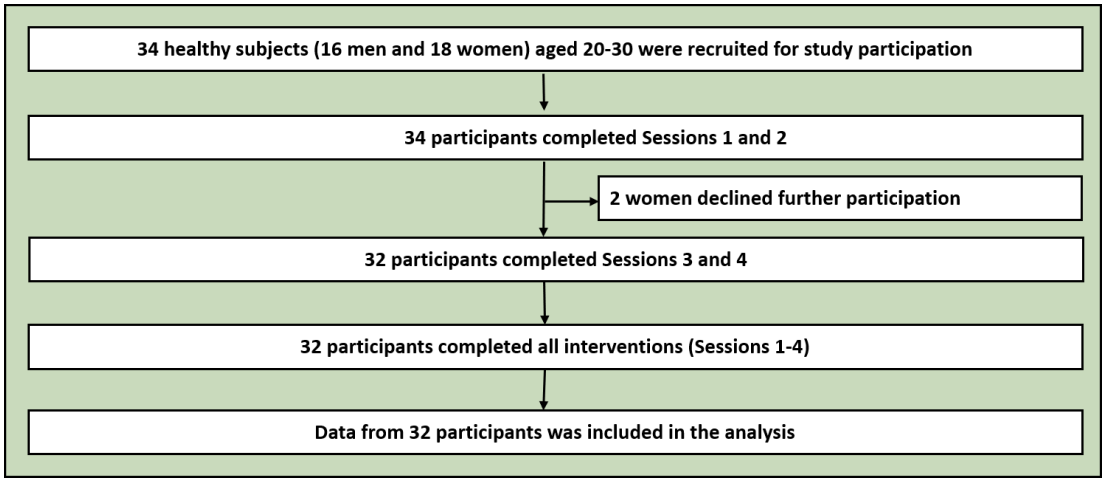


**Figure 1** Study flowchart.

Laser pulses were delivered to the dorsum of the left hand. After each stimulus, the laser beam target was shifted by approximately 1 cm in a random direction to avoid nociceptor fatigue or sensitisation. The ascending method of limits (in steps of 0.25 J) was applied for each subject to determine the laser energies: two laser energies that evoked subjective ratings of ~4 (ie, mild to moderate pain) and 7 (ie, moderate to severe pain) on a numerical rating scale (NRS) ranging from 0 ('no pain') to 10 ('the worst pain imaginable') were determined by increasing the laser energy in steps of 0.25 J until the target ratings were obtained. This procedure was repeated three times, and the average energy was used in the following procedures of the experiment for each subject. Notably, previous research demonstrated that the analgesic effect of VR was pronounced among patients who experienced moderate to severe pain.[15] To delve into the potential moderating role of pain intensity on the analgesic efficacy of VR combined with synchronous TENS, we incorporated two distinct levels of painful stimuli: one representing mild to moderate pain (ie, low pain) and the other representing moderate to severe pain (ie, high pain). Across subjects, two laser energies were as follows: E1, 3.30 (0.63) J for all 34 subjects and 3.25 (0.61) J for the 32 subjects included in the final analysis; E2, 3.82 (0.55) J for all 34 subjects and 3.78 (0.53) J for the 32 subjects included in the final analysis.

VR was provided through a head-mounted display (Pico Neo 3, Pico, China); the two different VR scenarios were developed by Ultimate Therapeutics, China. In the first scenario (~8 min), subjects entered a VR environment where they passively viewed the deep ocean scene, including whales, tridacna, and other rare marine organisms, with soft nature sounds played in the background. In the second scenario (~8 min), subjects were instructed to relax through abdominal breathing and muscle relaxation when viewing the seashore scene, including flying seagulls, sailboats, and rhythmic waves. Subjects could look around in a 360° virtual environment while the background sounds were emitted through headphones.

TENS was generated by a constant current electrical stimulator (Sanxia Technique, China) and delivered through a pair of round surface electrodes (diameter: 16 mm; interelectrode distance: 3 cm) placed over the radial nerve at the left wrist. Two different types of TENS were used in the experiment. Both TENS types consisted of a series of bidirectional square-wave pulses (pulse width: 0.2 ms; pulse frequency: 100 Hz). The stimulus intensity of conventional TENS was individually adjusted to elicit a strong but non-painful tingling sensation underneath the TENS electrodes and remained constant during the whole stimulation period.[4 5] To combine VR and TENS synchronously, the intensity of synchronous TENS was modulated to synchronise with the loudness of the sound in the VR environment. Specifically, to ensure the perceived TENS, sensations are more natural and realistic, the intensity of synchronous TENS changed every 200 ms and remained constant during this period. To mitigate the potential impact of stimulus intensity on the analgesic effects induced by different types of TENS, the total stimulus intensity of synchronous TENS was maintained at a similar level to that of conventional TENS in each subject. The duration of each type of TENS stimulus was ~16 min, the same as the duration of VR scenarios.

### Experimental design

The experiment was performed using a within-subject repeated-measures design (figure 2). Each subject participated in four sessions (figure 2A). Four types of interventions were randomly assigned to these sessions, including control, VR alone, a combination of VR with conventional TENS, and a combination of VR with synchronous TENS. To minimise the possible influence of the persistent analgesic effect between successive sessions on the outcomes, four sessions were conducted on two consecutive days (first day: sessions 1 and 2, second day: sessions 3 and 4), and subjects were required to rest for ~30 min between sessions. Please note that the two combination interventions (ie, VR with conventional TENS and VR with synchronous TENS) were conducted on two different days. In total, 34 subjects completed both sessions 1 and 2. Out of these participants, 32 subjects (16 men and 16 women; mean (SD) age 24.56 (2.79) years; age range 20–30 years) completed all four sessions (ie, sessions 1–4). Ultimately, the data from these 32 subjects were used in the final analysis.

In each session, we collected pain perception, pain unpleasantness, positive and negative affect scores, and EEG data from all subjects before and after the intervention (figure 2B). During the EEG data acquisition, 40 laser pulses at two different intensities were delivered to the dorsum of the left hand to elicit a painful pinprick sensation for each subject (figure 2C). Each intensity level consisted of 20 trials, with the order of stimulus intensities pseudo-randomised. The interstimulus interval varied randomly between 19 s and 21 s with a rectangular distribution. Each trial started with a 5 s presentation of a white cross centred on the screen. This was followed by the delivery of the laser stimulus, which lasted for 4 ms. Three seconds after the laser stimulus, a visual cue was presented to inform subjects to rate the intensity of pain perception within 5 s on the 0–10 NRS. Then, another visual cue was presented to inform subjects to rate the intensity of unpleasantness within 5 s on the same 0–10 NRS. The next trial started in 1–3 s, and the duration of the whole EEG data recording session lasted ~14 min. To assess the subject's current positive and negative affect, they were instructed to fill out the Chinese version of the Positive and Negative Affect Schedule (PANAS).[16 17] PANAS consists of two 10-item scales designed to assess positive affect (enthusiastic, interested, determined, excited, inspired, alert, active, strong, proud, and attentive) and negative affect (scared, afraid, upset, distressed, jittery, nervous, ashamed, guilty, irritable, and hostile). Participants were asked to rate the extent

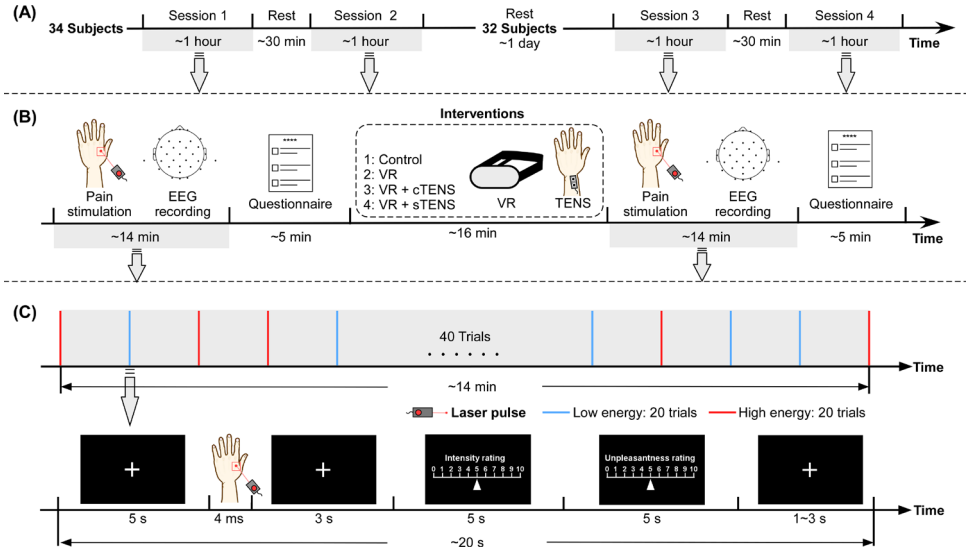


**Figure 2** Experimental design. (A) The experiment was performed using a within-subject repeated-measures design. Each subject participated in four sessions, which were conducted in two consecutive days (first day: sessions 1 and 2, second day: sessions 3 and 4). Subjects were required to rest for~30 min between sessions. (B) In each session, perceived pain intensity, unpleasantness, electroencephalographic (EEG) data, and positive and negative affects were collected from all subjects before and after the intervention. One control condition and three types of interventions, including the VR alone, the combination of VR with conventional TENS, and the combination of VR with synchronous TENS, were randomly assigned to each session. (C) During the EEG data acquisition, 40 laser pulses at two stimulus intensities were delivered to the dorsum of the left hand for each subject. For each stimulus intensity, 20 trials were delivered. cTENS, conventional TENS; EEG, electroencephalographic; sTENS, synchronous TENS; TENS, transcutaneous electrical nerve stimulation; VR, virtual reality.

of their present emotional state using a 5-point rating scale (ranging from 1=very slightly or not at all to 5=extremely). The mean score for each domain was calculated to derive moment scores for positive affect and negative affect.

## EEG data recording

Subjects were seated in a comfortable chair in a silent and temperature-controlled room. They were asked to relax their muscles and focus their attention on the stimulation. EEG data were recorded using 32 Ag-AgCl scalp electrodes placed according to the international 10–20 system (ANT Neuro, the Netherlands; bandpass: 0.01–100 Hz; sampling rate: 1000 Hz). The CPz electrode served as the reference, and electrode impedances were kept below 10 kΩ.

## EEG data processing

EEG data were preprocessed using EEGLAB.[18] Continuous EEG data were band-pass filtered between 1 Hz and 30 Hz and segmented into epochs using a time window of 1500 ms (500 ms prestimulus and 1000 ms poststimulus). EEG trials were baseline-corrected in the time domain using the prestimulus interval (−500 to 0 ms). Trials contaminated by eye blinks and movements were corrected using an independent component analysis algorithm (runica).[18] After preprocessing, EEG epochs were re-referenced to the average of bilateral mastoids (M1 and M2).

## Laser-evoked brain potentials

Single-trial laser-evoked brain potential (LEP) waveforms were averaged across all trials for each subject, session, and stimulus intensity. Peak latencies and amplitudes of N2 and P2 waves, defined as the most negative and positive deflections between 0 ms and 500 ms after stimulus onset, were measured from each single-subject average waveform at Cz. Single-subject average LEP waveforms were averaged across subjects to obtain group-level LEP waveforms. Group-level scalp topographies at the peak latencies of N2 and P2 waves were computed by spline interpolation.

Time-frequency distributions (TFDs) of EEG epochs were obtained using a windowed Fourier transform (WFT) with a fixed 250 ms Hanning window for each subject, session, and stimulus intensity.[19] For each EEG epoch, the WFT yielded a complex time-frequency estimate $F(t,f)$ at each time-frequency point $(t,f)$, extending from −500 ms to 1000 ms (in steps of 1 ms) in the time domain and from 1 Hz to 30 Hz (in steps of 1 Hz) in the frequency domain. The resulting spectrogram, $p(t,f)=|F(t,f)|^2$, represents the signal power as a joint function of time and frequency at each time-frequency point. The spectrograms were baseline-corrected (reference interval: −400 ms to −100 ms relative to stimulus onset) at each frequency $f$ using the subtraction approach.[20] This reference interval was chosen to reduce the adverse influence of spectral estimates biased by windowing poststimulus activity and padding values. Region-of-interests were used to extract the magnitude of time-frequency brain responses (ie,

event-related potential (ERP) and event-related desynchronisation at alpha frequencies (α-ERD)). Magnitudes of ERP (1–400 ms, 1–10 Hz) and α-ERD (500–1000 ms, 8–13 Hz) were calculated by computing the mean of the top 20% time-frequency pixels, displaying the highest increase (for ERP) or decrease (α-ERD) for each subject in each experimental condition.[19]

### Statistical analysis

The power calculations were performed using analysis of variance (ANOVA, repeated measures, within factors) F-tests in G*power, a free online software for power analysis (http://www.gpower.hhu.de/en.html). Considering the within-subject repeated-measures design, an initial sample size of 24 subjects would be sufficient to detect a medium effect size ($f$=0.25) with a statistical power (1–β) of 0.80 at a significant level of α=0.05. To account for the potential effects of intervention randomisation and to compensate for potential attrition during follow-up, the sample size was increased to 34 subjects. This adjustment aimed to ensure that the study retained adequate statistical power and could effectively detect any significant effects within the experimental design.[21]

The preintervention differences were compared using one-way repeated-measures ANOVA with 'session' and 'stimulus intensity' as within-subject factors for pain intensity, unpleasantness, and electrophysiological responses. For positive and negative affect scores, the preintervention differences were compared using one-way repeated-measures ANOVA with 'session' as a within-subject factor. Post hoc paired sample t-tests were performed to compare the possible preintervention differences between interventions (Fisher's least significant difference (LSD) correction, p<0.05).

The possible effect of different interventions on perceptual (ie, pain intensity), emotional (ie, pain unpleasantness, positive and negative affect scores), and electrophysiological responses (ie, LEP amplitude, ERP, and α-ERD magnitudes) elicited by nociceptive stimulation were first evaluated by paired sample t-tests. Then, we calculated the difference between each measure before and after each intervention (difference=preintervention−postintervention). The resulting differences were compared using two-way repeated-measures ANOVA with 'session' and 'stimulus intensity' as within-subject factors for pain intensity, unpleasantness, and electrophysiological responses. For positive and negative affect scores, the resulting differences were compared using one-way repeated-measures ANOVA with 'session' as a within-subject factor. Post hoc paired sample t-tests were performed to compare the possible differences between interventions (Fisher's LSD correction, p<0.05). The relationship between combination intervention-induced behavioural changes (ie, pain intensity and unpleasantness) and electrophysiological changes (ie, LEP amplitude, ERP and α-ERD magnitudes) were assessed using Pearson correlation analysis.

## RESULTS

### Analgesic effect and emotional changes induced by the interventions

Regarding preintervention variables (ie, pain intensity and unpleasantness, positive and negative affect scores), the two-way repeated-measures ANOVA demonstrated a significant main effect of 'stimulus intensity' for both pain intensity and unpleasantness, and no other significant effects were observed (online supplemental table 1). Post hoc paired sample t-tests showed that the baseline pain intensity before the combination of VR with conventional TENS intervention was higher than that before the control condition when exposed to both low pain (t(31)=−2.463, p=0.020) and high pain stimuli (t(31)=−2.143, p=0.040). No other differences were observed.

Paired sample t-tests revealed that all three interventions resulted in a significant reduction in pain intensity (control: t(31)=−1.768, p=0.087; VR alone: t(31)=2.261, p=0.031; VR with conventional TENS: t(31)=4.991, p<0.001; VR with synchronous TENS: t(31)=6.267, p<0.001) and unpleasantness (control: t(31)=−1.228, p=0.229; VR alone: t(31) = 2.732, p=0.010; VR with conventional TENS: t(31)=4.946, p<0.001; VR with synchronous TENS: t(31)=4.768, p<0.001) when participants were exposed to low pain stimuli. When exposed to high pain stimuli, both combination interventions significantly decreased pain intensity (control: t(31)=−2.679, p=0.012; VR alone: t(31)=0.254, p=0.801; VR with conventional TENS: t(31)=5.333, p<0.001; VR with synchronous TENS: t(31)=5.458, p<0.001) and unpleasantness (control: t(31)=−1.075, p=0.291; VR alone: t(31)=1.279, p=0.211; VR with conventional TENS: t(31)=5.127, p<0.001; VR with synchronous TENS: t(31)=4.620, p<0.001). The control condition (t(31)=2.511, p=0.017), the VR-alone intervention (t(31)=3.180, p=0.003), and the synchronous combination intervention (t(31)=2.581, p=0.015) all led to a significant decrease in positive affect. However, the combination of VR and conventional TENS did not reach statistical significance in changing positive affect (t(31)=1.718, p=0.096). On the other hand, both combination interventions showed a significant reduction in negative affect (VR with conventional TENS: t(31)=2.879, p=0.007; VR with synchronous TENS: t(31)=2.729, p=0.010).

Two-way repeated-measures ANOVA showed a significant interaction effect for pain intensity and significant main effects of 'session' for pain intensity and unpleasantness (table 1). Post hoc paired sample t-tests showed that, when exposed to both low pain and high pain stimuli, all interventions induced greater reductions in pain intensity compared with the control condition (VR alone: t(31)= −2.921, p=0.006 (low pain), t(31)=−2.270, p=0.030 (high pain); VR with conventional TENS: t(31)=−4.646, p<0.001 (low pain), t(31)=−5.735, p<0.001 (high pain); VR with synchronous TENS: t(31)=−6.781, p<0.001 (low pain), t(31)=−5.883, p<0.001 (high pain); figure 3A,B). Both combination interventions showed a better analgesic effect than VR alone (VR with conventional TENS:

Table 1 ANOVA results for intervention-induced changes in pain intensity, unpleasantness, PANAS and EEG responses

| Variables | Effects | df | F value | P value | Partial $\eta^2$ |
|---|---|---|---|---|---|
| Pain intensity | Session | (3,93) | 26.513 | **<0.001** | 0.461 |
| | Stimulus intensity | (1,31) | 0.105 | 0.749 | 0.003 |
| | Session × stimulus intensity | (2.481,76.913) | 2.950 | **0.047** | 0.087 |
| Pain unpleasantness | Session | (2.065,64.028) | 11.612 | **<0.001** | 0.273 |
| | Stimulus intensity | (1,31) | 0.659 | 0.423 | 0.021 |
| | Session × stimulus intensity | (3,93) | 2.138 | 0.101 | 0.065 |
| PANAS: positive affect | Session | (3,93) | 0.339 | 0.797 | 0.011 |
| PANAS: negative affect | Session | (2.755,85.401) | 5.175 | **0.003** | 0.143 |
| N2 amplitude | Session | (2.603,80.686) | 5.771 | **0.002** | 0.157 |
| | Stimulus intensity | (1,31) | 1.191 | 0.283 | 0.037 |
| | Session × stimulus intensity | (2.676,82.950) | 0.156 | 0.908 | 0.005 |
| P2 amplitude | Session | (3,93) | 2.390 | 0.074 | 0.072 |
| | Stimulus intensity | (1,31) | 2.291 | 0.140 | 0.069 |
| | Session × stimulus intensity | (3,93) | 0.654 | 0.582 | 0.021 |
| ERP magnitude | Session | (3,93) | 7.091 | **<0.001** | 0.186 |
| | Stimulus intensity | (1,31) | 11.992 | **0.002** | 0.279 |
| | Session × stimulus intensity | (3,93) | 0.672 | 0.571 | 0.021 |
| α-ERD magnitude | Session | (2.030,62.935) | 1.454 | 0.241 | 0.045 |
| | Stimulus intensity | (1,31) | 7.661 | **0.009** | 0.198 |
| | Session × stimulus intensity | (1.775,55.022) | 0.297 | 0.718 | 0.009 |

Statistical p values with significant effects are highlighted in bold.
ANOVA, analysis of variance; EEG, electroencephalographic; ERP, event-related potential; PANAS, Positive and Negative Affect Schedule; α-ERD, event-related desynchronisation at alpha frequency.

t(31)=−2.397, p=0.023 (low pain), t(31)=−3.506, p=0.001 (high pain); VR with synchronous TENS: t(31)=−4.573, p<0.001 (low pain), t(31)=−4.613, p<0.001 (high pain); figure 3A,B). Notably, the combination of VR with synchronous TENS achieved a superior analgesic effect compared with the combination of VR with conventional TENS (t(31)=−2.677, p=0.012 (low pain), t(31)=−2.141, p=0.040 (high pain); figure 3A,B).

For unpleasantness (figure 3A,B), VR alone induced a greater reduction than the control condition (t(31)=−2.560, p=0.016) when exposed to low pain stimuli. Both combination interventions resulted in greater reductions in unpleasantness than the control condition (VR with conventional TENS: t(31)=−3.407, p=0.002 (low pain), t(31)=−3.977, p<0.001 (high pain); VR with synchronous TENS: t(31)=−3.977, p<0.001 (low pain), t(31)=−3.835, p=0.001 (high pain)) when exposed to both low pain and high pain stimuli. The synchronous combination led to a greater reduction in unpleasantness than VR alone when exposed to both low pain (t(31)=−2.589, p=0.015) and high pain (t(31)=−3.617, p=0.001) stimuli, and the combination of VR with conventional TENS led to a greater reduction in unpleasantness than the VR-alone intervention when exposed to high pain stimuli (t(31)=−3.289, p=0.003).

In addition, one-way repeated-measures ANOVA showed a significant main effect of 'session' for negative affect scores (table 1). Both combination interventions induced a significant reduction in negative affect compared with the control condition (VR with conventional TENS: t(31)=−2.804, p=0.009; VR with synchronous TENS: t(31)=−2.855, p=0.008) and the VR-alone condition (VR with conventional TENS: t(31)=−2.556, p=0.016; VR with synchronous TENS: t(31)=−2.045, p=0.049; figure 3C).

### Brain response changes induced by the interventions

Group-level LEP waveforms and scalp topographies of N2 and P2 waves are presented in figure 3D,E. The scalp topographies of the N2 wave showed maximal activity at the vertex and extended bilaterally towards the temporal regions, while the scalp topographies of the P2 wave were more centrally distributed. Regarding the N2 and P2 waves before the intervention, the two-way repeated-measures ANOVA revealed a significant main effect of 'stimulus intensity' (online supplemental table 1). However, no other significant effects were observed, and there were no significant preintervention differences between interventions. In addition, all interventions resulted in a significant decrease in N2 and P2 amplitudes

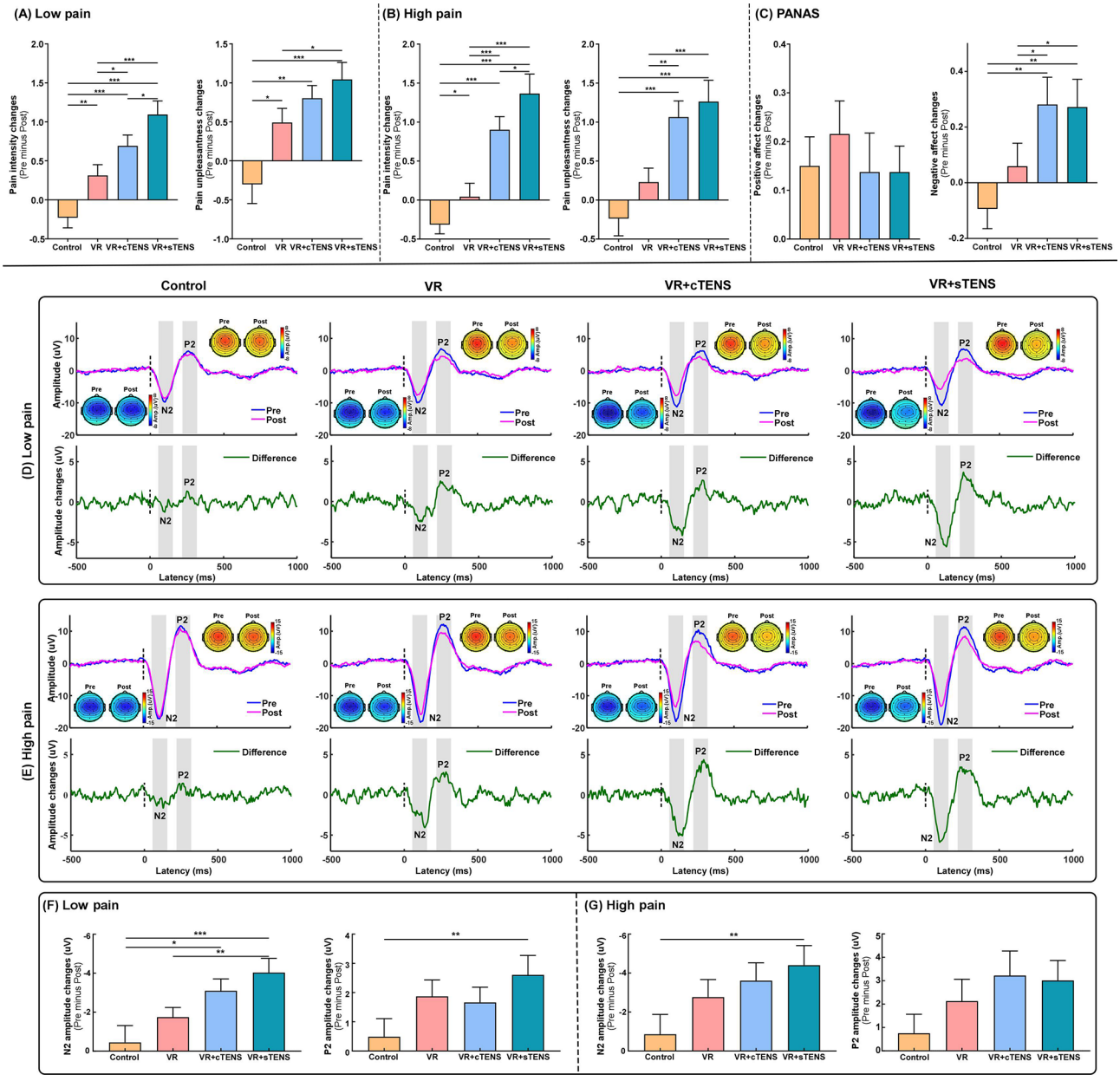


**Figure 3** Behavioural results and electroencephalographic results in the time domain. When exposed to (A) low pain and (B) high pain stimuli, both combination interventions showed a better analgesic effect than the VR-alone intervention. Notably, the combination of VR with synchronous TENS achieved a better analgesic effect than the combination of VR with conventional TENS. (C) Both combination interventions elicited a great reduction in negative affect than the VR-alone intervention. Group-level laser evoked potential waveforms and scalp topographies of the N2 and P2 waves elicited by (D) low pain and (E) high pain stimuli delivered to the left hand before (blue line) and after (purple line) interventions. (F) When exposed to low pain stimuli, the combination of VR with synchronous TENS induced a greater reduction in N2 amplitude than the VR-alone intervention. (G) When exposed to high pain stimuli, the combination of VR with synchronous TENS induced a greater reduction in N2 amplitude than the control condition. Bar graphs show the changes in behavioural variables, N2 and P2 amplitudes between preintervention and postintervention for different conditions. Error bars represent standard errors across subjects. cTENS, conventional TENS; PANAS, Positive and Negative Affect Schedule; sTENS, synchronous TENS; TENS, transcutaneous electrical nerve stimulation; VR, virtual reality. *p<0.05, **p<0.01, ***p<0.001.

when subjects were exposed to both low- and high-pain stimuli (all p<0.05).

Two-way repeated-measures ANOVA showed strong evidence for the main effect of 'session' on N2 amplitude (table 1). Post hoc paired sample t-tests (figure 3F,G) showed that the combination of VR with conventional TENS induced a greater reduction in N2 amplitude than the control condition when exposed to low pain stimuli (t(31)=2.624, p=0.013). The combination of VR with synchronous TENS resulted in greater reductions in both N2 (t(31)=4.567, p<0.001) and P2 (t(31)=−3.126, p=0.004) amplitudes when exposed to low pain stimuli, and a greater reduction in N2 amplitude (t(31)=2.899, p=0.007) when exposed to high pain stimuli than the

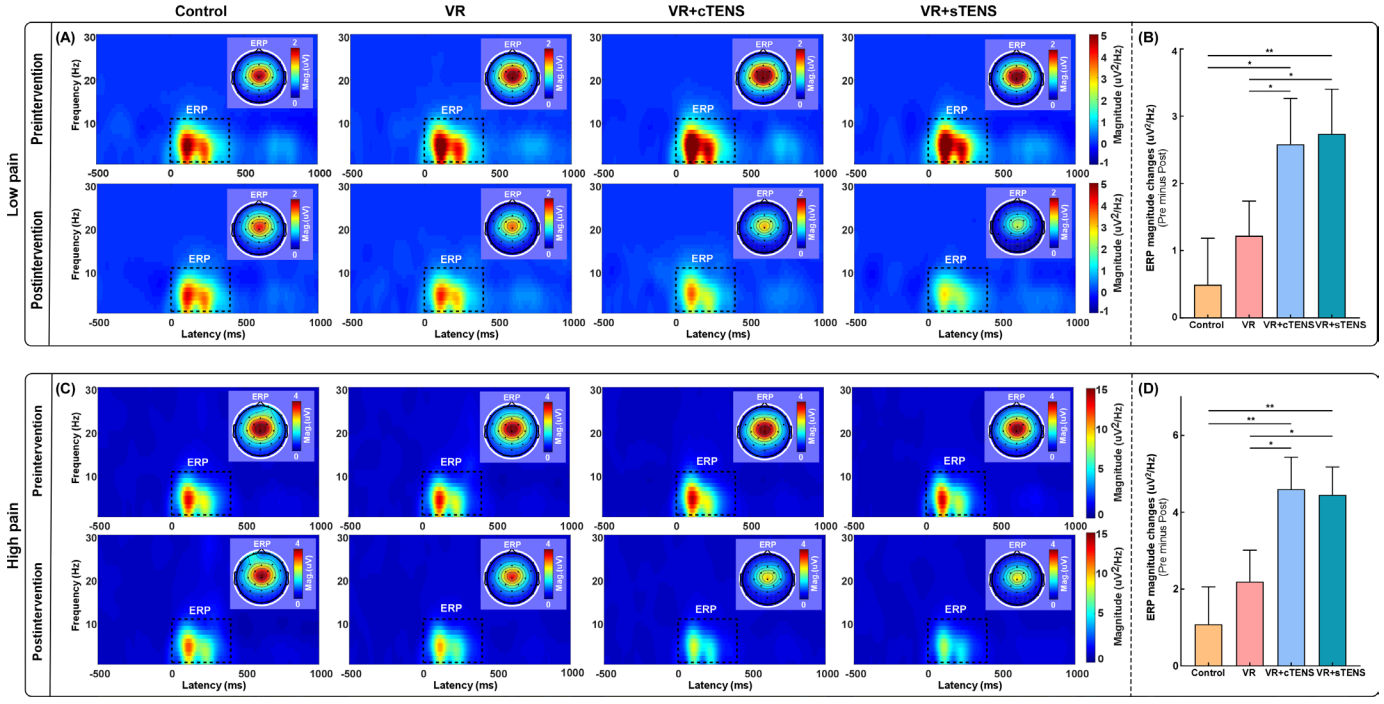


**Figure 4** Electroencephalographic results in the time-frequency domain. Group-level time-frequency distributions and scalp topographies of the ERP response elicited by (A) low pain and (C) high pain stimuli. The pain stimuli evoked a phase-locked ERP response (1–400 ms, 1–10 Hz, central electrode). When exposed to (B) low pain and (D) high pain stimuli, both combination interventions induced a greater reduction in ERP magnitude than the VR-alone intervention. Bar graphs show the changes in ERP magnitudes between preintervention and postintervention for different conditions. Error bars represent standard errors across subjects. cTENS, conventional TENS; ERP, event-related potential; sTENS, synchronous TENS; TENS, transcutaneous electrical nerve stimulation; VR, virtual reality. *p<0.05, **p≤0.01, ***p<0.001.

control condition. Furthermore, the synchronous combination led to a greater reduction in N2 amplitude than the VR-alone condition (t(31)=3.158, p=0.004) when exposed to low pain stimuli.

Figure 4A,C depict the group-level TFDs and scalp topographies of the ERP response. Laser stimuli evoked a prominent phase-locked brain response (ERP: 1–400 ms, 1–10 Hz, maximal at central midline electrodes) and a clear non-phase-locked response (α-ERD: 500–1000 ms, 8–13 Hz, maximal at the parietal-occipital electrodes). Regarding the ERP response and α-ERD magnitude before the intervention, the two-way repeated-measures ANOVA revealed significant main effects of 'stimulus intensity' (online supplemental table 1). Nonetheless, no other significant effects were observed. Subsequent post hoc paired sample t-tests detected that only α-ERD magnitude exhibited a significant preintervention difference between the combination of VR with conventional TENS condition and the control condition when exposed to low pain stimuli (t(31)=−2.698, p=0.011). No other significant preintervention differences were observed between interventions. In addition, all interventions resulted in a significant decrease in the magnitude of the ERP response when exposed to both low- and high-pain stimuli (all p<0.05). Only the synchronous combination intervention resulted in a significant decrease in the magnitude of α-ERD when exposed to both low pain (t(31)=2.254, p=0.031) and high pain stimuli (t(31)=3.599, p=0.001).

Two-way repeated measures ANOVA revealed strong evidence for the main effects of 'session' and 'stimulus intensity' on ERP magnitude (table 1). Post hoc paired sample t-tests (figure 4B,D) showed that both combination interventions led to greater reductions in the magnitude of the ERP response than the control condition (VR with conventional TENS: t(31)=−2.456, p=0.020 (low pain), t(31)=−2.894, p=0.007 (high pain); VR with synchronous TENS: t(31)=−3.397, p=0.002 (low pain), t(31)=−2.752, p=0.010 (high pain)) and the VR-alone condition (VR with conventional TENS: t(31)=−2.076, p=0.046 (low pain), t(31)=−2.234, p=0.033 (high pain); VR with synchronous TENS: t(31)=−2.400, p=0.023 (low pain), t(31)=−2.124, p=0.042 (high pain)) when exposed to both low- and high- pain stimuli. For α-ERD magnitude, two-way repeated-measures ANOVA revealed a significant main effect of 'intensity'. The interaction effect and the main effect of 'session' did not yield significance (table 1). Subsequent post hoc paired sample t-tests indicated that the synchronous combination resulted in a more pronounced decrease in α-ERD magnitude changes compared with the control condition (t(31)=−2.169, p=0.038) when exposed to low pain stimuli.

## Correlations results

The changes in the N2 amplitude induced by the synchronous combination intervention were negatively correlated with the changes in pain intensity (r=−0.433, p=0.013)

and unpleasantness (r=−0.421, p=0.016). Furthermore, the changes in ERP magnitude induced by the synchronous combination intervention were positively correlated with changes in unpleasantness (r=0.365, p=0.040). No other significant correlations were observed.

## DISCUSSION

### Main findings

In the present study, we proposed a novel approach to modulate pain by synchronously combining VR with TENS. We investigated its effectiveness in modulating experimental pain and the underlying neural mechanisms. We observed that both combination interventions had a better analgesic effect than the VR-alone intervention when exposed to low- and high-pain stimuli. Particularly, the synchronous combination of VR and TENS achieved an even better analgesic effect than the combination of VR with conventional TENS (figure 3). These effects were supported mainly by laser-evoked brain responses (figures 3 and 4). Both combination interventions induced a greater reduction in the magnitude of the ERP response than the VR-alone intervention when exposed to both low- and high-pain stimuli. The synchronous combination intervention led to a greater reduction in the N2 amplitude than the VR-alone intervention when exposed to low pain stimuli. We also found that both combination interventions significantly reduced subjects' negative affect than the VR-alone intervention (figure 3), which may contribute to their analgesic effects. Overall, these findings highlight the potential of this novel approach, the synchronous combination of VR and TENS, for improving pain management.

VR and TENS showed evident analgesic effects and have been widely applied in various painful conditions.[3 6 11 12] Preatoni *et al* demonstrated that synchronously combining visual and tactile stimuli could induce an embodiment illusion in neuropathic patients, resulting in a reduction in their neuropathic symptoms.[14] Building on this knowledge, we proposed two combination interventions and compared their analgesic effects. The first combination intervention involved applying VR and TENS simultaneously without altering any parameters of each technique. The second combination intervention focused on synchronising auditory (VR) and tactile (TENS) stimuli, aiming to create a more natural and realistic multisensory experience and enhance participants' immersion. As expected, both combination interventions resulted in greater pain intensity and negative affect reductions than the VR-alone intervention. Crucially, the synchronous combination intervention exhibited a greater reduction in pain intensity than the combination of VR with conventional TENS (figure 3). These findings provide evidence that combination interventions yield superior analgesic effects compared with the VR-alone intervention. Moreover, synchronising auditory (VR) and tactile (TENS) stimuli could improve the analgesic effect of the simple combination intervention.

The present study employed high-frequency conventional TENS and two different VR scenarios to modulate pain. Previous studies suggested that the analgesic effect of conventional TENS was commonly attributed to the gate control theory, which posited that the activation of large-diameter Aβ fibres resulted in a segmental inhibition of the transmission of nociceptive information at the spinal cord dorsal horn level.[3 22] Some researchers also detected a supraspinal descending inhibition mechanism for conventional TENS in animals and humans.[4 23] VR interventions have distinct mechanisms for pain modulation. In our study, VR scenario 1 mainly induced a strong sense of immersion that distracted subjects' attention away from painful stimuli. VR scenario 2, on the other hand, was designed primarily for mindfulness meditation with guided respiratory training to help individuals soften the experience of pain.[24] Additionally, the emotional arousal associated with the affective significance of the VR scenarios can also influence pain modulation for the VR intervention.[25 26]

Combining conventional TENS with VR interventions enables the modulation of multiple targets in pain processing and modulation pathways, such as the spinal cord and brainstem for TENS and attention, and emotion-related brain regions for VR. Therefore, this combined approach offers the potential to target and modulate various components of pain, including sensory, attentional, and emotional aspects, thus likely achieving a better analgesic effect than the VR-alone intervention.[14]

Notably, the synchronous combination intervention produced a better analgesic effect than the combination of VR with conventional TENS (figure 3A,B). This finding indicated that distinct mechanisms might be involved in the analgesic effect of the synchronous combination intervention. For example, the synchronous combination approach may provide a more immersive experience by creating a more natural and realistic sensation, leading to greater distraction or emotional regulation. In other words, increasing the immersive experience by synchronously combining VR and TENS has shown promise in attention and emotion modulation for pain management,[27 28] which may contribute to the enhanced analgesic effect of the synchronous combination intervention.

However, despite the observed superior analgesic effectiveness of VR when combined with synchronous TENS, in contrast to its combination with conventional TENS, and the identified correlations between N2 amplitude alterations induced by the synchronous intervention and changes in pain intensity, no substantial differences in neural responses were detected through EEG data between the two combined interventions, possibly due to the low signal-to-noise ratio of EEG data. Future investigations utilising EEG and functional MRI with a large sample size may yield deeper insights into the distinctive neural mechanisms underlying these two combination interventions.

## Limitations

Several limitations of the present study should be acknowledged. First, assessing the naturalness and pleasantness of the combination intervention would be necessary for future studies to provide valuable insights into the analgesic mechanism. Notably, previous studies suggested that perceiving pleasant sensations would be important to achieve a better analgesic effect and increase patients' motivation and treatment compliance.[14] Second, while the combination intervention showed superior analgesic effects compared with the VR-alone intervention, it would be valuable to explore whether the combination intervention could achieve better analgesic effects than the TENS-alone intervention. Furthermore, it is important to note that electrical stimulation sensations exhibit adaptation effects. To sustain the desired perceptual outcomes achieved through TENS, considering the adjustment of current intensity during the transition between the two VR scenarios in future studies holds promise for optimising the analgesic benefits of combination interventions. Third, as two different VR scenarios were utilised in the present study, it remains unknown which scenario, when combined with TENS, could yield the optimal analgesic effect. Fourth, TENS can lead to muscle contractions and, under certain conditions, induce pain relief. Since electromyography furnishes insights into the electrical activity generated by muscles during both contraction and relaxation, shedding light on the functionalities of both nerves and muscles, the simultaneous collection of electromyography and EEG data could provide more insights into the neural mechanisms underlying the intervention with TENS. Finally, it is important to note that the analgesic effect of the combination intervention was only assessed in healthy subjects experiencing experimental pain. Recent research has indicated that combining visual (VR) and tactile (TENS) stimuli synchronously can increase the naturalness and pleasantness of non-invasive electrical nerve stimulation,[14] leading to a reduction in pain perception among neuropathic patients.[29] Although the analgesic effects of both VR and TENS have been extensively demonstrated in various acute and chronic pain conditions,[15 30] the effectiveness of the combination intervention proposed by the present study in relieving acute or chronic pain conditions requires further investigation.

## Implications

In conclusion, the present study proposed a novel pain modulation strategy by combining VR with TENS synchronously and demonstrated its effectiveness in modulating experimental pain. The results contribute to novel insights into the development of effective pain treatments, which may help provide a foundation for developing personalised and comprehensive therapeutic interventions tailored to specific pain conditions.

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