

The analgesic effects and neural oscillatory mechanisms of virtual reality scenes based on distraction and mindfulness strategies in human volunteers

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Abstract

Background: Virtual reality (VR) has been widely used as a non-pharmacological adjunct to pain management. However, there is no consensus on what type of VR content is the best for pain alleviation and by what means VR modulates pain perception. We used three experiments to explore the analgesic effect of VR scenes in healthy adult volunteers.

Methods: We first compared the effect of immersive VR on pain perception with active (i.e. non-immersive, two-dimensional video) and passive (i.e. no VR or audiovisual input) controls at both subjective perceptual (Experiment 1) and electrophysiological (electroencephalography) levels (Experiment 2), and then explored possible analgesic mechanisms responsible for VR scenes conveying different strategies (e.g. exploration or mindfulness; Experiment 3).

Results: The multisensory experience of the VR environment lowered pain intensity and unpleasantness induced by contact heat stimuli when compared with two control conditions ($P=0.001$ and $P<0.001$, respectively). The reduced pain intensity rating correlated with decreased P2 amplitude ($r=0.433$, $P<0.001$) and increased pre-stimulus spontaneous gamma oscillations ($r=-0.339$, $P=0.004$) by 32-channel electroencephalography. A VR exploration scene induced a strong sense of immersion that was associated with increased pre-stimulus gamma oscillations ($r=0.529$, $P<0.001$), whereas a VR mindfulness meditation scene had a minor effect on immersive feelings but induced strong pre-stimulus alpha oscillations ($r=-0.550$, $P<0.001$), which led to a comparable analgesic effect.

Conclusions: Distinct neural mechanisms are responsible for VR-induced analgesia, deepening our understanding of the analgesic benefits of VR and its neural electrophysiological correlates. These findings support further development of digital healthcare.

Keywords: analgesia; digital healthcare; electroencephalography; mindfulness; pain; virtual reality

Editor's key points

- Virtual reality (VR) can be used to modify patients' experiences of pain. Two possible mechanisms (distraction and mindfulness-based emotional regulation) have been proposed, but neurological evidence is lacking.
- Adult human volunteers were subjected to 1) immersive VR vs non-immersive video vs no audio-visual input and subjective experience of pain; 2) immersive VR vs non-immersive video vs no audio-visual input and EEG responses to pain; and 3) immersive VR with distraction vs immersive VR with mindfulness.
- Immersive VR modified the subjective experience of pain compared with control conditions. The analgesic effects produced by VR distraction and mindfulness scenes were associated with different EEG signatures suggesting different neurological mechanisms.
- These findings may facilitate development of VR interventions for patients experiencing pain.

Virtual reality (VR) was invented in the 1970s to immerse users in an active three-dimensional (3D) virtual world. In the past few decades, affordable and miniaturised all-in-one head-mounted VR devices have become widely available and have been applied to digital healthcare, from medical training to pain management.^{1–3} Two decades ago, VR was first investigated as a non-pharmacological adjunct to burn wound care,^{4,5} where patients experienced pain reduction after playing a VR game of throwing snowballs at animated characters. The application of VR in pain management was rapidly extended to other pain conditions, such as cancer pain, dental treatment, and phantom limb pain.^{6–8}

Although there is no consensus about the best VR content for pain alleviation and by what means VR modulates pain perception, several psychological mechanisms have been proposed. Distraction is considered to be a dominant mechanism, which emphasises that VR offers an effective distractor for users to divert their attention from pain.⁹ Mindfulness-based emotional regulation is another proposed mechanism, as users usually report enhanced self-awareness and self-regulation of mood in the VR environment.^{10,11} These two mechanisms stress the importance of the top-down cognitive modulation by VR on pain processing.¹² However, neurological evidence is lacking. Previous studies suggested that increased power of gamma oscillations in the occipitoparietal cortex was associated with enhanced attention to sensory inputs.^{13,14} Therefore, one would expect increased gamma power in VR scenes with high immersion. However, if a VR scene is mindfulness-based, its modulation of alpha oscillations should be evident, as alpha synchronisation has been observed across a range of meditation studies.¹⁵

To provide a detailed investigation of the analgesic effects of different VR scenes and their neural mechanisms, we conducted three experiments on adult human volunteers. First, we compared the effect on pain perception and emotion of VR and control conditions at both the subjective perceptual (Experiment 1) and electrophysiological levels using electroencephalography (Experiment 2). Then, we explored whether

the analgesic effect produced by different strategies conveyed in the VR scenes could be explained by distinct neural mechanisms (Experiment 3). Based on previous findings, we hypothesised that (1) VR has a strong analgesic effect, which is supported by perceptual (i.e. the reduction of pain intensity and unpleasantness) and electrophysiological (i.e. the reduction of brain responses evoked by noxious stimuli by electroencephalography) evidence; (2) the analgesic mechanism of VR using a distraction strategy (i.e. scene exploration) is mainly associated with its modulation on spontaneous gamma oscillations, whereas the mindfulness-based VR scene reduces pain through its impact on spontaneous alpha oscillations by electroencephalography.

Methods

Healthy adult volunteers were recruited through local advertisements. None reported any peripheral or central nervous system diseases, psychiatric disorders, chronic pain, hearing loss, or visual impairment. All subjects gave their written informed consent before each experiment and were paid for their participation. The experimental procedures were approved by the Ethics Committee at the Institute of Psychology, Chinese Academy of Sciences (approval number: H21072; issue date: November 2021).

Experiment 1: VR and subjective perception**Subjects**

Thirty-one subjects were recruited for Experiment 1 (14 females and 17 males; mean age 27 [standard deviation, (SD) 11] yr [range: 19–49 yr]). The sample size for exploring the VR effect on pain perception was determined using G*Power software (version 3.1, available at <http://www.gpower.hhu.de/en.html>). We set statistical power at 0.8 with a medium effect size of $f=0.3$ and a significance level of 0.05. The prior test for repeated measures analysis of variance (ANOVA) with within factors yielded a minimum required sample size of 20.

Noxious stimuli

As shown in Figure 1a, subjects were seated comfortably with their right forearm resting on the table in front of them. Noxious contact heat stimuli were delivered via a thermode (Medoc Ltd, Ramat Yishai, Israel) fixed on the right forearm with a circular contact area of 27 mm in diameter (572 mm²). The temperature at the thermode surface was increased using a thermofoil at a rate of 70°C s⁻¹ and decreased using a Peltier element at a rate of 40°C s⁻¹. Before the formal experiment, a target temperature that evoked a subjective pain rating of 6 on a 0–10 numerical rating scale (NRS; 0: no pain, 10: pain as bad as it could be) was determined individually using a simplified staircase method.¹⁶ In the formal experiments, the temperature of the thermode for each stimulus was increased from baseline temperature (40°C) to the predefined target temperature and immediately decreased from the target temperature to baseline. Notably, the target temperature never exceeded 54°C because of safety considerations (e.g. avoiding skin burn). The thermode was fixed to the right medial forearm using an elastic Velcro strap, and the position of the thermode was slightly changed after each block to minimise nociceptor sensitisation or habituation.

Experimental conditions

As shown in Figure 1b, three experimental conditions were included in Experiment 1: the VR condition, the 2D condition, and the passive control condition. The VR condition was implemented using a program developed by Ultimate Therapeutics, Shanghai, China. This program contained two different scenes, allowing subjects to have an immersive nature experience. In one scene (Scene 1, 7 min), subjects experienced a deep ocean view, including whales, tridacna, and other rare marine organisms, with soft nature sounds playing in the background. In the other scene (Scene 2, 8 min), subjects experienced guided respiratory training by the seashore. These two scenes were played in sequence, as a combination of scenes exploring different strategies (scene exploration vs mindfulness meditation) may have a superior analgesic effect.^{9,17,18}

In the VR condition, subjects wearing a head-mounted display (PICO Neo 3, Pico Immersive, Beijing, China) and

headphones (Beats Solo 3, Beats Electronics LLC, Culver City, USA) were able to look around in a 360° virtual environment. In the 2D condition, which was the non-immersive version of the VR condition, subjects were presented with the same scenes through a 24-inch PC monitor (HKC, HKC Corporation Limited, Shenzhen, China) and headphones. This condition served as an active control, which allowed for direct comparison between scenes presented in immersive and non-immersive ways. In the passive control condition, no external audiovisual stimuli were provided. Subjects were asked to sit quietly in a chair and stay still for 15 min. This condition allowed us to determine the influence of audiovisual *per se* on pain modulation.

Procedures

As shown in Figure 1c, a within-subjects design was used in Experiment 1. After determining the target temperature, subjects underwent three blocked conditions (i.e. Control, 2D,

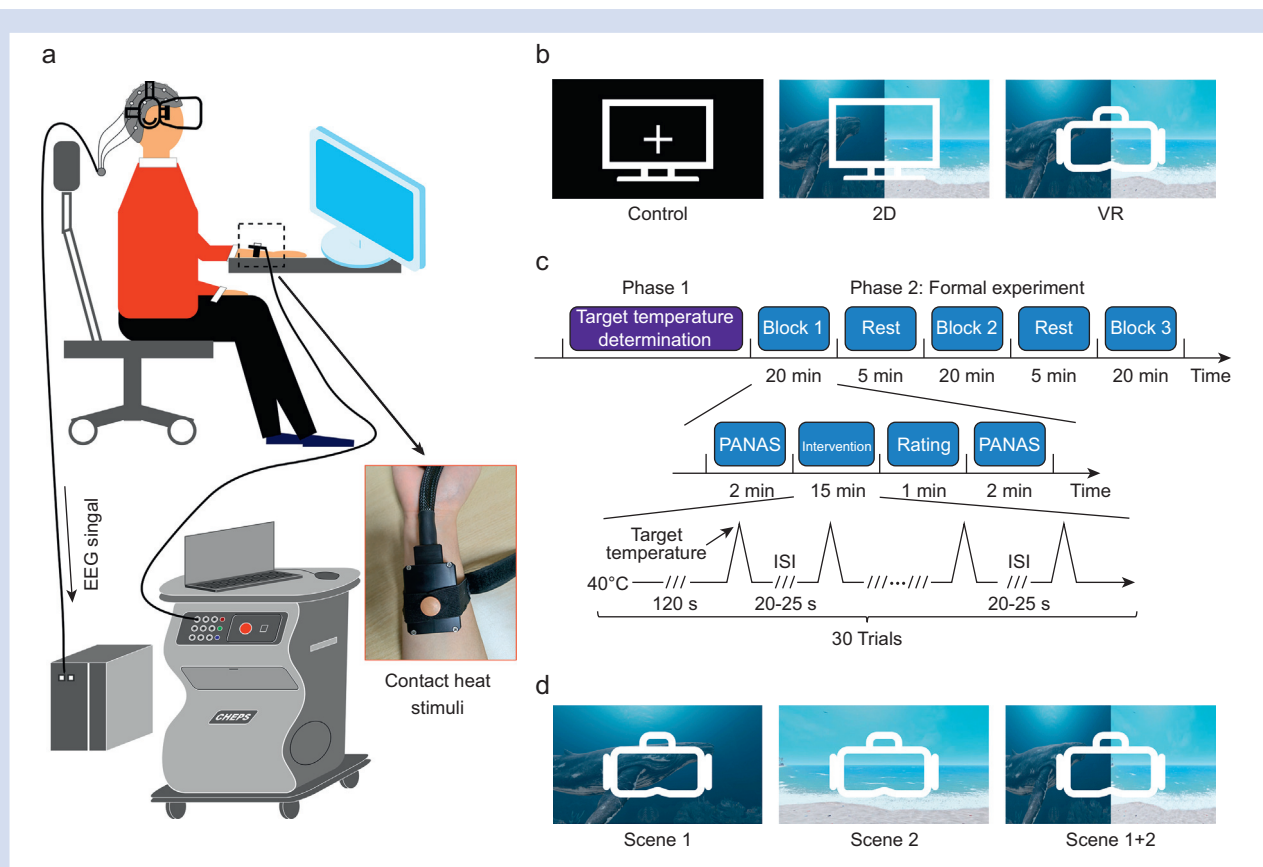


Fig 1. Outline of the experimental design. (a) Experimental setup schematic. A subject sat comfortably in a chair wearing a virtual reality (VR) device and headphones, and the contact heat thermode was fixed to the right forearm placed on the table. Simultaneous acquisition of 32-channel EEG during the whole process for Experiments 2 and 3. (b) Experimental conditions in Experiments 1 and 2. In the passive control condition, subjects were asked to look at the cross on the centre of the PC screen; in the two-dimensional (2D) condition, subjects were presented with the same video as in the VR condition via the PC monitor; in the VR condition, subjects experienced the VR program. (c) The experimental procedures of the three experiments. The target temperature was determined individually, and then three counterbalanced blocks with different conditions were administered one after another. In each block, subjects were presented with 30 stimuli during the intervention session, and they were asked to rate overall pain intensity and unpleasantness at the end of each block. Subjects were asked to complete the Positive and Negative Affect Scale (PANAS) both before and after the intervention in each block. (d) Experimental conditions in Experiment 3. Subjects experienced different scenes through VR. 2D, two-dimensional; ISI, interstimulus interval; PANAS, Positive and Negative Affect Scale; VR, virtual reality.

and VR). Each block lasted for 20 min and started with a measurement of current mood using the Positive and Negative Affect Scale (PANAS). The PANAS includes 20 items measuring both positive and negative affect in the moment (10 items for each, rated from 1='not at all' to 5='very strong'). Then, subjects underwent an intervention session, where no noxious stimuli were delivered in the first 2 min, and 30 contact heat stimuli were delivered in the following 13 min with a random interstimulus interval between 20 and 25 s. At the end of each block, subjects were asked to verbally report their pain intensity and unpleasantness (0: not unpleasant; 10: maximally unpleasant) on an 11-point NRS. Then, mood was assessed using the PANAS. Subjects were encouraged to take a 5-min break between each block. The presentation order of the three experimental blocks was counterbalanced across subjects.

Statistical analysis

To examine the effect of VR on pain perception and emotional states, one-way repeated measures ANOVA was conducted on both pain ratings (i.e. pain intensity and unpleasantness) and emotion changes (i.e. the differences in the PANAS before and after the intervention). Post hoc paired-sample *t*-tests were conducted when the main effect was significant, and Bonferroni correction was applied to address the issue of multiple comparisons.

Experiment 2: VR and electrophysiological changes

Subjects, stimuli, and experimental conditions

An additional 30 subjects were recruited for Experiment 2. However, six subjects were excluded because of incomplete data collection and poor EEG data quality, leaving a sample of 24 subjects (nine females and 15 males; mean age 24 [SD 4] yr [range: 19–33 yr]). The minimum required sample size was 20, which was determined using the same method and parameters as in Experiment 1. The stimuli and experimental conditions were the same as in Experiment 1.

Procedures, EEG data collection, and preprocessing

Experiment 2 followed the same procedure as in Experiment 1. In addition, EEG was recorded during the whole experiment (see Fig. 1a), using 32 Ag–AgCl scalp electrodes placed according to the International 10–20 system (ANT Neuro, Hengelo, the Netherlands; bandpass: 0.01–500 Hz; sampling rate: 1000 Hz). The CPz electrode was used as the online reference, and all electrode impedances were kept lower than 10 k Ω during the experiment.

EEG data were preprocessed using EEGLAB,¹⁹ an open-source toolbox running in the MATLAB environment. Continuous EEG data were bandpass filtered between 1 and 100 Hz. For the time-domain analysis, EEG epochs were extracted using a window analysis time of 2000 ms (500 ms before and 1500 ms after stimulus onset), and the baseline was corrected using the pre-stimulus interval. For the frequency-domain analysis, EEG epochs were extracted using a window analysis time of 16 000 ms before the stimulus onset (–16 000 ms–0 ms). Trials contaminated by eye blinks and movements were corrected using an independent component analysis algorithm (*runica* in EEGLAB). After pre-processing, EEG epochs were re-referenced to the average of bilateral mastoids (M1 and M2).

Time- and frequency-domain analyses

To extract the typical contact heat evoked potentials (CHEPs), preprocessed EEG data were further bandpass filtered between 1 and 30 Hz to eliminate the high-frequency noises. Single-subject CHEP waveforms were obtained by averaging epochs for each experimental condition. Amplitudes of N2 and P2 waves, defined as the mean value within 50 ms centred at the most negative and positive deflections between 150 and 1000 ms after stimulus onset, were measured from single-subject average waveforms at Cz, respectively.²⁰ To increase the signal-to-noise ratio and eliminate the potential influence of linear drift on amplitude estimation, we also calculated the N2–P2 peak-to-peak amplitude for each subject. Single-subject average CHEP waveforms were subsequently averaged across subjects for each experimental condition to obtain group-level CHEP waveforms. Group-level scalp topographies at the peak of N2 and P2 waves were computed by spline interpolation. In addition to the above time-domain analysis, time-frequency analysis^{20–22} was also performed to comprehensively explore the effect of VR on pain reduction neurologically (see Supplementary Materials for details). A frequency-domain analysis was also conducted to investigate the effect of VR on spontaneous brain oscillations. Preprocessed EEG data before the stimulus onset (i.e. extending from –16,000 ms–0 ms) were transformed to the frequency domain using a discrete Fourier transform,²¹ yielding an EEG spectrum ranging from 1 to 100 Hz for each experimental condition and each subject. Single-subject EEG spectra were subsequently averaged across subjects to obtain group-level spectra of spontaneous EEG oscillations for each experimental condition.

Statistical analysis

In addition to the statistical analysis of behavioural data, one-way repeated measures ANOVA was used to compare CHEP amplitude, time-frequency feature magnitude, and spectral power of brain oscillations among three conditions. The relationship between brain activities and subjective pain perception was assessed using the Pearson correlation on within-subject centralised data, that is, subtracting the mean from each data point to minimise the random effect between subjects.^{23,24}

To reveal how spontaneous EEG oscillations and stimulus-evoked brain responses influence pain perception under the three conditions, a mediation analysis using the Multilevel Mediation and Moderation (M3) Toolbox^{24,25} was performed. There were five paths in the mediation model, and each effect was described in detail below. The independent variable (X) in the model was the power of spontaneous EEG oscillations, and the dependent variable (Y) was the subjective pain ratings. The total effect of X on Y reflected the effects of spontaneous EEG oscillations on pain ratings and was referred to as path c. The direct effect of X on Y or the relationship from X to Y controlled for M was referred to as path c'. The other three paths of interest were the relationship from X to M (path a), the relationship from M to Y (path b), and the mediation effect (path a*b). The mediation analysis allowed us to test the mediation effects of contact heat-evoked brain responses on the relationship between spontaneous EEG oscillations on perceived pain ratings.

Experiment 3: VR effects of scene exploration and mindfulness meditation

Subjects and stimuli

An additional 27 subjects were recruited for Experiment 3. Three subjects were excluded because of incomplete data collection

and poor EEG data quality, leaving a sample of 24 subjects (13 females and 11 males; mean age 25 [SD 2] yr, [range 19–32 yr]). The minimum required sample size was 20, which was determined using the same method and parameters as in Experiment 1. The stimuli were the same as in Experiments 1 and 2.

Experimental conditions

To further assess whether different VR strategies produce analgesic effects via distinct neural mechanisms, we distinguished the two VR scenes used in Experiments 1 and 2 (immersive nature experience and guided respiratory training by the seashore) and set up three experimental blocked conditions in Experiment 3, that is, Scene 1 (scene exploration), Scene 2 (mindfulness meditation), and Scene 1+2 (scene exploration and mindfulness meditation). For each block, the scene continuously played for 15 min. The immersive level associated with each scene was evaluated subjectively after each block on an 11-point NRS (0: not immersive; 10 maximally immersive).

Procedures, EEG data collection, and analyses

As shown in Figure 1d, Experiment 3 followed the same procedure as Experiment 2, except that all three blocks were administered in a VR environment. EEG data were collected and analysed with the same criteria and procedures as in Experiment 2.

Statistical analysis

In line with the statistical analysis described in Experiment 2, one-way repeated measures ANOVA was conducted on pain ratings, emotion changes, immersion ratings, and brain activities in Experiment 3. The relationship between spontaneous

EEG oscillations and immersion ratings was assessed using the Pearson correlation on within-subject centralised data.

Results

Experiment 1: VR and subjective perception

The pain intensity and unpleasantness ratings in response to contact heat stimuli are shown in Figure 2a. A condition effect was found in both pain intensity ($F_{(2,60)}=18.146$, $P<0.001$, $\eta_p^2=0.377$) and pain unpleasantness ($F_{(2,60)}=16.300$, $P<0.001$, $\eta_p^2=0.352$). Post hoc analysis showed that subjects reported less pain and unpleasantness in the VR condition than in the control and 2D conditions (all $P<0.01$). No significant difference between the control condition and 2D condition was found.

Subjects' positive and negative emotion changes associated with interventions are shown in Figure 2b. A difference among the three conditions was found in both positive ($F_{(2,60)}=6.794$, $P=0.002$, $\eta_p^2=0.185$) and negative ($F_{(2,60)}=3.900$, $P=0.026$, $\eta_p^2=0.115$) emotion changes. Post hoc analysis suggested that the main effect was derived from the difference between the control and VR conditions (positive emotion change: $P<0.001$; negative emotion change: $P=0.06$). Specifically, positive emotion was decreased in the control condition, whereas positive emotion was maintained, and negative emotion was decreased in the VR condition. For detailed results of Experiment 1, see Supplementary Table S1.

Experiment 2: VR and electrophysiological changes

Similar results of subjective pain ratings and self-reported emotion ratings were obtained in Experiment 2 compared with Experiment 1 (see Supplementary Figs S1 and S2).

Group-level CHEP waveforms and scalp topographies of N2 and P2 waves are shown in Figure 3a. Although N2 amplitudes

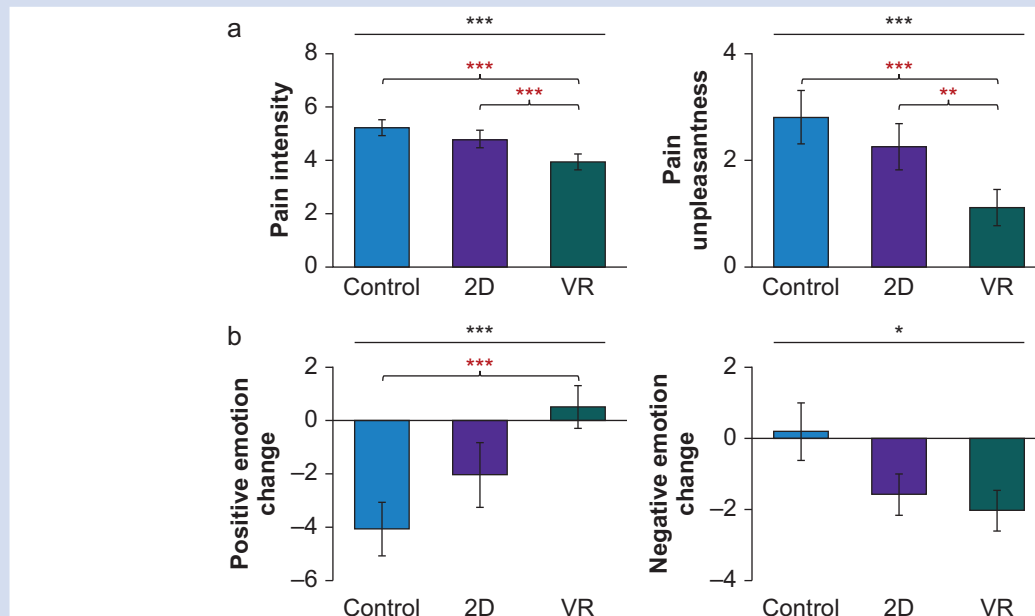


Fig 2. Subjective pain ratings and changes in self-reported emotion in three conditions (i.e. control, two-dimensional [2D], and virtual reality [VR]) of Experiment 1. (a) The comparisons of subjective ratings of pain intensity (left) and unpleasantness (right). (b) The comparisons of positive (left) and negative (right) emotion changes associated with the intervention. Error bars represent standard errors. Significant main effects and post hoc pairwise comparisons were labelled with black and red asterisks, respectively. 2D, two-dimensional; VR, virtual reality. * $P<0.05$. ** $P<0.01$. *** $P<0.001$.

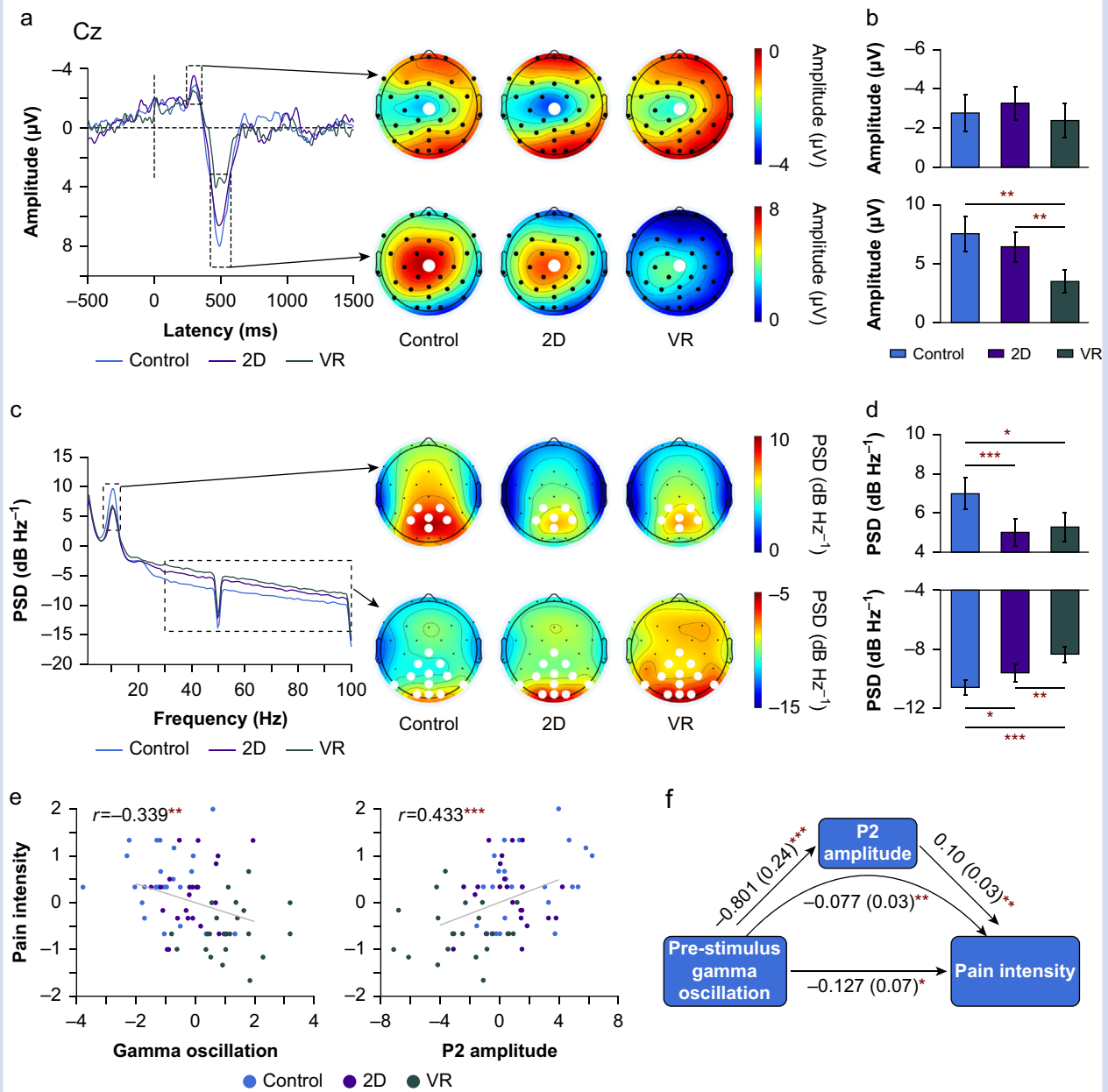


Fig 3. EEG results of Experiment 2. (a) Group-level contact heat evoked potential waveforms at Cz (referenced to bilateral mastoids) and scalp topographies of N2 and P2 waves in the three conditions (i.e. control, two dimensional [2D], and virtual reality [VR]). (b) Comparisons of N2 and P2 amplitudes of the three conditions. (c) Power spectral density (PSD) of spontaneous EEG oscillations (left) and scalp topographies of EEG spectra at alpha and gamma bands for the three conditions. (d) Comparisons of spectral powers of spontaneous alpha and gamma oscillations in the three conditions. (e) Correlations between subjective pain intensity ratings and brain activities (left: spectral powers of spontaneous gamma oscillations; right: P2 amplitudes) on within-subject centralised data. (f) The mediation path diagram for P2 amplitude of spontaneous gamma oscillation power on pain intensity. The three conditions were the same as those in Experiment 1. The mean standardised path coefficient is shown with standard error in parentheses. Error bars represent standard errors. 2D, two-dimensional; PSD, power spectral density; VR, virtual reality. * $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$.

were comparable in the three conditions ($F_{(2,46)}=0.955$, $P=0.392$), a significant condition difference was observed for P2 amplitudes ($F_{(2,46)}=14.22$, $P < 0.001$, $\eta_p^2=0.382$) and N2–P2 peak-to-peak amplitudes ($F_{(2,46)}=6.817$, $P=0.003$, $\eta_p^2=0.229$). Post hoc analyses revealed that the P2 amplitude and N2–P2 peak-to-

peak amplitude in the VR condition were significantly smaller than those in the control and 2D conditions (P2: both $P < 0.01$, see Fig. 3b; N2–P2: both $P < 0.05$, see Supplementary Fig. S3). Group-level time-frequency distributions and scalp topographies of the low-frequency event-related potential

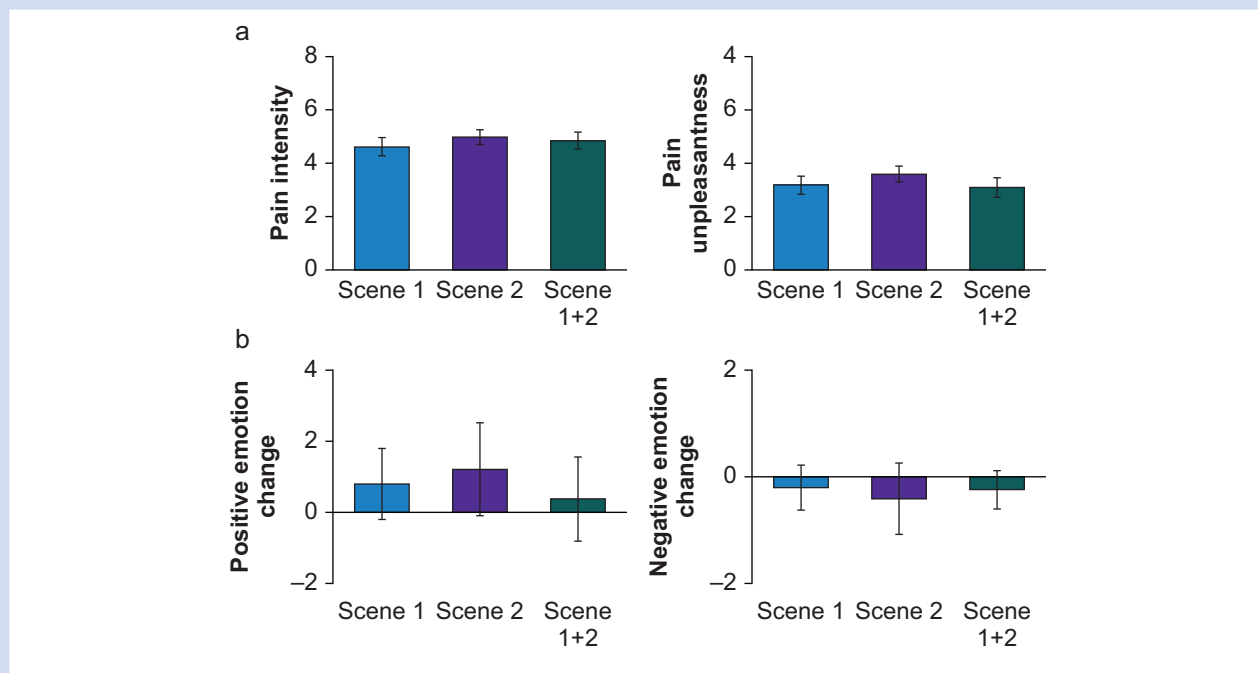


Fig 4. Subjective pain ratings and changes in self-reported emotion in three virtual reality scenes (i.e. Scene 1: scene exploration; Scene 2: mindfulness meditation; Scene 1+2: scene exploration and mindfulness meditation) of Experiment 3. (a) The comparisons of subjective ratings of pain intensity (left) and unpleasantness (right). (b) The comparisons of positive (left) and negative (right) emotion changes associated with the intervention. Error bars represent standard errors.

(ERP) response are shown in [Supplementary Figures S4 and S5](#). A significant main effect of condition on ERP magnitude (400–600 ms, 1–4 Hz, maximal at central midline electrodes; $F_{(2,46)}=7.678$, $P=0.005$, $\eta_p^2=0.25$) was found, in which the ERP magnitude was significantly smaller in the VR condition than in the other two conditions (both $P<0.05$).

[Figure 3c](#) shows EEG spectra of spontaneous activities for all conditions. As shown in [Figure 3d](#), the spectral powers were significantly different in the three conditions at both alpha (8–12 Hz; $F_{(2,46)}=11.637$, $P<0.001$, $\eta_p^2=0.336$) and gamma (30–100 Hz; $F_{(2,46)}=21.609$, $P<0.001$, $\eta_p^2=0.484$) bands. Post hoc analyses showed that the spectral power of alpha oscillations was significantly smaller in the 2D and VR conditions than in the control condition (both $P<0.05$), whereas no significant difference was observed between the 2D and VR conditions. The spectral power of gamma oscillations was significantly larger in the VR condition than in the control and 2D conditions and significantly larger in the 2D condition than in the control condition (all $P<0.05$).

As shown in [Figure 3e](#), subjective pain intensity ratings were negatively correlated with the power of spontaneous gamma oscillations ($r=-0.339$, $P=0.004$) and positively correlated with amplitudes of P2 wave ($r=0.433$, $P<0.001$). That is, with the increase of pain intensity, there was a corresponding decrease of the power of gamma oscillations and an increase of the P2 amplitudes. P2 amplitudes significantly mediated the link between spontaneous gamma oscillations and pain intensity ratings (see [Fig. 3f](#)). For more detailed results of Experiment 2, please see [Supplementary Table S2](#).

Experiment 3: VR effects of scene exploration and mindfulness meditation

As shown in [Figure 4](#), no significant condition difference was found among the three VR scenes (Scene 1, Scene 2, and Scene 1+2) on subjective pain ratings or emotion changes (all $P>0.05$).

Group-level CHEP waveforms and scalp topographies of N2 and P2 waves are shown in [Figure 5a](#). No significant difference in the three VR scenes was found for either the N2 or the P2 amplitude (see [Fig. 5b](#)). The N2–P2 peak-to-peak amplitude was slightly different in the three VR scenes, as the amplitude in Scene 1+2 (scene exploration and mindfulness meditation) was slightly lower than in Scene 1 (scene exploration) and Scene 2 (mindfulness meditation). However, the difference was not statistically significant ($F_{(2,46)}=1.928$, $P=0.157$; see [Supplementary Figs S6 and S7](#)).

[Figure 5c](#) shows EEG spectra of spontaneous activities for all three VR scenes. As shown in [Figure 5d](#), the spectral powers were significantly different among the three VR scenes at both alpha (8–12 Hz; $F_{(2,46)}=13.639$, $P<0.001$, $\eta_p^2=0.37$) and gamma (30–100 Hz; $F_{(2,46)}=29.857$, $P<0.001$, $\eta_p^2=0.565$) bands. Post hoc analyses showed that the spectral power of alpha oscillations was significantly smaller in Scene 1 and Scene 1+2 than in Scene 2 (both $P<0.001$), whereas no significant difference was observed between Scene 1 and Scene 1+2. Moreover, the spectral power of gamma oscillations was significantly larger in Scene 1 and Scene 1+2 than in Scene 2 (both $P<0.001$), whereas no significant difference was observed between Scene 1 and Scene 1+2.

The immersion ratings were significantly different in the three VR scenes ($F_{(2,46)}=9.729$, $P<0.001$, $\eta_p^2=0.297$, see Fig. 5e). Post hoc analysis revealed that the immersion rating for Scene 2 was lower than for Scene 1 and Scene 1+2 (both $P<0.01$), whereas no significant difference was observed between Scene 1 and Scene 1+2. Subjective

immersion ratings were negatively correlated with spectral powers of spontaneous alpha oscillations ($r=-0.550$, $P<0.001$) but positively correlated with spectral powers of spontaneous gamma oscillations ($r=0.529$, $P<0.001$; Fig. 5f). As the subjective immersion ratings increased, there was a decrease of the power of alpha oscillations and an increase

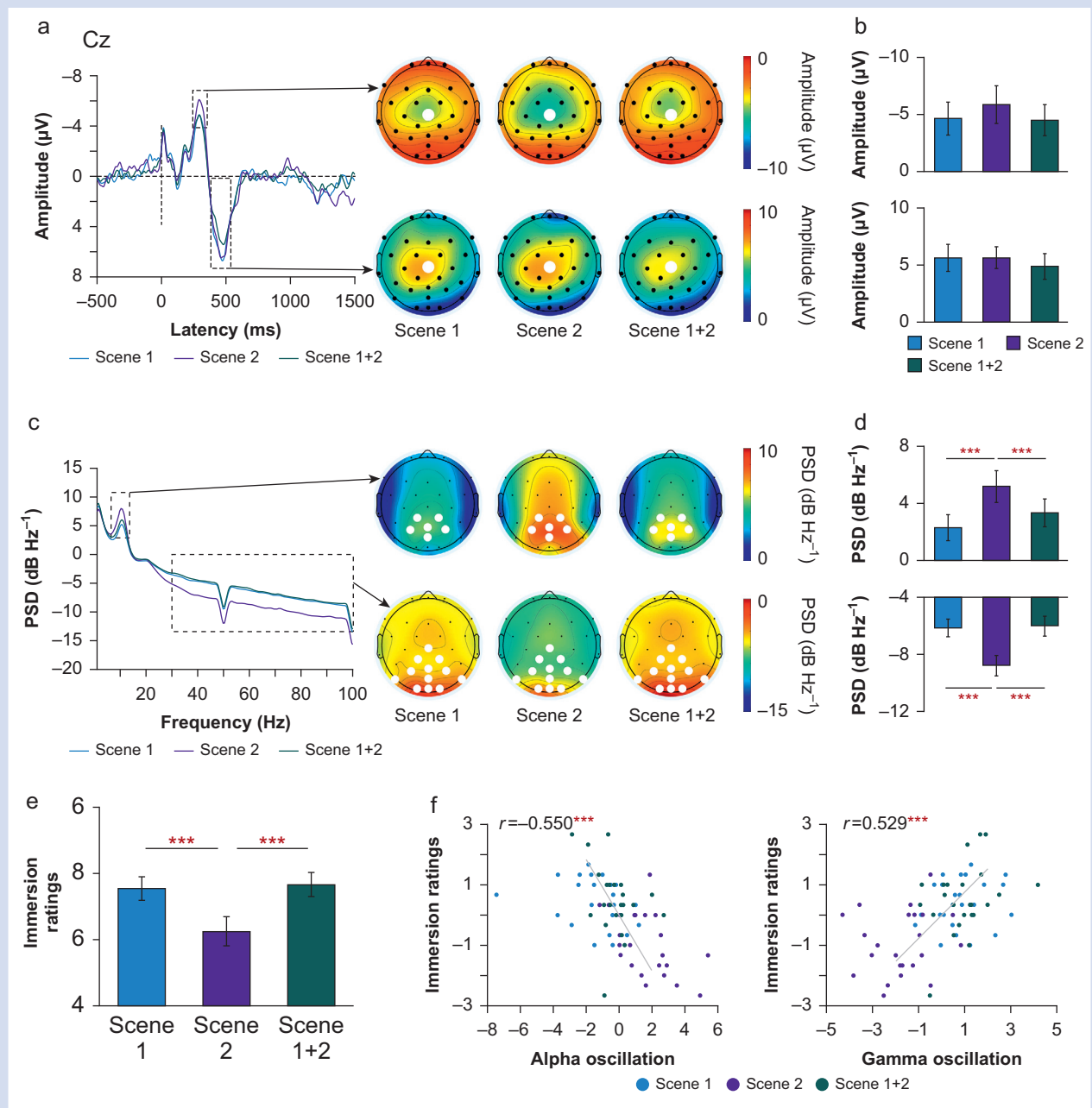


Fig 5. EEG results of Experiment 3. (a) Group-level contact heat evoked potential waveforms at Cz (referenced to bilateral mastoids) and scalp topographies of N2 and P2 waves in the three virtual reality (VR) scene conditions (i.e. Scene 1, Scene 2, and Scene 1+2). (b) Comparisons of N2 and P2 amplitudes of the three VR scenes. (c) The power spectral density of spontaneous EEG oscillations (left) and the scalp topographies of spectral powers of alpha and gamma oscillations for the three VR scenes. (d) Comparisons of spectral powers of spontaneous alpha and gamma oscillations in the three VR scenes. (e) Comparisons of immersion ratings in the three VR scenes. (f) Correlations between subjective immersion ratings and spontaneous EEG spectral powers (left: alpha oscillations; right: gamma oscillations) on within-subject centralised data. Error bars represent standard errors. PSD, power spectral density. *** $P<0.001$.

of the power of gamma oscillations. For more detailed statistical results of Experiment 3, see [Supplementary Table S3](#).

Discussion

We compared the modulatory effects of VR with its active (i.e. non-immersive, 2D video) and passive (i.e. no VR or audiovisual input) controls on subjective ratings and electrophysiological responses to contact heat pain in three complementary experiments. The multisensory experience of an immersive VR environment effectively lowered the pain intensity and unpleasantness induced by noxious stimuli and was likely to maintain positive emotion and decrease negative emotion (Experiments 1 and 2). Moreover, the lowered pain intensity rating was correlated with the decreased P2 amplitude and the increased spontaneous EEG gamma oscillation power (Experiment 2). More importantly, the analgesic effects produced by different VR scenes appear to be associated with distinct neural mechanisms (Experiment 3). Specifically, VR Scene 1 (scene exploration) and Scene 1+2 (scene exploration and mindfulness meditation) induced a strong sense of immersion that was correlated with increased power of spontaneous gamma oscillations. In contrast, Scene 2 (mindfulness meditation) induced a low sense of immersion but was correlated with increased power of spontaneous alpha oscillations, which also led to a comparable analgesic effect. These findings deepen our understanding of the analgesic benefits of VR and its neural electrophysiological correlates, which should prove helpful in pain management.

In line with previous studies, our subjects reported less pain and unpleasantness towards noxious stimuli when they were in the VR condition than in the other two conditions.^{26,27} This could be partly because the multisensory information provided in the VR condition offered an effective distraction,^{9,28} and partly because the immersive VR environment modulated mental state and mood, which further altered pain processing.^{29,30} However, it is hard to distinguish these two possibilities, as the distraction effect is often accompanied by emotional arousal associated with the affective significance of the distractor.³¹ Notably, pain ratings in the 2D condition (the active control) and control condition (the passive control) were not statistically significantly different. This is probably because the multisensory information used in our study was not effective enough in gaining attention and modulating emotion when it was presented in a non-immersive way. Nevertheless, these results highlighted the superiority of immersive VR in pain management.^{9,17,26}

The analgesic effect of VR was further confirmed by the ERP results, where the P2 amplitude (and N2–P2 peak-to-peak amplitude and ERP magnitude in the time-frequency domain) was smaller in the VR condition than in the 2D and control conditions. Additionally, there was a significantly positive correlation between the P2 amplitude and the intensity of pain perception. The P2 component evoked by noxious stimuli reflecting neural activation in bilateral operculo-insular cortex and anterior cingulate cortex is believed to be related to processing of the cognitive and affective dimensions of pain.³² Therefore, the smaller P2 amplitude in the VR condition compared with the other two conditions could reflect the top-down modulation of pain perception via

distraction and emotion modulation at the electrophysiological level.

It has been suggested that spontaneous EEG gamma oscillations are correlated with sustained attention to external stimuli³³ and immersive level.^{34,35} Our results agreed with these findings, as spontaneous gamma oscillations were the largest in the most immersive condition (i.e. the VR condition; Experiment 2), and there was a positive correlation between spontaneous gamma oscillations and self-reported immersion scores (Experiment 3). We therefore speculate that the increased gamma oscillations and immersion level in the VR condition (Experiment 2) were mainly attributable to scene exploration (i.e. Scene 1). More importantly, we found a mediation effect of P2 amplitude in the link between spontaneous gamma oscillations and perceived pain intensity, which may suggest a possible neural pathway to explain VR-induced analgesia. Specifically, subjects may experience a strong sense of involvement in the immersive VR environment for scene exploration, which induced an increase of spontaneous gamma oscillations. The increased spontaneous gamma oscillations sequentially decreased the neuronal activities in P2-related brain areas, such as bilateral operculo-insular cortex and anterior cingulate cortex,³⁶ which in turn resulted in the reduction of pain perception.^{22,37}

In contrast to the results of spontaneous gamma oscillations, the VR and 2D conditions both decreased spontaneous alpha oscillations when compared with the control condition in Experiment 2. The observed decrease of spontaneous alpha oscillations can be considered as a combining result of two different effects. One was the expected enhancement effect associated with the mindfulness meditation in Scene 2, and the other was the attenuation effect related to increased arousal induced by audiovisual inputs in the two scenes. The latter played a stronger influence on spontaneous alpha oscillations than the former, when two scenes were presented to subjects sequentially. Increased spontaneous alpha oscillations were observed, however, when the mindfulness-based scene (i.e. Scene 2) was presented alone in Experiment 3. This finding indicates an alternative neural mechanism responsible for the analgesic effect induced by mindfulness-based VR. Indeed, in addition to a strong sense of involvement, VR scenes may also provide a sense of pain control as a result of enhanced self-awareness.^{10,18} In the present study, subjects underwent mindfulness meditation with guided respiratory training in Scene 2. This approach provides a way for the users to use breath awareness and a deep body scan to help soften the experience of pain, and the increased alpha oscillation may imply that subjects had successfully entered a meditative state,¹⁵ which has also been reported to be effective for pain.^{38–40}

We acknowledge several limitations in the present study that need further investigation. Firstly, the specific contribution of distraction and emotion to VR-induced analgesia is not fully understood and deserves further consideration with strict experimental design. Secondly, we did not measure mindfulness level directly in the present study, which calls for further investigations with either behavioural or physiological measures of breathing or heart rate under VR scenes with the strategy of mindfulness meditation. Thirdly, the present study was limited to healthy subjects with experimental contact heat pain; so our findings should be generalised with caution. Future studies could include investigations on acute or chronic

pain patients to assess VR-induced analgesia in different pain conditions.

In conclusion, we show an effect of virtual reality on pain reduction and emotional regulation. Our results highlight that the analgesic effects produced by different virtual reality scenes might be associated with distinct neural mechanisms. As a low-cost and portable device, virtual reality can be easily implemented in pain management in different cultures and contexts. Understanding the merits of virtual reality-induced analgesia and its neural mechanisms could guide development of different virtual reality scenes for better pain management.

Authors' contributions

Study design: JL, LH, XL

Data collection: JL, HY, YX, BM

Primary data analysis: JL

Checking of data analysis: LH, XL

Drafting of manuscript: JL, XL

Critical revision: LH, KM, XL

Critically reviewed the content and approved the final version of the manuscript for publication: all authors

Acknowledgements

We thank Luandi Yao and Qiang Pang for their assistance in developing VR scenes that were used in this study.

Declaration of interest

The authors declare that they have no conflicts of interest.

Funding

National Natural Science Foundation of China (No. 32171077 to XL, 32071061 to LH). XL is supported by a grant from the Youth Innovation Promotion Association, CAS. Beijing Natural Science Foundation (JQ22018 to LH). Scientific Foundation of Institute of Psychology, Chinese Academy of Sciences (E2CX4015 to XL and LH).

Data availability statement

The data are available via reasonable requests to the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2023.09.001>.

References

1. Yetwin AK, Mahrer NE, Bell TS, Gold JI. Heart rate variability biofeedback therapy for children and adolescents with chronic pain: a pilot study. *J Pediatr Nurs* 2022; **66**: 151–9
2. Trost Z, France C, Anam M, Shum C. Virtual reality approaches to pain: toward a state of the science. *Pain* 2021; **162**: 325–31
3. Falah J, Khan S, Alfalah T, et al. Virtual reality medical training system for anatomy education. *Science and Information Conference* 2014: 752–8
4. Hoffman HG, Doctor JN, Patterson DR, Carrougner GJ, Furness 3rd TA. Virtual reality as an adjunctive pain control during burn wound care in adolescent patients. *Pain* 2000; **85**: 305–9
5. Hoffman HG, Patterson DR, Carrougner GJ, Sharar SR. Effectiveness of virtual reality-based pain control with multiple treatments. *Clin J Pain* 2001; **17**: 229–35
6. Chirico A, Lucidi F, De Laurentiis M, Milanese C, Napoli A, Giordano A. Virtual reality in health system: beyond entertainment. A mini-review on the efficacy of VR during cancer treatment. *J Cell Physiol* 2016; **231**: 275–87
7. Wiederhold MD, Gao K, Wiederhold BK. Clinical use of virtual reality distraction system to reduce anxiety and pain in dental procedures. *Cyberpsychol Behav Soc Netw* 2014; **17**: 359–65
8. Murray CD, Pettifer S, Howard T, et al. The treatment of phantom limb pain using immersive virtual reality: three case studies. *Disabil Rehabil* 2007; **29**: 1465–9
9. Indovina P, Barone D, Gallo L, Chirico A, De Pietro G, Giordano A. Virtual reality as a distraction intervention to relieve pain and distress during medical procedures: a comprehensive literature review. *Clin J Pain* 2018; **34**: 858–77
10. Mahrer NE, Gold JI. The use of virtual reality for pain control: a review. *Curr Pain Headache Rep* 2009; **13**: 100–9
11. Colloca L, Raghuraman N, Wang Y, et al. Virtual reality: physiological and behavioral mechanisms to increase individual pain tolerance limits. *Pain* 2020; **161**: 2010–21
12. Sharar SR, Alamdari A, Hoffer C, Hoffman HG, Jensen MP, Patterson DR. Circumplex model of affect: a measure of pleasure and arousal during virtual reality distraction analgesia. *Games Health J* 2016; **5**: 197–202
13. Akimoto Y, Kanno A, Kambara T, et al. Spatiotemporal dynamics of high-gamma activities during a 3-stimulus visual oddball task. *PLoS One* 2013; **8**, e59969
14. Ramot M, Fisch L, Harel M, et al. A widely distributed spectral signature of task-negative electrocortical responses revealed during a visuomotor task in the human cortex. *J Neurosci* 2012; **32**: 10458–69
15. Lomas T, Ivtzan I, Fu CH. A systematic review of the neurophysiology of mindfulness on EEG oscillations. *Neurosci Biobehav Rev* 2015; **57**: 401–10
16. Greenspan JD. Threshold determination protocols. In: Schmidt RF, Willis WD, editors. *Encyclopedia of pain*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2007. p. 2479–82
17. Hadjiat Y, Marchand S. Virtual reality and the mediation of acute and chronic pain in adult and pediatric populations: research developments. *Front Pain Res (Lausanne)* 2022; **3**, 840921
18. Loreto-Quijada D, Gutierrez-Maldonado J, Nieto R, et al. Differential effects of two virtual reality interventions: distraction versus pain control. *Cyberpsychol Behav Soc Netw* 2014; **17**: 353–8
19. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* 2004; **134**: 9–21
20. Hu L, Xiao P, Zhang ZG, Mouraux A, Iannetti GD. Single-trial time-frequency analysis of electrocortical signals:

- baseline correction and beyond. *Neuroimage* 2014; **84**: 876–87
21. Hu L, Zhang Z. *EEG signal processing and feature extraction*. Singapore: Springer Nature; 2019
 22. Hu L, Iannetti GD. Neural indicators of perceptual variability of pain across species. *Proc Natl Acad Sci U S A* 2019; **116**: 1782–91
 23. Vuorre M, Bolger N. Within-subject mediation analysis for experimental data in cognitive psychology and neuroscience. *Behav Res Methods* 2018; **50**: 2125–43
 24. Atlas LY, Bolger N, Lindquist MA, Wager TD. Brain mediators of predictive cue effects on perceived pain. *J Neurosci* 2010; **30**: 12964–77
 25. Wang H, Guo Y, Tu Y, et al. Neural processes responsible for the translation of sustained nociceptive inputs into subjective pain experience. *Cereb Cortex* 2023; **33**: 634–50
 26. Lier EJ, Oosterman JM, Assmann R, de Vries M, van Goor H. The effect of Virtual Reality on evoked potentials following painful electrical stimuli and subjective pain. *Sci Rep* 2020; **10**: 9067
 27. Rousseaux F, Panda R, Toussaint C, et al. Virtual reality hypnosis in the management of pain: self-reported and neurophysiological measures in healthy subjects. *Eur J Pain* 2023; **27**: 148–62
 28. Pourmand A, Davis S, Marchak A, Whiteside T, Sikka N. Virtual reality as a clinical tool for pain management. *Curr Pain Headache Rep* 2018; **22**: 53
 29. Wiech K, Lin CS, Brodersen KH, Bingel U, Ploner M, Tracey I. Anterior insula integrates information about salience into perceptual decisions about pain. *J Neurosci* 2010; **30**: 16324–31
 30. Hoffman HG, Richards TL, Van Oostrom T, et al. The analgesic effects of opioids and immersive virtual reality distraction: evidence from subjective and functional brain imaging assessments. *Anesth Analg* 2007; **105**: 1776. –83, table of contents
 31. Vuilleumier P. How brains beware: neural mechanisms of emotional attention. *Trends Cogn Sci* 2005; **9**: 585–94
 32. Mouraux A, Iannetti GD. Across-trial averaging of event-related EEG responses and beyond. *Magn Reson Imaging* 2008; **26**: 1041–54
 33. Clayton MS, Yeung N, Cohen Kadosh R. The roles of cortical oscillations in sustained attention. *Trends Cogn Sci* 2015; **19**: 188–95
 34. Škola F, Liarakapis F. Examining the effect of body ownership in immersive virtual and augmented reality environments. *Vis Comput* 2016; **32**: 761–70
 35. McMahan T, Parberry I, Parsons TD. Modality specific assessment of video game player's experience using the Emotiv. *Entertain Comput* 2015; **7**: 1–6
 36. Tu Y, Zhang Z, Tan A, et al. Alpha and gamma oscillation amplitudes synergistically predict the perception of forthcoming nociceptive stimuli. *Hum Brain Mapp* 2016; **37**: 501–14
 37. Valentini E, Hu L, Chakrabarti B, Hu Y, Aglioti SM, Iannetti GD. The primary somatosensory cortex largely contributes to the early part of the cortical response elicited by nociceptive stimuli. *Neuroimage* 2012; **59**: 1571–81
 38. Brandel MG, Lin C, Hannel D, Khazen O, Pilitsis JG, Ben-Haim S. Mindfulness meditation in the treatment of chronic pain. *Neurosurg Clin N Am* 2022; **33**: 275–9
 39. O'Connor S, Mayne A, Hood B. Virtual reality-based mindfulness for chronic pain management: a scoping review. *Pain Manag Nurs* 2022; **23**: 359–69
 40. Soares LO, Ferreira GE, Costa LOP, Nogueira LC, Meziat-Filho N, Reis FJJ. Meditation for adults with non-specific low back pain: a systematic review and meta-analysis. *Scand J Pain* 2022; **22**: 26–39

Handling Editor: Kate Leslie