

Original Article

Movement-induced hypoalgesia: behavioral characteristics and neural mechanisms

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Pain is essential for our survival because it helps to protect us from severe injuries. Nociceptive signals may be exacerbated by continued physical activities but can also be interrupted or overridden by physical movements, a process called *movement-induced hypoalgesia*. Several neural mechanisms have been proposed to account for this effect, including the reafference principle, non-nociceptive interference, and top-down descending modulation. Given that the hypoalgesic effects of these mechanisms temporally overlap during movement execution, it is unclear whether movement-induced hypoalgesia results from a single neural mechanism or from the joint action of multiple neural mechanisms. To address this question, we conducted five experiments on 129 healthy humans by assessing the hypoalgesic effect after movement execution. Combining psychophysics and electroencephalographic recordings, we quantified the relationship between the strength of voluntary movement and the hypoalgesic effect, as well as the temporal and spatial characteristics of the hypoalgesic effect. Our findings demonstrated that movement-induced hypoalgesia results from the joint action of multiple neural mechanisms. This investigation is the first to disentangle the distinct contributions of different neural mechanisms to the hypoalgesic effect of voluntary movement, which extends our understanding of sensory attenuation arising from voluntary movement and may prove instrumental in developing new strategies for pain management.

Keywords: pain; hypoalgesia; voluntary movement; sensory attenuation; electroencephalography

Introduction

Pain sensations have a basic biological function: to direct an organism's attention to injury and protect it from further injury by triggering or inhibiting movement. The relationship between pain and movement is complex. When we touch a hot saucepan, we recoil in pain. When we twist an ankle, we avoid movement of that body part. Such responses have protective functions and instantiate adaptations to evolutionary selection pressures.^{1–3} However, there are circumstances in which nociceptive signals appear to be inhibited in spite of the continued use of an injured body part. Movement-induced hypoalgesia refers to the process by which

nociceptive signals are interrupted or overridden by physical movement. The mechanisms underlying movement-induced hypoalgesia may be deployed through feedback from the physical movement itself, a phenomenon associated with sensory gating or sensory attenuation.^{4–6}

The sensory attenuation of afferent inputs (e.g., nociceptive inputs) induced by voluntary movement is conventionally held to prevent cognitive overload during movement execution and to free limited cognitive resources to attend to unpredicted, external events in the environment.⁷ The underlying neural mechanism of sensory attenuation during voluntary movement fits well with a conceptual model, suggesting that a copy of the expected

sensory results of a motor command or “an efference copy” is generated to anticipate sensory feedback from the movement (i.e., reafference⁸). When the reafference and the efference copy of the original motor command are of equal magnitude, reafferent information is eliminated from the sensory signal, and no sensory information is transmitted to the next levels of processing.⁹ Additionally, the sensory attenuation of nociceptive inputs induced by voluntary movement can also be explained by other neural mechanisms. One is associated with non-nociceptive interference, which is predicted by the gate control theory of pain. This explanation holds that voluntary movement and its somatosensory feedback should activate large-diameter A α and A β fibers, which inhibit the nociceptive volley transmitted via small-diameter A δ and C fibers innervating spatially adjacent skin areas.^{10,11} Another is the top-down supraspinal descending inhibition mechanism; for example, sensory attenuation may arise from the anticipation of afferent inputs.^{12,13}

The hypoalgesic effect of voluntary movement during both movement preparation and execution is well documented. For instance, subjective pain perception and brain responses elicited by nociceptive stimuli (e.g., laser-evoked potentials (LEPs)) were significantly attenuated by the preparation of voluntary movement¹⁴ and by moving the limb where nociceptive stimuli were applied.^{15,16} However, because the hypoalgesic effects associated with different neural mechanisms are temporally overlapping, existing studies are unable to determine whether movement-induced hypoalgesia results from a single neural mechanism or the joint action of multiple neural mechanisms. Isolating the independent and combined benefits of different hypoalgesic mechanisms remains one of the most significant challenges in this emerging field.

One strategy for disentangling the effects of multiple mechanisms is to examine the differential time courses and spatial extensions of coexistent neural mechanisms (Fig. 1). First, according to the reafference principle, the hypoalgesic effect should be confined to spatially adjacent skin areas innervated by reafferent nerves and should diminish with the termination of the motor command^{5,8} or with a short delay after repeated exposure to a systematic delay between movement and the actual somatosensory feedback,¹⁷ thus producing a spatially localized, transient, and reversible hypoalgesic effect. Second,

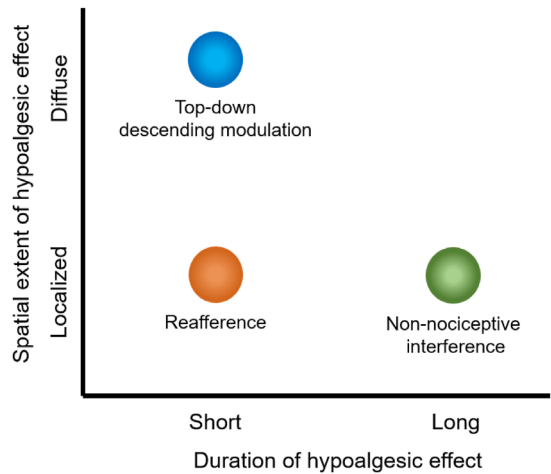


Figure 1. A simplified scheme of differential temporal and spatial hypoalgesic effects predicted by three pain inhibition neural mechanisms. According to the reafference principle (the orange dot), the hypoalgesic effect should be confined to spatially adjacent skin areas innervated by the reafferent nerves and should diminish with the termination of the motor command (short: <10 s). The non-nociceptive interference associated with the gate control theory of pain (the green dot) predicts a hypoalgesic effect that should be restricted to the innervating spatially adjacent skin areas but that persists for a few seconds (long: 10–30 s) after the termination of somatosensory feedback. The top-down descending modulation (the blue dot) possibly arising from anticipation or attention about future events or outcomes should produce a spatially diffuse and transient hypoalgesic effect (short: <10 s).

in line with the non-nociceptive interference, the hypoalgesic effect should be restricted to the innervating spatially adjacent skin areas but persist after the termination of the somatosensory feedback,^{11,18} thus producing a spatially localized but sustained hypoalgesic effect for at least a few seconds (e.g., 30 seconds). Third, the supraspinal descending inhibition mechanism arising from anticipation or attention about future events or outcomes should produce a spatially diffuse and transient hypoalgesic effect.¹⁹

To isolate the respective hypoalgesic effects of voluntary movement associated with different neural mechanisms, we conducted a series of experiments in which subjects were instructed to shake their left or right hand for a short period of time (i.e., 5 s) before receiving a nociceptive laser stimulus delivered on their left hand. The different potential neural mechanisms underlying hypoalgesia were disentangled by applying nociceptive laser

stimuli at different times and on different sites after the execution of voluntary movement. Temporal and spatial characteristics of movement-induced hypoalgesia were investigated, and we probed the relationship between voluntary movement intensity and its hypoalgesic effect by manipulating the strength of the movement. We also recorded brain electroencephalography (EEG) in order to provide objective evidence of the hypoalgesic effect after movement execution. The use of EEG provided neural evidence of (1) cortical activities in response to painful laser stimulation (i.e., LEPs), verifying our behavioral results, and (2) brain oscillations that reflect top-down descending modulation of hand movement and somatosensory feedback on pain processing.

Materials and methods

We performed five experiments on 129 healthy subjects to investigate the effects of movement-induced hypoalgesia. To determine the required sample sizes for sufficient power to detect the hypoalgesic effect, *a priori* power analysis was conducted using G*power software (version 3.1) with a significant level at 0.05 by setting statistical power at 0.9 with a large effect size ($\eta_p^2 = 0.14$). Each subject only participated in one experiment to rule out the potential influence of the experience in the experiment on the subsequent experiments. Experimental designs are detailed below, separately for each experiment. On the basis of self-report, all subjects have declared no neurological and pain-related diseases, no psychiatric disorders, nor the current use of any medication. They gave their written informed consent and were paid for their participation. All procedures were in accordance with the ethical standards of the local ethics committee.

Experiment 1

Subjects. Behavioral data were collected from 15 healthy volunteers (7 females) aged from 19 to 26 years (the mean $\pm$ SD = 22.1 $\pm$ 1.9 years).

Nociceptive stimuli. Nociceptive-specific radiant-heat stimuli were generated by an infrared neodymium yttrium aluminum perovskite (Nd:YAP) laser with a wavelength of 1.34 μ m (Electronic Engineering, Italy). At this wavelength, laser pulses directly activate nociceptive terminals in the most superficial skin layers.²⁰ Laser pulses were directed to a circular area (diameter $\approx$ 4 cm) on the dorsum

of the subject's left hand. A He-Ne laser was pointed to the area to be stimulated. The laser beam was then transmitted via an optic fiber with its diameter set at approximately 7 mm ($\approx$ 38 mm²) by focusing lenses. The laser pulse duration was 4 milliseconds. After each stimulus, the target of the laser beam was shifted by at least 1 cm in a random direction to avoid nociceptor fatigue or sensitization. Subjects were instructed to rate the intensity of pain elicited by each laser stimulus on a numerical rating scale (NRS) ranging from 0 (no sensation) to 10 (the worst pain imaginable), with 4 being the pinprick pain threshold.²¹ The energy of laser stimuli to be used in the experiment was individually determined by increasing the stimulus energy in steps of 0.25 J, until a rating of 7 out of 10 was obtained, which represented a moderate level of pain. The energies used in the present experiment were 4.0 $\pm$ 0.2 J across all subjects, ranging from 3.75 to 4.5 J.

Experimental design. Subjects were seated in a comfortable chair in a silent, temperature-controlled room. They were instructed to focus on the laser stimuli, keep their eyes open, and gaze at fixation on the screen in front of them during the experiment. As illustrated in Figure 2A, the experiment was composed of three blocks of trials, with each block administered under one of the three experimental conditions: control, S1_low, or S1_high. For the control condition, subjects were asked to rest their left hands on a table throughout the whole block. For the S1_low and S1_high conditions, subjects were asked to shake their left hands with a maximal range of 5 s at low ($\sim$ 1 Hz) and high ($\sim$ 5 Hz) frequencies, respectively. Each cycle of handshaking consisted of a rapid motion of the hand away from the body, followed by a return to the original hand position, with minimal whole arm movement. Videos showing such movements were recorded for afterward inspections. Then, subjects were instructed to rest their left hands on the table after they saw a visual cue of "STOP" appeared in the center of the screen. To ensure that subjects could successfully shake their hands at the required frequency in the S1_low and S1_high conditions, a practice session was included before the formal experiment. During the practice session, subjects were instructed to shake their left hands along with a tracking signal (beeps) presented at either 1 or 5 Hz for a total duration of 5 s in each trial (see

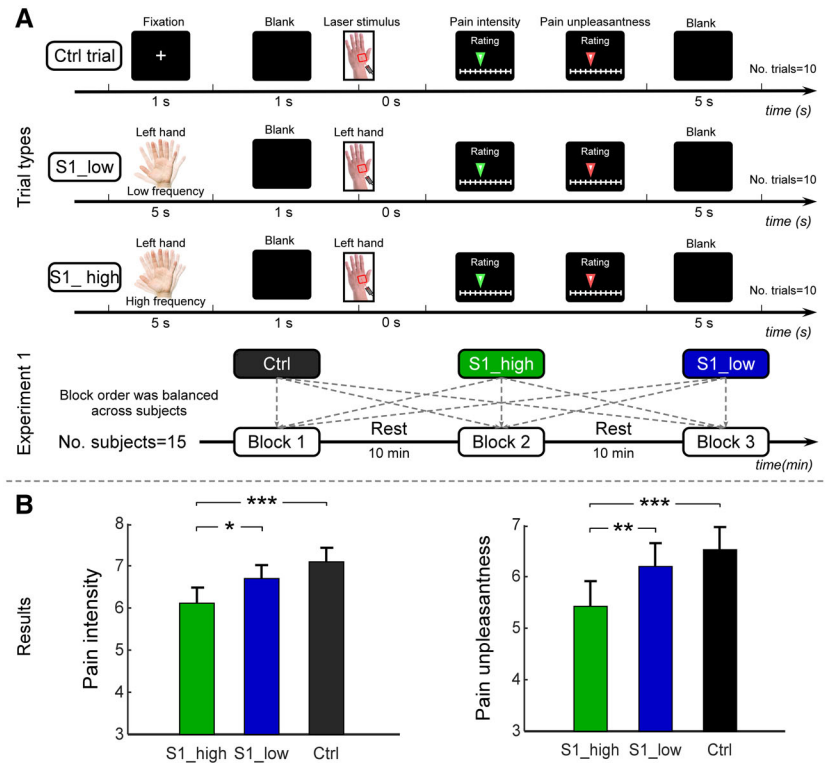


Figure 2. Experimental design and behavioral results of Experiment 1. (A) Experimental design. The experiment is composed of three blocks, each of which contains a distinct trial type (i.e., control, S1_low, or S1_high). (B) The comparison of subjective ratings of pain intensity (left) and unpleasantness (right) between different experimental conditions. * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$. Data are the mean $\pm$ SEM.

Supplementary videos for demo examples, online only). The beep was a 1000-Hz pure tone with a duration of 50 milliseconds. This phase of the practice session was then followed by a phase in which the tracking signal was removed. Subjects could stop practicing once the experimenter confirmed that they could successfully shake their hands at approximately the same frequency without the tracking signal. With the help of the recorded videos, a further qualitative comparison in terms of the frequency of handshaking between the two experimental conditions (i.e., slow versus fast) was conducted by another experimenter after the whole experiment. To rule out the confound introduced by auditory stimuli, no tracking signal was presented during the formal experiment.

For each trial, a fixation was presented once the subjects rested their left hands on the table, and a laser stimulus was delivered on the dorsum of their left hands 1 s after the termination of handshaking

(i.e., the appearance of the fixation on the screen). A visual cue was presented after the laser stimulation prompted the subjects to rate pain intensity (no sensation–the worst pain imaginable) and unpleasantness (no unpleasantness–most unpleasantness) on the same 0–10 NRS. The next trial started 5 s after the subjects responded. Each block contained 12 trials, including two practice trials, which were not used for the following statistical analysis, and 10 experimental trials. The order of three blocks was counterbalanced across subjects, and there was a 10-min break between consecutive blocks.

Experiment 2

Subjects. Behavioral data were collected from 24 healthy volunteers (14 females) aged 19–25 years (the mean $\pm$ SD = 21.9 $\pm$ 1.7 years).

Experimental design. The experiment was composed of three consecutive blocks of trials (Fig. 3A

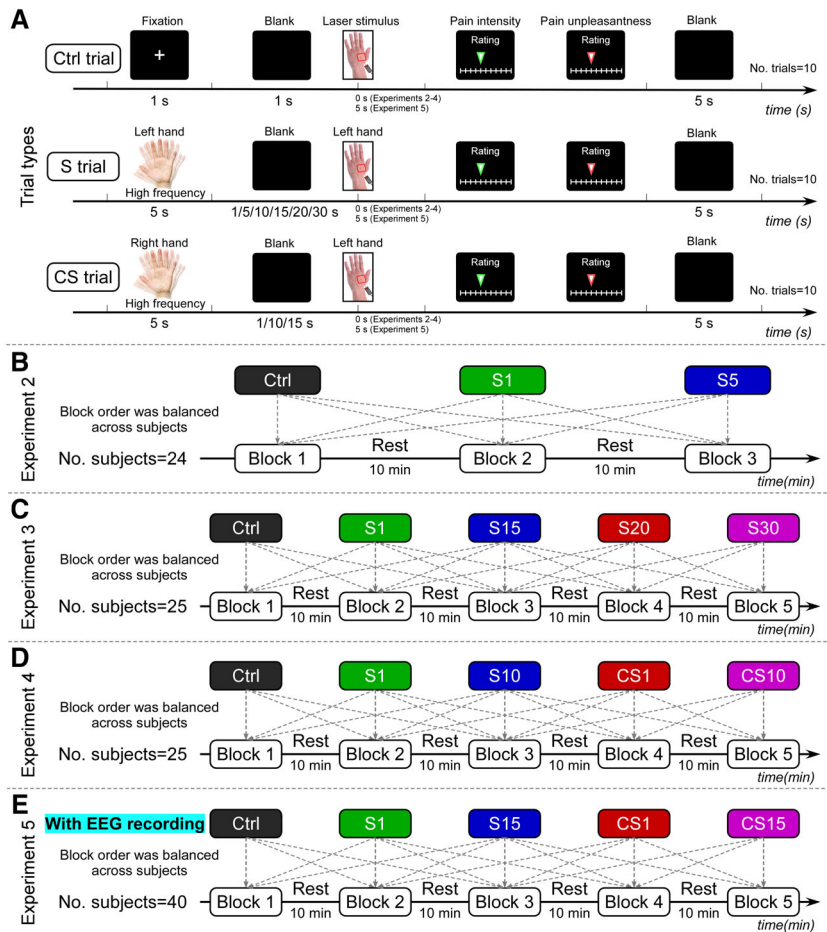


Figure 3. The experimental design of Experiments 2–5. (A) Trial types. The control trials were identical to those in Experiment 1. The S trials were composed of the S1, S5, S10, S15, S20, and S30 trials. The CS trials were composed of the CS1, CS10, and CS15 trials. (B) Experiment 2 is composed of three blocks, each of which contains a distinct trial type (i.e., control, S1, or S5). (C) Experiment 3 is composed of five blocks, each of which contains a distinct trial type (i.e., control, S1, S15, S20, or S30). (D) Experiment 4 is composed of five blocks, each of which contains a distinct trial type (i.e., control, S1, S10, CS1, or CS10). (E) Experiment 5 is composed of five blocks, each of which contains a distinct trial type (i.e., control, S1, S15, CS1, or CS15). EEG data were continuously recorded using 64 scalp electrodes in Experiment 5.

and B). The order of three blocks was counterbalanced across subjects, and there was a 10-min break between consecutive blocks. Within each block, data were collected under one of the three experimental conditions: control, S1, or S5. For the control condition, subjects were asked to rest their left hands on a table throughout the whole block. For the S1 and S5 conditions, subjects were asked to shake their left hands with a maximal range of 5 s at a high frequency before resting them on the table. A practice session with a tracking signal at 5 Hz was

included before the formal experiment to ensure that subjects could successfully shake their hands at the required frequency. For each trial, a fixation was presented once the subjects rested their left hands on the table, and a laser stimulus was delivered on the dorsum of their left hands 1 or 5 s after the termination of handshaking, respectively. The energy of laser stimuli used in this experiment was individually determined to a moderate level of pain (i.e., at a rating of 7 out of 10) as in Experiment 1. The energies of laser stimuli were 4.0 ± 0.3 J across all

subjects, ranging from 3.5 to 4.5 J in the present experiment. The rest of the experimental procedures were identical to that of Experiment 1.

Experiment 3

Subjects. Behavioral data were collected from 25 healthy volunteers (14 females) aged 19–27 years (the mean $\pm$ SD = 22.5 $\pm$ 2.3 years).

Experimental design. The experiment was composed of five blocks of trials, each administered under one of the five experimental conditions: control, S1, S15, S20, or S30 (Fig. 3A and C). The order of five blocks was counterbalanced across subjects, and there was a 10-min break between consecutive blocks. For the S1, S15, S20, and S30 conditions, subjects were asked to shake their left hands with a maximal range of 5 s at a high frequency as that in Experiment 1 before resting their left hands on the table. A laser stimulus was delivered on the dorsum of their left hands 1, 15, 20, or 30 s after the termination of handshaking, respectively. The energy of laser stimuli used in this experiment was individually determined to a moderate level of pain (i.e., at a rating of 7 out of 10) as in Experiment 1. The energies of laser stimuli were 4.2 ± 0.3 J across all subjects, ranging from 3.75 to 4.5 J in the present experiment. The rest of the experimental procedures were identical to that of Experiment 1.

Experiment 4

Subjects. Behavioral data were collected from 25 healthy volunteers (14 females) aged 19–28 years (the mean $\pm$ SD = 23.6 $\pm$ 2.4 years).

Experimental design. The experiment was composed of five blocks of trials, each administered under one of the five experimental conditions: control, S1, S10, CS1, or CS10 (Fig. 3A and D). The order of five blocks was counterbalanced across subjects, and there was a 10-min break between consecutive blocks. For the S1 and S10 conditions, subjects were asked to shake their left hands with a maximal range of 5 s at a high frequency as that in Experiment 1 before resting their left hands on the table. A laser stimulus was delivered on the dorsum of their left hands 1 or 10 s after the termination of handshaking, respectively. For the CS1 and CS10 conditions, subjects were asked to shake their right hands with a maximal range of 5 s at a high frequency as that in Experiment 1, and a laser

stimulus was delivered on the dorsum of their left hands 1 or 10 s after the termination of handshaking, respectively. The energy of laser stimuli used in this experiment was individually determined to a moderate level of pain (i.e., at a rating of 7 out of 10) as in Experiment 1. The energies of laser stimuli were 4.2 ± 0.4 J across all subjects, ranging from 3.0 to 4.5 J in the present experiment. The rest of the experimental procedures were identical to that of Experiment 1.

Experiment 5

Subjects. Behavioral and EEG data were collected from 40 healthy volunteers (23 females) aged 20–27 years (the mean $\pm$ SD = 22.7 $\pm$ 1.9 years).

Experimental design. The experiment was composed of five blocks of trials, each administered under one of the five experimental conditions: control, S1, S15, CS1, or CS15 (Fig. 3A and E). The order of five blocks was counterbalanced across subjects, and there was a 10-min break between consecutive blocks. The experimental procedures were identical to those of Experiment 4, except that instead of the S10 and CS10 conditions, the S15 and CS15 conditions were included, in which the temporal delay between the termination of handshaking and laser stimulus was 15 s in both conditions. In addition, a visual cue was presented 5 s after each laser stimulus prompted the subjects to rate pain intensity and unpleasantness on the same 0–10 NRS. The energy of laser stimuli used in this experiment was individually determined to a moderate level of pain (i.e., at a rating of 7 out of 10) as in Experiment 1. The energies of laser stimuli were 3.5 ± 0.4 J across all subjects, ranging from 2.75 to 4.5 J in the present experiment.

EEG recording. EEG data were recorded using 64 Ag-AgCl scalp electrodes placed according to the International 10–20 system (Brain Products GmbH; passband: 0.01–100 Hz; sampling rate: 1000 Hz). The nose was used as the reference, and electrode impedances were kept lower than 10 k Ω . To monitor ocular movements and eye blinks, electrooculographic signals were simultaneously recorded from two electrodes: one placed over the lower eyelid of the left eye, the other placed 1 cm lateral to the outer corner of the left orbit.

EEG preprocessing. EEG data were processed using EEGLAB,²² an open-source toolbox running

in the MATLAB (Mathworks, Carlsbad, CA) environment. Continuous EEG data were band-pass filtered between 1 and 30 hertz. EEG epochs were extracted using a window analysis time of 3000 ms (1000 ms before and 2000 ms after the onset of laser stimuli) and baseline corrected using the prestimulus interval. Trials contaminated by eye-blinks and movements were corrected using an independent component analysis algorithm.²²

Time-domain analysis. EEG epochs in each condition were averaged in the time domain, thus yielding five average waveforms time-locked to laser stimuli for each subject. The N1, N2, and P2 amplitudes were measured from the averaged LEP waveform of each subject. The N2 and P2 waves were defined as the most negative and positive deflections between 150 and 500 ms after laser stimulation at the central electrode (Cz-nose), respectively.²³ The N1 wave was defined as the most negative deflection preceding the N2 wave, which showed a contralateral central scalp distribution. A bipolar montage, that is, central electrode contralateral to the stimulated side referenced to Fz (C4-Fz), was adopted to optimally detect the N1 wave.^{24,25} Single-subject average waveforms were subsequently averaged across subjects to obtain group-level waveforms. Group-level scalp topographies of these LEP waves were computed by spline interpolation.

Prestimulus EEG oscillations. To assess the modulation of voluntary movement of spontaneous EEG oscillations, we extracted prestimulus EEG signals from a time window ranging from -1000 to 0 ms relative to the laser stimulus onset. For each subject, prestimulus EEG signals were transformed to the frequency domain using a discrete Fourier transform, yielding an EEG spectrum ranging from 1 to 30 hertz. Single-subject EEG spectra were averaged across subjects to obtain group-level prestimulus EEG spectra for each experimental condition. Since prestimulus alpha oscillations have been shown to be modulated by hand movement and somatosensory feedback,²⁶ we tested the *a priori* hypothesis that the modulation of voluntary movement on pain perception was influenced by prestimulus alpha oscillations. Specifically, the spectral amplitude of alpha oscillations was extracted at 8–12 Hz from bilateral centroparietal regions (i.e.,

C3, CP3, C4, and CP4) for the following statistical analysis.

To localize the sources of spontaneous alpha oscillations, we used a beamforming algorithm known as dynamic imaging of coherent sources,²⁷ implemented in FieldTrip.²⁸ This algorithm computes a spatial filter based on a leadfield matrix and a cross-spectral density matrix. The leadfield matrix, containing coefficients that reflect the mapping between current sources and scalp potential differences, was computed for a three-dimensional grid with a 1-cm resolution, using a realistically shaped three-shell boundary-element volume conduction model based on the Montreal Neurological Institute template brain. The cross-spectral density matrix was computed for alpha oscillations (i.e., 8–12 Hz) using a multitaper frequency transformation. The estimated power in source space yielded an estimate of the neural sources of spontaneous alpha oscillations for each experimental condition.

Statistical analysis

For all experiments, subjective ratings of pain intensity and unpleasantness were compared using one-way repeated-measures analysis of variance (ANOVA) with a within-subject factor of condition. The normality assumption was tested and met using the Shapiro–Wilk test ($P > 0.05$). Greenhouse–Geisser adjustments were used in light of violations of sphericity. When the main effect was significant ($P < 0.05$), post-hoc paired-sample *t*-tests were performed, and Bonferroni correction was applied for multiple comparisons. Partial eta-squared (η_p^2) was calculated to reflect the effect size. For Experiment 5, the same statistical analyses were conducted on the N1, N2, and P2 amplitudes, as well as the spectral amplitude of prestimulus alpha oscillations. To demonstrate the brain regions with movement-induced changes of spontaneous alpha oscillations, point-by-point one-way repeated-measures ANOVA was performed for each electrode at the scalp level and for each grid point at the source level. This procedure yielded a scalp topography and a source distribution of *F* values representing the significance level of the modulation of voluntary movement on alpha oscillations, respectively. To account for the multiple comparisons, a false discovery rate procedure was performed.

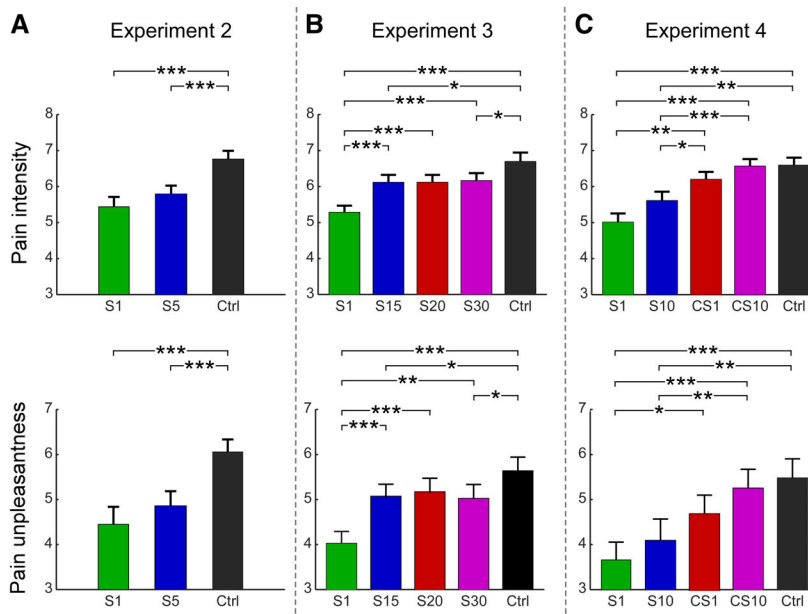


Figure 4. Behavioral results of Experiments 2–4. (A–C) The comparison of subjective ratings of pain intensity (top) and unpleasantness (bottom) between different experimental conditions in Experiments 2–4. * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$. Data are the mean $\pm$ SEM.

Results

The strength of voluntary movement modulates the hypoalgesic effect

In Experiment 1, we assessed the relationship between the strength of the voluntary movement and the hypoalgesic effect by manipulating the frequency of handshaking (Fig. 2A). Subjects were asked to rest their left hands on a table throughout the whole block (control condition) or shake their left hands for 5 s at either a low (S1_low condition) or high frequency (S1_high condition). For each trial, a nociceptive laser stimulus was delivered 1 s after the termination of hand movement, and subjects were instructed to provide self-reports of pain intensity and unpleasantness.

One-way repeated-measures ANOVA showed strong evidence for a main effect of condition for both pain intensity ($F(2,28) = 9.70$, $P = 0.001$, $\eta_p^2 = 0.41$) and unpleasantness ($F(2,28) = 11.89$, $P < 0.001$, $\eta_p^2 = 0.46$) (Fig. 2B; Table S1, online only). Post-hoc paired-sample t -tests showed that pain intensity and unpleasantness in the S1_high condition were significantly lower than those in the S1_low (intensity: $P = 0.033$; and unpleasant-

ness: $P = 0.005$) and control (intensity: $P = 0.004$; and unpleasantness: $P = 0.001$) conditions. These results suggest that the more vigorous the movements are (i.e., a higher frequency of handshaking), the stronger the hypoalgesic effect of voluntary movement is.

The temporal characteristics of the hypoalgesic effect of voluntary movement

Both Experiments 2 and 3 aimed to explore the temporal characteristics of the hypoalgesic effect of voluntary movement by manipulating the temporal delay between handshaking and nociceptive laser stimuli (short delays in Experiment 2 and long delays in Experiment 3).

In Experiment 2, subjects were asked to shake their left hands for 5 s, and a nociceptive laser stimulus was delivered 1 or 5 s after the termination of hand movement for the S1 and S5 conditions, respectively (Fig. 3A and B). One-way repeated-measures ANOVA showed strong evidence for a main effect of condition for both pain intensity ($F(2,46) = 16.80$, $P < 0.001$, $\eta_p^2 = 0.42$) and unpleasantness ($F(2,46) = 18.95$, $P < 0.001$, $\eta_p^2 = 0.45$) (Fig. 4A; Table S2, online only).

Post-hoc paired-sample *t*-tests showed that pain intensity and unpleasantness in the control condition were significantly higher than those in the S1 and S5 conditions (all $P < 0.001$). No significant difference between the S1 and S5 conditions was observed for either pain intensity or unpleasantness (both $P > 0.3$). These results indicate that the hypoalgesic effect of voluntary movement is strong when the temporal delay between handshaking and nociceptive laser stimuli is short (e.g., less than 5 s).

In Experiment 3, the temporal delay between handshaking and nociceptive laser stimuli was 1, 15, 20, and 30 s for S1, S15, S20, and S30 conditions, respectively (Fig. 3A and C). One-way repeated-measures ANOVA showed strong evidence for a main effect of condition for both pain intensity ($F(4,96) = 19.88$, $P < 0.001$, $\eta_p^2 = 0.45$) and unpleasantness ($F(4,96) = 16.78$, $P < 0.001$, $\eta_p^2 = 0.41$) (Fig. 4B; Table S3, online only). Post-hoc paired-sample *t*-tests showed that pain intensity and unpleasantness in the control condition were significantly higher than those in the S1 (both $P < 0.001$), S15 (intensity: $P = 0.019$; and unpleasantness: $P = 0.048$), and S30 (intensity: $P = 0.036$; and unpleasantness: $P = 0.011$) conditions. Pain intensity in the control condition was marginally higher than that in the S20 condition ($P = 0.051$). In addition, pain intensity and unpleasantness in the S1 condition were significantly lower than those in the S15 (both $P < 0.001$), S20 (intensity: $P < 0.001$; and unpleasantness: $P = 0.003$), and S30 (both $P < 0.001$) conditions. No significant difference was observed for either pain intensity or unpleasantness in the S15, S20, and S30 conditions (all $P > 0.9$). These results indicate that when the temporal delay between handshaking and nociceptive laser stimuli is long (i.e., from 15 to 30 s), the hypoalgesic effect of voluntary movement is evident but obviously weaker than the short temporal delay (i.e., 1 and 5 s).

Spatial characteristics of the hypoalgesic effect of voluntary movement

Both Experiments 4 and 5 aimed to investigate the spatial characteristics of the hypoalgesic effect of voluntary movement by manipulating the stimulated side (i.e., nociceptive laser stimuli were delivered on the hand ipsilateral or contralateral to the shaken one). Whereas only behavioral data

were collected in Experiment 4, we coupled psychophysics with high-density EEG recordings in Experiment 5.

In Experiment 4, a nociceptive laser stimulus was delivered on the left-hand dorsum 1 or 10 s after the termination of left-hand movement for the S1 and S10 conditions, respectively. By contrast, a nociceptive laser stimulus was delivered on the left-hand dorsum 1 or 10 s after the termination of right-hand movement for the CS1 and CS10 conditions, respectively (Fig. 3A and D). One-way repeated-measures ANOVA showed strong evidence for a main effect of condition for both pain intensity ($F(4,96) = 18.32$, $P < 0.001$, $\eta_p^2 = 0.43$) and unpleasantness ($F(4,96) = 13.00$, $P < 0.001$, $\eta_p^2 = 0.35$) (Fig. 4C; Table S4, online only). Post-hoc paired-sample *t*-tests showed that pain intensity and unpleasantness in the control condition were significantly higher than those in the S1 (both $P \leq 0.001$) and S10 (intensity: $P = 0.007$; and unpleasantness: $P = 0.004$) conditions, but not than those in the CS1 and CS10 conditions (all $P \geq 0.09$). Pain intensity and unpleasantness in the S1 condition were significantly lower than those in the CS1 (intensity: $P = 0.002$; and unpleasantness: $P = 0.041$) and CS10 (both $P < 0.001$) conditions. Pain intensity in the S10 condition was significantly lower than that in the CS1 ($P = 0.035$) and CS10 ($P < 0.001$) conditions and pain unpleasantness in the S10 condition was significantly lower than that in the CS10 condition ($P = 0.008$). These results indicate that the hypoalgesic effect of voluntary movement is greatly influenced by the stimulated side: the hypoalgesic effect is much stronger when nociceptive laser stimuli are delivered on the same hand with voluntary movement than on the other hand. Importantly, there was a clear trend that self-reports in the CS1 condition were smaller than in the control condition (unpleasantness: uncorrected $P = 0.009$ and Bonferroni-corrected $P = 0.09$), suggesting a possible spatially diffuse and transient hypoalgesic effect.

To assess whether the spatially diffuse and transient hypoalgesic effect is evident, we collected psychophysical data from an additional group of 40 subjects in Experiment 5. The experimental design was similar to that of Experiment 4, except that instead of the S10 and CS10 conditions, the S15 and CS15 conditions were included in Experiment 5, in which a nociceptive laser stimulus was delivered 15 s after the termination of voluntary

movement (Fig. 3A and E). One-way repeated-measures ANOVA showed strong evidence for a main effect of condition for both pain intensity ($F(4,156) = 48.62$, $P < 0.001$, $\eta_p^2 = 0.56$) and unpleasantness ($F(4,156) = 35.22$, $P < 0.001$, $\eta_p^2 = 0.48$) (Fig. 5A; Table S5, online only). Post-hoc paired-sample t -tests showed that pain intensity and unpleasantness in the control condition were significantly higher than those in the S1 (both $P < 0.001$), S15 (both $P < 0.001$), and CS1 (intensity: $P = 0.050$; and unpleasantness: $P = 0.025$) conditions, but not than those in the CS15 condition (both $P \geq 0.15$). Pain intensity and unpleasantness in the S1 condition were significantly lower than those in the S15, CS1, and CS15 conditions (all $P < 0.001$). Pain intensity and unpleasantness in the S15 condition were significantly lower than those in the CS1 (intensity: $P = 0.002$; and unpleasantness: $P = 0.041$) and CS15 (intensity: $P = 0.004$; and unpleasantness: $P = 0.014$) conditions. Similar to Experiment 4, these results suggest that the hypoalgesic effect of voluntary movement is greatly influenced by the stimulated side. Importantly, there is a clear hypoalgesic effect in the CS1 condition, demonstrating the existence of the spatially diffuse and transient hypoalgesic effect of voluntary movement. Moreover, different from the observation in Experiment 4, where self-reports of pain perception between the S1 and S10 conditions were insignificant, we found that self-reports between the S1 and S15 conditions were significantly different in Experiment 5 (in line with the observation in Experiment 3). This observation suggests that the hypoalgesic effect is stronger when the temporal delay was shorter than 10 s but much weaker when the temporal delay is longer than 15 seconds.

The modulation of voluntary movement on pain-related brain responses

Group-level LEPs and scalp topographies of the N1, N2, and P2 waves are shown in Figure 5B and C. In line with previous observations,^{23,29} scalp topographies of the earliest activity in LEPs (i.e., the N1 wave) showed a clear negative maximum on the central electrodes overlying the hemisphere contralateral to the stimulated side. Scalp topographies of the N2 wave were maximal at the vertex and extended bilaterally toward temporal regions, and scalp topographies of the P2 wave were more centrally distributed.

There were clear modulations of voluntary movement on the N1, N2, and P2 waves, and one-way repeated-measures ANOVA showed strong evidence for a main effect of condition for the N1 ($F(4,156) = 5.98$, $P < 0.001$, $\eta_p^2 = 0.13$), N2 ($F(4,156) = 10.17$, $P < 0.001$, $\eta_p^2 = 0.20$), and P2 ($F(4,156) = 16.34$, $P < 0.001$, $\eta_p^2 = 0.29$) amplitudes (Fig. 5D; Table S5, online only). Post-hoc paired-sample t -tests showed that the N1 amplitude in the S1 condition was significantly lower than those in all other conditions (all $P < 0.05$), and no significant condition difference was observed between the S15, CS1, CS15, and control conditions (all $P > 0.9$). Since the N1 wave represents somatosensory-specific activities maximally reflecting the incoming nociceptive inputs,³⁰ the N1 results suggest that in the S1 condition, the nociceptive information has been greatly attenuated before reaching the cerebral cortex.

The N2 amplitude in the S1 condition was significantly lower than those in the S15, CS15, and control conditions (all $P < 0.001$) and marginally lower than that in the CS1 condition ($P = 0.084$). Furthermore, the N2 amplitude in the CS1 condition was significantly lower than that in the control condition ($P = 0.015$). In other words, the N2 amplitude was reduced when the temporal delay between handshaking and nociceptive laser stimuli was short (i.e., 1 s), regardless of whether laser stimuli were delivered on the same or a different hand with voluntary movement. Considering that the N2 wave is highly associated with attentional factors,^{31,32} the modulation of voluntary movement on the N2 amplitude would reflect the top-down descending pain inhibition, thus providing additional evidence to support the existence of the spatially diffuse and transient hypoalgesic effect of voluntary movement.

The P2 amplitude in the S1 condition was significantly lower than those in all other conditions (all $P \leq 0.001$). In addition, the P2 amplitude in the S15 condition was significantly lower than that in the control condition ($P = 0.039$), and marginally lower than that in the CS15 condition (uncorrected $P = 0.0065$ and Bonferroni-corrected $P = 0.065$). The P2 amplitude in the CS1 condition was significantly lower than that in the CS15 condition ($P = 0.025$). These results suggest the coexistence of a spatially localized hypoalgesic effect that may persist for a period of time (i.e., S15 condition) and

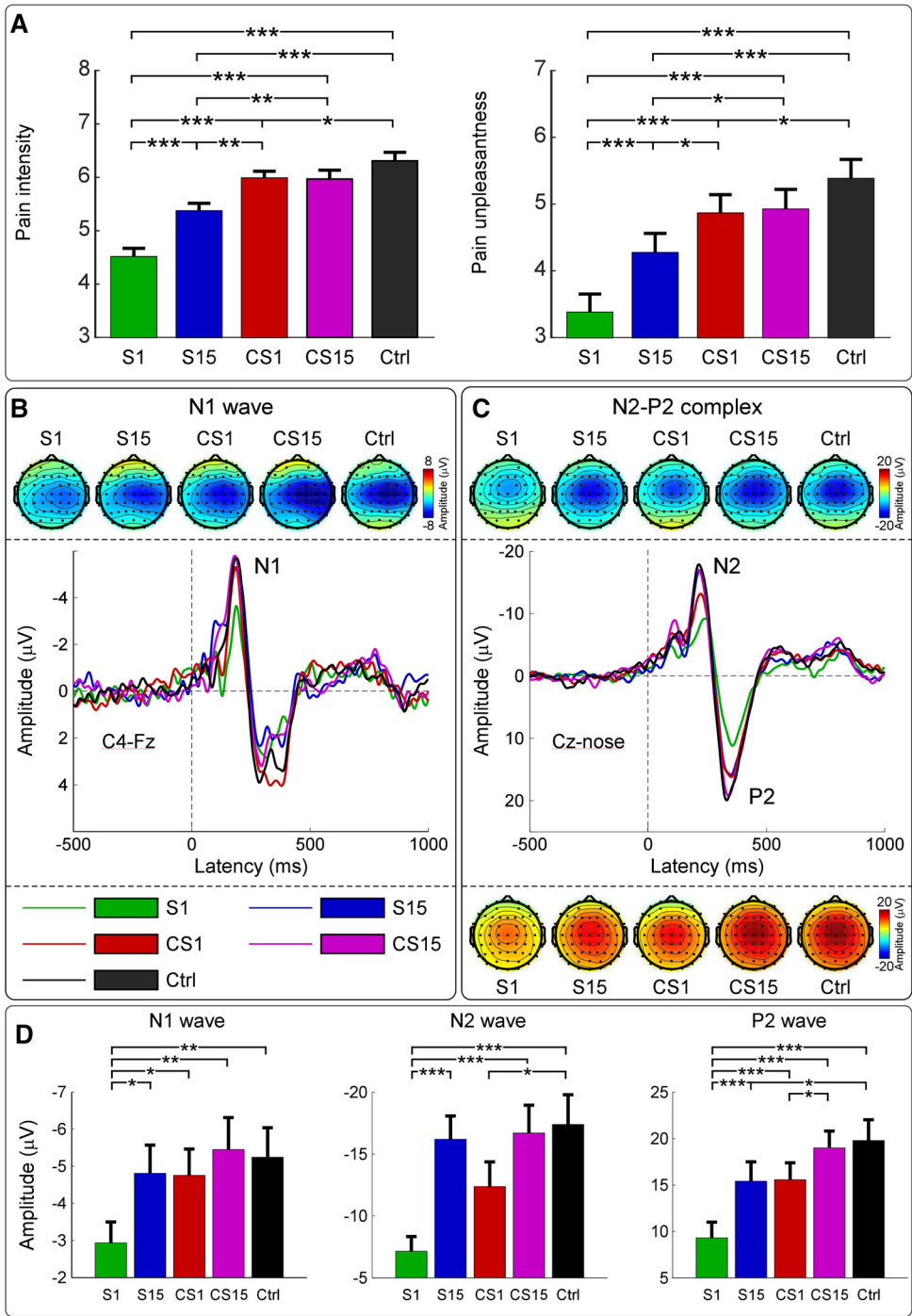


Figure 5. Behavioral and electrophysiological results of Experiment 5. (A) The comparison of subjective ratings of pain intensity (left) and unpleasantness (right) between different experimental conditions. (B and C) Group-level LEP waveforms and scalp topographies of the N1, N2, and P2 waves are displayed for each experimental condition. (D) The comparison of the N1, N2, and P2 amplitudes between different experimental conditions. * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$. Data are the mean $\pm$ SEM.

a spatially diffuse and transient hypoalgesic effect (i.e., CS1 condition).

The modulation of voluntary movement on spontaneous EEG oscillations

Group-level spectra of spontaneous EEG oscillations, together with the statistical results, are shown in Figure 6. Clear differences of spectral amplitude among experimental conditions were observed at alpha frequencies (8–12 Hz, Fig. 6A).

One-way repeated-measures ANOVA showed strong evidence for the main effect of condition for the spectral amplitude of alpha oscillations ($F(4,156) = 15.15$, $P < 0.001$, $\eta_p^2 = 0.28$). Post-hoc paired-sample *t*-tests showed that the spectral amplitude of alpha oscillations in the S1 condition was significantly lower than those in the S15, CS15, and control conditions (all $P < 0.001$). In addition, the spectral amplitude of alpha oscillations in the CS1 condition was significantly lower than those in the S15 ($P = 0.006$), CS15 ($P = 0.002$), and control ($P < 0.001$) conditions (Fig. 6B). At the scalp level, the modulation of voluntary movement on alpha oscillations was maximal at bilateral central regions (Fig. 6B). At the source level, such modulation was observed at bilateral primary sensorimotor cortices (S1/M1, Fig. 6C). These results showed that voluntary movement induced a clear change in the spontaneous brain state, that is, a decrease in the spectral amplitude of alpha oscillations in bilateral S1/M1, which could play an active role in the top-down inhibitory control of the nociceptive information.^{33,34} Therefore, the modulation of voluntary movement on the functional state of bilateral S1/M1 provides an electrophysiological basis for the spatially diffuse and transient hypoalgesic effect of voluntary movement.

Discussion

In the present study, a series of experiments were conducted on 129 healthy subjects to disentangle the underlying mechanisms of movement-induced hypoalgesia. First, the frequency of handshaking was manipulated in Experiment 1, and we observed that more vigorous movements confer more significant hypoalgesic benefits (Fig. 2B). Second, the temporal delay between handshaking and nociceptive laser stimuli was manipulated in Experiments 2 and 3 to quantify the temporal characteristics of the hypoalgesic effect. When the temporal delay was

short (e.g., less than 15 s), the hypoalgesic effect of voluntary movement was strong but decreased rapidly. When the temporal delay was long (e.g., from 15 to 30 s), the hypoalgesic effect was weak but sustained (Fig. 4A and B). These observations suggest the coexistence of two different hypoalgesic effects: one is strong but transient, and the other is weak but sustained. Third, the stimulated side (nociceptive laser stimuli were delivered on the hand ipsilateral or contralateral to the shaken one) was manipulated in Experiments 4 and 5 to quantify the spatial characteristics of the hypoalgesic effect. When nociceptive laser stimuli were delivered on the same hand with voluntary movement, the hypoalgesic effect was much stronger than when they were delivered on the other hand. Additionally, if the temporal delay between handshaking and nociceptive laser stimuli was very short (i.e., 1 s), there was a weak hypoalgesic effect even when laser stimuli were delivered on the hand without voluntary movement (Figs. 4C and 5A). These observations suggest the existence of another hypoalgesic effect, which is weak but spatially diffuse, besides the two spatially localized hypoalgesic effects observed in Experiments 2 and 3. The coexistence of distinct hypoalgesic effects of voluntary movement was also supported by electrophysiological evidence in Experiment 5 (i.e., the modulation of voluntary movement on the N1, N2, and P2 amplitudes, Fig. 5D). Moreover, clear modulation of voluntary movement on spontaneous alpha oscillations was observed in Experiment 5 (Fig. 6), suggesting changes in the functional state of bilateral primary sensorimotor cortices due to voluntary movement, which could play an active role in the top-down inhibitory control of the nociceptive information.

The hypoalgesic effect associated with the reafference principle

The hypoalgesic effect of voluntary movement was strongly modulated by the frequency of handshaking. Please note that this novel observation was similar to findings in previous studies that the magnitude of exercise-induced hypoalgesia was affected by exercise intensity (see Ref. 35 for a review), although our experimental design did not follow the exercise protocols commonly used in previous work (e.g., Ref. 36). This hypoalgesic effect observed in the present study rapidly decreased within a short

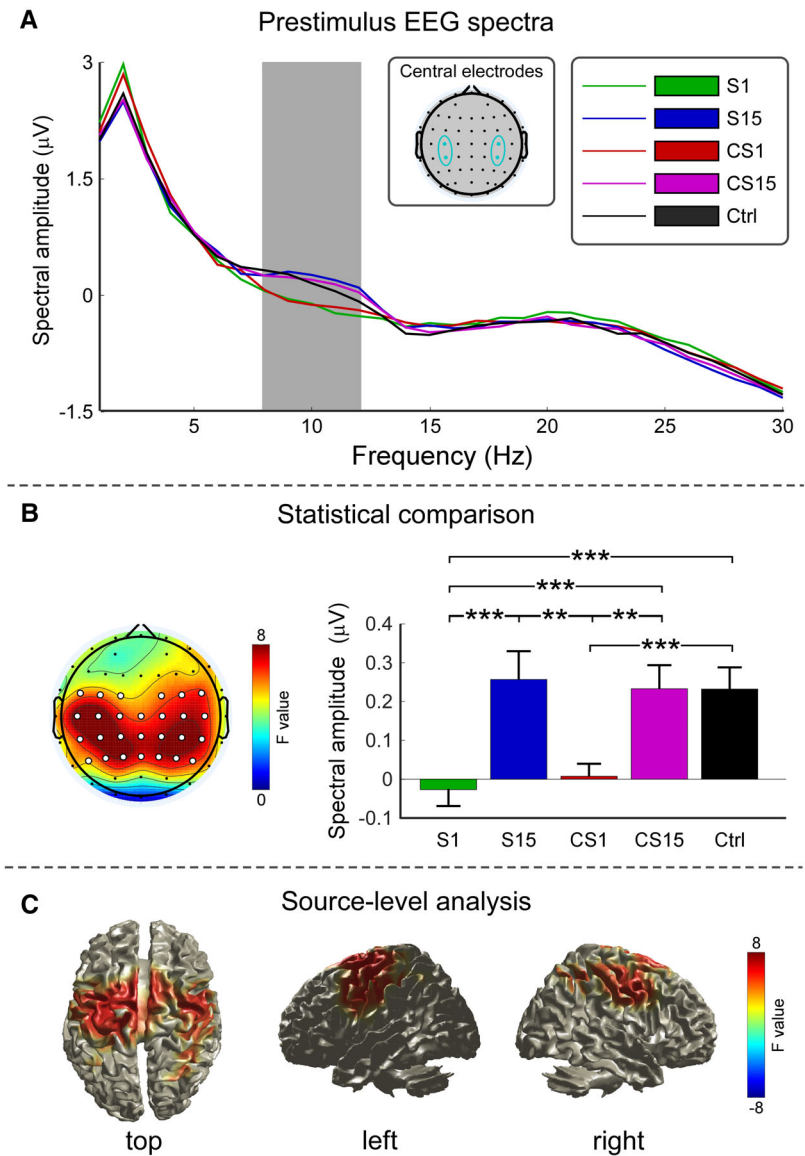


Figure 6. The effect of voluntary movement on spontaneous EEG oscillations (Experiment 5). (A) Group-level spectra of spontaneous EEG oscillations at bilateral central electrodes are displayed for each condition. A clear difference of spectral amplitude was observed at alpha frequencies (8–12 Hz, the gray area). (B) The comparison of the spectral amplitude of alpha oscillations between different conditions. $**P \leq 0.01$; $***P \leq 0.001$. Data are the mean $\pm$ SEM. The modulation of voluntary movement on alpha oscillations was maximal at bilateral central regions at the scalp level (electrodes with clear evidence for a main effect of condition are marked in white, $P < 0.05$, corrected using a false discovery rate (FDR) procedure). (C) The modulation of voluntary movement on alpha oscillations was maximal at bilateral primary sensorimotor cortices at the source level (brain regions with clear evidence for a main effect of condition are color-coded; FDR-corrected, $P < 0.05$).

time window and was largely confined to spatially adjacent skin areas of the innervated hand with voluntary movement (Fig. 4). These results revealed that voluntary movement confers a spatially local-

ized, transient, and reversible hypoalgesic effect. These hypoalgesic characteristics are associated with the reafference principle; that is, when a motor command is generated, an efference copy of this

command is utilized to predict the sensory consequence of the action.^{9,37} If the reafference due to self-generated action and an efference copy of the initial motor command are of equal magnitude, they cancel out.³⁸ In our case, it seems that an efference copy continues to function even after movement has ceased. One possibility is that motor commands generated along with repetitive motion persist for a short period of time in the absence of overt movement. Alternatively, it is also possible that the interruption of nociceptive signals driven by an efference copy is prolonged because of a refractory period in which the transmission of nociceptive signals cannot be reestablished immediately after the cessation of movement. The generation of such inhibition can be attributed to the descending motor commands, rather than the peripheral feedback from the motion itself,^{4,39} given that inhibitions occurred preferentially during active movement and were observed before the recording of electromyographic activity.⁴⁰

By recording the electrophysiological activity from the radial nerve of awake, behaving monkeys, Seki *et al.*⁴¹ found that cutaneous afferent inputs recorded from interneurons at the spinal cord were inhibited presynaptically during voluntary movement, thus effectively reducing synaptic transmission at the initial synapse. This observation suggests that the hypoalgesic effect associated with the reafference principle is spatially localized. Additionally, our brain continuously predicts the sensory consequences of its own body movements in an active fashion^{42,43} to dynamically minimize prediction errors.⁴⁴ Along with the dynamic property of the modulation of descending motor commands,^{7,45} this essential brain function accounts for why the reduction in sensory transmission caused by voluntary movement is transient and reversible.

The hypoalgesic effect associated with the non-nociceptive interference

The hypoalgesic effect of voluntary movement ipsilateral to nociceptive laser stimuli was sustained within a long time window, reaching a plateau with no further decline when the temporal delay between handshaking and nociceptive laser stimuli was relatively long (i.e., from 15 to 30 s, Fig. 4B). However, within this time window, no hypoalgesic effect was observed if nociceptive laser stimuli were delivered on the hand without voluntary

movement (i.e., CS15 condition in Experiment 5, Fig. 5). These findings suggest a spatially localized but sustained hypoalgesic effect, which cannot be explained by the reafference principle. Instead, they suggest an alternative mechanism, namely, the non-nociceptive interference, which is predicted by the gate control theory of pain. Indeed, handshaking and its somatosensory feedback should activate large-diameter A α and A β fibers, which inhibit the nociceptive volley transmitted via small-diameter A δ and C fibers innervating spatially adjacent skin areas.^{10,18}

This non-nociceptive interference is one of the neural mechanisms underlying the tactile-induced analgesia, in which the activation of tactile afferent nerve fibers inhibits the transmission of nociceptive inputs.^{46–48} Such an effect was maximal when tactile inputs were delivered homotopically to the same body territory of pain.¹⁸ This phenomenon fits well with our observation that the sustained hypoalgesic effect was only observed at the stimulated side ipsilateral to hand movement. Additionally, it has been demonstrated that tactile-induced analgesia can persist for up to hours in nonhuman animals^{49,50} and humans,¹⁸ which is consistent with our observation that the hypoalgesic effect persisted over a period of time after the execution of voluntary movement (e.g., up to 30 s, Fig. 4B).

The hypoalgesic effect associated with the top-down descending modulation

The combination of both the reafference principle and non-nociceptive interference is sufficient to explain most findings of the present study, with the exception of the weak spatially diffuse hypoalgesic effect; that is, a hypoalgesic effect was observed when there was a very short temporal delay between handshaking and nociceptive laser stimuli delivered on the hand without voluntary movement (i.e., CS1 condition in Experiments 4 and 5). Importantly, this weak spatially diffuse hypoalgesic effect was accompanied by the changes of the spectral amplitude of spontaneous alpha oscillations at bilateral central regions (Fig. 6). Specifically, voluntary movement induced a decrease in the spectral amplitude of alpha oscillations in bilateral S1/M1, and such modulation provides an electrophysiological basis for the top-down descending modulation of the nociceptive information.^{33,34}

The functional state of the cerebral cortex can be partly indexed by alpha oscillations, which would be dynamically modulated by hand movement and somatosensory feedback.²⁶ For instance, alpha oscillations at bilateral central regions have been demonstrated to be desynchronized by voluntary movement and somatosensory stimulation, which is characterized as the decreased amplitude of the oscillations.⁵¹ Such a decrease was encoded by temporal anticipation, which subserved as a plausible mechanism for biasing subsequent perception.⁵² This explanation is in line with our observation that, compared with the long temporal delays (e.g., 15 s), subjects tended to have higher temporal anticipation for the forthcoming stimuli when the temporal delay between handshaking and nociceptive laser stimuli was shorter (e.g., 1 s). Importantly, the modulation effect of anticipation on pain perception is transient and reversible,⁵³ which provided an apparent reason why the weak spatially diffuse hypoalgesic effect was only observed following a short temporal delay. Indeed, our results cannot exclude another possible explanation for the weak spatially diffuse hypoalgesic effect, which is attention modulation, for two reasons. First, drawing attention away from nociceptive laser stimuli during and after movement execution should reduce pain regardless of where the stimuli were delivered.^{31,54} Second, alpha oscillations, which are highly associated with the weak spatially diffuse hypoalgesic effect, could also be influenced by attention modulation.^{55–57}

In addition, the spatially diffuse hypoalgesic effect could be associated with changes in opioid and cannabinoid or cardiovascular systems,⁵⁸ which were commonly reported in previous studies investigating exercise-induced hypoalgesia.^{36,59,60} However, this is a remote possibility, as the present study did not focus on exercise per se. Instead, we were mainly interested in the specific connection between physical movement and pain experience. Therefore, we did not follow the protocols usually used in the exercise-based studies (e.g., varying the workloads or modes of exercise in a single bout of exercise^{36,61}). In addition, the temporal delay between movement and nociceptive stimuli in the present study (≤ 30 s) was markedly different from that in other exercise-based studies (e.g., > 30 min in Ref. 36). From this perspective, exercise-induced hypoalgesia described in the previous studies and

movement-induced hypoalgesia we observed might be different phenomena, and they could be driven by different mechanisms. In other words, different from exercise-induced hypoalgesia, sensory attenuation of nociceptive inputs related to voluntary movement (e.g., handshaking) is an immediate effect that is less likely to be attributed to changes in opioid and cannabinoid or cardiovascular systems.

Limitations

Although the present study provides solid evidence showing that movement can interrupt or override the nociceptive signals, several research questions related to this study need to be addressed in further investigations. First, all subjects in the present study were young and healthy, which would limit the generalization of our findings. In future studies, subjects from different age groups should be recruited to clarify whether movement-induced hypoalgesia could be modulated by the factor of age. Second, although the true purpose of the present study was not revealed to the subjects until they had completed all the tasks, subjects' expectation of pain relief may also contribute to the hypoalgesic effect, and we cannot rule out this possibility. Third, each of the three possible neural mechanisms underlying movement-induced hypoalgesia deserves an independent investigation to reveal its nature. For instance, on the basis of our observation that the hypoalgesic effect decreased dramatically at the first few seconds (< 10 s) and then reached a plateau (from 10 to 30 s)—a two-stage hypoalgesic effect, we speculated that it reflects a combined function of two mechanisms (i.e., refference principle and non-nociceptive interference). However, it is also possible that the two-stage hypoalgesic effect was the outcome of a single mechanism (e.g., non-nociceptive interference) showing two distinct decay patterns over time. To test this possibility, further investigations on the temporal characteristics of the non-nociceptive interference on pain processing are needed.

Conclusions

In summary, our findings suggest that voluntary movement can interrupt or override the nociceptive signals if there are urgent demands on an organism. Understanding and isolating the independent and combined benefits of different hypoalgesic mechanisms remains one of the most fundamental

challenges in pain research. The present study was the first investigation to disentangle the distinct contributions of multiple neural mechanisms underlying movement-induced hypoalgesia. Specifically, movement-induced hypoalgesia is a result of the joint action of multiple neural mechanisms, including, but not limited to, the reafference principle, non-nociceptive interference, and top-down descending modulation. These findings extend our understandings of sensory attenuation arising from voluntary movement by generalizing the phenomenon from movement preparation and execution stages to the stage after movement execution. Furthermore, our findings not only provide a theoretical basis for pain management that may shed new light on translational research, for example, using electrical stimulation to activate motor fibers or stimulating the primary motor cortex for pain reduction, but may also prove instrumental in developing new nonpharmaceutical strategies, for example, providing a guide to rapid hypoalgesia for people (especially for children) when they are experiencing limb pain after a sudden injury. The focus of such guidelines would be the identification of therapeutic movements that are effective but entirely benign to the injury itself.

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Supporting information

Additional supporting information may be found in the online version of this article.

Supplementary videos.

Table S1. Subjective ratings (mean $\pm$ SD) of pain intensity and unpleasantness for each experimental condition (S1_low, S1_high, and control) in Experiment 1.

Table S2. Subjective ratings (mean $\pm$ SD) of pain intensity and unpleasantness for each experimental condition (S1, S5, and control) in Experiment 2.

Table S3. Subjective ratings (mean $\pm$ SD) of pain intensity and unpleasantness for each experimental condition (S1, S15, S20, S30, and control) in Experiment 3.

Table S4. Subjective ratings (mean $\pm$ SD) of pain intensity and unpleasantness for each experimental condition (S1, S10, CS1, CS10, and control) in Experiment 4.

Table S5. Subjective ratings (mean $\pm$ SD) of pain intensity and unpleasantness, N1, N2, and P2 amplitudes, as well as the spectral amplitude of pres-timulus alpha oscillations (pre- α) for each experimental condition (S1, S15, CS1, CS15, and control) in Experiment 5.

Competing interests

The authors declare no competing interests.

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