

Analgesia induced by self-initiated electrotactile sensation is mediated by top-down modulations

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Abstract

It is well known that sensory perception can be attenuated when sensory stimuli are controlled by self-initiated actions. This phenomenon is explained by the consistency between forward models of anticipated action effects and actual sensory feedback. Specifically, the brain state related to the binding between motor processing and sensory perception would have inhibitory function by gating sensory information via top-down control. Since the brain state could casually influence the perception of subsequent stimuli of different sensory modalities, we hypothesize that pain evoked by nociceptive stimuli following the self-initiated tactile stimulation would be attenuated as compared to that following externally determined tactile stimulation. Here, we compared psychophysical and neurophysiological responses to identical nociceptive-specific laser stimuli in two different conditions: self-initiated tactile sensation condition (STS) and nonself-initiated tactile sensation condition (N-STs). We observed that pain intensity and unpleasantness, as well as laser-evoked brain responses, were significantly reduced in the STS condition compared to the N-STs condition. In addition, magnitudes of alpha and beta oscillations prior to laser onset were significantly larger in the STS condition than in the N-STs condition. These results confirmed that pain perception and pain-related brain responses were attenuated when the tactile stimulation was initiated by subjects' voluntary actions, and exploited neural oscillations reflecting the binding between motor processing and sensory feedback. Thus, our study elaborated the understanding of underlying neural mechanisms related to top-down modulations of the analgesic effect induced by self-initiated tactile sensation, which provided theoretical basis to improve the analgesic effect in various clinical applications.

Descriptors: Analgesia, Tactile sensation, Sensory attenuation, Top-down modulations, Alpha oscillations

The analgesic effect induced by tactile sensation is a well-known phenomenon (Igwea, Tabansi-Ochuogu, & Abaraogu, 2016; Johnson & Jones, 2017; Mancini, Beaumont, Hu, Haggard, & Iannetti, 2015); that is, pain resulting from afferent nociceptive inputs can be attenuated by simultaneous tactile input from the same area (Moran et al., 2011). This phenomenon has been attributed to the pain gating mechanism: tactile sensory inputs induced segmental inhibition of transmission of nociceptive inputs at the spinal level (Melzack & Wall, 1965). Based on this mechanism, some

nonpharmacological treatments, which were mainly achieved by delivering transcutaneous electrical stimulation, have been developed to relieve pain. These nonpharmacological treatments have been widely used in various clinical applications, and showed to be effective in relieving both acute and chronic pain (Elbadawy, 2017; Igwea et al., 2016; Johnson & Jones, 2017; Mancini et al., 2015; Moran et al., 2011; e.g., postoperative acute pain, chronic low back pain, dysmenorrhea, and labor pain).

Nevertheless, the analgesic effect induced by tactile sensation could be modulated by some top-down (subject-driven) factors, due to the existence of descending control of spinal circuitry from the brain (Heinricher, Tavares, Leith, & Lumb, 2009; Mendell, 2011) and possible cognitive modulation of pain in the brain (Miron, Duncan, & Bushnell, 1989; Rainville, Bao, & Chretien, 2005). Notably, humans can not only passively acquire external information (stimulus-driven), but also actively modulate the environment through voluntary actions (subject-driven) (Hauck, Dominick, Lorenz, Gerloff, & Engel, 2015; Valente, De Martino, Esposito, Goebel, & Formisano, 2011). Previous studies indicated that self-initiated action led to an attenuation of the perception of external sensory inputs (Bays, Flanagan, & Wolpert, 2006; Blake-More, Wolpert, & Frith, 1998; Hughes & Waszak, 2011; Mifsud,

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Beesley, Watson, & Whitford, 2016; Stenner, Bauer, Haggard, Heinze, & Dolan, 2014; Stenner, Bauer, Heinze, Haggard, & Dolan, 2015; Therrien, Richardson, & Balasubramaniam, 2011); that is, the perception of external sensory stimuli controlled by self-initiated action was reduced as compared to identical, externally generated stimuli. For example, when participants used their hands to control a robotic arm that delivered a tactile stimulus, they consistently rated the tactile stimulus as being less “tickly”, “intense”, and “pleasant,” compared to the identical tactile stimulus that was also delivered by the robotic arm but not controlled by the participants (Blakemore et al., 1998). Similarly, such self-generated sensory attenuation effect has also been reported in other sensory modalities (e.g., audition and vision; Hughes & Waszak, 2011; Mifsud et al., 2016; Stenner et al., 2015). The phenomenon that the perceived intensity of sensory stimuli is attenuated when these stimuli are initiated by the subject’s voluntary actions has been considered within the framework that links motor processing to sensory perception consequent to the action (Schutz-Bosbach & Prinz, 2007; Waszak, Cardoso-Leite, & Hughes, 2012; Wolpert, Ghahramani, & Jordan, 1995). It is often explained by the consistency between forward models of anticipated action effects and actual sensory feedback (forward models of sensory action outcome arising from motor processing; Sperry, 1950).

Based on the understanding that tactile sensation could relieve pain and that self-initiated action would lead to attenuated sensory perception (e.g., tactile sensation), we hypothesized that (1) analgesia due to self-initiated tactile sensation would be improved as compared to that induced by externally generated tactile sensation, since the brain state raised by the binding between motor processing and tactile sensation would have inhibitory function by gating nociceptive information via top-down control; and (2) the information that encoded such top-down modulation could be captured by EEG oscillations. To test these hypotheses, we compared subjects’ psychophysical and neurophysiological responses to identical nociceptive-specific laser stimuli in two different conditions: (1) the self-initiated tactile sensation condition (STS), in which participants were instructed to voluntarily press a key to initiate the presentation of tactile stimuli; and (2) the nonself-initiated tactile sensation condition (N-STs), in which the onset time of the tactile stimuli was not controlled by the subjects and randomly determined by a computer. Identical nociceptive-specific laser pulses were delivered 2–3 s after the initiation of the tactile stimulation in both conditions. In addition to the analysis of stimulus-evoked brain responses, we used time-frequency analysis to exploit neural oscillations, especially in the prestimulus interval, related to the top-down control of the analgesic effect induced by tactile sensation.

Method

Subjects

Twenty-one healthy right-handed volunteers (19 females, $M_{\text{age}} = 21.4$ years, age range: 18–24 years) participated in the experiment. All subjects gave their written informed consent and were paid for their participation. The experiment procedures were approved by the local ethics committee.

Experimental Design

Nociceptive stimulation. Nociceptive-specific radiant heat stimuli were generated by an infrared neodymium yttrium aluminum perovskite (Nd:YAP) laser with a wavelength of $1.34 \mu\text{m}$

(Electronic Engineering, Italy). At this wavelength, the laser pulses directly activate nociceptive terminals in the most superficial skin layers (Baumgartner, Cruccu, Iannetti, & Treede, 2005; Iannetti, Zambreanu, & Tracey, 2006). Laser pulses were delivered to a squared area ($4 \times 4 \text{ cm}^2$) on the left forearm. An HeNe laser pointed to the area to be stimulated. The laser beam was transmitted via an optic fiber, and its diameter was set at approximately 7 mm ($\approx 38 \text{ mm}^2$) by focusing lenses. The pulse duration was 4 ms. After each stimulus, the laser beam target was shifted by at least 1 cm in a random direction to avoid nociceptor fatigue or sensitization. Participants were asked to report the intensity of pain elicited by laser stimuli on a numerical rating scale (NRS) ranging from 0 (*no pain*) to 10 (*pain as bad as it could be*), with 4 denoting pinprick pain threshold. Before EEG data collection, 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 6 out of 10 was obtained.

Tactile stimulation. Transcutaneous electrical stimuli were generated by a multichannel electrical stimulator (type: SXC-4A, Sanxia Technique Inc., China), and delivered through a pair of Ag/AgCl surface electrodes (6 cm in distance between electrodes). Consisting of a series of rapidly succeeding constant-current, square-wave pulses (1-ms duration, 100 Hz), the electrical stimuli were applied to the left forearm for 4–6 s. The stimulus intensity ($1.00 \pm 0.18 \text{ mA}$) was twice the individual perceptual threshold, which was classically used to activate human A β fibers without the coactivation of A δ and C fibers (Garcia-Larrea, Lukasiewicz, & Mauguier, 1995; Hu et al., 2011; Sdrulla et al., 2015). These transcutaneous electrical stimuli were reported to elicit a tactile, but not painful, sensation.

Experimental procedures. A schematic illustration of the experimental design is shown in the left panel of Figure 1. The whole experiment was composed of three blocks in the same session, with 10 STS (+ laser) and 10 N-STs (+ laser) trials in each block (30 trials in total for each condition). In the STS condition, a trial started with a cue presented at the center of the screen, which prompted subjects to voluntarily press the *K* key using the right index finger to initiate the tactile stimulation, which lasted for 4–6 s. In the N-STs condition, the initiation of the tactile stimulation, which was blinded to the subjects, was fully determined by a computer. Trials in STS and N-STs conditions were delivered in a random order, and a laser pulse was delivered to the left forearm at 2–3 s after the initiation of the tactile stimulation (this information was provided to the subjects before the experiment). The presentation of all stimuli was controlled by E-Prime 2.0 software (Psychology Software Tools, Inc., Pittsburgh, PA). The time interval between the onset of tactile and laser stimuli was determined for two reasons. First, it was demonstrated that tactile stimuli delivered 1.5–1.7 s before the onset of the laser pulse could induce a clear analgesic effect and suppress both A δ fiber and C fiber laser-evoked potentials (Mancini et al., 2015). Second, a relatively long interval (i.e., 2–3 s) between the onset of tactile and laser stimuli could decrease the possibility that brain responses evoked by the two stimuli were temporally overlapped. At the end of the tactile stimulation, subjects were instructed to verbally report the intensity and unpleasantness of pain sensation evoked by the laser pulse, on the same 0–10 NRS. The interstimulus interval varied randomly between 3 and 5 s. For each subject and each condition, single-trial ratings of pain intensity and unpleasantness in all blocks were respectively averaged, and the obtained average ratings were

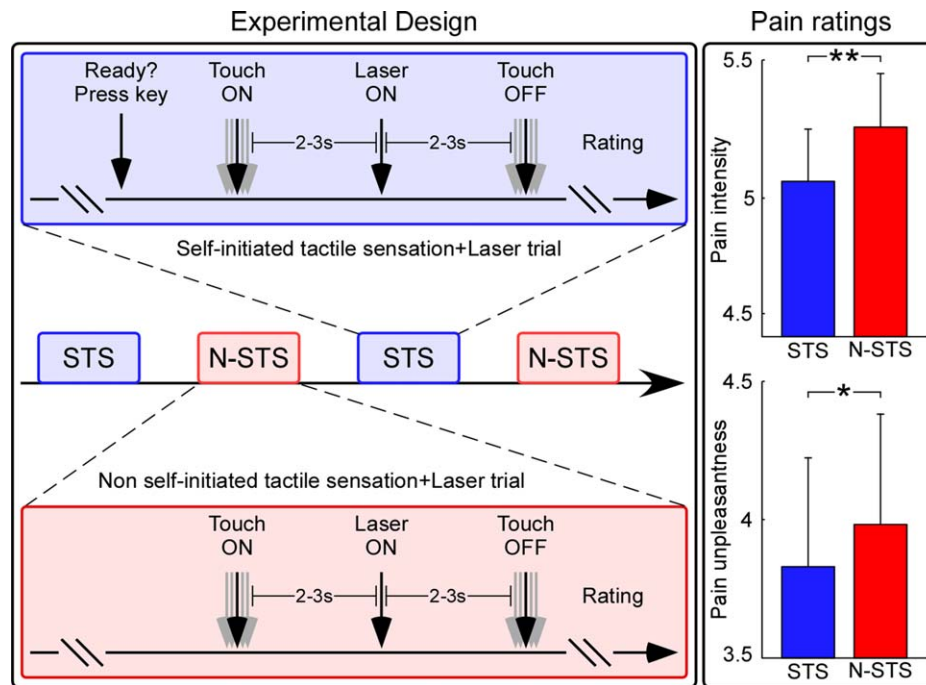


Figure 1. Experimental design and behavioral results. Each trial corresponded to one of the following two experimental conditions: self-initiated tactile sensation + laser (STS) and nonself-initiated tactile sensation + laser (N-STS). In the STS condition, subjects pressed the *K* key with the right index finger to initiate the tactile stimulation, which was composed of high-frequency electrical pulses (100 Hz; 1.00 ± 0.18 mA), and was delivered through a pair of electrodes for 4–6 s. In the N-STS condition, the initiation of the tactile stimulation (stimulus parameters were the same as those in the STS condition), which was blinded to the subjects, was determined by a computer. A laser pulse was delivered to subjects' left dorsum at 2–3 s after the initiation of the tactile stimulation. At the end of the tactile stimulation, subjects were instructed to verbally report the intensities of pain perception and pain unpleasantness evoked by the laser pulse. The average ratings of pain intensity (5.07 ± 0.17 vs. 5.30 ± 0.17 , $P_{\text{FDR}} < .01$) and pain unpleasantness (3.83 ± 0.29 vs. 3.98 ± 0.30 , $P_{\text{FDR}} = .05$) in the STS condition were significantly smaller than those in the N-STS condition.

compared between STS and N-STS conditions using a paired sample *t* test.

EEG Data Collection

Participants were seated in a comfortable chair in a silent, temperature-controlled room. They were instructed to focus on the stimuli, keep their eyes open, and gaze at a fixation point on the screen. A curtain was used to block the participants' view of their left forearm. EEG data were collected using 64 Ag-AgCl scalp electrodes placed according to the International 10-20 system (Brain Products GmbH; pass-band: 0.01–100 Hz using an infinite impulse response (IIR) filter with a cutoff slope of 12 dB/octave; sampling rate: 1000 Hz). The nose was used as the reference, and impedances of all electrodes were kept lower than 10 k Ω . To monitor ocular movements and eyeblinks, vertical and horizontal electrooculographic (EOG) signals were simultaneously recorded using two electrodes, one placed ~ 10 mm below the left eye and the other placed ~ 10 mm from the outer canthus of the left eye.

EEG Data Analysis

EEG data were processed using EEGLAB (Delorme & Makeig, 2004), an open source toolbox running in the MATLAB environment. Continuous EEG data were band-passed at 1–30 Hz, using a Hamming windowed sinc finite impulse response (FIR) filter (filter order: 3300; transition band width: 1 Hz; cutoff frequencies (-6 dB, half amplitude): $[0.5 \ 30.5]$ Hz). EEG epochs were extracted using a window analysis time of 3,000 ms (1,000 ms prestimulus

and 2,000 ms poststimulus) and baseline-corrected using the prestimulus interval. Four trials (one each for the 1st, 5th, 10th, and 17th subjects, respectively) in the STS condition and two trials (one each for the 5th and 10th subjects, respectively) in the N-STS condition with gross movement, artifacts were manually rejected. As a result, 29.9 ± 0.5 trials in the STS condition and 29.9 ± 0.3 trials in the N-STS condition were kept for the following analysis (the number of remaining trials was not significantly different between the two conditions: $P = .57$, paired sample *t* test). Furthermore, trials contaminated by eyeblinks and movements were corrected using an independent component analysis (ICA) algorithm (Delorme & Makeig, 2004), based on the following three criteria. First, independent components (ICs) of ocular artifacts showed smoothly decreasing EEG spectrum, with a dominant energy at low frequencies. Second, these ICs showed scalp topographies with strong far-frontal projections. Third, waveforms of these ICs showed strong similarity with the signals recorded from vertical and horizontal EOG electrodes. Note that ICs of ocular artifacts are usually in leading positions in the component array (because they tend to have a relatively large variance), and have a large EOG channel contribution as well as a frontal scalp distribution. Across subjects, 4 ± 2 ICs of ocular artifacts were identified and removed from the EEG signals.

For each subject, epochs corresponding to either STS or N-STS condition were respectively averaged, thus yielding two single-subject average waveforms (STS and N-STS), which were time-locked to the onset of laser stimuli. Single-subject average waveforms were subsequently averaged to obtain group-level waveforms. Group-level scalp topographies were computed by spline

interpolation. For each subject and each condition, peak latencies and amplitudes of the N2 and P2 waves were measured from the single-subject average waveforms (at Cz-nose), which were further compared between two experimental conditions using a paired sample *t* test.

Previous studies have well documented that sensory stimuli (including nociceptive stimuli) could not only evoke phase-locked responses (e.g., ERPs), but also induce nonphase-locked modulations of the magnitude of ongoing EEG oscillations, including event-related desynchronization (ERD) and synchronization (ERS) in different frequency bands (Hu, Xiao, Zhang, Mouraux, & Iannetti, 2014; Mouraux, Guerit, & Plaghki, 2003; Pfurtscheller & Lopes da Silva, 1999). These nonphase-locked responses that have been shown to capture important information particularly related to the cortical processing of nociceptive information (Hu, Peng, Valentini, Zhang, & Hu, 2013; Mouraux et al., 2003; Mouraux & Iannetti, 2008; Ploner, Gross, Timmermann, Pollok, & Schnitzler, 2006) would be completely lost using the across-trial averaging in the time domain. To explore both phase-locked and nonphase-locked brain responses elicited by laser stimuli, a time-frequency analysis was performed. Specifically, a time-frequency distribution (TFD) of the EEG time course was obtained using a windowed Fourier transform (WFT) with a fixed 250-ms Hanning window. The WFT yielded, for each time course, a complex time-frequency estimate $F(t, f)$ at each point (t, f) on the time-frequency plane, extending from $-1,000$ to $2,000$ ms (in steps of 1 ms) in the time domain, and from 1 to 30 Hz (in steps of 1 Hz) in the frequency domain. The resulting spectrogram $P(t, f) = |F(t, f)|^2$ represents the signal power as a joint function of time and frequency at each time-frequency point. When applied to single-trial EEG responses, the obtained TFDs contained brain responses both phase-locked and nonphase-locked to stimulus onsets (Mouraux & Iannetti, 2008).

To extract laser-elicited modulations of EEG oscillations on the time-frequency domain, the spectrograms were baseline-corrected (reference interval: -800 to -200 ms relative to laser stimulus onset) at each frequency f , using the subtraction approach, which avoids the positive bias introduced by the percentage approach (Hu et al., 2014). The reference interval was chosen to avoid the adverse influence of spectral estimates biased by windowing post-stimulus activity and padding values. In line with several previous studies (Iannetti, Hughes, Lee, & Mouraux, 2008; Mouraux et al., 2003), laser stimuli elicited a large phase-locked laser-evoked potentials (LEP) and a clear nonphase-locked alpha ERD response (alpha-ERD), which were respectively maximal at central and occipital electrodes. Based on these previous findings, two time-frequency regions of interest (ROIs) were defined on the baseline-corrected TFDs: LEP (100–400 ms and 1–10 Hz) and alpha-ERD (500–1,800 ms and 8–14 Hz). Note that LEP and alpha-ERD magnitudes were respectively measured at electrodes displaying maximal responses based on their respective scalp topographies, that is, at central electrodes (C1, C2, Cz, CPz) for LEP and at occipital electrodes (PO3, PO4, PO7, PO8, O1, O2) for alpha-ERD, and that similar selections of electrodes to extract LEP and alpha-ERD were reported in many previous studies (Iannetti et al., 2008; Mouraux et al., 2003; W. Peng, Hu, Zhang, & Hu, 2012; W. W. Peng et al., 2016). The mean magnitudes of time-frequency points within each ROI and across all selected electrodes were computed for each subject and condition, and then compared between two experimental conditions using a paired sample *t* test.

It should be noted that (a) the variance of baseline-corrected time-frequency features was jointly determined by the powers of

EEG oscillations not only in the poststimulus interval, but also in the prestimulus interval (Hu et al., 2013, 2014), and that (b) the neural substrate related to the top-down modulation of subsequent pain perception could be represented by the spontaneous EEG oscillations prior to the onset of nociceptive-specific laser stimuli (Babiloni et al., 2006; Tu et al., 2016). Therefore, we also extracted and compared time-frequency features from the TFDs that were not baseline-corrected. Specifically, four additional time-frequency ROIs were defined on the baseline-uncorrected TFDs: post-ERP (100–400 ms and 1–10 Hz), pre-alpha (-800 – 200 ms and 8–14 Hz), pre-beta (-800 – 200 ms and 15–25 Hz), and post-alpha (200–1,800 ms and 8–14 Hz). Note that their magnitudes were respectively measured at electrodes displaying maximal magnitudes, that is, at occipital electrodes (PO3, PO4, PO7, PO8, O1, O2) for pre-alpha, pre-beta, and post-alpha, and at central electrodes (C1, C2, Cz, CPz) for post-ERP. The mean magnitudes of time-frequency points within each ROI were computed for each subject and condition, and then compared between two experimental conditions using a paired sample *t* test. It should be noted that, to account for multiple comparisons, the significance level of all statistical tests was adjusted using a false discovery rate (FDR) procedure (Durka, Zygierec, Klekowicz, Ginter, & Blinowska, 2004).

Results

Behavioral Results

As displayed in the right panel of Figure 1, the subjective ratings of pain intensity and pain unpleasantness elicited by nociceptive-specific laser stimuli in the STS condition were significantly attenuated, compared with those in the N-STs condition (pain intensity: 5.07 ± 0.17 vs. 5.30 ± 0.17 , $P_{\text{FDR}} < .01$; pain unpleasantness: 3.83 ± 0.29 vs. 3.98 ± 0.30 , $P_{\text{FDR}} = .05$).

EEG Results

Figure 2 shows the group-level LEP waveforms (Cz-nose) in STS and N-STs conditions, together with the scalp topographies at peak latencies of N2 and P2 waves. The scalp topographies of N2 wave in both experimental conditions, along with their difference, were similarly maximal at the vertex and extended bilaterally toward temporal regions. In contrast, the scalp topographies of P2 wave in both experimental conditions, along with their difference, were more centrally distributed. Whereas N2 and P2 latencies were not significantly different (N2 latency: 248.23 ± 14.89 ms vs. 228.26 ± 5.82 ms, $P = .16$; P2 latency: 406.45 ± 27.20 ms vs. 367.43 ± 8.27 ms, $P = .14$), N2 and P2 amplitudes in the STS condition were significantly smaller, compared with those in the N-STs condition (N2 amplitude: -8.13 ± 1.22 μV vs. -9.48 ± 1.28 μV , $P_{\text{FDR}} < .01$; P2 amplitude: 7.16 ± 1.11 μV vs. 8.79 ± 1.36 μV , $P_{\text{FDR}} = .01$).

Figure 3 shows the group-level laser-elicited modulations of EEG oscillations (baseline-corrected TFDs) in STS and N-STs conditions, measured at central (C1, C2, Cz, CPz) and occipital electrodes (PO3, PO4, PO7, PO8, O1, O2). The scalp topographies of LEP response in both experimental conditions, along with their difference, were similarly maximal at the vertex. The similarity between the scalp topography of LEP in the time-frequency domain and the scalp topography of N2-P2 complex in the time domain (Figures 2 and 3) suggested that the neural activities reflected by the N2-P2 complex in the time domain corresponded to those reflected by the LEP response in the time-frequency

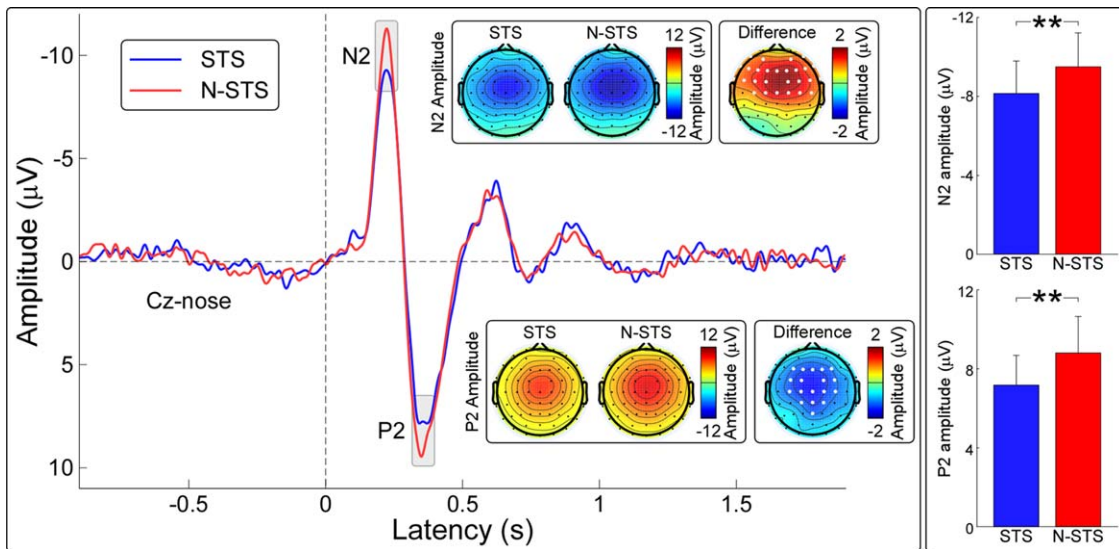


Figure 2. Comparison of laser-evoked potentials (LEPs) between STS and N-STS conditions. Displayed signals were group-level LEPs recorded from the vertex (Cz vs. nose) in both STS (blue line) and N-STS (red line) conditions. N2 and P2 amplitudes, measured at Cz-nose, were significantly smaller in the STS condition than those in the N-STS condition (N2 amplitude: $-8.13 \pm 1.22 \mu\text{V}$ vs. $-9.48 \pm 1.28 \mu\text{V}$, $P_{\text{FDR}} < .01$; P2 amplitude: $7.16 \pm 1.11 \mu\text{V}$ vs. $8.79 \pm 1.36 \mu\text{V}$, $P_{\text{FDR}} = .01$). Scalp topographies of N2 and P2 waves in the STS and N-STS conditions, as well as their differences (STS vs. N-STS, with enlarged dots representing electrodes with significant differences), are displayed at their peak latencies, respectively.

domain. In line with previous publications (Hu et al., 2013; Mouraux et al., 2003), the scalp topographies of alpha-ERD response in both experimental conditions were similarly maximal at the occipital region (Figure 3). As revealed by paired sample *t* test, (a) LEP

magnitude measured at central electrodes (C1, C2, Cz, CPz) was significantly smaller in the STS condition than that in the N-STS condition ($2.47 \pm 0.45 \mu\text{V}$ vs. $3.29 \pm 0.59 \mu\text{V}$, $P_{\text{FDR}} < .01$); and (b) alpha-ERD magnitude measured at occipital electrodes (PO3,

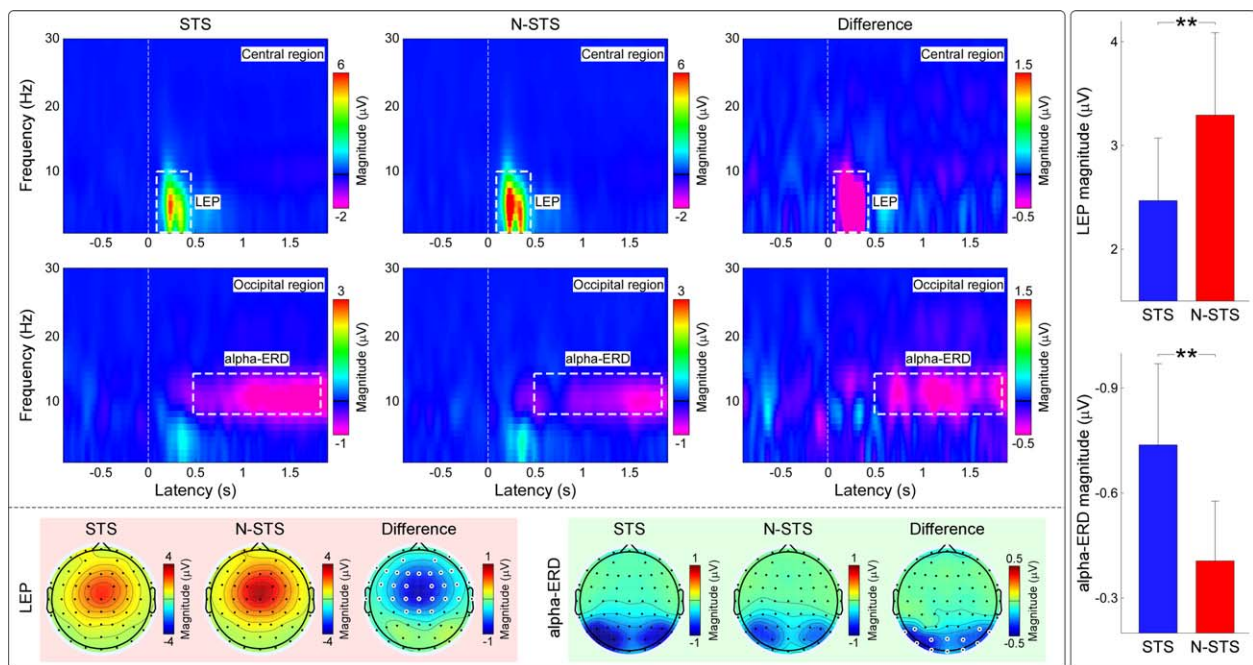


Figure 3. Comparison of laser-elicited modulations of EEG oscillations (baseline-corrected TFDs) between STS and N-STS conditions. Displayed signals show group-level baseline-corrected TFDs, recorded from central (top plots: C1, C2, Cz, CPz) and occipital electrodes (bottom plots: PO3, PO4, PO7, PO8, O1, O2), in both STS and N-STS conditions. LEP magnitude (measured at central electrodes) in the STS condition was significantly smaller than that in the N-STS condition ($2.47 \pm 0.45 \mu\text{V}$ vs. $3.29 \pm 0.59 \mu\text{V}$, $P_{\text{FDR}} < .01$). Alpha-ERD magnitude (measured at occipital electrodes) was significantly larger in the STS condition than that in the N-STS condition ($-0.74 \pm 0.17 \mu\text{V}$ vs. $-0.40 \pm 0.12 \mu\text{V}$, $P_{\text{FDR}} < .01$). Scalp topographies of response magnitudes in STS and N-STS conditions, together with their differences (STS vs. N-STS, with enlarged dots representing electrodes with significant differences), are displayed for each time-frequency feature (i.e., LEP and alpha-ERD).

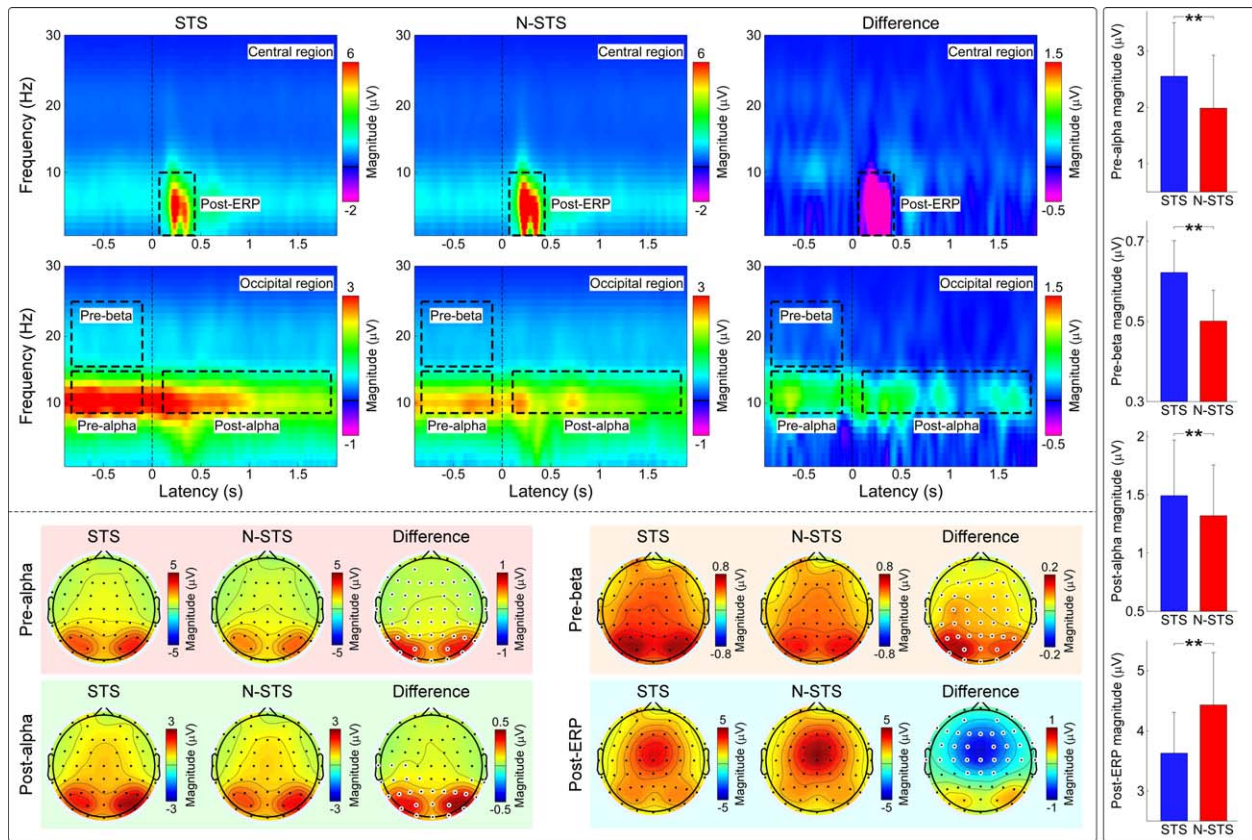


Figure 4. Comparison of EEG oscillations (baseline-uncorrected TFDs) between STS and N-STS conditions. Displayed signals show group-level baseline-uncorrected TFDs, recorded from central (top plots: C1, C2, Cz, CPz) and occipital electrodes (bottom plots: PO3, PO4, PO7, PO8, O1, O2), in both STS and N-STS conditions. Post-ERP magnitude (measured at central electrodes) in the STS condition was significantly smaller than that in the N-STS condition ($3.63 \pm 0.50 \mu\text{V}$ vs. $4.42 \pm 0.65 \mu\text{V}$, $P_{\text{FDR}} < .01$). Pre-alpha, pre-beta, and post-alpha magnitudes (measured at occipital electrodes) in the STS condition were all significantly larger than those in the N-STS condition (pre-alpha: $2.55 \pm 0.70 \mu\text{V}$ vs. $1.98 \pm 0.69 \mu\text{V}$, $P_{\text{FDR}} < .01$; pre-beta: $0.62 \pm 0.06 \mu\text{V}$ vs. $0.50 \pm 0.06 \mu\text{V}$, $P_{\text{FDR}} < .01$; post-alpha: $1.48 \pm 0.36 \mu\text{V}$ vs. $1.32 \pm 0.32 \mu\text{V}$, $P_{\text{FDR}} < .01$). Scalp topographies of the response magnitudes in STS and N-STS conditions, as well as their differences (STS vs. N-STS, with enlarged dots representing electrodes with significant differences), are displayed for each time-frequency feature (i.e., post-ERP, pre-alpha, pre-beta, and post-alpha).

PO4, PO7, PO8, O1, O2) was significantly enhanced in the STS condition compared to that in the N-STS condition ($-0.74 \pm 0.17 \mu\text{V}$ vs. $-0.40 \pm 0.12 \mu\text{V}$, $P_{\text{FDR}} < .01$).

Figure 4 displays the group-level EEG oscillations (baseline-uncorrected TFDs) in both STS and N-STS conditions, measured at central (C1, C2, Cz, CPz) and occipital electrodes (PO3, PO4, PO7, PO8, O1, O2). Similar to LEP response on the baseline-corrected TFDs (Figure 3), the scalp topographies of post-ERP response on the baseline-uncorrected TFDs in both experimental conditions, along with their difference, were similarly maximal at the vertex (Figure 4). The scalp topographies of pre-alpha, pre-beta, and post-alpha magnitudes in both experimental conditions, along with their between-conditions differences, were similarly maximal at the occipital region (Figure 4). As revealed by paired sample *t* test, (a) post-ERP magnitude measured at central electrodes (C1, C2, Cz, CPz) was significantly smaller in the STS condition than that in the N-STS condition ($3.63 \pm 0.50 \mu\text{V}$ vs. $4.42 \pm 0.65 \mu\text{V}$, $P_{\text{FDR}} < .01$); and (b) pre-alpha, pre-beta, and post-alpha magnitudes measured at occipital electrodes (PO3, PO4, PO7, PO8, O1, O2) were significantly larger in the STS condition than those in the N-STS condition (pre-alpha: $2.55 \pm 0.70 \mu\text{V}$ vs. $1.98 \pm 0.69 \mu\text{V}$, $P_{\text{FDR}} < .01$; pre-beta: $0.62 \pm 0.06 \mu\text{V}$ vs. $0.50 \pm 0.06 \mu\text{V}$, $P_{\text{FDR}} < .01$; post-alpha: $1.48 \pm 0.36 \mu\text{V}$ vs. $1.32 \pm 0.32 \mu\text{V}$, $P_{\text{FDR}} < .01$).

Discussion

We have obtained three main findings in the present study. First, subjective ratings of pain intensity and pain unpleasantness were significantly attenuated in the STS condition, compared with the N-STS condition (Figure 1). Second, laser-elicited brain responses, including N2 and P2 amplitudes in the time domain and LEP magnitudes in the time-frequency domain, were significantly smaller in the STS condition than those in the N-STS condition (Figure 2 and 3). Third, magnitudes of alpha and beta oscillations prior to the onset of laser stimuli, as well as poststimulus alpha oscillations, were significantly larger in the STS condition than those in the N-STS condition (Figure 4). These results demonstrated that the analgesic effect induced by tactile sensation was further enhanced when the tactile stimulation was initiated by the subject's voluntary actions, from the perspectives of both psychophysics and neurophysiology. The enhancement of analgesic effect was in line with the prestimulus enhancement of magnitudes of alpha and beta oscillations in the occipital region. This finding suggested that these oscillations could serve as the neurophysiological signature reflecting the binding between motor processing and sensory feedback, which execute inhibitory function by gating nociceptive information via top-down control. Our results would not only theoretically elaborate our understanding of the underlying neural

mechanisms related to the top-down modulations of the analgesic effect induced by self-initiated tactile sensation, but also in a practical sense help improve the analgesic effect of transcutaneous tactile stimulation in various clinical applications.

Many previous studies demonstrated that the perception of external sensory stimuli controlled by self-initiated action was reduced as compared to identical, externally generated stimuli (Mifsud et al., 2016; Stenner et al., 2014, 2015; Therrien et al., 2011). Such sensory attenuation effect was largely explained by the consistency between forward models of anticipated action effects and actual sensory feedback (Sperry, 1950; Waszak et al., 2012; Wolpert et al., 1995). These forward models involved the anticipatory modulation of sensory neural processing from motor actions, and self-initiated action-induced attenuation of sensory perception was mainly caused by top-down modulations mediated by motor-induced sensory anticipation (Chen et al., 2011; Kuhn, Seurinck, Fias, & Waszak, 2010). Here, top-down modulations refer to how our brains make use of information that has already been brought into the brain. This information could be encoded by neural oscillations (e.g., prestimulus alpha and beta oscillations in the occipital region), which could serve as the neurophysiological signature of the binding between motor processing and sensory feedback. In contrast to bottom-up processing, top-down modulation is a cognitive process (e.g., mediated by motor-induced sensory anticipation) that influences the lower-level functions (e.g., the perception of pain). Even though we have stated that the analgesic effect was mediated by top-down modulations, it remains an open question of whether the analgesic effect is caused by subcortical or corticocortical mechanisms. In the present study, we observed that, as compared to the condition that tactile sensation was externally initiated, self-initiated tactile sensation can effectively suppress both subjective pain perception (pain intensity and pain unpleasantness, Figure 1) and pain-related brain responses (N2 and P2 amplitudes in the time domain and LEP magnitudes in the time-frequency domain; Figure 2 and 3). These observations could not be easily explained by the anticipatory modulation of sensory neural processing from motor actions for two reasons. First, the delivery of the tactile stimulation, instead of the nociceptive stimulation, was directly controlled by self-initiated action in the STS condition (i.e., the binding was built between motor processing and tactile sensory feedback). Second, even though the anticipation level of tactile stimulation was different, the anticipation level of the following nociceptive stimuli would be similar between STS and N-STS conditions, considering that subjects were sure that the nociceptive-specific laser stimuli would be delivered 2–3 s after their perception of the initiation of the tactile stimulation.

Instead, since the binding between motor processing and tactile sensory feedback only existed in the STS condition, but not in the N-STS condition, we speculated that the brain state, which could be coded by neural oscillations, was markedly different between the two conditions. From the baseline-uncorrected TFDs, we observed that magnitudes of alpha and beta oscillations, maximal over occipital region, prior to the onset of laser stimuli were significantly larger in the STS condition than those in the N-STS condition (Figure 4). It is well known that the brain state could casually (at least partly) determine the perception of subsequent sensory stimuli (Chaumon & Busch, 2014; Jensen & Mazaheri, 2010; Kayser, McNair, & Kayser, 2016; Lou, Li, Philiastides, & Sajda, 2014), including nociceptive stimuli (Babiloni et al., 2006). For example, we have provided compelling evidence demonstrating that prestimulus alpha oscillations negatively modulated the perception of subsequent nociceptive stimuli in our previous study (Tu

et al., 2016). Therefore, it would be reasonable to interpret that our findings were driven by the difference of brain state, which was caused by the effect of self-initiated actions or nonself-initiated actions on the tactile inputs. In other words, our observations that analgesia due to self-initiated tactile sensation was enhanced as compared to that induced by externally generated tactile sensation were attributed to the difference of brain state between STS and N-STS conditions. In the STS condition, the brain state that coded the binding effect between motor processing and tactile sensory feedback would have inhibitory function by gating nociceptive information via top-down control. Importantly, such brain state related to the binding effect in the STS condition did not disappear immediately, since neural oscillations, especially alpha oscillations, were significantly different between STS and N-STS conditions, not only in the prestimulus interval, but also in the poststimulus interval (Figure 4). It should be noted that alpha oscillations were disrupted by the nociceptive inputs in the poststimulus interval, and the difference of alpha oscillations between STS and N-STS conditions weakened as time went on (Figure 4). Nevertheless, it remains unclear whether the brain state related to the binding effect would last longer or not, and this question deserves further investigation.

In line with previous studies (Hu et al., 2013; Mouraux et al., 2003; Ploner et al., 2006), nociceptive laser stimuli induced a transient suppression of EEG oscillations in the alpha frequency band (i.e., alpha-ERD) in both STS and N-STS conditions. The magnitude of alpha-ERD response, maximal over the occipital region, was significantly larger in the STS condition than that in the N-STS condition (the condition with a smaller intensity of pain perception has a larger magnitude of alpha-ERD, Figure 3). Nevertheless, it is contradictory with several previous studies documenting that the magnitude of nociceptive-induced alpha-ERD, which was hypothesized to play a crucial role in cortical integration and perception (Franciotti et al., 2009; W. Peng, Babiloni, Mao, & Hu, 2015), was significantly enhanced with the intensity of pain perception, that is, the larger the alpha-ERD magnitude, the stronger the pain perception (Hu et al., 2014; Ohara, Crone, Weiss, & Lenz, 2004; Tu et al., 2016). This contradiction is not physiologically based, but is largely due to the fact that the magnitude of alpha-ERD was jointly determined by the powers of prestimulus and poststimulus alpha oscillations, and the prestimulus alpha power had a greater influence on the resulting alpha-ERD variance (Hu et al., 2013). Therefore, to engage in more accurate interpretations of the observed modulations of neural oscillations related to a given mental state, it would be important to assess the respective contributions of prestimulus and poststimulus oscillations in determining the variability of nonphase-locked ERD and ERS. Note that it would be necessary to increase the number of subjects, as well as including more male subjects, to improve the reliability and validity of our findings. In addition, even though the skin-conducted potential could not contribute to any significant difference between STS and N-STS conditions, our raw data could be contaminated by this potential. Advanced techniques should be developed and applied to eliminate this contamination in the future.

In summary, we demonstrated that the analgesic effect induced by tactile sensation could be enhanced when the tactile stimulation was controlled by the subjects. Such enhancement was caused by the improvement of top-down control, which was encoded by prestimulus alpha and beta oscillations in the occipital region. Specifically, these neural oscillations prior to the onset of laser stimuli would serve as the neurophysiological signature of the binding between motor processing and sensory feedback, which would

execute inhibitory function by gating nociceptive information. These observations improved our understanding of the neural mechanisms related to the top-down modulations of the analgesic

effect induced by self-initiated tactile sensation, which provided theoretical basis for a practical approach via self-actions to improve the analgesic effect in clinical applications.

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