



Supraspinal neural mechanisms of the analgesic effect produced by transcutaneous electrical nerve stimulation

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Abstract

Although the analgesic effects of conventional transcutaneous electrical nerve stimulation (TENS) and acupuncture-like TENS are evident, their respective neural mechanisms in humans remain controversial. To elucidate and compare the supraspinal neural mechanisms of the analgesic effects produced by conventional TENS (high frequency and low intensity) and acupuncture-like TENS (low frequency and high intensity), we employed a between-subject sham-controlled experimental design with conventional, acupuncture-like, and sham TENS in 60 healthy human volunteers. In addition to assessing the TENS-induced changes of subjective ratings of perceived pain, we examined the TENS associated brainstem activities (fractional amplitude of low frequency fluctuations, fALFF) and their corresponding resting state functional connectivity (RSFC) with higher-order brain areas using functional magnetic resonance imaging. The analgesic effect of conventional TENS was only detected in the forearm that received TENS, coupled with decreased pons activity and RSFC between pons and contralateral primary somatosensory cortex. In contrast, acupuncture-like TENS produced a spatially diffuse analgesic effect, coupled with increased activities in both subnucleus reticularis dorsalis (SRD) and rostral ventromedial medulla (RVM), and decreased RSFC between SRD and medial frontal regions as well as between SRD and lingual gyrus. To sum up, our data demonstrated that conventional TENS and acupuncture-like TENS have different analgesic effects, which are mediated by different supraspinal neural mechanisms.

Keywords Transcutaneous electrical nerve stimulation (TENS) · Pain · Functional magnetic resonance imaging (fMRI) · Analgesic effect · Subnucleus reticularis dorsalis (SRD) · Rostral ventromedial medulla (RVM)

Introduction

Through delivering electrical pulses to activate peripheral somatosensory afferents, transcutaneous electrical nerve stimulation (TENS) has been widely offered as a non-invasive and non-addictive pain treatment in various acute

and chronic pain conditions (Hurlow et al. 2012; Johnson 2007; Mokhtari et al. 2020; Nnoaham and Kumbang 2008; Sluka and Walsh 2003; von Deneen et al. 2020). In practice, TENS can be implemented using different stimulus parameters to activate different populations of nerve fibers (Johnson 2007; Levin and Hui-Chan 1993). With electrical pulses of high frequency (~ 50–100 Hz) and low intensity (evoking a comfortable, nonpainful tingling sensation), conventional TENS activates large-diameter A β fibers, which inhibit the nociceptive volley transmitted via small-diameter A δ and C fibers innervating spatially adjacent skin areas (Johnson 2007; Jones and Johnson 2009; Sluka and Walsh 2003). In contrast, with electrical pulses of low frequency (~ 2–4 Hz) and high intensity (evoking a tolerable but painful sensation), acupuncture-like TENS activates small-diameter A δ and C fibers, which activate central nervous system structures resulting in a spatially diffuse analgesic effect (Johnson 2007; Jones and Johnson 2009; Sluka and Walsh 2003). Although the analgesic

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effects of conventional TENS and acupuncture-like TENS are evident, their respective neural mechanisms remain controversial.

The analgesic effect of conventional TENS was maximal when electrical pulses were delivered homotopically to the same body territory of pain (Johnson 2007; Peng et al. 2019). This phenomenon was usually explained by the gate control theory that the activation of large-diameter A β fibers results in a segmental inhibition of the transmission of nociceptive information at the spinal cord dorsal horn level (Melzack and Wall 1965). However, some animal studies suggested the existence of a supraspinal descending inhibition mechanism for conventional TENS (DeSantana et al. 2009; Kalra et al. 2001). For example, the analgesic effect of conventional TENS could be prevented by the blockade of opioid receptors in the rostral ventral medulla (RVM) (Kalra et al. 2001) or through the activation of ventrolateral periaqueductal gray (PAG) (DeSantana et al. 2009). In other words, the conventional TENS could produce an opioid-mediated antinociception via the descending pain inhibitory system that sends projections from the brainstem (where the PAG and RVM reside) to the spinal cord (DeSantana et al. 2009). It is likely that conventional TENS is contributed by the concomitance of both spinal and supraspinal neural mechanisms. However, this concomitant explanation of conventional TENS, especially for the involvement of the supraspinal neural mechanisms that was purely derived from animal pain models, has not been testified in humans.

In contrast, acupuncture-like TENS could produce a spatially diffuse analgesic effect, i.e., the analgesic effect was equally strong regardless whether electrical pulses were delivered to the same or different body territory of pain (Peng et al. 2019). There is no doubt that a supraspinal neural mechanism was involved in the generation of the spatially diffuse analgesic effect of acupuncture-like TENS. A possible explanation is that strong noxious inputs, produced by stimulating small-diameter A δ and C fibers by acupuncture-like TENS, could result in the release of endogenous opioids in the PAG-RVM network, which in turn produces a diffuse descending inhibition of the transmission of additional nociceptive information (DeSantana et al. 2009; Harper et al. 2018; Kalra et al. 2001; Knudsen et al. 2011). However, evidence from both animal and human studies also demonstrated that acupuncture-like TENS could act via the diffuse noxious inhibitory control (DNIC) system, through the activation of neurons in the subnucleus reticularis dorsalis (SRD) in the caudal-dorsal medulla (Le Bars et al. 1992; Villanueva et al. 1996; Youssef et al. 2016a, b). Even the two explanations are different, it is possible that the analgesic effect of acupuncture-like TENS is contributed by the concomitance of both supraspinal neural mechanisms. However, whether the RVM-related circuitry and SRD-related circuitry are simultaneously or independently involved in the

generation of the analgesic effect produced by acupuncture-like TENS remains unclear.

To elucidate and compare the supraspinal neural mechanisms of the analgesic effects (i.e., the analgesic effects that are associated with the activities in the brainstem) produced by conventional TENS and acupuncture-like TENS, we employed a between-subject sham-controlled experimental design in the present study. Conventional, acupuncture-like, and sham TENS were delivered to a population of 60 healthy human volunteers. Behavioral (e.g., perceived pain) and resting state functional magnetic resonance imaging (fMRI) data were collected before and after the TENS procedure. In addition to testing the TENS-induced changes of subjective ratings of perceived pain, we assessed the associated modulation of brainstem activities and their functional connectivity with higher-order brain areas. We also explored the possible correlations between behavioral data (e.g., perceived pain and tactile and pain thresholds) and neuroimaging variables (e.g., changes of regional brainstem activities and their functional connectivity with higher-order brain areas).

Materials and methods

Subjects

A total of 60 right-handed, healthy, and pain-free volunteers who never had TENS before were recruited through local advertisement (31 females; mean age 22.32 ± 2.75 years; age range 18–30 years). Subjects were assessed by the clinical interview, and were excluded if they had any contraindications (e.g., brain lesions, non-removable metallic implants, claustrophobia, etc.) for MRI scanning, any peripheral and central nervous system diseases, chronic pain, or if they were under any type of pain medication.

Sensory stimulation

Electrical stimuli for TENS were generated by a constant current electrical stimulator (Sanxia technique Inc., China), and delivered through two pairs of surface round electrodes (diameter: 16 mm; inter-electrode distance: 3 cm) placed over the median nerve on the left forearm. The conventional TENS (100 Hz) and acupuncture-like TENS (4 Hz) consisted of a series of constant-current square-wave pulses (pulse width = 2 ms). The stimulus intensity of conventional TENS was individually adjusted to elicit a strong but non-painful tingling sensation underneath the TENS electrodes, whereas the stimulus intensity of acupuncture-like TENS was adjusted to elicit a painful but tolerable sensation. To reduce the habituation effect of active TENS sensation, the stimulus intensities of both conventional TENS and acupuncture-like TENS were adjusted every 5 min during the

TENS session to ensure that the desired perceptual outcomes were maintained. No pulse was delivered in the sham TENS condition. The duration of the TENS session was 30 min for all types of TENS, and before the TENS session, subjects were given the following instruction: “You will now receive 30 min of TENS, and the TENS sensation could vary greatly among subjects: ranging from intense sensations to much weaker sensations, or even no sensation”. To reduce the possible influence of stimulation effects (e.g., the difference of stimulus intensity in different TENS conditions) on experimental results, we adopted a between-subject, placebo-controlled design. In addition, data from different subjects were collected at different time periods, and subjects could not communicate with each other about the sensation felt during the experiment.

Noxious contact heat stimuli were generated by a thermode (Contact Heat Evoked Potentials Stimulator: CHEPS, Medoc Ltd, Ramat Yishai, Israel) with a circular contact area of 5.7 cm². The thermode was fixed to the left or right forearm using an elastic Velcro strap provided with the equipment. To ensure that the pressure exerted by the thermode on the forearm was similar across subjects and stimulation sites, cautions were taken when placing the thermode by adjusting the length of the Velcro strap. In a preliminary session, the ascending method of limits was adopted for each subject to determine the stimulus intensity used in the experiment (delivered on the left forearm): starting from 32 °C, the thermode temperature was increased in steps of 0.5 °C/s until a rating of 70 out of 100 was obtained on a numerical rating scale (NRS) ranging from 0 (no pain) to 100 (unbearable pain). Please note that the ascending method of limits was repeated three times for each subject, and the average temperature was used for the following procedures of the experiment. In addition, the same procedures (the ascending method of limits) were performed for each subject to determine the pain threshold, i.e., the temperature at which pain begins to be felt (corresponding to 40 on the 0–100 NRS). During the experiment, ramp-and-hold stimuli, which consisted of an initial increase of temperature from 32 °C to the target temperature (corresponding to 70 on the 0–100 NRS), a 2-s hold at the target temperature, and a decrease of temperature to its baseline (i.e., 32 °C), was applied. The rates of temperature increase and decrease were 40 °C/s.

Tactile stimuli were delivered using Semmes–Weinstein monofilaments (Touch-Test™ 20 Piece Kit with an evaluator size of 1.65–6.65 and a target force of 0.008–300 g; North Coast Medical, Inc., USA) to determine the tactile threshold before TENS procedure for each subject (Bell-Krotoski 1995). The Touch-Test sensory evaluator was applied on the dorsum of left hand for each subject, and the filament was pressed at a 90° angle against the skin until it bowed and was held in place for 1.5 s. The subject was instructed to look away from the filament and report whether the stimulus

was felt or not. The method of limits (starting from 1.65, the evaluator size was gradually increased until the subject felt the stimulus and then gradually decreased until the subject could not feel the stimulus) was adopted and repeated three times for each subject. The geometric mean of three series of ascending and descending stimulus intensities was recorded as the tactile threshold.

Experimental design

A between-subject sham-controlled experimental design was used (Fig. 1). Subjects were randomly assigned to one of the three experimental groups (conventional TENS group, acupuncture-like TENS group, and sham TENS group). Age and gender were well matched between groups. The experiment consisted of three sessions, separated by a 5-min break: Pre-TENS (~30 min), TENS procedure (~30 min), and Post-TENS (~25 min). In both Pre-TENS and Post-TENS sessions, 14 noxious contact heat stimuli (i.e., ramp-and-hold stimuli) were delivered to both forearms (7 stimuli per forearm), which were followed by the MRI data acquisition (Pre-TENS session: structural and resting state functional MRI scanning, Post-TENS session: resting state functional MRI scanning only). The inter-stimulus interval varied randomly between 18 and 20 s. The order of stimulated forearms was pseudorandomized: in half of the subjects in each group the first seven stimuli were delivered to the left forearm; in the other half the first seven stimuli were delivered to the right forearm. Approximately 5 s after each contract heat stimulus, subjects were asked to verbally report pain intensity on the same 0–100 NRS. Please note that data from different subjects were collected at different time periods, and subjects were not able to communicate with each other about the sensation felt during the experiment.

MRI data acquisition

The MRI data were collected using a 3.0-Telsa MRI system (Discovery MR 750; General Electric Healthcare; Milwaukee; Wisc.) at the MRI Research Center, Institute of Psychology, Chinese Academy of Sciences. A standard birdcage 8-channel head coil with foam pads was used to minimize head motion and scanner noise. In the Pre-TENS session, T1-weighted 3D structural image was acquired using the gradient echo (3D SPGR) sequence with the following parameters: flip angle = 12°; in-plane matrix size = 256 × 256; in plane resolution = 1 × 1 mm²; slices = 256; slice thickness = 1 mm. In both Pre-TENS and Post-TENS sessions, resting-state fMRI data were acquired using a gradient echo planar imaging sequence with the following parameters: repetition time = 2000 ms; echo time = 30 ms; flip angle = 90°; data matrix = 64 × 64; in plane resolution = 3 × 3 mm²; slice thickness = 3.5 mm

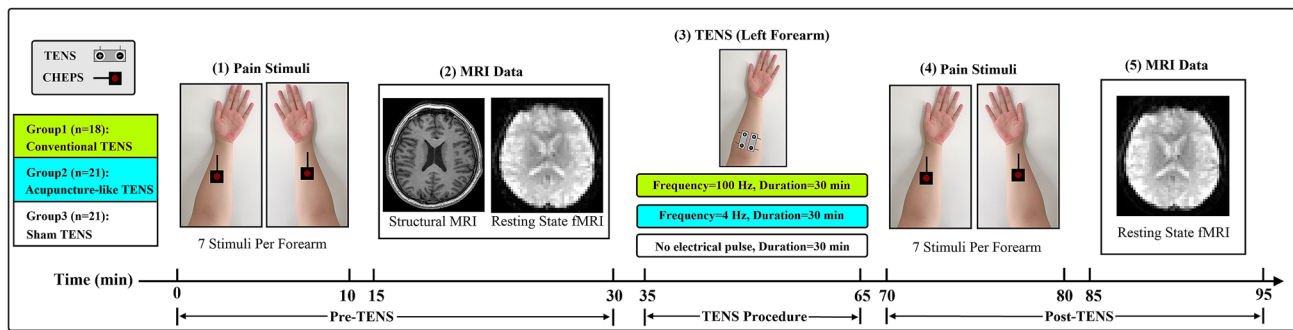


Fig. 1 Experimental design. 60 subjects were randomly assigned to three experimental groups: conventional TENS group ($n=18$), acupuncture-like TENS group ($n=21$), and sham TENS group ($n=21$). The experiment consisted of three sessions, separated by a 5-min break: Pre-TENS, TENS procedure, and Post-TENS. In both Pre-TENS and Post-TENS sessions, 14 noxious contact heat stimuli were delivered to both forearms (7 stimuli per forearm), which were followed by the MRI data acquisition. The order of stimulated forearms was pseudorandomized: in half of the subjects in each group the first seven stimuli were delivered to the left forearm; in the other half

the first seven stimuli were delivered to the right forearm. Approximately 5 s after each contract heat stimulus, subjects were asked to verbally report pain intensity on the same 0–100 NRS. In the TENS procedure, conventional TENS (100 Hz) and acupuncture-like TENS (4 Hz) were delivered transcutaneously to the median nerve on the left forearm (pulse width = 2 ms), while no electrical pulse was delivered in the sham TENS group. The duration of the TENS session was 30 min for all types of TENS. TENS transcutaneous electrical nerve stimulation, CHEPS contact heat evoked potential stimulator, NRS numerical rating scale

without slice spacing; volumes = 230. During the resting state fMRI data acquisition, subjects were instructed to keep their eyes open, look at the fixation cross on the screen, keep still, and not to think about anything systematically.

Resting state fMRI data preprocessing

Resting state fMRI data were analyzed using Data Processing and Analysis for (Resting-State) Brain Imaging (DPABI) software (Yan et al. 2016). The first ten volumes were discarded because of spin saturation effects and adaptation of subjects to their immediate environment. Images were slice timing corrected and spatially realigned. Subjects with head motion more than 2.0 mm of maximal translation (in any direction of x , y or z) or 2.0° of maximal rotation throughout the course of scanning were excluded from further analysis. The realigned images were co-registered to their corresponding structural images. Structural images were segmented into grey matter, white matter, and cerebrospinal fluid. White matter signal, cerebrospinal fluid signal, and Friston's-24 motion parameters (Friston et al. 1996) were regressed as nuisance covariates from the pre-processed resting-state fMRI data. The processed fMRI data were then normalized to the Montreal Neurological Institute (MNI) space (resampling voxel size = $3\text{ mm} \times 3\text{ mm} \times 3\text{ mm}$), spatially smoothed using a Gaussian kernel of 6-mm full width at half maximum (FWHM), and detrended to remove the linear drifts in the fMRI data. A Gaussian kernel of 4-mm FWHM was also applied in the preprocessing step to assess the reliability of the results.

Fractional amplitude of low frequency fluctuations (fALFF) analysis

Being defined as the ratio of power spectrum of low frequency fluctuations (0.01–0.08 Hz) to that of the entire frequency range (0–0.25 Hz), fALFF could be used to detect the intensity of regional spontaneous brain activity with high sensitivity and specificity (Feng et al. 2016; Xue et al. 2013; Yuan et al. 2013; Zou et al. 2008). To assess whether TENS-induced analgesic effects was associated with the regional spontaneous brainstem activity, fALFF analysis was performed, and the calculated fALFF values were compared using a two-way analysis of variance (ANOVA) with “time” (Pre-TENS and Post-TENS) as a within-subject factor and “group” (conventional TENS, acupuncture-like TENS, and sham TENS) as a between-subjects factor. When the main effect or the interaction between the two factors was significant, post hoc paired-sample t -tests were performed to assess the TENS-induced changes of regional spontaneous brainstem activity (Pre-TENS vs. Post-TENS) for each experimental group. Statistical maps were thresholded using the Gaussian random field (GRF) theory correction procedure (Chen et al. 2018; Nichols and Hayasaka 2003), as implemented in DPABI (Yan et al. 2016). The significance level was set at $p < 0.05$ corrected for multiple comparisons ($z > 2.3$, cluster significance: $p < 0.05$).

Resting state functional connectivity (RSFC) analysis

Brain regions showed significant TENS-induced changes of fALFF were selected as regions of interest (ROIs) for the functional connectivity analysis of resting-state fMRI

data. For each ROI, time series of spontaneous brain activity, which were averaged across all voxels of the ROI, were extracted in each subject, and individual-level correlation maps of all voxels that were positively or negatively correlated with the averaged time series were produced (Bi et al. 2017a, b). The resulting correlation maps were converted to Z value maps using Fisher's r -to- z transformation. Paired-sample t tests were performed to investigate TENS-induced RSFC changes of each ROI for each experimental group. Statistical maps were thresholded using the GRF theory correction procedure (Chen et al. 2018; Nichols and Hayasaka 2003; Yan et al. 2016), in which the significance level was set at $p < 0.05$ corrected for multiple comparisons ($z > 2.3$, cluster significance: $p < 0.05$).

Statistical analysis

The TENS-induced perceptual effect was evaluated by calculating the difference of pain perception between sessions ($\Delta \text{pain intensity}_{([\text{Post-TENS}]-[\text{Pre-TENS}])} = \text{pain intensity}_{(\text{Post-TENS})} - \text{pain intensity}_{(\text{Pre-TENS})}$). The resulting differences were compared using a two-way ANOVA, with “side” (contact heat stimulation of the forearms ipsilateral and contralateral to the TENS side) as a within-subject factor and “group” (conventional TENS, acupuncture-like TENS, and sham TENS) as a between-subjects factor. When the main effect or the interaction between the two factors was significant, post hoc independent-sample t -tests were performed to assess the differences of the analgesic effects of TENS types on the forearm ipsilateral or contralateral to the TENS side ($p < 0.05/6 = 0.0083$, Bonferroni correction), and post hoc paired-sample t -tests were performed to investigate the differences of the analgesic effects on the two forearms for each experimental group ($p < 0.05/6 = 0.0083$, Bonferroni correction).

The TENS-induced changes of brain activity and functional connectivity were respectively quantified by calculating the differences of both fALFF and RSFC values between sessions (i.e., $\Delta \text{fALFF}_{([\text{Post-TENS}]-[\text{Pre-TENS}])}$ or $\Delta \text{RSFC}_{([\text{Post-TENS}]-[\text{Pre-TENS}])}$ in each ROI). Two sample t -tests were performed to assess the differences of both TENS-induced fALFF and RSFC changes between active TENS (conventional TENS or acupuncture-like TENS) and sham TENS. To assess the possible relationship between $\Delta \text{pain intensity}_{([\text{Post-TENS}]-[\text{Pre-TENS}])}$ and $\Delta \text{fALFF}_{([\text{Post-TENS}]-[\text{Pre-TENS}])}$ or $\Delta \text{RSFC}_{([\text{Post-TENS}]-[\text{Pre-TENS}])}$, Pearson correlation analyses were performed for the forearm ipsilateral or contralateral to the TENS side in each experimental group. In addition, Pearson correlation analyses were performed (1) between tactile threshold and brain activity and functional connectivity (as well as TENS-induced changes of brain activity and functional connectivity) in conventional TENS group,

(2) between pain threshold and brain activity and functional connectivity (as well as TENS-induced changes of brain activity and functional connectivity) in acupuncture-like TENS group. Please note that conventional TENS and acupuncture-like TENS respectively activate large-diameter A β fibers and small-diameter A δ and C fibers, for which the detection sensitivity could be reflected by the tactile threshold (Cole et al. 2006; von Frey 1894) and pain threshold (Adriaensen et al. 1983; Hallin et al. 1982; Meh and Denišlić 1994). The possible correlations between these thresholds and brain activity/connectivity would provide a better understanding of their neural mechanisms (Palmer et al. 2004).

Results

Demographics

A total of 60 healthy subjects participated in the experiment, which included 18 subjects in the conventional TENS group (9 females, 9 males, age: 22.67 ± 3.74 years, education: 15.5 ± 2.12 years), 21 subjects in the acupuncture-like TENS group (12 females, 9 males, age: 21.95 ± 2.36 years, education: 15.86 ± 2.29 years), and 21 subjects in the sham TENS group (10 females, 11 males, age: 22.38 ± 2.13 years, education: 16 ± 1.48 years). One-way ANOVA showed no significant group difference of age ($F_{(2,57)} = 0.329$, $p = 0.721$, $\eta^2 = 0.011$) and education ($F_{(2,57)} = 0.320$, $p = 0.727$, $\eta^2 = 0.011$). Chi-Square test revealed no significant differences of gender between three groups (conventional TENS vs. acupuncture-like TENS: $p = 0.513$; conventional TENS vs. sham TENS: $p = 0.827$; acupuncture-like TENS vs. sham TENS: $p = 0.378$).

Effect of TENS on subjective pain perception

For the TENS-induced perceptual effect, two-way ANOVA revealed strong evidence for main effects of “group” ($F_{(2,57)} = 8.863$, $p < 0.001$, $\eta^2 = 0.237$) and “side” ($F_{(2,57)} = 13.926$, $p < 0.001$, $\eta^2 = 0.196$), but no evidence for their interaction ($F_{(2,57)} = 2.36$, $p = 0.104$, $\eta^2 = 0.076$) (Fig. 2). Post hoc independent-sample t -tests showed that, compared with sham TENS (ipsilateral side: 0.85 ± 5.10 points; contralateral side: 4.74 ± 6.59 points), acupuncture-like TENS significantly decreased the pain intensity for both forearms (ipsilateral side: -9.43 ± 14.12 points, $p = 0.004$; contralateral side: -6.64 ± 9.55 points, $p < 0.001$), while conventional TENS only decreased the pain intensity for the forearm ipsilateral to the TENS side (ipsilateral side: -12.92 ± 16.01 points, $p = 0.002$; contralateral side: -2.37 ± 11.98 points, $p = 0.034$, Bonferroni corrected threshold: $p < 0.05/6 = 0.0083$). In addition, post hoc paired-sample t -tests showed that the analgesic effects

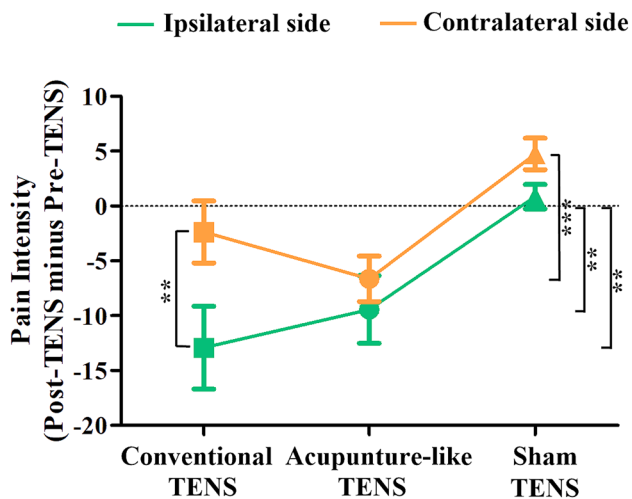


Fig. 2 Effect of TENS on subjective pain intensity. Acupuncture-like TENS decreased pain intensity in both forearms (i.e., ipsilateral and contralateral to the TENS side), while conventional TENS only decreased pain intensity in the forearm ipsilateral to the TENS side. TENS transcutaneous electrical nerve stimulation. ** $p < 0.01$; *** $p < 0.001$

of conventional TENS on the forearm ipsilateral to TENS side were significantly stronger than that contralateral to TENS side ($p = 0.005$, Bonferroni corrected threshold: $p < 0.05/6 = 0.0083$). However, the analgesic effects of acupuncture-like TENS on the two forearms were not significantly different ($p = 0.375$, Bonferroni corrected threshold: $p < 0.05/6 = 0.0083$).

Effect of TENS on fALFF

Two-way ANOVA showed that voxel-wise fALFF was significantly different between the three groups in a series of regions in the brainstem, including the midbrain, pons, and medulla, which contain the PAG, RVM, and SRD (Fig. 3a). Post hoc paired-sample t -tests revealed that acupuncture-like TENS increased fALFF in RVM and SRD (Fig. 3b, bottom panel; Table 1), while conventional TENS decreased fALFF in pons (Fig. 3b, top panel; Table 1), and no fALFF changes were observed after sham TENS. Please note that the results were almost identical no matter the 6-mm or the 4-mm smoothing kernel was adopted in the preprocessing step (Fig. 3b vs. Fig. 3c). TENS-induced changes of fALFF in RVM, SRD, and pons were summarized in Fig. 3d for a

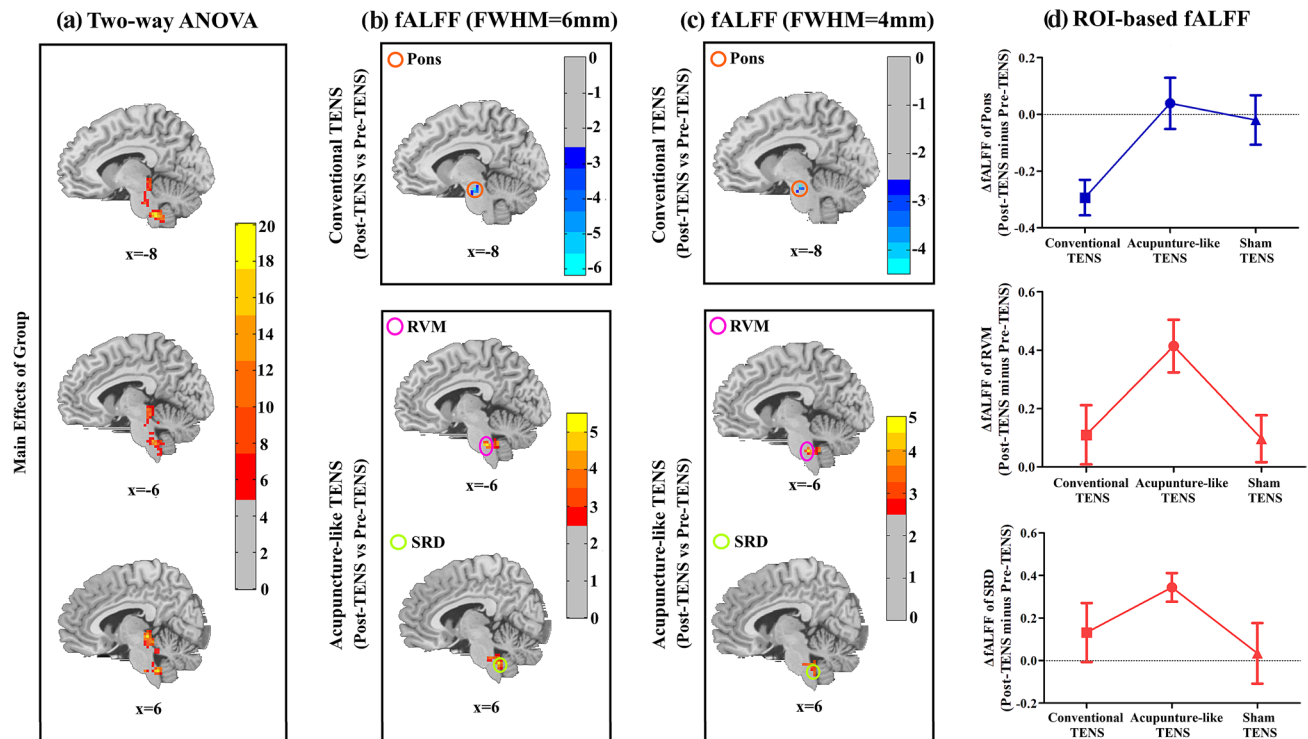


Fig. 3 Effect of TENS on fALFF. **a** Significant group difference of TENS-induced fALFF changes was observed in the midbrain, pons, and medulla, which contain the PAG, RVM, and SRD. **b–d** Acupuncture-like TENS increased fALFF in the RVM and SRD, while conventional TENS decreased fALFF in the pons. Please note that statistical results were almost identical no matter when the 6-mm

smoothing kernel or the 4-mm smoothing kernel were adopted in the preprocessing step. TENS transcutaneous electrical nerve stimulation, fALFF fractional amplitude of low frequency fluctuations, PAG periaqueductal gray, RVM rostral ventral medulla, SRD subnucleus reticularis dorsalis

Table 1 Clusters that exhibited TENS-induced fALFF changes

Brain area	Side	Peak voxel				Cluster size (voxels)
		<i>X</i>	<i>Y</i>	<i>Z</i>	<i>T</i> value	
<i>Clusters that exhibited decreased fALFF after conventional TENS</i>						
Pons	L/R	− 9	− 21	− 18	− 6.1627	32
<i>Clusters that exhibited increased fALFF after acupuncture-like TENS</i>						
SRD	L/R	6	− 42	− 42	5.0817	99
RVM	L/R	− 6	− 33	− 39	5.5249	

All the coordinates are located in the MNI space

TENS transcutaneous electrical nerve stimulation, fALFF fractional amplitude of low frequency fluctuations, SRD subnucleus reticularis dorsalis, RVM rostral ventromedial medulla, L left, R right

better visualization of the TENS-induced effect on spontaneous brain activity. Two-sample *t*-tests showed significant differences of TENS-induced changes of fALFF (i.e., $\Delta fALFF_{([Post-TENS]-[Pre-TENS])}$) between conventional TENS and sham TENS at the pons ($p=0.016$), and between acupuncture-like TENS and sham TENS at the RVM ($p=0.012$). The TENS-induced changes of fALFF at the SRD was marginally different between acupuncture-like TENS and sham TENS ($p=0.056$).

Effect of TENS on RSFC

ROI-based functional connectivity analysis showed that conventional TENS decreased RSFC between pons and right primary somatosensory cortex (SI) (Fig. 4a; Table 2), while acupuncture-like TENS decreased RSFC between SRD and supplementary motor area (SMA), middle cingulate cortex (MCC), medial prefrontal cortex (mPFC), as well as lingual gyrus (Fig. 4c; Table 2). No TENS-induced changes of RSFC between RVM and any other brain regions were observed (Fig. 4b). Two sample *t*-tests showed that TENS-induced changes of RSFC (i.e., $\Delta RSFC_{([Post-TENS]-[Pre-TENS])}$) between the SRD and medial frontal areas (i.e., SMA, MCC, and mPFC; $p=0.047$) or lingual gyrus ($p=0.008$) were significantly different between acupuncture-like TENS and sham TENS. No significant difference of TENS-induced changes of RSFC between the pons and right SI was observed between conventional TENS and sham TENS ($p=0.111$).

Correlations between behavioral data and neuroimaging variables

In conventional TENS group, tactile threshold measured by Touch-Test sensory evaluator was positively correlated with RSFC between pons and SI in the Pre-TENS session ($r=0.536$, $p=0.022$; Fig. 5a). In acupuncture-like TENS group, pain threshold was positively correlated with RSFC between SRD and lingual gyrus in the Pre-TENS session ($r=0.464$, $p=0.034$; Fig. 5b), and negatively correlated with

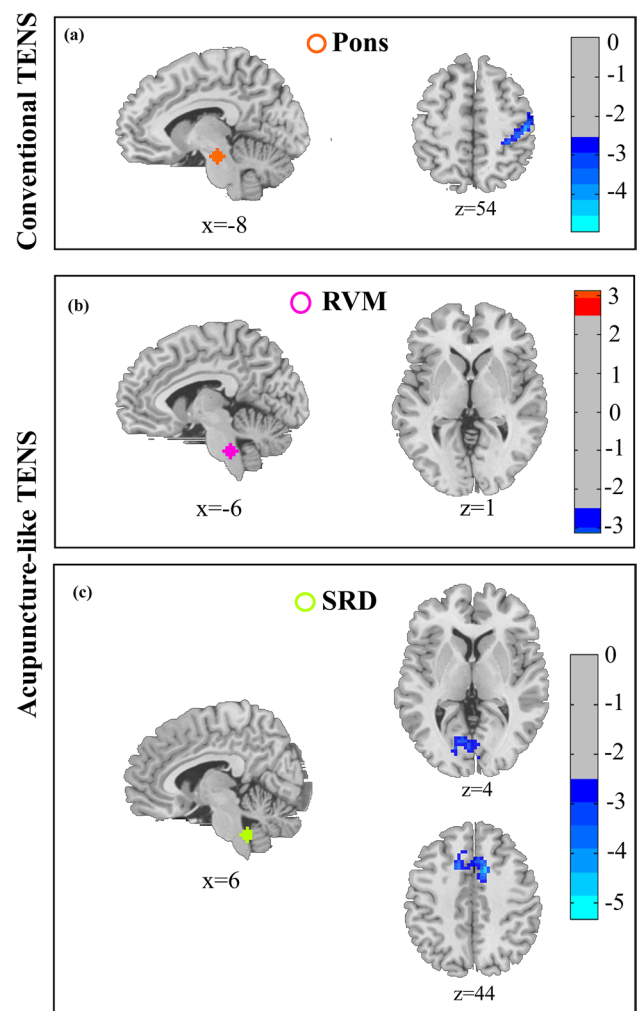


Fig. 4 Effect of TENS on ROI-based RSFC. **a** Conventional TENS decreased RSFC between pons and right SI. **c** Acupuncture-like TENS decreased RSFC between SRD and medial frontal areas (i.e., SMA, MCC, and mPFC), as well as lingual gyrus. **b** No RSFC changes of RVM were detected after acupuncture-like TENS. TENS transcutaneous electrical nerve stimulation, RSFC resting state functional connectivity, ROI region of interest, SI primary somatosensory cortex, SRD subnucleus reticularis dorsalis, SMA supplementary motor area, MCC middle cingulate cortex, mPFC medial prefrontal cortex, RVM rostral ventral medulla

Table 2 Clusters that exhibited TENS-induced RSFC changes

Brain area	Side	Peak voxel				Cluster size (voxels)
		X	Y	Z	T value	
<i>Clusters that exhibited decreased RSFC with pons after conventional TENS</i>						
SI	R	42	− 27	48	− 4.0101	167
<i>Clusters that exhibited decreased RSFC with SRD after acupuncture-like TENS</i>						
Frontal areas (SMA/MCC/mPFC)	L/R	12	12	45	− 4.4891	197
Lingual gyrus	L/R	− 15	− 78	− 6	− 4.1192	385

All the coordinates are located in the MNI space

TENS transcutaneous electrical nerve stimulation, RSFC resting state functional connectivity, SI primary somatosensory cortex, SRD subnucleus reticularis dorsalis, SMA supplementary motor area, MCC middle cingulate cortex, mPFC medial prefrontal cortex, L left, R right

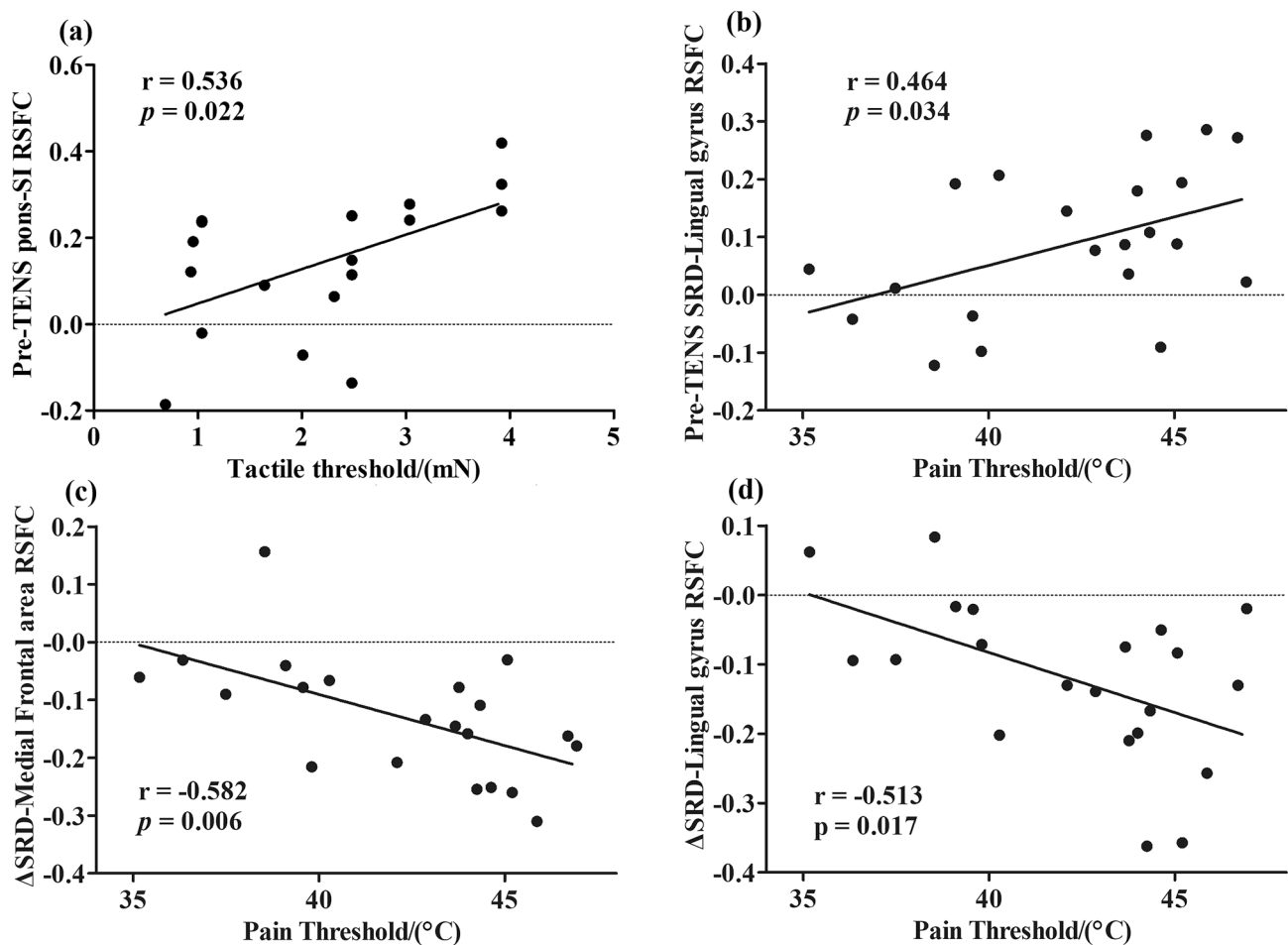


Fig. 5 Correlations between tactile/pain thresholds and neuroimaging variables. **a** In conventional TENS group, tactile threshold was positively correlated with pons-SI RSFC in the Pre-TENS session. **b** In acupuncture-like TENS group, pain threshold was positively correlated with SRD-lingual gyrus RSFC in the Pre-TENS session.

c In addition, pain threshold was negatively correlated with TENS-induced changes of RSFC between SRD and medial frontal areas, as well as **d** between SRD and lingual gyrus. TENS transcutaneous electrical nerve stimulation, SI primary somatosensory cortex, RSFC resting state functional connectivity, SRD subnucleus reticularis dorsalis

TENS-induced changes of RSFC between SRD and medial frontal areas (i.e., SMA, MCC, and mPFC; $r = -0.582$, $p = 0.006$; Fig. 5c) as well as between SRD and lingual gyrus ($r = -0.513$, $p = 0.017$; Fig. 5d). No other significant correlations were observed.

Discussion

Consistent with previous findings (Cho et al. 2014; Peng et al. 2019; Sabino et al. 2008), we showed that both conventional and acupuncture-like TENS produced an analgesic effect stronger than in the sham condition. Conventional TENS produced a spatially segmental analgesic effect, i.e., the analgesic effect was maximal when noxious contact heat stimuli were delivered homotopically to the same forearm that received the electrical pulses (Fig. 2). This spatially segmental analgesic effect was accompanied with decreased regional spontaneous brain activity in pons (Fig. 3) and decreased RSFC between pons and right SI (Fig. 4). Notably, tactile threshold was positively correlated with RSFC between pons and SI before the TENS procedure (Fig. 5). In contrast, acupuncture-like TENS produced a spatially diffuse analgesic effect, i.e., the analgesic effect was equally strong regardless whether noxious contact heat stimuli were delivered to the same or the different forearm that received the electrical pulses (Fig. 2). The spatially diffuse analgesic effect was associated with increased regional spontaneous brain activity in both RVM and SRD (Fig. 3) and decreased RSFC between SRD and medial frontal areas (e.g., SMA, MCC, and mPFC; Fig. 4). Importantly, pain threshold was significantly correlated with TENS-induced changes of RSFC within the SRD-related circuitry (Fig. 5). To sum up, conventional TENS and acupuncture-like TENS have different analgesic effects, which are mediated by different supraspinal neural mechanisms.

Supraspinal neural mechanism of conventional TENS

The observation that conventional TENS only decreased the subjective ratings of perceived pain in the forearm ipsilateral to the TENS side (Fig. 2) is in line with the gate control theory of pain (Melzack and Wall 1965): the activation of large-diameter A β fibers results in a segmental inhibition of the transmission of nociceptive information at the spinal cord dorsal horn level (Johnson 2007; Jones and Johnson 2009; Sluka et al. 1999, 2005). In addition to the spinal neural mechanism, we also observed that conventional TENS resulted in the decrease of regional spontaneous brain activity in pons (Fig. 3) and RSFC between pons and right SI (Fig. 4). Therefore, the analgesic effect of conventional TENS is likely to be contributed by the concomitance of

both spinal and supraspinal neural mechanisms. The concomitant contribution of both mechanisms has also been demonstrated in animal pain models, in which the analgesic effect of conventional TENS would be reduced by spinalization (Woolf et al. 1980) and by microinjection of the δ -opioid receptor antagonist naltrindole in both the spinal cord and brainstem (Kalra et al. 2001; Sluka et al. 1999). Since the pons sits between the medulla (where the RVM resides) and midbrain (where the PAG resides), it essentially forms an important bridge within the PAG-RVM network (Basbaum and Fields 1984). In addition, nuclei within the pons, such as the locus coeruleus, are involved in the control of pain through ascending projections to cortical brain areas and descending connections to the dorsal horn (Llorca-Torralba et al. 2016; Ossipov et al. 2014; Pertovaara 2006; Vila-Pueyo et al. 2018). Therefore, the pons would be a crucial area in the descending pain inhibitory system that is responsible for the analgesic effect of conventional TENS. Importantly, the pons-SI circuitry has been demonstrated to be also associated with pain modulation (Harper et al. 2018; Hougaard et al. 2017), e.g., increased RSFC between pons and SI was found during pain attacks (Hougaard et al. 2017). Accordingly, that the decreased RSFC between pons and SI is responsible for the analgesic effect of conventional TENS would be reasonable. However, we are aware that our observations (i.e., decreased regional spontaneous brain activity in pons and decreased RSFC between pons and right SI) could also reflect the modulation of the non-nociceptive somatosensory system by the long-lasting conventional TENS. The positive correlation between tactile threshold and RSFC between pons and SI in the Pre-TENS session (Fig. 5) would suggest that the pons-SI circuitry is likely to be responsible for the tactile information processing. In other words, we are not able to rule out the possibility that our observations are associated with the reduced neural processing of tactile information caused by repeated electrical pulses (i.e., habituation of the non-nociceptive somatosensory system) (Defrin et al. 2005; Pantaleao et al. 2011), and that the reduced tactile sensation is accompanied with the analgesic effect of conventional TENS.

Supraspinal neural mechanism of acupuncture-like TENS

In line with previous studies, we observed that acupuncture-like TENS produced a spatially diffuse analgesic effect (Fig. 2), in which the intensity of a painful stimulus (e.g., the noxious contact heat stimulus in the present study) is reduced by a second painful stimulus (e.g., acupuncture-like TENS in the present study) delivered at the same or a different body territory (Bars et al. 1979; Tang et al. 2015; Yarnitsky 2010). This phenomenon cannot be observed in patients with complete spinal cord transection (Albu et al.

2015; Roby-Brami et al. 1987) and in patients with lateral medullary lesions (but not in patients with thalamic vascular lesions) (De Broucker et al. 1990). Therefore, it is widely accepted that the circuitries lie within the brainstem are essential for the generation of the analgesic effect produced by acupuncture-like TENS (Bouhassira et al. 1992; DeSantana et al. 2009; Harper et al. 2018; Kalra et al. 2001; Knudsen et al. 2011; Villanueva et al. 1996). Some animal studies and human investigations showed that neural activity of SRD within the medulla played a crucial role in producing the spatially diffuse analgesic effect (Bouhassira et al. 1992; Villanueva et al. 1996). Consistent with this supraspinal neural mechanism, we observed that acupuncture-like TENS would result in the increased regional spontaneous brain activity in SRD (Fig. 3) and the decreased RSFC between SRD and medial frontal areas (e.g., SMA, MCC, and mPFC; Fig. 4). In addition to a previous human investigation showing that the DNIC analgesic effect was modulated by the strength of functional connectivity between SRD and prefrontal cortices (Youssef et al. 2016a), we found that pain threshold was not only positively correlated with RSFC between SRD and lingual gyrus in the Pre-TENS session, but also significantly correlated with TENS-induced changes of RSFC within the SRD-related circuitry (Fig. 5). This observation would suggest that SRD-related circuitry is responsible for the nociceptive information processing, which is crucial to determine the analgesic effect of acupuncture-like TENS. Altogether, acupuncture-like TENS could act via the activity of SRD, which receives inputs from higher-order brain regions (e.g., medial frontal brain areas) to modulate the transmission of nociceptive information through the descending inhibition (Villanueva et al. 1996).

In addition, the recruitment of the PAG-RVM network, i.e., acupuncture-like TENS would result in the release of endogenous opioids (e.g., binding to the μ -opioid receptors) in the PAG and RVM, was also believed to be a crucial supraspinal neural mechanism of the analgesic effect (DeSantana et al. 2009; Kalra et al. 2001). Indeed, we observed that acupuncture-like TENS increased regional spontaneous brain activity in RVM (Fig. 3). This observation is reasonable since the RVM, a final common relay in descending inhibition of nociception from supraspinal sites, receives inputs from higher-order brain areas (mainly from PAG) and sends descending inhibitory projections to the spinal cord to modulate the transmission of nociceptive inputs (Heinricher 1985). Please note that the analgesic effect of acupuncture-like TENS could be prevented by the blockade of opioid receptors in the RVM (Kalra et al. 2001). The increased regional spontaneous brain activity in RVM observed in the present study would reflect the enhancement of pain inhibition, thus producing the analgesic effect. However, acupuncture-like TENS did not elicit significant changes of RSFC between RVM with other brain areas,

even with regions in the descending pain inhibitory system (Fig. 4). This negative finding would suggest that the RVM-related circuitry would be less important in contributing to the analgesic effect of acupuncture-like TENS than the SRD-related circuitry. In other words, even the contribution of the RVM-related circuitry is non-negligible, the SRD-related circuitry plays a dominant role in producing the analgesic effect of acupuncture-like TENS.

Conclusion

Our data supported the involvement of different supraspinal neural mechanisms of the analgesic effects produced by conventional TENS and acupuncture-like TENS. In addition to the gate control theory of pain, the analgesic effect produced by conventional TENS was associated with the connectivity of the pons-related circuitry. In contrast, the analgesic effect generated by acupuncture-like TENS was contributed by both the SRD-related circuitry and the RVM. Indeed, whereas we focused on exploring the supraspinal neural mechanisms, the analgesic effects of both conventional TENS and acupuncture-like TENS would be associated with the descending inhibition via connections to the dorsal horn, for which the detailed mechanisms could be clarified by future work with combined spinal-brain fMRI.

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Author contributions All authors contributed to the study conception and design. The behavioral data were collected by YB and ZW. Data analyses were performed by YB. The first draft of the manuscript was written by YB and LH, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Institutional Review Board of the Institute of Psychology, Chinese Academy of Sciences, H18027) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All subjects provided written informed consent and were financially compensated for their participation.

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