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The transferable placebo effect from pain to emotion: Changes in behavior and EEG activity

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Abstract

Past studies indicate that the placebo expectation established by analgesic treatment significantly relieves pain perception, while ataractic treatment significantly alleviates unpleasant arousal evoked by negative picture processing. But it is unclear whether the placebo effect can be transferred from one domain to the other, namely from pain to emotion. In this study we led participants to believe in the analgesic effect of magnetic treatment equipment (the placebo) by secretly reducing the intensity of pain stimulus. Then, we examined if this placebo could significantly alter participants' negative affect evoked by watching unpleasant pictures. Our results indicated a significant transferable placebo effect that alleviated negative feelings. EEG recordings showed the transferable placebo treatment induced decreased P2 amplitude and increased N2 amplitude, with source location near the posterior cingulate.

Descriptors: Transferable placebo effect, Pain, Negative emotion, Expectation, Event-related potentials

The placebo effect has been widely found to be effective in the field of pain (Amanzio & Benedetti, 1999; Levine, Gordon, & Fields, 1978; Petrovic, Kalso, Petersson, & Ingvar, 2002; Zubieta et al., 2005), Parkinson's disease (Benedetti et al., 2004; de la Fuente-Fernandez et al., 2001; Pollo et al., 2002), and depression (Leuchter, Cook, Witte, Morgan, & Abrams, 2002; Mayberg et al., 2002) from both neuropharmacological and neuroanatomical viewpoints. However, its underlying psychological and neurobiological mechanisms are still poorly understood. Recent neuroimaging studies have revealed the brain basis of placebo effects on pain and emotion regulation (Petrovic et al., 2005; Wager et al., 2004). However, in these studies the investigators only focused on the placebo effect obtained within a single domain. That is, they either studied the analgesic effect of a pain-alleviating expectation (Kong et al., 2006; Matre, Casey, & Knardahl, 2006; Wager, Matre, & Casey, 2006) or the ataractic effect of an anxiety-reducing expectation (Petrovic et al., 2005). What is currently unclear is whether the placebo effect is transferable across domains, from pain to emotion. The present study addresses this issue by investigating whether the placebo expectation derived from pain relief can significantly impact the intensity of anxiety as well.

In Experiment 1, in the belief-establishing stage, participants were made to believe in the pain-alleviating effect of magnetic treatment equipment (the placebo). Unbeknownst to the participants, the supposed "analgesic" effect was actually due to our reduction of the intensity of the pain-evoking stimulus. In the testing stage of the transferable placebo effect, participants were told that the magnetic treatment equipment could also decrease the negative feelings induced by unpleasant pictures. Participants were required to evaluate the intensity of their negative feelings as they viewed unpleasant pictures with the placebo equipment turning on or off.

In this study, we explored the transferable effect of the placebo, first at the behavioral level (Experiment 1) and then at the electrophysiological level (Experiment 2). In Experiment 2, we used event-related potentials (ERPs), to test whether participants' subjective reports on emotional arousal reflected a response bias caused by experimenter demand, or whether they reflected underlying neural processes. Due to its good time resolution, ERP can provide precise time windows for us to monitor the time course of the perception and processing of unpleasant pictures. Previous research has shown that the early processing of visually presented emotional stimuli is related to P2 and N2, typically within 100–300 ms from stimulus onset (Ortigue et al., 2004; Pizzagalli, Regard, & Lehmann, 1999), and peaking at approximately 200 and 250 ms, respectively (Daffner et al., 2000; Tales, Newton, Troscianko, & Butler, 1999). Thus, if the transferable placebo effect were truly generated through internal emotional arousal, especially early automatic emotional arousal, then we would expect to observe significant ERP differences

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between the placebo and the control conditions, particularly in P2 and/or N2.

We wanted to investigate whether a *direct* analgesic placebo effect also existed in our experimental setup and, if so, how its perceptual and emotional components might relate to those of the transferable effect. Thus, in Experiment 3, we examined both the placebo's analgesic effect on painful laser stimulation (i.e., the direct analgesic placebo effect) and its ataractic effect on unpleasant picture processing (i.e., the transferable placebo effect).[1] During the testing of the placebo's analgesic effect, participants were asked to evaluate the sensory and then the affective pain of each pain stimulus, sequentially. These evaluations were then correlated with the reported negative emotional arousal induced by watching the unpleasant pictures. If the transferable placebo effect is a direct result of the conditioned anxiety-reducing responses established in the pain-placebo training phase, then we would expect the affective pain reduction obtained by the direct analgesic placebo effect to be highly correlated with reduction of visual unpleasantness. In contrast, if the transferable placebo effect is mainly caused by the interaction between placebo expectation and subsequent cognitive-affective processing to each target picture, then this correlation would be lower.

To sum up, we employed a transferable model of placebo effect in three experiments to test the following three questions in the present study: (1) Does placebo effect derived from pain relief have a significant impact on the processing of unpleasant pictures? (2) If the transferable effect of placebo does exist, then how do placebo treatments alter early visual emotional processing? (3) Is affective pain reduction correlated with reduction of visual unpleasantness? To address the first and third questions, we relied on participants' subjective evaluation of sensory and affective pain, and of the unpleasantness of negative pictures as the placebo equipment was turned on and off. To address the second question, we used ERPs, focusing particularly on the P2 and N2 amplitudes in the control and placebo conditions.

Experiment 1

Methods

Participants. Thirty-two right-handed subjects participated in Experiment 1. They reported normal or corrected-to-normal vision. They were randomly assigned to either the reinforced expectation group (age: 20.44 ± 0.89, 8 females, 8 males) or the verbal expectation group (age: 20.19 ± 0.83, 8 females, 8 males). All subjects were free of medication and gave written informed consent in accordance with the ethical guidelines of the Institute of Psychology, Chinese Academy of Sciences.

Stimulation. Pain stimulus was delivered by CO2 laser stimulator (DIMEI-300, Changchun Optoelectronic Technology Dimei Co., Ltd., Changchun, China). Spot diameter was 2.5 mm and pulse duration 100 ms. The output energy was kept below 300 mJ to avoid skin damage. The stimulus was applied to the dorsum of the right hand, with each presentation of the stimulus occurring at a different spot to avoid habituation. The subjects orally reported pain intensity using a visual analog scale ranging from 0 mm to 100 mm, with 0 indicating no pain, 100 indicating unbearable pain.

[1]We thank our anonymous reviewer for the suggestion to discuss this issue.

Thirty-six unpleasant pictures selected from the International Affective Picture System (IAPS) including snakes, spiders, and residues (Lang, Bradley, & Cuthbert, 2001) were used in the study. The pictures, sized 10 cm $\times$ 7 cm, were presented on a color computer monitor placed approximately 70 cm from subjects' eyes. These images subtended a visual angle of approximately 8.18° horizontally and 5.72° vertically.

Experimental Procedure

The reinforced expectation group. Participants in this group were told that they were taking part in a study on magnetic treatment equipment's effect on alleviation of pain and negative emotion. In fact, the presence of the equipment was a pretense, as we were only interested in studying the placebo effect. Participants were told that in accordance with the acupuncture point theory of traditional Chinese medicine, the magnetic equipment would exert an analgesic effect if it were connected with an electrode to the *Hegu* acupoint of the hand receiving pain stimulus. They were also told that if the magnetic equipment were connected with an electrode to the *Dazhui* acupoint located at the back of the neck, any negative emotional arousal would be reduced. Participants were told that in order for the equipment to operate, the electrode had to be clamped to it; once the electrode was disconnected, the equipment would not operate. Participants were able to clearly see at all times whether or not the electrode was clamped to the equipment.

After the instructions were given, participants underwent three experimental phases: (1) the pain accommodation phase; (2) the expectation manipulation phase based on pain; and (3) the test phase of placebo effect on negative emotional arousal.

In the accommodation phase, participants were familiarized with the laser pain by receiving two sequences of increasingly intense stimuli. Each sequence consisted of 6–7 stimuli, with output energy of 80 mJ, 120 mJ, 160 mJ, 200 mJ, 240 mJ, 280 mJ, and 300 mJ. To relieve any fears and uncertainties about the upcoming expectation manipulation phase, subjects were assured that the stimulus intensity used in the formal part of the experiment would not exceed the strongest stimuli used in the accommodation phase. In the expectation manipulation phase, participants received four blocks of painful laser stimulation. Participants were told that the intensity of the stimuli was uniform within and across each of the four blocks. In fact, however, stimuli intensity varied, with six low intensity stimuli (120 mJ) delivered in the first and third blocks while the clamp was connected to the electrode (indicating the equipment was turned on), and six high intensity stimuli (220 mJ) delivered in the second and fourth blocks while the clamp was disconnected (suggesting the equipment was turned off). Therefore, in our settings, participants didn't know the pain had been surreptitiously reduced in the placebo blocks, they were made to believe pain-reducing effect was caused by the placebo. This method has been employed by past studies (Colloca & Benedetti, 2006; Kong et al., 2006). In the final test phase, we used unpleasant pictures to test the placebo's transferable effect in alleviating negative feelings. After a brief practice block including eight unpleasant pictures, participants went through six blocks of unpleasant pictures. Three blocks were presented with the electrode connected to the equipment (the placebo condition, [p]), while the other three blocks were presented with the electrode disconnected to the equipment (the control condition, [c]). The sequence of the six blocks was arranged as c-p-c-p-c-p for half of the participants,

and p-c-p-c-p-c for the other half (order counterbalanced across participants). Each block contained 6 pictures and lasted for about 2 min. There was an inter-block rest of 1 min. Each picture was presented for 6 s with a random pre-stimulus interval that varied from 6 s to 10 s, during which a black screen with a cross was presented. Participants were asked to passively perceive the picture during its presentation and press the spacebar when the picture disappeared from the screen. Then, they were required to orally rate the unpleasantness elicited by the picture that had just been presented, using a 100-point scale with 0 indicating no unpleasantness and 100 indicating unbearable unpleasantness. Participants pressed the spacebar to advance to the next trial. For each participant, the 36 unpleasant pictures were randomly assigned to the six blocks, with the average emotional value of each block comparable. Several days after the experiment, the experimenter re-interviewed the participants and debriefed them about the true purpose of the experiment.

The verbal expectation group. In order to investigate whether verbal expectation, based purely on verbal induction and without pain-alleviating reinforcement, could also result in a detectable effect on alleviating unpleasantness, participants in this group were only verbally told that the placebo equipment could reduce negative emotional arousal. In order to keep the experimental setup comparable with that of the reinforced expectation group, the participants in this condition also experienced three phases: the pain accommodation phase, the pain assessment phase that was not related to the placebo equipment, and a test session of emotional placebo effect that was based purely on verbal instruction. Different from the reinforced expectation group, participants in this group were told that they would take part in two unrelated experimental parts: the pain-evaluating part and the emotion-alleviating part. This group received the same pain accommodation phase as the first group. The participants in this group then received the pain assessment phase in which, like the first group, they were also asked to report as accurately as possible their pain as the laser intensity switched between high and low level for four blocks of painful laser stimuli. But unlike the first group, this second group was not told anything about the magnetic treatment equipment. It was only during the emotion-alleviating part that participants were introduced to the magnetic treatment equipment and told about its supposed effect on negative emotional responses. The introduction of the magnetic treatment equipment and experimental procedure were identical as that given to the first group of participants.

The procedure of the experiment is depicted in Figure 1.

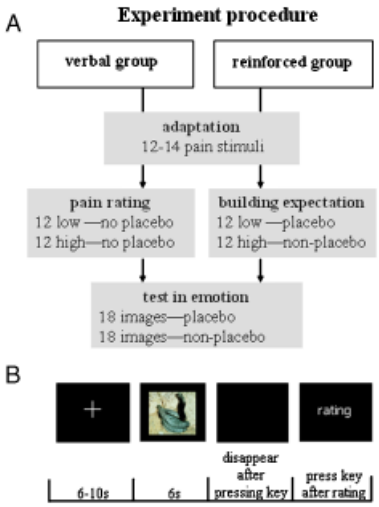

Figure 1. (A) There were two groups, the verbal expectation group and the reinforced expectation group. Each group involved three phases: accommodation, manipulation, and test. After accommodation to two increasing series of laser stimuli, participants in the two groups received laser stimuli at high and low intensities in the manipulation session. The verbal expectation group was asked to evaluate pain intensity. The reinforced expectation group received high intensity pain when the magnetic treatment equipment (the placebo) was turned off, but secretly reduced intensity pain when the placebo was turned on. The aim of this arrangement was to make participants in the expectation group establish a higher placebo expectation. During the test session, participants in the two groups both received six blocks of negative pictures in placebo and control conditions at high unpleasantness. The order of the blocks was counterbalanced across participants. (B) Timeline of events on each trial in the third phase. A fixation is presented first, followed by a photo. Then a black screen appears, remaining until the spacebar is pressed. Finally, participants provide a rating of their current negative affect.

Statistical Analysis

Unpleasantness ratings on negative pictures in the test phase were analyzed with a within-subjects factor (conditions: placebo vs. control) and a between-subjects factor (groups: verbal expectation group vs. reinforced expectation group) by means of repeated measures ANOVA. Post hoc analyses were conducted to explore the interaction effects. All the analysis was carried out using SPSS for Windows software, version 10.0.

Results

There was a significant main effect of the condition factor [$F(1,30) = 18.673$, $p < .001$, $\eta_p^2 = .384$] on mean unpleasantness ratings, indicating that unpleasantness ratings decreased with the placebo treatment. Condition × group interaction on Unpleasantness ratings was also significant, $F(1,30) = 5.28$, $p = .029$, $\eta_p^2 = .150$. Simple main effect test (paired t-test) revealed that unpleasantness ratings within the verbal expectation group were not significantly decreased in the placebo condition ($M \pm SD$: 50.623 ± 23.709) compared to control condition ($M \pm SD$: 53.69 ± 24.856), $t(15) = 1.617$, $p = .127$, whereas unpleasantness ratings within the reinforced expectation group were significantly decreased in the placebo condition relative to the control condition, $t(15) = 4.242$ ($M \pm SD$: control, 51.477 ± 22.562; placebo, 41.446 ± 21.511), $p < .001$. There were no significant between-subjects differences in either the control condition [$t(30) = 0.264$, $p = .794$] or placebo condition [$t(30) = 1.147$, $p = .261$]. This result is shown with a bar in Figure 2.

Experiment 2

According to Experiment 1, the transferable placebo effect was significant only in the reinforced expectation group. Therefore, in Experiment 2, we directly adopted the procedure used on the reinforced expectation group to detect how the transferable placebo effect influenced electroencephalogram (EEG) activities.

Methods

Subjects. Twenty right-handed participants participated in the study (age: 20.35 ± 1.09, ten females, ten males). They reported normal or corrected-to-normal vision. All were free of

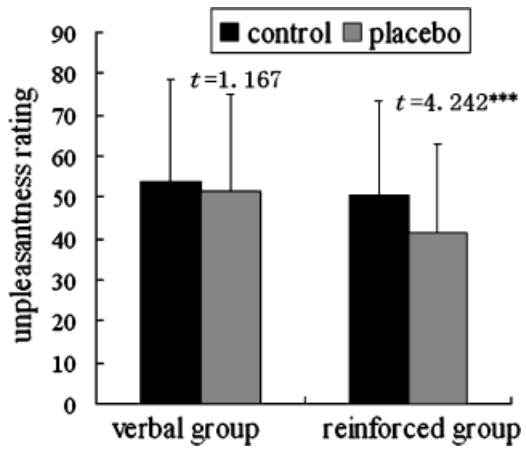

Figure 2. Unpleasantness ratings under placebo and control conditions in verbal expectation group and reinforced expectation group. Notably, placebo reductions in unpleasantness rating were significant only in the reinforced expectation group.

medication and gave written informed consent in accordance with the ethical guidelines of the Institute of Psychology, Chinese Academy of Sciences.

Stimulation. The intensity of pain stimuli and the size of negative emotion pictures were identical to the first experiment. In this experiment each picture was presented for 2 s with a random pre-stimulus interval that varied from 1.3 s to 1.7 s, during which a cross was presented. The purpose of shortening stimulus-presentation duration and pre-stimulus interval was to present sufficient stimuli to fulfill the requirements necessary for data analysis with an ERP setup. The participants orally rated the unpleasant feeling of each picture on a 100-point scale identical to Experiment 1.

Experimental Procedure

We continued to adopt the reinforced expectation paradigm to investigate the second question: how does the transferred placebo effect alter the electrophysiological activities of processing emotionally negative visual stimuli? Identical to the reinforced expectation group in Experiment 1, there were three phases in Experiment 2: the pain accommodation phase, the expectation manipulation phase, and the test phase of the transferable placebo effect. In order to make sure the experimental settings of the expectation manipulation phase and the test phase were as similar as possible, we had participants wear the elastic cap in both phases and told them that EEG activities were being recorded throughout. In actuality, EEG was only recorded in the third test phase. We selected 100 pictures from IAPS. Given the afferent accent of the emotional stimulus was not always centrally located, we created another 100 mirror images to counterbalance this. This resulted in a total of 200 pictures. The 100 original pictures were used in the first four blocks, with each containing 25 pictures. The 100 mirror images were used in the latter four blocks. The eight blocks were ordered c-p-c-p-c-p-c-p for half of the subjects and p-c-p-c-p-c-p-c for the other half.

EEG Recording

During participants' perception of unpleasant pictures, EEG was recorded from 64 scalp sites using Ag/AgCl electrodes mounted in an elastic cap (Neuroscan Inc., El Paso, TX, USA). The reference was the computed value of average mastoids. When the EEG was recording, all of the scalp sites and the right mastoid were referenced to the left mastoid. The average mastoids reference derivation for a given site was computed off-line using the formula $a' = a\text{-}(r/2)$, where a' is the desired value for a site with averaged mastoids reference, and a and r are the recorded values of this site and the right mastoid, respectively. The vertical electrooculogram (VEOG) and horizontal electrooculogram (HEOG) were recorded with two pairs of electrodes, one placed above and below the left eye, and another 10 mm from the outer canthi of both eyes. All interelectrode impedance was maintained at 0.5 kω. Signals were amplified with 0.05–100 Hz bandpass filter and digitized at 500 Hz. The EEG data from the placebo and control conditions were digitally filtered with 30 Hz low-pass and were epoched into periods of 1200 ms (including a 200 ms pre-stimulus baseline). Ocular artifacts were removed from the EEG signal using a regression procedure implemented in the Neuroscan software (Semlitsch, Anderer, Schuster, & Presslich, 1986). Trials with various artifacts were rejected, with a criterion of $\pm$ 75 mV. The peak amplitudes of the early components P2 and N2 were measured.

Analysis

We performed statistical comparisons by means of repeated measures ANOVA. All the analysis was carried out using SPSS for Windows software, version 10.0. The P2 component was mainly distributed over frontal electrodes and was analyzed accordingly at the following 14 sites: FP1, FP2, AF3, AF4, AF7, AF8, FPz, F1, F2, F3, F4, F5, F6, Fz. The N2 component, which was more broadly distributed, was analyzed at the following 20 sites: FPz, FP1, FP2, AF7, AF8, Fz, F1, F2, F5, F6, Cz, C1, C2, C5, C6, Pz, P1, P2, P5, P6. Thus the factors of P2 analysis were Condition (placebo vs. control) $\times$ Anterior-Posterior (FP and F) $\times$ Laterality (left1, left2, left3, midline, right1, right2, and right3). The factors of N2 analysis included Condition (placebo vs. control) $\times$ Laterality (left1, left2, midline, right1, and right2) $\times$ Anterior-Posterior (FP, F, C, and P). The Greenhouse–Geisser correction was used to compensate for sphericity violations.

In conducting EEG analysis, in addition to studying the whole group, we also analyzed the participants who showed a significant transferable placebo effect (the responders) and those who did not (the non-responders). The responders were defined as the higher half ($n = 10$) whose rating scores decreased by more than the mean group reduction, and the non-responders were the lower half ($n = 10$) whose rating scores decreased by less than the mean group reduction.

Dipole source analysis was carried out using Curry v4.6 software (Neurosoft, Inc., El Paso, TX, USA). Principle component analysis (PCA) was employed on the grand average ERP data to get the maximal signal–noise ratios for dipole modeling (Supek & Aine, 1993). The rotating dipole modeling was applied in dipole source analysis. According to PCA method, we used one dipole to reconstruct the sources of P2 (over the time range of 150–250 ms) and of N2 (over the time range of 200–300 ms) with a three-shell spherical model. The final reported coordinate was referred to the Talairach human brain atlas.

Results

Behavior results. T-test revealed that unpleasantness ratings were significantly lower in the placebo condition than the control condition, $t(19) = 5.09$ ($M \pm SD$: control, 52.676 $\pm$ 19.131; pla-

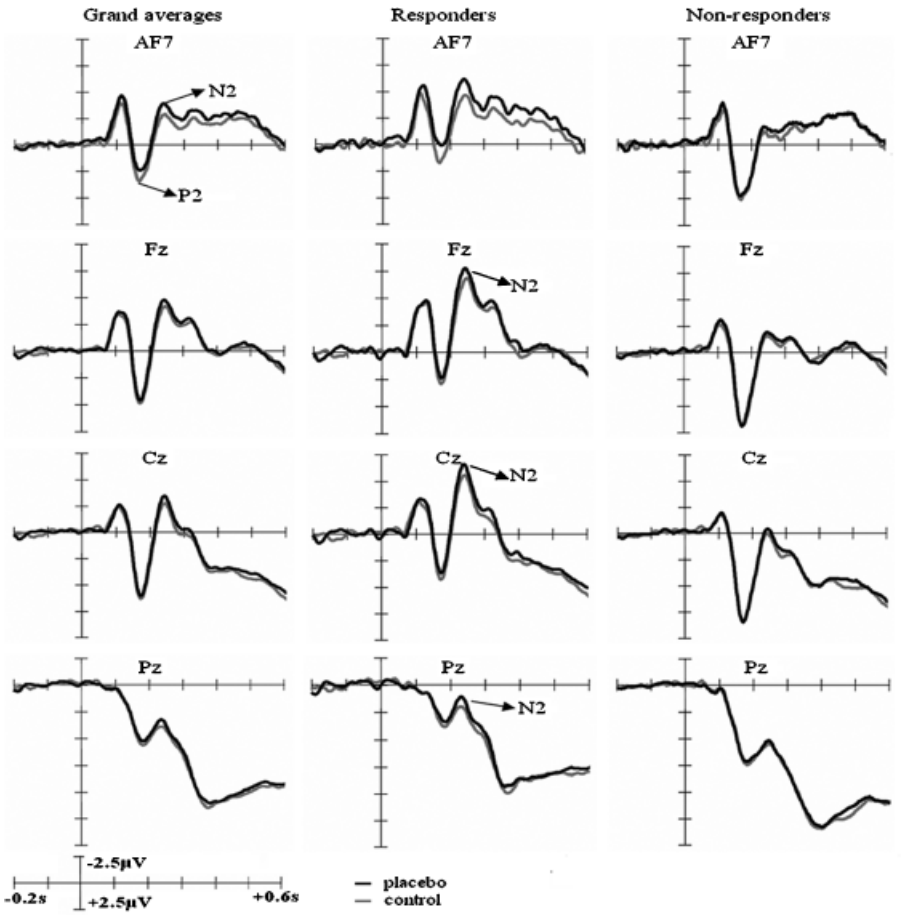

Figure 3. Left column: grand averages across all participants. Middle column: grand averages for the placebo responder group ($n = 10$). Right column: grand averages for non-responders ($n = 10$). Responses in the placebo condition are shown by the black lines, and responses in the control condition are shown by the gray lines.

cebo, 45.087 ± 18.704), $p < .001$. It was consistent with the results of Experiment 1.

ERPs. Figure 3 shows P2 and N2 in both placebo and control conditions across all 20 subjects. The placebo effect showed a trend towards significance for the P2 component, $F(1,19) = 3.624$, $p = .072$, $\eta_p^2 = .16$. The Condition × Anterior-Posterior interaction for P2 amplitude reached significance, $F(1,19) = 4.746$, $p = .042$, $\eta_p^2 = .2$. Laterality didn't interact with condition effect. Simple main effect test (paired t-test) revealed that the effect of Condition for P2 amplitude was significant at prefrontal locations, $t(19) = 2.470$ ($M \pm SD$: control, 43.876 ± 49.552; placebo, 37.421 ± 53.921), $p = .023$, $\eta_p^2 = .243$. The placebo effect was maximal at AF7. The results show that in the placebo condition, P2 amplitude was lower, while N2 amplitude was significantly higher, $F(1,228) = 11.592$, $p = .003$, $\eta_p^2 = .379$. The Condition × Anterior-Posterior interaction and condition × Laterality interaction were not significant. In the present study, the placebo effect on N2 amplitude was maximal at AF7.

Figure 3 also shows the placebo effect on the responder (10 subjects) and non-responder (10 subjects) subgroups. There was no placebo reduction in P2 amplitude in either responders or non-responders. N2 amplitude was more significantly augmented in the placebo condition for the responders, $F(1,108) = 23.343$, $p < .001$, $\eta_p^2 = .722$, the Condition × Anterior-Posterior and condition × Laterality interaction didn't reach significance. It appears that N2 was more sensitive to the placebo condition than P2.

Relationship of P2 and N2 amplitude to unpleasant ratings. The correlation between EEG activity patterns and changes in unpleasantness ratings of placebo was analyzed. Changes were calculated by subtracting ratings in the placebo condition from those in the control condition. The correlations between average changes in P2 ($r = .122$, $p = .608$) and N2 ($r = -.226$, $p = .339$) amplitude and changes in unpleasantness rating were not significant.

Source localization. Single source analysis showed that the dipole locations of P2 and N2 were close to the posterior cingulate cortex in both the control condition and placebo condition (Table 1 and Figure 4). This suggests that the negative emotional responses in the two conditions are related to this area.

Experiment 3

Methods

Subjects. Twenty-four right-handed participants participated in the study (age: 24 ± 1.89; 11 females, 13 males). They reported

Table 1. *Main Focus Provided by Curry 4.6 for P2 and N2*

		Talairach (x, y, z)	Residual Variance	Regions	
Control	P2	4, −62, 14	8.58%	Limbic lobe, Posterior cingulate	BA 23, range = 0
Condition	N2	2, −53, 25	6.53%	Limbic lobe, Cingulate gyrus	BA 31, range = 1
Placebo	P2	1, −60, 14	7.92%	Limbic lobe, Posterior cingulate	BA 23, range = 1
Condition	N2	2, −52, 23	6.82%	Limbic lobe, Posterior cingulate	BA 23, range = 2

normal or corrected-to-normal vision. All subjects were free of medication and gave written informed consent in accordance with the ethical guidelines of the Institute of Psychology, Chinese Academy of Sciences.

Stimulation. The settings for the pain stimuli used in Experiment 3 were identical to that used in Experiments 1 and 2. Each picture was presented for 4 s at full-screen size with a pre-stimulus interval of 3 s, during which a cross was presented. Participants were asked to passively perceive the picture during its presentation and press the spacebar when the picture disappeared from the screen. Then, they were required to orally rate the unpleasantness of the presented picture using the 100-point scale with 0 indicating no unpleasantness, 100 indicating unbearable unpleasantness. Then they pressed the spacebar to proceed to the next trial.

Experimental Procedure

Different from Experiments 1 and 2, in this experiment we examined the placebo effect on both pain and negative emotion in the test phase. There were two parts: section A and B. For the four blocks in section A, pain stimuli were administered first, followed by unpleasant pictures. Every block included 3 pain stimuli and 3 emotional pictures. The four blocks were ordered c-p-c-p for 6 subjects and p-c-p-c for the other 6 subjects. The participants were asked to give affective pain and sensory pain ratings for each pain stimulus, and give unpleasantness ratings for each unpleasant stimulus on a 100-point scale. In section B, the order of pain and emotional stimuli presentation was reversed, with unpleasant pictures presented first, followed by pain stimuli in each of the four blocks. The four blocks were ordered c-p-c-p for 6 subjects and p-c-p-c for the other 6 subjects. Different from section A, every block in section B included 5 emotion stimuli, not 3. This was done to increase the diversity and representativeness of image content. To explain the difference between intensity of pain and unpleasantness of pain to the subjects, standard instructions, as used by Price, McHaffie, and Larson (1989), were given: "We are interested in two aspects of sensory experience. One is the intensity, that is, how strong the stimulus is felt. The other is unpleasantness, or how disturbing the stimulus is for you. The distinction between these two aspects of sensory experience might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds, or how unpleasant it is to you. The intensity of the stimulus is like loudness, and the unpleasantness of the stimulus depends not only on intensity but also on other factors that may affect you. These are scales for measuring each of these two aspects of sensory experience. Although some sensory experiences may be equally intense and unpleasant, we would like you to judge these two aspects of your sensation independently."

Statistical Analysis

We performed statistical analysis using paired *t*-test and partial correlations which excluded the influences of two orders (i.e., the order of control condition vs. placebo condition and the order of pain stimuli vs. emotional stimuli). All the analysis was carried out using SPSS for Windows software, version 10.0.

Results

Statistical analysis revealed that the placebo expectation established in the reinforced stage not only induced evident placebo effect on sensory pain and affective pain, but also significantly decreased unpleasantness ratings induced by negative pictures. The results are shown in Table 2. Further partial correlation analysis showed that through the placebo treatment, changes in

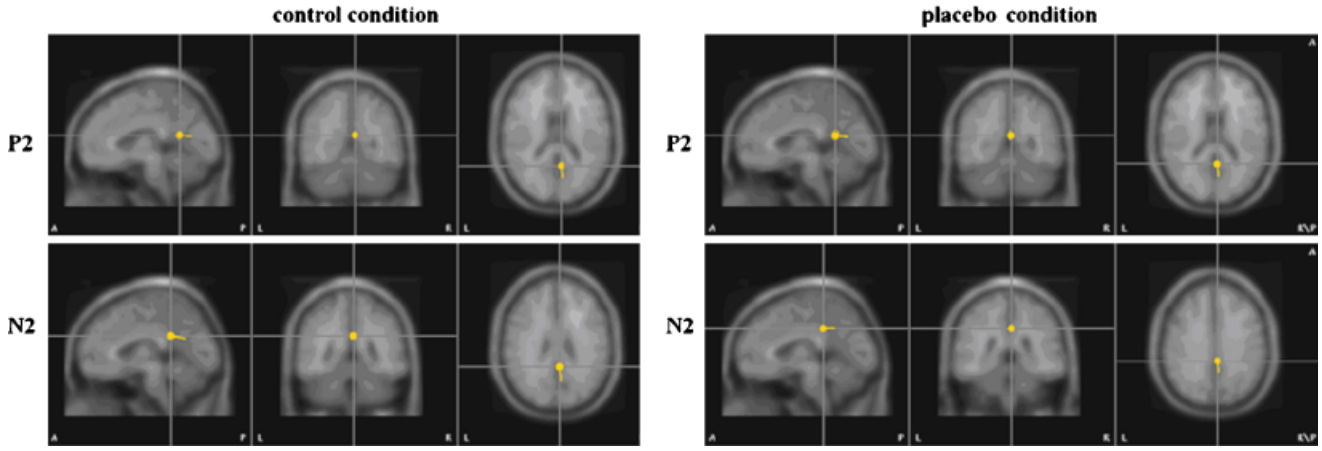

Figure 4. Dipole source localization for P2 and N2 is reconstructed on the three-shell head model. The main focus of each is close to the posterior cingulate represented by the dipole location.

Table 2. *Comparison of Control Condition and Placebo Condition*

	Control	Placebo	t	p
Sensory pain	33.462 ± 21.196	22.408 ± 13.795	4.430	.000
Affective pain	29.658 ± 20.995	23.202 ± 17.717	2.755	.011
Unpleasant emotion arousal	56.260 ± 22.119	51.302 ± 22.297	2.923	.008

sensory pain were significantly correlated with changes in affective pain ($r = .769$, $p < .001$). However, neither individual changes in sensory nor affective pain were correlated with changes in unpleasantness ratings of negative pictures ($r = -.085$, $p = .708$; $r = .136$, $p = .547$). The participants who showed greatest placebo analgesic effect did not manifest the most decease in visually-induced unpleasant feelings.

Discussion

This study showed that the placebo expectation established from pain alleviation did alter the level of negative emotional arousal caused by perceiving unpleasant pictures. Experiment 1 showed that the expectation, which was reinforced by actual analgesia, was transferable and could produce significant placebo effect on negative emotional arousal. However, the expectation that was merely induced by verbal instruction did not have such power. This finding was consistent with many past studies that obtained significant analgesic placebo effect through pain-reducing reinforcement (Colloca & Benedetti, 2006; Price et al., 1999). Although there is some experimental evidence showing expectations established by verbal instructions can also evoke significant placebo effect (Benedetti et al., 2003; Klinger, Soost, Flor, & Worm, 2007), reinforced expectation before formal placebo treatment is much more widely recommended and adopted in most studies (Kong et al., 2006; Petrovic et al., 2005; Wager et al., 2004). The results of the present study suggest that reinforced expectation before formal placebo treatment is necessary to induce significant transferable placebo effect. Experiment 3 further proved that the placebo expectation that was established from pain-reducing reinforcement not only induced significant placebo effect on pain, but also significant placebo effect on unpleasant feeling.

So far, two kinds of mechanisms have been proposed to account for the placebo effect: expectation (Kirsch, 2004; Price & Fields, 1997) and conditioning (Ader, 1997; Siegel, 2002). We believe that the transferable placebo effect investigated in this study was brought about mainly through expectation for three primary reasons. First of all, expectation is believed to play an important role when the placebo effect happens in conscious processes (e.g., pain perception and motor performance or emotional arousal in the present study). In contrast, conditioning is more widely cited to explain the placebo effect occurring unconsciously (such as hormone secretion) (Benedetti et al., 2003). The second reason that expectation seems to be supported in this study is that the procedure of transferable placebo effect is different from the typical experimental setting in which a single effect—whether analgesic or sedative—is induced in both the pre-experimental reinforcement stage and the experimental placebo treatment stage. Unlike conventional studies, here, we reinforced one placebo effect (the analgesic effect) in one experimental situation (receiving painful stimulation), but examined the placebo's other effect (the anti-anxiety effect) in another experimental situation (watching unpleasant pictures). With this cross-domain setup, we are able to separate the cognitive role played by the placebo from its conditioning role, allowing us to highlight and study the cognitive meaning of placebo expectations. Lastly, in Experiment 3, the reductions in affective pain were closely related to changes in sensory pain, but not related to reductions in visual unpleasantness. These results support the viewpoint that the reduction of affective pain based on the conditioning mechanism plays an important role in the placebo analgesia (McGlashan, 1969; Staats, Staats, & Hekmat, 2001; Vase, Robinson, Verne, & Price, 2003), but can't explain the transferred placebo effect on visual unpleasantness. Therefore, it is reasonable to conclude that it is not unconscious conditioning but conscious expectation that primarily contributes to the transferable placebo effect on unpleasant feelings. It is likely that the size of the transferable placebo effect is due to the interaction between placebo expectations and cognitive-affective processing of each target picture.

The transferable placebo expectation might modulate emotional response through regulating cognition processing (Knutson, Fong, Adams, Varner, & Hommer, 2001; Ochsner & Gross, 2005; Ochsner et al., 2004) and attentive control to threatening emotional stimuli (Pessoa, McKenna, Gutierrez, & Ungerleider, 2002). That is, the expectation for the efficacy of the placebo may help participants to anticipate the consequences of processing unpleasant pictures more optimistically and even enable them to tackle threatening stimuli more positively. Alternately, expectation of the placebo may enable participants to allocate less attentive resources to the threatening stimuli and consequently diminish the unpleasantness aroused by these stimuli. These possibilities are consistent with our EEG findings. EEG recordings showed the transferable placebo treatment was accompanied by increased N2 amplitude and decreased P2 amplitude. N2 amplitude has been found to be higher when perceiving positive/neutral pictures than negative ones (Carretie, Hinojosa, Martin-Loeches, Mercado, & Tapia, 2004), implying N2 amplitude is positively correlated with pictures perceived to be less emotionally negative. More importantly, enhanced N2 amplitude likely implies more positive expectation and cognitive control. For example, Carretie, Martin-Loeches, Hinojosa, and Mercado (2001) observed that N280 amplitude significantly increased in response to cues announcing positive and neutral targets, but not to cues announcing negative targets, implying increased N2 amplitude is related to positive expectation. Moser, Hajcak, Bukay, and Simons (2006) found that the intentional suppression of emotional responses to unpleasant stimuli was accompanied with enhanced N2 magnitudes relative to passively viewing, implying increased N2 amplitude could also be related to cognitive control and positive coping strategy. Unlike the increased N2, the P2 component decreased in the transferable placebo condition. Previous studies indicate that greater P2 amplitude is associated with more attentive processing in viewing negative pictures relative to neutral pictures (Carretie, Hinojosa, Martin-Loeches, Mercado, & Tapia, 2004; Huang & Luo, 2006). Furthermore, in placebo analgesia, lower P2 amplitudes were seen at midline electrodes in the placebo blocks than in control ones, perhaps reflecting reduced attention to painful stimuli (Garcia-Larrea, Frot, & Valeriani, 2003; Wager, Matre, & Casey, 2006).

The above analyses suggest that higher N2 amplitude might represent increased top-down cognitive regulation driven by expectation, whereas lower P2 amplitude might go with reduced attentional bias to threatening stimuli. Additionally, significant

differences between the transferable placebo condition and the control condition (i.e., P2 and N2) were observed within the first 150–300 ms, a duration brief enough to rule out the possibility that differences between the two conditions merely reflect a bias "to try to please the investigator" (Hajcak & Nieuwenhuis, 2006).

Single source analysis showed the dipole locations of P2 and N2 were close to the posterior cingulate cortex both in the control condition and placebo condition. This implies that the negative emotional responses in the two conditions are related to this area. A functional magnetic resonance imaging (fMRI) study (Maddock, Garrett, & Buonocore, 2003) also found that, compared to neutral words, both unpleasant and pleasant words activated the posterior cingulate cortex significantly more bilaterally.

Previous fMRI studies found reported pain was significantly correlated with brain activation (Petrovic et al., 2005; Wager et al., 2004). But in this study, the subjects who exhibited the largest placebo reduction in reported unpleasantness didn't show the largest P2/N2 placebo changes. This low brain–behavior correlation has also been observed in previous studies on pain–related placebo effect (Wager, Matre, & Casey, 2006). One factor that might account for this discrepancy is that the placebo effect on reported unpleasantness involved multiple components, only one of which has an effect on early emotion processing (Wager, Matre, & Casey, 2006). The existence of both early and late components would make the relationship between P2/N2 and reported effects difficult to detect. Such a factor may account for why the placebo analgesia had no significant correlation with the placebo anti-anxiety effect.

In sum, the present study suggests that placebo expectation built on analgesic experiences produces a transferable placebo effect on reported unpleasantness. The transferred placebo treatment also produces detectable amplitude decreases in the P2 component and increases in the N2 component of unpleasant stimuli. These observations imply a meaningful difference between the cross-modal placebo condition and the control condition in the early processing of negative pictures.

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