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A transferable anxiolytic placebo effect from noise to negative effect

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Abstract

Background: The placebo effect in relieving negative emotion arousal is poorly understood.

Aims: We examined whether placebo expectation established with noise stimuli could have a transferable anxiolytic effect on negative emotion arousal.

Methods: In Experiment 1, noise intensity was surreptitiously lowered during placebo condition in the preconditioning phase to reinforce placebo expectation, and the noise-relieving placebo effect was assessed in the testing phase. In Experiment 2, the same manipulation as in Experiment 1 was administered in the preconditioning phase, but the anxiolytic placebo effect was assessed in the testing phase using negative pictures.

Results: Intensity and annoyance by the noise in Experiment 1 were significantly reduced, and unpleasantness in Experiment 2 was also significantly reduced in the placebo condition.

Conclusion: Direct noise-relieving placebo effects and transferred anxiolytic placebo effects were found. The present study provides evidence that the placebo effect can be transferred from noise to emotion.

Introduction

It is valuable to investigate ways to regulate negative emotional reactions as they comprise some of the main causes of suffering and dysfunction (Beauregard et al., 2001). In this context, anxiolytic placebo effects are an important issue that is still poorly understood. Reinforcing placebo expectation is considered crucial in producing noticeable placebo effect (Colloca & Benedetti, 2006; Colloca et al., 2008; Kong et al., 2009). Petrovic et al. (2005) first studied the anxiolytic placebo effect by using a potent anxiolytic drug to reinforce placebo expectation, but this method may bring potential side effect of drugs and ethical issues relating to pharmaceutical experiments. Zhang et al. (2011, 2012) and Zhang & Luo (2009) utilized a transferable model to investigate the anxiolytic placebo effect: they first produced analgesic placebo expectations by surreptitiously manipulating the intensity of pain stimuli, and then examined whether this placebo expectation could be transferred to relieve negative emotion arousal. They found significantly decreased neural activity that correlated with emotion processing. This transferable paradigm could represent a useful approach considering the side effect of drugs and the limits in surreptitiously manipulating the intensity of emotion stimuli (Zhang & Luo, 2009; Zhang et al., 2011).

For the present study, we were particularly interested in the following questions: (1) could a noise stimulus be used to build placebo expectation, similar to a pain stimulus? (2) could placebo expectation generated with noise stimuli be transferred to relieve negative emotional arousal (Zhang & Luo, 2009)? As for the first question, noise intensity can be easily manipulated while keeping other features constant, which is similar to pain stimuli. Furthermore, noise stimuli may invoke less potential damage and fear and therefore find wider acceptance, which is advantageous over pain stimuli. Prior studies have demonstrated the existence of auditory-related placebo effects. One study (Dawes et al., 2013) confirmed that a hearing aid produced better sound quality, when it was labeled ‘‘new equipment’’ instead of ‘‘conventional equipment’’. Clinical studies for patients with hearing disorders found that placebo treatments were as effective as actual medical treatments (Dobie, 1999; Ge, et al., 2012; Lamm et al., 1998; Porubsky et al., 2007). As for the second question, if placebo expectation derived from noise relief can significantly impact anxiety intensity, such a transferable paradigm from noise to emotion would yield multiple advantages such as more convenient manipulations and fewer risks.

To investigate these issues, we devised two experiments. In Experiment 1, low-intensity noise stimuli were secretly delivered in the preconditioning training phase during placebo
condition while higher-intensity noise stimuli were provided in the control condition. In the subsequent test phase, placebo effects were assessed by administering the same intensity noise under both conditions. In Experiment 2, the same manipulation was used in the preconditioning training phase as in Experiment 1. Subsequently, the transferable placebo effects were assessed using emotional stimuli. If the subjects experienced significantly less emotional arousal under the placebo condition, a significant transferable placebo effect was obtained.

**Experiment 1**

**Methods**

**Subjects**

Forty-four undergraduate students (8 males and 36 females, mean age = 21 years) were recruited for the study. None of the subjects reported any hearing or mental disorders. The study was approved by the local ethics committee of the Institute of Psychology, Chinese Academy of Sciences, and written informed consent was obtained from all the subjects.

**Stimuli**

The auditory experimental stimuli consisted of four-second noise of a metal collision, and were divided into three sets: low-intensity set (62.7 dB, 64.8 dB, 66.4 dB, 68.6 dB, and 69.8 dB), high-intensity set (73.3 dB, 73.6 dB, 73.9 dB, 74.2 dB, and 74.5 dB), and the average-intensity set (66.4 dB, 69.1 dB, 70.0 dB, 72.1 dB, and 73.3 dB). The amplitude of the original noise was edited by CoolEdit 2.0 (San Jose, CA, US), and the intensity was assessed by a professional noise sound-level meter (Smart Sensor AR824, range 30–130 dB, error ±1.5 dB). The noise stimuli were presented via computer and the corresponding program was written using E-prime 2.0 (Sharpsburg, PA, US). A sham acupuncture-point magneto therapy apparatus (APMTA) without any real effect was used as placebo.

**Procedure**

Subjects were randomly assigned to a 2 (between-subjects factor: reinforced and non-reinforced group) × 2 (within-subjects factor: placebo and control condition) mixed design. The reinforced group was preconditioned with surreptitious administration of low-intensity noise stimuli in the placebo condition and told that the APMTA apparatus had a powerful noise-alleviating effect, while the non-reinforced group only received the same verbal information of the treatment. They were all told that the treatment with the APMTA would function only when it was turned on and would not function when the device is turned off.

The subjects were told that the aim was to check the effect of the APMTA on easing the experience of noise. They were also informed that the device was involved in the integrated Chinese–Western therapy, and stimulating the specific acupuncture point with magnetic power would treat the disease associated with this point. When the magnetic treatment was delivered to the Tinghui point (associated with hearing in the anterior inferior part of the tragus), the experience of intensity and annoyance due to the noise could be relieved. The experimenter directed the subjects to find the site of Tinghui by having them open their mouth and locate in the depression between ear and jaw until they could feel the point. This ritual manipulation was expected to strengthen the credibility of the instruction. Subsequently, the experimenter pasted an electrode patch on the Tinghui point that the subjects had located and told them that when the magnetic pinch of the APMTA was attached to the electrode patch, the device worked, and when it was disconnected, the APMTA would not work. The subjects could clearly see whether the device was connected throughout the experiment as the experimenter would connect the device before a turned-on condition block and disconnect before a turned-off block. Although the Tinghui point actually is relevant for auditory disease, the point received no stimulation, as the APMTA was not a real therapeutic instrument and the power was turned off all the time.

In the first phase of the formal experiment, the subjects practiced two blocks including two noise stimuli each, one block with the turned-on condition and the other with the turned-off condition. This allowed subjects to become familiar with the procedure. The practice phase was followed by the preconditioning and testing phase. The subjects were informed that they would hear 12 blocks of noises and each block presented five noises randomly. If the previous block was in the turned-on condition, the subsequent block would be in the turned-off conditions, thus the two conditions always alternated. The subjects were informed that when they were treated with the APMTA, they would feel less sensation intensity and annoyance by the noise; when they were not treated with the APMTA, they would feel no such relief. To alert the subjects whether they would be treated in a given block, an icon indicating that the APMTA was connected or disconnected appeared before presenting each block of noises, if the icon was ‘‘on’’, the experimenter would attach the magnetic pinch to the patch on subjects’ Tinghui Point, if it was ‘‘off’’, the experimenter would take down the pinch from the point. After six blocks (three turned on, three turned off), there was a 1-min rest period with soothing music, after which another six blocks were presented.

The subjects in neither group were informed that the first six blocks of noises were used to reinforce the placebo belief, and that the second six blocks were used to measure the placebo effect itself. In the preconditioning phase, the reinforced group heard low-intensity noise when the APMTA was connected and high-intensity noise when it was disconnected. This manipulation was aimed at reinforcing their placebo expectation. The non-reinforced group was presented with the average-intensity noise in both placebo and control condition; thus, their placebo expectation was not strengthened. Although the instruction and the total noise intensity given to two groups were the same, the reinforced group strengthened their placebo belief under the surreptitious arrangement while the non-reinforced group did not. In the testing phase, both groups heard the average intensity of noise in both connected and disconnected conditions; thus, if the experience of noise differed between the two groups, the placebo effect from the preconditioning manipulation can be confirmed (Figure 1).
After a block ended, the subjects were told that “as the volume of the sound increases, I can ask you how loud it sounds, or how unpleasant it is to you” according to the instructions by Price et al. (1989), so the subjects were asked to report the sensation intensity and annoyance of noise. The subjects were informed to use a scale with the score of 0–100, “0” meant no noise or annoyance, “100” meant unbearable noise or annoyance. In addition, the subjects were also told: “although the five noises of each block differ in intensity, the average intensity of noise among all blocks is same, if you feel lower sensation intensity and annoyance when the APMTA is connected compared with it is disconnected, you can think that is the work of the device”.

Statistics
A repeated-measures analysis of variance (ANOVA, using the SPSS 18.0 (Armonk, NY, US) package) was used to analyze data. A simple effect analysis was carried on the interaction effect of the change score between placebo and control condition. Price et al. (2005) suggested that the change score approach is a better reflection of placebo effect.

Results
For the testing phase, the main effect of the within-subjects factor (placebo versus control condition) was significant on the assessment of noise intensity, $F(1,42) = 50.555$, CI (99.9%), 0.070–14.233, $p<0.001$, and noise annoyance, $F(1,42) = 40.646$, CI (99.9%), 0.070–14.233, $p<0.001$. The main effect of the between-subjects factor (reinforced versus non-reinforced condition) was not significant on both scores of noise intensity, $F(1,42) = 0.060$, $p = 0.807$, CI (95%), 0.185–5.404; and noise annoyance, $F(1,42) = 0.407$, $p = 0.527$, CI (95%), 0.185–5.404. The interaction between the two factors was significant for the assessments of noise intensity, $F(1,42) = 17.533$, CI (99%), 0.070–14.233, $p<0.001$, and noise annoyance, $F(1,42) = 10.870$, CI (99%), 0.114–8.779, $p = 0.002$. We conducted a simple effect analysis with the change scores between control and placebo condition for the two groups. For the noise intensity, the change score between the two conditions in the reinforced group ($M \pm SD$: 7.379 ± 4.668) was significantly larger than in the non-reinforced group ($M \pm SD$: 1.909 ± 3.968), $t = 4.187$, CI (99.9%), −3.538 to 3.538, $p<0.001$. Similarly, for the noise annoyance, the change score between the two conditions in the reinforced group ($M \pm SD$: 7.712 ± 5.952) was significantly larger than that in the non-reinforced group ($M \pm SD$: 2.455 ± 4.530), $t = 3.297$, CI (99%), −2.698 to 2.698, $p = 0.002$. These findings indicate placebo effect more evident in the reinforced group than in the non-reinforced group. The results of the testing phase are presented in Figures 2 and 3.

Experiment 2

Methods
Subjects
Forty-three undergraduate students (14 males and 29 females, mean age = 22 years) were recruited for the study. None of the subjects reported any hearing or mental disorders.

Stimuli
The noise stimuli used in this experiment were the same as in Experiment 1. The emotional pictures were derived from the International Affective Picture System (IAPS). The APMTA device from Experiment 1 was also used as placebo in Experiment 2.

Procedure
The pictures of negative emotion were used in the testing phase to examine whether the belief of placebo built in the
reinforced phase could relieve the negative emotional arousal via a mode of transference. Similar to Experiment 1, subjects were randomly assigned to a 2 (between-subjects factor: reinforced and non-reinforced group) × 2 (within-subjects factor: placebo and control condition) mixed design.

In this experiment, we stressed the relief functions of both noise and unpleasantness of the APMTA. The subjects were told that, on one hand, the treatment was applied on the Tinghui point to relieve the experience of noise, and on the other hand, the treatment applied on Hegu point (located in the middle of the second metacarpal on the back of the hand close to the thumb) would inhibit the arousal of negative emotion. The way to find the Tinghui point was the same as in Experiment 1. The subjects were then told that the Hegu point was in the depression between the thumb and index finger and were directed to palpate it. Similar to Experiment 1, both acupuncture points are assigned certain functions as the instructions suggested; however, the APMTA was a sham device and throughout the entire experiment the power was disconnected, so that no real treatment resulted from the device.

The subjects performed two practice blocks, each containing two noises before the formal experiment: in one block, the APMTA was “turned on”; and in the other, it was “turned off”. For the actual experiment, the subjects were instructed that they would hear six blocks of noises (three connected and three disconnected) with each block playing five noises. A one-minute break was followed, during which soft music was played. After the break, six blocks of emotional pictures (three blocks with and three blocks without placebo) were
presented to the subjects with each block containing five pictures. The subjects were told that when they received treatment with the APMTA (i.e. the device was turned on), they would experience less unpleasantness, which did not imply that the negative emotion would completely disappear; and when the device was turned off, they would feel no relief from the negative emotion.

Compared to the Experiment 1, the subjects made the assessment after each noise or picture stimulus was presented in Experiment 2; this modification should more accurately reflect the subjects’ immediate mental experience. The assessment of noise was identical to Experiment 1 with standard instructions to assess noise intensity and annoyance. A scale from 0 to 100 points was used to assess the negative emotional pictures with 0 indicating “no unpleasantness” and 100 referring to “unbearable unpleasantness”.

Statistics
Experiment 2 used the same statistical methods as Experiment 1.

Results
For the testing phase, the main effect of the within-subjects factor (placebo versus control condition) was significant for the arousal of negative emotion, $F(1, 41) = 85.392$, CI (99.9%), 0.070–14.291, $p<0.001$. The main effect of the between-subjects factor was not significant, $F(1, 41) = 1.511$, CI (95%), 0.185–5.414, $p = 0.226$. while the interaction between the two factors was significant, $F(1, 41) = 5.671$, CI (95%), 0.185–5.414, $p = 0.022$. The results are shown in Figure 4. The change score of unpleasantness between the control and placebo condition was analyzed for the two groups, confirming that for the change score between the two conditions in the reinforced group (M ± SD: 10.085 ± 6.350) was significantly larger than in the non-reinforced group (M ± SD: 5.952 ± 4.978), $t = 2.381$, CI (95%), 2.020–2.020, $p = 0.022$. This result indicates anxiolytic placebo effect was stronger in the reinforced group than in the non-reinforced group.

Discussion
In this study, we provide the first report of transferable placebo effect from noise to negative emotions, and we show that a direct placebo effect of alleviating noise experience and a transferable placebo effect alleviating negative emotions can be evoked.

Experiment 1 indicates that a noise placebo effect exists in the auditory system and provides the foundation for investigating the transferred anxiolytic placebo effect from noise to emotion. There is a possibility that differences in noise intensity and annoyance between the placebo and control treatment may reflect demand characteristics—a desire to please the investigators instead of a true placebo effect. However, as the placebo effect was significantly larger in the reinforcement group than in the non-reinforcement group indicates that when removing the effect of verbal instruction, the preconditioning training itself could produce a true placebo effect. Other studies provide evidence that the auditory placebo effect exists (Cracknell & Mills, 2008; Dawes et al., 2011; Ge et al., 2012; Geers et al., 2005; Lamm et al., 1998; Thomsen et al., 1981). As the surreptitious manipulation of noise intensity in the preconditioning phase proved to be more flexible and less frightening than the use of pain stimuli, we believe that the application of noise stimuli for establishing transferable placebo expectations holds great promise.

In Experiment 2, we observed the reliable transfer of placebo effects from noise to emotion. The reinforcement group showed larger reduction of unpleasantness than the control group. This finding indicates that a true transferable effect occurred and excludes the possibility that the placebo effect simply represents the tendency to please the investigators as discussed above. In previous studies, we found transferred anxiolytic placebo effect from pain to emotion
(Zhang & Luo, 2009; Zhang et al., 2011, 2012). The present study provides additional evidence for the existence of a transferred anxiolytic placebo effect from noise to emotion. This finding suggests that the transferable placebo effects may be a common cross-domain phenomenon and not just confined to the transfer from pain to emotion.

Two mechanisms have been proposed to account for the placebo effect: expectation and conditioning. We believe that expectation directly produces the anxiolytic placebo effect, and conditioning through prior noise-relieving experience further strengthened the expectation effect. In the transferable paradigm, we reinforced the noise-relieving effect in the preconditioning phase, but examined the anxiolytic placebo effect in the test phase. Thus, we cannot conclude that the anxiolytic placebo response is produced by conditioning due to this mismatch (i.e., different sense modality in the two phases). Some researchers have also discussed that conditioning may be a means of altering expectations by providing experience (Rescorla, 1988), or that the conditioning effect on placebo analgesia may be mediated by expectancy (Kirsch et al., 2014). Colloca & Miller (2011) especially stress that it is necessary to overcome the strict dichotomy; decoding the information from various forms of learning such as the conditioning, verbal communication and observation all contribute to generating expectation and then placebo response. In the present study, the transferable paradigm of the placebo effect may add further evidence for understanding the mechanism of the placebo effect.

There may be some implications for clinical practice in view of a salient transferable placebo effect. First, although considering the patient’s informed consent clinical practices could not use placebo effect as primary aims at present, the direct or transferable placebo effect could be considered fully in active therapy to optimize the therapeutic effect in clinical practice. Rigorous ritual of therapy, supportive patient–clinician relationship and so on could be potential links to set up placebo expectation. This placebo expectation would likely produce a magnifying healing power. Second, for more specific examples of transferable placebo effect, if a person finds slow abdominal breathing or meditation training could relieve his hypertension, then he would believe these trainings is necessary to overcome the strict dichotomy; decoding the information from various forms of learning such as the conditioning, verbal communication and observation all contribute to generating expectation and then placebo response. In the present study, the transferable paradigm of the placebo effect may add further evidence for understanding the mechanism of the placebo effect.

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**Declaration of interest**

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