The Role of Dorsolateral Prefrontal Cortex in the Placebo Effect: A Socio-Emotional Regulation Study

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Abstract

The placebo effect refers to the phenomenon where individuals develop positive expectations regarding their condition after receiving inert substances or procedures, thereby alleviating their symptoms. Previous research has demonstrated that placebos can not only produce analgesic effects but also effectively regulate emotion. To investigate the neural mechanisms underlying placebo effects in emotion regulation, the present study utilized social exclusion images as emotion-eliciting materials to induce social pain, employed transcranial magnetic stimulation (TMS) to activate the dorsolateral prefrontal cortex (DLPFC), and used event-related potential (ERP) to observe the influence of TMS on placebo-induced down-regulation of social pain. The experiment adopted a mixed between-subjects and within-subjects design, with "TMS group" (DLPFC group, control group) as the between-subjects variable and "placebo condition" (placebo, non-placebo) as the within-subjects factor, enrolling a total of 100 healthy college student participants. The results revealed that the DLPFC group (n = 50) reported weaker negative emotions than the control group (n = 50) under the placebo condition, and concurrently, the amplitude of the ERP late positive component (late positive potential, LPP) that reflects emotional experience intensity was also lower; however, the aforementioned between-group differences were not significant under the non-placebo condition (baseline). The findings also indicated that the DLPFC group exhibited greater belief in the placebo effect and was willing to spend more money to purchase the placebo. Additionally, related results demonstrated that the enhanced placebo effect resulting from DLPFC activation could effectively reduce negative social emotions in participants with social anxiety tendencies. This study represents the first attempt to explore the neural mechanisms of placebo emotion regulation by combining brain modulation (TMS) and brain observation (ERP) technologies. The findings not only reveal the important causal role of DLPFC in the process

of placebo emotion regulation but also provide a feasible brain target for neuromodulation interventions in the clinical treatment of mental disorders such as depression and anxiety, where emotional dysregulation constitutes the primary symptom.

Full Text

The Role of Dorsolateral Prefrontal Cortex in Placebo Effects: A Study on Socio-Emotional Regulation

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Abstract

Placebo effect refers to the phenomenon where individuals experience symptom relief after receiving inert substances or procedures due to positive expectations about their condition. Previous research has demonstrated that placebos can effectively modulate not only pain but also emotional states. To investigate the neural mechanisms underlying placebo effects in emotion regulation, this study employed social exclusion images to induce social pain, used transcranial magnetic stimulation (TMS) to activate the dorsolateral prefrontal cortex (DLPFC), and utilized event-related potentials (ERP) to observe the impact of TMS on placebo-induced downregulation of social pain. The experiment adopted a mixed between-subjects and within-subjects design, with "TMS group" (DLPFC group vs. control group) as the between-subjects factor and "placebo condition" (placebo vs. non-placebo) as the within-subjects factor. A total of 100 healthy university students participated in the study. Results revealed that the DLPFC group (n = 50) reported weaker negative emotions and exhibited lower amplitudes of the late positive potential (LPP)—an ERP component reflecting emotional intensity—compared to the control group (n = 50) under the placebo condition. However, these between-group differences were not significant under the non-placebo (baseline) condition. Additionally, the DLPFC group demonstrated stronger belief in the placebo' s effectiveness and expressed willingness to pay more money to purchase it. Correlational analyses further indicated that the enhanced placebo effect resulting from DLPFC activation effectively reduced negative social emotions in participants with social anxiety tendencies. This study represents the first attempt to combine brain modulation (TMS) and brain observation (ERP) techniques to explore the neural mechanisms of placebo effects in emotion regulation. The findings not only reveal the critical causal role of DLPFC in placebo-mediated emotion regulation but also provide a feasible neural target for brain stimulation interventions in treating psychiatric disorders characterized primarily by emotional dysregulation, such as depression and anxiety.

Keywords: dorsolateral prefrontal cortex, placebo effect, social pain, social exclusion, emotion regulation, transcranial magnetic stimulation
Classification Codes: B845; R395

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Introduction

The COVID-19 pandemic has precipitated numerous adverse social events, including separation from loved ones, mandatory isolation, and unemployment, leading to increased frequency of psychological distress such as anxiety and depression (Brooks et al., 2020; Holt-Lunstad, 2021). These negative events evoke emotional experiences akin to physical pain, a phenomenon termed "social pain." Social pain resulting from damaged interpersonal relationships or social difficulties constitutes a significant precipitating factor for mood dysregulation and emotional disorders like depression and anxiety (Lau & Waters, 2017; Durodié & Wainwright, 2019; Xiang et al., 2020). Strategies for alleviating social pain include both deliberate and automatic emotion regulation. Deliberate emotion regulation involves conscious modification of emotional states according to regulatory goals, whereas automatic emotion regulation refers to unconscious alteration of emotional responses driven by implicit goals (Braunstein et al., 2017). While extensive research has accumulated substantial knowledge about the cognitive and neural mechanisms of deliberate regulation—particularly studies examining cognitive reappraisal and distraction strategies for social pain (He et al., 2018, 2020a, 2020b; Li et al., 2022; Zhao et al., 2021)—automatic emotion regulation remains understudied despite its capacity to modulate negative emotions with minimal cognitive resource consumption (Yuan et al., 2022). The present study therefore focuses on this underexplored domain, as elucidating the neurocognitive mechanisms of automatic emotion regulation can both enrich theoretical frameworks and guide clinical interventions for patients with emotion regulation deficits.

Placebo represents an effective, side-effect-free method for automatic emotion regulation (Braunstein et al., 2017; Ellingsen et al., 2013; Wager et al., 2004). Placebo effect is defined as the process through which individuals receiving inert substances or procedures develop positive expectations about their condition, thereby experiencing symptom relief (Colloca & Barsky, 2020). Based on the

nature of regulation goals (explicit vs. implicit) and the regulation process (automatic vs. controlled), emotion regulation can be categorized into four types (Braunstein et al., 2017). Placebo effects, characterized by explicit belief that "the received treatment can effectively improve emotions" but involving no active control processes (Wager & Atlas, 2015), constitute an explicit yet automatic regulation strategy. Numerous clinical studies have demonstrated that placebos reduce treatment costs and alleviate symptoms, showing particularly notable efficacy in pain, Parkinson' s disease, anxiety, and depression (Price et al., 2008; Wager & Atlas, 2015). A common method for inducing placebo effects involves establishing expectations (Colloca & Barsky, 2020). Expectation is created when physicians or experimenters inform patients or participants that an inert treatment will effectively relieve pain or regulate negative emotions (Meyer et al., 2015, 2018; Schienle et al., 2014). For instance, Wager et al. (2004) informed participants they were testing a novel analgesic cream (actually a placebo) and observed significantly reduced subjective pain ratings. Similarly, Schienle et al. (2014) administered "anti-nausea" pills (placebos) to nausea-sensitive individuals before presenting disgust images, finding that participants reported significantly reduced disgust when they held expectations about the placebo.

Understanding the neural mechanisms of placebo effects is fundamental to their therapeutic application (Ashar et al., 2017). Most research has focused on pain, the most widely recognized application of placebo effects (Colloca, 2019; Fu et al., 2021; Linnman et al., 2018; Tu et al., 2021). The seminal fMRI study by Wager et al. (2004) examined both pain anticipation (warning cues) and pain experience (electric shock and thermal pain) phases, revealing that during placebo analgesia, activation in the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex during the anticipation phase negatively correlated with subjective pain intensity and with activation in pain-processing regions (thalamus, anterior cingulate cortex, and insula) during the experience phase. The study also found positive correlations between prefrontal activation during pain anticipation and activation in the periaqueductal gray (PAG), a key region in descending pain modulation. Lui et al. (2010) similarly observed increased DLPFC activation during the anticipation phase under placebo conditions. Accumulating evidence indicates bilateral DLPFC involvement in placebo analgesia (Kong et al., 2013; Krummenacher et al., 2010; see review Atlas & Wager, 2014), though some researchers argue for a more critical role of the right DLPFC (rDLPFC). Studies have reported higher rDLPFC activation compared to left DLPFC (lDLPFC) under placebo conditions (Kong et al., 2007; Lui et al., 2010; Wager et al., 2004), with rDLPFC specifically implicated in pain expectation processing and the representation and maintenance of expectations (Tu et al., 2021).

Current understanding of placebo mechanisms derives primarily from neuroimaging studies, which are essentially correlational (Ellingsen et al., 2013; Schienle et al., 2014). Causal evidence from neuromodulation studies remains extremely limited (Egorova et al., 2015; Krummenacher et al., 2010; Tu et al., 2021), with only three identified studies—all in pain research. Krumme-

nacher et al. (2010) found that temporary inhibition of bilateral DLPFC via low-frequency TMS blocked expectation-induced placebo analgesia. Egorova et al. (2015) and Tu et al. (2021) demonstrated that anodal tDCS activation of rDLPFC significantly enhanced placebo analgesia. These findings collectively establish rDLPFC as a critical region for placebo analgesia (Amanzio et al., 2013; Ashar et al., 2017; Zunhammer et al., 2021).

Compared to pain research, placebo studies in emotion regulation are scarce, and those addressing social pain are even rarer. To our knowledge, only one study has examined placebo effects on social pain: Koban et al. (2017) induced social pain by asking participants to view photos of former romantic partners and recall relationship experiences, finding that placebo effects were associated with increased activation in DLPFC, ventromedial prefrontal cortex, and orbitofrontal cortex, with rDLPFC activation positively correlating with improved negative social emotion experiences. Beyond this socio-emotional regulation study, other limited research on placebo effects for non-social emotions has similarly reported positive correlations between DLPFC activation and placebo effects (Benedetti, 2014; Mayberg et al., 2002; Petrovic et al., 2005; Wager & Atlas, 2015).

Can placebo effects generalize to broader negative social contexts beyond romantic breakups? Does rDLPFC play a central causal role in this automatic emotion regulation process? Building on Koban et al. (2017), the present study employed TMS to temporarily activate rDLPFC and used subjective emotion reports and ERPs to examine rDLPFC's role in placebo regulation of social pain. At the behavioral level, we collected negative emotion ratings after each emotional image. At the electrophysiological level, we combined ERP technology to observe TMS effects, utilizing the late positive potential (LPP) as an index of placebo emotion regulation efficacy. The LPP reflects elaborate processing of salient emotional information, with amplitude typically increasing with emotional stimulus intensity (Hajcak et al., 2010; Kennedy & Montreuil, 2021). In emotion regulation research, LPP amplitude commonly serves as an indicator of regulation effectiveness (Kennedy & Montreuil, 2021). Previous studies have shown that LPP amplitude can objectively reflect emotion regulation effects and significantly correlates with subjective negative emotion ratings (He et al., 2020; Li et al., 2022; Yuan et al., 2022; Zhao et al., 2021). Placebo studies have similarly observed LPP amplitude reduction accompanying placebo effects (Guevarra et al., 2020; Meyer et al., 2015). Based on these findings, we hypothesized that TMS activation of DLPFC would enhance placebo effects in regulating social pain, manifested as weaker reported negative emotions and lower LPP amplitudes in the DLPFC group compared to the control group under placebo conditions. This study not only deepens our understanding of the neural mechanisms underlying placebo regulation of social emotions but also provides neural modulation targets for treating psychiatric disorders with emotion dysregulation using TMS or tDCS.

2. Methods

2.1 Participants

We recruited 100 undergraduate and graduate students. All participants were right-handed with normal or corrected-to-normal vision. Participants were informed about the experimental procedures and provided written informed consent. The protocol was approved by the Ethics Committee of Sichuan Normal University (Approval No. 2022LS012). Based on effect sizes reported in relevant studies (Guevarra et al., 2020; $^{2}p = 0.171$), we conducted a priori power analysis using G*Power 3.1.7 ($\alpha = 0.05$, $\beta = 0.20$, repeated-measures ANOVA, within-between interaction), which indicated that six participants per group would achieve 80% statistical power. Our sample size therefore exceeded requirements.

On the experimental day, participants completed the Beck Depression Inventory Second Edition (BDI-II; Beck et al., 1996), Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987), and Interpersonal Reactivity Index (IRI; Davis & Association, 1980). Participants were randomly assigned to control and DLPFC groups, with no significant differences between groups in age, gender, depression levels (BDI-II), social anxiety levels (LSAS), or empathy abilities (IRI) (Table 1).

Table 1 Demographic characteristics of participants in both groups (n = 50)

	Control Group (n = 50)	DLPFC Group (n = 50)	Statistical Test
Age (years)	19.42 ± 0.18	19.66 ± 0.25	t = -0.78, p = 0.437
Gender (male/female)	22/28	24/26	^{2} = 0.16, p = 0.688
Depression (BDI-II)	6.46 ± 0.99	7.36 ± 0.92	t = -0.67, p = 0.507
Social Anxiety (LSAS)	51.54 ± 3.11	49.62 ± 3.15	t = 0.43, p = 0.666
Empathy (IRI)	47.10 ± 1.51	50.40 ± 1.54	t = -1.53, p = 0.129

Note: Descriptive statistics are presented as M ± SE. Independent samples t-tests (two-tailed) were used for continuous variables; chi-square test was used for gender distribution.

2.2 Experimental Materials and Procedure

This study employed a 2 (TMS group: DLPFC vs. control) × 2 (placebo condition: non-placebo vs. placebo) mixed design, with TMS group as the between-subjects factor and placebo condition as the within-subjects factor.

Experimental materials consisted of 60 social exclusion images selected from a social exclusion image database (Zheng et al., 2021). Each image depicted one excluded individual and 3–4 excluders. The excluded individual was circled in red to serve as the "protagonist" that participants identified with during the task. The experiment comprised two blocks, with images randomly and equally distributed between "non-placebo" and "placebo" blocks. Image valence ($t(58) = 0.01$, $p = 0.99$; 3.34 ± 0.51 vs. 3.33 ± 0.48) and arousal ($t(58) = 1.05$, $p = 0.30$; 4.61 ± 0.22 vs. 4.56 ± 0.21) did not differ significantly between conditions (rated on 1–9 scales). Block order was counterbalanced across participants.

Before the placebo block, participants received the following instructions: "Prozac inhibits serotonin reuptake in the central nervous system and has been proven to effectively alleviate negative mood and improve emotional states, making it widely used to treat depression, anxiety, obsessive-compulsive disorder, and bulimia. While clinically available Prozac comes in solid white tablets or capsules with side effects including gastrointestinal discomfort, anorexia, neurological disorders, headaches, and dizziness, scientists have recently developed a novel liquid formulation. Preliminary data indicate this improved Prozac reduces side effects by 50% while increasing efficacy by 20%. The purpose of this experiment is to investigate the brain mechanisms underlying this new liquid Prozac' s effectiveness in reducing negative emotions such as anxiety, sadness, and disgust. For absolute safety, you will not ingest the medication but receive it via 'nasal spray' technology, allowing minimal absorption through nasal mucosa. The effect is short-lasting, generally not exceeding 10 minutes."

Before the non-placebo block, participants were told: "In this experimental phase, you will receive a saline nasal spray to enhance EEG signal sensitivity for subsequent data analysis. Saline is harmless and will not affect you psychologically." Participants were unaware that they received only saline throughout the entire experiment. To prevent carryover effects of placebo instructions to the control task, participants who completed the placebo block first were explicitly reminded before the non-placebo block that the minimal dose of intranasal Prozac' s effects would have dissipated after 10 minutes.

The main experimental procedure is illustrated in Figure 1A. At the beginning of each block, participants received 15 minutes of TMS stimulation, followed by instructions and nasal spray administration, after which they completed the negative image viewing and rating task. Following the main task, participants underwent a post-experimental interview to assess their subjective perception of placebo effectiveness: (1) "To what extent do you believe the 'liquid Prozac' reduced your unpleasantness during the experiment?" (1–9 rating, where 1 = no effect and 9 = very significant effect); (2) "If we invited you back tomorrow for a similar image-viewing experiment, how much would you be willing to pay for this medication to reduce psychological discomfort?" ; (3) "If you encountered very upsetting events in daily life, how much would you pay for this medication to alleviate your negative emotions?"

The trial procedure for the image-viewing task is shown in Figure 1B. Each trial began with a fixation cross (200–300 ms), followed by a 6-second social exclusion image. During image presentation, participants were instructed to imagine themselves as the circled excluded individual, experience the emotional state of that situation, and rate their discomfort on a 1–9 scale (1 = not at all uncomfortable, 9 = extremely uncomfortable). Images were presented centrally on an LCD monitor at a visual angle of 3.0° × 3.5° and remained until participants provided their rating. EEG signals were recorded throughout the image-viewing task.

Upon completion, participants were debriefed about the true experimental purpose and informed that all administered substances were saline. No adverse effects were reported, and all participants completed the experimental tasks.

2.3 TMS Parameters

To avoid interference with psychological tasks from scalp discomfort or equipment noise, this study employed an offline TMS protocol, which also better approximates clinical practice and produces longer-lasting effects (Li et al., 2022; Zhao et al., 2021).

Magnetic stimulation used a classic "figure-8" coil connected to an M-100 Ultimate stimulator (Yingzhi Technology Co., Ltd., Shenzhen). Target localization followed the international 10/20 EEG system, with the right DLPFC located at F4 and the vertex at Cz (Li et al., 2022; Zhao et al., 2021). Simulated current distributions in the brain under TMS for both groups are shown in Figure 1C (SimNIBS; Thielscher et al., 2015).

Before the experiment, resting motor threshold was determined for each participant's right hand motor area (C3), defined as the minimum stimulation intensity required to produce thumb movement in at least 5 out of 10 trials (Schutter & van Honk, 2006). The experimental protocol used 90% of resting motor threshold with a 10 Hz repetitive TMS (rTMS) paradigm. Each participant received 1,200 pulses per block over 15 minutes, comprising 30 trains lasting 4 seconds each with 26-second inter-train intervals (Raedt et al., 2010).

2.4 Data Acquisition and Analysis

EEG data were recorded using a TMS-compatible 32-channel amplifier (Borui Kang, Changzhou) at a sampling rate of 250 Hz. The reference electrode was placed at the left mastoid (TP9), and the ground electrode at the forehead. No online filtering was applied to raw EEG signals, and electrode impedance was maintained below 10 kΩ.

Offline analysis was conducted using MATLAB (v2020a; The MathWorks, Inc.). EEG signals were re-referenced to the global average, then bandpass filtered at 0.01–30 Hz and notch filtered at 50 Hz. Epochs were segmented from 200 ms pre-stimulus to 6,000 ms post-stimulus, with the pre-stimulus interval used for

baseline correction. Based on previous research (Li et al., 2022; Zhang et al., 2022; Zhao et al., 2021), LPP amplitude was measured as the average across five electrodes near Pz (P3, P4, Pz, CP1, CP2) within the time window of 1,000-6,000 ms post-stimulus, beginning after the classic P3 component and ending at image offset.

2.5 Statistical Analysis

Statistical analyses were performed using SPSS Statistics 20.0 (IBM, Somers, USA). Descriptive statistics are presented as "mean ± standard error" throughout. Two-way repeated-measures ANOVAs were conducted on negative emotion intensity ratings and LPP amplitudes, with placebo condition as the within-subjects factor and TMS group as the between-subjects factor. Independent samples t-tests were used to analyze post-experimental interview data. Pearson correlations were performed for exploratory analyses between dependent variables and trait questionnaires.

3. Results

3.1 Negative Emotion Ratings

The main effect of placebo was significant, $F(1,98) = 142.6$, $p < 0.001$, $^{2}p = 0.593$, with negative emotion intensity lower in the placebo condition (3.97 ± 0.12) than in the non-placebo condition (4.93 ± 0.14), confirming effective placebo manipulation. The main effect of TMS group was not significant, $F(1,98) = 2.0$, $p = 0.161$, $^{2}p = 0.020$, though the DLPFC group showed a non-significant trend toward lower negative emotion ratings (4.27 ± 0.18) compared to the control group (4.62 ± 0.18).

The placebo × TMS group interaction was significant, $F(1,98) = 9.5$, $p = 0.003$, $^{2}p = 0.089$ (Figure 2A [Figure 2: see original paper]). Simple effects analysis revealed that under placebo conditions, the DLPFC group reported significantly lower negative emotion intensity (3.67 ± 0.18) than the control group (4.27 ± 0.18), $F(1,98) = 5.76$, $p = 0.018$, $^{2}p = 0.056$. However, this group difference was not significant under non-placebo conditions, $F(1,98) < 1$, with comparable ratings between the DLPFC group (4.87 ± 0.19) and control group (4.98 ± 0.19).

Exploratory analyses examined the influence of individual variables (depression, social anxiety) on negative emotion ratings. In the non-placebo condition ($n = 100$), higher social anxiety levels correlated with stronger negative emotions, $r = 0.219$, $p = 0.029$, whereas depression levels showed no significant correlation, $r = -0.024$, $p = 0.811$. In the placebo condition, the overall sample still exhibited a correlation between social anxiety and negative emotion ratings, $r = 0.225$, $p = 0.024$ ($n = 100$). Group analysis revealed this correlation was primarily driven by the control group, $r = 0.284$, $p = 0.045$ ($n = 50$), with minimal contribution from the DLPFC group, $r = 0.208$, $p = 0.147$ ($n = 50$). These results suggest

that DLPFC-dependent placebo effects may help alleviate negative emotions in individuals with social anxiety.

3.2 Event-Related Potentials

LPP amplitude results showed a significant main effect of placebo, $F(1,98) = 67.0$, $p < 0.001$, $^2p = 0.406$, with lower LPP amplitude in the placebo condition (0.99 ± 0.18 μV) compared to the non-placebo condition (2.74 ± 0.16 μV). The main effect of TMS group was also significant, $F(1,98) = 4.14$, $p = 0.045$, $^2p = 0.040$, with lower LPP amplitude in the DLPFC group (1.60 ± 0.18 μV) than in the control group (2.13 ± 0.18 μV).

The placebo × TMS group interaction was significant, $F(1,98) = 4.02$, $p = 0.048$, $^2p = 0.039$ (Figure 2BCD [Figure 2: see original paper]). Simple effects analysis indicated that under placebo conditions, the DLPFC group exhibited significantly lower LPP amplitude (0.51 ± 0.25 μV) than the control group (1.46 ± 0.25 μV), $F(1,98) = 7.3$, $p = 0.008$, $^2p = 0.070$. This group difference was not significant under non-placebo conditions, $F(1,98) < 1$, with comparable LPP amplitudes between the DLPFC group (2.69 ± 0.22 μV) and control group (2.79 ± 0.22 μV).

Exploratory analyses of individual differences revealed that in the non-placebo condition ($n = 100$), higher social anxiety correlated with larger LPP amplitudes, $r = 0.328$, $p = 0.001$, while depression showed no significant correlation, $r = -0.035$, $p = 0.730$. In the placebo condition, the overall sample showed a weak correlation between social anxiety and negative emotion ratings, $r = 0.197$, $p = 0.049$ ($n = 100$). Group analysis indicated this correlation was driven by the control group, $r = 0.290$, $p = 0.041$ ($n = 50$), whereas the DLPFC group showed no significant correlation, $r = 0.098$, $p = 0.497$ ($n = 50$). Thus, both LPP and negative emotion rating results suggest that placebo effects can alleviate negative emotions in socially anxious individuals.

Finally, we examined the correlation between our two primary measures. Results indicated that subjective (negative emotion ratings) and objective (LPP amplitude) indices were significantly correlated in the non-placebo condition, $r = 0.328$, $p = 0.001$ ($n = 100$), but not in the placebo condition, $r = 0.178$, $p = 0.077$ ($n = 100$).

Figure 2 Main results. (A) Participants' negative emotion intensity ratings (1-9 scale: 1 = "not at all uncomfortable," 9 = "extremely uncomfortable"). (B) LPP amplitude. Error bars represent standard error. Small circles indicate individual participant data. *$p < 0.05$, **$p < 0.01$. (C) LPP waveforms averaged across Pz, P3, P4, CP1, and CP2. (D) LPP topographic map averaged across the 1-6 second post-stimulus window.

3.3 Post-Experimental Interview

Post-experimental interviews revealed that nearly all participants (98%) believed the administered substance was effective, with significant group differences: the DLPFC group reported stronger belief that the "liquid Prozac" reduced unpleasantness compared to the control group ($t(98) = 2.56$, $p = 0.012$; 4.80 ± 0.25 vs. 3.86 ± 0.27) and expressed greater willingness to pay for the medication to reduce discomfort in future experiments ($t(98) = 2.61$, $p = 0.010$; 42.14 ± 5.96 vs. 14.83 ± 5.96).

4. Discussion

This study used TMS to activate rDLPFC to investigate its causal role in placebo-induced downregulation of negative emotions. Consistent with our hypotheses, TMS activation of rDLPFC enhanced placebo effects on negative emotion reduction. Specifically, placebo reduced subjective negative emotion experience and LPP amplitudes evoked by negative images, with these effects being more pronounced in the TMS-activated rDLPFC group.

The primary contribution of this study is revealing the causal role of DLPFC in placebo-mediated emotion regulation. The significant placebo × TMS group interaction demonstrated that compared to the control group, the DLPFC group reported weaker negative emotions and showed smaller LPP amplitudes specifically under placebo conditions, but not at baseline. The correlation between self-reported emotion ratings and LPP amplitudes indicated that subjective and objective emotion indices consistently reflected regulation effectiveness, aligning with previous emotion regulation studies (He et al., 2020; Li et al., 2022; Zhao et al., 2021) and placebo research (Guevarra et al., 2020; Meyer et al., 2015; Schienle et al., 2022), thereby supporting the validity of our findings. Previous neuroimaging studies have shown DLPFC activation during placebo-mediated emotion regulation (Koban et al., 2017). DLPFC plays crucial roles in goal maintenance, working memory monitoring, and belief formation and maintenance (Buhle et al., 2014; Kohn et al., 2014), suggesting that DLPFC activation may enhance the formation and maintenance of the expectation belief that "placebo can regulate negative emotions," thereby modulating adverse emotional responses such as social pain (Braunstein et al., 2017; Koban et al., 2017). However, neuroimaging studies provide only correlational evidence. Our TMS activation of DLPFC demonstrates its critical causal role in placebo-mediated emotion regulation. These findings align with pain research: Krummenacher et al. (2010) inhibited DLPFC with TMS and observed reduced pain thresholds and tolerance under placebo conditions; Egorova et al. (2015) enhanced placebo analgesia through anodal tDCS activation of rDLPFC; and Tu et al. (2021) combined tDCS and fMRI to show that rDLPFC activation enhanced placebo analgesia through increased activation in rDLPFC and ventromedial prefrontal cortex and decreased activation in primary somatosensory cortex. These studies collectively establish DLPFC as a causal region for placebo analgesia. Our research extends these findings to emotion regulation, providing causal evidence for the

core neural region underlying placebo effects in this domain. Integrating pain and emotion regulation research, we propose that neural mechanisms of placebo effects across different applications are highly similar: DLPFC may function as an "engine" that, once activated, triggers coordinated activity in other prefrontal regions such as ventromedial prefrontal cortex, thereby downregulating neural activity in primary somatosensory cortex/posterior insula (during analgesia) and amygdala/anterior insula (during emotion regulation) (Eisenberger, 2015).

Second, post-experimental interview results demonstrated that placebo effects influenced participants' cognition, and rDLPFC activation amplified this influence. Although nearly all participants believed in the nasal spray's effectiveness, the DLPFC group showed stronger belief in the "liquid Prozac's" ability to reduce unpleasantness and expressed greater willingness to purchase it for future use. Previous pain studies have similarly found higher effectiveness ratings and purchase intentions for medications used under placebo conditions (Geuter et al., 2013; Guevarra et al., 2020; Buhle et al., 2012). Our findings confirm the effectiveness of our placebo manipulation and suggest that placebo can alter broader cognitive processes beyond emotion, including drug efficacy expectations and value assessments. Research has shown that placebo can reduce test anxiety and enhance self-management (Schaefer et al., 2019) and increase belief in exercise benefits (Wang et al., 2022). Our study indicates these cognitive effects can be enhanced through DLPFC activation. However, since we did not match consumption values between TMS groups, we advise cautious interpretation of these "willingness-to-pay" measures.

Finally, our results suggest that DLPFC-dependent placebo effects may reduce negative social emotions in individuals with social anxiety tendencies. Although social anxiety correlated positively with negative emotion intensity and LPP amplitude at baseline across all 100 participants, this correlation was significantly attenuated under placebo conditions following DLPFC activation. Previous research indicates that higher social anxiety is associated with greater sensitivity to social exclusion (Heeren et al., 2017) and more negative expectations of social feedback (Gu et al., 2020). Critically, individuals with social anxiety show impaired deliberate emotion regulation (Brühl et al., 2014; Heeren et al., 2017; Kivity & Huppert, 2019; Dryman & Heimberg, 2018). For example, high socially anxious individuals use cognitive reappraisal less frequently and less effectively than healthy controls (Blalock et al., 2016; Goldin et al., 2009). Automatic regulation methods like placebo may therefore represent effective interventions for social anxiety. Notably, our conclusion is based on correlational analyses; future research should employ stronger manipulations to directly compare placebo (automatic regulation) and cognitive reappraisal (deliberate regulation) in socially anxious populations and explore clinical applications.

Future research should address several limitations and extend our findings. First, verify whether DLPFC activation enhances placebo effects established through conditioning. While our study demonstrated rDLPFC's role in expectation-

based placebo effects (Colloca & Barsky, 2020), its involvement in conditioning-based placebo effects remains unknown. Second, investigate the duration of TMS-enhanced placebo effects. We measured only immediate effects of single-session TMS, which induces neural plasticity changes lasting approximately 30 minutes (Valero-Cabré et al., 2017). Future studies should examine multi-session TMS protocols to enhance placebo efficacy and slow its decay. Third, incorporate additional measures of placebo emotion regulation. fMRI studies have shown reduced activation in emotion-processing regions including amygdala, thalamus, insula, and anterior cingulate cortex during placebo effects (Koban, Kross, et al., 2017; Peciña et al., 2015; Petrovic et al., 2005; Rütgen et al., 2015; Schienle et al., 2014, 2017). Eye-tracking research has demonstrated increased fixation frequency on aversive stimuli following placebo administration (Schienle et al., 2016). Additionally, emotion regulation studies have shown changes in pupillary diameter (Robinson et al., 2021) and skin conductance (Raio et al., 2013). Future research should combine multiple measurement modalities to comprehensively assess placebo emotion regulation.

5. Conclusion

This study is the first to combine neuromodulation and neuroimaging techniques to reveal the causal role of DLPFC in placebo-mediated negative emotion regulation. We demonstrated that TMS activation of rDLPFC enhances placebo emotion regulation effects, manifested as reduced subjective negative emotion experience and decreased objective LPP amplitude. These findings establish DLPFC' s central role in placebo emotion regulation and provide neural intervention targets for treating psychiatric disorders characterized by emotion dysregulation, such as social anxiety, depression, and generalized anxiety disorder.

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English Title and Abstract

The Role of Dorsolateral Prefrontal Cortex on Placebo Effect of Regulating Social Pain: A TMS Study

Under the influence of the novel coronavirus epidemic, negative social events such as separation of family or friends and home isolation have increased. These events can cause negative emotion experiences similar to physical pain, thus they are called social pain. Placebo effect refers to the positive response to inert treatment with no specific therapeutic properties, which has been shown to be one of the effective ways to alleviate social pain. Studies have shown that the dorsolateral prefrontal cortex (DLPFC) plays a key role in placebo effect. Therefore, this study aimed to explore whether activating DLPFC by using transcranial magnetic stimulation (TMS) could improve the ability of placebo effects to regulate social pain. Besides, we also combined neuroimaging and neuromodulation techniques to provide bidirectional evidence for the role of the DLPFC on placebo effects.

We recruited a total of 100 participants to finish the task of negative emotional rating of social exclusion images. Among them, 50 participants were stimulated by TMS at the right DLPFC (rDLPFC), while the others were assigned to the sham group. This study contained two independent variables. The between-subject variable was TMS group (rDLPFC-activated group or sham group) and the within-subject variable was placebo type (no-placebo and placebo). All participants received nasal spray in two blocks. In the no-placebo condition, participants were instructed that they would receive a saline nasal spray which

helped to improve physiological readings; in the placebo block, participants were told to administrate an intranasal fluoxetine spray (saline nasal spray in fact) that could reduce unpleasantness within 10 minutes. To strengthen the expectation of intranasal fluoxetine, participants viewed a professional introduction to fluoxetine' s clinical and academic usage including downregulating negative emotion, such as fear, anxiety, and disgust. Participants who received the placebo block first would be reminded that fluoxetine' s effect was over before the next block to reduce carry-over effects.

Self-reported negative emotional and electroencephalogram data were recorded. There was a significant two-way interaction of TMS group and placebo type. Results showed that compared with the sham group, participants in the rDLPFC-activated group reported less negative emotional feeling and had a lower amplitude of the late positive potential (LPP) in the placebo condition, a component that reflects emotional intensity, suggesting that activating rDLPFC can improve the ability of placebo effect to regulate social pain.

The above finding suggested that activating DLPFC can improve the placebo effect of regulating negative emotion. Moreover, this study is the first attempt to investigate the enhancement of placebo effects by using TMS on emotion regulation. The findings not only support the critical role of DLPFC on placebo effect using neuroimaging and neuromodulation techniques, but also provide a potential brain target for treating emotional regulation deficits in patients with psychiatric disorders.

Key words: dorsolateral prefrontal cortex, placebo effect, social pain, social exclusion, emotion regulation, transcranial magnetic stimulation

Note: Figure translations are in progress. See original paper for figures.