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Affective processing and non-invasive brain stimulation, volume II

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Affective processing and non-invasive brain stimulation, volume II

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Editorial: Affective processing and non-invasive brain stimulation, volume II

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Editorial on the Research Topic
Affective processing and non-invasive brain stimulation, volume II

Affective processing plays a crucial role in human life. Deficits in affective processing are accompanied by mental problems including depression, anxiety, and addiction. Non-invasive brain stimulation methodologies such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have become more and more popular in modulating a wide range of cognitive processing. This Research Topic aggregated several reviews, research articles, case reports, and research proposals aiming at identifying the neural correlates of affective processing and how these neural correlates are modulated by non-invasive brain stimulation.

Neural correlates of affective processing

Quickly and accurately identifying facial expressions plays an important role in social interactions. Song et al. investigated the influence of emotional contextual information (fearful, happy, and neutral scenes) on the neural processing of fearful expressions during the early stages of facial recognition based on the face-specific N170 component derived from the event-related potential (ERP) method. Their findings suggest that people allocate more attention to the processing of facial information when the valence between emotional context and expression conflicts.

Although extensive research has focused on the detection of uncertain threat signals in anxious individuals, little has been done to investigate the detection of uncertain safety signals in people with anxiety. Jin et al. compared 16 subjects with high trait anxiety and 16 with low trait anxiety during a modified cue-target task in certain and uncertain stimulus blocks based on the ERP components P2 and N2 that reflect early attentional allocation and association learning, respectively. They reported distinctive attentional biases between high and low-trait anxiety individuals, as well as association learning in uncertain conditions in high-trait anxiety individuals.

Outcome evaluation plays an important role in reward learning and decision-making and is related to the benefits of both self and others. Tan et al. examined both behavioral and neural correlates of outcome evaluation by gambling for the self and charity, respectively.

They employed two ERP components FRN and P3 to reflect the early and middle/late neural processing of outcomes, respectively. They reported that people tended to optimize strategies for themselves rather than for charity. Based on their ERP results, they concluded that people focus more on charity-outcome in the early stage, and more on self-outcome in the middle and late stages. The differences between self-outcome and charity-outcome varied with the reward magnitude. More specifically, people pay similar attention to small self-outcome and charity-outcome, but more attention to larger self-outcome than larger charity-outcome.

Cognitive reappraisal is one of the core treatment components of cognitive behavioral therapy and is the gold standard treatment for major depressive disorders. Wang et al. proposed a novel cognitive bias model that hypothesizes that cognitive reappraisal training may improve the generation ability of cognitive reappraisal with altered prefrontal–amygdala functional activation/connectivity, thus reducing negative cognitive bias (negative attention bias, negative memory bias, negative interpretation bias, and/or negative rumination bias) and alleviating depressive symptoms.

Non-invasive brain stimulation and its effects

People who use methamphetamine for a long time may become less able to control their actions and more likely to act impulsively. Liu Q. et al. found that high-frequency repetitive TMS (HF-rTMS) on the left dorsolateral prefrontal cortex (DLPFC) is a promising intervention for reducing impulsivity and cue-induced craving in patients with methamphetamine use disorders. In their study, patients underwent five sessions of HF-rTMS on the left DLPFC per week for 4 consecutive weeks, while controls received no rTMS intervention.

Non-invasive brain stimulation methods are well-accepted in both academic and clinical domains focusing on not only affective processing but also the other cognitive processing. Qi et al. systematically reviewed the existing literature on the effects of tDCS on motor skills learning of healthy adults and discussed the underlying neurophysiological mechanism that influences motor skills learning. They included 11 studies in their meta-analysis and showed that tDCS can help healthy adults improve motor skills learning through activating different brain regions including the primary motor cortex, left DLPFC, and right cerebellum.

Cryptococcal meningitis is a central nervous system disease caused by a novel Cryptococcus infection that leads to subacute or chronic inflammatory changes in the nervous system. In a case study, Liu Y. et al. examined a 72-year-old woman diagnosed with Cryptococcal meningitis and severe cognitive impairment and disabilities. They reported a large improvement in cognitive functions, especially executive functions, after receiving anti-infectious and rTMS.

Novel methods

Non-invasive brain stimulation should not be limited to TMS and tDCS methods. Adding noise to a system to improve a weak signal's throughput has been shown to improve sensory perception and even higher-order processing such as working memory. To understand whether stochastic resonance can broadly improve cognition, Sherman et al. investigated the performance of different cognitive tasks while applying auditory white noise and/or noisy galvanic vestibular stimulation. They found that some subjects exhibited cognitive changes with the addition of noise but the rest subjects did not. Their findings suggest that using noise to improve cognition is not applicable to a broad population; however, the effect of noise differs across individuals.

Machine learning is very promising in clinical usage. In order to improve diagnosis in clinical patients by using the functional connection methods, Zhao et al. developed a new multi-view brain network feature enhancement method based on a self-attention mechanism graph convolutional network (SA-GCN). This method enhances node features through the connection relationship among different nodes, and then extracts deep-seated and more discriminative features. They reported that SA-GCN effectively extracts more discriminative features and achieves the best classification accuracy (79.9%) for the diagnosis of autism spectrum disorder. Their new methods have the potential to be applied to patients with other disorders including problems of affective processing.

In summary, our Research Topic may help to delineate the neural correlates of affective processing as well as the influences of non-invasive brain stimulations on neural processing including affective processing, and may help to propose potential empirical interventions for clinical disorders.

Author contributions

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Early Influence of Emotional Scenes on the Encoding of Fearful Expressions With Different Intensities: An Event-Related Potential Study

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Contextual affective information influences the processing of facial expressions at the relatively early stages of face processing, but the effect of the context on the processing of facial expressions with varying intensities remains unclear. In this study, we investigated the influence of emotional scenes (fearful, happy, and neutral) on the processing of fear expressions at different levels of intensity (high, medium, and low) during the early stages of facial recognition using event-related potential (ERP) technology. EEG data were collected while participants performed a fearful facial expression recognition task. The results showed that (1) the recognition of high-intensity fear expression was higher than that of medium- and low-intensity fear expressions. Facial expression recognition was the highest when faces appeared in fearful scenes. (2) Emotional scenes modulated the amplitudes of N170 for fear expressions with different intensities. Specifically, the N170 amplitude, induced by high-intensity fear expressions, was significantly higher than that induced by low-intensity fear expressions when faces appeared in both neutral and fearful scenes. No significant differences were found between the N170 amplitudes induced by high-, medium-, and low-intensity fear expressions when faces appeared in happy scenes. These results suggest that individuals may tend to allocate their attention resources to the processing of face information when the valence between emotional context and expression conflicts i.e., when the conflict is absent (fear scene and fearful faces) or is low (neutral scene and fearful faces).

Keywords: emotional scenes, intensity, fear expression, ERP, N170, P1

Abbreviations: ERP, event-related potential; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; STS, superior temporal sulcus; rSTS, right superior temporal sulcus; LPP, late positive potential; EOG, electrooculography; EPN, early posterior negativity.

INTRODUCTION

Accurately identifying facial expressions is important for social interactions in the human. In daily life, however, facial expressions are always presented with specific contextual information. Facial expression recognition is extremely affected by context, such as body postures (Aviezer et al., 2010; Rajhans et al., 2016), emotional voices (Langeslag et al., 2019), self-related sentences (Aguado et al., 2019; Li S. et al., 2019), the task relevance (Mirabella, 2018; Mancini et al., 2020; Mancini et al., 2022), and emotional scenes (Righart and de Gelder, 2006; Righart and Gelder, 2008a,b; Qiang et al., 2015; Bai et al., 2017; Fernández-Martín et al., 2017; Xu et al., 2017). How does the human brain process facial expressions? Many studies primarily used the prototypical, posed facial expressions provided by volunteers at the request of researchers; but, emotional facial expressions typically arise dynamically from a neutral expression, and this expression strengthens or weakens depending on the situation. For example, a smile may transition into a laugh or mild anger may intensify to rage. Therefore, investigating the influence of emotional context on facial expression recognition, at different expression intensities, is of a great importance.

Accordingly, our brains respond quickly to changes in expression intensity (Leleu et al., 2018). Using an electroencephalogram (EEG), an earlier study demonstrated that maximum amplitude of P1 was attained before the participants confirmed seeing "fear image" in a fear detection task. P1 was observed to peak at about 100 ms after the onset of facial expressions in the occipito-temporal visual cortex (Foti et al., 2010; Luo et al., 2010). Empirical evidence shows that threatening faces induce a greater P1 amplitude than neutral faces (Luo et al., 2010; Smith et al., 2013; Xia et al., 2014), which reflects the rapid detection of threatening information and negative processing bias. However, the intensity effect of P1 is rarely studied.

Studies have also reported that the amplitude of the face-specific component, N170, is enhanced by the intensities of the expressions (Leppänen et al., 2007). According to the traditional view, N170 is sensitive to the structural coding of facial expression and insensitive to the emotional content of facial expression (Martin and Amanda, 2002; Holmes et al., 2003). However, Leppänen et al. (2007) investigated the electrocortical responses to fearful and happy emotional expressions at three levels of intensity (50, 100, 150%), but the intensity effect was only observed following exposure to fear expressions. Similarly, in a study of three negative facial expressions, including fear, disgust, and anger, with different intensities ranging from 50 to 150% with increments of 50%, the amplitudes of N170 were reported to significantly increase as the levels of intensity increased (Sprengelmeyer and Jentzsch, 2006). These studies suggest that the enhancement of the intensity-related N170 amplitude may be sensitive to negative faces. In general, studies that have investigated the intensity effect of isolated facial expressions have demonstrated that expressions with clearer meanings are associated with larger ERP amplitudes, i.e., P1 or N170, during the early processing stages of facial expression.

Righart and de Gelder (2006) were the first to provide electrophysiological evidence showing that context impacts expression processing during the early stages, reporting that the modulation effect of context on expression processing was reflected in the face-specific N170 component. Specifically, they demonstrated that faces without any context evoked the largest N170, and faces (especially fearful faces) in fearful scenes elicited a more negative N170 than faces in neutral scenes (Righart and de Gelder, 2006). These results indicate that scenes affect the early encoding of the face. In a subsequent study, Righart and Gelder (2008b) further clarified the modulation effect of scenes on face processing in an explicit expression discrimination task; showing that faces in fearful scenes induce a more negative N170 than faces in happy and neutral scenes, and fearful faces in fearful scenes evoked a more negative N170 than fearful faces in happy scenes. Both studies partially supported the affective congruency effect. Hietanen and Astikainen (2013) reported a clearer affective congruency effect using the emotional priming paradigm. According to the affective congruency effect, the N170 was stronger for happy expressions primed by positive scenes than N170 for happy expressions primed by negative scenes. Additionally, N170 was stronger for sad expressions primed by negative scenes than N170 for sad expressions primed by positive scenes (Hietanen and Astikainen, 2013). The scene pictures selected by Righart and de Gelder (2006) and Righart and Gelder (2008a) had the same emotional content as the facial expression (e.g., fearful scenes and fearful faces); therefore, they were closer in semantic level.

Recently, multiple studies investigated the influence of context on expression processing using expressions with ambiguous emotional meanings, such as neutral expressions, and found that they were rated more positively in positive contexts and more negatively in negative contexts (Wieser et al., 2014; Li S. et al., 2019). ERP and fMRI studies have also provided evidence of the influence of emotional context on the processing of expressions with ambiguous emotional meanings in the temporal process and the activation of specific brain regions (Schwarz et al., 2013; Wieser et al., 2014; Li S. et al., 2019). This indicates that influence of emotional context on facial expression with different intensities may be varied. Recently, a few studies have provided preliminary evidence of the effect of scenes on expression with different intensities at the behavioral level (Tae-Ho et al., 2012; Li S. et al., 2019). They discovered that the recognition of expressions was largely dependent on the information of emotional scenes (i.e., affective congruency) and affected by the personality traits (e.g., anxiety) of the participants. However, the effects of emotional context on expression processing at varying intensities have yet to be identified.

In this study, we investigated the influence of scenes on the recognition of fear expressions with different intensities using ERP. By presenting integrated pictures of fear expressions with varying intensities (high, medium, and low) and scenes with different valences (fear, neutral, and happy), the subjects were required to identify whether the expression presented on the background of the scene was fear or not. The recognition rate and response time to fear expressions were recorded, and the early components, P1 and N170, were analyzed. We hypothesized that (1) the recognition rate of facial expressions would increase with fear intensity, (2) the recognition rate

would be the highest in fearful scenes, happy scene would make fear recognition difficult, and (3) the emotional scenes in which the fear expression appeared would affect the early processing stages of fear expression with different intensities. For N170, we hypothesized that the amplitude evoked by fear expression with higher intensity would be more negative and influenced by the scenes. In addition, fear expression evoked more negative N170 than neutral expression, and the amplitude became more negative as expression intensity increased. And the right lateralized effect for the processing of faces would be observed. We also hypothesized that the faces in fearful scenes would evoke a greater P1 than faces in neutral scenes, and smaller P1 than faces in happy scenes.

MATERIALS AND METHODS

Participants

The sample size in this study was estimated using G*power (version 3.1.9.7). The moderate effect $f = 0.25$ (corresponding η_p^2 is about 0.06), which is expected to reach 0.80 statistical test strength ($\alpha = 0.05$), was used, and the minimum number of planned samples needed was 22 subjects. To prevent possible loss of subjects, 25 physically and mentally healthy undergraduates from the University of Jinan were recruited. Participants were all right-handed with normal or corrected visual acuity. The handedness was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). In addition, all participants completed the Beck Anxiety Inventory (Beck and Steer, 1993) before the experiment to ensure that participants could maintain emotional stability during tasks. Scores < 30 points (25.56 ± 2.92), indicated that participants had no severe anxiety. Three participants were excluded because of too many artifact trials (<40 trials per condition). For the final sample, the average age was 19.97 years ($SD = 1.67$; 14 females and eight males). Verbal and written informed consents from all participants prior to the experiment were obtained. Participants were informed that they had the right to terminate the experiment at any time. All participants were received a gift for their participation. The experiment lasted for approximately one and a half hours. This study was approved by the ethics committee of the School of Education and Psychology, University of Jinan.

Stimuli

In total, 60 emotional scene images, including 20 fearful, neutral, and pleasant scenes, were used in the current study. Most of scene images were selected from the International Affective Picture System, and some were obtained from the internet.[1] Twenty-two participants were recruited to evaluate the valence (1 = very unpleasant, 9 = very pleasant) and arousal (1 = very calm, 9 = extremely arousing) of each emotional scene image using a 9-point scale. In term of valence, the results showed that pleasant scenes scored significantly higher than neutral scenes, which in turns scored significantly higher than fearful scenes (pleasant scenes: $M = 7.27$, $SE = 0.17$, neutral scenes: $M = 4.88$, $SE = 0.13$, fearful scenes: $M = 2.76$, $SE = 0.23$, $ps < 0.05$). In addition, fearful and pleasant scenes were more emotionally arousing than neutral scenes (fearful scenes: $M = 6.70$, $SE = 0.36$, pleasant scenes: $M = 6.34$, $SE = 0.19$, neutral scenes: $M = 4.46$, $SE = 0.20$, $ps < 0.05$). There was no difference in arousal between fearful scenes and pleasant scenes [the scores on valence ratings and arousal rating are presented in Appendix A (**Supplementary Material**)].

Facial expressions were selected from the NimStim database (Tottenham et al., 2009), and 20 pairs of images (fearful and neutral expressions) from 20 individual actors (10 women) were selected to create the different intensities of fearful facial expressions [the actor numbers are presented in Appendix B (**Supplementary Material**)]. Hair, clothing and other non-face items of the actors were not included. FantaMorphing software[2] was used to combine the prototypical fearful expressions with the neutral expressions of the same actor. Facial intensities included images ranging from 0 to 100% with 10% increments between consecutive images, and 220 different images depicting 20 different actors with 11 levels of fearful facial expressions were used within each continuum (**Figure 1**). However, a 10% increment in facial expression intensity is small. Therefore, to evoke a stable ERP waveform, the 11 levels of different intensities were further divided into three groups: low intensity (0, 10, 20, 30%), medium intensity (40, 50, 50, 60%), and high intensity (70, 80, 90, 100%) fearful expressions. A pilot study was conducted to ensure the rationality of this groping.

In the pilot study, ten undergraduate volunteers were asked to indicate if the facial expression was fear or not. The results showed a significant difference among the three intensities; the percentage of recognition of high intense fearful expressions was higher than the percentage of recognition of medium intense fearful expressions, which in turns was higher than the percentage of recognition of low intense fearful expressions (high: $M = 78.30$, $SE = 2.79$, medium: $M = 34.77$, $SE = 3.19$, low: $M = 10.60$, $SE = 2.63$, $ps < 0.05$). To ensure that the number of facial expressions in each group was consistent, the facial expressions with 50% intensity were repeated once so that there were 80 images for low, medium, and high intensity expressions, respectively. All scene and face images were adjusted until they reached a similar luminance, size, and color depth, etc. Facial images were 255*315 pixels and appeared against scene images that were 1.024*768 pixels.

Procedure

An experiment of 3 (Scene type: fearful, neutral, pleasant) * 3 (Expression intensity: low, medium, high) was designed, and all variables were within-subject factors.

Practice trials were performed to ensure that the participants were familiar with the experimental procedures; these trials were not included in the formal experiment. Overall, there were 720 face-scene compounds: 240 for each group of face intensity, 80 for each experiment condition. For each condition, such as the low-face-intensity and fearful-scene compound condition, the 80 images of facial expressions were shown once, while the

[1] https://image.baidu.com/

[2] http://www.fantamorph.com

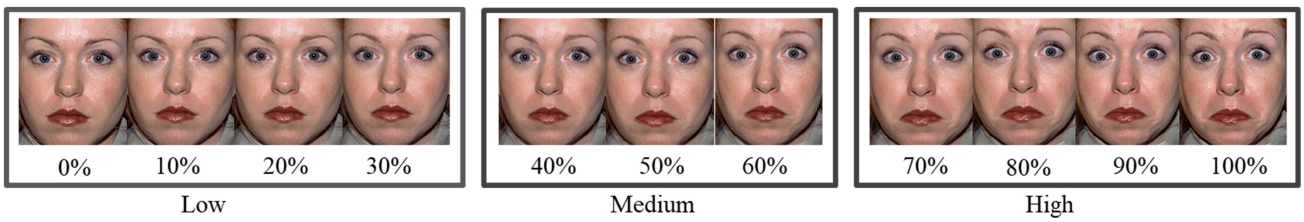

FIGURE 1 | Illustration of fearful facial expressions with different intensities. The image has been obtained from a public database with the publish permission.

20 scenes were shown four times to produce the compounds. The study was divided into three parts, and participants were given two opportunities to rest. During each part, 240 trials were presented to the subjects, including 80 facial expressions (28 trials for two kinds of intensity and 24 trials for one kind, three intensities balanced in three parts) in 3 emotional scenes. For each condition (low, medium, high), there was an equal number of trials (24 + 28 + 28 = 80 trails). Trials were presented randomly, and the order of the three parts of the experiment was counterbalanced across participants.

During the experiment, participants were seated on a comfortable chair that was located about 70 cm away from the computer screen in an electrically shielded and sound-attenuated room. A single trial was performed as follows: each trial started with a fixation mark (+), which varied randomly between 400 and 600 ms. The face-scene compound was presented for 800 ms, followed by a gray blank screen until the participant pressed the button for a response. Next, a white fixation mark (*) was presented for 600 ms (**Figure 2**). Participants were instructed to indicate as quickly as possible if the facial expression was fear or not. The experimental design was based on one previous study (Righart and de Gelder, 2006). E-prime 2.0 was used for stimuli presentation and to record behavioral results. The integrated images were presented at the center of screen with a visual angle of 29.94° × 22.45° to scene images and 7.46° × 9.21° to facial expression images.

Behavioral Data Analysis

The fearful facial expression recognition rate and reaction time were analyzed, and extreme data of reaction time that exceeded three standard deviations were excluded. The proportion of rejected data for each participant was 1.97 ± 0.78% ($M \pm SD$). A two-way repeated measures ANOVA was conducted using scene type (fearful, neutral, pleasant) and expression intensity (high, medium, low) as the within-subject factors (SPSS v. 17).

Electrophysiological Recordings and Analysis

Electroencephalogram data was collected continuously by a 64 Ag/AgCl electrode cap according to the International 10–20 system. All electrodes were referenced online to Cz. Impedance of each electrode was maintained below 10 kΩ during the experiment. Two electrodes were placed approximately 1 cm outside the canthus to record the horizontal electrooculography, and two electrodes were placed about 1 cm above and below the left eye to record the vertical electrooculography (EOG). The EEG and EOG were amplified and digitalized using a Neuroscan Synamp2 (Neuroscan Ltd., Charlotte, NC28269, United States) Amplifier with a band-pass of 0.01–400 Hz and a sampling rate of 1,000 Hz.

Offline, Curry7 (Compumedics Neuroscan United States, Ltd.) was used for data processing. All EEG data were re-referenced to an average reference and filtered with the band pass of 0.1∼30 Hz. Trials with EOG artifacts were corrected using the covariance-based artifact correction algorithms (0 for the Lower threshold, and 200 μV for the Upper one). Afterward, the data contaminated with other artifacts (peak-to-peak deflection exceeding ±100 μV) were excluded from averaging. Next, the EEG recording was segmented into epochs of 1,000 ms starting at 200 ms before stimulus onset. The trials left in each condition were all higher than 60% (low intensity in pleasant: $M \pm SD$ = 69.10 ± 5.53; medium intensity in pleasant: $M \pm SD$ = 67.34 ± 6.26; high intensity in pleasant: $M \pm SD$ = 70.08 ± 2.41; low intensity in neutral: $M \pm SD$ = 66.57 ± 5.28; medium intensity in neutral: $M \pm SD$ = 68.29 ± 6.55; high intensity in neutral: $M \pm SD$ = 71.17 ± 3.37; low intensity in fear: $M \pm SD$ = 63.42 ± 7.89; medium intensity in fear: $M \pm SD$ = 63.33 ± 6.34; high intensity in fear: $M \pm SD$ = 61.86 ± 5.21).

According to previous related studies (Frenkel and Bar-Haim, 2011; Qiang et al., 2015; Malaia et al., 2019), P1 was analyzed for PO3, PO4, O1, and O2 and N170 was analyzed for P7, P8, PO7, and PO8. ERP analyses focused on the peak amplitudes in the following time windows: 60∼140 ms (P1) and 130∼200 ms (N170). All ERP data were analyzed using three-way-repeated measures ANOVA with scene type (fearful, neutral, pleasant), expression intensity (high, medium, low) and hemisphere (left, right) as the within-subject factors. The Greenhouse-Geisser correction was applied where sphericity was violated. When the main effect or an interaction was significant, pairwise comparisons were performed with the Bonferroni correction (SPSS v. 17).

RESULTS

Behavioral Data

There was a significant main effect of fearful expression intensity [$F_{(2,48)}$ = 64,14, $p < 0.001$, η^2 = 0.73] on the recognition rate. The recognition rate of high intensity fearful expressions

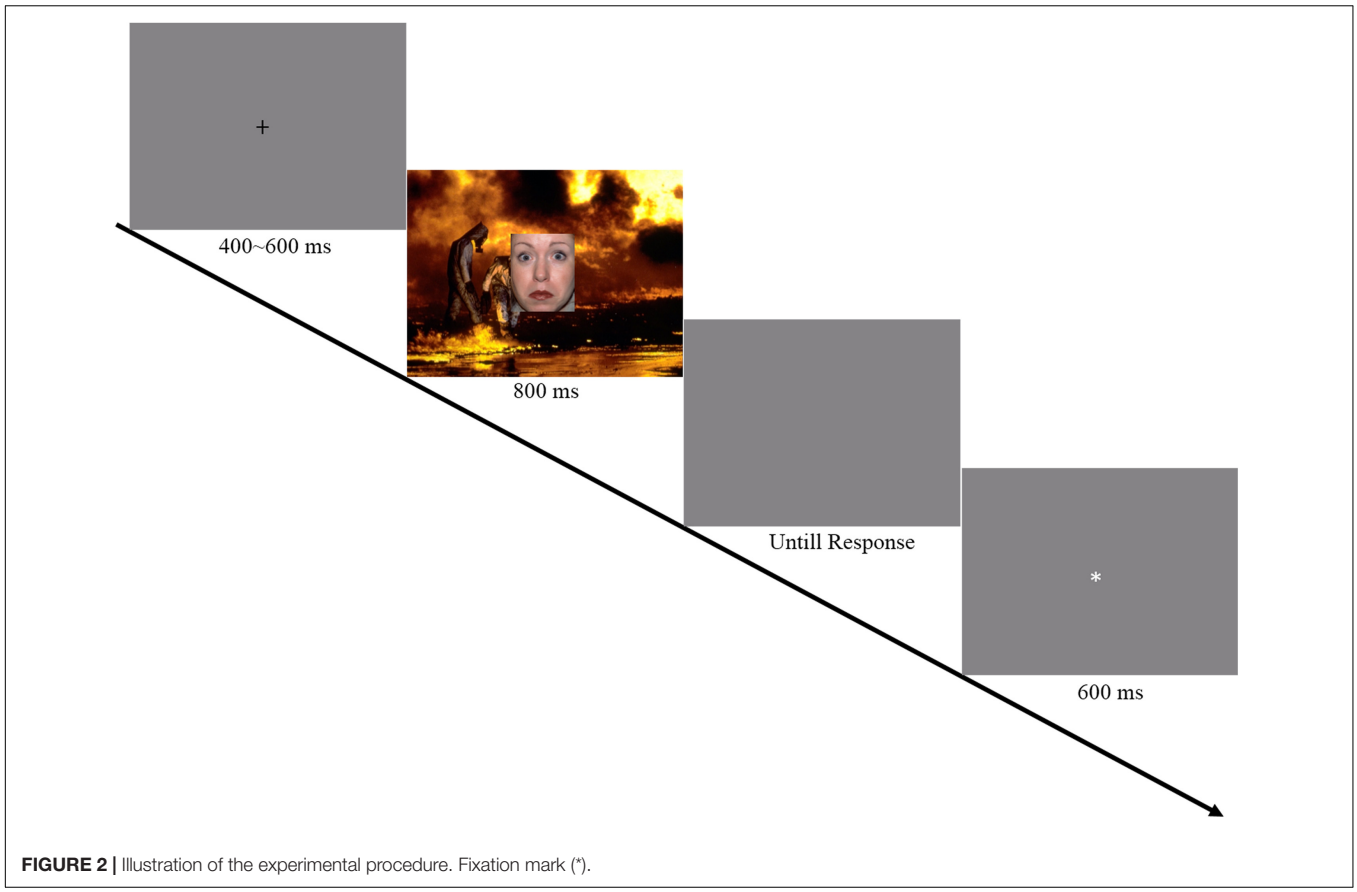

FIGURE 2 | Illustration of the experimental procedure. Fixation mark (*).

was significantly higher than that of medium intensity fearful expressions, and the recognition rate of medium intensity fearful expressions were significantly higher than that of low intensity fearful expressions (high vs. medium: $p < 0.001$; medium vs. low: $p < 0.001$). There was a significant main effect of emotional scenes [$F_{(2,48)} = 5.57$, $p = 0.006$, $\eta^2 = 0.19$] on the recognition rate, and the *post-hoc* comparison showed that the recognition rate of fearful expressions in fearful scenes was significantly larger than that of neutral scenes (fearful vs. neutral scenes: $p = 0.019$). The recognition rate of fearful expressions in fearful scenes was higher than that of fearful expressions in pleasant scenes; however, this difference was not significant (fearful vs. pleasant scenes: $p = 0.128$). There was no interaction between emotional scene type and facial expression intensity [$F_{(4,96)} = 1.74$, $p = 0.147$, $\eta^2 = 0.068$]. No differences were found in reaction time ($ps > 0.05$). The reaction time and recognition rate of fearful facial expressions is shown in **Figure 3**.

Event-Related Potential Data

P1

A significant emotional scene effect [$F_{(2,42)} = 8.62$, $p < 0.001$, $\eta^2 = 0.29$] was observed on the amplitude of P1. The P1 amplitudes induced by fearful and pleasant scenes were significantly higher than the P1 amplitude induced by neutral scenes (fearful vs. neutral scenes: $p = 0.003$; pleasant vs. neutral scenes: $p = 0.008$). There was no significant main effect of fearful expressions intensities [$F_{(2,42)} = 0.39$, $p = 0.682$, $\eta^2 = 0.018$] on the P1 amplitude. Neither the hemisphere effect nor the interaction between fearful expression intensities and emotional scenes were significant [$F_{(4,84)} = 0.42$, $p = 0.796$, $\eta^2 = 0.019$].

N170 (130–200 ms)

A main effect was found for emotional scenes [$F_{(2,42)} = 11.07$, $p < 0.001$, $\eta^2 = 0.35$] on the amplitude of N170. *Post-hoc* tests confirmed that the amplitude of N170 in neutral scene was significantly higher than the N170 amplitude in pleasant and fearful scenes (neutral vs. pleasant scenes: $p = 0.007$; neutral vs. fearful scenes: $p = 0.001$). There was a significant main intensity effect [$F_{(2,42)} = 8.05$, $p < 0.001$, $\eta^2 = 0.30$] on the N170 amplitude, and *post-hoc* analyses demonstrated that the N170 amplitude in high intense fearful facial expression was higher than that in medium and low intense fearful facial expressions (high vs. medium: $p = 0.001$; high vs. low: $p = 0.039$) (**Figure 4**). Finally, there was a significant main effect of hemisphere [$F_{(1,21)} = 15.93$, $p < 0.001$, $\eta^2 = 0.43$], on the N170 amplitude; the N170 amplitude was higher in the right hemisphere than that in the left hemisphere (right: $M = -8.30$; Left: $M = -5.12$, $p < 0.001$).

In addition, there was a significant interaction between emotional scenes and fearful facial expression intensities [$F_{(4,84)} = 3.67$, $p = 0.010$, $\eta^2 = 0.15$] on the N170 amplitude. In neutral scenes, N170 for high intensity fearful facial expressions was higher than that for medium intensity fearful facial

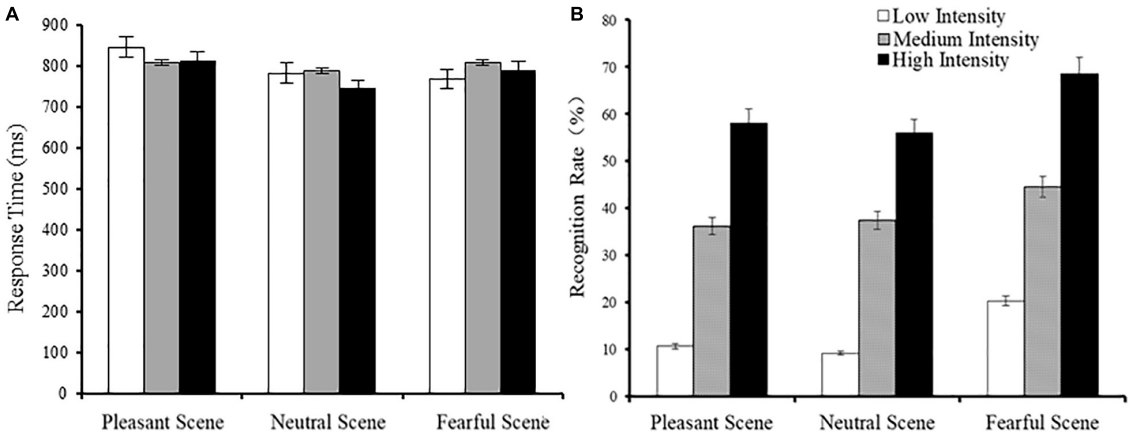

FIGURE 3 | Response time **(A)** and fearful expression recognition rate **(B)** when faces appeared in different scenes ($M \pm SE$).

expressions (high vs. medium: $p < 0.001$). In fearful scenes, the N170 amplitude for high intensity fearful facial expressions was higher than that for low intensity fearful facial expressions (high vs. low: $p = 0.026$), but no differences were found in the pleasant scenes ($ps > 0.05$). However, for low intense fearful expressions, the N170 amplitude was more negative when faces appeared in neutral scenes than the N170 amplitude when faces appeared in fearful and pleasant scenes (neutral vs. fearful scenes: $p = 0.002$; neutral vs. pleasant scenes: $p < 0.001$). The same result was observed for high intensity fearful expressions (neutral vs. fear scenes: $p = 0.001$; neutral vs. happy cenes: $p = 0.015$), but this result was not significant for medium intensity fearful expressions (**Figure 5**, $ps > 0.05$).

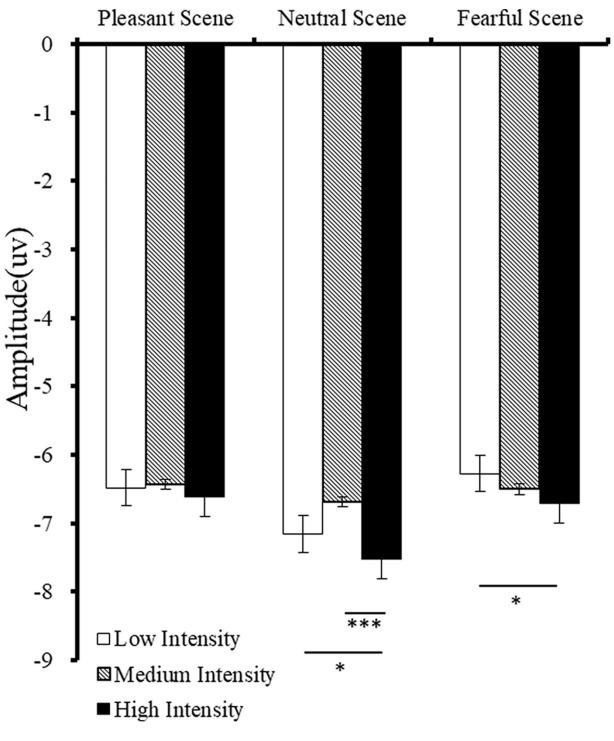

FIGURE 4 | Mean amplitudes of N170 for different fearful facial expression intensities in different scenes. Error bars indicate standard errors, $^{*}p < 0.05$. $^{***}p < 0.001$.

DISCUSSION

The current study investigated the influence of scenes on the processing of fear expression with different intensities when faces appeared in different scenes. The behavioral results showed that the recognition rate of fear expressions with high intensity was significantly higher than that for medium and low fear expressions. Additionally, the expression recognition rate was the highest when faces appeared in fearful scenes, indicating that scenes influence the recognition of fear expressions. The ERP results showed that the amplitude of N170 was more negative for faces with high intensity when fearful face appeared in fearful and neutral scenes than the amplitude of N170 for faces with low intensity when fearful faces appeared in fearful and neutral scenes; however, no significant results were observed when faces appeared in happy scenes, suggesting that emotional scenes modulate the processing of facial expressions with different intensities.

At the behavioral level, we found that as the intensity of fear expressions increased, the recognition rate of the expressions also increased, indicating that intensity played an important role in expression recognition (Leppänen et al., 2007; Gao and Maurer, 2010; Chen et al., 2020), which is consistent with the ERP results of this study demonstrating that the N170 amplitude increased with the intensity of fearful expressions. In addition, the context of scenes played an important role in facial expression recognition, as the recognition rate of fearful expressions appearing in fearful scenes was significantly higher than that in neutral scenes, reflecting the affective congruency effect (Righart and Gelder, 2008b). However, there was no interaction between scene and intensity level of fearful expressions, and the recognition rate of medium and low intensity fearful

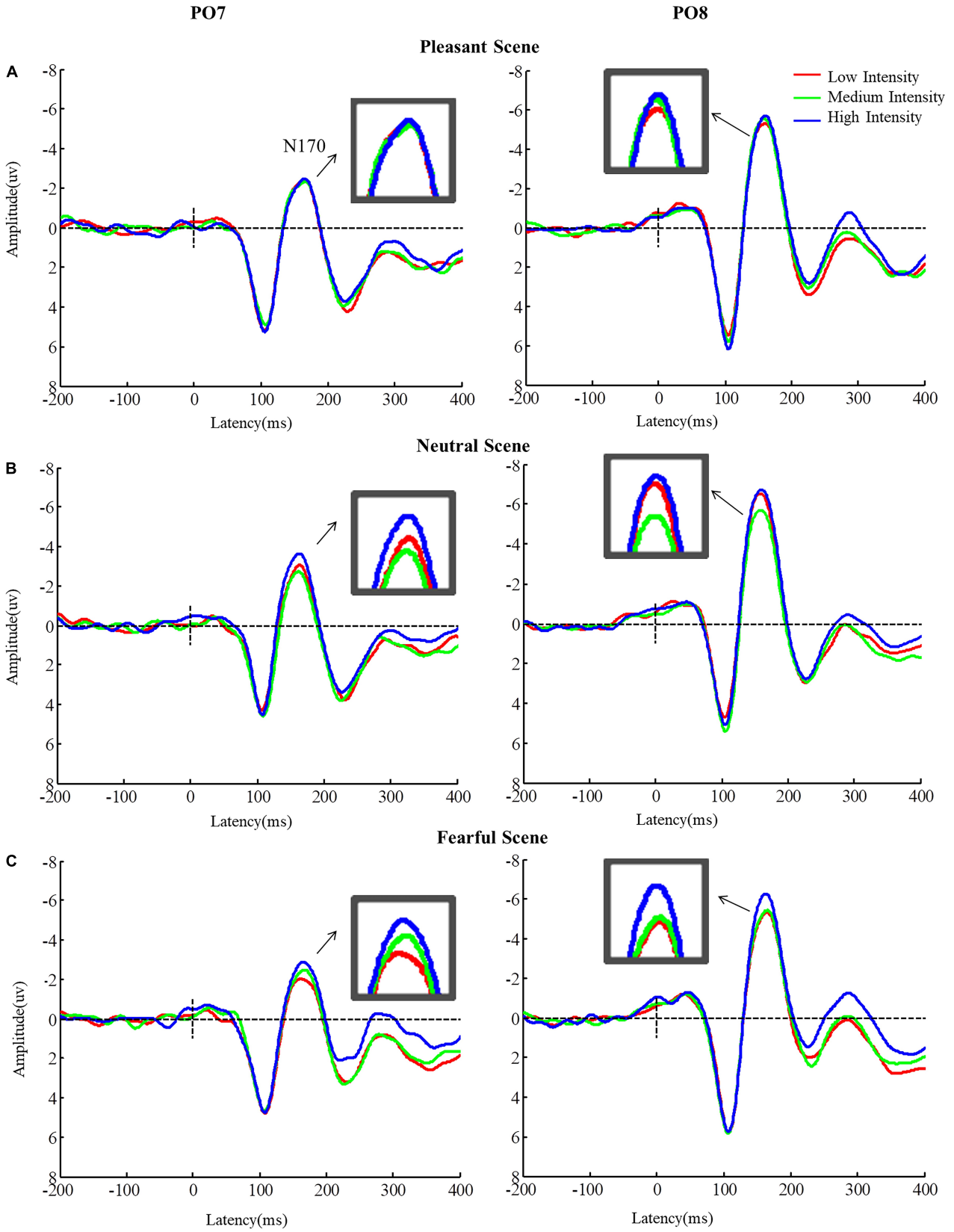

FIGURE 5 | Grand Average N170 amplitudes for **(A)** low intensity, **(B)** medium intensity, and **(C)** high intensity fearful facial expressions in different emotional scenes.

expressions were not affected by the types of scene. Previous studies on expressions with ambiguous emotional meanings (e.g., neutral) found that context affected the perception of expressions, reflected in the ratings of valence and arousal levels; for example, the valence ratings in a positive context were more positive, while those in a negative context were more negative (Wieser et al., 2014). In the current study, the participants were asked to indicate whether the expression was fearful or not, and the response times showed no significant difference among all conditions; therefore, the setting of the task may have been too easy and the embedding of the face stimuli in the context does not appear very realistic/naturalistic, which may explain why no interaction was observed.

In addition, recent studies showed that the emotional content of faces interferes with actions only when task-relevant, i.e., the effect of emotions is context-dependent (Mirabella, 2018; Mancini et al., 2020, 2022). Mirabella (2018) and Mancini et al. (2020) showed that task-irrelevant facial emotional expressions did not influence healthy people's motor readiness. Mancini et al. (2022) showed that the same effect also occur on inhibitory control, i.e., participants made more commission errors for happy than for fearful expressions only when emotional expressions are task relevant. In our case, the faces were always task relevant, which might reflect the neat result regarding the recognition rate. However, such effect was unlikely to be linked to changes in the N170. These changes occur much earlier than the behavioral responses. In future studies, task-irrelevant conditions (e.g., judge the scene and not the facial expression) should be added to investigate further the effect of emotional scenes on the recognition of expressions intensity.

At the level of ERPs, our results demonstrated that the influence of emotional scene information on fearful expression processing with different intensities was first reflected in the N170 component. In neutral scenes, the N170 amplitude induced by high-intensity fearful expression was stronger than that of medium-and low-intensity fearful expressions. In fearful scenes, the N170 amplitude induced by high-intensity fearful expressions was stronger than that induced by low-intensity fearful expressions. However, no significant difference was found for N170 when faces appeared in happy scenes. Previous studies that have investigated the intensity effect of isolated facial expressions have shown that high-intensity fearful expressions evoked stronger N170 amplitudes (Leppänen et al., 2007). After adding the emotional scene information, we found that the N170 amplitude was modulated by the emotional context. When the emotional context and the expression did not conflict (fearful faces in fearful scenes), or when the conflict between the emotional context and the expression was not too high (fearful faces in neutral scenes), the N170 amplitude differed according to different emotional intensities. When the conflict was highest (fearful faces in happy scenes), the N170 amplitude did not different. A recent study (Chen et al., 2020) showed that N170 amplitude induced by low- and high- intensities fearful expressions on negative scene was greater than the same expressions on the positive scene, which seems to be inconsistent with our findings. The most likely possibility is that facial expressions in our study didn't be grayscaled for maintaining higher ecological validity, and, therefore, the effect from emotional scenes was weakened. Thus, our results are in line with the characteristics of N170 component, which is more sensitive to facial expression (Bruno, 2014). Additionally, studies have shown that the amplitude of N170 is regulated by attention, and when attention was directed to emotional faces, a larger N170 component was induced (Holmes et al., 2003). Similarly, fMRI studies using the target point detection task have reported that when the target point was presented on the left or right side of the emotional face, the activation of the fusiform gyrus was weakened under the effective clue condition (Brassen et al., 2010). Although some studies have found a significant negative correlation between STS activation and N170 amplitude, source localization analyses have indicated that the fusiform gyrus may be the intracephalic activation region corresponding to N170 (Herrmann et al., 2005), and this may relate to the functional connection between STS and the fusiform gyrus. Therefore, one possible explanation for the results of this study is that the emotional scene information triggered a shift in attention. It has been reported that emotional scenes trigger attention transfer as evidenced by participants paying attention to the emotional scene information when asked to judge the orientation of the stripe stimulus on both sides of an emotional scene (Erthal et al., 2005). Furthermore, the isolated face-induced N170 amplitude was greater than that in the condition when the face appeared in the scene (Righart and de Gelder, 2006), suggesting the presentation of the scene distracted the attention resources for face processing. In the present study, conflicting situations were more likely to trigger more noticeable shifts of attention than consistent and non-conflicting situations, resulting in reduced individual attention to emotional faces; therefore, no intensity effects of expressions were observed. Although not explicitly reported in the study by Righart and Gelder (2008a) it was found that the conflicting situation (fearful face presented in a happy scene) induced the smallest N170 (Righart and Gelder, 2008a).

From the level of the individual experimental condition (**Figure 4**), the high-intensity fearful expressions evoked the largest amplitude of N170 when faces appeared in neutral scenes. Suggesting that the fearful scenes cause a more obvious attention transfer than neutral scenes and consequently does not reflect the affective congruency effect reported in previous studies (Righart and Gelder, 2008b; Hietanen and Astikainen, 2013). Additionally, when the emotional priming paradigm was used, the affective congruency effect reflected in the N170 was reported steadily (Hietanen and Astikainen, 2013). The processing of both positive and negative expressions showed the affective congruency effect; this was probably because in the priming paradigm, the primed scenes are processed first, allowing subjects to pay more attention to the subsequently presented faces. The possibility of attention transfer was small, indicating that attention transfer may play a more important role under the experimental condition when expressions were embedded in the background of scenes. In future studies, emotional scene priming and point detection paradigms could be combined (Yang et al., 2012) to further clarify the role of attention in the process of scene influence on expression processing, and the relationship between intensity of facial expression and exposure duration in the perception of

complex scenes (Shakespeare et al., 2014) need to be clarified. In the current study, P1 induced by fearful and pleasurable scenes were significantly higher than that induced by neutral scenes; however, the main effect of face intensity was not significant, indicating that P1 reflects the rapid detection of threatening or evolutionary significant stimuli, and intensive-related information may be further encoded by the later N170 component (Luo et al., 2010).

The current study examined the influence of scenes on fearful expressions with different intensities on the early stage of face processing and partially demonstrated the affective congruency effect–that is, when fearful faces appeared in fearful scenes, the intensity effect was significant. Additionally, our results also revealed that the intensity effect was significant when fearful faces were presented in neutral scenes and partially in fear scenes. Differently, the intensity effect was not significant when the fearful faces were presented in a pleasant context, indicating that the participants paid less attention to the face in the conflicted situation.

While our study highlights several important findings, there are limitations that need to be addressed. First, the study focused on fearful expressions, and the division level of fearful expressions was a gradual change from neutral to fearful. To keep the number of each facial intensity consistency, one level in medium was represented twice as much than the other level. Therefore, the conditions are not exactly comparable. In addition, as there was no positive expression, it was impossible to prove whether the scene had the emotional suppression effect on positive expressions of different intensities in the early processing stage of facial recognition. Second, the fearful expressions selected in this study were all closed-mouth versions. High-intensity fearful expressions in real life are more likely to be accompanied by mouth opening and tooth exposure. Expression with an open mouth elicits a stronger emotional feeling, and the expressions with exposed teeth evoke a greater N170 amplitude, indicating that low levels of visual features have an important impact on the processing of emotional expressions (Dasilva et al., 2016). Furthermore, negative (e.g., angry) open-mouth expressions induce greater early posterior negativity (EPN) than closed-mouth expressions, indicating a higher degree of automatic capture of early attention resources (Langeslag et al., 2018). Therefore, using fearful expressions with natural open mouths may improve the ecological validity of this study. Finally, in addition to scene information from outside of the facial expressions, information of the expression observer, such as personality traits and emotional states, may also affect the processing of fear expressions with different intensities (Wieser and Brosch, 2012). For example, people with high anxiety show a negative bias toward fear expressions (Torrence and Troup, 2018). Thus, it is necessary to further examine the impact of the internal information of the expression observer.

CONCLUSION

This study investigated the influence of emotional context information on fearful facial expression recognition with different intensities. The two major conclusions are: (1) As a function of fear facial expression intensity, the accuracy of facial recognition was enhanced, where fear scenes increase the recognition of fear expressions; (2) the early coding of fearful expressions with different intensities was affected by emotional scenes. Under the valence conflict condition between scenes and expressions, individuals do not need to allocate their attention to face processing probably because of a pop out effect.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of University of Jinan. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS and CF conceived and designed the study. SS and MW prepared the manuscript, conducted the experiments, and analysed the data. CF reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2022.866253/full#supplementary-material

REFERENCES

Aguado, L., Dieguez-Risco, T., Villalba-García, C., and Hinojosa, J. A. (2019). Double-checking emotions: valence and emotion category in contextual integration of facial expressions of emotion. *Biol. Psychol.* 146:107723. doi: 10.1016/j.biopsycho.2019.107723

Aviezer, H., Ran, R. H., Ryan, J., Grady, C., Susskind, J., Anderson, A., et al. (2010). Angry, disgusted, or afraid? studies on the malleability of emotion perception. *Psychol. Sci.* 19, 724–732. doi: 10.1111/j.1467-9280.2008.02148.x

Bai, L., Mao, W., Wang, R., and Zhang, W. (2017). The effect of emotional scene and body expression on facial expression recognition. *Acta Psychol. Sin.* 49, 1172–1183. doi: 10.3724/sp.j.1041.2017.01172

Beck, A. T., and Steer, R. A. (1993). *Beck Anxiety Inventory Manual*. San Antonio, TX: Psychological Corporation

Brassen, S., Gamer, M., Rose, M., and Büchel, C. (2010). The influence of directed covert attention on emotional face processing. *Neuroimage* 50, 545–551. doi: 10.1016/j.neuroimage.2009.12.073

Bruno, R. (2014). Understanding face perception by means of human electrophysiology. *Trends Cogn. Sci.* 18, 310–318. doi: 10.1016/j.tics.2014.02.013

Chen, T. J., Wang, Y., Feng, C. Z., and Feng, W. F. (2020). Early integration of affectively contextual information when processing low-intensity fearful faces: behavioral and electrophysiological evidence. *Int. J. Psychophysiol.* 156, 1–9. doi: 10.1016/j.ijpsycho.2020.07.001

Dasilva, E. B., Crager, K., Geisler, D., Newbern, P., Orem, B., and Puce, A. (2016). Something to sink your teeth into: the presence of teeth augments ERPs to mouth expressions. *Neuroimage* 127, 227–241. doi: 10.1016/j.neuroimage.2015.12.020

Erthal, F. S., Oliveira, L. D., Mocaiber, I., Pereira, M. G., Machado-Pinheiro, W., Volchan, E., et al. (2005). Load-dependent modulation of affective picture processing. *Cogn. Affect. Behav. Neurosci.* 5, 388–395. doi: 10.3758/cabn.5.4.388

Fernández-Martín, A., Gutiérrez-García, A., Capafons, J., and Calvo, M. G. (2017). Adaptive attunement of selective covert attention to evolutionary-relevant emotional visual scenes. *Conscious. Cogn.* 51, 223–235. doi: 10.1016/j.concog.2017.03.011

Foti, D., Hajcak, G., and Dien, J. (2010). Differentiating neural responses to emotional pictures: evidence from temporal-spatial PCA. *Psychophysiology* 46, 521–530. doi: 10.1111/j.1469-8986.2009.00796.x

Frenkel, T. I., and Bar-Haim, Y. (2011). Neural activation during the processing of ambiguous fearful facial expressions: an ERP study in anxious and nonanxious individuals. *Biol. Psychol.* 88, 188–195. doi: 10.1016/j.biopsycho.2011.08.001

Gao, X., and Maurer, D. (2010). A happy story: developmental changes in children's sensitivity to facial expressions of varying intensities. *J. Exp. Child Psychol.* 107, 67–86. doi: 10.1016/j.jecp.2010.05.003

Herrmann, M. J., Ehlis, A. C., Muehlberger, A., and Fallgatter, A. J. (2005). Source localization of early stages of face processing. *Brain Topogr.* 18, 77–85. doi: 10.1007/s10548-005-0277-7

Hietanen, J. K., and Astikainen, P. (2013). N170 response to facial expressions is modulated by the affective congruency between the emotional expression and preceding affective picture. *Biol. Psychol.* 92, 114–124. doi: 10.1016/j.biopsycho.2012.10.005

Holmes, A., Vuilleumier, P., and Eimer, M. (2003). The processing of emotional facial expression is gated by spatial attention: evidence from event-related brain potentials. *Cognit. Brain Res.* 16, 174–184. doi: 10.1016/s0926-6410(02)00268-9

Langeslag, S. J. E., Gootjes, L., and van Strien, J. W. (2018). The effect of mouth opening in emotional faces on subjective experience and the early posterior negativity amplitude. *Brain Cogn.* 127, 51–59. doi: 10.1016/j.bandc.2018.10.003

Langeslag, S. J. E., Gootjes, L., and Van Strien, J. W. (2019). The effect of mouth opening in emotional faces on subjective experience and the early posterior negativity amplitude. *Brain Cogn.* 127, 51–59

Leleu, A., Dzhelyova, M., Rossion, B., Brochard, R., Durand, K., Schaal, B., et al. (2018). Tuning functions for automatic detection of brief changes of facial expression in the human brain. *Neuroimage* 179, 235–251. doi: 10.1016/j.neuroimage.2018.06.048

Leppänen, J. M., Kauppinen, P., Peltola, M. J., and Hietanen, J. K. (2007). Differential electrocortical responses to increasing intensities of fearful and happy emotional expressions. *Brain Res.* 1166, 103–109. doi: 10.1016/j.brainres.2007.06.060

Li, S., Zhu, X., Ding, R., Ren, J., and Luo, W. (2019). The effect of emotional and self-referential contexts on ERP responses towards surprised faces. *Biol. Psychol.* 146:107728. doi: 10.1016/j.biopsycho.2019.107728

Luo, W., Feng, W., He, W., Wang, N. Y., and Luo, Y. J. (2010). Three stages of facial expression processing: ERP study with rapid serial visual presentation. *Neuroimage* 49, 1857–1867. doi: 10.1016/j.neuroimage.2009.09.018

Malaia, E., Cockerham, D., and Rublein, K. (2019). Visual integration of fear and anger emotional cues by children on the autism spectrum and neurotypical peers: an EEG study. *Neuropsychologia* 126, 138–146. doi: 10.1016/j.neuropsychologia.2017.06.014

Mancini, C., Falciati, L., Maioli, C., and Mirabella, G. (2020). Threatening facial expressions impact goal-directed actions only if task-relevant. *Brain Sci.* 10:794. doi: 10.3390/brainsci10110794

Mancini, C., Falciati, L., Maioli, C., and Mirabella, G. (2022). Happy facial expressions impair inhibitory control with respect to fearful facial expressions but only when task-relevant. *Emotion* 22, 142–152. doi: 10.1037/emo0001058

Martin, E., and Amanda, H. (2002). An ERP study on the time course of emotional face processing. *Neuroreport* 13:427. doi: 10.1097/00001756-200203250-00013

Mirabella, G. (2018). The weight of emotions in decision-making: how fearful and happy facial stimuli modulate action readiness of goal-directed actions. *Front. Psychol.* 9:1334. doi: 10.3389/fpsyg.2018.01334

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113. doi: 10.1016/0028-3932(71)90067-4

Qiang, X., Yaping, Y., Entao, Z., Fuqiang, Q., Wenyi, L., and Ningjian, L. (2015). Emotional conflict in facial expression processing during scene viewing: an ERP study. *Brain Res.* 1608, 138–146. doi: 10.1016/j.brainres.2015.02.047

Rajhans, P., Jessen, S., Missana, M., and Grossmann, T. (2016). Putting the face in context: body expressions impact facial emotion processing in human infants. *Dev. Cogn. Neurosci.* 19, 115–121. doi: 10.1016/j.dcn.2016.01.004

Righart, R., and de Gelder, B. (2006). Context influences early perceptual analysis of faces–an electrophysiological study. *Cereb. Cortex* 16, 1249–1257. doi: 10.1093/cercor/bhj066

Righart, R., and Gelder, B. D. (2008a). Rapid influence of emotional scenes on encoding of facial expressions: an ERP study. *Soc. Cogn. Affect. Neurosci.* 3, 270–278. doi: 10.1093/scan/nsn021

Righart, R., and Gelder, B. D. (2008b). Recognition of facial expressions is influenced by emotional scene gist. *Cogn. Affect. Behav. Neurosci.* 8, 264–272. doi: 10.3758/cabn.8.3.264

Schwarz, K. A., Wieser, M. J., Gerdes, A. B., Muhlberger, A., and Pauli, P. (2013). Why are you looking like that? How the context influences evaluation and processing of human faces. *Soc. Cogn. Affect. Neurosci.* 8, 438–445. doi: 10.1093/scan/nss013

Shakespeare, T. J., Yong, K., Chris, F., Kim, L. G., Warrington, E. K., and Crutch, S. J. (2014). Corrigendum: scene perception in posterior cortical atrophy: categorization, description and fixation patterns. *Front. Hum. Neurosci.* 8:908. doi: 10.3389/fnhum.2014.00908

Smith, E., Weinberg, A., Moran, T., and Hajcak, G. (2013). Electrocortical responses to NIMSTIM facial expressions of emotion. *Int. J. Psychophysiol.* 88, 17–25. doi: 10.1016/j.ijpsycho.2012.12.004

Sprengelmeyer, R., and Jentzsch, I. (2006). Event related potentials and the perception of intensity in facial expressions. *Neuropsychologia* 44, 2899–2906. doi: 10.1016/j.neuropsychologia.2006.06.020

Tae-Ho, L., June-Seek, C., and Seok, C. Y. (2012). Context modulation of facial emotion perception differed by individual difference. *PLoS One* 7:e32987. doi: 10.1371/journal.pone.0032987

Torrence, R. D., and Troup, L. J. (2018). Event-related potentials of attentional bias toward faces in the dot-probe task: a systematic review. *Psychophysiology* 55:e13051. doi: 10.1111/psyp.13051

Tottenham, N., Tanaka, J. W., Leon, A. C., Mccarry, T., Nurse, M., Hare, T. A., et al. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Res.* 168, 242–249. doi: 10.1016/j.psychres.2008.05.006

Wieser, M. J., and Brosch, T. (2012). Faces in context: a review and systematization of contextual influences on affective face processing. *Front. Psychol.* 3:471. doi: 10.3389/fpsyg.2012.00471

Wieser, M. J., Gerdes, A. B. M., Bungel, I., Schwarz, K. A., Muhlberger, A., and Pauli, P. (2014). Not so harmless anymore: how context impacts the perception and electrocortical processing of neutral faces. *Neuroimage* 92, 74–82. doi: 10.1016/j.neuroimage.2014.01.022

Xia, M., Li, X., Ye, C., and Li, H. (2014). The ERPs for the facial expression processing. *Adv. Psychol. Sci.* 22, 1556–1563.

Xu, Q., Yang, Y., Tan, Q., and Zhang, L. (2017). Facial expressions in context: electrophysiological correlates of the emotional congruency of facial expressions and background scenes. *Front. Psychol.* 8:2175. doi: 10.3389/fpsyg.2017.02175

Yang, H., Dong, M., Chen, S., and Zheng, X. (2012). The effect of early attention allocation on location-based attention toward a later threat: an ERP study. *Neurosci. Lett.* 523, 62–66. doi: 10.1016/j.neulet.2012.06.042

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Early Safety Discrimination Under Uncertainty in Trait Anxiety: An Event-Related Potential Study

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Detection of safety-threat signals during uncertainty is an important mechanism of developmental anxiety disorder (AD). Although extensive research has focused on the detection of uncertain threat signals in anxious individuals, relatively little attention has been given to the identification of safety signals during uncertainty, which is an important way to relieve anxiety in individuals with AD. To investigate this phenomenon, 16 subjects with high trait anxiety (HTA) and 16 with low trait anxiety (LTA) completed a modified cue-target task in certain and uncertain stimulus blocks. In the uncertain block, the cue was followed by a threat picture or safety picture in 20% of trials, respectively; in the certain block, the cue could be followed by a threat picture or a safety picture on 100% of trials. Behavioral responses and event-related potentials (ERPs) were recorded. The ERP results demonstrated that LTA participants exhibited larger P2 amplitudes in the detection of safety cues than of threat cues during the uncertain block, whereas HTA participants showed significant P2 amplitudes between the safety and threat cues during the certain block, impairing the detection of safety stimuli during uncertainty. However, all participants exhibited greater N2 amplitudes following threat cues in certainty or uncertainty conditions. These findings pertaining to the P2 amplitude suggested distinctive attentional biases between HTA and LTA individuals, whereas the N2 amplitude showed association learning in uncertain conditions, compensating for safety-threat detection in HTA individuals.

Keywords: safety, uncertainty, high trait anxiety, event-related potentials, threat

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INTRODUCTION

According to environmental cues, safety-threat detection helps individuals to initiate adaptive behavioral responses. Previous studies have indicated that detection of threat stimuli during uncertainty, compared to certainty, increases behavioral avoidance and subjective distress (Shankman et al., 2011; Bennett et al., 2018). Cognitive neuroscience studies further show evidence that in anticipation of uncertain threat stimuli relative to certain threat stimuli, N100 and P3 (Nelson et al., 2015) were enhanced along with greater P2 (Huang et al., 2017) and SPN responses (Johnen and Harrison, 2020), eliciting larger insula and amygdala responses (Kastner-Dorn et al., 2018). These studies indicated that uncertainty alters threat anticipation processing.

Abnormal threat anticipation processing serves as the fundamental mechanism of anxiety disorders (ADs) (Geng et al., 2018). Some studies using subjective estimation have found that individuals with high trait anxiety (HTA) perceive future threat events as more likely to happen than

do healthy controls (Castillo and Calvo, 2000). Neuroimaging studies provide further the evidence that individuals with HTA are associated with heightened anticipation activity of threat stimuli compared to that of safety stimuli (Veerapa et al., 2020). Compared to healthy controls, heightened reactivity to uncertain threat stimuli was more prominent in individuals with ADs (Simmons et al., 2013). Specifically, anxious individuals show increased amygdala activation (Williams et al., 2015), lower bed nucleus of the stria terminalis-amygdala connectivity (Clauss et al., 2019) in response to the uncertain threat cues, and positive correlation between state anxiety and N1 peak during the processing of uncertain cues (Yang et al., 2020).

These studies examined the behavioral and brain response to uncertainty cues, which were equally likely to be followed by threat or safety stimulus (Williams et al., 2015; Clauss et al., 2019), or only presented threat stimuli (Stegmann et al., 2019). Although the experimental paradigms were constructed using uncertain conditions, it was impossible to detect safety during the uncertain contexts. However, detecting safety signals under uncertainty is a ubiquitous way to relieve anxiety in daily life. For example, although novel coronavirus pneumonia may happen unpredictably, people may avoid misfortune by engaging in certain preventive behaviors, such as wearing masks and washing hands frequently. Further, a small number of studies have shown that experimental manipulation of safety learning reduces indices of state anxiety (Fonteyne et al., 2009; Cho, 2021). However, despite the importance of detection safety signals in uncertain situations, neural mechanisms to detect safety signals during uncertainty remain unclear.

Moreover, previous studies have found inconsistent results regarding anxious individuals utilizing safety cues (Spiegler et al., 2019). It was reported that safety signals reduced fear-potentiated startle in HTA individuals relative to LTA individuals (Jovanovic et al., 2005), whereas another study failed to reduce the fear response (Grillon and Ameli, 2001). In addition, theoretical paradigms also differ: some researchers have proposed a bottom-up processing mechanism in anxiety, where discrimination between safety and threat information occurs at the early stages of processing (Mogg and Bradley, 1998; Bar-Haim et al., 2007). Other studies hypothesized that distinguishing between safety and threat cues occur during the later stages of processing (Mogg et al., 2000), in which anxious individuals have top-down processing in threat-safety detection (Eysenck et al., 2007). These conflicting findings may reflect methodological differences (Denefrio et al., 2019).

Importantly, previous studies indicate that the effect of uncertainty on safety-threat detection seems to occur only in the first second after detection (Lin et al., 2015). In this case, event-related potentials (ERPs) can be sufficient to capture the time course of the uncertainty effect precisely and accurately, including two distinct processes at the early and late stages. Several electroencephalogram (EEG) components have been used to determine whether uncertainty-linked attention was affected, including P2 and N2. The first was P2, which is a positive-energy reading related to selective attention in early sensory processes, which peaks from 150 to 275 ms after stimulus presentation (Johnen and Harrison, 2020). One study found that emotionally uncertain cues elicited larger P2 amplitudes than did certain ones (Huang et al., 2017). Another study observed no P2 amplitude differences between the certain and uncertain conditions (Johnen and Harrison, 2020). Another ERP component, N2 is a negative-energy reading occurring over the frontal midline regions 200–350 ms after stimulation, reflecting attention control (Basten et al., 2011). Previous studies have found that N2 amplitudes under uncertain conditions are larger than those under certain ones (Gole et al., 2011), while other studies have found that N2 amplitudes under certain conditions are larger than those under uncertain ones (Lin et al., 2014; Peng et al., 2020). Thus, it is not clear whether anxiety influences safety-threat detection in the time course of brain activity.

Therefore, the present study combined the ERP technique (Yang et al., 2020) with the modified cue-target paradigm to examine the effect of trait anxiety on the sensitivity of safety-threat signals during uncertainty. This study is an extension of a previous one with more nuanced in the investigation of the effects of uncertainty on safety-threat detection in HTA individuals, which has been identified as a severe risk factor for ADs. Uncertainty was elicited by cues signaling different association degrees about whether a forthcoming stimulus would be safety or threat. Thus, the present study chose four graphics as detection cues, corresponding to 100% association safety condition (certain safety condition), 100% association threat condition (certain threat condition), 20% association safety condition (uncertain safety condition), and 20% association threat condition (uncertain threat condition). According to the safety signal hypothesis (Seligman and Binik, 1997), uncertainty makes safety signals lose safety function, and previous results report that anxiety-linked attention bias occurs at the early stage (Williams et al., 1992), hence, we hypothesized that, during the early stage, attention patterns would differ between the HTA and LTA groups. Meanwhile, based on the reinforcement sensitivity theory (Corr, 2002) that association learning enhances sensory discrimination of threat and safety cues (Kass et al., 2013; Stegmann et al., 2021), we hypothesized that at the later stage, HTA and LTA individuals would exhibit similar attention bias in the uncertain conditions.

MATERIALS AND METHODS

Participants

High trait anxiety and LTA individuals aged 18–23 years were selected from a pool of nearly 400 undergraduate students based on their scores on the State-Trait Anxiety Inventory (STAI) trait scale scores, a self-evaluated questionnaire (Spielberger, 2010). Individuals scoring in the top and bottom 10 percentiles of the sample's distribution were invited to participate in the experiment. Participants within these percentiles were only excluded if they had a history of an affective disorder. After two subjects were excluded due to excessive EEG artifacts, 16 participants were allocated to the HTA group [nine females, STAI score, mean $\pm$ standard deviation (SD): 54.62 $\pm$ 4.27), and 16 to the LTA group (eight females, STAI score: 27.5 $\pm$ 3.86]. There was a significant difference in STAI scores between the

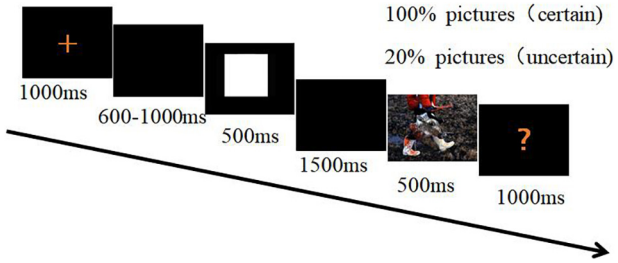

FIGURE 1 | The procedure of the modified cue-target task.

groups, $t(30) = 29.07$, $p < 0.001$. The groups did not differ in age, $t(30) < 1$. The mean age of the entire cohort was 20.16 ± 1.90 years. The study was approved by the Research Ethics Review Board of South China Normal University, and all participants signed an informed consent form for participation in the experiment.

Procedure and Stimulus Materials

The stimuli and procedures were the same as those in our previous study (Jin et al., 2013). Subjects viewed 40 neutral and 40 negative pictures selected from the International Affective Picture System (IAPS) (Lang et al., 2008). The selection was based on normative valence and arousal evaluation using a 9-point scale ranging from "1" (extremely unpleasant) to "9" (extremely pleasant) and "1" (low excitement) to "9" (high excitement), respectively, as reported in the study by Lang et al. (2008). Neutral and negative pictures were selected for safety and threat stimuli respectively. In accordance with the IAPS scoring, comparison using *t*-tests indicated significant differences between the safety and threat stimuli in valence [threat: 1.88 ± 0.34, safety: 4.98 ± 0.32; $t(78) = -41.69$, $p < 0.001$] and in arousal [threat: 6.32 ± 0.63, safety: 2.92 ± 0.61; $t(78) = 24.58$, $p < 0.001$]. Stimuli were presented in two blocks. In the certain block, a square cue was always followed by the presentation of a threat picture or a hexagon cue was always followed by a safety picture. In the uncertain block, a circle cue was paired with a threat picture or a triangle cue was paired with a safety picture 20% of the time. A blank-screen appeared during the remaining 80% of time. There were four fixed associations between cues and pictures. The stimuli presentation within each block was randomized. There were 100 trials in both certain and uncertain blocks. The cues were randomly counterbalanced across subjects.

A 500-ms cue signaled a safety or threat picture. The cue was followed by a 1,500-ms blank-screen interval before a threat or safety picture was shown. Each picture was shown for 500 ms and was followed by a red question mark on the screen. Termination of the red question mark was initiated by pressing a key within 1,000 ms. The subjects were required to indicate for each picture whether they perceived it as threat or safety (**Figure 1**). Half of the subjects were instructed to press the "F" key on the keyboard with their left index finger as accurately and quickly as possible following a threat picture, and to press the "J" key with their right index fingers when the red question mark followed a safety picture. The assignment of the response hands was reversed for the other half of the subjects. After each question mark, an inter-trial interval was randomly set for 4, 5, or 6 s.

Electroencephalogram Recording

The EEGs were recorded with Brain Amp DC amplifiers. Recordings were made from 30 scalp locations in accordance with the international extended 10–20 system (FP1, FP2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, TP7, CP3, CPz, CP4, TP8, P7, P3, Pz, P4, P8, O1, Oz, and O2). The left and right mastoids were recorded online, with the reference electrode attached over the left mastoid. The EEG data were re-referenced offline and calibrated to an averaged mastoid reference. The vertical electrooculogram (EOG) recording electrodes were positioned above and below the left eye, while the horizontal EOG recording electrodes were positioned at the outer canthus of both eyes. Scalp impedances were maintained below 5 kΩ. The signal was filtered offline using a band-pass of 0.1–30.0 Hz. The sampling rate was 500 Hz/channel. Trials with EOG artifacts (mean EOG voltage exceeding ± 75 μV) and those contaminated with artifacts due to peak-to-peak deflection exceeding ± 75 μV were excluded from averaging.

Event-Related Potential Analyses

We only analyzed a cue-locked period because the identification of ERPs requires an adequate number of trials, which were not in the uncertain picture block. ERPs were time-locked to the cue onset. EEG activity was separately averaged for each condition (i.e., certain/threat, certain/safety, uncertain/threat, uncertain/safety). We used a 500-ms cue onset to evoke a priming effect. Based on Williams' attentional bias of anxiety in the early aspects of processing, we did not expect to observe a slow wave (i.e., SPN) between the cue and target stimulus. Thus, the ERP epoch length was 700 ms with a pre-stimulus baseline of 200 ms. We observed the prominent N1 (time window: 110–150 ms), P2 (time window: 180–240 ms), and N2 (time window: 270–340 ms) components (see **Figure 2**). These components were robustly found in the midline, therefore, only three electrode sites (Fz, Cz, and Pz) were selected for analysis. A mixed-model analysis of variance (ANOVA) was used with the groups (two levels: HTA and LTA) as a between-subject factor, certainty (two levels: certain and uncertain), stimulus type (two levels: threat and safety), and electrode sites (three levels: Fz, Cz, and Pz) for ERP mean amplitudes as within-subject factors. As this study was interested in the effect of trait anxiety on the sensitivity of safety-threat signals during uncertainty, our analyses mainly focused on group-related interaction effects. The Greenhouse-Geisser correction was applied to adjust the degrees of freedom of the F-ratios.

RESULTS

Behavioral Data

All subjects achieved a mean accuracy of 96.1% in identifying threat and safety stimuli, irrespective of certainty (certain or uncertain). Reaction time analysis was conducted on the trials

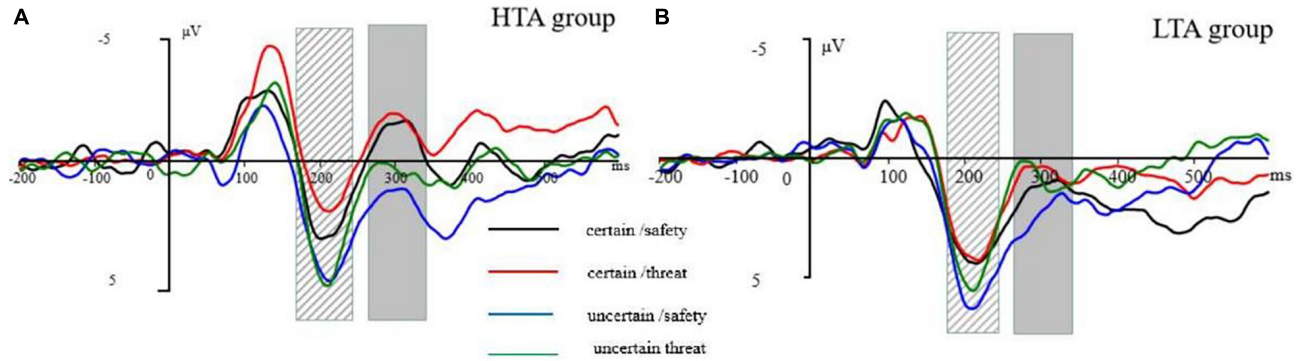

FIGURE 2 | (A) Grand-averaged P2 waveform at electrode Cz. **(B)** Grand-averaged N2 waveform at electrode Cz. The striped column is P2 at 180–240 ms following the cue onset. The gray column is N2 at 270–340 ms following the cue onset. The cue-ERP for certain-safety (black line), certain-threat (red line), uncertain-safety (blue line), and uncertain-threat (green line) conditions in the high trait anxiety (HTA) group (left) and the low trait anxiety (LTA) group (right).

with correct responses. The reaction time (mean ± standard deviation) of the HTA and LTA groups was: 305.03 ± 24.23 ms and 319.38 ± 24.17 ms, respectively. The difference between the groups was not significant.

Event-Related Potential Data

In the N1 time window (110–150 ms), a mixed-model ANOVA conducted on the amplitudes demonstrated very significant main effects for type, $F_{(1,\ 30)} = 16.70$, $p < 0.001$, $\eta_p^2 = 0.36$, with larger amplitudes for the threat (−2.00 ± 0.49 μV) than safety (−1.23 ± 0.49 μV) cues; electrode site, $F_{(2,\ 60)} = 10.45$, $p < 0.001$, $\eta_p^2 = 0.26$, with Fz showing more negative amplitudes (−2.34 ± 0.60 μV) than Cz (−2.066 ± 0.54 μV) and Pz (−0.45 ± 0.49 μV). Furthermore, there was a significant electrode site by group interaction, $F_{(2,\ 60)} = 4.86$, $p < 0.05$, $\eta_p^2 = 0.14$. The simple effect analysis of the electrode site by group interaction effect revealed no significant group effect. Although there was a significant three-way interaction of certainty by type by electrode site, $F_{(2,\ 60)} = 6.38$, $p < 0.05$, $\eta_p^2 = 0.18$, no group interaction was observed for the component (**Figure 2**), therefore, N1 was not further addressed.

Three main effects reached a significance level in the P2 time window (180–240 ms): type, $F_{(1,\ 30)} = 9.15$, $p < 0.01$, $\eta_p^2 = 0.23$, with larger amplitudes for the safety (3.70 ± 0.46 μV) than threat (3.08 ± 0.45 μV) cues; certainty, $F_{(1,\ 30)} = 13.18$, $p < 0.001$, $\eta_p^2 = 0.31$, with larger amplitudes for the uncertain condition (3.93 ± 0.48 μV) than the certain condition (2.84 ± 0.45 μV); and electrode site, $F_{(2,\ 60)} = 3.42$, $p < 0.05$, $\eta_p^2 = 0.10$. Significant three-way interactions of certainty by electrode site by group [$F_{(2,\ 60)} = 3.43$, $p < 0.05$, $\eta_p^2 = 0.10$] and type by certainty by group were observed [$F_{(1,\ 30)} = 4.48$, $p < 0.05$, $\eta_p^2 = 0.13$] were significant. A further simple effect analysis (**Figure 3A**) indicated that, in the HTA group, the P2 amplitudes were larger for safety cues (2.66 ± 0.67 μV) than those for threat cues (1.61 ± 0.69 μV) under the certain condition, [$F_{(1,\ 15)} = 6.38$, $p < 0.05$, $\eta_p^2 = 0.40$], while the amplitudes associated with safety (3.66 ± 0.90 μV) and threat (3.53 ± 0.74 μV) cues were comparable under the uncertain condition [$F_{(1,\ 15)} = 0.71$, $p > 0.05$]. Analyses in the LTA group revealed a significant effect for the type under the uncertain condition, [$F_{(1,\ 15)} = 7.27$, $p < 0.05$, $\eta_p^2 = 0.25$], indicating larger P2 amplitudes for safety cues (4.75 ± 0.51 μV) than threat cues (3.79 ± 0. 61 μV).

The main effect of the threat cue (0.16 ± 0.65 μV) was significantly more negative than that of the safety cues (0.91 ± 0.64 μV) in the N2 time window [270–340 ms; $F_{(1,\ 30)} = 9.60$, $p < 0.01$, $\eta_p^2 = 0.24$]. The certainty main effect indicated that the N2 amplitudes for an uncertain cue (1.27 ± 0.70 μV) were less negative than those of the certain cue [-0.20 ± 0.63 μV; $F_{(1,\ 30)} = 11.92$, $p < 0.01$, $\eta_p^2 = 0.28$]. The site main effect differed significantly between the electrodes [$F_{(2,\ 60)} = 31.01$, $p < 0.001$, $\eta_p^2 = 0.51$], with Fz showing more negative amplitudes (−1.62 ± 0.84 μV) than Cz (0.49 ± 0.75 μV) and Pz (2.74 ± 0.50 μV). More importantly, a four-way interaction of group, certainty, type, and electrode site was significant [$F_{(2,\ 60)} = 5.47$, $p < 0.01$, $\eta_p^2 = 0.15$]. Further simple analysis (**Figure 3B**) found that the type effect was significant at Cz across certainty conditions: in the HTA group, a significantly larger N2 amplitude was observed in anticipation of a negative stimulus (−0.63 ± 1.12 μV) than for neutral ones (−0.49 ± 1.01 μV) during both the certain condition [$F_{(1,30)} = 12.24$, $p < 0.001$, $\eta_p^2 = 0.01$] and the uncertain condition [$F_{(1,30)} = 14.31$, $p < 0.001$, $\eta_p^2 = 0.12$], with a more negative N2 amplitude in anticipation of a threat stimulus (0.92 ± 1.21 μV) than for a safety one (1.65 ± 1.23 μV). Similarly, in the LTA group, a more negative N2 amplitude was observed in anticipation of a threat stimulus than a safety stimulus during the certain condition [$F_{(1,30)} = 20.37$, $p < 0.001$, $\eta_p^2 = 0.07$] and during the uncertain condition [$F_{(1,30)} = 5.26$, $p < 0.05$, $\eta_p^2 = 0.45$].

Figures 4A,B illustrates the topographies of difference waves (subtraction of the safety cue ERPs from the threat cue ERPs) at the 180–240 and 270–340 ms intervals after the cue onset. The various wave topographies at the 180–240 ms interval under the uncertain condition in the HTA group and under the certain condition in the LTA group were sky blue, indicating that the amplitudes generated by the threat and safety cues in this time window were similar, resulting in a difference of almost zero. ANOVA results for the wave difference at the 180–240 ms interval showed that the interaction between certainty,

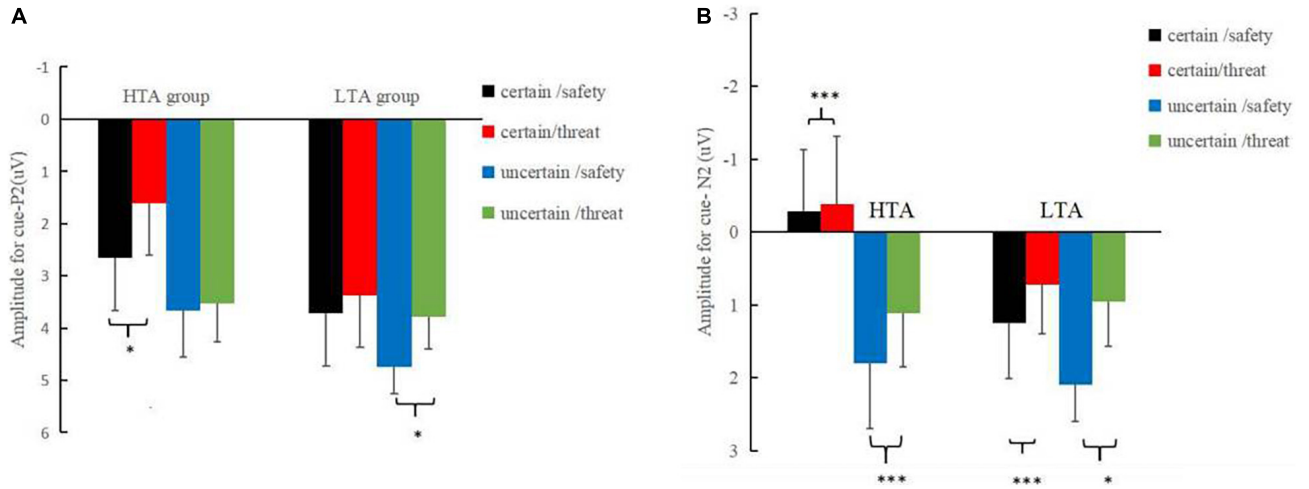

FIGURE 3 | (A) Corresponding mean amplitudes and standard errors for cue-P2. **(B)** Corresponding mean amplitudes and standard errors for cue-N2. Certain-safety (black), certain-threat (red), uncertain-safety (blue), and uncertain-threat (green) trials, respectively in the LTA and HTA groups (*$p < 0.05$, ***$p < 0.001$).

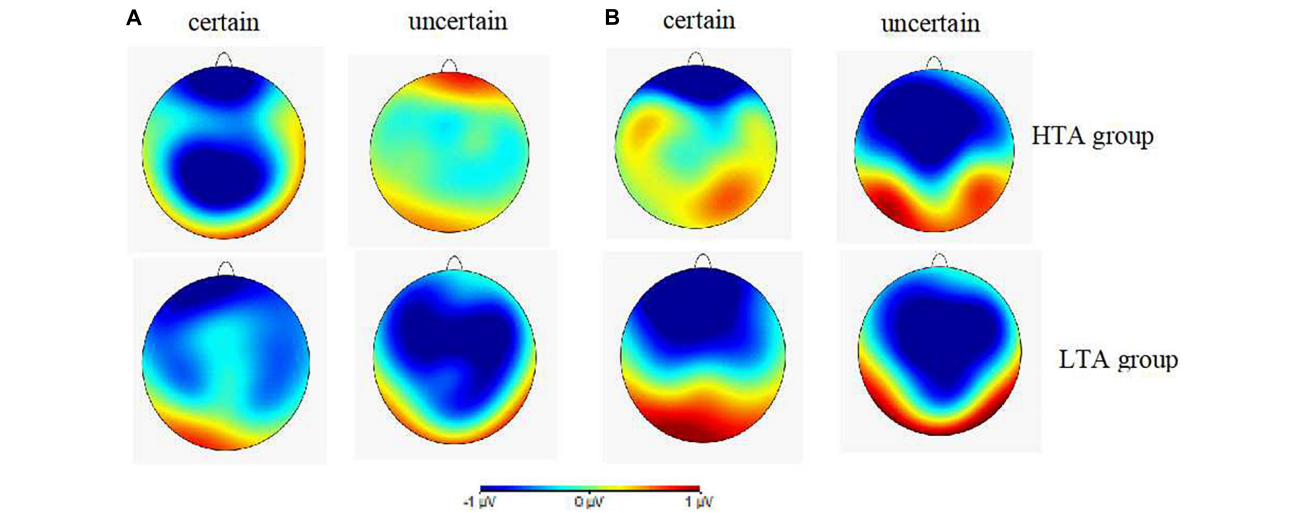

FIGURE 4 | (A) Topographic maps showing voltage differences between certain and uncertain trials (threat minus safety) for cue-P2 at 180–240 ms after the cue onset. **(B)** Topographic maps showing voltage differences between certain and uncertain trials (threat minus safety) for cue-N2 at 270–340 ms after the cue onset for the HTA (up) and LTA (below) groups.

electrode site, and group was significant [$F_{(2, 60)} = 3.25$, $p < 0.05$, $\eta_p^2 = 0.10$]. Simple effect analysis in the HTA group revealed that the amplitude at Pz was smaller under uncertain cues (-0.11 ± 0.41 μV) than certain ones (-1.67 ± 0.45 μV), $F_{(1,30)} = 6.09$, $p < 0.05$. This result was consistent with the P2 ERP results detailed above. ANOVA results for the wave differences at the 270–340 ms interval demonstrated a significant main effect for certainty [$F_{(1,30)} = 15.66$, $p < 0.001$, $\eta_p^2 = 0.34$]. The *post hoc* pairwise comparisons showed that the uncertain cues (-1.19 ± 0.24 μV) elicited larger N2 amplitudes than the certain ones (-0.31 ± 0.29 μV). Thus, topography of difference waves reflected distinct anticipation between the HTA an LTA groups during the different certainty contexts.

DISCUSSION

Using ERP measures, the present study investigated the effects of trait anxiety on safety-threat detection during an uncertain condition. P2 results revealed that individuals with LTA exhibited a higher anticipation for safety than for threat cues during the uncertain conditions, whereas HTA individuals showed significance between safety cues and threat cues during the certain conditions, and uncertain conditions elicited similar anticipation responses for the upcoming threat and safety stimuli, suggesting attention bias at the early stage. Moreover, N2 results showed that HTA individual discrimination between safety and threat cues was similar to those of LTA individuals, indicating

that association learning enhances attention control during uncertainty in those with HTA.

The P2 is related to the allocation of attention in the early sensory processes (Gupta et al., 2019). Our study found a larger P2 amplitude during the uncertain condition than during the certain condition, which was consistent with the results of previous studies (Dieterich et al., 2016). Importantly, we found some evidence that HTA and LTA individuals have different attention allocation patterns during uncertainty. During uncertain conditions, LTA individuals showed differential threat-safety cue responses in P2 amplitudes. By contrast, HTA individuals showed no differential effects during uncertain conditions. These data suggest that LTA individuals demonstrate selective attention, which involves paying more attention to safety cues to ensure that these signals receive processing priority (Richards et al., 2014). Meanwhile, HTA individuals exhibited significant difference in P2 amplitudes during the certain condition, whereas they showed attention deficiency, which involves impaired discrimination between threat and safety cues during uncertain conditions; this was seen as no significant difference in P2 amplitudes. Our results were in line with those of a study that has shown that anxiety-liked individuals display increased threat generalization and less differentiation in uncertain contexts (Morriss et al., 2016). A similar effect has been observed for individuals with AD (Lissek et al., 2009; Grasser and Jovanovic, 2021). The safety-signal theory accounts for this observation (Seligman and Binik, 1997), which indicates that safety cues lose their safe signal function during uncertainty in individuals with HTA.

Interestingly, the uncertain cue-target picture pairing had a larger N2 amplitude for threat cues than for safety cues in both HTA and LTA participants. On one hand, this was a surprising finding, considering that N2 indicates inefficient attention control correlates with HTA (Bishop, 2009; Berggren and Derakshan, 2013). Uncertainty amplified the effects (Ran et al., 2016). The fact that both HTA and LTA individuals demonstrated high N2 amplitudes indicated significant discrimination between safety and threat cues. This may be because association learning strengthened affective electromyographic reactions in individuals with high anxiety (Corr, 2002), HTA individuals exhibited increased activations in the frontoparietal systems and had higher activation of the dorsolateral prefrontal cortex (Basten et al., 2011), which may be a compensatory mechanism for HTA individuals to achieve the same level of performance processing like LTA individuals.

In addition, although our ERP results revealed no group differences, HTA and LTA individuals demonstrated different initial safety sensitivity in P2, whereas in the N2 amplitudes, HTA and LTA individuals exhibited similar negative biases. A cognitive motivation of the anxiety model (Mogg and Bradley, 1998) is ideal to explain the differences and similarities in ERPs between the HTA and LTA individuals observed in this study. From the perspective of safety motivation, the safety-threat detection comprises the pre-evaluation stage, wherein subjects need to evaluate the stimulus based on the environmental cues. Previous studies have found that HTA individuals generated greater state anxiety than LTA individuals in an uncertain context (Williams et al., 2015), and uncertainty raises initial allocation attention bias (Peng et al., 2012), HTA individuals generalize anxiety, which disable the evaluation of the unpredictable stimuli, whereas LTA individuals use maximum attention resources to detect safety cues during uncertainty. However, after several trials, as all individuals build an association between the cue and target, they orient toward actual threat and direct their attention for the current goal task.

Some limitations of the present study should be mentioned. First, we studied the EEG response of HTA individuals and not subjects with clinically diagnosed ADs. This means that our current findings may not extend to individuals with ADs. Future studies should add such subjects to compare brain pattern differences among HTA individuals, LTA individuals and individuals with clinical anxiety to better explain this processing bias phenomenon. Second, our sample size was small. Future research should recruit higher numbers of HTA and LTA individuals. Third, although some studies (Bacigalupo and Luck, 2018) have shown that there was no significant difference in early and late trials of the association learning, EEG was averaged by early and late trials due to no time segments for the trials. Future studies will split into several sub-blocks to examine association learning dynamics of EEG effects.

P2 results revealed distinctive attentional biases between HTA and LTA individuals, whereas individuals with HTA exhibited negative biases in N2 like LTA individuals, in whom association learning may be a compensatory safety-threat detection mechanism.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Review Board of South China Normal University (Approval Number: SCNU-PSY-2021-112). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YJ and XZ: conceptualization, methodology, writing—original draft preparation and review and editing. LZ and WC: data collection. YJ: data analysis. XZ: supervision. All authors have read and agreed to the published version of the manuscript.

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REFERENCES

Bacigalupo, F., and Luck, S. J. (2018). Event-related potential components as measures of aversive conditioning in humans. *Psychophysiology* 55:e13015. doi: 10.1111/psyp.13015

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., and van IJzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychol. Bull.* 133, 1–24. doi: 10.1037/0033-2909.133.1.1

Basten, U., Stelzel, C., and Fiebach, C. J. (2011). Trait anxiety modulates the neural efficiency of inhibitory control. *J. Cogn. Neurosci.* 23, 3132–3145. doi: 10.1162/jocn_a_00003

Bennett, K. P., Dickmann, J. S., and Larson, C. L. (2018). If or when? Uncertainty's role in anxious anticipation. *Psychophysiology* 55:e13066. doi: 10.1111/psyp.13066

Berggren, N., and Derakshan, N. (2013). Attentional control deficits in trait anxiety: why you see them and why you don't. *Biol. Psychol.* 92, 440–446. doi: 10.1016/j.biopsycho.2012.03.007

Bishop, S. J. (2009). Trait anxiety and impoverished prefrontal control of attention. *Nat. Neurosci.* 12, 92–98. doi: 10.1038/nn.2242

Castillo, M. D., and Calvo, M. G. (2000). Anxiety gives priority to anticipation of threatening events. *Eur. Psychol.* 5, 234–244. doi: 10.1027/1016-9040.5.3.234

Cho, H. (2021). *Learning to Feel Safe: A Translational Study of the Influence of Safety Learning on Anxiety-Related Overgeneralized Fear*. New York, NY: City University of New York.

Clauss, J. A., Avery, S. N., Benningfield, M. M., and Blackford, J. U. (2019). Social anxiety is associated with BNST response to unpredictability. *Depress. Anxiety* 36, 666–675. doi: 10.1002/da.22891

Corr, P. J. (2002). J.A. Gray's reinforcement sensitivity theory: tests of the joint subsystems hypothesis of anxiety and impulsivity. *Pers. Individ. Dif.* 33, 511–532. doi: 10.1016/S0191-8869(01)00170-2

Denefrio, S., Myruski, S., Mennin, D., and Dennis-Tiwary, T. A. (2019). When neutral is not neutral: neurophysiological evidence for reduced discrimination between aversive and non-aversive information in generalized anxiety disorder. *Motiv. Emot.* 43, 325–338. doi: 10.1007/s11031-018-9732-0

Dieterich, R., Endrass, T., and Kathmann, N. (2016). Uncertainty is associated with increased selective attention and sustained stimulus processing. *Cogn. Affect. Behav. Neurosci.* 16, 447–456. doi: 10.3758/s13415-016-0405-8

Eysenck, M. W., Derakshan, N., Santos, R., and Calvo, M. G. (2007). Anxiety and cognitive performance: attentional control theory. *Emotion* 7, 336–353. doi: 10.1037/1528-3542.7.2.336

Fonteyne, R., Vervliet, B., Hermans, D., Baeyens, F., and Vansteenwegen, D. (2009). Reducing chronic anxiety by making the threatening event predictable: an experimental approach. *Behav. Res. Ther.* 47, 830–839. doi: 10.1016/j.brat.2009.06.011

Geng, H., Wang, Y., Gu, R., Luo, Y. J., Xu, P., Huang, Y., et al. (2018). Altered brain activation and connectivity during anticipation of uncertain threat in trait anxiety. *Hum. Brain Mapp.* 39, 3898–3914. doi: 10.1002/hbm.24219

Gole, M., Schäfer, A., and Schienle, A. (2011). Event-related potentials during exposure to aversion and its anticipation: the moderating effect of intolerance of uncertainty. *Neurosci. Lett.* 507, 112–117. doi: 10.1016/j.neulet.2011.11.054

Grasser, L. R., and Jovanovic, T. (2021). Safety learning during development: implications for development of psychopathology. *Behav. Brain Res.* 408:113297. doi: 10.1016/j.bbr.2021.113297

Grillon, C., and Ameli, R. (2001). Conditioned inhibition of fear-potentiated startle and skin conductance in humans. *Psychophysiology* 38, 807–815. doi: 10.1111/1469-8986.3850807

Gupta, R. S., Kujawa, A., and Vago, D. R. (2019). The neural chronometry of threat-related attentional bias: event-related potential (ERP) evidence for early and late stages of selective attentional processing. *Int. J. Psychophysiol.* 146, 20–42. doi: 10.1016/j.ijpsycho.2019.08.006

Huang, Y., Shang, Q., Dai, S., and Ma, Q. (2017). Dread of uncertain pain: an event-related potential study. *PLoS One* 12:e0182489. doi: 10.1371/journal.pone.0182489

Jin, Y., Yan, K., Zhang, Y., Jiang, Y., Tao, R., and Zheng, X. (2013). Gender differences in detecting unanticipated stimuli: an ERP Study. *Neurosci. Lett.* 538, 38–42. doi: 10.1016/j.neulet.2013.01.020

Johnen, A. K., and Harrison, N. R. (2020). Level of uncertainty about the affective nature of a pictorial stimulus influences anticipatory neural processes: an event-related potential (ERP) study. *Neuropsychologia* 146:107525. doi: 10.1016/j.neuropsychologia.2020.107525

Jovanovic, T., Keyes, M., Fiallos, A., Myers, K. M., Davis, M., and Duncan, E. J. (2005). Fear potentiation and fear inhibition in a human fear-potentiated startle paradigm. *Biol. Psychiatry* 57, 1559–1564. doi: 10.1016/j.biopsych.2005.02.025

Kass, M. D., Rosenthal, M. C., Pottackal, J., and McGann, J. P. (2013). Fear learning enhances neural responses to threat-predictive sensory stimuli. *Science* 342, 1389–1392. doi: 10.1126/science.1244916

Kastner-Dorn, A. K., Andreatta, M., Pauli, P., and Wieser, M. J. (2018). Hypervigilance during anxiety and selective attention during fear: using steady-state visual evoked potentials (ssVEPs) to disentangle attention mechanisms during predictable and unpredictable threat. *Cortex* 106, 120–131. doi: 10.1016/j.cortex.2018.05.008

Lang, P. J., Bradley, M. M., and Cuthbert, B. N. (2008). *International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. Technical Report A-8*. Gainesville, FL: University of Florida.

Lin, H., Gao, H., You, J., Liang, J., Ma, J., Yang, N., et al. (2014). Larger N2 and smaller early contingent negative variation during the processing of uncertainty about future emotional events. *Int. J. Psychophysiol.* 94, 292–297. doi: 10.1016/j.ijpsycho.2014.10.004

Lin, H., Jin, H., Liang, J., Yin, R., Liu, T., and Wang, Y. (2015). Effects of uncertainty on ERPs to emotional pictures depend on emotional valence. *Front. Psychol.* 6:1927. doi: 10.3389/fpsyg.2015.01927

Lissek, S., Rabin, S. J., McDowell, D. J., Dvir, S., Bradford, D. E., Geraci, M., et al. (2009). Impaired discriminative fear-conditioning resulting from elevated fear responding to learned safety cues among individuals with panic disorder. *Behav. Res. Ther.* 47, 111–118. doi: 10.1016/j.brat.2008.10.017

Mogg, K., and Bradley, B. P. (1998). A cognitive-motivational analysis of anxiety. *Behav. Res. Ther.* 36, 809–848. doi: 10.1016/S0005-7967(98)00063-1

Mogg, K., McNamara, J., Powys, M., Rawlinson, H., Seiffer, A., and Bradley, B. P. (2000). Selective attention to threat: a test of two cognitive models of anxiety. *Cogn. Emot.* 14, 375–399. doi: 10.1080/026999300378888

Morriss, J., Macdonald, B., and van Reekum, C. M. (2016). What is going on around here? Intolerance of uncertainty predicts threat generalization. *PLoS One* 11:e0154494. doi: 10.1371/journal.pone.0154494

Nelson, B. D., Hajcak, G., and Shankman, S. A. (2015). Event-related potentials to acoustic startle probes during the anticipation of predictable and unpredictable threat. *Psychophysiology* 52, 887–894. doi: 10.1111/psyp.12418

Peng, M., De Beuckelaer, A., Yuan, L., and Zhou, R. (2012). The processing of anticipated and unanticipated fearful faces: an ERP study. *Neurosci. Lett.* 526, 85–90. doi: 10.1016/j.neulet.2012.08.009

Peng, S., Xuan, B., and Li, P. (2020). Fearful faces modulate cognitive control under varying levels of uncertainty: an event-related potential study. *Brain Cogn.* 141:105550. doi: 10.1016/j.bandc.2020.105550

Ran, G., Chen, X., Zhang, Q., Ma, Y., and Zhang, X. (2016). Attention Modulates neural responses to unpredictable emotional faces in dorsolateral prefrontal cortex. *Front. Hum. Neurosci.* 10:332. doi: 10.3389/fnhum.2016.00332

Richards, H. J., Benson, V., Donnelly, N., and Hadwin, J. A. (2014). Exploring the function of selective attention and hypervigilance for threat in anxiety. *Clin. Psychol. Rev.* 34, 1–13. doi: 10.1016/j.cpr.2013.10.006

Seligman, M. E., and Binik, Y. M. (1997). "The safety signal hypothesis," in *Operant-Pavlovian Interactions*, eds H. Davis and H. M. B. Hurwitz (Hillsdale, NJ: Lawrence Erlbaum Associates), 165–187.

Shankman, S. A., Robison-Andrew, E. J., Nelson, B. D., Altman, S. E., and Campbell, M. L. (2011). Effects of predictability of shock timing and intensity on aversive responses. *Int. J. Psychophysiol.* 80, 112–118. doi: 10.1016/j.ijpsycho.2011.02.008

Simmons, A. N., Flagan, T. M., Wittmann, M., Strigo, I. A., Matthews, S. C., Donovan, H., et al. (2013). The effects of temporal unpredictability in anticipation of negative events in combat veterans with PTSD. *J. Affect. Disord.* 146, 426–432. doi: 10.1016/j.jad.2012.08.006

Spiegler, K. M., Smith, I. M., and Pang, K. C. H. (2019). Danger and safety signals independently influence persistent pathological avoidance in anxiety-vulnerable Wistar Kyoto rats: a role for impaired configural learning in anxiety vulnerability. *Behav. Brain Res.* 356, 78–88. doi: 10.1016/j.bbr.2018.07.025

Spielberger, C. D. (2010). *State-Trait Anxiety Inventory*. Hoboken, NJ: Wiley Online Library. doi: 10.1002/9780470479216.corpsy0943

Stegmann, Y., Andreatta, M., Pauli, P., and Wieser, M. J. (2021). Associative learning shapes visual discrimination in a web-based classical conditioning task. *Sci. Rep.* 11:15762. doi: 10.1038/s41598-021-95200-6

Stegmann, Y., Reicherts, P., Andreatta, M., Pauli, P., and Wieser, M. J. (2019). The effect of trait anxiety on attentional mechanisms in combined context and cue conditioning and extinction learning. *Sci. Rep.* 9:8855. doi: 10.1038/s41598-019-45239-3

Veerapa, E., Grandgenevre, P., El Fayoumi, M., Vinnac, B., Haelewyn, O., Szaffarczyk, S., et al. (2020). Attentional bias towards negative stimuli in healthy individuals and the effects of trait anxiety. *Sci. Rep.* 10:11826. doi: 10.1038/s41598-020-68490-5

Williams, J. M. G., Watts, F. N., MacLeod, C., and Mathews, A. (1992). *Cognitive Psychology and Emotional Disorders*. Chichester: Wiley. doi: 10.1007/BF03060482

Williams, L. E., Oler, J. A., Fox, A. S., McFarlin, D. R., Rogers, G. M., Jesson, M. A., et al. (2015). Fear of the unknown: uncertain anticipation reveals amygdala alterations in childhood anxiety disorders. *Neuropsychopharmacology* 40, 1428–1435. doi: 10.1038/npp.2014.328

Yang, S., Zhang, M., Xu, J., Wang, L., and Wang, Y. (2020). The electrophysiology correlation of the cognitive bias in anxiety under uncertainty. *Sci. Rep.* 10:11354. doi: 10.1038/s41598-020-68427-y

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Multi-View Feature Enhancement Based on Self-Attention Mechanism Graph Convolutional Network for Autism Spectrum Disorder Diagnosis

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Functional connectivity (FC) network based on resting-state functional magnetic resonance imaging (rs-fMRI) has become an important tool to explore and understand the brain, which can provide objective basis for the diagnosis of neurodegenerative diseases, such as autism spectrum disorder (ASD). However, most functional connectivity (FC) networks only consider the unilateral features of nodes or edges, and the interaction between them is ignored. In fact, their integration can provide more comprehensive and crucial information in the diagnosis. To address this issue, a new multi-view brain network feature enhancement method based on self-attention mechanism graph convolutional network (SA-GCN) is proposed in this article, which can enhance node features through the connection relationship among different nodes, and then extract deep-seated and more discriminative features. Specifically, we first plug the pooling operation of self-attention mechanism into graph convolutional network (GCN), which can consider the node features and topology of graph network at the same time and then capture more discriminative features. In addition, the sample size is augmented by a "sliding window" strategy, which is beneficial to avoid overfitting and enhance the generalization ability. Furthermore, to fully explore the complex connection relationship among brain regions, we constructed the low-order functional graph network (Lo-FGN) and the high-order functional graph network (Ho-FGN) and enhance the features of the two functional graph networks (FGNs) based on SA-GCN. The experimental results on benchmark datasets show that: (1) SA-GCN can play a role in feature enhancement and can effectively extract more discriminative features, and (2) the integration of Lo-FGN and Ho-FGN can achieve the best ASD classification accuracy (79.9%), which reveals the information complementarity between them.

Keywords: resting-state functional magnetic resonance imaging (rs-fMRI), graph convolutional network (GCN), pooling operation, feature enhancement, autism spectrum disorder (ASD)

INTRODUCTION

Brain disease is regarded as a public health challenge with an alarming proportion (Yao et al., 2021). Among them, autism spectrum disorder (ASD) is a complex genetic heterogeneous neurological disease with high incidence rate, usually coexisting with other diseases (Lord et al., 2020; Hiremath et al., 2021). According to the latest report of the Centers for Disease Control and Prevention, there is one autistic in every 44 American children (Maenner et al., 2021). So far, there is no effective method to completely cure autism, and the rehabilitation treatment of autism is a lifelong training, which causes heavy economic burden to the families and society (Eslami et al., 2019; Zhao et al., 2020). Thus, early diagnosis and intervention of autism is of great clinical and social value (Zhao et al., 2018; Wang et al., 2019; Hiremath et al., 2021).

Resting-state functional magnetic resonance imaging (rs-fMRI) based on blood oxygen level dependent (BOLD) signal imaging is an important tool to explore brain mechanism and pathology (Chen et al., 2016; Gan et al., 2021). Rs-fMRI can realize non-invasive study of brain function high spatial resolution, which cannot only reflect the local spatial function information of the brain, but also maintain detailed functional connectivity maps of the brain (Zhi et al., 2018). Rs-fMRI has been widely used to detect and characterize functional interconnection among different region of interests (ROIs), revealing potential patterns to distinguish between patients and healthy controls (Yao et al., 2021).

Currently, many extracting feature methods based on rs-fMRI are presented from different angles for disease diagnosis. Generally, they can be divided into two categories.

The first category focuses on extracting the features from each brain region without considering their connection relationship to each other; that is, the time-domain and frequency-domain features of each brain region of interest (ROI) are directly extracted based on the original BOLD. For example, Sartipi et al. (2018) proposed that based on generalized autoregressive conditional heteroscedasticity, the time-frequency sub-bands obtained by decomposing the brain ROI of subjects were extracted to diagnose ASD; Sidhu (2019) proposed the local linear embedding method, and the information measure of potential neuronal activity was extracted from BOLD time series for disease classification; Easson and McIntosh (2019) measured the variability of resting BOLD based on mean square continuous difference of time series and evaluated its complexity based on sample entropy to find predictors of ASD diagnosis. The above methods rely on brain ROIs, and the pathogenesis of brain diseases is explored by measuring the activities of various brain regions to assist the diagnosis of ASD. However, such methods ignore the connections among brain ROIs. Since the brain is a complex biological information system, each brain area is not isolated, but is interconnected on multiple spatial and temporal scales, working in coordination, the relationship among brain areas contains rich useful information for disease diagnosis.

The second category is committed to explore the functional connectivity among ROIs, through constructing functional connectivity (FC) network and conduct classification according to the differences in FC patterns among brain ROIs. For example, Zhang et al. (2020) learned multi-view features with multiatlas-based FC network to improve MCI diagnosis; Zhou et al. (2018) enhanced the high-order FC network based on regularization learning framework to identify the patients with MCI and ASD; Zhao et al. (2021) extracted the temporal-invariant properties contained in low-order and high-order dynamic FC networks based on the central moment method, revealing that different networks can identify the fingerprint of the autistic brain at different connection levels; Wang N. et al. (2022) identified ASD using multi-point clustering and nested feature extraction of rs-fMRI. Despite the effectiveness of the above methods captures features, they ignore the features of each brain ROIs and do not organically integrate the features of nodes (each brain region) and edges (the connection relationship among brain regions), and thus, they cannot extract relatively comprehensive and powerful discriminative features. Therefore, how to enhance the node features through the connection relationship between nodes and realize the organic combination of nodes and edges is an important research topic for ASD diagnosis.

In recent years, graph convolutional network (GCN) has achieved great success in dealing with non-Euclidean spatial data in the form of graph data (Xu et al., 2020, 2022; Li L. et al., 2021; Song et al., 2021; Ghorbani et al., 2022). GCN is able to automatically extract feature of brain network through an end-to-end manner, which is used for the recognition and classification of brain disease (Wang et al., 2021; Zhu et al., 2022). Specifically, GCN has the capability of transmitting, aggregating, and updating the node information in the graph, which can use the connection relationship of the nodes in the graph to enhance the node features, explicitly capture the node information and topology of the graph network, and mine useful brain connection network patterns for disease classification (Ktena et al., 2018). For example, Cao et al. (2021) used DeepGCN to identify ASD from multi-site resting-state data; Wang Y. et al. (2022) conducted diagnosis of ASD based on multi-spectral convolution network and ensemble learning. However, the existing GCNs still have some drawbacks listed as following when applied to brain FC networks.

(1) For high-dimensional small sample, GCN may not work well. A large number of training samples are often required for GCN training to avoid overfitting, which is hard to be satisfied in the single site of medical imaging. For example, the Autism Brain Imaging Data Exchange (ABIDE) database consists of 17 international imaging sites, of which New York University site has the most rs-fMRI data, including only 92 subjects (Di Martino et al., 2014). To solve this problem, previous studies usually collect data from multiple sites and put multiple data sources together (Cao et al., 2021). However, the problem of inconsistent parameters of multiple data sources may affect the learning performance of GCN.

(2) GCNs generally focus on the node information in the brain function connectivity network, but ignore the network topology and lack efficient graph pooling operation. GCN for graph classification mainly predicts the class labels of the whole graph by combining the learning methods of graph convolution layer, graph pooling layer, and readout layer (Pan et al., 2015,

2017; Ying et al., 2018; Zhang et al., 2018). Among them, the graph volume layer is responsible for accurate high-level node representation, whereas the graph pool layer learns the hierarchical representation of the network and reduces the parameters (Lee et al., 2019).

(3) In terms of graph network construction, previous studies usually start from a single level and then to extract features. They ignored two facts in the setting of node feature matrix and adjacency matrix of initial graph network. First, in the selection of node features, the FC network reflecting the connection relationship between nodes is considered, while ignoring the original blood oxygen signals in each brain region (Song et al., 2021); second, in the topological structure of the graph network, the connection between the two brain regions is considered, whereas the deep connection among nodes is ignored. For the ease of understanding, we use social networks as an analogy. Each brain region is regarded as an individual. In addition to its own unique features, each individual also has his/her own friends. Previous studies have focused on the interaction between individuals and their friends, but ignored individual unique features and the interaction between the circle of friends.

To handle the above issues, we propose a novel multi-view brain network feature enhancement method based on self-attention mechanism graph convolutional network (SA-GCN). Specifically, we first adopt the "sliding window" strategy to expand the sample size, i.e., the whole rs-fMRI time series is divided into multiple overlapping sub-segments by "sliding window" methods, and each sub-segment constructs a graph network, so that more samples are generated from one rs-fMRI time series for improving the overfitting problem caused by small samples and solved the problem of inconsistent parameters of multiple data sources in previous studies, making the experimental performance more stable; Then, we facilitate the graph pooling operation *via* self-attention mechanism in GCN, which considers both node features and network topology, and can filter useless informatics, leave more advanced, deeper and more discriminative node features; Furthermore, two different levels of FGN, i.e., Lo-FGN and Ho-FGN, are constructed from fMRI data to comprehensively capture the information contained in the brain network. The Lo-FGN reflects the changes of original BOLD in each brain region in terms of node features, and the connection strength between two brain regions in terms of network structure. The Ho-FGN reflects the interaction among brain regions in terms of node features and the deeper connection among multiple brain regions in terms of network structure. Finally, the multi-level features extracted based on SA-GCN are fused to realize the information complementarity between features, which is helpful to identify brain diseases, such as autism.

The rest of this article is organized as follows. In the Introduction section, we introduce related works of GCN in graph-level processing tasks. In the Proposed Methods section, our approach is described in detail, including data augmentation, self-attention pooling operations, and network construction. In the Experiments part, we present the experimental results, discuss different feature evaluation methods, and compare our strategy with other state-of-the-arts. Finally, conclusions are given.

INTRODUCTION OF GRAPH CONVOLUTIONAL NETWORK

At present, GCN is one of the favorites in graph data learning tasks, which has wide applicability and is suitable for nodes and graphs with any topological structure (Rubinov and Sporns, 2010; Zhou et al., 2020; Li X. et al., 2021). Here, we focus on GCN for graph level tasks. GCN is essentially Laplacian smoothing on the network, which takes the weighted sum of neighbors and self-expressions of each node as the feature (Parisot et al., 2018; Shao et al., 2021).

The typical architecture of graph-level task GCN is shown in **Figure 1**. Firstly, the node feature matrix and adjacency matrix of the initial graph network are input into GCN; Then, the graph convolution operation is conducted at each layer to characterize the local structure of the node, and extract high-level node representation (Gu et al., 2021); After that, the graph pooling operation is facilitated to learn the hierarchical representation of the network (Henaff et al., 2015); Finally, with certain loss functions, gradient back propagation is used to train the network. All convolution layers share the same adjacency matrix. To increase non-linearity, the *ReLU* activation function is added after each layer. The iterative update operation can be expressed as:

$$X^{(l+1)} = ReLu\left(pooling\left(\hat{D}^{-1/2}\hat{A}\hat{D}^{-1/2}X^{(l)}W^{(l)}\right)\right) \quad (1)$$

where $A \in R^{n\times n}$ is an adjacency matrix, which defines the connection between nodes, and in an undirected graph $A_{\mathrm{i,j}} = A_{\mathrm{j,i}}$. $I_{\mathrm{n}}\epsilon R^{n\times n}$is an identity matrix, and $\hat{A} = A + I_{\mathrm{n}}$. $\boldsymbol{D}$ is a diagonal matrix, $D_{\mathrm{i,j}}$ represents the degree of the $i-th$ node and $\hat{D}_{\mathrm{ii}} = \sum_{\mathrm{j}} \hat{A}_{ij}$. $\boldsymbol{W}$ is the trainable weight, $X^{(l)}$ is the $l-th$ node feature matrix, where $X^{(0)}$ is the original node feature matrix. The complete GCN can be obtained after L iterations of training (Parisot et al., 2018; Gu et al., 2021).

Although GCN can do feature extraction and enhancement by considering both nodes and edges in the graph network, it cannot be directly applied to our task. Specifically, there are two limitations: (1) The performance of GCN heavily depends on training samples, and our sample size is small. To solve this problem, we must expand the sample size; (2) Previous graph pooling methods either only consider the topology of graphs, or have high spatial complexity (Defferrard et al., 2016; Rhee et al., 2017; Cangea et al., 2018; Ying et al., 2018; Zhang et al., 2018). To reduce the learning parameters and computational complexity, it is necessary to improve the graph pooling operation. To tackle these two problems, we give the corresponding solutions in the proposed methods.

PROPOSED METHODS

To make GCN adapts to our task and data, we propose a novel multi-view brain network feature enhancement method based on GCN with self-attention mechanism (SA-GCN). The overall framework of our model is illustrated in **Figure 2**. To be specific,

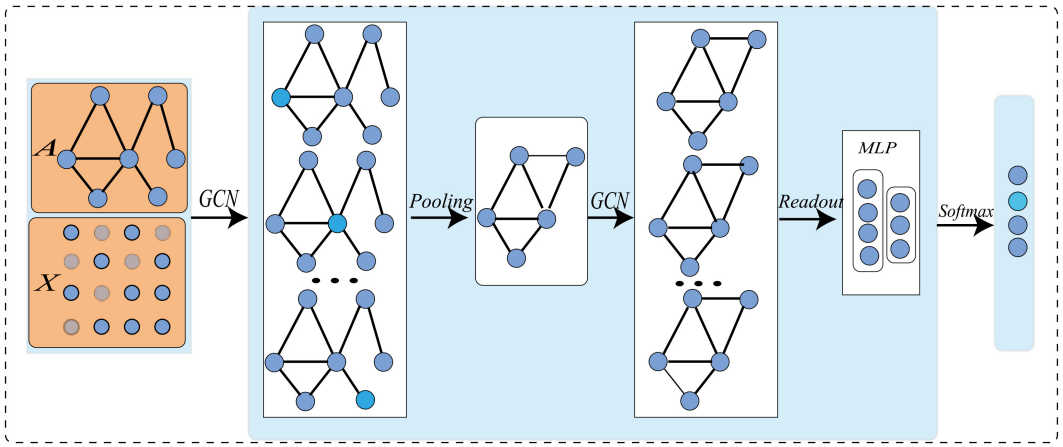

FIGURE 1 | GCN with pooling layer and readout layer for graph level tasks.

we first use the "sliding window" strategy to enlarge the sample size, and the low-order functional graph network (Lo-FGN) and high-order functional graph network (Ho-FGN) are constructed; Then, the pooling operation of self-attention mechanism is added to the GCN architecture to extract more discriminative features; Finally, the Lo-FGN and Ho-FGN are integrated based on SA-GCN to capture more comprehensive and discriminative features. **Figure 2** illustrates the overall framework of our model.

Data Augmentation

To solve the small sample size of rs-fMRI data, we adopt a "sliding window" method for data augmentation, as shown in **Figure 3**, where the abscissa represents the acquisition time of the fMRI time series, and the ordinate represents the blood oxygen signal in the brain region. For each subject, the average rs-fMRI time series of all voxels in the $i-th$ brain ROI is defined as follows:

$$x_{\mathrm{i}} = (x_{\mathrm{i}1}, x_{\mathrm{i}2}, \ldots, x_{\mathrm{i}N})\ (i = 1, 2, \ldots, R) \tag{2}$$

where R is the total number of regions of interest and N represents the total number of image volumes during rs-fMRI scanning. The whole rs-fMRI time series is divided into K overlapping sub-segments. Each sub-rs-fMRI time series can build a graph network. The value of K is calculated according to the following:

$$K = ((M - W)/s) + 1 \tag{3}$$

where M is the length of the entire rs-fMRI time series, and W is the length of the sliding window. To ensure that each sub-window owns relatively more rs-fMRI time information, W can be set to a relatively large value, and s is the step length of each slide of the sliding window. Therefore, the augmentation of the experimental data can be achieved through the "sliding window" method.

Pooling Operation for Graph Classification

To better reflect the hierarchical structure of the input data and reduce the learning parameters for higher computation efficiency, we add the self-attention pooling operation after the graph convolution. The network architecture is shown in **Figure 4**. The updating formulas of node feature matrix and adjacency matrix are given by equation (4):

$$\left(\hat{A}^{(l+1)}, X^{(l+1)}\right) = ReLu\left(SAGPool\left(GCN\left(\hat{A}^{(l)}, X^{(l)}\right)\right)\right) \tag{4}$$

To understand the pooling operations in the graph network, **Figure 5** shows the changes in brain connectivity before and after the pooling, where thickness of lines represents the strength of connectivity among brain regions, and the fork sign represents that the pooling operation can discard some less important nodes and retain the nodes with more discriminative features. From **Figure 5**, self-attention graph pooling method cannot only use relatively few parameters to learn hierarchical representation in end-to-end manner, but also use self-attention to distinguish among nodes that should be deleted and retained. SA-GCN not only considers the node features, but also reflects the topology of the graph, which is conducive to improve the accuracy of downstream classification task.

Construction of Multi-Level Graph Network

Feature extraction based on GCN requires the construction of function graph network from fMRI data. The complete function graph network includes two parts: node feature matrix and adjacency matrix. Conventional methods ignore the complementarity of features among different levels. Our method constructs the function graph network from multiple levels, as shown in **Figure 6**, where the left part is the construction process of low-order functional graph network (Lo-FGN), and the right part illustrates the construction of high-order functional graph network (Ho-FGN).

Construction of Low-Order Functional Graph Network

Let $x_{\mathrm{i}}(l)$ and $x_j(l)$ represent the subsequences of the $i-th$ and $j-th$ ROI in the $l-th$ window, respectively. The correlation between time series is calculated by Pearson correlation to obtain

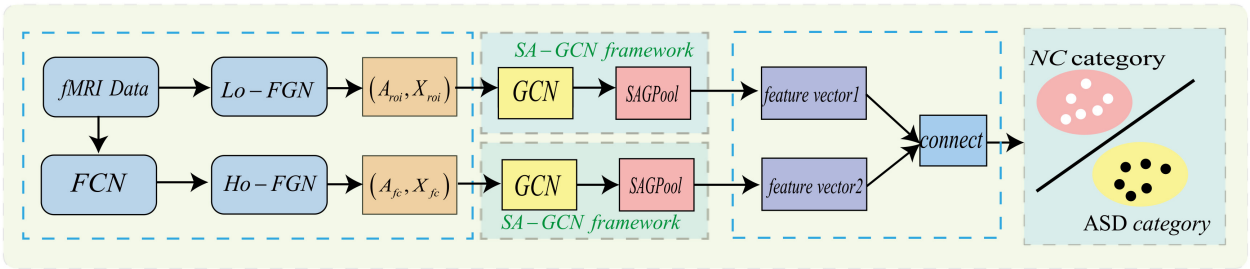

FIGURE 2 | Overall frame diagram, where *FCN*: functional connectivity networks; *Lo – FGN*: Low-order functional graph network; *Ho – FGN*: High – order functional graph network; A_{roi} represents the adjacency matrix of Lo-FGN; X_{roi} represents the node feature matrix of Lo-FGN, others are the same as above.

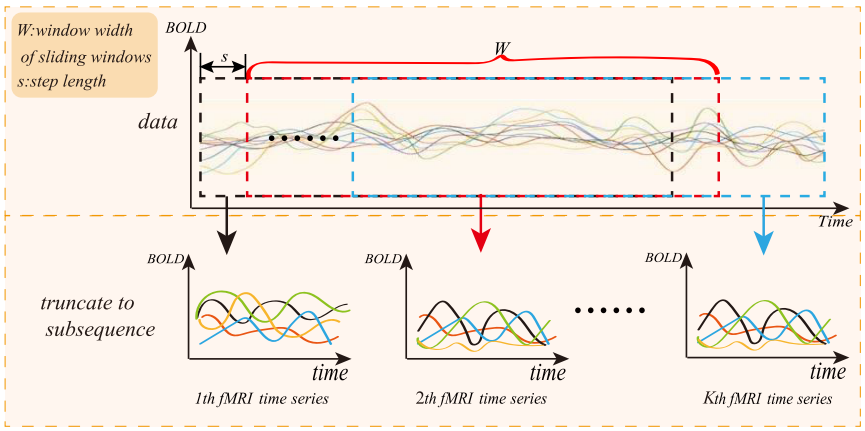

FIGURE 3 | Sliding window method diagram.

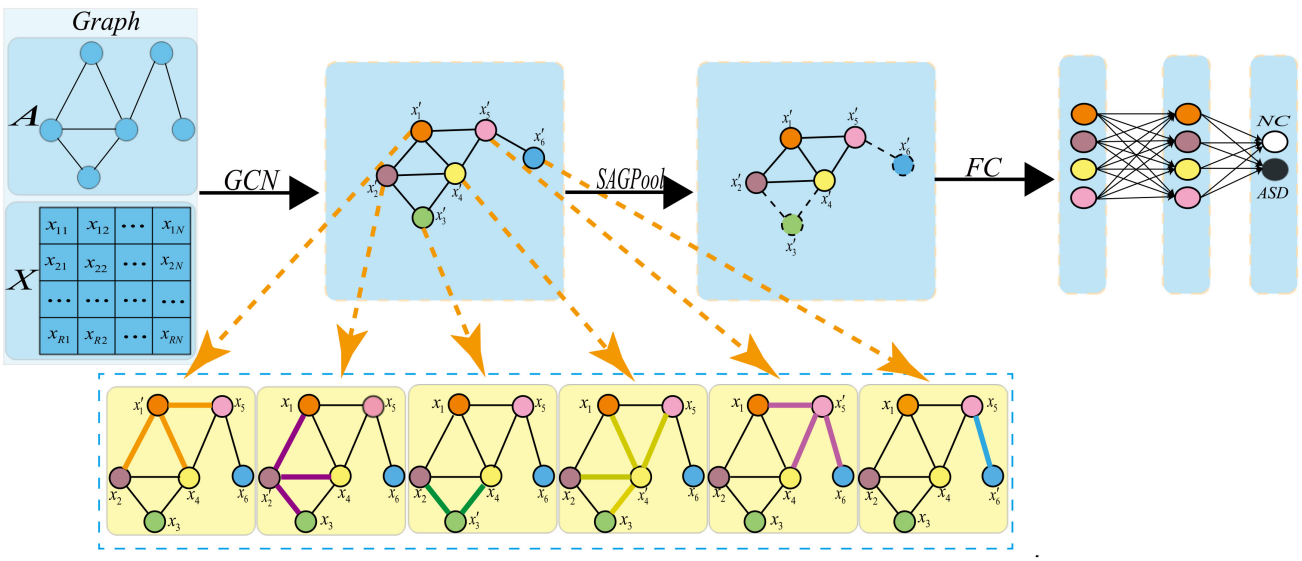

FIGURE 4 | Pooling operation. Where x_i represents the feature vector of the $i-th$ node, x_i' represents the feature vector of the $i-th$ new node obtained after the graph convolution. After the pooling operation, a new graph is obtained, in which the dotted line indicates that the corresponding node should be discarded.

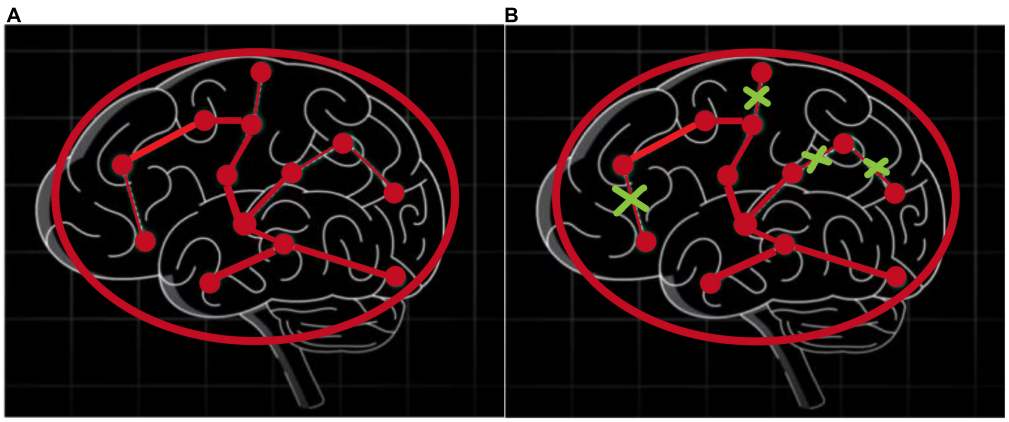

FIGURE 5 | Self-attention graph pooling method diagram, where **(A)** represents the connectivity among brain regions before the pooling operation, **(B)** represents the connectivity among brain regions after the pooling operation, and thickness of lines represents the strength of connectivity among brain regions, the fork sign represents that the pooling operation can discard some less important nodes and retain the nodes with more discriminative features.

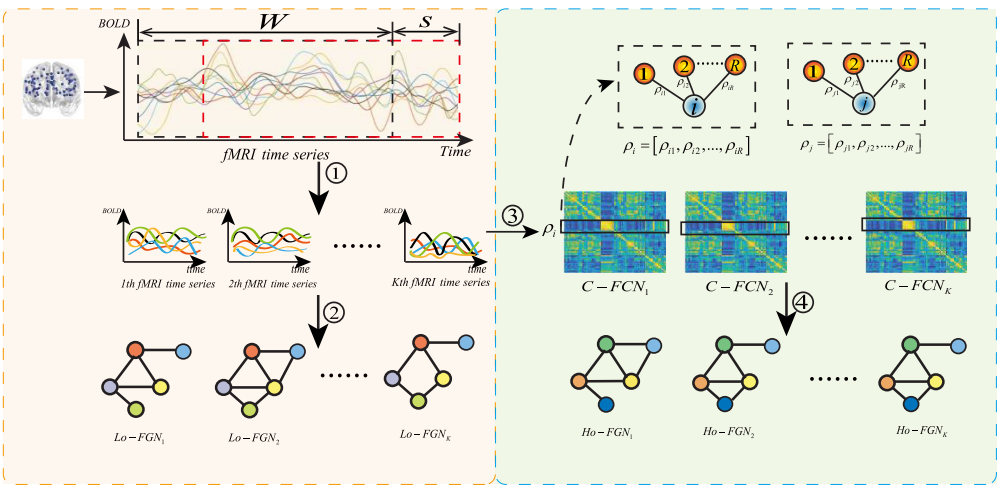

FIGURE 6 | Construction of multi-level function graph network, where ① represents get K sub fMRI time series; ② represents the construction of Lo-FGN from fMRI time series; ③ represents the use of Pearson correlation to build a functional connectivity network (FCN); ④ represents the construction of Ho-FGN from FCN. ρ_i represents Pearson correlation between the $i-th$ ROI and other ROIs.$C-FCN_i$ represents the $i-th$ traditional functional connectivity network.

FC, and the FC is thresholded by adjusting parameters to obtain the adjacency matrix of Lo-FGN, that is:

$$A_{\mathrm{Lo}} = \varphi\left(corr(x_{\mathrm{i}}(l), x_{\mathrm{j}}(l))\right) = \left(\rho_{\mathrm{ij}}(l)\right)_{1\le l\le K, 1\le i,j\le R} \quad (5)$$

where φ denotes a thresholding operation.

To capture the temporal changes in the original BOLD in the brain area and avoid the timing structure of rs-fMRI is being destructed, we take the mean and variance of the original data X_{roi} as the node features X_{Lo} of Lo-FGN as:

$$X_{Lo} = (mean(X), var(X)) \quad (6)$$

Construction of High-Order Functional Graph Network

To characterize the organizational features of the brain and reflect the functional connectivity interaction mode among multiple ROIs, we explore the connection relationship of edges in the graph network to enhance discrimination ability of node features. Based on the "one-time Pearson correlation," the high-order function connection (Ho-FC) is obtained based on the idea of "correlation of correlation," and the Ho-FC is thresholded by adjusting parameters to obtain the adjacency matrix of the Ho-FGN as follows:

$$A_{Ho} = \varphi\left(\rho\left(\rho_{\mathrm{ij}}(l)\right)\right)_{1\le l\le K, 1\le i,j\le R} \quad (7)$$

To better capture the deep-seated node features, the functional connectivity matrix is used as the node feature matrix of Ho-FGN, that is:

$$X_{Ho} = \left(\rho_{\mathrm{ij}}(l)\right)_{1\le l\le K, 1\le i,j\le R} \quad (8)$$

EXPERIMENTS ANALYSIS

Experimental Data

The rs-fMRI dataset used in this article is from the ABIDE database, which consists of 17 international imaging sites (Di Martino et al., 2014). To mitigate data heterogeneity, the rs-fMRI data of NUY site with the largest sample size are selected to verify the feasibility of our proposed method. Specifically, rs-fMRI scanning data of 45 patients with ASD and 47 normal control (NC) subjects were included. The subjects ages are between 7 and 15 years, and there are no excessive head movements in any three directions, displacement less than 1.5 mm or angular rotation less than 1.5°. The detailed demographic information of these subjects is summarized in **Table 1**. There are no significant differences in age, gender, IQ, diagnostic interview, and diagnostic observation ($p > 0.05$) between the two groups.

The data acquisition and preprocessing follow a standard pipeline, including head movement, normalization, denoising, and other processes and related parameters, which same as some previous pieces of literature (Murdaugh et al., 2012; Satterthwaite et al., 2013; Yan et al., 2013; Washington et al., 2014; Leung et al., 2015; Lin et al., 2015; Ray et al., 2015; Urbain et al., 2016; Reinhart and Nguyen, 2019). Finally, we use the automatic anatomical marker (AAL) map to divide the brain into 116 brain ROIs and calculate the mean value of rs-fMRI time series of each brain ROI, which is represented by the data matrix $X \in R^{170\times116}$ for subsequent experiments. Note that 170 represents the total volume of time images and 116 is the total number of all brain ROIs.

Evaluation Methodology

To verify the effectiveness of the method, we conducted eight experiments based on rs-fMRI data. In the experiment, ASD and NC are considered as positive and negative classes, respectively. All experiments were evaluated by 10 times of fivefold cross-validation. Specifically, we first divide all subjects into 5 subsets (roughly the same size). Then, we take one subset as the test set and the other four subsets as the training data. This process is repeated 10 times to avoid the deviation of random data division in cross-validation. The classification results of all iterations are averaged and evaluated by six metrics: classification accuracy (ACC), sensitivity or true positive rate (TPR), specificity or true negative rate (TNR), positive predictive value (PPV), negative predictive value (NPV), and F1 score. In addition, we performed the statistical significance test (t-test) on the accuracy obtained by seven comparison methods and SA-GCN, and the p-values of the test are also listed in **Table 2**. When the p-value is less than 0.05, it indicates that there is a significant difference between the two methods.

TABLE 1 | Demographic information of the subjects.

Characteristic	ASD	NC	*p*-values
Gender (M/F)	36/9	36/11	0.2135[a]
Age (mean ± SD)	11.1±2.3	11.0±2.3	0.773[b]
FIQ (mean ± SD)	106.8±17.4	113.3±14.1	0.0510[b]
ADI-R (mean ± SD)	32.2±14.3[c]	–	–
ADOS (mean ± SD)	13.7±5.0	–	–
FD (mean ± SD)	0.14±0.05	0.15±0.07	0.36[b]

M, male; F, female; FIQ, Full Intelligence Quotient; ADI-R, Autism Diagnostic Interview-Revised; ADOS, autism diagnostic observation schedule.
[a]The p-value was obtained by χ2-test.
[b]The p-value was obtained by two-sample two-tailed t-test.
[c]Two patients do not have the ADI-R score.

Influence of Parameters on Feature Extraction

Since the proposed SA-GCN is a deep learning method, to avoid overfitting, the "sliding window" strategy is adopted to increase the sample size. There are two free parameters, namely, sliding window width (W) and translation step size (s), which may affect the final classification performance. We set the range of these parameters to $W \in [120, 125, 130, 135, 140, 145]$, $s \in [5, 6, 7, 8]$. In addition, in the process of constructing Lo-FGN and Ho-FGN, because the brain network is considered to have sparse connection structure, the adjacency matrix is thresholded by adjusting parameters. In the construction of Lo-FGN, the range of threshold L_{corr} is set as $L_{corr} \in \{(-0.4, 0.4), (-0.45, 0.45), \ldots, (-0.65, 0.65)\}$. In the construction of Ho-FGN, the range of threshold H_{corr} is set as $H_{\text{corr}} \in \{(-0.4, 0.4), (-0.45, 0.45), \ldots, (-0.65, 0.65)\}$. To check the influence of threshold L_{corr} and H_{corr} on the results, we make $t = L_{\text{corr}} = H_{\text{corr}}$ for comparative experiment, as shown in **Figure 7**.

From **Figure 7**, we have the following conclusions: (1) The classification performance is quite sensitive to free parameters, so it is necessary to continuously adjust parameters to obtain the best performance. We can see that when $W = 130, s = 5, L_{corr} = H_{corr} = 0.6$, the maximum value of ACC is 79.9%, and when $W = 125, s = 6, L_{corr} = H_{corr} = 0.6$, the minimum value of ACC is 63.3%; (2) Different thresholds determine different network topologies, which can provide different useful information for ASD identification and obtain different classification performances.

Comparison for Autism Spectrum Disorder Diagnosis Using Different Feature Extraction

To verify the effectiveness of the proposed method, we set $W = 130, s = 5, t = L_{corr} = H_{corr} = 0.6$ and conducted extensive experimental comparison based on the following eight methods. **Table 2** shows the average classification performance of the above eight methods. Among them, the conventional brain network (CBN) represents the use of the mean and variance of the time series of rs-fMRI as the characteristics; $GCN_{(Lo)}$ indicates that the constructed $Lo - FGN$ is sent into the GCN network architecture; $SA - GCN_{(Lo)}$ indicates that $Lo - FGN$ is sent into the GCN network architecture with self-attention pooling operation; FCN represents the characteristics of traditional FC network based on Pearson correlation; " + " denotes the fusion operation and the other expressions of similarity.

From **Table 2**, we can draw three conclusions: (1) The feature extraction using GCN architecture is superior to the traditional feature extraction methods, indicating that GCN can enhance the node features through the connection among nodes, and

TABLE 2 | ASD classification results with different feature strategies.

Model	ACC (%)	*P*-value	TPR (%)	TNR (%)	PPV (%)	NPV (%)	F1 (%)
CBN	65.4 ± 0.01	0.0161498	67.3 ± 0.12	62.7 ± 0.06	59.8 ± 0.01	71.2 ± 0.06	63.0 ± 0.01
$GCN_{(Lo)}$	68.0 ± 0.01	0.0034533	67.8 ± 0.12	66.5 ± 0.04	67.3 ± 0.01	68.1 ± 0.01	67.0 ± 0.04
$SA - GCN_{(Lo)}$	73.0 ± 0.03	0.0306230	65.0 ± 0.07	81.0 ± 0.01	79.6 ± 0.08	71.0 ± 0.08	69.4 ± 0.04
FCN	72.6 ± 0.02	0.0301950	88.2 ± 0.02	56.0 ± 0.07	64.3 ± 0.05	87.9 ± 0.05	74.0 ± 0.01
$GCN_{(Ho)}$	74.5 ± 0.01	0.0462659	74.7 ± 0.02	74.4 ± 0.04	76.5 ± 0.03	75.0 ± 0.01	75.0 ± 0.08
$SA - GCN_{(Ho)}$	75.0 ± 0.04	0.0453326	70.1 ± 0.12	77.3 ± 0.05	77.9 ± 0.01	74.0 ± 0.01	72.0 ± 0.04
$GCN_{(Lo)} + GCN_{(Ho)}$	77.0 ± 0.01	0.0421363	71.3 ± 0.08	78.5 ± 0.04	77.9 ± 0.02	74.7 ± 0.07	73.6 ± 0.04
$SA - GCN_{(Lo)} + SA - GCN_{(Ho)}$	**79.9 ± 0.03**	/	**75.6 ± 0.03**	**78.6 ± 0.04**	**78.7 ± 0.01**	**78.6 ± 0.01**	**76.1 ± 0.04**

The bold values represent the results of our proposed method under different evaluation metrics.

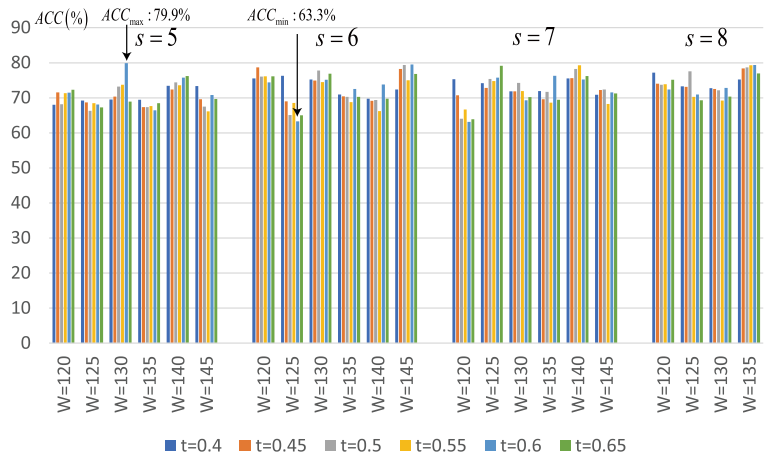

FIGURE 7 | Average classification accuracy (ACC) of SA-GCN with different free parameter combinations (i.e., *W, s,* and *t*).

has strong feature extraction ability; (2) the GCN with pooling operation *via* self-attention mechanism can take into account node features and network topology structure and extract more discriminative features; (3) for Lo-FGN and Ho-FGN, the performance of feature extraction and feature layer fusion based on SA-GCN achieves the best performance, indicating that the effectiveness of feature fusion.

The Most Distinguishing Features in Autism Spectrum Disorder Diagnosis

To further analyze the pooling operation in GCN with self-attention mechanism, we fed the test datasets into the SA-GCN architecture and counted the probability of occurrence of each node in the remaining nodes after the pooling operation of all test sets scored based on the self-attention mechanism to rank the nodes' importance, as shown in **Table 3**.

The top 10 nodes (ROIs) of the Lo-FGN screened by the SA-GCN architecture are VIIB-Cb.R, VIIB-Cb.L, HIP.R, II-Cb.R, VIII-Cb.R, II-Cb.L, VIII-Cb.L, I-Cb.L, PreCG.L, and THA.R, as shown in **Figure 8**. Some studies have shown that all these brain regions are associated with ASD.

The top 10 nodes (ROIs) of the Ho-FGN filtered by the SA-GCN architecture are INS.L, PUT.L, SFGmed.R, PAL.L, PAL.R, PUT.R, THA.L, THA.R, SFGmed.L, and INS.R, as shown in **Figure 9**. It has been shown that there are significant differences between autistic and normal individuals in SFGmed and INS; SFGmed belongs to the DMN, which is widely believed to play an important role in higher cognitive functions, and abnormalities in the DMN can be observed in a range of neurological disorders (Murdaugh et al., 2012; Washington et al., 2014); INS is highly associated with communication and affective

TABLE 3 | The 10 most discriminating features and their frequency of occurrence.

$SA - GCN_{(Lo)}$		$SA - GCN_{(Ho)}$	
ROI	**Probability of occurrence**	**ROI**	**Probability of occurrence**
VIIB-Cb.R	0.7717	INS.L	0.7554
VIIB-Cb.L	0.7704	PUT.L	0.7337
HIP.R	0.7663	SFGmed.R	0.73505
II-Cb.R	0.7649	PAL.L	0.7269
VIII-Cb.R	0.7541	PAL.R	0.71875
II-Cb.L	0.7527	PUT.R	0.7174
VIII-Cb.L	0.7412	THA.L	0.7119
I-Cb.L	0.72146	THA.R	0.7119
PreCG.L	0.7269	SFGmed.L	0.70106
THA.R	0.7228	INS.R	0.649

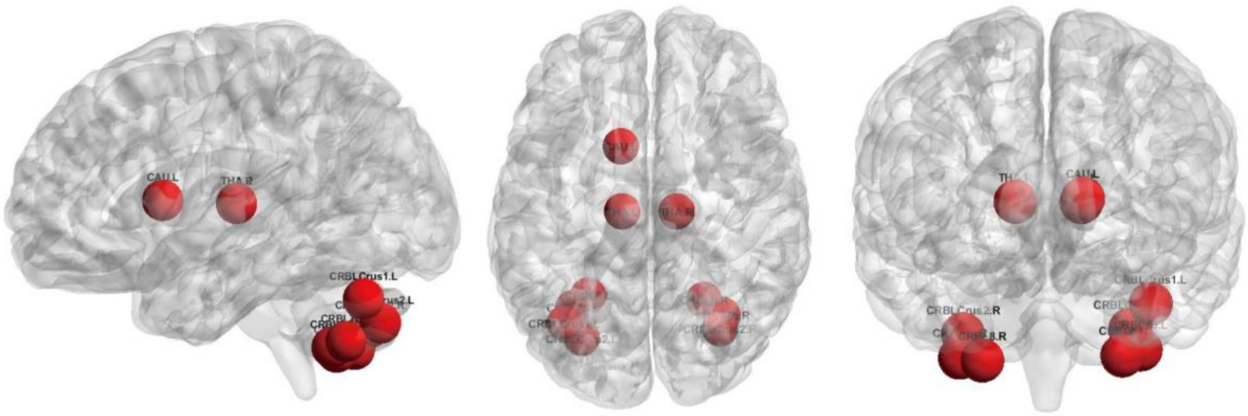

FIGURE 8 | The top 10 nodes (ROIs) of the Lo-FGN screened by the SA-GCN architecture.

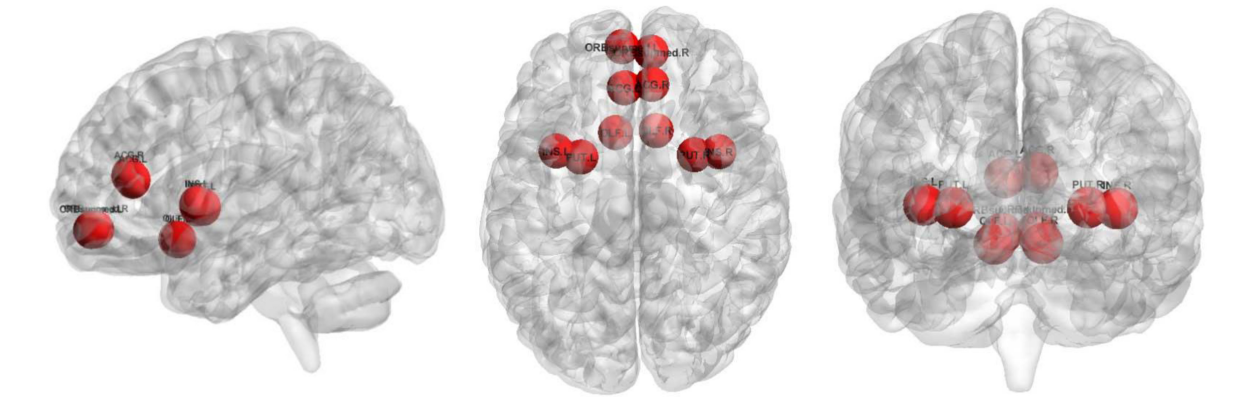

FIGURE 9 | The top 10 nodes (ROIs) of the Ho-FGN screened by the SA-GCN architecture.

deficits in ASD (Leung et al., 2015; Urbain et al., 2016). In summary, our proposed method can extract deeper and more discriminative features.

CONCLUSION

In this article, we propose a novel multi-view feature enhancement method based on SA-GCN. Multi-view discriminative features are extracted from the constructed Lo-FGN and Ho-FGN based on SA-GCN, respectively, and feature layer fusion enables the model to achieve the best classification results. The experimental results show that (1) with the "sliding window" strategy, the sample size can be effectively expanded to avoid the overfitting problem; (2) compared with the other methods, the pooling operation in GCN with self-attention mechanism can extract deeper and more discriminative features, which can help to explore disease-related information for ASD diagnosis; (3) complementary information among features can be achieved from multiple perspectives to improve the disease identification rate.

Finally, SA-GCN can be easily extended for diagnosis of other highly heterogeneous neurodevelopmental disorders, such as Alzheimer's disease, and depressive illness. Of course, the findings of this study are still preliminary and require further study in the future. As for future work, we plan to extend SA-GCN to other modalities in brain connectomics.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: http://fcon_1000.projects.nitrc.org/indi/abide/abide_I.html.

AUTHOR CONTRIBUTIONS

FZ: conceptualization, methodology, and writing-review and editing. NL: conceptualization, software, writing-original draft, methodology, formal analysis, investigation, and validation. HP: validation. XC, YL, HZ, NM, and DC: writing-review and editing. All authors contributed to the article and approved the submitted version.

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REFERENCES

Cangea, C., Veličković, P., Jovanović, N., Kipf, T., and Liò, P. (2018). Towards sparse hierarchical graph classifiers. *arXiv* [preprint]. doi: arXiv:1811.01287

Cao, M., Yang, M., Qin, C., Zhu, X., Chen, Y., Wang, J., et al. (2021). Using DeepGCN to identify the autism spectrum disorder from multi-site resting-state data. *Biomed. Signal Proc. Control* 70:103015. doi: 10.1016/j.bspc.2021.103015

Chen, X., Zhang, H., Gao, Y., Wee, C.-Y., Li, G., and Shen, D. (2016). High-order resting-state functional connectivity network for MCI classification. *Hum. Brain Mapp.* 37, 3282–3296. doi: 10.1002/hbm.23240

Defferrard, M., Bresson, X., and Vandergheynst, P. (2016). Convolutional neural networks on graphs with fast localized spectral filtering. *Adv. Neural Inform. Proc. Syst.* 29, 3844–3852.

Di Martino, A., Yan, C. G., Li, Q., Denio, E., Castellanos, F. X., Alaerts, K., et al. (2014). The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Mol. Psychiatr.* 19, 659–667. doi: 10.1038/mp.2013.78

Easson, A. K., and McIntosh, A. R. (2019). BOLD signal variability and complexity in children and adolescents with and without autism spectrum disorder. *Dev. Cogn. Neurosci.* 36:100630. doi: 10.1016/j.dcn.2019.100630

Eslami, T., Mirjalili, V., Fong, A., Laird, A. R., and Saeed, F. (2019). ASD-DiagNet: a hybrid learning approach for detection of autism spectrum disorder using fMRI data. *Front. Neuroinform.* 13:70. doi: 10.3389/fninf.2019.00070

Gan, J., Peng, Z., Zhu, X., Hu, R., Ma, J., and Wu, G. (2021). Brain functional connectivity analysis based on multi-graph fusion. *Med. Image Anal.* 71:102057. doi: 10.1016/j.media.2021.102057

Ghorbani, M., Kazi, A., Baghshah, M. S., Rabiee, H. R., and Navab, N. (2022). Ra-gcn: graph convolutional network for disease prediction problems with imbalanced data. *Medical Image Analysis* 75, 102272. doi: 10.1016/j.media.2021.102272

Gu, P., Xu, X., Luo, Y., Wang, P., and Lu, J. (2021). "BCN-GCN: A Novel Brain Connectivity Network Classification Method via Graph Convolution Neural Network for Alzheimer's Disease," in *International Conference on Neural Information Processing*, (Cham: Springer), 657–668. doi: 10.3233/JAD-201163

Henaff, M., Bruna, J., and LeCun, Y. (2015). Deep convolutional networks on graph-structured data. *arXiv* [preprint]. doi: arXiv:1506.05163

Hiremath, C. S., Sagar, K. J. V., Yamini, B. K., Girimaji, A. S., Kumar, R., Sravanti, S. L., et al. (2021). Emerging behavioral and neuroimaging biomarkers for early and accurate characterization of autism spectrum disorders: a systematic review. *Transl. Psychiatr.* 11, 1–12. doi: 10.1038/s41398-020-01178-6

Ktena, S. I., Parisot, S., Ferrante, E., Rajchl, M., Lee, M., Glocker, B., et al. (2018). Metric learning with spectral graph convolutions on brain connectivity networks. *NeuroImage* 169, 431–442. doi: 10.1016/j.neuroimage.2017.12.052

Lee, J.,Lee, I., and Kang, J. (2019). "Self-attention graph pooling," in *36th International Conference on Machine Learning, ICML 2019*, (Washington, DC: IMLS).

Leung, R. C., Pang, E. W., Cassel, D., Brian, J. A., Smith, M. L., and Taylor, M. J. (2015). Early neural activation during facial affect processing in adolescents with Autism Spectrum Disorder. *NeuroImage: Clin.* 7, 203–212. doi: 10.1016/j.nicl.2014.11.009

Li, L., Jiang, H., Wen, G., Cao, P., Xu, M., Liu, X., et al. (2021). TE-HI-GCN: an Ensemble of Transfer Hierarchical Graph Convolutional Networks for Disorder Diagnosis. *Neuroinformatics* 1–23. [Epub ahead of print]. doi: 10.1007/s12021-021-09548-1

Li, X., Zhou, Y., Dvornek, N., Zhang, M., Gao, S., Zhuang, J., et al. (2021). Braingnn: Interpretable brain graph neural network for fmri analysis. *Med. Image Anal.* 74:102233. doi: 10.1016/j.media.2021.102233

Lin, H. Y., Tseng, W. Y. I., Lai, M. C., Matsuo, K., and Gau, S. S. F. (2015). Altered resting-state frontoparietal control network in children with attention-deficit/hyperactivity disorder. *J. Int. Neuropsychol. Soc.* 21, 271–284.

Lord, C., Brugha, T. S., Charman, T., Cusack, J., Dumas, G., Frazier, T., et al. (2020). Autism spectrum disorder. *Nat. Rev. Dis. Prim.* 6, 1–23. doi: 10.1038/s41572-019-0138-4

Maenner, M. J., Shaw, K. A., Bakian, A. V., Bilder, D. A., Durkin, M. S., Esler, A., et al. (2021). Prevalence and characteristics of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites. *United States, 2018. MMWR Surveill. Sum.* 70, 1-16. doi: 10.15585/mmwr.ss7011a1

Murdaugh, D. L., Shinkareva, S. V., Deshpande, H. R., Wang, J., Pennick, M. R., and Kana, R. K. (2012). Differential deactivation during mentalizing and classification of autism based on default mode network connectivity. *PloS one* 7:e50064. doi: 10.1371/journal.pone.0050064

Pan, S., Wu, J., Zhu, X., Long, G., and Zhang, C. (2017). "Task sensitive feature exploration and learning for multitask graph classification,". *IEEE Transac. Cybernet.* 47, 744–758.

Pan, S., Wu, J., Zhu, X., Zhang, C., and Philip, S. Y. (2015). Joint structure feature exploration and regularization for multi-task graph classification. *IEEE Transactions Knowl. Data Eng.* 28, 715–728. doi: 10.1109/TKDE.2015.2492567

Parisot, S., Ktena, S. I., Ferrante, E., Lee, M., Guerrero, R., Glocker, B., et al. (2018). Disease prediction using graph convolutional networks: application to autism spectrum disorder and Alzheimer's disease. *Med. Image Anal.* 48, 117–130. doi: 10.1016/j.media.2018.06.001

Ray, S., Gohel, S., and Biswal, B. B. (2015). Altered functional connectivity strength in abstinent chronic cocaine smokers compared to healthy controls. *Brain Connect.* 5, 476–486. doi: 10.1089/brain.2014.0240

Reinhart, R. M., and Nguyen, J. A. (2019). Working memory revived in older adults by synchronizing rhythmic brain circuits. *Nat. Neurosci.* 22, 820–827. doi: 10.1038/s41593-019-0371-x

Rhee, S., Seo, S., and Kim, S. (2017). Hybrid approach of relation network and localized graph convolutional filtering for breast cancer subtype classification. *arXiv* [preprint]. doi: arXiv:1711.05859

Rubinov, M., and Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage* 52, 1059–1069. doi: 10.1016/j.neuroimage.2009.10.003

Sartipi, S., Shayesteh, M. G., and Kalbkhani, H. (2018). "Diagnosing of Autism Spectrum Disorder based on GARCH Variance Series for rs-fMRI data[C]//," in *2018 9th International Symposium on Telecommunications (IST)*.

Satterthwaite, T. D., Elliott, M. A., Gerraty, R. T., Ruparel, K., Loughead, J., Calkins, M. E., et al. (2013). An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *Neuroimage* 64, 240–256. doi: 10.1016/j.neuroimage.2012.08.052

Shao, L., Fu, C., You, Y., and Fu, D. (2021). Classification of ASD based on fMRI data with deep learning. *Cogn. Neurodynam.* 15, 961–974. doi: 10.1007/s11571-021-09683-0

Sidhu, G. (2019). Locally linear embedding and fMRI feature selection in psychiatric classification. *IEEE J. Transl. Eng. Health Medicine* 7, 1–11. doi: 10.1109/JTEHM.2019.2936348

Song, X., Zhou, F., Frangi, A. F., Cao, J., Xiao, X., Lei, Y., et al. (2021). Graph convolution network with similarity awareness and adaptive calibration for disease-induced deterioration prediction. *Med. Image Anal.* 69:101947. doi: 10.1016/j.media.2020.101947

Urbain, C., Vogan, V. M., Ye, A. X., Pang, E. W., Doesburg, S. M., and Taylor, M. J. (2016). Desynchronization of fronto-temporal networks during working memory processing in autism. *Hum. Brain Mapp.* 37, 153–164. doi: 10.1002/hbm.23021

Wang, L., Li, K., and Hu, X. P. (2021). Graph convolutional network for fMRI analysis based on connectivity neighborhood. *Netw. Neurosci.* 5, 83–95. doi: 10.1162/netn_a_00171

Wang, M., Zhang, D., Huang, J., Yap, P. T., Shen, D., and Liu, M. (2019). Identifying autism spectrum disorder with multi-site fMRI via low-rank

domain adaptation. *IEEE Transac. Med. Imaging* 39, 644–655. doi: 10.1109/TMI.2019.2933160

Wang, N., Yao, D., Ma, L., and Liu, M. (2022). Multi-site clustering and nested feature extraction for identifying autism spectrum disorder with resting-state fMRI. *Med. Image Anal.* 75:102279. doi: 10.1016/j.media.2021.102279

Wang, Y., Liu, J., Xiang, Y., Wang, J., Chen, Q., and Chong, J. (2022). MAGE: automatic diagnosis of autism spectrum disorders using multi-atlas graph convolutional networks and ensemble learning. *Neurocomputing* 469, 346–353. doi: 10.1016/j.neucom.2020.06.152

Washington, S. D., Gordon, E. M., Brar, J., Warburton, S., Sawyer, A. T., Wolfe, A., et al. (2014). Dysmaturation of the default mode network in autism. *Hum. Brain Mapp.* 35, 1284–1296. doi: 10.1002/hbm.22252

Xu, H., Wang, H., Yuan, C., Zhai, Q., Tian, X., Wu, L., et al. (2020). Identifying diseases that cause psychological trauma and social avoidance by GCN-Xgboost. *BMC Bioinform.* 21:1–16. doi: 10.1186/s12859-020-03847-1

Xu, R., Li, Y., Wang, C., Xu, S., Meng, W., and Zhang, X. (2022). Instance segmentation of biological images using graph convolutional network. *Eng. Appl. Artif. Intell.* 110:104739. doi: 10.1016/j.engappai.2022.104739

Yan, C. G., Cheung, B., Kelly, C., Colcombe, S., Craddock, R. C., Di Martino, A., et al. (2013). A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. *Neuroimage* 76, 183–201. doi: 10.1016/j.neuroimage.2013.03.004

Yao, D., Sui, J., Wang, M., Yang, E., Jiaerken, Y., Luo, N., et al. (2021). A mutual multi-scale triplet graph convolutional network for classification of brain disorders using functional or structural connectivity. *IEEE Transac. Med. Imaging* 40, 1279–1289. doi: 10.1109/TMI.2021.3051604

Ying, Z., You, J., Morris, C., Ren, X., Hamilton, W., and Leskovec, J. (2018). Hierarchical graph representation learning with differentiable pooling. *Adv. Neural Inform. Processing systems* 31, 1–5. doi: 10.3390/s21186070

Zhang, M., Cui, Z., Neumann, M., and Chen, Y. (2018). ""An end-to-end deep learning architecture for graph classification,"," in *The Thirty-Second AAAI Conference on Artificial Intelligence*, (Washington: Washington University).

Zhang, Y., Zhang, H., Adeli, E., Chen, X., Liu, M., and Shen, D. (2020). Multiview feature learning with multiatlas-based functional connectivity networks for MCI diagnosis. *IEEE Transac. Cybernet.* [Epub ahead ofprint]. doi: 10.1109/TCYB.2020.3016953

Zhao, F., Chen, Z., Rekik, I., Lee, S. W., and Shen, D. (2020). Diagnosis of autism spectrum disorder using central-moment features from low-and high-order dynamic resting-state functional connectivity networks. *Front. Neurosci.* 14:258. doi: 10.3389/fnins.2020.00258

Zhao, F., Zhang, H., Rekik, I., An, Z., and Shen, D. (2018). Diagnosis of autism spectrum disorders using multi-level high-order functional networks derived from resting-state functional MRI. *Front. Hum. Neurosci.* 12:184. doi: 10.3389/fnhum.2018.00184

Zhao, F., Zhang, X., Thung, K. H., Mao, N., Lee, S. W., and Shen, D. (2021). Constructing Multi-view High-order Functional Connectivity Networks for Diagnosis of Autism Spectrum Disorder. *IEEE Transac. Biomed. Eng.* 69, 1237–1250.

Zhi, D., Calhoun, V. D., Lv, L., Ma, X., Ke, Q., Fu, Z., et al. (2018). Aberrant dynamic functional network connectivity and graph properties in major depressive disorder. *Front. Psychiatr.* 9:339. doi: 10.3389/fpsyt.2018.00339

Zhou, J., Cui, G., Hu, S., Zhang, Z., Yang, C., Liu, Z., et al. (2020). Graph neural networks: a review of methods and applications. *AI Open* 1, 57–81. doi: 10.1016/j.aiopen.2021.01.001

Zhou, Y., Zhang, L., Teng, S., Qiao, L., and Shen, D. (2018). Improving sparsity and modularity of high-order functional connectivity networks for MCI and ASD identification. *Front. Neurosci.* 12:959. doi: 10.3389/fnins.2018.00959

Zhu, Y., Ma, J., Yuan, C., and Zhu, X. (2022). Interpretable learning based dynamic graph convolutional networks for alzheimer's disease analysis. *Inform. Fusion* 77, 53–61. doi: 10.1016/j.inffus.2021.07.013

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The antidepressant effect of cognitive reappraisal training on individuals cognitively vulnerable to depression: Could cognitive bias be modified through the prefrontal–amygdala circuits?

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Cognitive reappraisal (CR) is one of the core treatment components of cognitive behavioral therapy (CBT) and is the gold standard treatment for major depressive disorders. Accumulating evidence indicates that cognitive reappraisal could function as a protective factor of cognitive vulnerability to depression. However, the neural mechanism by which CR training reduces cognitive vulnerability to depression is unclear. There is ample evidence that the prefrontal–amygdala circuit is involved in CR. This study proposes a novel cognitive bias model of CR training which hypothesizes that CR training may improve the generation ability of CR with altered prefrontal–amygdala functional activation/connectivity, thus reducing negative cognitive bias (negative attention bias, negative memory bias, negative interpretation bias, and/or negative rumination bias) and alleviating depressive symptoms. This study aims to (1) explore whether there is abnormal CR strategy generation ability in individuals who are cognitively vulnerable to depression; (2) test the hypothesis that CR training alleviates depressive symptoms through the mediators of cognitive bias (interpretation bias and/or rumination bias); (3) explore the neural mechanism by which CR training may enhance the ability of CR strategy generation; and (4) examine the short- and long-term effects of CR training on the reduction in depressive symptoms in individuals who are cognitively vulnerable to depression following intervention and 6 months later. The study is promising, providing theoretical and practical evidence for the early intervention of depression-vulnerable individuals.

KEYWORDS

antidepressant effect, cognitive reappraisal training, cognitively vulnerable to depression, prefrontal-amygdala circuit, cognitive bias

Introduction

Depressive disorder is an affective mental disorder with depressive mood and anhedonia as the defining symptoms. It may cause functional disability, seriously affect social functioning and quality of life, and create a heavy socioeconomic burden. The disease burden of depressive disorders accounts for 10.3% of the total disease burden (Smith, 2014), which is estimated to be the cause of the world's top disease burden in 2030. Therefore, early identification and intervention to reduce disease burden is currently the focus of research on depressive disorders.

According to the cognitive vulnerability–stress theory of depression, cognitive vulnerability can interact with stress to increase the likelihood of depression (Abramson et al., 1989, 1999). Cognitive vulnerability manifests as negative cognitive biases, such as biases in attention, interpretation, and rumination (Dai and Feng, 2008; Chen and Feng, 2015; Zhang and Feng, 2016; Yan et al., 2017). The combined cognitive bias hypothesis in depression proposed that negative attention bias can lead to interpretation bias, which in turn induces rumination and subsequently more depressive symptoms. This hypothesis is supported empirically by path analyses of these variables (attention bias→interpretation bias→rumination→depressive symptoms; Everaert et al., 2012, 2017).

Cognitive reappraisal (CR), which changes the affective regulation process of emotional responses through the reinterpretation of the meaning of emotional stimuli, represents a core technique of cognitive behavioral treatment (CBT), the gold standard psychotherapy of depressive disorder (Shore et al., 2017). Typically, depressed individuals manifest deficits in the habitual use of CR strategies. Compared with other emotion regulation strategies (e.g., emotion expression suppression), deficits in positive CR (the frequency with which individuals interpret stressful life events as positive rather than threatening) are specific factors that can predict depressive symptoms (Garnefski et al., 2005) and positive emotions initially and depression and anxiety symptoms 3–6 months later (Nowlan et al., 2016). In contrast, frequent use of CR may have beneficial effects that protect individuals from depression vulnerability. Frequent use of CR can modify an individual's interpretation bias, dampen rumination bias, and thus alleviate depression symptoms (attention bias→interpretation bias→CR→rumination→depressive symptoms) (Everaert et al., 2017). CR frequency mediated the relationship between interpretation biases and depressive symptoms in individuals at high familial risk for depression and alleviated the negative impact of interpretation bias on depressive symptoms (interpretation bias→CR→depressive symptoms) (Sfärlea et al., 2021). Depression-resilient individuals tend to use CR to assign a new emotional meaning to stressful events (Knyazev et al., 2017), whereas adolescents with parents having a history of depression (depression-vulnerable individuals) who frequently use CR as an emotion regulation strategy will experience less depression and have higher positive emotions (Kudinova et al., 2018). Specifically, CR was positively linked with the ability to inhibit negative content during a negative affective priming task in individuals with low rumination (Daches and Mor, 2015). Individuals who frequently use CR can better inhibit the interference of distracting negative stimuli (Cohen et al., 2012) and have fewer depressive symptoms in response to unpredictable stress (Troy et al., 2013). The ability to generate a non-negative CR predicts fewer stress responses (lower cortisol levels) when faced with depression-related acute stress (Tsumura et al., 2015). Therefore, the CR ability may have a positive impact on reducing depressive symptoms through inhibition or compensation of negative cognitive bias (e.g., interpretation bias and/or rumination bias) as well as through reduction of physiological arousal.

Notably, previous studies utilizing self-report measures, such as the Emotion Regulation Questionnaire (ERQ) (Gross and John, 2003) and Cognitive Emotion Regulation Questionnaire (CERQ), mainly measure an individual's tendency, such as frequency (trait) and extent (state), to use CR strategies specified by the developers of the questionnaire in daily life. However, CR tendency reflects typical behavioral patterns rather than capacity for best performance (e.g., CR ability) (Perchtold et al., 2017). Furthermore, self-reported CR tendency is moderately correlated with personality factors such as self-acceptance and environmental mastery (r = 0.35 and 0.41) (Gross and John, 2003), which may influence the motivation to use CR strategies and cannot objectively quantify the ability of the individual to generate a CR strategy. In contrast, CR ability, which is also termed reappraisal effectiveness (RE), can be experimentally measured by changes in spontaneous emotion responses after the individual is required to adopt a CR strategy compared to passively viewing emotional stimuli (Troy et al., 2010). A previous study demonstrated that deficits in experimentally measured CR ability are manifested in individuals with mild to moderate symptoms of depression (Zhang et al., 2016), patients in depressive episodes (Compare et al., 2014; Wang et al., 2014; Smoski et al., 2015; Wang et al., 2015), and patients in remission from depression (Ehring et al., 2008), and they can be predictive of depressive symptoms after treatment (Radkovsky et al., 2014).

One other issue of concern for CR ability is that most previous CR tasks required the subjects to generate new CR strategies of emotional stimuli under guidance rather than spontaneously (Khodadadifar et al., 2022), making it impossible to directly measure an individual's spontaneous tendency to produce and maintain a CR strategy. According to the recent empirical literature, CR ability can be operationalized as either RE or reappraisal inventiveness (RI) (Zeier et al., 2021), with RI independent of RE (Zeier et al., 2020). RI is defined as the

flexibility and semantic fluency of individuals in generating new emotional appraisals in response to specific emotion-inducing scenes, which is measured with the Reappraisal Inventiveness Test (RIT) (Weber et al., 2013). Despite the well-acknowledged effectiveness of CRs, the launching of CRs is found to be more difficult due to default preferences in the decision to regulate emotions (Suri et al., 2015). The performance of the RIT task includes RIT-fluency (the number of reappraisals generated) and RIT-flexibility (the number of categories of different reappraisals), which will be transformed into RIT scores. Thus, a higher RIT score represents greater CR abilities to generate abundant and diverse strategies to regulate emotion. Studies found that a greater RI predicts lower chronic stress levels in women and depressive symptoms in men (Perchtold et al., 2017, 2019). Greater RI, especially that which generates alternative (creative) reappraisal strategies, predicts immediate, and long-lasting beneficial effects (< 10 min vs. 3 days) in transforming negative emotion into positive emotion (Wu et al., 2019). Furthermore, the reduced ability of individuals with depressive symptoms to generate a CR strategy was observed (Perchtold et al., 2017). Therefore, the RI index is necessary for objective measurement of CR ability, and the improvement in RI may be beneficial to emotional health.

Intervention studies demonstrated that individuals' CR ability can be improved through training and could predict changes in depressive symptoms. CR training could alleviate depressive symptoms and negative emotions, improve happiness and life satisfaction in patients with depression (Berking et al., 2013; Ehret et al., 2014; Weytens et al., 2014), and decrease short- and long-term negative emotions in healthy individuals (Denny and Ochsner, 2014). Enhancement of self-reported CR frequency after CR training compared to the wait-list control condition (WLC) could reduce the depressive symptom severity of depressed patients (Berking et al., 2019). The change in CR tendency after CBT could predict a decrease in depressive symptoms in patients with depressive disorder (Forkmann et al., 2014). A meta-analysis of emotion regulation intervention in clinical populations showed improvement in emotion regulation (including CR) tendencies (Moore et al., 2022). However, studies of the antidepressant effect of CR training on cognitively vulnerable individuals with depression are still lacking. Yuan et al. (2014) proposed that the use of CR training could reduce the vulnerability of adolescents to negative emotions, whose development stage is prone to emotional disturbances. Thus, empirical evidence for the training effects of CR on cognitively vulnerable individuals is still needed.

Notably, the neural mechanism of CR training effects is still unclear. First, deficits in CR for depressed individuals are related to aberrant activities in frontal cognitive control regions, which modulate the emotion generation regions (Khodadadifar et al., 2022), and abnormalities in the structural covariance of the emotion regulation network (Wu X. et al., 2017). (1) Cognitive control regions: The dorsolateral prefrontal lobe (dlPFC) and the ventrolateral prefrontal lobe (vlPFC) are responsible for storing and choosing appropriate CR strategies, respectively (Morawetz et al., 2016). The dorsal medial prefrontal lobe (dmPFC) is mainly responsible for monitoring and reflecting changes in an emotional state, modifying the initial emotion appraisal in adaptation to current situations/goals (top-down control of emotion) (Phillips et al., 2003). (2) Emotion generation regions, the ventral medial prefrontal cortex (vmPFC), are mainly responsible for the initial appraisal of emotional stimuli and spontaneous emotional responses (Phillips et al., 2003). The amygdala plays a major role in the effective relevance (valence) of positive and negative stimuli (Fadok et al., 2018), and its volume (especially the right side) is positively associated with CR ability (Hermann et al., 2014). The functional interactions between prefrontal subregions (dlPFC/vlPFC/dmPFC) and the amygdala probably act through the vmPFC, which has direct structural connections with prefrontal subregions and with the amygdala (D'Arbeloff et al., 2018). When depressed patients regulated negative emotion using CR, lower activation of the dlPFC, the vlPFC, and the dmPFC and higher activation of the amygdala and the vmPFC were found during the downregulation of negative emotion, and higher activation of the medial prefrontal cortex (mPFC) and lower activation of the amygdala were found during the upregulation of negative emotion (Belden et al., 2015; Picó-Pérez et al., 2017; Stephanou et al., 2017; Zilverstand et al., 2017; Radke et al., 2018). In contrast, the IFG and dlPFC/dmPFC/vmPFC effective functional connectivity (FC) patterns are indicative of reappraisal effectiveness (RE) (Morawetz et al., 2017), and the hypoactivity of the IFG in patients with depression modulated by motivation disposition during CR may interfere with inhibitory IFG-dlPFC coupling (Wang et al., 2014, 2017).

Second, there were fewer evidence indicating neural abnormalities underlying the CR abilities of individuals vulnerable to depression. Previous evidence indicated strengthened dmPFC-amygdala and vmPFC-amygdala resting-state functional connectivities in stress-vulnerable individuals with high harm avoidance (HA) personality traits (Baeken et al., 2014). In healthy individuals, stronger coupling of the dmPFC-amygdala under task-induced stress showed an enhanced immune response (Muscatell et al., 2015), which may suggest stress vulnerability. Furthermore, the associations between lower left-lateralized vlPFC activation and decreased RI ability (e.g., RIT-fluency) of individuals with depressive symptoms and chronic stress were observed, supporting the deficits in reappraisal inventiveness in individuals vulnerable to depression (Papousek et al., 2017; Perchtold et al., 2017). In contrast, the inverse relationship between the functional activities of vmPFC and amygdala in stress-resilient individuals showed more effective control over emotion response (decreased versus increased activation of amygdala) when confronted with

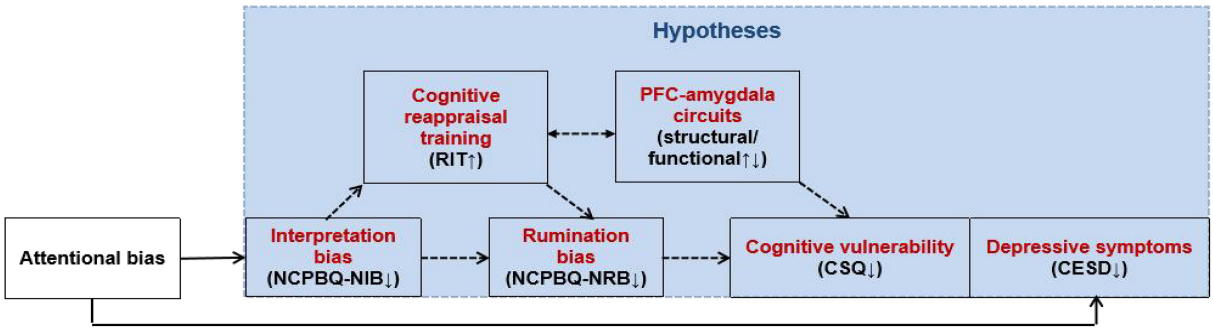

FIGURE 1
Antidepressant mechanism of CR training on individuals cognitively vulnerable to depression.

repeated task-induced stress compared to stress-vulnerable individuals (Wang et al., 2013).

In summary, this evidence may suggest abnormalities in the prefrontal–amygdala circuits for individuals cognitively vulnerable to depression, which may lead to heightened initial affect appraisal (vmPFC↑, vmPFC-amygdala coupling↓), failure to store, generate, and monitor the need for implementing CR strategies (dlPFC/vlPFC/dmPFC↓, dlPFC/vlPFC/dmPFC-amygdala coupling↑), and selection of appropriate contextual CR strategies (IFG↓, IFG-dlPFC coupling↓).

On the other hand, the frequent user of CR showed stronger downregulation of amygdala activation to negative emotion stimuli (Kanske et al., 2012), and CR in healthy individuals can attenuate the excitatory connectivity from the dlPFC to the inferior frontal gyrus (IFG) and increase the inhibitory connectivity from the IFG to the dlPFC, which supports the selection of appropriate alternative CR strategies (reinterpretations) in the IFG, and afterward, inhibition of original interpretations maintained and monitored in the dlPFC (Morawetz et al., 2016). Neurofeedback-guided CR training targeting the left vlPFC improved the frequency of CR strategy use (indexed with ERQ) as well as depression symptoms (Keller et al., 2021). Therefore, CR training may enhance CR ability by changing the functional activity/connectivity pattern of prefrontal-amygdala circuits, which then alleviates cognitive biases and thus depressive symptoms.

Researchers suggested that specific measures using lab-based tasks may be more sensitive to detect training effects (Cohen and Ochsner, 2018). Therefore, in this study, we will combine the RIT, CR training, and fMRI, as well as self-report measures (cognitive/emotion/symptoms) to address the following aims: (1) to examine whether the CR ability (reappraisal inventiveness) of the population with cognitive vulnerability to depression is abnormal; (2) to test the hypothesis that CR training alleviates depressive symptoms through the mediators of cognitive bias (e.g., interpretation bias and/or rumination bias); (3) to investigate the neural substrates (structural/functional) of prefrontal–amygdala circuits through which CR training improves the ability to generate a CR strategy; and (4) to examine the short- and/or long-term effects of CR training on reducing depression symptoms in cognitively vulnerable individuals immediately after intervention and/or 6 months to provide theoretical and practical evidence for early intervention in these populations. We postulate that CR training improves CR ability (RIT) by changing the brain activity/function connectivity of the prefrontal-amygdala circuits, thereby reducing negative cognitive biases (NCPBQ-NIB, NCPBQ-NRB, and CSQ) and improving depression symptoms (CESD) (**Figure 1**).

Methods

Using RIT and CR training in combination with fMRI, we will explore (1) the deficits in CR ability (indexed with RIT) for the depression-vulnerable group; (2) the short- and long-term antidepressant effects of CR training on depression-vulnerable populations; (3) whether it is feasible to reduce negative cognitive biases (negative interpretation bias and/or negative rumination bias) and depressive symptoms of depression by improving reappraisal inventiveness; and (4) the changes in the prefrontal–amygdala circuit induced by CR training, including changes in the functional activation and connectivity of the regions of interest (prefrontal cortex and amygdala) before and shortly after CR training and changes in the volumes of these regions of interest (prefrontal cortex and amygdala) long after CR training (6 months later) (**Figure 2**).

Procedure

The effects of cognitive reappraisal inventiveness on individuals cognitively vulnerable to depression

Individuals cognitively vulnerable to depression will be screened using the Cognitive Style Questionnaire (CSQ)

developed based on the hopelessness theory and the weakest link method. The weakest link method (Abela and Sarin, 2002) will be used to screen individuals with cognitive vulnerability to depression; it showed the value in predicting changes in depression (Reilly et al., 2012). By using a group of individuals cognitively vulnerable to depression and a normal control group as research participants, we will determine, using the RIT, whether individuals cognitively vulnerable to depression have defects in CR inventiveness before training.

Neural mechanism of improvements in cognitive reappraisal inventiveness in individuals cognitively vulnerable to depression through cognitive reappraisal training

Using the group of individuals cognitively vulnerable to depression (divided into intervention and waiting subgroups) and the normal control group as research participants, we will conduct a 4-week (2 sessions/week) CR training program for the intervention subgroup, and before and after training, the intervention and waiting-list control subgroups will undergo fMRI to examine whether CR training can improve reappraisal inventiveness and depression symptoms by regulating the function of the prefrontal–amygdala circuit.

Short- and long-term antidepressant effects of cognitive reappraisal training on individuals cognitively vulnerable to depression

Through follow-up immediately after intervention or 6 months after the intervention, we will validate the hypothesis of the reduction in cognitive vulnerability to depression and depression symptoms through improvements in reappraisal inventiveness with CR training by constructing a hierarchical linear model (HLM) analysis and mediating/modulating effect analyses.

Subjects

The study protocol is in accordance with the Declaration of Helsinki and was approved by the ethical committee of the University. All voluntary participants have to provide informed written consent before the initiation of the study procedures.

Group of individuals cognitively vulnerable to depression

Of the recruited healthy subjects, those with an average weakest link score plus 1 standard deviation will be assigned to the group of individuals cognitively vulnerable to depression, and whether they have affective disorders and other axis I diseases will be determined by two experienced psychiatrists using the Structured Clinical Interview for DSM Disorders (SCID).

The inclusion criteria are as follows: participants (a) with average CSQ weakest link score plus 1 standard deviation; (b) with Han ethnicity; (c) aged 18–25 years; (d) who are right-handed; (e) with normal or corrected vision; (f) who are local community residents; (g) who can understand the content of the study, are willing to participate, and are committed to completing the entire experiment; (h) have signed informed consent form.

The weakest link composite score of CSQ will be calculated as follows: (1) calculating the scores for the 3 subscales (causes, consequences, and self-worth) of CSQ; (2) standardizing the scores for the 3 subscales and converting them to standard scores, based on which the standard scores for the 3 subscales for each individual are then ranked, in which the highest of the 3 subscale scores represents the final score for each individual's weakest link; and (3) calculating the average weakest link scores for all individuals. The score is further used to screen individuals in the cognitively vulnerable to depression group (mean score plus 1 standard derivation) or those in the not cognitively vulnerable to depression group (the mean score minus 1 standard derivation).

The exclusion criteria are as follows: participants (a) who meet the diagnostic criteria for depression or other axis diseases; (b) with a history of taking any antidepressants or antipsychotics; (c) with a history of alcohol or drug abuse or dependence; (d) with a history of central nervous system diseases, e.g., head injury or epilepsy; (f) with a history of multiple sclerosis or major physical diseases; (g) with a history of electroshock therapy; (h) with a history of mental illness in first-degree relatives; and (i) with contraindications to MRI.

Normal control group

Of the recruited healthy subjects, those with an average weakest link score minus 1 standard deviation will compose the group of individuals without cognitive vulnerability to depression, i.e., the normal control group. Individuals in the normal control group will be interviewed by two experienced psychiatrists using the SCID to exclude those suffering from depression and other axis I diseases. Ultimately, the control group will comprise 30 subjects, and the control group and the intervention and waiting subgroups of the group of individuals cognitively vulnerable to depression will be homogenous in terms of demographic variables and depression symptoms.

The inclusion criteria are described as follows: participants (a) with average CSQ weakest link score minus 1 standard deviation; (b) with Han ethnicity; (c) aged 18–25 years; (d) who are right-handed; (e) who have normal or corrected vision; (f) who are local community residents; (g) who can understand the content of the study, are willing to participate, and are committed to completing the entire experiment; and (h) who signed an informed consent form.

The exclusion criteria are described as follows: participants (a) who meet the diagnostic criteria for

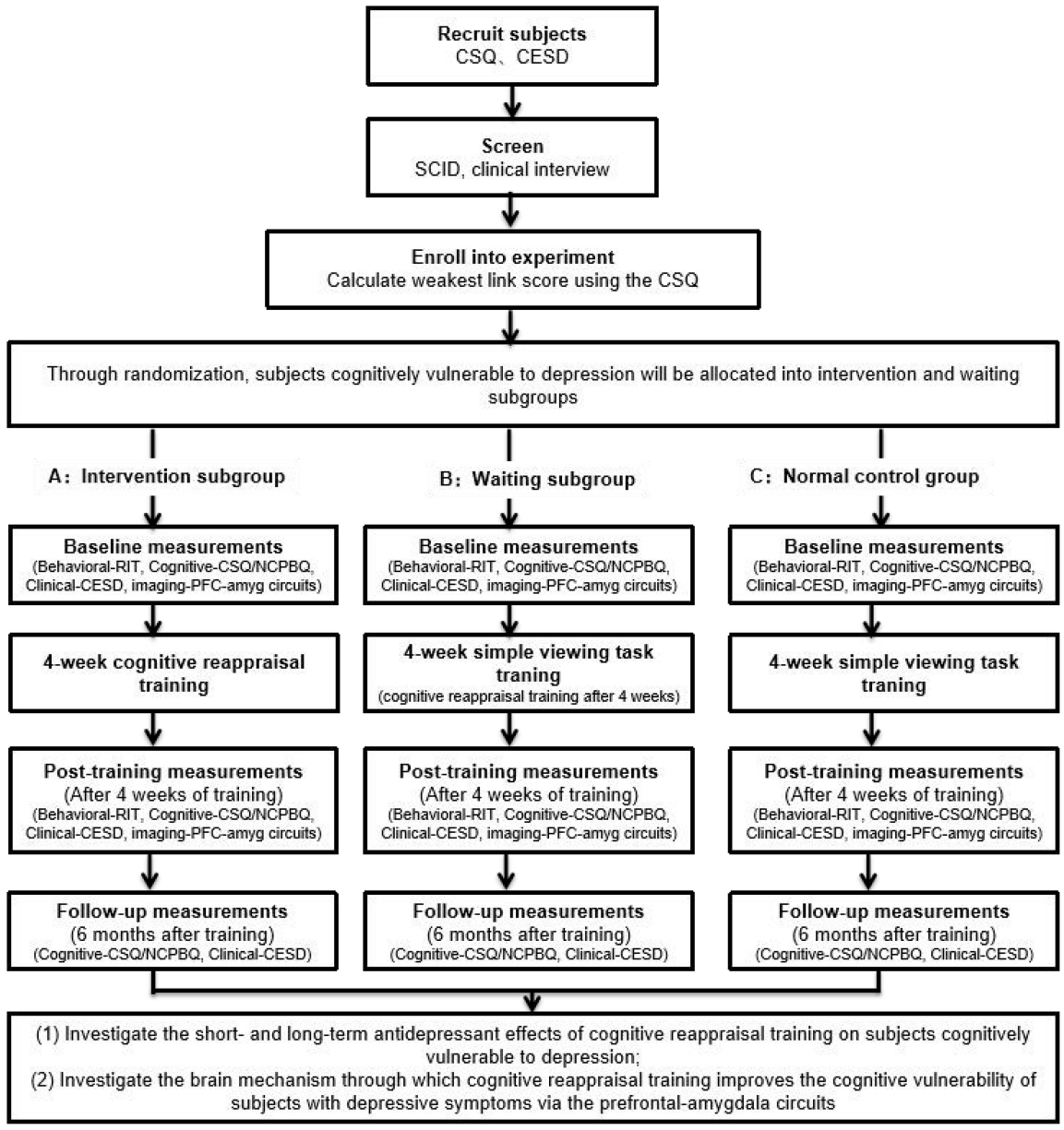

FIGURE 2
The flow diagram of the current study summarizing the randomized controlled trial design, recruitment of participants, and collected measures.

depression or other axis diseases; (b) history of taking any antidepressants or antipsychotics; (c) history of alcohol or drug abuse or dependence; (d) history of central nervous system diseases, e.g., head injury or epilepsy; (e) history of multiple sclerosis or major physical diseases; (f) history of electroshock therapy; (g) history of mental illness in first-degree relatives; and (h) contraindications to MRI.

Sample size calculation: An *a priori* power analysis found that a sample size of 75 participants per group (N = 150) would be sufficient with a medium effect size (Cohen's d = 0.0.39) and 65% power (computed with G*power 3.1). These estimates were based on previous research examining changes in HRSD/BDI-II scores before and after CR training when compared to the waiting-list control condition (Berking et al., 2019). Since the sample size projection considered an anticipated 20% dropout rate, the target sample size was 188 patients.

Randomization to treatment will be completed with a computer-generated list of random numbers, and each

FIGURE 3
Schematic diagram of a computerized CR task. Adapted from https://699pic.com/.

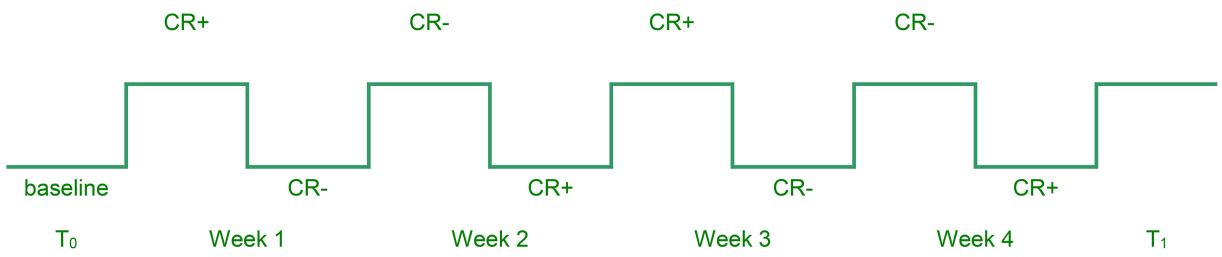

FIGURE 4
CR training process: one session as an example (4 weeks, 2 sessions/week).

participant will be randomly assigned to either the intervention group or the control group with a 1:1 allocation and double-blinded. The randomization will minimize group differences in demographic factors and instrument scores (Pocock and Simon, 1975).

Cognitive reappraisal training

Stimuli

After preliminary experiments, a total of 48 positive and negative emotion pictures were selected from the Chinese Affective Picture System (CAPS), which showed high internal consistencies of valence, arousal, and dominance (0.982, 0.979, and 0.980) (Bai et al., 2005). A block design will be adopted, in which each task block contains one type of CR task, with the same number of positive and negative emotion pictures with comparable arousal.

Task

The CR task for each participant will include 3 conditions: simple viewing (baseline), CR + (emotion upregulation), and CR- (emotion downregulation). The CR task starts with the baseline condition, and then the order of CR + and CR- tasks will be counterbalanced across the participants. The task was designed based on our previous study of the CR ability of patients diagnosed with depressive disorder (Wang et al., 2014, 2017). To motivate the participants to generate reappraisal strategies, the practice before the formal CR task will give the participants two examples that provide creative reappraisal strategies vs. objective descriptions of the emotion stimuli pictures (Wu X. et al., 2017, Wu et al., 2022) and then require the participants to reappraise each of the four emotion pictures (2 for the emotion upregulation condition and 2 for the emotion downregulation condition See details below) and type their strategies in the blank under each picture on the computer screen.

Simple viewing task (baseline)

The participants will be instructed to naturally view the emotion stimuli pictures in sequence and rate their emotional arousal after each picture. The following instructions will be provided at the beginning of the task: "When a fixation point ' + ' appears in the center of the screen, please keep your eyes on the fixation point. When the fixation point disappears, a picture appears; please look at the picture. After the picture disappears, please evaluate your emotional intensity at this time based on the instructions provided."

Cognitive reappraisal + task (emotion upregulation)

The participants will be instructed to enhance their emotions while viewing stimuli pictures and rate their emotional

arousal after each picture. The following instructions will be provided at the beginning of the task: "When a fixation point ' + ' appears in the center of the screen, please keep your eyes on the fixation point. When the fixation point disappears, a picture will appear. Please imagine yourself in the picture and fully experience the emotion the scene evokes. After the picture disappears, please evaluate your emotional intensity at this time based on the instructions provided."

Cognitive reappraisal-task (emotion downregulation)

The participants will be instructed to weaken their emotions while viewing stimulus pictures and rate their emotional arousal after each picture. The following instructions will be provided at the beginning of the task: "When a fixation point ' + ' appears in the center of the screen, please keep your eyes on the fixation point. When the fixation point disappears, a picture will appear. Please keep an objective attitude and try not to feel any emotion from the picture. After the picture disappears, please evaluate your emotional intensity at this time based on the instructions provided" (**Figure 3**).

The emotional regulation effectiveness of CR can be calculated by subtracting the emotional intensity for the simple viewing task from that for the CR + task or CR- task. The upregulation effect ($arousal_{CR+}$ - $arousal_{baseline}$) and the downregulation effect ($arousal_{baseline}$ - $arousal_{CR-}$) can be obtained before (T_0) and after (T_1) CR training while MRI is performed (T_0 and T_1).

Training procedure

The training includes 8 sessions (2 sessions/week) within 4 weeks. Each session is divided into 9 blocks (20 trials/block, 180 trials in total). The order of the experimental content is counterbalanced, i.e., in each block, one-half of the subjects start with a CR + task and the other half start with a CR- task. In each session, pictures with different valences are randomly presented in trials. Each trial lasts 18–21 s: first, a fixation point is presented for 2 s at the center of the screen which the participant fixes; then, a positive or negative emotion picture is presented on the screen and the subject is asked to focus on the emotion picture for 8 s to allow emotional arousal. After the picture disappears, the subject is asked to report his/her emotional intensity at the moment on a 1–9 scale within 4–7 s, during which the subject's reaction time of key press is recorded. If the subject does not press the key in the allotted time, the interface screen will continue (**Figure 4**).

After the experiment, the subject is asked about his/her conformity to the instructions (manipulation check). Both the quantitative and qualitative CR manipulation checks will be conducted by the experimenter to confirm that they obeyed CR training instructions (Rood et al., 2012). After each block, participants briefly state the content coming into mind during that block (recorded by the experimenter after the informed written consent by the participants) and the degree to which they reappraise the emotional pictures during that block on a 0–100 rating scale.

Primary outcome

The structured clinical interview for DSM-IV-TR Axis Disorders (SCID-I) will be used to diagnose and screen for major depressive disorders and exclude other DSM-IV axis I mental disorders when recruiting subjects. Demographic information, including gender, age, ethnicity, education, and duration of illness (months), will be collected using a questionnaire.

Center for epidemiologic studies depression scale

The center for epidemiologic studies depression scale (CESD) will be used by subjects to self-evaluate their current depressive symptoms (within a week), focusing on depressive emotions or mood rather than somatic symptoms. Subjects with depressive symptoms will undergo preliminary screening to facilitate further diagnosis. The scale contains 20 items in 4 dimensions (negative emotions, positive emotions, physical symptoms, and interpersonal relationships) that are scored on a 4-level scale ("no or rarely, less than once a day," "sometimes or only a small part of the time in 1 day," "frequently or half of the time in 1 day," and "most of the time or all the time in 1 day"); the higher the score is, the more severe the level of depression.

Secondary outcomes

Negative cognitive bias

Cognitive style questionnaire

The CSQ will be used to screen subjects in the group of individuals cognitively vulnerable to depression and the group of individuals not cognitively vulnerable to depression. The CSQ was developed based on the hopelessness theory and was designed to be used to assess an individual's negative cognitive styles, mainly including the individual's perceptions of the causes, consequences, and self-worth after an event. The Chinese-translated version of the CSQ has good internal reliability (Cronbach's alpha coefficient = 0.94), satisfactory 8-week test–retest reliability (reliability = 0.59), and good construct validity for the four-factor model (CFI = 0.91, RMSEA = 0.09), which included general-local causes, stable-temporary causes, consequences, and self-worth (Chen et al., 2014).

Negative cognitive processing bias questionnaire

The negative cognitive processing bias questionnaire (NCPBQ) contains 4 dimensions, i.e., negative attention bias (NAB), negative memory bias (NMB), negative interpretation bias (NIB), and negative rumination bias (NRB), using a Likert 4-point scale from 1 (completely disagree) to 4 (completely agree). The NCPBQ has good internal reliability (Cronbach's alpha coefficient = 0.89), split-half reliability (r = 0.87), construct validity for a four-factor model that explained 50.152% of the total variation (CFI = 0.92, RMSEA = 0.05), and criterion validity coefficients of 0.395 (relative to the Beck Depression Self-Rating Scale) and 0.548 (relative to the Dysfunctional Attitude Questionnaire) (Yan et al., 2017). The negative interpretation bias (NIB) and the negative rumination bias (NRB) subscales will be utilized in the mediation analyses.

Reappraisal ability/tendency

Reappraisal inventiveness test

RIT includes 4 scenes that can trigger emotions. Participants are asked to imagine themselves in the scene as vividly as possible within a specified time (3 min), after which they are asked to think of reappraisals that can change the induced emotion within 20 s and then record the reappraisals in 3 min. RIT was scored on two scales: (a) RIT-fluency was indicated by the number of reappraisals generated and (b) RIT-flexibility was indicated by the number of categories of different reappraisals (Weber et al., 2013). To improve the internal validity of the test, we set the induced emotions to sad and happy. Before the test, the subjects will be given examples to illustrate how to generate as many reappraisals as possible for a given emotional stimulus so that they can transfer to the formal test.

Emotion regulation questionnaire

The ERQ was developed by Gross and contains a total of 10 items in 2 dimensions, a CR and expression inhibition (EI) (Gross and John, 2003). It is scored through a 5-point scale (1 = strongly disagree and 5 = strongly agree); the higher the score, the more likely the subject is to use this emotion regulation strategy. The Chinese-translated version of the ERQ has good test–retest reliability (r = 0.82 and 0.79) and internal reliability (Cronbach's alpha coefficient = 0.85 and 0.77) for the CR and EI subscales, split-half reliability (reliability = 0.87), and construct validity for the two-factor model (CFI = 0.96, RMSEA = 0.09), with completely standardized factor loadings of all items higher than 0. 55 at a statistically significant level (Wang et al., 2007). The ERQ will be utilized to verify the construct validity of the RIT indexes.

Brain structure and functional imaging

Brain structure and functional imaging data will be collected on a Siemens 3.0T scanner from the affiliated hospital of the university. During the scan, each participant will be in a supine position, with foam under the head to minimize head movement, and will be wearing headphones to reduce noise interference. A standard orthogonal single-channel head coil will be used. Conventional T1WI and T2WI imaging, echo-planar imaging (EPI), and whole-brain 3D magnetization-prepared rapid gradient-echo (MPRAGE) imaging will be conducted for each subject by a radiologist. The experimental stimulus will be presented by connecting a liquid-crystal display (LCD) screen outside the scanning channel to the E-prime stimulus presentation and the response recording system, and each participant will view the presentation through a reflective mirror attached to the head coil. During the experiment, the participant will use a joystick to enter their ratings while the system automatically records the participant's response to the CR tasks.

The scanning sequence will be as follows: **(1)** The axial T1-FLAIR sequence, parallel to the anterior-posterior joint line; pulse repetition time/echo time (TR/TE) = 500 ms/14 ms; slice thickness = 4 mm; field of view (FOV) = 240 mm × 240 mm; and matrix = 256 × 160; **(2)** sagittal T2-FLAIR will be scanned at the same location using gradient-echo echo-planar imaging (EPI) with the following parameters: TR/TE = 3,000 ms/40 ms; FOV = 240 mm × 240 mm; matrix = 128 × 128; 30 consecutive images at each time point; and slice thickness = 4 mm; if no abnormality is observed in plain scans, resting-state scans will be performed; **(3)** a total of 176 consecutive slices in the sagittal position will be acquired to cover the entire brain through an MPRAGE sequence for subsequent 3D reconstruction and spatial alignment with the following parameters: TR/TE = 1,970 ms/3.93 ms; flip angle = 15°; slice thickness = 1.70 mm; interval = 0.85 mm; FOV = 250 mm × 250 mm; and matrix = 448 × 512; and **(4)** task-state blood-oxygen-level-dependent (BOLD) functional images will be acquired using the EPI sequence, with the same position as that for anatomical images and the following parameters: TR/TE = 2,000 ms/30 ms; number of slices = 36; slice spacing = 33; FOV = 240 mm × 240 mm; and matrix = 64 × 64.

Regions of interest (ROIs): The structural and functional activities of the dlPFC, the vlPFC, the dmPFC, and the vmPFC, as well as the amygdala, will be analyzed. The functional connectivities between these regions and subcortical regions (amygdala) will be analyzed based on the time series of these ROIs.

Statistical analysis

Behavioral and self-report data

Intervention effect analysis

A 3 (group: CR = cognitively vulnerable intervention subgroup; WC = cognitively vulnerable waiting-list control subgroup; NC = normal control group) × 3 (time point: T_0 = pretraining, T_1 = post-training, T_2 = 6-month follow-up) mixed design will be adopted. Using the HLM analysis, as well as mediating/modulating effect analyses, we will investigate (1) hypothesis 1, whether the changes in negative cognitive biases and depressive symptoms across time 1 and time 2 differ significantly among groups and (2) hypothesis 2, whether the changes in negative cognitive bias (negative interpretation bias and/or negative rumination bias) pre- and post-training could predict depression symptoms at T_1 and/or T_2.

To test hypothesis 1, we will conduct an HLM analysis with time (0 = pretraining; 1 = post-training), group (0 = CR; 1 = WC; 2 = NC), and the interaction between time and group as predictor variables and the with CESD score as the outcome variable. To test hypothesis 2, we will conduct mediating/modulating effect analyses among CR ability (RIT) and tendency (ERQ), negative cognitive bias (NCPBQ), cognitive vulnerability (CSQ), and depressive symptoms (CESD) at T_1 and/or T_2. The HLM and mediating/modulating effect analyses will be conducted in SPSS (Statistical Product and Service Solutions) software version 22.0 (SPSS, Inc., Chicago, IL, United States) combined with the PROCESS Macro (Hayes, 2012).

Neuroimaging data

Data preprocessing

Structural data preprocessing: The raw data will be analyzed with the CAT (Computational Anatomy Toolbox) 12 toolbox.[1] (1) Segmentation: The T1-weighted image for each pair of participants will be normalized to a template MNI space using DARTEL normalization and segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). (2) Check data quality: The written data will be checked to exclude those with artifacts or orientation errors. (3) The GM images will be smoothed using a Gaussian kernel of 8 mm full-width half-height (FWHM) and then entered into the statistical analysis.

Functional data preprocessing: The raw data will be formatted using MRIcro software[2] and the data will be preprocessed using the internationally accepted software Statistical Parametric Mapping 12 (SPM12) (Wellcome Trust Center for Neuroimaging.[3] (1) Functional data for the first 10 repetition times (TRs) will be excluded to eliminate the effects of subject maladaptation and longitudinal magnetization relaxation not reaching the steady state. (2) Head movement correction: This will be performed to reduce the interference of noise signals caused by the subject's head movement during the scanning process, and data with head motion exceeding 1.5 mm or a rotation angle exceeding 1.5° will be excluded. (3) Time point correction: This will be performed to standardize the images collected at different time points to the same time point based on the time modulation effect of the hemodynamic function on each functional image. (4) Alignment: To address the differences in the anatomical structure of different individuals, each subject's functional images and templates will be aligned so that the individual's brain is aligned to the standard Montreal Neurological Institute (MNI) space for functional localization of activation zones. (5) Gaussian smoothing: The full width at half maximum value will be set to 8 mm to improve the signal-to-noise ratio of images.

Data analysis

(1) Analysis of the morphological characteristics of brain structure: Voxel-based morphometry (VBM) will be adopted to calculate the concentration and volume of each voxel in different brain tissues (gray matter, white matter, and cerebrospinal fluid) using templates for the whole brain and different brain tissues created based on 3D data, and the volumes of ROIs will be compared between different groups to examine (1) whether the volumes of ROIs before and after CR training differ significantly and (2) if the volumes of ROIs differ significantly, whether the changes in the volumes of the ROIs can predict depressive symptoms immediately after training (T_1) or 6 months later (T_2).

(2) Region of interest analysis: The anatomical localization of functional images will be determined with reference to the anatomical maps of the brain in Talairach coordinates and based on the opinions of experienced neuroimagers. Using MARSbar software, the prefrontal subregions (dlPFC/dmPFC/vlPFC/vmPFC) and the amygdala will be extracted as BOLD signals of ROIs by subtraction between the baseline and CR (±) conditions. The data will then be exported to SPSS for statistical processing, in which the activation of the region of interest will be used as a predictor of depressive symptom scores to investigate (1) whether the activation levels of regions of interest (prefrontal lobe and the amygdala and its subregions) before and after CR training differ significantly and (2) if the activation levels do differ significantly, whether the changes in the activation levels of the regions of interest can predict depressive symptoms (T_1 and T_2).

(3) Functional connectivity analysis: Taking the amygdala as the seed point and the average time series within the seed point as the reference time series, we will perform "one point to multipoint" linear correlation analysis with the

1 https://neuro-jena.github.io/cat/
2 http://www.mricro.com
3 http://www.fil.ion.ucl.ac.uk/spm/software/spm12/

time series of each ROI. Using the average signals of head movement, the white matter, the cerebrospinal fluid, and the whole brain as covariates and using the prefrontal-amygdala FCs as predictors of depressive symptom scores, we will use between-group *t*-tests, combined with correlation analyses and path analyses, to examine (1) whether the FCs between the prefrontal subregions (dlPFC/vlPFC/dmPFC/vmPFC) and the amygdala before and after CR training differ significantly and (2) if the prefrontal-amygdala FCs do differ significantly, whether the FCs could predict depressive symptoms (T_1 and T_2). The FCs between ROIs, cognitive bias (CSQ/NCPBQ), CR ability (RIT), and tendency (ERQ) will then be entered into path analyses to verify the cognitive bias model of CR training.

Discussion

CR is one of the key components of CBT, and accumulating evidence suggests that CR training as a standalone treatment is effective for depressed patients to improve negative effects and enhance wellbeing (Berking et al., 2013; Ehret et al., 2014; Weytens et al., 2014). Prior studies found that individuals with cognitive vulnerability are at high risk for depression, which merits attention considering the prevalence of depression. Nonetheless, as a highly accessible and cost-effective intervention, the mood-lifting effects of CR for cognitively vulnerable individuals are unknown. Therefore, the current study could provide support for the potential of CR training for the prevention of depression in vulnerable groups. Of note, with the progress of e-mental health, CR training is promising to be developed into a cost-effective computerized program that is easy to implement for counselors and is suitable for early interventions of cognitively vulnerable individuals to depression.

Furthermore, despite ample evidence for the role of the prefrontal–amygdala circuit in CR, as well as prefrontal–amygdala dysfunction in CR deficits in patients with depression, the impact of CR training on hypothesized neural targets remains unclear, especially the cause–effect relationship between these regions during CR training. Based on previous evidence, we propose that CR training may involve increased top-down cognitive control areas (such as dlPFC, vlPFC, and dmPFC) and reduced bottom-up emotion responding areas (such as vmPFC and amygdala), as well as strengthened interactions between the PFC and the subcortical regions (mainly the amygdala). In addition, the hypothesis about the changes after CR training is exploratory and without strong *a priori* evidence; however, the structural changes of CR training may be of clinical significance. The current study aims to reveal the neural substrates of CR training, which remain largely unknown yet and have the potential to inform techniques, such as real-time fMRI neurofeedback (Zweerings et al., 2020; Keller et al., 2021), to precisely impact the neural targets underlying CR and amplify the effects of CR training.

This study also proposes a novel cognitive bias model of CR training (CR training→cognitive bias↓→cognitive vulnerability to depression↓), which hypothesizes that CR training may improve CR ability (effectiveness and incentives) and reduce cognitive bias (negative interpretation bias and/or negative rumination bias), which then alleviates the depressive symptoms. We adopt a process-based approach, which emphasizes the primary cognitive process underlying intervention (Forgeard et al., 2011) and assesses the effectiveness of the training using behavioral (RIT), cognitive (CSQ/NCPBQ), and clinical (CESD) assessments, along with measures of task-related brain activity/FCs before and after the training. This approach may provide proof-of-concept evidence for the cognitive bias model of CR training. In summary, the following scientific questions are expected to be answered: whether CR training will change prefrontal–amygdala FCs in the short term and the structure of the regions among the circuits in the long term (6 months later). The current study is promising to provide a novel approach to the intervention of depression vulnerability and insights into the underlying neurocognitive mechanism.

Limitations

First, we include the process measures of cognitive bias (negative interpretation bias and/or negative rumination bias) to evaluate the intervention effects, which should be interpreted as exploratory. More solid progress will depend on a systematic examination of the neural network mechanism involved in CR training effectiveness. The neural signature of the cognitive control and emotion regulation network during CR, such as global metrics and topological characteristics (Pan et al., 2018), is needed. However, connectome-based predictive modeling of distributed neural networks during CR has not revealed a meaningful whole-brain signature of CR tendency (Pan et al., 2018; Burr et al., 2020). Therefore, more evidence is needed to explore the neural network mechanism of CR training, which may provide more perspectives on the neural and cognitive targets of CR training.

Second, evidence of both clinical effectiveness and cost effectiveness of CR training is necessary for future studies to test the feasibility of CR training in primary care, as well as in clinical settings for vulnerable individuals with depression, and generalize CR training to those populations that may benefit from training. Therefore, various context-specific CR training programs should be forged into well-specified protocols that could be tested in randomized controlled trials to provide such evidence. Furthermore, further studies comparing CR training

with other components of CBT as well as its whole package are warranted to assess its cost-effectiveness.

Conclusion

This study is expected to provide initial evidence on the intervention effect of CR training on cognitively vulnerable individuals with depression through the mediating role of cognitive bias (negative interpretation bias and/or negative rumination bias) with the underlying prefrontal–amygdala structural/functional neural substrates.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Third Military Medical University. Written informed consent was not provided because no participant has been recruited and/or included in the study at the time of submission.

Author contributions

XW and ZF conceived and designed the study. XW drafted the manuscript. All authors revised the manuscript, approved the final version of the manuscript, and agreed to authorship contributions.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Abela, J. R. Z., and Sarin, S. (2002). Cognitive Vulnerability to Hopelessness Depression: A Chain Is Only as Strong as Its Weakest Link. *Cogn. Ther. Res.* 26, 811–829. doi: 10.1023/A:1021245618183

Abramson, L. Y., Alloy, L. B., Hogan, M. E., Whitehouse, W. G., Donovan, P., Rose, D. T., et al. (1999). Cognitive vulnerability to depression: Theory and evidence. *J. Cogn. Psychother.* 13, 5–20. doi: 10.1891/0889-8391.13.1.5

Abramson, L. Y., Metalsky, G. I., and Alloy, L. B. (1989). Hopelessness depression: A theory-based subtype of depression. *Psychol. Rev.* 96, 358–372. doi: 10.1037/0033-295X.96.2.358

Baeken, C., Marinazzo, D., Van Schuerbeek, P., Wu, G. R., De Mey, J., Luypaert, R., et al. (2014). Left and right amygdala - mediofrontal cortical functional connectivity is differentially modulated by harm avoidance. *PLoS One* 9:e95740. doi: 10.1371/journal.pone.0095740

Bai, L., Ma, H., Huang, Y., and Luo, Y. (2005). The Development of Native Chinese Affective Picture System—A pretest in 46 College Students. *Chin. Ment. Health J.* 19, 719–722.

Belden, A. C., Pagliaccio, D., Murphy, E. R., Luby, J. L., and Barch, D. M. (2015). Neural Activation During Cognitive Emotion Regulation in Previously Depressed Compared to Healthy Children: Evidence of Specific Alterations. *J. Am. Acad. Child Adolesc. Psychiatry* 54, 771–781. doi: 10.1016/j.jaac.2015.06.014

Berking, M., Ebert, D., Cuijpers, P., and Hofmann, S. G. (2013). Emotion Regulation Skills Training Enhances the Efficacy of Inpatient Cognitive Behavioral Therapy for Major Depressive Disorder: A Randomized Controlled Trial. *Psychother. Psychosomat.* 82, 234–245. doi: 10.1159/000348448

Berking, M., Eichler, E., Luhmann, M., Diedrich, A., Hiller, W., and Rief, W. (2019). Affect regulation training reduces symptom severity in depression – A randomized controlled trial. *PLoS One* 14:e220436. doi: 10.1371/journal.pone.0220436

Burr, D. A., D'Arbeloff, T., Elliott, M. L., Knodt, A. R., Brigidi, B. D., and Hariri, A. R. (2020). Functional connectivity predicts the dispositional use of expressive suppression but not cognitive reappraisal. *Brain Behav.* 10:e1493. doi: 10.1002/brb3.1493

Chen, J., Zhou, L., Yan, L., and Su, L. (2014). Psychometric Properties of the Short-form Version of the Cognitive Style Questionnaire. *Chin. J. Clin. Psychol.* 22, 1046–1049.

Chen, X., and Feng, Z. (2015). Trait rumination and executive control function deficiency. *Chin. J. Clin. Psychol.* 6, 1065–1069.

Cohen, N., Henik, A., and Moyal, N. (2012). Executive control attenuates emotional effects-For high reappraisers only? *Emotion* 12, 970–979. doi: 10.1037/a0026890

Cohen, N., and Ochsner, K. N. (2018). From surviving to thriving in the face of threats: The emerging science of emotion regulation training. *Curr. Opin. Behav. Sci.* 24, 143–155. doi: 10.1016/j.cobeha.2018.08.007

Compare, A., Zarbo, C., Shonin, E., Van Gordon, W., and Marconi, C. (2014). Emotional Regulation and Depression: A Potential Mediator between Heart and Mind. *Cardiovasc. Psychiatry Neurol.* 2014:324374. doi: 10.1155/2014/324374

Daches, S., and Mor, N. (2015). Brooding moderates the link between reappraisal and inhibition of negative information. *Cogn. Emot.* 29, 923–934. doi: 10.1080/02699931.2014.955839

Dai, Q., and Feng, Z. (2008). Attentional bias of depressed patients. *Adv. Psychol. Sci.* 2, 260–265.

D'Arbeloff, T. C., Kim, M. J., Knodt, A. R., Radtke, S. R., Brigidi, B. D., and Hariri, A. R. (2018). Microstructural integrity of a pathway

connecting the prefrontal cortex and amygdala moderates the association between cognitive reappraisal and negative emotions. *Emotion* 18, 912–915. doi: 10.1037/emo0000447

Denny, B. T., and Ochsner, K. N. (2014). Behavioral effects of longitudinal training in cognitive reappraisal. *Emotion* 14, 425–433. doi: 10.1037/a0035276

Ehret, A. M., Kowalsky, J., Rief, W., Hiller, W., and Berking, M. (2014). Reducing symptoms of major depressive disorder through a systematic training of general emotion regulation skills: Protocol of a randomized controlled trial. *BMC Psychiatry* 14:20. doi: 10.1186/1471-244X-14-20

Ehring, T., Fischer, S., Schnülle, J., Bösterling, A., and Tuschen-Caffier, B. (2008). Characteristics of emotion regulation in recovered depressed versus never depressed individuals. *Personal. Individ. Diff.* 44, 1574–1584. doi: 10.1016/j.paid.2008.01.013

Everaert, J., Grahek, I., Duyck, W., Buelens, J., Van den Bergh, N., and Koster, E. H. (2017). Mapping the interplay among cognitive biases, emotion regulation, and depressive symptoms. *Cogn. Emot.* 31, 726–735. doi: 10.1080/02699931.2016.1144561

Everaert, J., Koster, E. H. W., and Derakshan, N. (2012). The combined cognitive bias hypothesis in depression. *Clin. Psychol. Rev.* 32, 413–424. doi: 10.1016/j.cpr.2012.04.003

Fadok, J. P., Markovic, M., Tovote, P., and Lüthi, A. (2018). New perspectives on central amygdala function. *Curr. Opin. Neurobiol.* 49, 141–147. doi: 10.1016/j.conb.2018.02.009

Forgeard, M. J. C., Haigh, E. A. P., Beck, A. T., Davidson, R. J., Henn, F. A., Maier, S. F., et al. (2011). Beyond depression: Toward a process-based approach to research, diagnosis, and treatment. *Clin. Psychol. Sci. Prac.* 18, 275–299. doi: 10.1111/j.1468-2850.2011.01259.x

Forkmann, T., Scherer, A., Pawelzik, M., Mainz, V., Drueke, B., Boecker, M., et al. (2014). Does cognitive behavior therapy alter emotion regulation in inpatients with a depressive disorder? *Psychol. Res. Behav. Manage.* 7, 147–153. doi: 10.2147/PRBM.S59421

Garnefski, N., Kraaij, V., and van Etten, M. (2005). Specificity of relations between adolescents' cognitive emotion regulation strategies and Internalizing and Externalizing psychopathology. *J. Adolesc.* 28, 619–631. doi: 10.1016/j.adolescence.2004.12.009

Gross, J. J., and John, O. P. (2003). Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *J. Personal. Soc. Psychol.* 85, 348–362. doi: 10.1037/0022-3514.85.2.348

Hayes, A. F. (2012). *PROCESS: A versatile computational tool for observed variable mediation, moderation, and conditional process modeling* [White paper]. Available online at: http://www.afhayes.com/public/process2012.pdf

Hermann, A., Bieber, A., Keck, T., Vaitl, D., and Stark, R. (2014). Brain structural basis of cognitive reappraisal and expressive suppression. *Soc. Cogn. Affect. Neurosci.* 9, 1435–1442. doi: 10.1093/scan/nst130

Kanske, P., Heissler, J., Schonfelder, S., and Wessa, M. (2012). Neural correlates of emotion regulation deficits in remitted depression: The influence of regulation strategy, habitual regulation use, and emotional valence. *Neuroimage* 61, 686–693. doi: 10.1016/j.neuroimage.2012.03.089

Keller, M., Zweerings, J., Klasen, M., Zvyagintsev, M., Iglesias, J., Mendoza Quiñones, R., et al. (2021). fMRI Neurofeedback-Enhanced Cognitive Reappraisal Training in Depression: A Double-Blind Comparison of Left and Right vlPFC Regulation. *Front. Psychiatry* 12:715898. doi: 10.3389/fpsyt.2021.715898

Khodadadifar, T., Soltaninejad, Z., Ebneabbasi, A., Eickhoff, C. R., Sorg, C., Van Eimeren, T., et al. (2022). In search of convergent regional brain abnormality in cognitive emotion regulation: A transdiagnostic neuroimaging meta-analysis. *Hum. Brain Mapp.* 43, 1309–1325. doi: 10.1002/hbm.25722

Knyazev, G. G., Bazovkina, D. V., Savostyanov, A. N., Naumenko, V. S., Kuznetsova, V. B., and Proshina, E. A. (2017). Suppression mediates the effect of 5-HTTLPR by stress interaction on depression. *Scand. J. Psychol.* 58, 373–378. doi: 10.1111/sjop.12389

Kudinova, A. Y., James, K., and Gibb, B. E. (2018). Cognitive Reappraisal and Depression in Children with a Parent History of Depression. *J. Abnormal Child Psychol.* 46, 849–856. doi: 10.1007/s10802-017-0333-2

Moore, R., Gillanders, D., and Stuart, S. (2022). The Impact of Group Emotion Regulation Interventions on Emotion Regulation Ability: A Systematic Review. *J. Clin. Med.* 11:2519. doi: 10.3390/jcm11092519

Morawetz, C., Bode, S., Baudewig, J., and Heekeren, H. R. (2017). Effective amygdala-prefrontal connectivity predicts individual differences in successful emotion regulation. *Soc. Cogn. Affect. Neurosci.* 12, 569–585. doi: 10.1093/scan/nsw169

Morawetz, C., Bode, S., Baudewig, J., Kirilina, E., and Heekeren, H. R. (2016). Changes in Effective Connectivity Between Dorsal and Ventral Prefrontal Regions Moderate Emotion Regulation. *Cereb. Cortex* 26, 1923–1937. doi: 10.1093/cercor/bhv005

Muscatell, K. A., Dedovic, K., Slavich, G. M., Jarcho, M. R., Breen, E. C., Bower, J. E., et al. (2015). Greater amygdala activity and dorsomedial prefrontal–amygdala coupling are associated with enhanced inflammatory responses to stress. *Brain Behav. Immun.* 43, 46–53. doi: 10.1016/j.bbi.2014.06.201

Nowlan, J. S., Wuthrich, V. M., and Rapee, R. M. (2016). The impact of positive reappraisal on positive (and negative) emotion among older adults. *Int. Psychogeriatr.* 28, 681–693. doi: 10.1017/S1041610215002057

Pan, J., Zhan, L., Hu, C., Yang, J., Wang, C., Gu, L., et al. (2018). Emotion Regulation and Complex Brain Networks: Association Between Expressive Suppression and Efficiency in the Fronto-Parietal Network and Default-Mode Network. *Front. Hum. Neurosci.* 12:70. doi: 10.3389/fnhum.2018.00070

Papousek, I., Weiss, E. M., Perchtold, C. M., Weber, H., de Assunção, V. L., Schulter, G., et al. (2017). The capacity for generating cognitive reappraisals is reflected in asymmetric activation of frontal brain regions. *Brain Imaging Behav.* 11, 577–590. doi: 10.1007/s11682-016-9537-2

Perchtold, C. M., Fink, A., Rominger, C., Weber, H., de Assunção, V. L., Schulter, G., et al. (2017). Reappraisal inventiveness: Impact of appropriate brain activation during efforts to generate alternative appraisals on the perception of chronic stress in women. *Anxiety Stress Coping* 31, 206–221. doi: 10.1080/10615806.2017.1419205

Perchtold, C. M., Papousek, I., Fink, A., Weber, H., Rominger, C., and Weiss, E. M. (2019). Gender Differences in Generating Cognitive Reappraisals for Threatening Situations: Reappraisal Capacity Shields Against Depressive Symptoms in Men, but Not Women. *Front. Psychol.* 10:553. doi: 10.3389/fpsyg.2019.00553

Phillips, M. L., Drevets, W. C., Rauch, S. L., and Lane, R. (2003). Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol. Psychiatry* 54, 515–528. doi: 10.1016/S0006-3223(03)00171-9

Picó-Pérez, M., Radua, J., Steward, T., Menchón, J. M., and Soriano-Mas, C. (2017). Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 79, 96–104. doi: 10.1016/j.pnpbp.2017.06.001

Pocock, S. J., and Simon, R. (1975). Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 31, 103–115. doi: 10.2307/2529712

Radke, S., Hoffstaedter, F., Löffler, L., Kogler, L., Schneider, F., Blechert, J., et al. (2018). Imaging the up's and down's of emotion regulation in lifetime depression. *Brain Imaging Behav.* 12, 156–167. doi: 10.1007/s11682-017-9682-2

Radkovsky, A., McArdle, J. J., Bockting, C. L., and Berking, M. (2014). Successful emotion regulation skills application predicts subsequent reduction of symptom severity during treatment of major depressive disorder. *J. Consult. Clin. Psychol.* 82, 248–262. doi: 10.1037/a0035828

Reilly, L. C., Ciesla, J. A., Felton, J. W., Weitlauf, A. S., and Anderson, N. L. (2012). Cognitive vulnerability to depression: A comparison of the weakest link, keystone and additive models. *Cogn. Emot.* 26, 521–533. doi: 10.1080/02699931.2011.595776

Rood, L., Roelofs, J., Bögels, S. M., and Arntz, A. (2012). The Effects of Experimentally Induced Rumination, Positive Reappraisal, Acceptance, and Distancing When Thinking About a Stressful Event on Affect States in Adolescents. *J. Abnorm. Child Psychol.* 40, 73–84. doi: 10.1007/s10802-011-9544-0

Sfärlea, A., Takano, K., Buhl, C., Loechner, J., Greimel, E., Salemink, E., et al. (2021). Emotion Regulation as a Mediator in the Relationship Between Cognitive Biases and Depressive Symptoms in Depressed, At-risk and Healthy Children and Adolescents. *Res. Child Adolesc. Psychopathol.* 49, 1345–1358. doi: 10.1007/s10802-021-00814-z

Shore, T., Cohen Kadosh, K., Lommen, M., Cooper, M., and Lau, J. Y. F. (2017). Investigating the effectiveness of brief cognitive reappraisal training to reduce fear in adolescents. *Cogn. Emot.* 31, 806–815. doi: 10.1080/02699931.2016.1159542

Smith, K. (2014). Mental health: A world of depression. *Nature* 515, 180–181. doi: 10.1038/515180a

Smoski, M. J., Keng, S., Ji, J. L., Moore, T., Minkel, J., and Dichter, G. S. (2015). Neural indicators of emotion regulation via acceptance vs. reappraisal in remitted major depressive disorder. *Soc. Cogn. Affect. Neurosci.* 10, 1187–1194. doi: 10.1093/scan/nsv003

Stephanou, K., Davey, C. G., Kerestes, R., Whittle, S., and Harrison, B. J. (2017). Hard to look on the bright side: Neural correlates of impaired emotion regulation in depressed youth. *Soc. Cogn. Affect. Neurosci.* 12, 1138–1148. doi: 10.1093/scan/nsx039

Suri, G., Whittaker, K., and Gross, J. J. (2015). Launching reappraisal: It's less common than you might think. *Emotion* 15, 73–77. doi: 10.1037/emo0000011

Troy, A. S., Shallcross, A. J., and Mauss, I. B. (2013). A Person-by-Situation Approach to Emotion Regulation: Cognitive Reappraisal Can Either Help or Hurt. Depending on the Context. *Psychol. Sci.* 24, 2505–2514. doi: 10.1177/0956797613496434

Troy, A. S., Wilhelm, F. H., Shallcross, A. J., and Mauss, I. B. (2010). Seeing the silver lining: Cognitive reappraisal ability moderates the relationship between stress and depressive symptoms. *Emotion* 10, 783–795. doi: 10.1037/a0020262

Tsumura, H., Sensaki, J., and Shimada, H. (2015). Stress-induced cortisol is associated with generation of non-negative interpretations during cognitive reappraisal. *BioPsychoSoc. Med.* 9:23. doi: 10.1186/s13030-015-0049-x

Wang, L., Liu, H., Li, Z., and Du, W. (2007). Reliability and validity of emotion regulation questionnaire Chinese revised version. *Chin. J. Health Psychol.* 15, 503–505.

Wang, L., Paul, N., Stanton, S. J., Greeson, J. M., and Smoski, M. J. (2013). Loss of Sustained Activity in the Ventromedial Prefrontal Cortex in Response to Repeated Stress in Individuals with Early-Life Emotional Abuse: Implications for Depression Vulnerability. *Front. Psychol.* 4:320. doi: 10.3389/fpsyg.2013.00320

Wang, X., Feng, Z., Zhou, D., Lei, X., Liao, T., Zhang, L., et al. (2014). Dissociable Self Effects for Emotion Regulation: A Study of Chinese Major Depressive Outpatients. *Biomed. Res. Int.* 2014:390865. doi: 10.1155/2014/390865

Wang, X., Jiang, C., Li, J., and Feng, Z. (2015). Neural substrates of abnormal positive emotion regulation in depressed patients. *Chin. J. Clin. Psychol.* 23, 615–620.

Wang, X., Zhou, X., Dai, Q., Ji, B., and Feng, Z. (2017). The Role of Motivation in Cognitive Reappraisal for Depressed Patients. *Front. Hum. Neurosci.* 11:516. doi: 10.3389/fnhum.2017.00516

Weber, H., Loureiro De Assunção, V., Martin, C., Westmeyer, H., and Geisler, F. C. (2013). Reappraisal inventiveness: The ability to create different reappraisals of critical situations. *Cogn. Emot.* 28, 345–360. doi: 10.1080/02699931.2013.832152

Weytens, F., Luminet, O., Verhofstadt, L. L., and Mikolajczak, M. (2014). An integrative theory-driven positive emotion regulation intervention. *PLoS One* 9:e95677. doi: 10.1371/journal.pone.0095677

Wu, H., Sun, H., Wang, C., Yu, L., Li, Y., Peng, H., et al. (2017). Abnormalities in the structural covariance of emotion regulation networks in major depressive disorder. *J. Psychiatric. Res.* 84, 237–242. doi: 10.1016/j.jpsychires.2016.10.001

Wu, X., Guo, T., Tan, T., Zhang, W., Qin, S., Fan, J., et al. (2019). Superior emotional regulating effects of creative cognitive reappraisal. *Neuroimage* 200, 540–551. doi: 10.1016/j.neuroimage.2019.06.061

Wu, X., Guo, T., Tang, T., Shi, B., and Luo, J. (2017). Role of Creativity in the Effectiveness of Cognitive Reappraisal. *Front. Psychol.* 8:1598. doi: 10.3389/fpsyg.2017.01598

Wu, X., Xiao, F., and Luo, J. (2022). The neural mechanism and transfer effect of creative cognitive reappraisal in negative emotion regulation. *Adv. Psychol. Sci.* 30, 477–485. doi: 10.3724/SP.J.1042.2022.00477

Yan, X., Zhang, R., and Feng, Z. (2017). Development of negative cognitive processing bias questionnaire. *J. Army Med. Univers.* 39, 2329–2334.

Yuan, J., Liu, Y., and Yang, J. (2014). The influences of emotional coping style and cognitive training on adolescents' vulnerability to affective disturbances. *Adv. Psychol. Sci.* 22, 1062–1074. doi: 10.3724/SP.J.1042.2014.01062

Zeier, P., Meine, L. E., and Wessa, M. (2021). It's worth the trouble: Stressor exposure is related to increased cognitive reappraisal ability. *Stress and Health* [Epub ahead of print]. doi: 10.1002/smi.3101

Zeier, P., Sandner, M., and Wessa, M. (2020). Script-based Reappraisal Test introducing a new paradigm to investigate the effect of reappraisal inventiveness on reappraisal effectiveness. *Cogn. Emot.* 34, 793–799. doi: 10.1080/02699931.2019.1663153

Zhang, J., and Feng, Z. (2016). Interpretation bias under different conditions of self-relevance in individuals with depressed mood. *J. Army Med. Univers.* 38, 647–651.

Zhang, K., Wang, C., and Wang, J. (2016). The effectiveness of reappraisal and distractive emotion regulation in depression patients: ERPs study. *Psychol. Explor.* 36, 245–250.

Zilverstand, A., Parvaz, M. A., and Goldstein, R. Z. (2017). Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. *Neuroimage* 151, 105–116. doi: 10.1016/j.neuroimage.2016.06.009

Zweerings, J., Sarkheil, P., Keller, M., Dyck, M., Klasen, M., Becker, B., et al. (2020). Rt-fMRI neurofeedback-guided cognitive reappraisal training modulates amygdala responsivity in posttraumatic stress disorder. *NeuroImage Clin.* 28:102483. doi: 10.1016/j.nicl.2020.102483

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High-frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex may reduce impulsivity in patients with methamphetamine use disorders: A pilot study

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Background: Individuals who use methamphetamine (MA) for a long period of time may experience decreased inhibition and increased impulsivity. In order to reduce impulsivity or improve inhibitory control ability, high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) has attracted much attention of researchers. Recent studies on addiction have shown that rTMS can stimulate different brain regions to produce different therapeutic effects. Recent work also suggests that HF-rTMS over right dorsolateral prefrontal cortex (DLPFC) does not affect the impulsivity of patients with alcohol use disorder; while HF-rTMS over left DLPFC could improve the impulsivity of patients with alcohol use disorder and cigarette smokers. However, it should be noted that empirical studies applying HF-rTMS over left DLPFC of patients with MA use disorders (MAUD) (to evaluate its effect on impulsivity) are still lacking.

Methods: Twenty-nine patients with MAUD underwent five sessions of HF-rTMS on the left DLPFC per week for 4 consecutive weeks. The cue-induced craving and stop-signal and NoGo task were assessed pre-rTMS and post-rTMS (at the end of the 4-week rTMS treatment). In addition, 29 healthy controls were recruited. There was no rTMS intervention for the controls, the performance of the stop-signal and NoGo task was evaluated on them.

Results: In total, HF-rTMS of the left DLPFC significantly decreased MA-dependent patients' cue-induced craving and stop-signal reaction time (SSRT). For SSRT, the pre-test of experimental group was significantly higher

than the score of control group. In the experimental group, the pre-test score was significantly higher than the post-test score. For Go and stop-signal delay (SSD), the pre-test scores of the experimental group was significantly lower than the scores of the control group. No significant difference was found between the pre-test and the post-test scores of the experimental group.

Conclusion: Add-on HF-rTMS of left DLPFC may be an effective intervention for reducing impulsivity and cue-induced craving of patients with MAUD. Future research with a control group of MAUD that does not undergo the treatment is needed to confirm the effectiveness.

KEYWORDS

rTMS, left DLPFC, MAUD, craving, impulsivity

Introduction

Methamphetamine (MA) is a highly addictive and euphoric stimulant, which represents one of the largest illegal drugs in the world, and it has become more prevalent than other amphetamine derivatives (Jones et al., 2022). Among the registered drug abusers, there are approximately 1.35 million MA abusers, accounting for 56.1% of all drug abusers (People's Republic of China Central Government | Ministry of Public Security, 2019). Generally, the use of amphetamine-like stimulants, including MA, is a major matter of public concern, representing the second most used substance after marijuana according to the United Nations Office on Drugs and Crime. It has been reported that repeated intake of MA would lead to drug addiction, the inability to control intake, strong drug craving, and the reduced prefrontal cortex function (Perry and Carroll, 2008; Koob and Volkow, 2010; Jentsch and Pennington, 2014; Sjoerds et al., 2014).

Impulsivity can be defined behaviorally as "actions, which are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation, mainly resulting in undesirable consequences" (Dawe et al., 2004; Dalley and Robbins, 2017). The inability to stop an initiated response can be evaluated by a stop-signal task (SST) (Verbruggen and Logan, 2008). The task determines the time required between the Go signal and the stop signal for participants being capable of stopping the initiated response within a 50% probability range (i.e., stop-signal reaction time). That is to say, the higher the stop-signal reaction-time (SSRT), the more impulsive the individual is (Hamilton et al., 2015). Previous studies have shown that individuals with substance use disorders (including MA) exhibit an impaired performance on stop-signal impulsivity tasks (Lipszyc and Schachar, 2010; Smith et al., 2014). This may be attributed to the chronic damage of the substance to the dopaminergic and serotonergic prefrontal-subcortical networks, which is related to motor control (Volkow et al., 2001), and therefore, may affect performance on response inhibition task.

In order to reduce impulsivity or improve inhibitory control ability, transcranial magnetic stimulation (TMS) has attracted much attention of researchers (Bellamoli et al., 2014). TMS is a robust magnetic pulse generated by an electromagnetic coil, which can penetrate the skull and alter neural activity of the skull base tissue. Pulses delivered in series are called repetitive TMS (rTMS). Depending on the pulse frequency, either inhibitory [low-frequency (LF) $\leq$ 1 Hz] or excitatory [high-frequency (HF) $\geq$ 5 Hz] effects can be produced (Rossi et al., 2009; Guse et al., 2010). Effects of rTMS treatment include enhancing the release of dopamine in the limbic circuit of the brain and affecting the excitability of the brain nerves, ultimately lead to changes in neural adaptation (Strafella et al., 2001), continuous changes in cortical plasticity (Hallett, 2007), and reorganization of network functional connections (Philip et al., 2018). The dorsolateral prefrontal cortex (DLPFC) is frequently selected as the target region in inhibitory control networks (Ridderinkhof et al., 2004). Previous studies that applied HF-rTMS over DLPFC of patients with substance use disorders have obtained inconsistent results on impulsivity measures: for instance, it has been shown that while one-time frequency of 10 Hz does not improve accuracy on the Go-NoGo task (Herremans et al., 2013); quartic frequency of 10 Hz stimuli could improve accuracy on the Go-NoGo task (Del Felice et al., 2016) in alcohol-dependent patients. In nicotine-dependent patients, a single-frequency of 10 or 20 Hz could improve performance of a delay discounting task (Sheffer et al., 2013), which demonstrates that it could reduce impulsivity in patients with nicotine use disorders. Another study uses the 2-choice oddball paradigm, and the results show that low-frequency rTMS could attenuate the craving and impulsivity of patients with MAUD (Yuan et al., 2020). Up to now, no study has

examined the effects of HF-rTMS on impulsivity in patients with MAUD, as measured by the stop-signal and NoGo task.

rTMS could reduce cue-induced craving in patients with MAUD (Liu et al., 2017, 2020b), and some studies have shown that craving is positively correlated with impulsivity (Mathew et al., 2015; Li et al., 2021). Recent work also suggests that after the first treatment, there is no change in craving of patients with MAUD, while after 5 HF-rTMS treatment, there is a significant reduction in craving; while sham stimulation does not have the same effect (Su et al., 2017). In addition to reducing cravings, it suggests that long-term HF rTMS can improve withdrawal symptoms, anxiety and depression scores, sleep quality and cognition in patients with MA or heroin use disorders (Su et al., 2017; Liang et al., 2018; Lin et al., 2019). Other studies have shown that HF-rTMS of the left DLPFC may be an effective intervention for the treatment of cocaine use disorder symptoms such as anhedonia and craving, which needs to be further explored in larger placebo-controlled studies (Terraneo et al., 2016; Pettorruso et al., 2018).

In the present study, we investigated the effects of HF-rTMS on impulsivity of patients with MAUD. We hypothesized that repeated add-on HF-rTMS of left DLPFC may be effective in improving impulse control ability in patients with MAUD, as well as reducing their cue-induced craving. Therefore, we proposed that patients with MAUD who received HF-rTMS would show no difference in impulsivity compared with healthy controls (HCs). In the present study, we recruited 29 patients with MAUD and 29 HCs. Patients with MAUD were assessed with the stop-signal and NoGo task 1 day before and 1 day after HF-rTMS treatment, and healthy controls were assessed at baseline.

Methods

Participants

A total of 29 male patients with MAUD, right-handed, and were admitted to an addiction rehabilitation center in Zhejiang Province (China), were recruited. Inclusion criteria were as follows:(1) patients who aged 18–65 years old; (2) patients who had a recurrent history of MAUD (DSM-V diagnosis, urine test was positive on admission, abstinence thereafter); (3) patients with a mild or higher level of drug craving; (4) patients who signed the written informed consent form; (5) patients who had not received TMS treatment at 6 months prior to the experiment; (6) patients who did not receive other therapeutic strategies, such as pharmacological or psychological treatment, etc., during the study. Exclusion criteria were as follows: (1) patients with neurological disorders; (2) patients with cardiovascular diseases; (3) patients with other serious physical diseases; (4) patients with psychiatric disorders; (5) patients with a history of brain injury; (6) patients with a history of epilepsy; (7) pacemaker wearers; (8) participants who, according to an investigator's judgment, were not eligible or had a poor compliance. Withdrawal and termination criteria were as follows: (1) serious violations of the clinical trial protocol; (2) participants who could not follow the protocol for treatment and had a poor compliance; (3) intolerable adverse events; (4) subjects who voluntarily withdrew the study at any time. An investigator determined whether a participant needs to withdraw or continue the trial based on the above-mentioned criteria. Every effort must be made to complete the efficacy and safety checklists specified in the protocol at the time of withdrawal from the trial, and to fully document the reasons for withdrawal and adverse effects. An investigator attempted to suggest or provide new or alternative treatment methods to participants based on their clinical conditions. In addition, 29 male HCs without a history of major neurological or psychiatric diseases from a volunteer group in Brain and Cognitive Neuroscience at Liaoning Normal University (Dalian, China) were recruited, the two groups were matched for education and age. The study was approved by the Ethics Committee of Nanjing Normal University (Nanjing, China; Approval No. 2017-004) and was registered in the Chinese Clinical Trial Registration Center (no. ChiCTR17013610[1]), and the written informed consent forms were signed by all participants prior to beginning the study (**Figure 1A**).

Assessment of cue-induced craving

For the assessment of cue-induced craving, participants watched a video about MA use for 5 min, the evaluation was performed as described previously (Liu et al., 2020b).

Participants were asked to express their desire to use drugs immediately and mark it on the visual analogue scale of 0–100. The question was scored as follows: What is the level of your craving for MA? (0 indicates absolutely unwilling and 100 represents extremely tendentious). Participants' data were fully kept confidential and were not be provided to the judiciary, and the authenticity of videos was evaluated.

Implementation of the HF-rTMS and study design

Consistent with previous study (Liu et al., 2020a), the stimulation protocol included 20 weekdays (once a day, 5 days on, 2 days off/week, 10 Hz frequency, pulse intensity 100% of the resting motor threshold, 5 s on, 10 s off, repeated for 40 times, 2,000 pulses) and targeted the left DLPFC, which was performed in this study. During the operation, the stimulus intensity was

1 http://www.chictr.org.cn

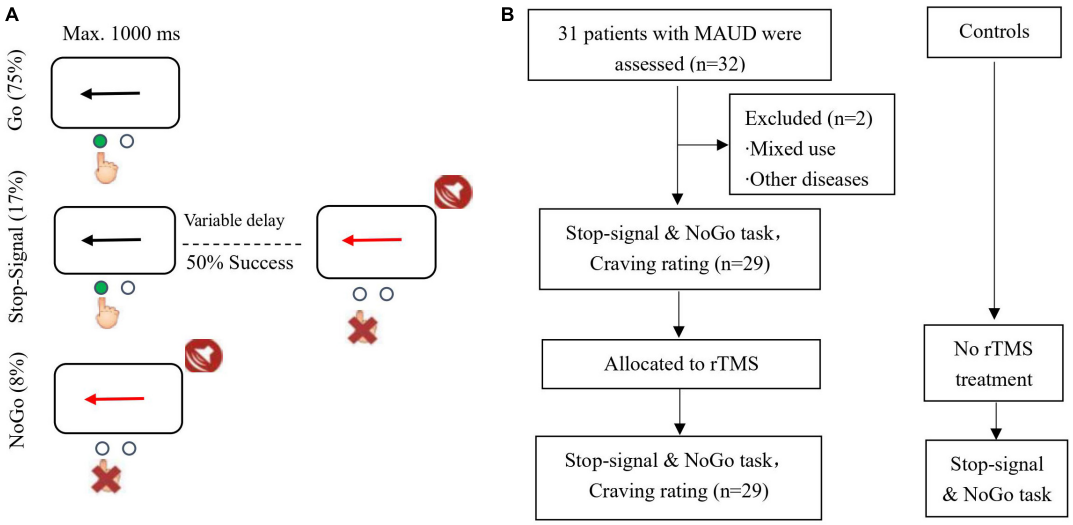

FIGURE 1
(A) Task and stimuli. **(B)** Study design. MAUD, methamphetamine use disorder.

adjusted according to participants' tolerability, single-pulse TMS was used to measure the motor threshold of the motor cortex, and it was adjusted until the response of thumb muscle was observed in 5 out of 10 stimuli. During the treatment, the coil was placed in the left prefrontal area, 5 cm away from the scalp area of the measured movement threshold (Liu et al., 2017, 2019). The HF-rTMS was applied on the left DLPFC using a CCY-IA TMS device (Yiruide Biotechnology Co., Ltd., Wuhan, China) and a circular coil was used.

Before commencing the study, an investigator screened MA addicts who were voluntarily participated, excluded those cases with contraindications to TMS, obtained their consent, and collected their basic data, including their full-name, age, years of drug use, maximum amount of drug consumption per session, maximum amount of use per month, and type of addiction (excluding mixed use of other drugs, such as heroin and marijuana). Then, an investigator assessed the craving scores of the experimental group and eliminated participants with craving scores of < 40. Twenty-nine patients with MAUD underwent five sessions of HF-rTMS on the left DLPFC per week for 4 consecutive weeks. The cue-induced craving and stop-signal and NoGo task were assessed pre-rTMS and post-rTMS (at the end of the 4-week rTMS treatment). However, HCs were not asked to receive TMS treatment and only the stop signal and NoGo task was conducted. During treatment, participants might experience discomfort or side effects. Therefore, we used a self-rating scale for patient-perceived side effects. The side effects included headache, neck pain, scalp pain, tingling sensation, itching, burning sensation, skin redness, sleepiness, lack of concentration and changes in mood, discomfort at the site of stimulation, etc. Each side effect was scored on a scale of 1–10. After each treatment, side effects were monitored.

Stop-signal and NoGo task: This task consisted of randomly interspersed NoGo and stop-signal trials with inclusion of 360 Go (75%), 40 NoGo (8%), and 80 stop-signal trials (17%). In the Go trials, participants responded to the black arrow (1000 ms) in the left and right directions by pressing a button with their right hand. Participants could respond to the questions with either the index finger (pressing the left arrow) or the middle finger (pressing the right arrow). In the stop-signal trials, the initial response was prompted by the left or right black arrow, while when the stop-signal was delayed, the arrow color changed to red and appeared simultaneously with the sound. At this time, participants were asked to avoid responding. The stop-signal delay (SSD) maintained a successful inhibition of 50% by using an ascending or descending algorithm with an initial estimation of 250 ms varying from trial to trial (Chamberlain et al., 2007). SSD indicates the time interval between response signal and stop signal. This is similar to the tracking algorithm used in a previous stop-signal task imaging study (Cubillo et al., 2014). In the NoGo task, participants were asked to avoid responding to the red arrow (1000 ms) and the accompanying beep, which would be equivalent to a 0 s SSD. SSRT indicates the time from the appearance of the stop signal to the completion of the stop task, i.e., the internal reaction time of the subject when successfully suppresses an action impulse. SSRT is the most important indicator in the stop signal task, responding to the subject's reaction speed to the stop signal. Most studies have used it as a direct indicator of response inhibition ability to assess whether the subject has a deficit in response inhibition. A higher SSRT has been suggested to represent that participant has a longer stop-signal response time, a poorer behavioral inhibition, and a higher impulsivity. In contrast, a lower SSRT

indicates that participants have a shorter stop signal response time, a better behavioral inhibition, and they can promptly inhibit impulsive behaviors. Participants were asked to operate with their right hand and ensure that they fully understood the cognitive task before performing it, so that they could respond as quickly as possible and ensure the accuracy. The participants were asked to remain quiet and not to interact with each other while waiting. They were asked to stay focused during the task. The stop-signal and NoGo task are shown in **Figure 1B**.

Statistical analysis

Statistical analysis was performed using the SPSS 19.0 software (IBM Corp., Armonk, NY, United States). The independent-sample *t*-test was used to compare differences in demographic variables between the experimental and control groups. The independent-sample *t*-test was employed to compare differences in the performance of the stop-signal and NoGo task between the experimental group and the control group. The paired *t*-test was utilized to compare differences in stop-signal and NoGo task between the pre and post experimental group. Pearson correlation analysis was adopted to analyze the relationship between experiment variables (craving, SSRT, Go, SSD, etc.) and demographic variables. $p < 0.05$ was considered statistically significant.

Results

Participants' demographic characteristics

The participants' demographic characteristics are listed in **Table 1**, and no significant difference could be found in age and education between the experimental group and the control group ($M \pm$ SEM).

TABLE 1 Participants' demographic characteristics ($M \pm SEM$).

Variable	Experimental group	Control group	*t*	*P*
Sex	Male	Male	–	–
Age (years)	35.66 ± 1.49	36.55 ± 1.80	0.38	0.70
Education (years)	8.90 ± 0.39	9.69 ± 0.39	1.66	0.10
Duration of drug use (years)	8.86 ± 0.63	–	–	–
Maximum usage per session (g)	0.93 ± 0.09	–	–	–
Monthly usage (g)	16.31 ± 2.41	–	–	–

There was no significant difference in age [$t(56) = 0.38$, $p = 0.70$] and education [$t(56) = 1.66$, $p = 0.10$] between the experimental group and the control group.

Comparison between the pre-test experimental group and the control group

The independent-sample *t*-test was employed to compare SSRT, Go, and SSD between the experimental group (pre-test) and the control group. For SSRT, the pre-test of experimental group ($M = 285.53$, SEM = 7.90) was significantly higher than the score of control group ($M = 257.59$, SEM = 6.71), $t(56) = 2.38$, $p < 0.05$. Therefore, it suggested that patients with long-term MAUD showed decreased inhibitory control ability. For Go, the pre-test of experimental group ($M = 490.19$, SEM = 16.48) was significantly lower than the baseline score of control group ($M = 555.74$, SEM = 17.06), $t(56) = 3.31$, $p < 0.01$. The Go reaction time of patients with MAUD was significantly lower than that of health control, suggesting that patients with MAUD were deficient in behavioral inhibition and showed more inhibition control disorders. This finding is consistent with previous research (Qi et al., 2022), which reports impaired inhibitory control in internet addiction disorder. For SSD, the pre-test of experimental group ($M = 204.66$, SEM = 20.42) was significantly lower than the baseline score of control group ($M = 298.15$, SEM = 17.18), $t(56) = 3.68$, $p < 0.001$.

Comparison between pre- and post-test scores of the experimental group

The paired *t*-test was used to compare craving score between the experimental group of pre- (65.17 ± 3.20) and post-test (35.86 ± 3.20). It was revealed that HF-rTMS of the left DLPFC decreased craving score [$t(28) = 7.33$, $p < 0.001$] of patients with MAUD.

The paired *t*-test was utilized to compare the SSRT, Go, and SSD between the experimental group of pre-test and post-test. For SSRT, the pre-test experimental group ($M = 285.53$, SEM = 7.90) was significantly higher than the post-test experimental group ($M = 249.62$, SEM = 12.11), $t(28) = 2.77$, $p < 0.05$. This indicated that HF-rTMS intervention could reduce impulsivity and improve inhibitory control ability of patients with MAUD. For Go, there was no significant difference between the pre-test experimental group ($M = 490.19$, SEM = 16.48) and the post-test experimental group ($M = 483.25$, SEM = 20.17), $t(28) = 0.71$, $p = 0.49$. For SSD, there was no significant difference between the pre-test experimental group ($M = 204.66$, SEM = 20.42) and the post-test experimental group ($M = 233.63$, SEM = 27.03), $t(28) = -1.63$, $p = 0.12$, (**Figure 2**).

In conclusion, the HF-rTMS treatment had an effect on SSRT, but not on Go and SSD in the stop-signal and NoGo task of patients with MAUD.

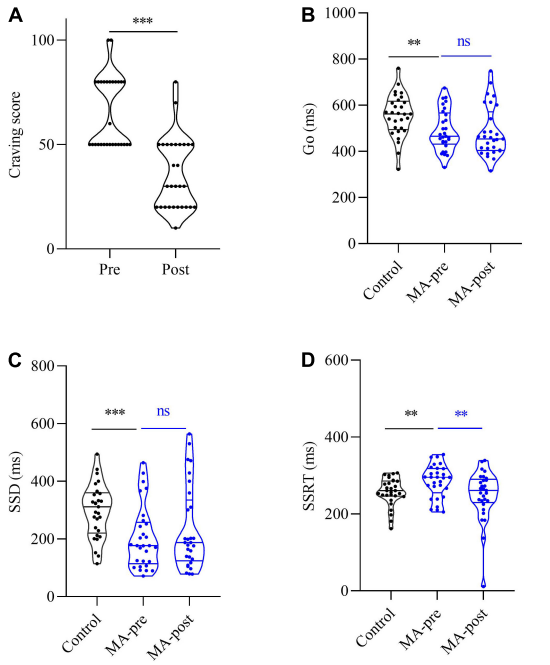

FIGURE 2
Comparison craving score between the experimental group of pre- and post-test. **(A)** The pre-test was significantly higher than the post-test score of the experimental group [$t(28) = 7.33$, $p < 0.001$] of patients with MAUD. Comparison of SST and NoGo between experimental and control groups. **(B)** For Go, the pre-test of the experimental group was significantly lower than the score of the control group [$t(56) = 3.31$, $p < 0.01$], and the post-test of the experimental group was also significantly lower than the score of the control group [t (56) = 3.21, $p < 0.01$]. No significant difference was found between the pre-test and the post-test scores of the experimental group [$t(28) = 0.71$, $p = 0.49$]. **(C)** For SSD, the pre-test of the experimental group was significantly lower than the score of the control group [$t(56) = 3.68$, $p < 0.001$], and the post-test of the experimental group was also significantly lower than the score of the control group [$t(56) = 2.32$, $p < 0.05$]. No significant difference was found between the pre-test and the post-test scores of the experimental group. **(D)** For SSRT, the pre-test of the experimental group was significantly higher than the score of the control group [$t(56) = 2.38$, $p < 0.05$]. There was no significant difference between the post-test of the experimental group and the score of the control group [$t(56) = 0.54$, $p > 0.05$]. The pre-test was significantly higher than the post-test score of the experimental group [$t(28) = 2.77$, $p < 0.05$]. [$t(28) = -1.63$, $p = 0.12$]. The symbol * represents $p < 0.05$, ** represents p < 0.01, and *** represents $p < 0.001$.

Correlation between test scores and demographic variables

Pearson correlation analysis was used to analyze the correlation between SSRT, Go, SSD and demographic variables in the experimental group. The results showed that pre- SSRT was significantly positively correlated with age ($r = 0.57$, $p < 0.01$) (**Figure 3**). This indicated that the older the participants, the greater the SSRT; while post-SSRT

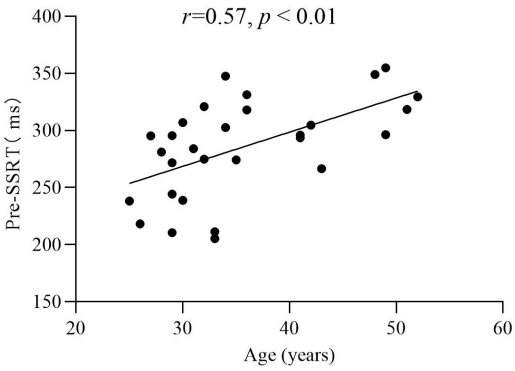

FIGURE 3
Correlation analysis of the pre-SSRT and age in the experimental group ($r = 0.57$, $p < 0.01$).

($r = 0.03$, $p > 0.05$), pre- ($r = -0.08$, $p > 0.05$), post-Go ($r = -0.13$, $p > 0.05$), pre- ($r = -0.28$, $p > 0.05$), and post-SSD ($r = -0.11$, $p > 0.05$), these variables were not significantly correlated with age. The correlation between pre-SSRT and years of drug use ($r = -0.03$, $p > 0.05$), maximum consumption per time ($r = -0.06$, $p > 0.05$), and monthly use ($r = 0.14$, $p > 0.05$), respectively, was not significant. The correlation between post-SSRT and years of drug use ($r = 0.03$, $p > 0.05$), maximum consumption pre time ($r = -0.12$, $p > 0.05$), and monthly use ($r = -0.04$, $p > 0.05$), respectively, was not significant. The pre- and post-test differences of SSRT, Go and SSD were not significantly correlated with any demographic variables (all $p > 0.05$).

Safety and tolerability

In the experimental group, a total of 580 treatments were performed. There were 9 cases of mild headache after stimulation (1.6%) of 3 subjects, 2 reported 4 times and 1 reported 1 time, 6 cases of scalp pain (1.0%) of 2 subjects who reported 3 times respectively, 10 cases of sleepiness (1.7%) of 6 subjects, 4 reported 2 times and 2 reported 1 time, and 12 cases of discomfort after treatment (2.1%) of 9 subjects, 6 reported 1 time and 3 reported 2 times. Three subjects reported both headaches and discomfort after treatment. All of these discomforts disappeared in the follow-up 1 week later.

Discussion

The present study aimed to investigate the effects of repeated HF-rTMS treatment on impulsivity in patients with MAUD. The HF-rTMS treatment was well tolerated and no serious side effects could be observed. The stop-signal and NoGo task

was used to evaluate the impulsivity of patients with MAUD before and after HF-rTMS treatment. The results of the present study suggested that repeated HF-rTMS may be effective in reducing drug-induced craving in patients with MAUD, as well as improving their impulse control ability.

To our knowledge, this study is the first to assess the influences of HF-rTMS treatment on impulsivity in patients with MAUD, as measured by the stop-signal and NoGo task. One study explored the effects of HF-rTMS on impulsivity tasks in patients with alcohol use disorder using three tasks simultaneously—SST, Go-NoGo and delay discounting task. It was found that HF-rTMS did not improve alcohol use disorder patients' performance on impulsivity tasks (Schluter et al., 2019), and participants in the study only received 10 treatments; whereas participants in our study received five sessions of HF-rTMS on the left DLPFC per week for 4 consecutive weeks of the therapy. It might be also due to the different clinical statuses of treated participants (i.e., a poorer clinical status requires more stimulation to achieve a greater efficacy).

We will briefly outline the limitations of this study. First, our study was the absence of a sham control group receiving routine rehabilitation treatment without rTMS intervention. The patients of MAUD did not use MA during rTMS treatment, but they did normal rehabilitation exercises. Thus, the results observed in the patients of MA group could not be solely attributed to the unique effects of rTMS. Second, the study lacked associated impulsivity scales to measure impulsivity in patients with MAUD; in the future studies, some impulsivity scales should be added, such as the Barratt Impulsiveness Scale Version 11 (BIS-11), of which is able to assess motor impulsivity, cognitive impulsivity, and unplanned impulsivity of participants. Third, to some extent, in the absence of a sham control group, the placebo effect may still exist in the experiment group, the experiment perhaps is only a pilot study at present. Finally, as participants in this study were all in the same brigade in a rehabilitation center, they might exchange their physical feelings with each other during the HF-rTMS treatment.

The current study suggested that HF-rTMS might reduce impulsivity and craving of patients with MAUD. It was also found in previous research that HF-rTMS could reduce the craving of patients with heroin usage (Shen et al., 2016). However, the underlying neurophysiological mechanism has remained elusive. Psychostimulants has the potential to cause changes in the prefrontal cortex network, thereby increasing impulsive behavior (Volkow et al., 2001; Badiani et al., 2011; Ersche et al., 2011); while HF-rTMS could facilitate cortical excitability (Peterchev et al., 2012), thus improve the inhibitory control ability of addicts. In addition, it is highly crucial to indicate whether intermittent theta-burst stimulation could achieve the same effect. Thus, further studies need to be carried out to eliminate the above-mentioned deficiencies and to confirm our findings.

Conclusion

The research revealed that add-on HF-rTMS of left DLPFC might be an effective intervention for reducing impulsivity and cue-induced craving of patients with MAUD. Furthermore, future studies are required to explore the underlying cognitive and neural mechanisms.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was approved by the Ethics Committee of Nanjing Normal University (Nanjing, China; Approval No. 2017-004) and was registered in the Chinese Clinical Trial Registration Center (http://www.chictr.org.cn; no. ChiCTR17013610), and the written informed consent forms were signed by all participants prior to beginning the study.

Author contributions

QL, DD, and YS: conceptualization. YS: funding acquisition and supervision. QL and XX: investigation and writing – original draft. QL and DD: methodology. QL: project administration. QL, HC, LZ, ZZ, and DD: writing – review and editing. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Badiani, A., Belin, D., Epstein, D., Calu, D., and Shaham, Y. (2011). Opiate versus psychostimulant addiction: the differences do matter. *Nat. Rev. Neurosci.* 12, 685–700. doi: 10.1038/nrn3104

Bellamoli, E., Manganotti, P., Schwartz, R. P., Rimondo, C., Gomma, M., and Serpelloni, G. (2014). rTMS in the treatment of drug addiction: an update about human studies. *Behav. Neurol.* 2014:815215. doi: 10.1155/2014/815215

Dalley, J. W., and Robbins, T. W. (2017). Fractionating impulsivity: neuropsychiatric implications. *Nat. Rev. Neurosci.* 18, 158–171. doi: 10.1038/nrn.2017.8

Dawe, S., Gullo, M. J., and Loxton, N. J. (2004). Reward drive and rash impulsiveness as dimensions of impulsivity: implications for substance misuse. *Addict. Behav.* 29, 1389–1405. doi: 10.1016/j.addbeh.2004.06.004

Chamberlain, S. R., Del Campo, N., Dowson, J., Müller, U., Clark, L., Robbins, T. W., et al. (2007). Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder. *Biol. Psychiatry* 62, 977–984. doi: 10.1016/j.biopsych.2007.03.003

Cubillo, A., Smith, A. B., Barrett, N., Giampietro, V., Brammer, M. J., Simmons, A., et al. (2014). Shared and drug-specific effects of atomoxetine and methylphenidate on inhibitory brain dysfunction in medication-naive ADHD boys. *Cereb. Cortex* 24, 174–185. doi: 10.1093/cercor/bhs296

Del Felice, A., Bellamoli, E., Formaggio, E., Manganotti, P., Masiero, S., Cuoghi, G., et al. (2016). Neurophysiological, psychological and behavioural correlates of rTMS treatment in alcohol dependence. *Drug Alcohol Depend.* 158, 147–153. doi: 10.1016/j.drugalcdep.2015.11.018

Ersche, K. D., Barnes, A., Jones, P. S., Morein-Zamir, S., Robbins, T. W., and Bullmore, E. T. (2011). Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. *Brain* 134, 2013–2024. doi: 10.1093/brain/awr138

Guse, B., Falkai, P., and Wobrock, T. (2010). Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. *J. Neural Transm.* 117, 105–122. doi: 10.1007/s00702-009-0333-7

Hallett, M. (2007). Transcranial magnetic stimulation: a primer. *Neuron* 55, 187–199. doi: 10.1016/j.neuron.2007.06.026

Hamilton, K. R., Littlefield, A. K., Anastasio, N. C., Cunningham, K. A., Fink, L., Wing, V. C., et al. (2015). Rapid-response impulsivity: definitions, measurement issues, and clinical implications. *Personal. Disord.* 6:168. doi: 10.1037/per0000100

Herremans, S. C., Vanderhasselt, M. A., De Raedt, R., and Baeken, C. (2013). Reduced intra-individual reaction time variability during a go–NoGo task in detoxified alcohol-dependent patients after one right-sided dorsolateral prefrontal HF-rTMS session. *Alcohol Alcohol.* 48, 552–557. doi: 10.1093/alcalc/agt054

Jentsch, J. D., and Pennington, Z. T. (2014). Reward, interrupted: inhibitory control and its relevance to addictions. *Neuropharmacology* 76, 479–486. doi: 10.1016/j.neuropharm.2013.05.022

Jones, C. M., Houry, D., Han, B., Baldwin, G., Vivolo-Kantor, A., and Compton, W. M. (2022). Methamphetamine use in the United States: epidemiological update and implications for prevention, treatment, and harm reduction. *Ann. N. Y. Acad. Sci.* 1508, 3–22. doi: 10.1111/nyas.14688

Koob, G. F., and Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology* 35, 217–238. doi: 10.1038/npp.2009.110

Li, J., Weidacker, K., Mandali, A., Zhang, Y., Whiteford, S., Ren, Q., et al. (2021). Impulsivity and craving in subjects with opioid use disorder on methadone maintenance treatment. *Drug Alcohol Depend.* 219:108483. doi: 10.1016/j.drugalcdep.2020.108483

Liang, Y., Wang, L., and Yuan, T. F. (2018). Targeting withdrawal symptoms in men addicted to methamphetamine with transcranial magnetic stimulation: a randomized clinical trial. *JAMA Psychiatry* 75, 1199–1201. doi: 10.1001/jamapsychiatry.2018.2383

Lin, J., Liu, X., Li, H., Yu, L., Shen, M., Lou, Y., et al. (2019). Chronic repetitive transcranial magnetic stimulation (rTMS) on sleeping quality and mood status in drug dependent male inpatients during abstinence. *Sleep Med.* 58, 7–12. doi: 10.1016/j.sleep.2019.01.052

Lipszyc, J., and Schachar, R. (2010). Inhibitory control and psychopathology: a meta-analysis of studies using the stop signal task. *J. Int. Neuropsychol. Soc.* 16, 1064–1076. doi: 10.1017/S1355617710000895

Liu, Q., Shen, Y., Cao, X., Li, Y., Chen, Y., Yang, W., et al. (2017). Either at left or right, both high and low frequency rTMS of dorsolateral prefrontal cortex decreases cue induced craving for methamphetamine. *Am. J. Addict.* 26, 776–779. doi: 10.1111/ajad.12638

Liu, T., Li, Y., Shen, Y., Liu, X., and Yuan, T. F. (2019). Gender does not matter: add-on repetitive transcranial magnetic stimulation treatment for female methamphetamine dependents. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 92, 70–75. doi: 10.1016/j.pnpbp.2018.12.018

Liu, X., Zhao, X., Shen, Y., Liu, T., Liu, Q., Tang, L., et al. (2020b). The effects of DLPFC-targeted repetitive transcranial magnetic stimulation on craving in male methamphetamine patients. *Clin. Transl. Med.* 10:e48. doi: 10.1002/ctm2.48

Liu, X., Zhao, X., Liu, T., Liu, Q., Tang, L., Zhang, H., et al. (2020a). The effects of repetitive transcranial magnetic stimulation on cue-induced craving in male patients with heroin use disorder. *EBioMedicine* 56:102809. doi: 10.1016/j.ebiom.2020.102809

Mathew, A. R., Burris, J. L., Froeliger, B., Saladin, M. E., and Carpenter, M. J. (2015). Impulsivity and cigarette craving among adolescent daily and occasional smokers. *Addict. Behav.* 45, 134–138. doi: 10.1016/j.addbeh.2015.01.032

People's Republic of China Central Government | Ministry of Public Security (2019). *China Drug Situation Report*. Available online at: http://www.gov.cn/xinwen/2019-06/18/content_5401230.htm (accessed June 18, 2019).

Perry, J. L., and Carroll, M. E. (2008). The role of impulsive behavior in drug abuse. *Psychopharmacology* 200, 1–26. doi: 10.1007/s00213-008-1173-0

Peterchev, A. V., Wagner, T. A., Miranda, P. C., Nitsche, M. A., Paulus, W., Lisanby, S. H., et al. (2012). Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting practices. *Brain Stimul.* 5, 435–453. doi: 10.1016/j.brs.2011.10.001

Pettorruso, M., Spagnolo, P. A., Leggio, L., Janiri, L., Di Giannantonio, M., Gallimberti, L., et al. (2018). Repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex may improve symptoms of anhedonia in individuals with cocaine use disorder: a pilot study. *Brain Stimul.* 11, 1195–1197. doi: 10.1016/j.brs.2018.06.001

Philip, N. S., Barredo, J., van 't Wout-Frank, M., Tyrka, A. R., Price, L. H., and Carpenter, L. L. (2018). Network mechanisms of clinical response to transcranial magnetic stimulation in posttraumatic stress disorder and major depressive disorder. *Biol. Psychiatry* 83, 263–272. doi: 10.1016/j.biopsych.2017.07.021

Qi, Y., Liu, Y., Yan, Z., Hu, S., Zhang, X., Zhao, J., et al. (2022). Slow-wave EEG activity correlates with impaired inhibitory control in internet addiction disorder. *Int. J. Environ. Res. Public Health* 19:2686. doi: 10.3390/ijerph19052686

Ridderinkhof, K. R., van den Wildenberg, W. P., Segalowitz, S. J., and Carter, C. S. (2004). Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain Cogn.* 56, 129–140. doi: 10.1016/j.bandc.2004.09.016

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., and Safety of Tms Consensus Group (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin. Neurophysiol.* 120, 2008–2039. doi: 10.1016/j.clinph.2009.08.016

Schluter, R. S., van Holst, R. J., and Goudriaan, A. E. (2019). Effects of ten sessions of high frequency repetitive transcranial magnetic stimulation (HF-rTMS) add-on treatment on impulsivity in alcohol use disorder. *Front. Neurosci.* 13:1257. doi: 10.3389/fnins.2019.01257

Sheffer, C. E., Mennemeier, M., Landes, R. D., Bickel, W. K., Brackman, S., Dornhoffer, J., et al. (2013). Neuromodulation of delay discounting, the reflection effect, and cigarette consumption. *J. Subst. Abuse Treat.* 45, 206–214. doi: 10.1016/j.jsat.2013.01.012

Shen, Y., Cao, X., Tan, T., Shan, C., Wang, Y., Pan, J., et al. (2016). 10-Hz repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex reduces heroin cue craving in long-term addicts. *Biol. Psychiatry* 80, e13–e14. doi: 10.1016/j.biopsych.2016.02.006

Sjoerds, Z., Van den Brink, W., Beekman, A. T., Penninx, B. W., and Veltman, D. J. (2014). Response inhibition in alcohol-dependent patients and patients with depression/anxiety: a functional magnetic resonance imaging study. *Psychol. Med.* 44, 1713–1725. doi: 10.1017/S0033291713002274

Smith, J. L., Mattick, R. P., Jamadar, S. D., and Iredale, J. M. (2014). Deficits in behavioural inhibition in substance abuse and addiction: a meta-analysis. *Drug Alcohol Depend.* 145, 1–33. doi: 10.1016/j.drugalcdep.2014.08.009

Strafella, A. P., Paus, T., Barrett, J., and Dagher, A. (2001). Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J. Neurosci.* 21:RC157. doi: 10.1523/JNEUROSCI.21-15-j0003.2001

Su, H., Zhong, N., Gan, H., Wang, J., Han, H., Chen, T., et al. (2017). High frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex for methamphetamine use disorders: a randomised clinical trial. *Drug Alcohol Depend.* 175, 84–91. doi: 10.1016/j.drugalcdep.2017.01.037

Terraneo, A., Leggio, L., Saladini, M., Ermani, M., Bonci, A., and Gallimberti, L. (2016). Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: a pilot study. *Eur. Neuropsychopharmacol.* 26, 37–44. doi: 10.1016/j.euroneuro.2015.11.011

Verbruggen, F., and Logan, G. D. (2008). Response inhibition in the stop-signal paradigm. *Trends Cogn. Sci.* 12, 418–424. doi: 10.1016/j.tics.2008.07.005

Volkow, N. D., Chang, L., Wang, G. J., Fowler, J. S., Franceschi, D., Sedler, M., et al. (2001). Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. *J. Neurosci.* 21, 9414–9418. doi: 10.1523/JNEUROSCI.21-23-09414.2001

Yuan, J., Liu, W., Liang, Q., Cao, X., Lucas, M. V., and Yuan, T. F. (2020). Effect of low-frequency repetitive transcranial magnetic stimulation on impulse inhibition in abstinent patients with methamphetamine addiction: a randomized clinical trial. *JAMA Netw. Open* 3:e200910. doi: 10.1001/jamanetworkopen.2020.0910

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Effects of transcranial direct current stimulation on motor skills learning in healthy adults through the activation of different brain regions: A systematic review

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Objective: This systematic review aims to analyze existing literature of the effects of transcranial direct current stimulation (tDCS) on motor skills learning of healthy adults and discuss the underlying neurophysiological mechanism that influences motor skills learning.

Methods: This systematic review has followed the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses. The PubMed, EBSCO, and Web of Science databases were systematically searched for relevant studies that were published from database inception to May 2022. Studies were included based on the Participants, Intervention, Comparison, Outcomes, and Setting inclusion strategy. The risk of bias was evaluated by using the Review manager 5.4 tool. The quality of each study was assessed with the Physiotherapy Evidence Database (PEDro) scale.

Results: The electronic search produced 142 studies. Only 11 studies were included after filtering. These studies performed well in terms of distribution, blinding availability and selective reporting. They reported that tDCS significantly improved motor skills learning. The main outcomes measure were the improvement of the motor sequence tasks and specific motor skills. Nine studies showed that tDCS interventions reduced reaction time to complete motor sequence tasks in healthy adults and two studies showed that tDCS interventions improved golf putting task performance.

Conclusion: The included studies showed that tDCS can help healthy adults to improve the motor skills learning by activating different brain regions, such as the primary motor cortex, left dorsolateral prefrontal cortex and right cerebellum. However, the number of included studies was limited, and the sample sizes were small. Therefore, more studies are urgently needed to validate the results of current studies and further explore the underlying neurophysiological mechanisms of tDCS in the future.

KEYWORDS

transcranial direct current stimulation, motor skills learning, primary motor cortex, cerebellum, dorsolateral prefrontal cortex, neural circuitry

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique that uses a stable, low-intensity direct current (1-2 mA) to regulate the activity of cortical neurons (Nitsche et al., 2008). The components of tDCS consist of a battery-powered stimulator and two or more electrodes (anode and cathode) placed on the scalp (Jamil et al., 2017). The current passes through the scalp, through the outer layer of the cortex, and then reaches the cortex, where it regulates the membrane polarity of neurons in a certain area under the neural tissue of the cerebral cortex (Fertonani and Miniussi, 2017). Subthreshold stimulation provided by tDCS can depolarize or hyperpolarize the resting membrane potential of neurons, which depends on the stimulation parameters of tDCS and the neuron direction related to the induced electric field (Sudbrack-Oliveira et al., 2021). tDCS is non-invasive, efficient, simple to operate and inexpensive with numerous applications in various fields. Anodal tDCS (a-tDCS) usually aims to increase the excitability of the targeted cortical regions by depolarizing the membrane potential of neurons, whereas cathodal tDCS (c-tDCS) frequently inhibits the neural excitability of the targeted brain regions (Nitsche et al., 2003a).

Motor skills are needed for daily life activities. They are the ability to complete target actions during human movement. Motor skills learning is a process in which the human body receives various signal stimuli and establishes complex conditioned reflexes under the guidance of the cerebral cortex. It is also a process of establishing a balance between excitation and inhibition in the cerebral cortex (Shmuelof et al., 2012). Motor skills learning adaptation is related to the functional connectivity of the brain network, which is defined as a dependency relationship reflecting the degree of non-directional synchronization between two brain regions (Polanía et al., 2011), particularly brain regions, such as the primary motor cortex (M1), cerebellum, supplementary motor area (SMA) and dorsolateral prefrontal cortex (DLPFC) (Landi et al., 2011). Studies have demonstrated that tDCS can increase synaptic plasticity and enhance the functional connection of premotor, motor and sensorimotor regions (Kuo et al., 2014). The above mechanisms have a positive effect on brain activities in motor skills learning and promote motor skills learning. In recent years, researchers have investigated the effect of tDCS on the exercise performance of healthy individuals, and found that tDCS can improve a variety of physical functions, including muscle fatigue (Angius et al., 2016), motor skills learning (Ehsani et al., 2016), motor sensation (Olma et al., 2013), balance control (Saruco et al., 2017) and muscle strength (Abdelmoula et al., 2016). When a-tDCS acts on the M1 region, it can significantly increase the performance level of motor learning and promote the acquisition and maintenance of motor skills (Nitsche et al., 2003b). C-tDCS can also improve performance in motor learning and golf putting practice by acting on the left DLPFC region (Zhu et al., 2015). Given the effective impact of tDCS on motor skills learning, a systematic review of published studies could provide valuable summaries of the effects of tDCS on motor skills learning.

Therefore, this study aims to review systematically the peer-reviewed publications available to date on the effects of tDCS on motor skills learning in healthy adults, then discusses its underlying neurophysiological mechanisms. This review provides an improved understanding of the research work on this topic and will eventually help optimize the application of tDCS in promoting motor skills learning in the future.

Methods

The method of this review was developed under the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Cochrane Handbook for Systematic Reviews of Interventions (Cumpston et al., 2019).

Search strategy

In this systematic review, the three databases of PubMed, Web of Science and EBSCO were comprehensively searched up to May 2022. The phrases "motor skills," "motor learning" and "memory" were separately combined with the phrases "transcranial direct current stimulation" or "tDCS" in all databases. The Boolean operators "AND" and "OR" were used to combine keywords based on the recommendations of each database. All search results were imported into the EndNote reference manager (EndNote X9, USA, Stanford) to collect and find duplicate records automatically.

Eligibility criteria and article selection

Studies were included following the inclusion criteria of the Participants, Intervention, Comparison, Outcomes, and Study design.

1. Participants: The participants were healthy adults without a history of musculoskeletal injury and obvious neurological diseases. The age range of healthy adults is 18–56 years old.
2. Intervention: The intervention method was tDCS regardless of stimulation type, intensity, duration or electrode position.
3. Comparison: The comparison was with sham tDCS.
4. Outcomes: The main outcomes measure were the improvement of the motor sequence tasks and specific motor skills, such as serial reaction time task (SRTT),

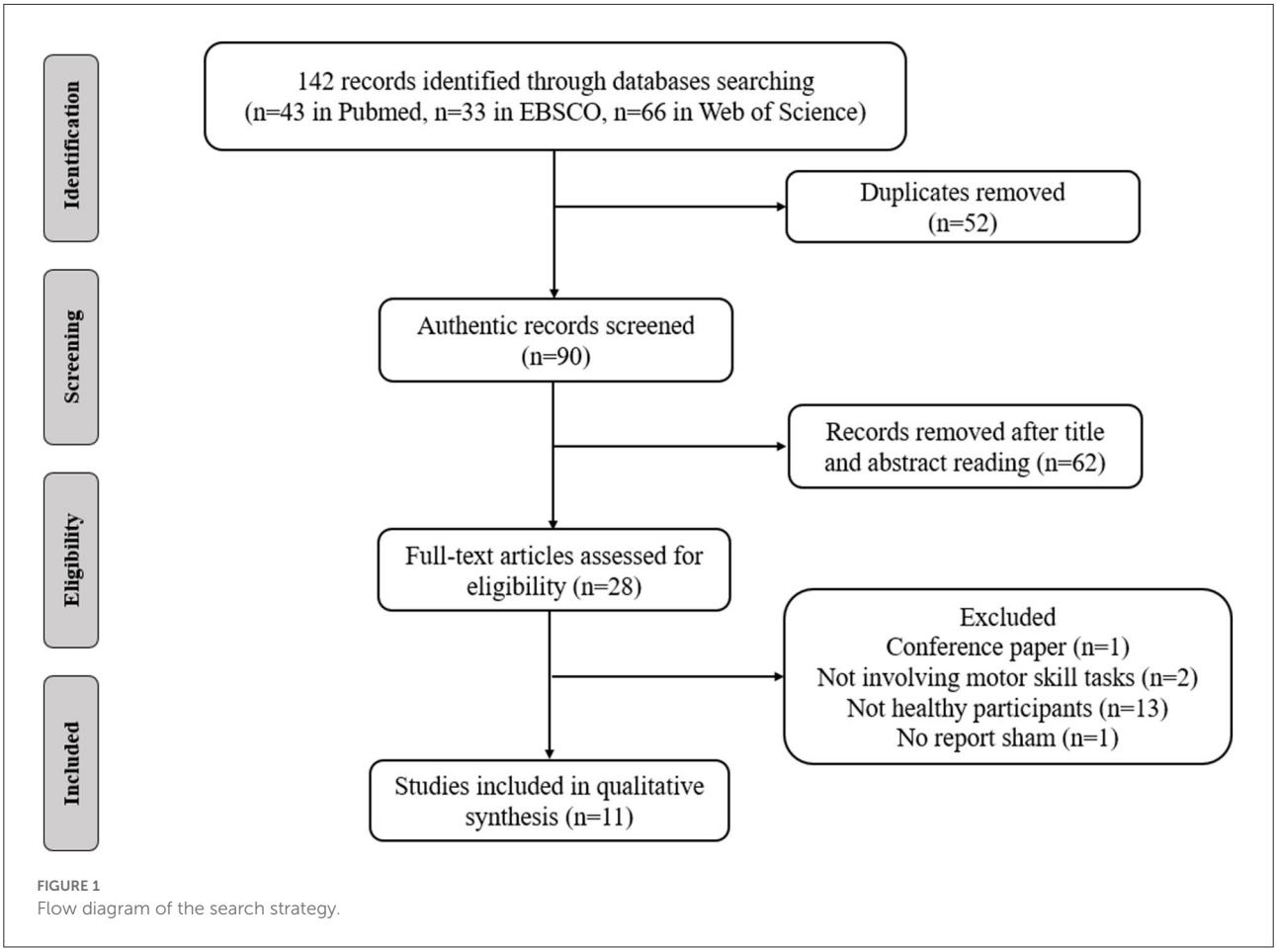

FIGURE 1
Flow diagram of the search strategy.

sequential finger tapping tasks (SFTT), sequential visual isometric pinch task (SVIPT), and golf putting tasks. Improvements in motor skills learning are assessed through sequential task reaction times and golf putting scores.

5. Study design: The study included randomized, crossover, and sham controlled designs. Animal studies and non-English studies were excluded. Comments, case reports, letters, opinions and conference abstracts were also removed (Figure 1).

Two researchers independently examined the search results and resolved differences through discussion (QS and ZL). The abstracts and full texts of relevant articles were read carefully and only those that qualified were selected. Then, the researcher further confirmed the selected articles and discussed possible disagreements. If disagreements remained, a fifth researcher was consulted, and the results were evaluated (XW).

Data extraction

Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) was used to summarize the original data from the included articles. The author, sample, age, anodal/cathodal location, current intensity, electrode size, current density, duration, work tasks, and main outcome measures were all summarized.

Quality and risk-of-bias assessments

The Physiotherapy Evidence Database (PEDro) scale was used to evaluate the quality of each study (Maher et al., 2003) (Figure 2). Studies with a PEDro score <6 were considered to be of low quality. Each study's risk of bias was evaluated by using the Review Manager 5.4, which is based on the Cochrane Handbook for Systematic Reviews of Interventions (Cumpston et al., 2019). The risk of bias for each study was determined as "low risk," "high risk," or "unclear risk." Researchers independently assessed the PEDro score and risk of bias of each study. If disagreements remained, a second researcher was consulted to establish a final consensus.

Results

These databases yielded 142 related articles (43 in PubMed, 33 in EBSCO and 66 in Web of Science). After removing

1. Eligibility criteria were specified.
2. Subjects were randomly allocated to groups.
3. Allocation was concealed.
4. The groups were similar at baseline regarding the most important prognostic indicators.
5. There was blinding of all subjects.
6. There was blinding of all therapists who administered the therapy.
7. There was blinding of all assessors who measured at least one key outcome.
8. Measurements of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
9. All subjects for whom outcome measurements were available received the treatment or control condition as allocated, or where this was not the case, data for at least one key outcome were analyzed by "intention to treat".
10. The results of between-group statistical comparisons are reported for at least one key outcome.
11. The study provides both point measurements and measurements of variability for at least one key outcome.

FIGURE 2
PEDro scale.

TABLE 1 Stimulation protocols and main outcomes of the studies investigating the effect of tDCS on motor skills learning.

References	Sample	Age (year)	Anode Locations	Cathode Locations	Current (mA)	Electrode size (cm)	Current Density (mA/cm^2)	Duration (min)	Task	Outcome measure
Tecchio et al. (2010)	47	24-34	R M1	R Arm	1	7 × 5	0.03	15	SFTT	RTs for correct trials↓
Ferrucci et al. (2013)	21	20-49	R Cerebellar	R Arm	2	7 × 5	0.06	20	SRTT	RTs for correct trials ↓
Marquez et al. (2013)	30	20-27	R M1	R Arm	1	5 × 5	0.04	20	SFTT	RTs for correct trials↓
Cantarero et al. (2015)	33	24-31	R Cerebellar	R Buccinator	2	5 × 5	0.08	20	SVIPT	RTs for correct trials ↓
Zhu et al. (2015)	27	18-24	R Supraorbital	L DLPFC	1.5	5 × 5	0.06	15-20	Golf putting task	Number of successful putts ↑
Soekadar et al. (2015)	40	18-56	L M1	R Supraorbital	1	4 × 6	0.04	15	SRTT	RTs for correct trials ↓
Apolinario-Souza et al. (2016)	32	18-35	L M1	R Supraorbital	1	5 × 5	0.04	20	SFTT	RTs for correct trials ↓
Wessel et al. (2016)	38	20-28	R Cerebellar	R Buccinator	2	5 × 5	0.08	20	SFTT	RTs for correct trials ↓
Debarnot et al. (2019)	48	20-27	L M1	L Supraorbital	2	5 × 5	0.08	13	SRTT	RTs for correct trials ↓
Parma et al. (2021)	48	18-40	L M1	R M1	1.5	5 × 5	0.06	20	Golf putting task	Number of successful putts↑
Nakashima et al. (2021)	19	21-37	L DLPFC	R Forehead	2	7 × 5	0.06	20	SRTT	RTs for correct trials↓

R, right; L, left; M1, primary Motor Cortex; DLPFC, dorsolateral prefrontal cortex; RT, reaction time; SRTT, serial reaction time task; SFTT, sequential finger tapping tasks; SVIPT, sequential visual isometric pinch task. ↑ Means increase and ↓ means decrease.

duplicate publications and identifying irrelevant studies by reviewing the titles, abstracts and full texts of the articles, 11 articles were included in this systematic review. These studies investigated the effects of tDCS on motor skills learning.

Effects of tDCS on motor skills learning

Eleven studies investigated the effects of tDCS on motor skill learning. A total of 383 people were recruited (Table 1).

Among the studies, four studies applied tDCS on the left M1 region (Soekadar et al., 2015; Apolinario-Souza et al., 2016; Debarnot et al., 2019; Parma et al., 2021). Two studies applied tDCS on the right M1 region (Tecchio et al., 2010; Marquez et al., 2013). Three studies applied tDCS on the right cerebellum (Ferrucci et al., 2013; Cantarero et al., 2015; Wessel et al., 2016) and two studies applied tDCS on the left DLPFC region (Zhu et al., 2015; Nakashima et al., 2021) (Figure 3). The current intensity of four studies was 1 mA (Tecchio et al., 2010; Marquez et al., 2013; Soekadar et al., 2015; Apolinario-Souza et al., 2016).

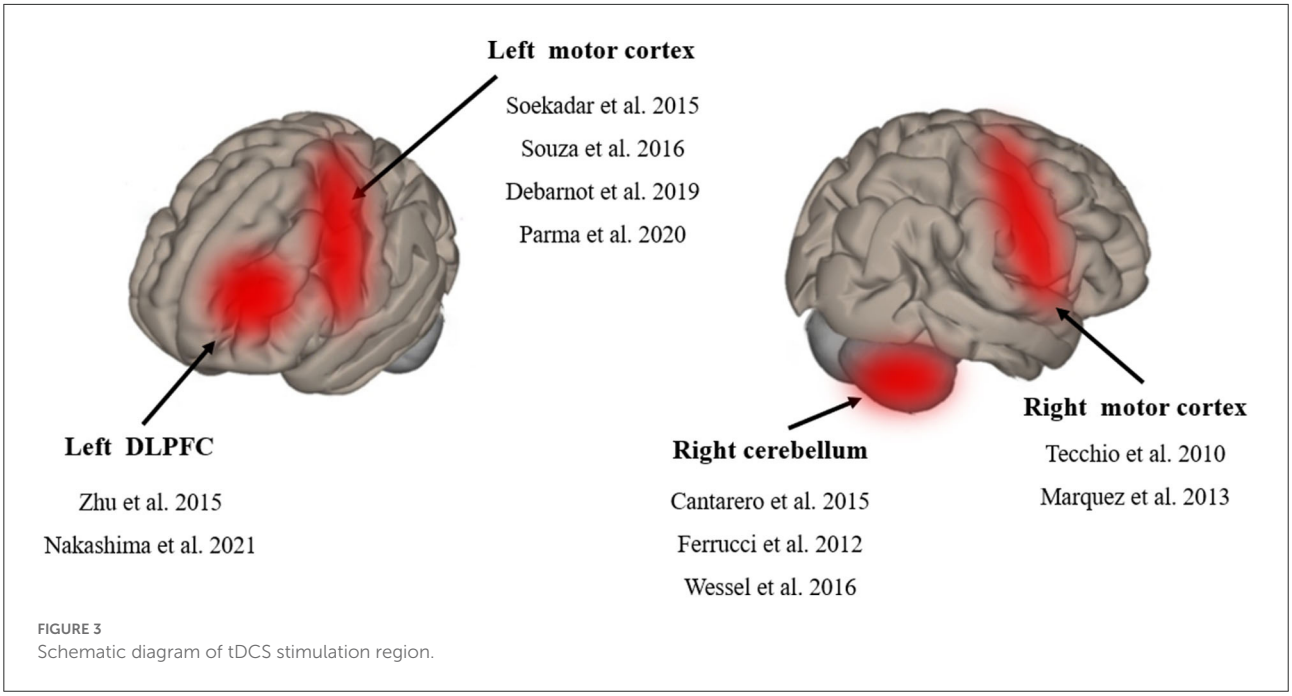

FIGURE 3
Schematic diagram of tDCS stimulation region.

TABLE 2 Characterization of the main motor paradigms described in this Systematic Review.

Motor sequence task	Description
Serial Reaction Time Task (SRTT)	Participants responded to visual cues presented on the screen by pressing the relevant keyboard response. The location of visual cues was either presented in repeated sequences or at random.
Sequential Finger Tapping Tasks (SFTT)	A sequence of elements in a specific order that presented a specific finger movement was presented on the screen. Participants were required to perform the representative key operations as quickly and accurately as possible.
Sequential Visual Isometric Pinch Task (SVIPT)	Participants used their thumb and index finger to squeeze an isometric force sensor to control the movement of the pointer on the computer screen. The goal is to move the cursor as rapidly and correctly as possible between the beginning point and the target area's numbered sequence.

The current intensity of five studies was 2 mA and that of two studies was 1.5 mA (Zhu et al., 2015; Parma et al., 2021). The electrode size in seven studies was 25 cm^2 (Marquez et al., 2013; Cantarero et al., 2015; Zhu et al., 2015; Apolinario-Souza et al., 2016; Wessel et al., 2016; Debarnot et al., 2019; Parma et al., 2021). The electrode size in three studies was 35 cm^2 (Tecchio et al., 2010; Kantak et al., 2012; Nakashima et al., 2021) and that in one study was 24 cm^2 (Soekadar et al., 2015). The current density of 11 studies ranged from 0.03 to 0.08 mA/cm^2. The duration of stimulation in 10 studies was 15 to 20 min (Tecchio et al., 2010; Ferrucci et al., 2013; Marquez et al., 2013; Cantarero et al., 2015; Soekadar et al., 2015; Zhu et al., 2015; Apolinario-Souza et al., 2016; Wessel et al., 2016; Nakashima et al., 2021; Parma et al., 2021) and that in one study was 13 min (Debarnot et al., 2019). The number of montages for all studies was two electrodes.

At present, the most frequently tasks of investigating motor skills learning in the experimental environment are SRTT, SFTT and SVIPT (see Table 2 for details). Tecchio et al. (2010), Marquez et al. (2013), Soekadar et al. (2015), Apolinario-Souza et al. (2016) and Debarnot et al. (2019) found that compared with the sham condition, a-tDCS acting on the left and right M1 region could reduce the RTs for correct trials. Parma et al. (2021) reported that compared with the sham condition, a-tDCS acting on the left M1 region could increase golf putting performance. Ferrucci et al. (2013), Cantarero et al. (2015) and Wessel et al. (2016) discovered that compared with the sham condition, a-tDCS acting on the right cerebellar region could reduce the RTs for correct trials. Nakashima et al. (2021) showed that compared with the sham condition, a-tDCS acting the left DLPFC region also could reduce the RTs for correct trials. Meanwhile, Zhu et al. (2015) reported that compared with the sham condition, c-tDCS acting on the left DLPFC region also could improve golf putting performance. These phenomena demonstrated that increasing the excitability of a region involved in action observation

promoted motor skills acquisition, and the results differed under the stimulation from different electrode polarities for the same region.

Risk of bias and quality of evidence

Figure 4 provides the summary risk of bias graph. In the risk-of-bias assessment, three studies maintained a low risk of bias in all domains tested, whereas the other studies revealed a certain high or unclear risk. All studies used randomization for random sequence generation. Six studies applied double blinding, and three studies utilized single blinding. Only two studies presented a high risk of incomplete outcome data. Complete data were not collected from one individual due to vertigo under stimulation. One sub-ject in the main experiment had to be excluded from the study due to vertigo under stimulation.

Two participants dropped out before the end of one study, resulting in incomplete data results (Marquez et al., 2013). All studies were evaluated to have a minimal risk of bias in terms of selective reporting. In addition, the PEDro score of all the studies exceeded 6, indicating that all of the included studies were of excellent quality. In a word, the investigations performed well in terms of allocation, blinding effectiveness, selective reporting, order effects avoidance, well-tolerated stimulation maintenance, and absence of side effects.

Discussion

This study comprehensively evaluated the literature on the effects of tDCS on motor skills learning. The 11 included studies all demonstrated that tDCS can increase motor skills learning in healthy individuals by activating multiple brain regions, such as M1, left DLPFC and right cerebellum. However, owing to the small sample sizes, different tDCS parameters and other factors of the studies, these findings need to be validated and confirmed in future investigations. In the review, the underlying neurophysiological mechanism of tDCS were explored and future research directions were speculated.

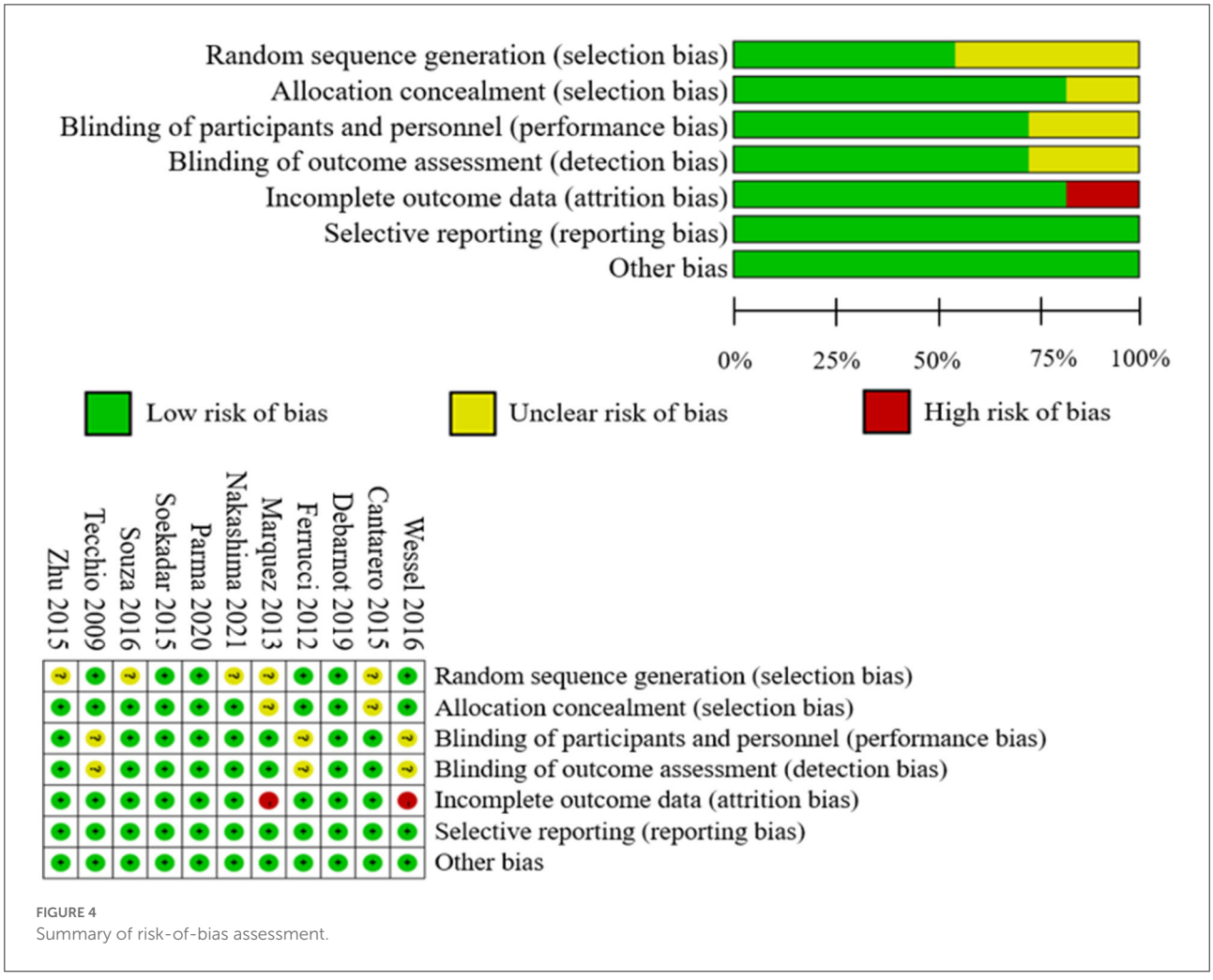

FIGURE 4
Summary of risk-of-bias assessment.

Influence of different electrode polarities on tDCS-induced motor skills learning and its possible explanation

The benefits of tDCS in increasing physical performance has been gradually studied in recent years (Lattari et al., 2020). These benefits include delaying muscle fatigue, increasing muscle strength, promoting motor skills learning and improving motor sensation (Machado et al., 2019).

Since Nitsche and Paulus (2000) reported the impact of transcranial low current on human M1 region, excitatory/inhibitory effects have been widely associated with anodal/cathodal current stimulation, respectively (Nitsche and Paulus, 2000). A-tDCS usually aims to depolarize the neuronal membrane potential to increase excitability in the target region, and the c-tDCS aims to hyperpolarize the neuronal membrane potential to inhibit excitability in the target region. Moreover, it should be pay attention that neuronal morphology (Nitsche and Paulus, 2000; Radman et al., 2009) and axonal orientation may be factors worth being considered when interpreting tDCS induced responses. Notably, the location of cathode and anode can also affect the differences in tDCS results. For example, Zhu et al. (2015) found that c-tDCS improved subjects' golf putting performance when the left DLPFC was stimulated by tDCS. However, Nakashima et al. (2021) found that a-tDCS was effective. Specifically, Zhu et al. (2015) placed the cathode contact on the subject's left DLPFC region and the anode contact on the right supraorbital region. While Nakashima et al. (2021) placed the anode on the subject's left DLPFC and the cathode on the right forehead. Although the current densities were the same in both studies, differences in the placement of the cathode and anode positions may have contributed to the differences in results.

Therefore, the differences in experimental tDCS results may be related to the high variability amongst individuals in terms of local circuit organization, basic functional levels, mental states, neurotransmitter levels, baseline neurophysiological states and genetic aspects (Machado et al., 2019). In addition, electrode shape and the montage (which includes the currents, locations and polarity of the electrodes), the stimulated brain region, and the brain state among other parameters can also influence the stimulation effect. Further research is needed to verify the effect of these factors on the stimulation of tDCS.

Influences of different brain regions on tDCS-induced motor skills learning

Motor skills learning is a process wherein human body receives various signal stimuli and establishes complex conditioned reflex under the guidance of the cerebral cortex, and through practice to improve the ability of motor movement. The learning and adaptation of motor skills are associated with functional and structural changes in the brain distribution network including M1, somatosensory (S1), dorsal (PMd) and ventral premotor (PMv), SMA and posterior parietal cortex (PPC), as well as the cerebellum and basal ganglia (Landi et al., 2011). Stimulating brain regions associated with motor skills learning may have the same effects. The stimulating parameters for promoting motor skills learning are relatively variable. For example, most studies used the duration of 15 min to 20 min, and the polar plate is mostly 25 cm^2. Previous works utilized commonly used valence motor skills learning tasks, including SRTT, SFTT and SVIPT (Ma et al., 2021). However, when these indicators were applied to evaluate motor skills learning, the task evaluation setting was relatively simple and ignored multidimensional and complex motor skills. Therefore, the improvement brought by tDCS was less than that expected. However, the main results of these studies suggested that tDCS has the potential to improve motor skills learning, and its effects should be further confirmed in future studies with increased sample sizes and rigors.

The motor cortex of the brain, involved in the execution and regulation of movement, it is mainly composed of three parts including M1 region, SMA region and premotor area (PMA). In view of the complexity involved in motor skills, multiple regions of the brain may be involved in the regulation and limitation of motor skills, including M1, DLPFC, SMA and the cerebellum (Machado et al., 2019). In addition, their basic principles may be different, so most studies on motor skills learning do not provide clear assumptions. For example, the reason placing electrodes at specific locations in the brain to stimulate or inhibit a given brain region can improve motor skills is unclear.

M1 region, the key brain region regulating human and animal motor execution, memory formation and motor skills consolidation, is the most associated region with motor skills and widely used in brain science (Fritsch et al., 2010). The M1 region has been found to be the main brain region stimulated by tDCS to improve motor skills learning and acquisition. tDCS is used on the M1 region to increase its excitability, which may lead to the continuous neural drive of neurons. In addition, under the condition of a-tDCS, the axons direction of the M1 region is perpendicular to the electrode surface, which can improve the excitability of neurons. M1 regulates the ability of the fingers to perform skilled, complex motor sequences (Rathelot and Strick, 2009), such as finger tapping tasks (Yu and Tomonaga, 2015). The action of a-tDCS on the M1 region can significantly increase the functional connection of the premotor, motor and sensorimotor regions of the cerebral hemisphere and induce the connectivity between the left and right hemispheres to change (Yang et al., 2021). Therefore, tDCS regulates the functional connection between the complex networks of the brain. tDCS can cause changes in the substances such as neurotransmitters, through

a neuroplasticity model, which is based on the principle that current intensity leads to alterations in neuronal synapses and that local neuronal transmission causes the enhancement or weakening of synaptic transmission efficiency (Nwaroh et al., 2020). Glutamate (Glu) and γ-aminobutyric acid (GABA) are the two main neurotransmitters. Glu is an excitatory neurotransmitter, and GABA is an inhibitory neurotransmitter. Glu plays a key role in the maintenance of the synapses plasticity and promotes learning and memory by changing the efficacy of synaptic transmission and efficacy of the formation and function of cytoskeleton. Studies have shown that during or after tDCS, the levels of metabolites changed, such as increased excitatory neurotransmitters Glu and decreased inhibitory neurotransmitters GABA, especially in the cortical regions (Nwaroh et al., 2020). GABA plays an important regulatory role in skills learning. Therefore, the action of a-tDCS on the left M1 region could improve motor skills learning (Parma et al., 2021). In addition, some researchers believe that tDCS acted on M1 region affects motor performance by improving long-term changes in brain excitability and activity, through enhancing synaptic plasticity.

DLPFC is another region of interest that has always been a key candidate for working memory and interference control (Machado et al., 2019). Contemporary motor skills learning theory holds that motor learning can be obtained explicitly or implicitly (Zhu et al., 2015). Explicit motor learning is the language analysis aspect of learning through working memory management (Maxwell et al., 2003). By contrast, implicit motor learning reduces the involvement of language analysis in motor control by encouraging limited dependence on working memory. Compared with explicit motor learning, this form of learning has been proven to reduce awareness of the movements involved and increase neural efficiency (Zhu et al., 2015). A study showed that the DLPFC appears to be important to the neural basis of implicit motor learning, because the performance of patients with DLPFC lesions in practice tasks did not improve while the low-frequency repetitive transcranial magnetic stimulation (TMS) on the DLPFC improved motor learning, which suggested that DLPFC was a part of the neuronal matrix responsible for sequence learning (Hosp et al., 2011). Meanwhile, the action of tDCS on the left DLPFC demonstrated its clinical application in the treatment of depressive states, psychiatric symptoms, and the rehabilitation of cerebral infarction (Santos Ferreira et al., 2019). Zhu et al. (2015) and Nakashima et al. (2021) found that applying tDCS on the left DLPFC could improve implicit motor learning behavior (Zhu et al., 2015; Nakashima et al., 2021). In addition, Nakashima et al. (2021) found that a-tDCS improved implicit motor learning. However, Zhu et al. (2015) reported that c-tDCS improved implicit motor learning. Although the two studies had a consistent region of action, their tDCS intervention parameters were not completely consistent and their motor skills measures were inconsistent, which may account for the different results.

Cerebellum, an important motor regulation center, contributes to the regulation of programmed motor learning and plays important roles in establishing motor skills, perception, and motor behavior (Ehsani et al., 2016). The cerebellum helps control motor and non-motor behaviors, including learning, posture and balance, coordination, cognition, emotion, and language (Caligiore et al., 2017). The cerebellum is considered to be an alternative site to the M1 region for tDCS stimulation to promote motor learning (Oldrati and Schutter, 2018). In the process of motor learning, the cerebellum appears to play a crucial role in reducing errors associated with the needs of a new environment (Galea et al., 2011). The forming of motor skills is encoded by a large subcortical network that primarily involves the cerebellum (Ramnani, 2006). Clinical studies have shown that patients with damaged cerebellum have significantly impaired ability to learn new motor skills and poor ability to adapt to new environments (Criscimagna-Hemminger et al., 2010). These results revealed that the cerebellum was essential to the feedforward process required for motor adaptation. Ferrucci et al. (2013) and Cantarero et al. (2015) found that tDCS enhanced motor skills when it acted on the cerebellum, which was likely due to the increased excitability of cerebellar neurons, significant changes in the neural activity of interconnected parietal lobe network of the brain and the enhanced temporal complexity of distributed brain networks that modulated neural activity in interconnected cortical regions (Rastogi et al., 2017), thus improving motor skills.

The disadvantages of tDCS, and the advantages of other non-invasive neuromodulation techniques

As a type of transcranial electrical stimulation, tDCS has defects. For example, it has a narrow action range and low spatial resolution, which make accurately stimulating deep brain regions difficult. Differences in electrode size, current parameters, stimulation duration and electrode position in different studies often have other adverse effects on the results (Rampersad et al., 2019). Meanwhile, the focus of the stimulating electric field itself is low, which is mainly manifested by the reduction in the intensity of the electromagnetic field with the increase in the distance from the head surface. Furthermore, numerous regions in the superficial cortex are directly involved in the body's cognition and behavior and participate in the whole brain (Bikson and Dmochowski, 2020; Lee et al., 2020). The network connection between tDCS stimulation regions and their inability to focus on deep brain regions may adversely affect the final results. Given that different regions of the brain may be related to different motor learning processes, the simultaneous electrical stimulation of these regions with the proper polarity and current intensity may optimize the relevant effects of tDCS.

In this regard, bilateral M1 combined with PFC stimulation has been successfully applied. However, due to the inherent low focus of this technique, only a few effects related to its concomitant stimulation of different brain regions have been described in the literature. In the future, new non-invasive brain stimulation methods were needed to investigate its prospect in improving motor skills. The section on TI has been removed.

Shortages of the review and prospect of tDCS research

The included studies generally showed that tDCS can promote motor skills learning. However, the results of this systematic review should be interpreted with caution given that the included studies had some methodological limitations. Firstly, the research sample size included in this review was relatively small. Secondly, the selection of tDCS parameters in different studies was diverse. The diversification of parameters led to diversified results. Therefore, a standardized tDCS scheme, a research design with increased rigor and advanced neural modeling technology for testing the effectiveness of tDCS in motor skills learning are urgently needed in future studies. Thirdly, this review only focuses on the effect of tDCS on motor skills learning in healthy adults. We need to further focus on exploring new directions for the treatment of neurological diseases and strengthen restorative treatments after stroke or other injuries affecting motor function.

The neurophysiological mechanisms of tDCS in motor skills are still unclear, and further researches are needed to estimate the target of tDCS by using neural modeling techniques combined with the participants' brain magnetic resonance images to correlate doses with the observed functional improvement. Notably, gender bias was found in the effect of tDCS on motor skills learning, but no research until now has reported how gender affects the effects of tDCS on motor skills, and this topic is also worth exploring in the future. In addition, the publication of negative results on the efficacy of tDCS can be encouraged to critique the implementation of tDCS for the potential publication bias, and such criticisms will eventually help optimize the tDCS intervention scheme.

In brief, although the mechanisms through which tDCS improves motor skills learning remains uncertain, several possible explanations exist and reflected in the change of cerebral excitability, the regulation of neurotransmitters, the increase in synaptic plasticity, the change in regional cerebral blood flow (rCBF) in the brain and the adjustment of brain network functional connections to regulate brain function (Bandeira et al., 2021). Improving cortical excitability and enhancing synaptic plasticity in target brain regions play key roles in regulating neural circuits (Nitsche et al., 2008). Specifically, the current delivered by tDCS may enhance synaptic connections between cortical neuronal structures, resulting in continuous changes in neural activity that can increase the degree of the synchronous discharge of motor units and further affect neural circuit regulation in motor skills and improve body functions (Patel et al., 2019).

Conclusion

The existing research show that tDCS acted on multiple brain regions (including M1, DLPFC and cerebellum) can help improve motor skills learning, and its underlying neurophysiological mechanisms are related to the changes in cerebral excitability, neurotransmitters, synaptic plasticity, and brain network functional connections. However, future studies with large sample sizes and experimental designs with increased rigor are needed to confirm the current findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

SQ contributed to study design, data collection, drafting, and revising the manuscript. YL and XW contributed to supervising study design, completing data analysis and interpretation, and revising the manuscript. ZL and ZW revised the manuscript. All authors have read and approved the final version of the manuscript and agree with the order of the presentation of the authors.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2022.1021375/full#supplementary-material

References

Abdelmoula, A., Baudry, S., and Duchateau, J. (2016). Anodal transcranial direct current stimulation enhances time to task failure of a submaximal contraction of elbow flexors without changing corticospinal excitability. *Neuroscience* 322, 94–103. doi: 10.1016/j.neuroscience.2016.02.025

Angius, L., Pageaux, B., Hopker, J., Marcora, S. M., and Mauger, A. R. (2016). Transcranial direct current stimulation improves isometric time to exhaustion of the knee extensors. *Neuroscience* 339, 363–375. doi: 10.1016/j.neuroscience.2016.10.028

Apolinario-Souza, T., Romano-Silva, M. A., de Miranda, D. M., Malloy-Diniz, L. F., Benda, R. N., Ugrinowitsch, H., et al. (2016). The primary motor cortex is associated with learning the absolute, but not relative, timing dimension of a task: a tDCS study. *Physiol. Behav.* 160, 18–25. doi: 10.1016/j.physbeh.2016.03.025

Bandeira, I. D., Lins-Silva, D. H., Barouh, J. L., Faria-Guimarães, D., Dorea-Bandeira, I., Souza, L. S., et al. (2021). Neuroplasticity and non-invasive brain stimulation in the developing brain. *Prog. Brain Res.* 264, 57–89. doi: 10.1016/bs.pbr.2021.04.003

Bikson, M., and Dmochowski, J. (2020). What it means to go deep with non-invasive brain stimulation. *Clin. Neurophysiol.* 131, 752–754. doi: 10.1016/j.clinph.2019.12.003

Caligiore, D., Pezzulo, G., Baldassarre, G., Bostan, A. C., Strick, P. L., Doya, K., et al. (2017). Consensus paper: towards a systems-level view of cerebellar function: the interplay between cerebellum, basal ganglia, and cortex. *Cerebellum* 16, 203–229. doi: 10.1007/s12311-016-0763-3

Cantarero, G., Spampinato, D., Reis, J., Ajagbe, L., Thompson, T., Kulkarni, K., et al. (2015). Cerebellar direct current stimulation enhances on-line motor skill acquisition through an effect on accuracy. *J. Neurosci.* 35, 3285–3290. doi: 10.1523/JNEUROSCI.2885-14.2015

Criscimagna-Hemminger, S. E., Bastian, A. J., and Shadmehr, R. (2010). Size of error affects cerebellar contributions to motor learning. *J. Neurophysiol.* 103, 2275–2284. doi: 10.1152/jn.00822.2009

Cumpston, M., Li, T., Page, M. J., Chandler, J., Welch, V. A., Higgins, J. P., et al. (2019). Updated guidance for trusted systematic reviews: a new edition of the cochrane handbook for systematic reviews of interventions. *Cochrane Database Syst. Rev. 10*, Ed000142. doi: 10.1002/14651858.ED000142

Debarnot, U., Neveu, R., Samaha, Y., Saruco, E., Macintyre, T., and Guillot, A. (2019). Acquisition and consolidation of implicit motor learning with physical and mental practice across multiple days of anodal tDCS. *Neurobiol. Learn. Mem.* 164, 107062. doi: 10.1016/j.nlm.2019.107062

Ehsani, F., Bakhtiary, A. H., Jaberzadeh, S., Talimkhani, A., and Hajihasani, A. (2016). Differential effects of primary motor cortex and cerebellar transcranial direct current stimulation on motor learning in healthy individuals: a randomized double-blind sham-controlled study. *Neurosci. Res.* 112, 10–19. doi: 10.1016/j.neures.2016.06.003

Ferrucci, R., Brunoni, A. R., Parazzini, M., Vergari, M., Rossi, E., Fumagalli, M., et al. (2013). Modulating human procedural learning by cerebellar transcranial direct current stimulation. *Cerebellum* 12, 485–492. doi: 10.1007/s12311-012-0436-9

Fertonani, A., and Miniussi, C. (2017). Transcranial electrical stimulation: what we know and do not know about mechanisms. *Neuroscientist* 23, 109–123. doi: 10.1177/1073858416631966

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., et al. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron* 66, 198–204. doi: 10.1016/j.neuron.2010.03.035

Galea, J. M., Vazquez, A., Pasricha, N., de Xivry, J. J., and Celnik, P. (2011). Dissociating the roles of the cerebellum and motor cortex during adaptive learning: the motor cortex retains what the cerebellum learns. *Cereb. Cortex* 21, 1761–1770. doi: 10.1093/cercor/bhq246

Hosp, J. A., Pekanovic, A., Rioult-Pedotti, M. S., and Luft, A. R. (2011). Dopaminergic projections from midbrain to primary motor cortex mediate motor skill learning. *J. Neurosci.* 31, 2481–2487. doi: 10.1523/JNEUROSCI.5411-10.2011

Jamil, A., Batsikadze, G., Kuo, H. I., Labruna, L., Hasan, A., Paulus, W., et al. (2017). Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. *J. Physiol.* 595, 1273–1288. doi: 10.1113/JP272738

Kantak, S. S., Mummidisetty, C. K., and Stinear, J. W. (2012). Primary motor and premotor cortex in implicit sequence learning - evidence for competition between implicit and explicit human motor memory systems. *Eur. J. Neurosci.* 36, 2710–2715. doi: 10.1111/j.1460-9568.2012.08175.x

Kuo, M. F., Paulus, W., and Nitsche, M. A. (2014). Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *Neuroimage,* 85, 948–960. doi: 10.1016/j.neuroimage.2013.05.117

Landi, S. M., Baguear, F., and Della-Maggiore, V. (2011). One week of motor adaptation induces structural changes in primary motor cortex that predict long-term memory one year later. *J. Neurosci.* 31, 11808–11813. doi: 10.1523/JNEUROSCI.2253-11.2011

Lattari, E., Rosa Filho, B. J., Fonseca Junior, S. J., Murillo-Rodriguez, E., Rocha, N., Machado, S., et al. (2020). Effects on volume load and ratings of perceived exertion in individuals' advanced weight training after transcranial direct current stimulation. *J. Strength Cond. Res.* 34, 89–96. doi: 10.1519/JSC.0000000000002434

Lee, S., Lee, C., Park, J., and Im, C. H. (2020). Individually customized transcranial temporal interference stimulation for focused modulation of deep brain structures: a simulation study with different head models. *Sci. Rep.* 10, 11730. doi: 10.1038/s41598-020-68660-5

Ma, R., Xia, X., Zhang, W., Lu, Z., Wu, Q., Cui, J., et al. (2021). High gamma and beta temporal interference stimulation in the human motor cortex improves motor functions. *Front. Neurosci.* 15, 800436. doi: 10.1101/2021.03.26.437107

Machado, D., Unal, G., Andrade, S. M., Moreira, A., Altimari, L. R., Brunoni, A. R., et al. (2019). Effect of transcranial direct current stimulation on exercise performance: a systematic review and meta-analysis. *Brain Stimul.* 12, 593–605. doi: 10.1016/j.brs.2018.12.227

Maher, C. G., Sherrington, C., Herbert, R. D., Moseley, A. M., and Elkins, M. (2003). Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys. Ther.* 83, 713–721. doi: 10.1093/ptj/83.8.713

Marquez, C. M. S., Zhang, X., Swinnen, S. P., Meesen, R., and Wenderoth, N. (2013). Task-specific effect of transcranial direct current stimulation on motor learning. *Front. Hum. Neurosci.* 7, 333 doi: 10.3389/fnhum.2013.00333

Maxwell, J. P., Masters, R. S., and Eves, F. F. (2003). The role of working memory in motor learning and performance. *Conscious. Cogn.* 12, 376–402. doi: 10.1016/S1053-8100(03)00005-9

Nakashima, S., Koeda, M., Ikeda, Y., Hama, T., Funayama, T., Akiyama, T., et al. (2021). Effects of anodal transcranial direct current stimulation on implicit motor learning and language-related brain function: An fMRI study. *Psychiatry Clin. Neurosci.* 75, 200–207. doi: 10.1111/pcn.13208

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., et al. (2008). Transcranial direct current stimulation: state of the art 2008. *Brain Stimul.* 1, 206–223. doi: 10.1016/j.brs.2008.06.004

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., et al. (2003a). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J. Physiol.* 553, 293–301. doi: 10.1113/jphysiol.2003.049916

Nitsche, M. A., and Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J. Physiol.* 527, 633–639. doi: 10.1111/j.1469-7793.2000.t01-1-00633.x

Nitsche, M. A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., et al. (2003b). Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. *J. Cogn. Neurosci.* 15, 619–626. doi: 10.1162/089892903321662994

Nwaroh, C., Giuffre, A., Cole, L., Bell, T., Carlson, H. L., MacMaster, F. P., et al. (2020). Effects of transcranial direct current stimulation on gaba and glx in children: a pilot study. *PLoS ONE* 15:e0222620. doi: 10.1371/journal.pone.0222620

Oldrati, V., and Schutter, D. (2018). Targeting the human cerebellum with transcranial direct current stimulation to modulate behavior: a meta-analysis. *Cerebellum* 17, 228–236. doi: 10.1007/s12311-017-0877-2

Olma, M. C., Dargie, R. A., Behrens, J. R., Kraft, A., Irlbacher, K., Fahle, M., et al. (2013). Long-term effects of serial anodal tDCS on motion perception in subjects with occipital stroke measured in the unaffected visual hemifield. *Front. Hum. Neurosci.* 7, 314. doi: 10.3389/fnhum.2013.00314

Parma, J. O., Profeta, V., Andrade, A. G. P., Lage, G. M., and Apolinário-Souza, T. (2021). TDCS of the primary motor cortex: learning the absolute dimension of a complex motor task. *J. Mot. Behav.* 53, 431–444. doi: 10.1080/00222895.2020.1792823

Patel, R., Ashcroft, J., Patel, A., Ashrafian, H., Woods, A. J., Singh, H., et al. (2019). The impact of transcranial direct current stimulation on upper-limb motor performance in healthy adults: a systematic review and meta-analysis. *Front. Neurosci.* 13, 1213. doi: 10.3389/fnins.2019.01213

Polanía, R., Paulus, W., Antal, A., and Nitsche, M. A. (2011). Introducing graph theory to track for neuroplastic alterations in the resting human brain: a transcranial direct current stimulation study. *Neuroimage* 54, 2287–2296. doi: 10.1016/j.neuroimage.2010.09.085

Radman, T., Ramos, R. L., Brumberg, J. C., and Bikson, M. (2009). Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. *Brain Stimul, 2(4), 215-228* 228.e211–213. doi: 10.1016/j.brs.2009.03.007

Ramnani, N. (2006). The primate cortico-cerebellar system: anatomy and function. *Nat. Rev. Neurosci.* 7, 511–522. doi: 10.1038/nrn1953

Rampersad, S., Roig-Solvas, B., Yarossi, M., Kulkarni, P. P., Santarnecchi, E., Dorval, A. D., et al. (2019). Prospects for transcranial temporal interference stimulation in humans: a computational study. *Neuroimage* 202, 116124. doi: 10.1016/j.neuroimage.2019.116124

Rastogi, A., Cash, R., Dunlop, K., Vesia, M., Kucyi, A., Ghahremani, A., et al. (2017). Modulation of cognitive cerebello-cerebral functional connectivity by lateral cerebellar continuous theta burst stimulation. *Neuroimage* 158, 48–57. doi: 10.1016/j.neuroimage.2017.06.048

Rathelot, J. A., and Strick, P. L. (2009). Subdivisions of primary motor cortex based on cortico-motoneuronal cells. *Proc. Natl. Acad. Sci. USA.* 106, 918–923. doi: 10.1073/pnas.0808362106

Santos Ferreira, I., Teixeira Costa, B., Lima Ramos, C., Lucena, P., Thibaut, A., and Fregni, F. (2019). Searching for the optimal tDCS target for motor rehabilitation. *J. Neuroeng. Rehabil.* 16, 90. doi: 10.1186/s12984-019-0561-5

Saruco, E., Di Rienzo, F., Nunez-Nagy, S., Rubio-Gonzalez, M. A., Jackson, P. L., Collet, C., et al. (2017). Anodal tDCS over the primary motor cortex improves motor imagery benefits on postural control: a pilot study. *Sci. Rep.* 7, 480. doi: 10.1038/s41598-017-00509-w

Shmuelof, L., Krakauer, J. W., and Mazzoni, P. (2012). How is a motor skill learned? change and invariance at the levels of task success and trajectory control. *J. Neurophysiol.* 108, 578–594. doi: 10.1152/jn.00856.2011

Soekadar, S. R., Witkowski, M., Birbaumer, N., and Cohen, L. G. (2015). Enhancing hebbian learning to control brain oscillatory activity. *Cereb. Cortex* 25, 2409–2415. doi: 10.1093/cercor/bhu043

Sudbrack-Oliveira, P., Razza, L. B., and Brunoni, A. R. (2021). Non-invasive cortical stimulation: transcranial direct current stimulation (tDCS). *Int. Rev. Neurobiol.* 159, 1–22. doi: 10.1016/bs.irn.2021.01.001

Tecchio, F., Zappasodi, F., Assenza, G., Tombini, M., Vollaro, S., Barbati, G., et al. (2010). Anodal transcranial direct current stimulation enhances procedural consolidation. *J. Neurophysiol.* 104, 1134–1140. doi: 10.1152/jn.00661.2009

Wessel, M. J., Zimerman, M., Timmermann, J. E., Heise, K. F., Gerloff, C., and Hummel, F. C. (2016). Enhancing consolidation of a new temporal motor skill by cerebellar noninvasive stimulation. *Cereb. Cortex* 26, 1660–1667. doi: 10.1093/cercor/bhu335

Yang, K., Xi, X., Wang, T., Wang, J., Kong, W., Zhao, Y. B., et al. (2021). Effects of transcranial direct current stimulation on brain network connectivity and complexity in motor imagery. *Neurosci. Lett.* 757, 135968. doi: 10.1016/j.neulet.2021.135968

Yu, L., and Tomonaga, M. (2015). Interactional synchrony in chimpanzees: examination through a finger-tapping experiment. *Sci. Rep.* 5, 10218. doi: 10.1038/srep10218

Zhu, F. F., Yeung, A. Y., Poolton, J. M., Lee, T. M., Leung, G. K., and Masters, R. S. (2015). Cathodal transcranial direct current stimulation over left dorsolateral prefrontal cortex area promotes implicit motor learning in a golf putting task. *Brain Stimul.* 8, 784–786. doi: 10.1016/j.brs.2015.02.005

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Risk decision: The self-charity discrepancies in electrophysiological responses to outcome evaluation

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Previous studies have examined the outcome evaluation related to the self and other, and recent research has explored the outcome evaluation of the self and other with pro-social implications. However, the evaluation processing of outcomes in the group in need remains unclear. This study has examined the neural mechanisms of evaluative processing by gambling for the self and charity, respectively. At the behavioral level, when participants make decisions for themselves, they made riskier decisions following the gain than loss in small outcomes and engage in more risky behaviors following the loss than gain in large outcomes. However, magnitude and valence did not affect the next risky behavior when participants made decisions for the charity. At the neurophysiological level, the results found that the FRN was larger for the charity outcome than for the self-outcome. For FRN, the valence difference of small outcomes was smaller than that of large outcomes. The P3 response was larger for the self-outcome than for the charity outcome. Meanwhile, compared with the small outcome, the self-charity discrepancies have a significant difference in large outcomes. In addition, the FRN amplitude for self in large outcomes was negatively correlated with the upcoming risky choices, regardless of outcome valence. The behavioral results suggest that people are more likely to optimize strategies for themselves than for the charity. The ERP findings indicated that people focus more on charity outcome than self-outcome in the early stage. In the middle and late stages, people turn attention to their outcomes, and the difference between self's and charity's outcome varies with the magnitude. Specifically, it is only in large outcomes that people engage more emotional attention or motivation in their outcomes, but self and charity outcomes had a similar emotional engagement in small outcomes.

KEYWORDS

self, charity, outcome evaluation, gambling task, event-related potential

Introduction

It is crucial for people to make decisions quickly according to their behavioral outcomes. The rapid evaluation of outcome is an important cognitive function. Studies have identified FRN and P3 as ERP components related to outcome evaluative processing (Wang et al., 2017; Yang et al., 2018; Liu et al., 2020). For example, FRN and P3 not only represent indicators of early, middle and late processing of outcome evaluation, but also reflect the emotional or motivational level and the allocation of attention resources, respectively (Liu et al., 2020). Among them, FRN is a negative deflection that stems from frontocentral recording sites and peaks 250–300 ms after feedback stimulus (Yeung et al., 2005). The FRN is primarily considered as an indicator of emotional or motivational significance of feedback stimuli or reward prediction errors (Li et al., 2018). Gehring and Willoughby (2002) found that FRN reflects the emotional or motivational significance aroused by the current events. For example, outcomes of the self-executing condition elicited the larger FRN response than those of the observing condition, because of more emotional and motivational relevance in the self-executing condition (Yu and Zhou, 2006). In addition, the FRN is also associated with reward prediction errors, which trigger the greater FRN response when the outcome is worse (vs. better) than expected (Holroyd and Coles, 2002). P3 is a positive component that reaches its peak within 300–600 ms after the feedback stimulus and locates at centroparietal sites (Wu and Zhou, 2009). It is closely related to the allocation of attention resources and the motivational or emotional significance of outcomes (Nieuwenhuis et al., 2005). Self-relevant stimuli preferentially obtain attention resources and have the advantage of processing (Gray et al., 2004; Tacikowski and Nowicka, 2010). In outcome evaluation, self's outcomes have greater emotional and motivational value and can elicit a larger P3 amplitude than others' outcomes (Yu and Zhou, 2006).

A large number of studies have explored the neural mechanisms of the self-other decision-making and found that people pay more attention to their than others' outcomes (Itagaki and Katayama, 2008; Fukushima and Hiraki, 2009; Leng and Zhou, 2010; Tong et al., 2021). Specifically, Yu and Zhou (2006) found that the FRN effect (loss minus gain) elicited by the self-execution condition was larger than the observation condition. Fukushima and Hiraki (2009) further found that one's own outcomes elicited a greater FRN effect than that elicited by observing competitors' outcomes. Itagaki and Katayama (2008) further found that the FRN response to one's own outcomes was greater than that to observing outcomes for partners and competitors. From the perspective of interpersonal relationships, studies found that self-outcomes elicited larger FRN and P3 responses compared to observing friends and strangers (Leng and Zhou, 2010; Tong et al., 2021). Similarly, gambling for oneself elicited a greater brain response than gambling for others, and people allocate more emotional and cognitive resources to their outcomes (He et al., 2018; Liu et al., 2020; Xu, 2021). These results showed obvious the self-other discrepancies.

Prosocial decisions aim to help others in need (Shariff et al., 2016). Decision-making has prosocial implications when the beneficiary is the others or groups in need (Zlatev et al., 2020). However, the other people involved in the previous study did not have prosocial implications, just a stranger not in need or a friend (Itagaki and Katayama, 2008; Fukushima and Hiraki, 2009; Leng and Zhou, 2010; He et al., 2018; Tong et al., 2021). A few studies have explored the outcome evaluation of others with prosocial implications (Liu et al., 2020). However, Liu et al. (2020) only investigated the neural mechanism of outcomes related to a stranger in need, and the outcome evaluation of the group in need is still unclear. Studies have found that people have different psychological and behavioral responses toward single and numerous people who need help (Slovic, 2010). Specifically, people had more emotional experiences with the individual in need and were inclined to help a single individual in need than group in need (Kogut and Ritov, 2005; Small et al., 2007). Given the difference between the individual and group in need, it is necessary to examine self-other decision-making from a group perspective.

Recently, a study explored self-charity discrepancies in risk preference and found that people are more likely to choose the risky option when making decisions for themselves than for charity or a homeless stranger (Zlatev et al., 2020). However, the above study did not explore the neural mechanisms underlying the evaluative processing of one's own and charity's outcomes. Additionally, feedback evaluation was influenced by outcome magnitude (Goyer et al., 2008; Gu et al., 2011), but the magnitude effect on the self–other decision-making is also unclear. Therefore, we used ERP techniques to explore the evaluation processing of self and charity. It can help understand the neural mechanism between self and others and enrich the outcome evaluation from the group perspective.

A study found that making decisions for charity was less risky than making decisions for oneself (Zlatev et al., 2020). Therefore, we assumed that the risk rate of making decisions for oneself was significantly higher than that of making decisions for charity. Slovic (2010) found that multiple beneficiaries reduced people's emotional involvement, we expected that self-elicited larger FRN and P3 responses than charity. Meanwhile, Liu et al. (2020) found that empathic concern only moderated the FRN response and that the valence effect of the FRN was as strong for the stranger outcome in the high-empathy condition (i.e., the stranger-in-need condition) as it was for self-outcome. However, researches have found that people generate relatively less empathy for group in need than the individual in need

(Small et al., 2007; Erlandsson et al., 2015). We expected that self-outcome had a larger valence effect on the FRN than the charity outcome. Moreover, compared with small outcomes, large outcomes can bring a larger reward level and have a higher emotional arousal (Xu et al., 2018). We expected outcomes of self and charity to respond differently to different magnitudes.

Materials and methods

Participants

A power analysis (G*Power 3.1) suggested that 16 participants would ensure 80% statistical power in the case of small to medium effect sizes (Faul et al., 2007). All participants received 25 yuan for participation and were awarded up to 15 yuan based on their task choice. A total of 35 college students were recruited from Hunan Normal University, and four of them were excluded from the subsequent analysis due to a lack of valid trials for a certain condition, including 31 valid subjects (M_{age} = 19.45, SD = 1.20, 16 female). All participants had no history of neurological or psychiatric disorders. They had normal or corrected vision and were right-handed.

Procedure

Participants were required to perform a gambling task for themselves and charity (China Charity Federation). The task was to choose between the numbers 9 and 99, and the credits they selected could be gained or lost according to the feedback after making the choice (Yang et al., 2018). The credits for the same beneficiary kept accumulating during the task. The credits accumulated in the task can be converted into cash in a certain proportion and determined participants' and the charity's reward. Among them, we made real and anonymous donations to charity. The whole experiment included a practice and a formal experiment. The practice experiment included 16 trials. Only after the participants completely understood the task rules did they start the formal experiment. The formal task consists of two blocks (480 trials), 240 trials each. However, what the participants did not know was that the probability of winning or losing feedback was 0.5. That is, a block had 120 positive and negative feedback in the experiment setting. However, because each participant had the different number of small and large outcomes, we could only achieve a similar total number of positive and negative feedback in each participant's choice number of the large and small outcomes. The average number of trials for each condition was shown in **Table 1**. Each block began with a cue (for self and charity). Each trial started from the central fixation point of 1200 ms, and then the participants were asked to press F or J on the keyboard to choose between 9 and 99. Then, the selected option was highlighted in red and displayed for 500 ms. Thereafter, blank rectangles were randomly presented at 800–1200 ms on the screen. Positive or negative feedback was presented in the rectangle of the selected number (see **Figure 1**).

TABLE 1 The mean trials and discarded trials of all the experimental conditions.

Conditions		Gain	Loss
Charity	Small outcome	63.32 (5.06)	61.39 (4.84)
	Large outcome	57.23 (4.91)	58.06 (4.32)
Self	Small outcome	67.39 (3.74)	67.45 (3.26)
	Large outcome	52.81 (2.55)	52.35 (2.03)

The value in parentheses is the mean of discarded trials in the EEG analysis.

EEG recording and analysis

We used 32 scalp sites of Brain Products to record the electrical activity of the brain. A horizontal electrooculogram (EOG) was recorded by placing electrodes above both eyes. Meanwhile, the sampling rate was 500 Hz/channel, and the filter bandpass was 0.05–100 Hz. The impedance between all electrodes and scalp was less than 5 kΩ. The online reference electrode is Fz, and the offline reference is the average of the left and right mastoids. After the continuous recording of EEG data, offline analysis was performed. EEG data were analyzed using the EEGLAB toolkit. First, the data are filtered with parameters from 0.1 to 30 Hz (filter slopes: 24 dB/octave). Then, ICA was used to remove EOG and artifacts. Then, the data was segmented for a period from 200 ms before feedback onset to 1000 ms. Finally, we excluded artifacts with wave amplitude greater than ±100 μV. Combined with a visual inspection of brain topography and waveform and based on the previous literature and experimental purposes (Hu et al., 2017; Yang et al., 2018; Liu et al., 2020), we calculated the mean values of FRN amplitude within 220–310 ms window after the outcome feedbacks were presented and used the mean value within 310–420 ms time window to calculate P3. F3, Fz, F4, FC1, FC2, C3, Cz, and C4 were selected as the analytical electrodes of FRN, while C3, Cz, C4, CP1, CP2, Pz, P3, and P4 were selected as the analytical electrodes of P3. After data processing, we determined the average trials under each condition ("charity-small gain": 58.26, "charity-small loss": 56.55, "charity-large gain": 52.32, "charity-large loss: 53.74, "self-small gain": 63.65, "self-small loss": 64.19, "self-large gain": 50.26, "self-large loss": 50.32, $F(7, 240) = 1.77$, $p = 0.094$). We performed the average amplitude of FRN and P3 on 2 (beneficiary: self vs. charity) × 2 (valence: gain vs. negative) × 2 (magnitude: large vs. small) repeated-measures analysis of variance (ANOVA). All data analyses were performed using SPSS 26.

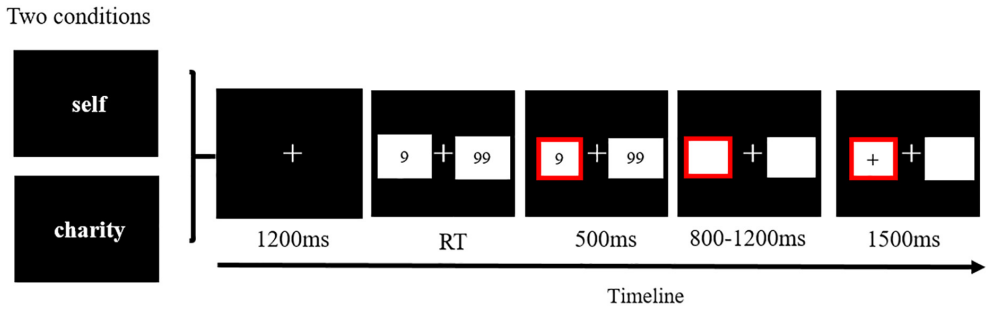

FIGURE 1
An illustration of a single trial.

Results

Behavior results

We define 99 as the risky option (Yang et al., 2018). The paired sample *t*-test was used to compare the ratio of risky choices among the self and charity, but there was not significant difference [$t(30) = 1.30$, $p = 0.204$]. We further examined the effect of feedback on the next risk-taking behavior, and the ratio of 99 on the next trial was chosen by the participants as the dependent variable. We conducted a 2 (beneficiary: self vs. charity) × 2 (valence: gain vs. loss) × 2 (magnitude: large vs. small) repeated-measures ANOVA. The main effect of the magnitude was significant [$F(1,30) = 19.77$, $p < 0.001$, $\eta_p^2 = 0.40$]. Consistent with previous studies (Yang et al., 2018), participants chose more high-risk options following a large outcome than a small outcome (54.1 ± 19.0% vs. 37.8 ± 17.7%). The interaction between magnitude and valence was significant [$F(1,30) = 8.96$, $p = 0.005$, $\eta_p^2 = 0.23$]. More importantly, the effect was moderated by beneficiary [$F(1,30) = 9.42$, $p = 0.005$, $\eta_p^2 = 0.24$]. When the beneficiary was oneself, the interaction between magnitude and valence was significant [$F(1,30) = 25.95$, $p < 0.001$, $\eta_p^2 = 0.46$]. This simple effect found that participants were more likely to choose high-risk options following small positive outcomes than small negative outcomes (40.7 ± 20.6% vs. 32.2 ± 18.6%), but participants chose fewer high-risk options following large positive outcomes than large negative outcomes (48.8 ± 20.8% vs. 58.0 ± 18.4%). The interaction between magnitude and valence was not significant when the beneficiary was the charity [$F(1,30) = 0.10$, $p = 0.756$]. Other effects were not significant [$Fs(1,30) < 1.19$, $ps > 0.29$].

The FRN results

The main effect of the beneficiary was significant [$F(1,30) = 7.05$, $p = 0.013$, $\eta_p^2 = 0.19$], and the FRN elicited by the charity was larger than self (5.74 ± 3.54 μV vs. 7.06 ± 3.94 μV) (see Figure 2). The main effect of the magnitude was significant [$F(1,30) = 57.92$, $p < 0.001$, $\eta_p^2 = 0.66$], and the FRN elicited by small outcomes was larger than that elicited by large outcomes (4.48 ± 3.44 μV vs. 8.33 ± 4.05 μV), which was consistent with the previous studies (Gu et al., 2011). Also consistent with the previous findings (Yang et al., 2018), the main effect of valence was significant [$F(1,30) = 36.68$, $p < 0.001$, $\eta_p^2 = 0.55$], and the loss outcomes elicited a larger FRN than the gain outcomes (5.33 ± 2.99 μV vs. 7.48 ± 4.15 μV). The interaction between magnitude and valence was significant [$F(1,30) = 8.15$, $p = 0.008$, $\eta_p^2 = 0.21$], and the valence difference in the small outcomes [5.16 ± 3.99 μV vs. 3.80 ± 3.24 μV, $F(1,30) = 10.24$, $p = 0.003$, $\eta_p^2 = 0.25$] was smaller than the valence difference of large outcomes [9.80 ± 4.84 μV vs. 6.86 ± 3.59 μV, $F(1,30) = 37.90$, $p < 0.001$, $\eta_p^2 = 0.56$]. To explore the interaction further, we analyzed the mean amplitude of the FRN on the difference waves (loss minus gain). We found that the FRN effect (loss minus gain) of large outcomes was larger than that of small outcomes [−2.94 ± 2.66 μV vs. −1.35 ± 2.35 μV, t (30) = 2.86, $p = 0.008$, d = 1.04] (see Figure 3). Other interactions were not significant [$Fs(1,30) < 1.62$, $ps > 0.21$]. The total mean waveforms for all conditions were shown in Figure 4.

The P3 results

The main effect of the beneficiary was significant [$F(1,30) = 10.43$, $p = 0.003$, $\eta_p^2 = 0.26$], and P3 amplitude elicited by self was larger than charity (11.29 ± 5.64 μV vs. 8.78 ± 4.34 μV). The main effect of magnitude was significant [$F(1,30) = 56.31$, $p < 0.001$, $\eta_p^2 = 0.65$], and the P3 elicited by large outcomes was larger than that elicited by small outcomes (13.03 ± 5.85 μV vs. 7.04 ± 4.11 μV), which was consistent with the previous studies (Liu et al., 2020). Consistent with the previous findings (Kou et al., 2022), the main effect of valence was significant [$F(1,30) = 22.19$, $p < 0.001$, $\eta_p^2 = 0.43$], and gain outcomes elicited larger P3 amplitude (10.70 ± 4.86 μV vs. 9.37 ± 4.34 μV) than the loss outcomes.

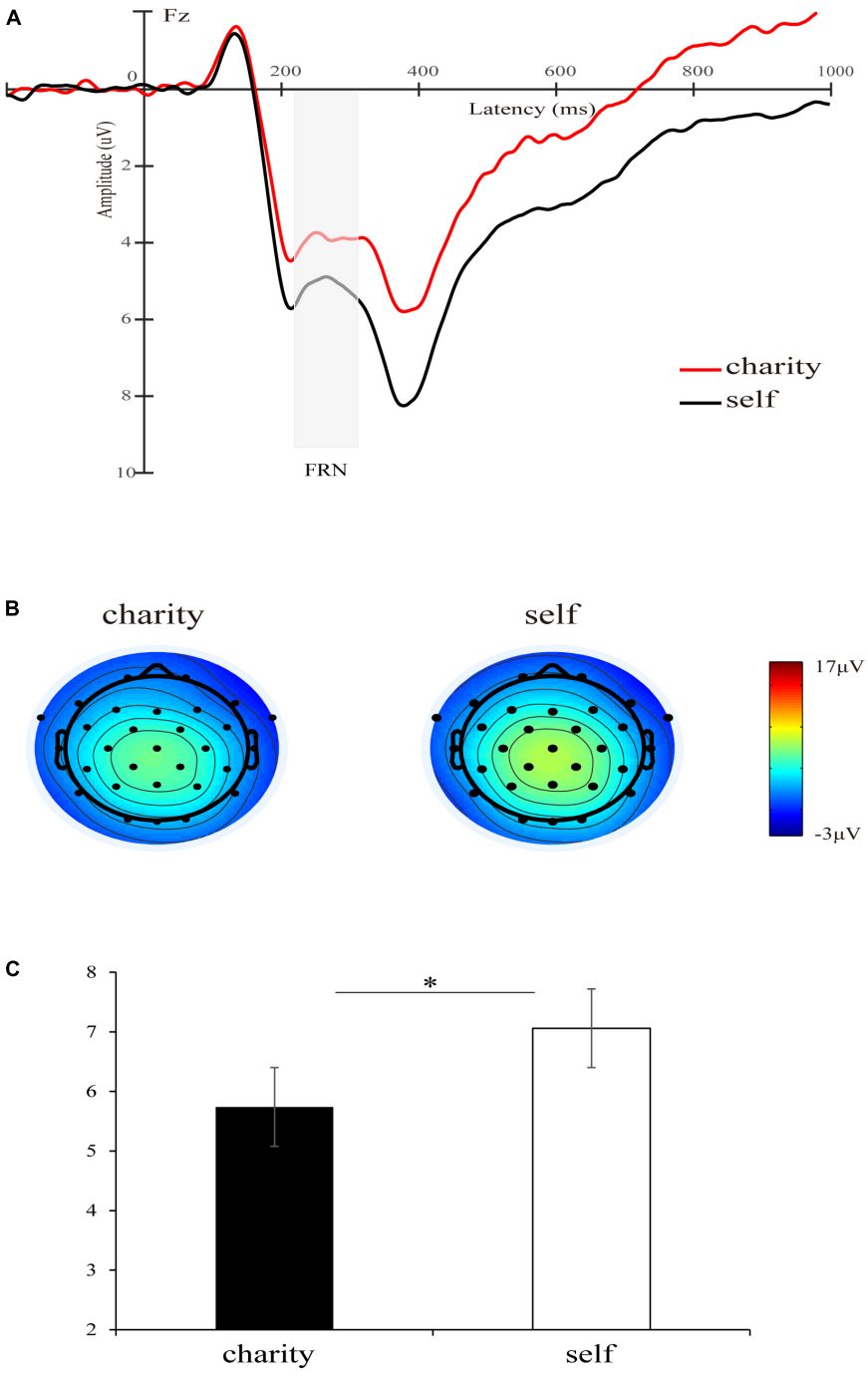

FIGURE 2
(A) Grand-average ERP waveforms of FRN at Fz electrode site, the gray area highlights the 220–310 ms time window for calculating the mean value of the FRN amplitude. The red line represents the waveform of the charity and the black represents the waveform of self. **(B)** Topographic maps of charity and self-condition. **(C)** The bar graphs and standard errors show the mean values of FRN for charity and self-condition. *$p < 0.05$.

The interaction between beneficiary and magnitude was significant [$F(1,30) = 6.32$, $p = 0.018$, $\eta_p^2 = 0.17$]. There was no significant difference between self and charity in small outcomes [7.82 ± 4.76 μV vs. 6.26 ± 4.59 μV, $F(1,30) = 3.82$, $p = 0.060$, $\eta_p^2 = 0.11$], but the difference between self and charity was significant in large outcomes [14.76 ± 7.04 μV vs. 11.29 ± 5.68 μV, $F(1,30) = 13.99$, $p = 0.001$, $\eta_p^2 = 0.32$] (see Figure 5). Other interactions were not significant [Fs $(1,30) < 1$,

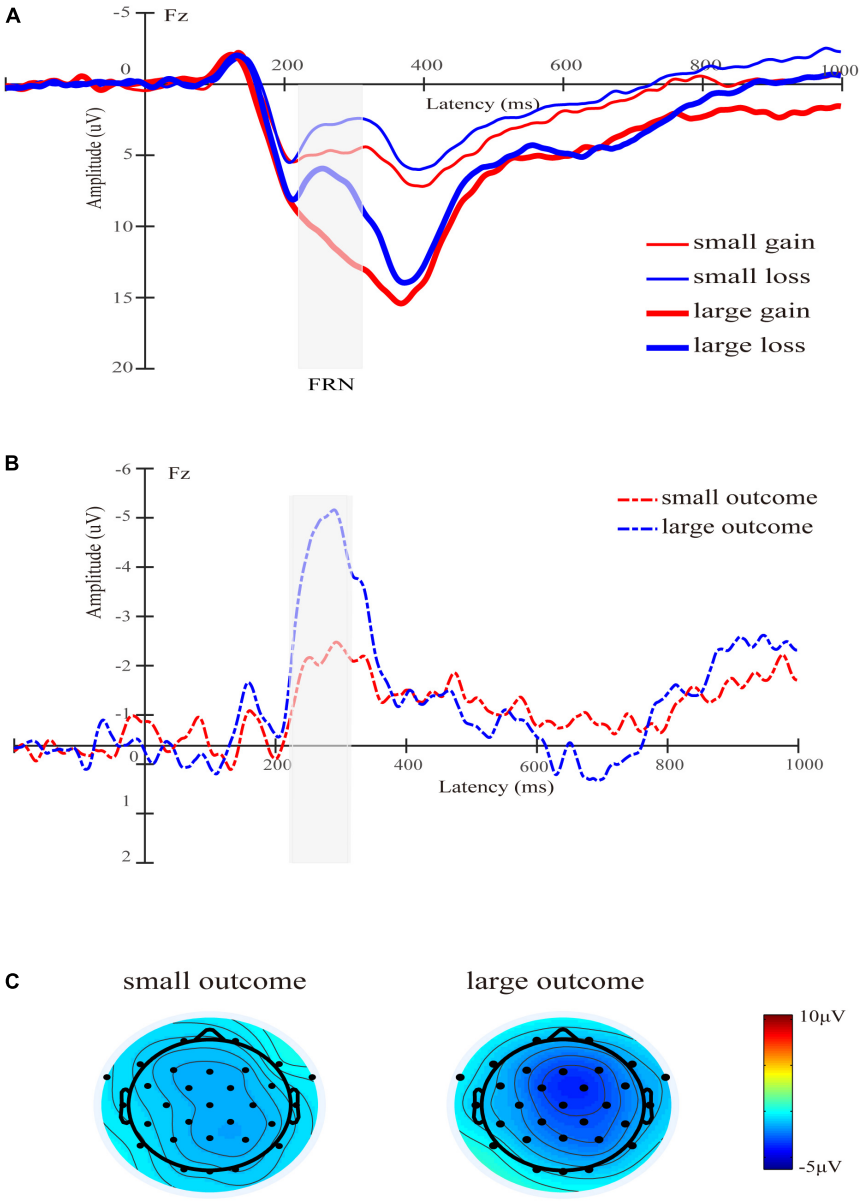

FIGURE 3
(A) Grand-average ERP waveforms of FRN at Fz electrode site. The gray area highlights the 220–310 ms time window for calculating the mean value of FRN. The thin red line represents the waveform with a small gain condition, the thin blue line represents the waveform with a small loss condition, the thick red line represents the waveform with a large gain condition, and the thick blue line represents the waveform with a large loss condition. **(B)** The difference wave of FRN in the 220–310 ms time window (loss minus gain). **(C)** The scalp topographies of the difference for small and large outcomes are presented.

ps > 0.46]. The total average P3 waveforms for all conditions were shown in Figure 6.

Correlation analysis

Some studies have shown that FRN is related to the risky decision of the next trial (Hewig et al., 2007; Kiat et al., 2016), and the interaction between magnitude and valence has also been found on the FRN amplitude, which is consistent with the behavioral results. Therefore, we conducted the correlation analysis between FRN and behavior. The separate correlation analyses were conducted between magnitude and valence according to the different beneficiaries. This result found that FRN amplitudes were significantly negatively correlated with both positive and negative large outcomes involving the self (r_{gain} = −0.50, p = 0.004, r_{loss} = −0.39, p = 0.032), but this pattern of correlation was absent in small outcomes (r_{gain} = 0.04,

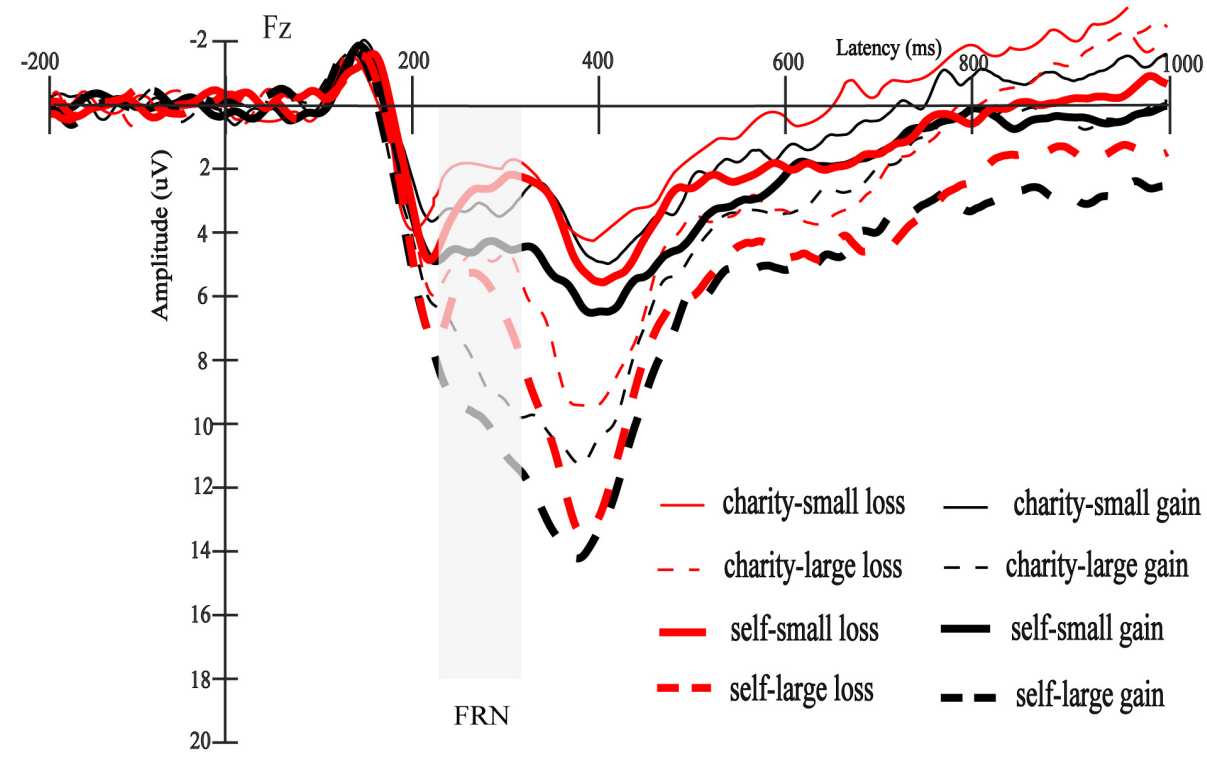

FIGURE 4
The total average FRN waveforms for all conditions.

$p = 0.833$, $r_{loss} = -0.28$, $p = 0.122$). Meanwhile, we also found a related trend between FRN amplitudes and large positive outcomes involving the charity ($r_{gain} = -0.32$, $p = 0.082$). The correlation analysis results were shown in **Table 2**.

Discussion

This study examined outcome evaluation related to self and charity. This result showed that self and charity have similar risk-taking behaviors. Our findings indicate that the outcomes of the charity and self are different at two stages of evaluation. The results are discussed in detail by risky ratio, FRN and P3, respectively.

The results showed that the risky behavior between self and charity was similar, which is inconsistent with the hypothesis. Zlatev et al. (2020) found that people were more likely to take risks when making decisions for themselves than for charity or stranger-in-need. In contrast, Liu et al. (2020) found that the stranger-in-need and self were similar in risky behaviors involving outcome evaluation. This may be caused by differences in the operational definition of risky behavior. The risky option was a larger reward with a probability of 75% and $0 with a probability of 25%, while the non-risky option was a small, certain reward (Zlatev et al., 2020). However, both large and small rewards had a 50% chance of loss or gain in the outcome evaluations (Liu et al., 2020), which were consistent with our study. Studies have shown that probability affects risk-taking behavior (Sun et al., 2009). Therefore, the probability of risky behaviors in studies may cause inconsistency in results. In addition, at the behavioral level, when participants made decisions for themselves, they are more likely to seek risk to maximize their self-interest after positive feedback than negative feedback in the small outcome. However, they were more likely to choose the high-risk option after high-risk choice with negative feedback in the large outcome, which is consistent with previous studies (Schuermann et al., 2012). High-risk behavior may be intended to avoid negative consequences in the future, since conservative behavior after the large loss cannot compensate for the loss. And people are more willing to protect the money they have had and to act more conservatively after the large gain. When participants made decisions for the charity, this risk-taking behavior was unaffected by the magnitude and valence of the feedback, i.e., the same strategy was used for both large and small outcomes. This suggests that people are more likely to optimize decisions for their own interests than for the charity's interests.

FRN reflects emotional or motivational evaluation of the current outcome at an early stage (Gehring and Willoughby,

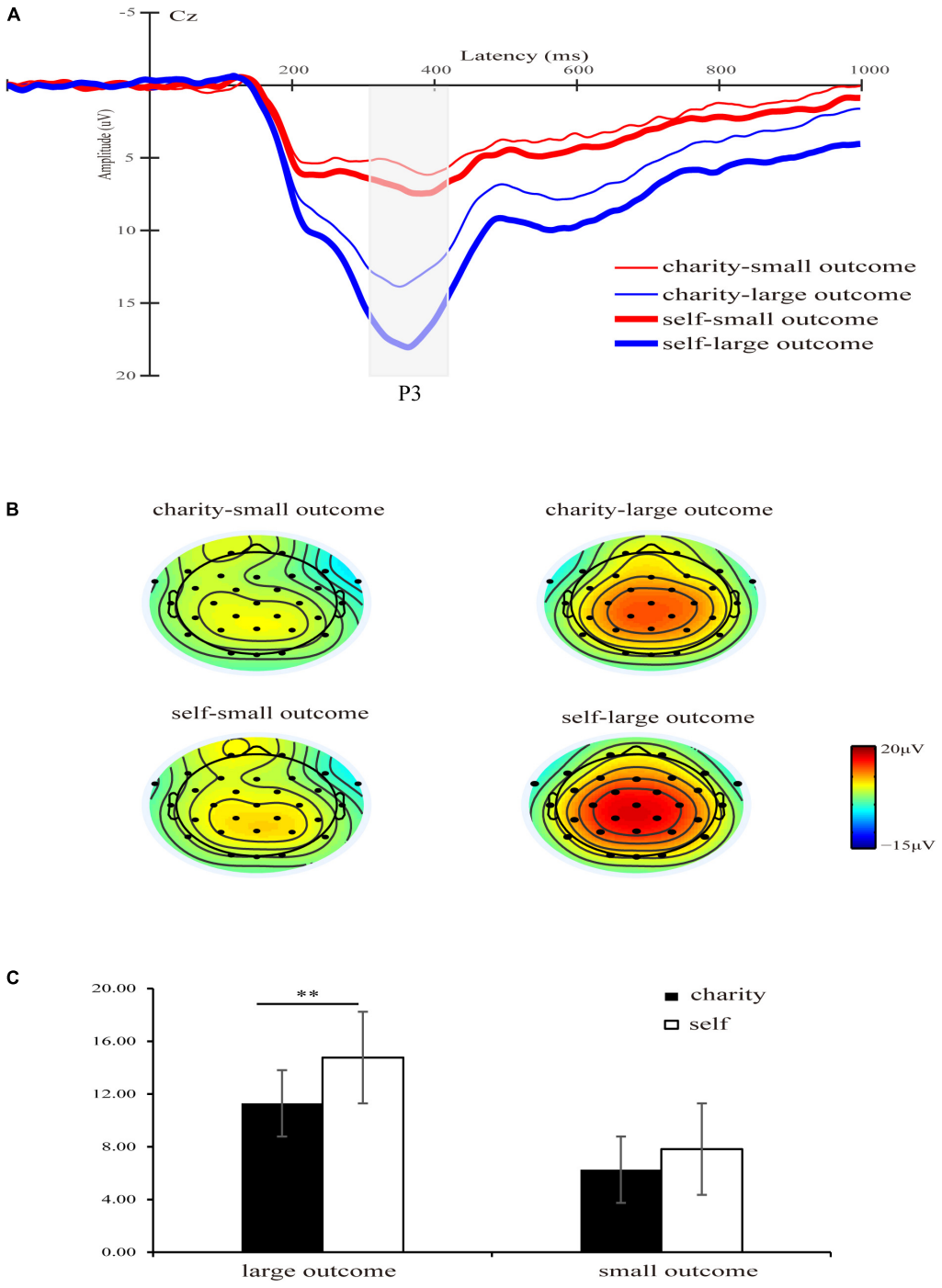

FIGURE 5
(A) Grand-average ERP waveforms of P3 at Cz electrode site, the gray area highlights the 310–420 ms time window for calculating the mean value of the P3 amplitude. The thin red line represents the waveform with a charity-small outcome condition, the thin blue line represents the waveform with a charity-large outcome condition, the thick red line represents the waveform with a self-small outcome condition, and the thick blue line represents the waveform with a self-large outcome condition. **(B)** Topographic maps of P3 of each condition. **(C)** The bar graphs and standard errors show the mean values of P3 for each condition. $^{**}p < 0.01$.

2002). We found that charity outcomes elicited greater FRN responses than self-outcomes. This was inconsistent with our hypothesis that people had stronger emotional concern toward single rather than multiple beneficiaries (Slovic, 2010). This may be because, compared with individualism, collectivism is more about collective than individual interests (Chen et al.,

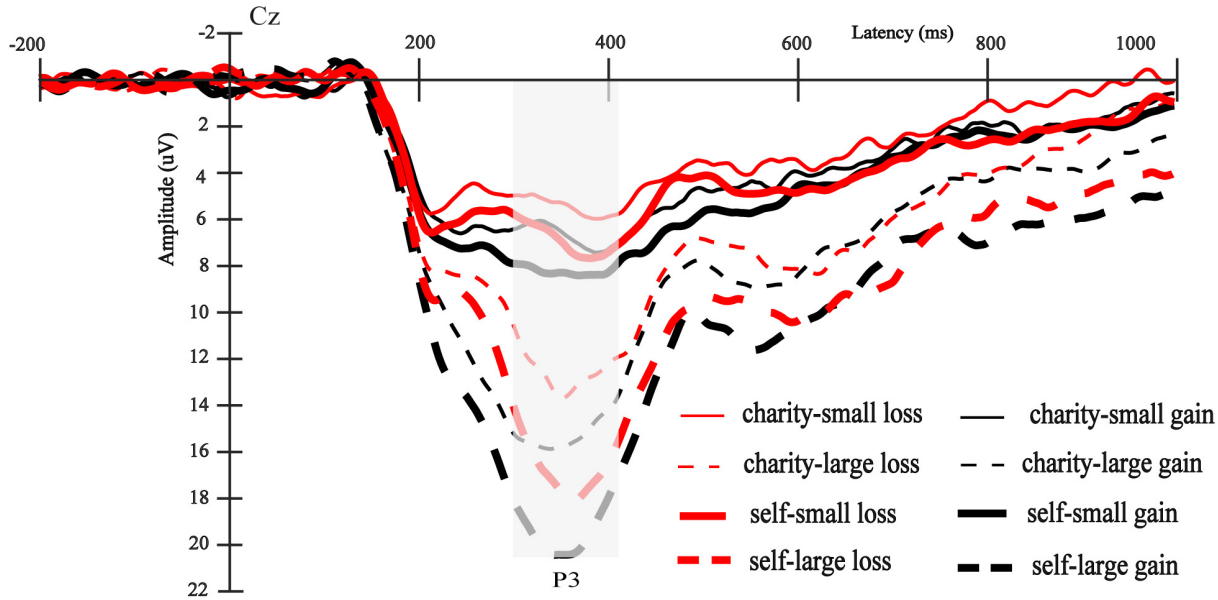

FIGURE 6
The total average P3 waveforms for all conditions.

TABLE 2 Correlation analysis results.

Conditions		*r*	*p*
Charity	+9	−0.11	0.543
	−9	0.13	0.503
	+99	−0.32	0.082
	−99	−0.15	0.434
Self	+9	0.04	0.833
	−9	−0.28	0.122
	+99	−0.50**	0.004
	−99	−0.39*	0.032

Correlation coefficient is statistically significant at $^{*}p < 0.05$, $^{**}p < 0.01$.

1997). Chinese participants recruited by this experiment would pay more emotional attention to the collective outcomes. Another possible explanation is that this represents a difference in expected errors. According to the reinforcement learning-error-related negativity theory, FRN is sensitive to expectancy violations (Holroyd and Coles, 2002; Hewig et al., 2011). In other word, this causes a greater FRN response when the actual outcomes do not match the expected outcomes. The homo economicus assumption holds that humans are self-interested actors (Smith, 1776). People are more likely to expect their own outcomes from this assumption. Thus, this gap between actual outcomes and previous expectations triggered a larger FRN response when charity outcomes were presented.

The results found that loss elicited a larger FRN response than gain for large outcomes, while this effect was weaker for small outcomes. This was consistent with previous studies (Yang et al., 2018). Some studies have shown that the FRN showed a relatively positive deflection in the reward condition (San Martín et al., 2010). Positive emotions induce activities of the midbrain dopamine system, which makes the brain more sensitive to rewards, leading to the positive deflection for FRN (Mushtaq et al., 2016). This suggests that gain induces a smaller FRN response than loss. The magnitude of the outcome is the index of the level of emotion or motivation and has different benefit levels (San Martín, 2012). The reduction of the reward level also decreases people's emotions and motivation levels. Therefore, the FRN effect for large outcomes is larger than the FRN effect for small outcomes. This suggests that FRN can recognize the rank of outcomes, and large outcomes carry greater weight in emotional and motivational relevance.

However, the results found that the FRN effect of charity was as strong as that of self, which was inconsistent with the hypothesis. The greater the number of people in need, the less empathy generates (Erlandsson et al., 2015). In other words, charity can evoke less empathy than an individual in need, which can lead to differences in emotional salience between the self and charity. But Chinese people pay more attention to group interests generally (Chen et al., 1997), which may compensate for this difference between self and charity. Therefore, the FRN effects of charity and self were similar. There is another possible explanation. From the perspective of expectancy violation, some studies have found that people always expect the outcome of helping others to be successful, so the failed feedback induces a stronger FRN than the successful feedback when helping

others (Gan et al., 2016, 2022). In the same way, people also expect to get better self-outcomes to maximize the self-interest, so loss also induces a greater FRN response than gain. In short, people have the same expectations of themselves and charity outcomes, so the FRN effects of charity and self are similar.

Moreover, charity and self-outcomes were not affected by the magnitude in the FRN amplitude. This is not consistent with the hypothesis. A possible reason is that the participants' concern for group interests reduced the discrepancy between the charity and themselves in different magnitudes. Another factor might be that the charity is pro-social. Studies have shown that prosocial behaviors can experience vicarious rewards, such as happiness (Dunn et al., 2008; Aknin et al., 2013). Specifically, prosocial behavior refers to the involvement of the ventromedial prefrontal cortex (VMPFC) (Morelli et al., 2015), which monitors the subjective value of behavioral outcomes and guides decision-making by increasing the motivational significance of behaviors (Carlson et al., 2016). These results indicate that charitable outcomes will activate people's higher motivational relevance and emotion levels. Therefore, for both large and small outcomes, the FRN response of charitable outcomes was greater than that of self-outcomes. In other words, this prosocial involvement weakens hierarchically magnitude sensitivity in the early stage. Interestingly, the FRN amplitude for self in large outcomes was negatively associated with possibility of making risky decisions on the next trial, while this correlation was absent in small outcomes. High-risk decisions may also reflect the motivational or emotional significance compared with low-risk decision (Schuermann et al., 2012), and larger outcomes also activate greater levels of emotion or motivation (San Martín, 2012). Thus, the FRN amplitude was significantly negatively correlated with large outcomes for the self. However, small outcomes reduce people's motivational or emotional level, which weakens the correlation between FRN amplitude and future risky behaviors.

P3 reflects the significance of emotion or motivation, which can process current events in a relatively accurate manner (Nieuwenhuis et al., 2005). It was found that self-outcomes evoked larger P3 amplitude than charity outcomes, which was consistent with the previous studies that self-interest evoked greater motivational or emotional significance (Yu and Zhou, 2006). This suggests that, in the middle and later stages, participants focus more on self-outcomes and allocate more attention resources to themselves. Importantly, we found that self-elicited larger P3 amplitude than charity for large outcomes. However, with small outcomes, the difference disappears. The motivational significance can be measured by the magnitude of the outcomes (San Martín, 2012). Specifically, the magnitude of the outcomes represents different levels of reward, and large outcomes activate greater interests and have stronger motivational significance and emotional response than the small ones. Self-gains and losses in large outcomes are associated with higher levels of self-interest, evoking higher levels of emotion and motivation. Consequently, this increases the level of emotion and motivation for self-outcomes. However, small outcomes reduce the level of reward and people's arousal to self-interest, which makes people have a similar P3 amplitude for self and charity in small outcomes.

Our study has several limitations. First, our risk behavior mainly involves binary gambling tasks. However, in everyday life, we face situations more complex than simple binary game tasks. Meanwhile, this paradigm lacks real-life scenarios, which may make it difficult to generalize the experimental results to real life. So, future research could explore differences in outcome evaluation by asking participants to perform more complex decision tasks or more realistic tasks for themselves and charity. Moreover, our sample comes from China with a collectivist culture. Compared with Chinese participants who focus on collective interests, participants from western cultures may show different outcome processing. Therefore, future cross-cultural research needs to confirm this difference in outcome evaluation between self and charity. Although we have attributed the self-charity discrepancies in electrophysiological responses to emotional or motivational salience, expectancy violations as mentioned in the discussion may also play a role. Particularly, P3 is related to action updating (Donchin and Coles, 1988; Yang et al., 2018). The action updating may also has a potential impact in outcome evaluation. Future research could examine the effect of other factors, such as action updating, given that P3 has various cognitive functions. Finally, we did not directly compare individuals in need with charity and could not account for the difference in outcome evaluation between individuals and groups with prosocial implications. Future research can explore the difference between individual and group levels.

Conclusion

This study has used ERP technology to explore differences in outcome evaluation between self and charity. People are more likely to adjust strategies for their own outcomes than for charity outcomes from behavioral results. Meanwhile, in the early stage, individuals paid more emotional investment to charity than to their outcomes (FRN as the indicator). In the middle and later stages, individuals focus more on their outcomes than on the outcomes of the charity (P3 as the indicator). Moreover, the difference in emotional or motivational concerns between self and charity was only moderated by the magnitude in the middle and late stages. In other words, individuals focus more on their outcomes than on the outcomes of the charity in large outcomes, while

self and charity have similar emotional or motivational concerns for small outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Board of Hunan Normal University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MT, ML, and YZ designed the experiment. MT, HL, and CY carried out the experiments. MT, ML, and JL analyzed the data. MT and GZ wrote the manuscript. All authors edited and approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Aknin, L. B., Barrington-Leigh, C. P., Dunn, E. W., Helliwell, J. F., Burns, J., and Biswas-Diener, R. (2013). Prosocial spending and well-being: cross-cultural evidence for a psychological universal. *J. Pers. Soc. Psychol.* 104, 635–652. doi: 10.1037/a0031578

Carlson, R. W., Aknin, L. B., and Liotti, M. (2016). When is giving an impulse? An ERP investigation of intuitive prosocial behavior. *Soc. Cogn. Affect. Neurosci.* 11, 1121–1129.

Chen, C. C., Meindl, J. R., and Hunt, R. G. (1997). Testing the effects of vertical and horizontal collectivism: a study of reward allocation preferences in China. *J. Cross Cult. Psychol.* 28, 44–70. doi: 10.1177/0022022197281003

Donchin, E., and Coles, M. G. (1988). Is the P300 component a manifestation of context updating? *Behav. Brain Sci.* 11, 357–374. doi: 10.1017/S0140525X00058027

Dunn, E. W., Aknin, L. B., and Norton, M. I. (2008). Spending money on others promotes happiness. *Science* 319, 1687–1688. doi: 10.1126/science.1150952

Erlandsson, A., Björklund, F., and Bäckström, M. (2015). Emotional reactions, perceived impact and perceived responsibility mediate the identifiable victim effect, proportion dominance effect and in-group effect respectively. *Organ. Behav. Hum. Decis. Process.* 127, 1–14. doi: 10.1016/j.obhdp.2014.11.003

Faul, F., Erdfelder, E., Lang, A.-G., and Buchner, A. (2007). G* Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav. Res. Methods* 39, 175–191. doi: 10.3758/BF03193146

Fukushima, H., and Hiraki, K. (2009). Whose loss is it? Human electrophysiological correlates of non-self reward processing. *Soc. Neurosci.* 4, 261–275. doi: 10.1080/17470910802625009

Gan, T., Wang, L., Zhang, L., Fang, W., and Gu, R. (2016). The neural correlates of evaluating the outcome of prosocial-helping decisions. *Neuroreport* 27, 1293–1298. doi: 10.1097/WNR.0000000000000696

Gan, T., Zhang, Y., Zhang, L., and Gu, R. (2022). Neural sensitivity to helping outcome predicts helping decision in real life. *Neuropsychologia* 173:108291. doi: 10.1016/j.neuropsychologia.2022.108291

Gehring, W. J., and Willoughby, A. R. (2002). The medial frontal cortex and the rapid processing of monetary gains and losses. *Science* 295, 2279–2282. doi: 10.1126/science.1066893

Goyer, J. P., Woldorff, M. G., and Huettel, S. A. (2008). Rapid electrophysiological brain responses are influenced by both valence and magnitude of monetary rewards. *J. Cogn. Neurosci.* 20, 2058–2069. doi: 10.1162/jocn.2008.20134

Gray, H. M., Ambady, N., Lowenthal, W. T., and Deldin, P. (2004). P300 as an index of attention to self-relevant stimuli. *J. Exp. Soc. Psychol.* 40, 216–224. doi: 10.1016/S0022-1031(03)00092-1

Gu, R., Lei, Z., Broster, L., Wu, T., Jiang, Y., and Luo, Y.-J. (2011). Beyond valence and magnitude: a flexible evaluative coding system in the brain. *Neuropsychologia* 49, 3891–3897. doi: 10.1016/j.neuropsychologia.2011.10.006

He, Q., Sun, Q., Shi, Z., Zhang, X., and Hu, F. (2018). Effect of social distance on outcome evaluation in self–other decision-making: evidence from event-related potentials. *Neuroreport* 29, 1499–1503. doi: 10.1097/WNR.0000000000001141

Hewig, J., Kretschmer, N., Trippe, R. H., Hecht, H., Coles, M. G., and Holroyd, C. B. (2011). Why humans deviate from rational choice. *Psychophysiology* 48, 507–514. doi: 10.1111/j.1469-8986.2010.01081.x

Hewig, J., Trippe, R., Hecht, H., Coles, M. G., Holroyd, C. B., and Miltner, W. H. (2007). Decision-making in blackjack: an electrophysiological analysis. *Cereb. Cortex* 17, 865–877. doi: 10.1093/cercor/bhk040

Holroyd, C. B., and Coles, M. G. (2002). The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychol. Rev.* 109, 679–709. doi: 10.1037/0033-295X.109.4.679

Hu, X., Xu, Z., and Mai, X. (2017). Social value orientation modulates the processing of outcome evaluation involving others. *Soc. Cogn. Affect. Neurosci.* 12, 1730–1739. doi: 10.1093/scan/nsx102

Itagaki, S., and Katayama, J. (2008). Self-relevant criteria determine the evaluation of outcomes induced by others. *Neuroreport* 19, 383–387. doi: 10.1097/WNR.0b013e3282f556e8

Kiat, J., Straley, E., and Cheadle, J. E. (2016). Escalating risk and the moderating effect of resistance to peer influence on the P200 and feedback-related negativity. *Soc. Cogn. Affect. Neurosci.* 11, 377–386. doi: 10.1093/scan/nsv121

Kogut, T., and Ritov, I. (2005). The "identified victim" effect: an identified group, or just a single individual? *J. Behav. Decis. Mak.* 18, 157–167. doi: 10.1002/bdm.492

Kou, M., Zhang, H., Lv, Y., and Luo, W. (2022). The effects of depression tendency and social comparison on adolescent self-evaluation. *Neuropsychologia* 170:108236. doi: 10.1016/j.neuropsychologia.2022.108236

Leng, Y., and Zhou, X. (2010). Modulation of the brain activity in outcome evaluation by interpersonal relationship: an ERP study. *Neuropsychologia* 48, 448–455. doi: 10.1016/j.neuropsychologia.2009.10.002

Li, D., Li, P., and Li, H. (2018). The updated theories of feedback-related negativity in the last decade. *Adv. Psychol. Sci.* 26, 1642–1650. doi: 10.3724/SP.J.1042.2018.01642

Liu, X., Hu, X., Shi, K., and Mai, X. (2020). Your losses are mine: the influence of empathic concern on evaluative processing of others' outcomes. *Cogn. Affect. Behav. Neurosci.* 20, 481–492. doi: 10.3758/s13415-020-00779-4

Morelli, S. A., Sacchet, M. D., and Zaki, J. (2015). Common and distinct neural correlates of personal and vicarious reward: a quantitative meta-analysis. *Neuroimage* 112, 244–253. doi: 10.1016/j.neuroimage.2014.12.056

Mushtaq, F., Wilkie, R. M., Mon-Williams, M. A., and Schaefer, A. (2016). Randomised prior feedback modulates neural signals of outcome monitoring. *Neuroimage* 125, 868–879. doi: 10.1016/j.neuroimage.2015.10.046

Nieuwenhuis, S., Aston-Jones, G., and Cohen, J. D. (2005). Decision making, the P3, and the locus coeruleus–norepinephrine system. *Psychol. Bull.* 131, 510–532. doi: 10.1037/0033-2909.131.4.510

San Martín, R. (2012). Event-related potential studies of outcome processing and feedback-guided learning. *Front. Hum. Neurosci.* 6:304–321. doi: 10.3389/fnhum.2012.00304

San Martín, R., Manes, F., Hurtado, E., Isla, P., and Ibañez, A. (2010). Size and probability of rewards modulate the feedback error-related negativity associated with wins but not losses in a monetarily rewarded gambling task. *Neuroimage* 51, 1194–1204. doi: 10.1016/j.neuroimage.2010.03.031

Schuermann, B., Endrass, T., and Kathmann, N. (2012). Neural correlates of feedback processing in decision-making under risk. *Front. Hum. Neurosci.* 6:204. doi: 10.3389/fnhum.2012.00204

Shariff, A. F., Willard, A. K., Andersen, T., and Norenzayan, A. (2016). Religious priming: a meta-analysis with a focus on prosociality. *Pers. Soc. Psychol. Rev.* 20, 27–48. doi: 10.1177/1088868314568811

Slovic, P. (2010). "If I look at the mass I will never act": psychic numbing and genocide. *Judgm. Decis. Mak.* 2, 79–95. doi: 10.1007/978-90-481-8647-1_3

Small, D. A., Loewenstein, G., and Slovic, P. (2007). Sympathy and callousness: the impact of deliberative thought on donations to identifiable and statistical victims. *Organ. Behav. Hum. Decis. Process.* 102, 143–153. doi: 10.1016/j.obhdp.2006.01.005

Smith, A. (1776). *The Wealth of Nations*. New York, NY: Modern Library.

Sun, Y., Xu, J.-H., and Chen, X.-Y. (2009). The effects of cover stories, framing, and probability on risk preference in investment decision-making. *Acta Psychol. Sin.* 41, 189–195. doi: 10.3724/SP.J.1041.2019.00189

Tacikowski, P., and Nowicka, A. (2010). Allocation of attention to self-name and self-face: an ERP study. *Biol. Psychol.* 84, 318–324. doi: 10.1016/j.biopsycho.2010.03.009

Tong, Y., Xiting, H., Caizhen, Y., Liming, X., and Anguo, F. (2021). Influence of an individual's own gains and losses on the evaluation of friends' gambling results: evidence from ERPs. *Acta Psychol. Sin.* 53, 651–666. doi: 10.3724/SP.J.1041.2021.00651

Wang, Y., Kuhlman, D. M., Roberts, K., Yuan, B., Zhang, Z., Zhang, W., et al. (2017). Social value orientation modulates the FRN and P300 in the chicken game. *Biol. Psychol.* 127, 89–98. doi: 10.1016/j.biopsycho.2017.04.012

Wu, Y., and Zhou, X. (2009). The P300 and reward valence, magnitude, and expectancy in outcome evaluation. *Brain Res.* 1286, 114–122. doi: 10.1016/j.brainres.2009.06.032

Xu, S. (2021). Self–other discrepancies in electrophysiological response to outcome evaluation in the balloon analogue risk task. *Int. J. Psychophysiol.* 170, 6–11. doi: 10.1016/j.ijpsycho.2021.09.010

Xu, S., Pan, Y., Qu, Z., Fang, Z., Yang, Z., and Yang, F. (2018). Differential effects of real versus hypothetical monetary reward magnitude on risk-taking behavior and brain activity. *Sci. Rep.* 8:3712. doi: 10.1038/s41598-018-21820-0

Yang, Z., Sedikides, C., Gu, R., Luo, Y. L., Wang, Y., and Cai, H. (2018). Narcissism and risky decisions: a neurophysiological approach. *Soc. Cogn. Affect. Neurosci.* 13, 889–897. doi: 10.1093/scan/nsy053

Yeung, N., Holroyd, C. B., and Cohen, J. D. (2005). ERP correlates of feedback and reward processing in the presence and absence of response choice. *Cereb. Cortex* 15, 535–544. doi: 10.1093/cercor/bhh153

Yu, R., and Zhou, X. (2006). Brain responses to outcomes of one's own and other's performance in a gambling task. *Neuroreport* 17, 1747–1751. doi: 10.1097/01.wnr.0000239960.98813.50

Zlatev, J. J., Kupor, D. M., Laurin, K., and Miller, D. T. (2020). Being "good" or "good enough": prosocial risk and the structure of moral self-regard. *J. Pers. Soc. Psychol.* 118, 242–253. doi: 10.1037/pspa0000175

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A case study of repetitive transcranial magnetic stimulation for cryptococcal meningitis combined with cognitive impairment

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Cryptococcal meningitis (CM) is a central nervous system disease caused by a novel *Cryptococcus* infection that leads to subacute or chronic inflammatory changes in the nervous system. In this study, we present the case of a woman aged 72 years with CM and severe cognitive impairment and disabilities. The cognitive assessment indicated that, although her cognitive function was impaired, especially executive function, it largely improved after receiving anti-infectious and repetitive transcranial magnetic stimulation, which can alter the membrane potential of the cortical nerve cells by triggering long-term potentiation and depression, modulating and releasing hormones, reducing the level of neuroinflammatory and peripheral blood cytokines, promoting nerve regeneration and synaptic remodeling, and changing the activity of the neural circuitry of the dorsolateral prefrontal cortex. We argue that this case provides a novel method of treatment for patients with CM in conjunction with cognitive impairments.

KEYWORDS

cryptococcal meningitis, repetitive transcranial magnetic stimulation, cognitive impairment, rehabilitation, inflammatory cytokines

Introduction

Cryptococcal meningitis (CM) is a central nervous system disease caused by a novel mesophilic *Cryptococcus* that can penetrate the blood–brain barrier through a specific mechanism (Wang et al., 2013). As the primary target of the novel *Cryptococcus* is the central nervous system, *Cryptococcus* infections can easily result in subacute or chronic inflammatory changes in the central nervous system. Furthermore, long-term use of immunosuppressants, immunodeficiencies, severe trauma, and systemic

chronic diseases is associated with a high infection rate, and people with a normal immune function who carry individual susceptibility factors are also prone to infection. Studies showed that the complement system and glucuronide xylose rush glycan are related to individual susceptibility (Vecchiarelli et al., 2013). In addition to the common symptoms of CM, which are caused by increased intracranial pressure (ICP), infection with the novel *Cryptococcus* can cause brain parenchymal damage, with corresponding clinical manifestations including hemiplegia, epilepsy, mental disorders, and cognitive impairment (Mao et al., 2017). The diagnostic accuracy can be improved by combining repeated cerebrospinal fluid (CSF) bacterial smears, latex agglutination tests, and imaging.

Anti-infective medication involves the administration of flucytosine, and amphotericin B with high sensitivity is prioritized in the treatment of CM. Supportive therapy according to symptoms, such as dehydration, lowering ICP, and neuroprotection, can yield better outcomes. Additionally, it is crucial to initiate early and proper rehabilitation for dysfunction after infection. A study on 27 patients with CM found significantly worse executive function performance in patients with ventriculomegaly (VM) than in those without VM (Traino et al., 2019). Another study showed that the related inflammatory cytokines [growth-related oncogenes; interleukin (IL)-10, IL-2, and IL-8; macrophage inflammatory protein-1β; and tumor necrosis factor (TNF)-α] were negatively correlated with the Montreal Cognitive Assessment (MoCA) score of patients, whereas the MoCA score was significantly positively correlated with dementia-related factors (αβ42 and total tau) (Tao et al., 2022). In addition, Lu et al. reported an indirect relationship between neuropsychological performance and CSF antigen titer: the higher CSF cryptococcal-antigen titer on admission may be associated with poorer cognitive function (Lu et al., 2011).

In addition to conventional drug therapy and cognitive therapy, repetitive transcranial magnetic stimulation (rTMS) has been widely used in clinical practice in recent years to improve the cognitive function of patients with cognitive impairment. rTMS can reduce the levels of inflammatory cytokines such as IL-8, IL-10, and TNF-α (Xu, 2021). In this study, a patient with CM combined with cognitive impairment as the main manifestation underwent rTMS-based therapy, and satisfactory clinical effects were obtained.

Clinical summary

A 72-year-old woman with a middle school education who presented with headache, dizziness, nausea, and vomiting was admitted to a local hospital. In August 2021, she was diagnosed with tuberculous meningitis and underwent antituberculosis therapy. However, her symptoms did not disappear. After being discharged from the local hospital, she visited the neurology department of our hospital. CSF analysis and India ink staining of the CSF revealed *Cryptococcus*, and she was diagnosed with CM. She received antifungal therapy [fluconazole (10 mg/kg/day) and 5-fluorocytosine (100 mg/kg/day)] for almost 2 months before being affected by rapidly progressive dementia caused by central nervous system infection. On 25 November 2021, she began to show signs of confusion, an inability to speak, limited limb movements, an inability to walk, an inability to eat independently, signs of nausea without vomiting, and signs of incontinence, but she could still open her eyes when called and lacked limb convulsions. She was then hospitalized in our department. A lumbar puncture and CSF analysis were performed, which revealed an ICP of >200 mmH_2O, a white blood cell (WBC) count of 7.4 cells/μl. a glucose level of 1.83 mmol/L, a protein level of 2,496 mg/L, and a chlorine level of 112.3 mmol/L. which suggested an inflammation. India ink staining of the CSF revealed *Cryptococcus* and CSF culture revealed *Cryptococcus neoformans*. Moreover, multiple intracranial lesions with meningeal enhancement were observed on brain magnetic resonance imaging (MRI; Figure 1). During hospitalization, the consciousness and mental state of the patient gradually improved after antifungal treatment with fluconazole and fluoropyrimidine, and cognitive function assessments revealed that the cognitive dysfunction of the patient persisted (Mini-Mental State Examination: 11 points, MoCA: 7 points); hence, the patient was referred to the Department of Rehabilitation Medicine for appropriate treatment while she demonstrated a weakness of the lower limbs and gait disturbance. After 2 weeks of receiving rTMS treatment, the condition of the patient was reevaluated, which revealed that all cognitive functions had significantly improved. The patient was conscious

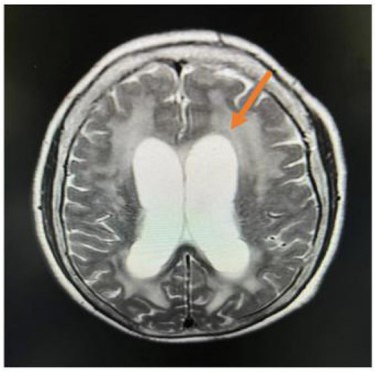

FIGURE 1
Brain MRI in T2-weighted sequence, taken on 30 November 2021, revealing hydrocephalus, ischemic changes in the bilateral frontoparietal occipital lobe, age-related brain changes, and ventriculomegaly where indicated by the orange arrow.

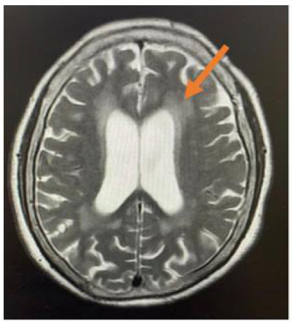

FIGURE 2
Brain MRI took on 3 March 2022, revealing significantly reduced ventricles.

and responded slowly. Her ICP reached >200 mmH_2O, and she had a WBC count of 11.83 cells/μl, a glucose level of 2.37 mmol/L, a protein level of 2,111 mg/L, and avchlorine level of 114.6 mmol/L. Additionally, the brain MRI images taken on 03 March 2022 revealed a significant reduction in the ventricles (MRI; Figure 2). Though the CSF culture was negative and cognitive function improved after rTMS therapy, we did not found a significant decline in inflammatory signals.

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in the article.

Assessment method

The Beijing version of the MoCA was used to screen the cognitive function of patients, which includes 11 examination items in eight cognitive domains (attention and concentration, executive function, memory, language, visual structural skills, abstract thinking, calculation, and orientation).

The Loewenstein Occupational Therapy Cognitive Assessment (LOTCA) was used to evaluate the functions of patients such as orientation, perception, optic-motor organization, and thinking operation.

The Rivermead Behavioral Memory Test (RBMT) was used to measure the behavioral memory function in daily life, which includes 12 items (including remembering names, remembering concealed objects, remembering appointments, picture recognition, story immediate recall, remembering directions and dates, routes delayed recall, and letters delayed recall).

Treatments

First, the medications of the patients were continued. According to previous studies, the effect of medications is limited. Other studies indicated that cognitive impairment is the primary complication in individuals with CM. When only anti-infective medications are taken, it takes >1 month to observe signs of improvement in cognitive dysfunction (Mao et al., 2017). To further improve the treatment effects, we added rTMS therapy to the previous treatment protocol. The patient was informed of the risks and advantages of rTMS therapy prior to treatment, and consent was obtained from the patient and her family before initiating the treatments. For rTMS therapy, we used the butterfly coil D-B80 with a stronger focus (Mag Pro R30; Mag Venture; Denmark). The motor threshold (MT) of the patient was measured during the initial treatment. The stimulation site was selected as the left dorsolateral prefrontal cortex (DLPFC) of the patient. The stimulation intensity was set to 100% MT, and the stimulation frequency was 20 Hz. Each training session involved 20 stimulation pulses with a total of 50 trains, and the interval between each train was 30 s. A total of 1,000 stimulation pulses were used in a single treatment, which took approximately 25 min per session. The patient was treated for 14 consecutive days, with one treatment session per day.

Summary

Before rTMS treatment, the cognitive scale assessment results of the patient (Tables 1–3) indicated that the patient had severe cognitive impairment, and the MoCA assessment results revealed that the cognitive function of the patient was severely impaired; visuospatial and executive functions, object naming function, and abstract thinking function were severely reduced; and language function, short-term memory, and delayed recall function were impaired. The findings of the tests conducted using LOTCA and RBMT were identical in that the patients had a functional impairment and dysfunction in thinking operations, learning imitation, attention, and concentration. The scores on the aforementioned scales met the requirements for significant cognitive impairment.

The patient underwent a second evaluation of her cognitive performance after 2 weeks of rTMS treatment. The results showed that the cognitive function of the patient was greatly improved, and each subscore of the evaluation was very close to normal. The comprehensive analysis of assessment results and clinical observations revealed that the visuospatial function of the patient was significantly improved, and she could distinguish between her left and right limbs and identify the corresponding

TABLE 1 The assessment results of MoCA.

Project	Visuospatial and executive function	Object naming function	Attention	Language	Thinking function	Delayed memory	Orientation	Total
Before	0/5	0/3	1/6	1/3	0/2	1/5	4/6	7/30
After	4/5	2/3	5/6	2/3	1/2	3/5	5/6	22/30

TABLE 2 The assessment results of LOTCA.

Project	Orientation	Visual perception	Spatial perception	Motor praxis	Visuomotor organization	Logic	Attention and concentration	Total
Before	2/16	8/16	6/12	7/12	13/28	9/35	2/4	47/123
After	12/16	11/16	11/12	11/12	21/28	23/35	3/4	92/123

relationship between the front and the back and the left and the right of a picture. Meanwhile, the executive function, which includes drawing and imitating sketching, also improved. Time cognition and language function also significantly improved, and the patient could accurately express the current year, month, and season; tell the current time according to the clock; and name simple things. Furthermore, the memory function of the patient significantly improved; she was able to remember some basic phrases and complex routes and could execute simple recall tasks after a delay. However, the recall of complex tasks still required further improvement. In terms of learning and attention, the patient could learn how to use a calculator and imitate and copy graphics; in terms of logical thinking, the patient could classify simple objects and respond to straightforward logical questions.

Discussion

The clinical symptoms of CM are diverse, and they are often accompanied by irregular fever, increased ICP, blurred vision, gait disturbance, headache, and vomiting. Inflammation can also cause cranial nerve and brain parenchymal damage, leading to a series of problems such as cognitive dysfunction. Due to the insidious onset of cognitive dysfunction and the less prominent manifestation of single cognitive dysfunction, CM is easily misdiagnosed or ignored clinically. As a result, prompt treatment can be delayed, which negatively impacts the prognosis of the patient.

Once the cognitive function is disrupted, abilities such as attention, speech, and execution are limited and impaired to varying degrees, which has a significant impact on the daily lives of the patients. Currently, medication therapy or corresponding cognitive training is typically used to treat cognitive impairment. However, it usually takes a prolonged time to achieve therapeutic effects, and the adverse effects of the medications are significant. Hence, it is crucial to identify innovative, effective, and side-effect-free therapy options. In recent years, TMS has shown significant clinical effects in improving post-stroke cognitive impairment (PSCI) (Hu et al., 2012). It generates induced currents through stimulation coils in specific brain regions and stimulates the cortex. Thus, it can achieve transmembrane, transcortical, and cortical networks, altering the membrane potential of cortical nerve cells by triggering synaptic long-term potentiation (LTP) and long-term depression (LTD). The distant effects of rTMS therapy may result in functional modifications of the distant cortex at the stimulation site so that the goals of in-depth treatment could be accomplished (Liu et al., 2017). Previous studies suggested that altering the membrane potential of the cortical nerve cells by triggering LTP and LTD, modulating and releasing hormones, reducing the level of neuroinflammatory and peripheral blood cytokines, promoting nerve regeneration and synaptic remodeling, and changing the activity of the neural circuitry of the DLPFC may be involved in the mechanism of rTMS.

Several previous studies showed that rTMS can modulate the release of neurohormones, such as regulation of dopamine synthesis and release, and restore the function of cerebral cortical networks. A study using animal models reported that rTMS could upregulate the expression of GAP-43, Syp, and neurotrophic factors, suggesting that it can promote nerve regeneration and synaptic remodeling (Koch et al., 2014).

TABLE 3 The assessment results of RBMT (delayed recall/immediate recall).

Project	First and second names (D)	Belongings (D)	Appointments (D)	Route (I)	Route (D)	Novel task (I)	Novel task (D)	Orientation	Time	Face recognition	Picture recognition	Total
Before	0/2	1/1	0/1	0/1	0/1	1/1	0/1	0/1	0/1	0/1	0/1	2/12
After	2/2	1/1	1/1	0/1	0/1	1/1	1/1	1/1	0/1	1/1	1/1	9/12

In addition, among healthy young people, multiple sessions of high-frequency rTMS over the left DLPFC can increase resource recruitment of cognitive control and enhance resource efficiency, thus deploying for conflict resolution during multiple stages of cognitive control processing. The left dorsal frontal lobe area is involved in cognitive and emotional function (Li, 2017). Various studies reported that the application of rTMS to the left DLPFC improves emotional and cognitive functions. Furthermore, studies on the neuropathological analysis of AD brains revealed that neuroinflammation is an important driving force for neurodegeneration and AD progression (Motta et al., 2020), which is associated with significantly increased levels of CSF IL-4, IL-6, IL-8, and granulocyte colony-stimulating factor. A previous study suggested that the levels of CRP, TNF-α, IL-1β, IL-6, and IL-8 in the peripheral blood of patients with mild cognitive impairment (MCI) were higher than those in the normal population. A previous study also showed that rTMS therapy could decrease the levels of inflammatory cytokines (such as TNF-α, IL-2, IL-1β) (Li and Cheng, 2018; Lu et al., 2022), which can cross the blood–brain barrier, and high levels can affect the normal metabolism of monoamine neurotransmitters in the brain. In this case, the use of rTMS therapy on the patient led to better performance on the cognitive scale assessment results of the patient, but we did not observe a significant correlation between cognitive function and a change in inflammatory cytokines. A limitation of the current study is that neuroinflammatory biomarkers of the patients were not examined, as peripheral biomarkers are easily affected by other factors such as infectious disease. As a limitation, additional correlations, such as biomarkers and inflammatory cytokines, will require further studies. In addition, rTMS can also be complemented with the assessment of a putative marker of central cholinergic transmission. Short latency afferent inhibition (SAI) is a paired-pulse TMS protocol involving the inhibition of motor-evoked potentials by afferent sensory impulses. Previous findings pointed out that SAI is a putative marker of central cholinergic transmission, which can be modulated by ongoing recognition memory, specifically for the retrieval process (Sun and Zhao, 2021). Taken together, it could be applied not only in healthy subjects but also in patients with neurodegenerative diseases, such as Parkinson's or Alzheimer's disease, whose SAI is significantly impaired (Bonnì et al., 2017).

Combined with clinical data, the possible mechanisms promoting the recovery of cognitive functions in different dimensions after CM through rTMS treatment were explored, as discussed below.

Memory function can be divided into instantaneous memory, short-term memory, and long-term memory according to the time of information extraction, and these three types of memories are related to each other. High-frequency rTMS has been demonstrated to increase delayed memory function in patients with MCI, reduce memory encoding time, and boost

memory storage modules in healthy individuals (Martorana et al., 2009). According to functional MRI results, high-frequency rTMS can enhance memory performance by boosting the functional connectivity of the hippocampal-cortical network (Floel and Cohen, 2007). In parallel, animal studies showed that rTMS could improve synaptic ultrastructure in the hippocampal CA1 region and enhance the mRNA and protein expression of brain-derived neurotrophic factor, N-methyl-D-aspartic acid receptor, and synaptophysin so that it could further affect synaptic plasticity (Wang and Voss, 2015), enhance the modulation of hippocampus function *via* the dopaminergic system, and increase the memory storage (Floel and Cohen, 2007). The findings of our analysis showed that the delayed and instantaneous memory of the patient had improved to some degree, indicating that high-frequency rTMS may have a certain curative effect on the improvement of memory function.

Time perception and memory function are inseparable. Objective data are transformed into a time interval representation through the memory process, and decisions are made by comparing the current time interval with the time image stored in long-term memory. The dorsolateral prefrontal cortex, the cerebellum, the basal ganglia, and the auxiliary motor areas are the primary brain regions involved in the cognitive processing of time perception (Wang et al., 2015). Previous research demonstrated that the DLPFC, which serves as the primary memory of the internal clock, receives input from the cerebellum and the basal ganglia to create a time interval representation and encodes the temporal representation before storing it in memory (Yin et al., 2008). Additionally, some researchers discovered that time perception within 1 s is controlled by the cortico-basal ganglia-thalamic network. This was discovered by stimulating the cerebellum site (Gironell et al., 2005). Other studies in this area revealed that stimulating the primary audiovisual cortex of the parietal lobe could positively affect audiovisual time perception (Lee et al., 2007). Thus, when investigating the stimulation targets for time cognition, a comprehensive analysis of the time perception conditions of the patient should be done to determine the optimal stimulation site for treatment. If necessary, stimulation of multiple sites can be performed to enhance these effects.

Visuospatial ability. The three cognitive skills of attentiveness, orientation, and execution make up the visuospatial ability, which indicates the ability to point and focus on spatial information. Functional imaging of the human brain has revealed that functional regions such as the dorsolateral frontal cortex, the anterior cingulate gyrus, and the parietal cortex play a major role in the activation of visuospatial networks (Mifsud et al., 2014). In one study, subjects underwent theta-burst repetitive TMS (cTBS) to stimulate their bilateral dorsolateral prefrontal cortex and inflict "virtual damage." Patients whose right DLPFC was stimulated displayed decreased alertness and executive function, whereas those whose left DLPFC was stimulated displayed decreased orientation function. Hence, it can be assumed that the bilateral DLPFC are both the centers for the initiation and regulation of the visuospatial attention process (Sturm and Willmes, 2001). The high-frequency rTMS employed in this study had an excitatory effect on the neural activity of the stimulation site as opposed to the inhibitory function of cTBS. The distant effect induced by TMS also resulted in the excitation of brain activity in the posterior parietal lobe, in addition to the LTP effect of the left DLPFC. The frontoparietal loop of the conductive pathway of the patient, which is primarily concerned with determining the spatial location of items, is further activated by the excitatory action (Xu et al., 2013). In this case, we selected high-frequency stimulation to activate the left DLPFC of the patient according to the theory of the interhemispheric competition model of brain injury. It could be speculated that the right DLPFC was in a suppressed state at this time. However, the second evaluation results of this case demonstrated that the actual effect is contradictory to the prognosis, in which inhibition of the right DLPFC did not cause a decline in vigilance and executive function. In turn, the concentration and executive function performance of the patient greatly improved after TMS. This outcome currently fails to explain the mechanism, and further investigation is required.

Language is a unique high-level cognitive function in human beings. According to functional MRI studies based on several baseline tasks, the overall functional network of the frontal-parietal-subcortical regions is more functionally employed than Wernicke's and Broca's areas for language processing, where the dorsolateral prefrontal cortex plays a major role in the process of detecting incorrect language information and suppressing nontarget languages (Yantis et al., 2002). In this case, during the second cognitive evaluation of the patient, the language function had significantly improved, and the usage of incorrect and random words had significantly decreased. It may be inferred that high-frequency rTMS could encourage the rearrangement of the language function of the patient and enhance the connectivity between synapses in the neural networks of language centers. According to a study, white matter integration around the left hemisphere is strengthened after high-frequency stimulation of the frontal lobe. Simultaneously, the functional connection between the white matter and the reward processing center of the brain, such as the hippocampus and the caudate nucleus, is enhanced (Hu, 2015).

Executive function. To ensure the general control of specific targets by the cognitive system in a more flexible and optimized manner, the executive function, as an important high-level cognitive processing of individuals, is in charge of coordinating various cognitive resources and procedures in the process of completing complex cognitive tasks. The dorsolateral prefrontal cortex is an important center of the executive control network. Some studies showed that healthy individuals could gain better results in executive function, as measured by the Stroop test, after high-frequency rTMS (Martorana et al., 2009). Other

studies also demonstrated that the Stroop test scores were significantly improved after 4 weeks of high-frequency rTMS stimulation on the left dorsolateral prefrontal lobe in individuals with PSCI compared with those before treatment and 2 weeks after treatment (Vanderhasselt et al., 2006). In this case, the executive function of the patient significantly improved after consecutive rTMS therapy. In addition, elevated neurometabolic research suggests that biological markers that affect the cognitive executive function of a person, such as N-acetyl aspartate and choline complexes, are markedly elevated in patients with executive dysfunction (Wang and Voss, 2015). In conclusion, high-frequency rTMS can effectively regulate synaptic plasticity, enhance neural excitability, induce arousal of the cortex in cerebral function areas, and activate networks of executive control in the frontal lobe.

According to related studies on TMS paired with event-related potentials, the amplitudes of N2 and N450, two significant components closely associated with cognitive control and conflict monitoring, can be enlarged by rTMS in the course of completing tasks, while incorrect electroencephalogram signals can be modified by rTMS during task execution (Yin et al., 2018). The NoGo-N2 potential, which reflects the number of cognitive resources used in the early stages of response inhibition, is one of the waveforms implicated in response inhibition. According to a previous study, high-frequency rTMS can stimulate the entire neural circuit involved in response inhibition and significantly improve cognitive function in patients with deficits in response inhibition (Zhou et al., 2017).

Conclusion

Anti-infective therapy should be primarily addressed for the treatment of CM so that the cognitive impairments and other symptoms of the patients might be improved after controlling the infection. Additionally, rTMS therapy might improve the cognitive performance of the patient in different categories, including memory function, time perception, visuospatial cognition, speech, and executive function. This case provides a novel treatment method for patients with CM in conjunction with cognitive impairment, and our findings serve as a foundation for future clinical investigations. However, it is essential to increase the patient sample size to conduct a thorough analysis because of the limitations of case studies on individual differences. Finally, further exploration and research could be conducted on the selection of precise stimulation targets and stimulation parameters in rTMS, as well as analysis combined with imaging examinations, neurophysiology, and other clinical techniques.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in the article.

Author contributions

YLi: data curation, formal analysis, visualization, writing—original draft, and writing—review and editing. LF: data curation, formal analysis, investigation, visualization, writing—original draft, and writing—review and editing. XJ: data curation, formal analysis, investigation, writing—original draft, and writing—review and editing. YLu: conceptualization, data curation, formal analysis, supervision, validation, visualization, and writing—review and editing. YL: data curation, investigation, writing—original draft, and writing—review and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Bonnì, S., Ponzo, V., Di Lorenzo, F., Caltagirone, C., and Koch, G. (2017). Real-time activation of central cholinergic circuits during recognition memory. *Eur. J. Neurosci.* 45, 1485–1489. doi: 10.1111/ejn.13588

Floel, A., and Cohen, L. G. (2007). Contribution of noninvasive cortical stimulation to the study of memory functions. *Brain Res. Rev.* 53, 250–259. doi: 10.1016/j.brainresrev.2006.08.006

Gironell, A., Rami, L., Kulisevsky, J., and García-Sánchez, C. (2005). Lack of prefrontal repetitive transcranial magnetic stimulation effects in time production processing. *Eur. J. Neurol.* 12, 891–896. doi: 10.1111/j.1468-1331.2005.01093.x

Hu, D. M., Cheng, X. R., Zhou, W. X., Zhang, W. X., and Zhou, L. C. (2012). Treatment of Post Stroke Cognitive Impairment by rTMS Prog. *Physiol. Sci.* 43, 411–416.

Hu, J. H. (2015). *Research on cognitive control in language information processing and its neural Mechanism* (Doctor dissertation). University of Electronic Science and Technology of China.

Koch, G., Di Lorenzo, F., Bonnì, S., Giacobbe, V., Bozzali, M., Caltagirone, A., et al. (2014). Dopaminergic modulation of cortical plasticity in Alzheimer's disease patients. *Neuropsychopharmacology* 39, 2654–2661. doi: 10.1038/npp.2014.119

Lee, K. H., Egleston, P. N., Brown, W. H., Gregory, A. N., Barker, A. T., Woodruff, P. W., et al. (2007). The role of the cerebellum in subsecond time perception: evidence from repetitive transcranial magnetic stimulation. *J. Cogn. Neurosci.* 19, 147–157. doi: 10.1162/jocn.2007.19.1.147

Li, Y. M. (2017). *The effects of high frequency repetitive transcranial magnetic stimulation over the left DLPFC on the cognitive function in healthy young people and its electrophysiological, metabolic mechanism* (Doctor dissertation). Neurology. Hebei Medical University.

Li, Z. M., and Cheng, Z. H. (2018). Peripheral inflammatory markers in the patients with mild cognitive impairment:a meta-analysis. *Chin. J. Behav. Med. Brain Sci.* 27, 955–960. doi: 10.3760/cma.j.issn.1674-6554.2018.10.019

Liu, H., Han, X. H., and Huang, X. L. (2017). The influencing factors and mechanism ofrepeated transcranial magnetic stimulation in regulating cortical excitability. *Chin. J. Rehabil. Med.* 32, 354–358.

Lu, C. H., Chen, H. L., Chang, W. N., Tsai, N. W., Wang, H. C., Yang, T. M., et al. (2011). Assessing the chronic neuropsychologic sequelae of human immunodeficiency virus-negative cryptococcal meningitis by using diffusion tensor imaging. *AJNR Am. J. Neuroradiol.* 32, 1333–1339. doi: 10.3174/ajnr.A2489

Lu, L., Zhou, J. J., and Zhang, Y. (2022). Efficacy and mechanism of repetitive transcranial magnetic stimulation combined with agomelatine in the treatment of deprSunession with insomnia. *J. North Sichuan Med. Coll.* 37, 358–361.

Mao, L. Y., Tang, Y. M., Ding, J., and Wang, X. (2017). Cryptococcal meningitis with cognitive impairment as the initial manifestation: a case report. *Chin. J. Clin. Med.* 24, 3920–3923.

Martorana, A., Mori, F., Esposito, Z., Kusayanagi, H., Monteleone, F., Codecà, C., et al. (2009). Dopamine modulates cholinergic cortical excitability in Alzheimer's disease patients. *Neuropsychopharmacology.* 34, 2323–2328. doi: 10.1038/npp.2009.60

Mifsud, G., Zammit, C., Muscat, R., Di Giovanni, G., and Valentino, M. (2014). Oligodendrocyte pathophysiology and treatment strategies in cerebral ischemia. *CNS Neurosci. Ther.* 20, 603–612. doi: 10.1111/cns.12263

Motta, C., Finardi, A., Toniolo, S., Di Lorenzo, F., Scaricamazza, E., Loizzo, A., et al. (2020). Protective role of cerebrospinal fluid inflammatory cytokines in patients with amnestic mild cognitive impairment and early Alzheimer's disease carrying apolipoprotein E4 genotype. *J. Alzheimers Dis.* 76, 681–689. doi: 10.3233/JAD-191250

Sturm, W., and Willmes, K. (2001). On the functional neuroanatomy of intrinsic and phasic alertness. *Neuroimage.* 14, S76–S84. doi: 10.1006/nimg.2001.0839

Sun, Z. M., and Zhao, Z. J. (2021). Application of Transcranial Magnetic Stimulation in Alzheimer's Disease. *China For. Med. Treat.* 40, 1–4.

Tao, R., Peng, X., Liu, X., Su, J., Lang, G., Huang, Y., et al. (2022). Lenalidomide improves cognitive function and reduces immune reconstitution inflammatory syndrome in HIV-1-related cryptococcal meningitis. *J. Inflamm. Res.* 15, 2891–2899. doi: 10.2147/JIR.S353463

Traino, K., Snow, J., Ham, L., Summers, A., Segalà, L., Shirazi, T., et al. (2019). HIV-negative cryptococcal meningoencephalitis results in a persistent frontal-subcortical syndrome. *Sci. Rep.* 9, 18442. doi: 10.1038/s41598-019-54876-7

Vanderhasselt, M. A., De Raedt, R., Baeken, C., Leyman, L., and D'haenen, H. (2006). The influence of rTMS over the left dorsolateral prefrontal cortex on Stroop task performance. *Exp. Brain Res.* 169, 279–282. doi: 10.1007/s00221-005-0344-z

Vecchiarelli, A., Pericolini, E., Gabrielli, E., Kenno, S., Perito, S., Cenci, E., et al. (2013). Elucidating the immunological function of the Cryptococcus neoformans capsule. *Future Microbiol.* 8, 1107–1116. doi: 10.2217/fmb.13.84

Wang, F., Chang, G. M., Yu, Q., and Geng, X. (2015). The neuroprotection of repetitive transcranial magnetic stimulation pre-treatment in vascular dementia rats. *J. Mol. Neurosci.* 56, 198–204. doi: 10.1007/s12031-014-0480-7

Wang, J. X., and Voss, J. L. (2015). Long-lasting enhancements of memory and hippocampal-cortical functional connectivity following multiple-day targeted noninvasive stimulation. *Hippocampus.* 25, 877–883. doi: 10.1002/hipo.22416

Wang, Y. C., He, J. Y., Bu, H., Zou, Y. L., and Ding, W. T. (2013). Cryptococcal meningitis . *Chin J Contemp Neurol Neurosurg.* 13, 16–23.

Xu, G. Q., Lan, Y., Zhao, J. L., Chen, Z. H., and Huang, D. F. (2013). Modulatory effects of continuous theta burst stimulation over dorsolateral prefrontal cortex on visuospatial attention. *Chin. J. Rehabil. Med.* 28, 806–810.

Xu, J. B. (2021). Effects of repeated transcranial magnetic stimulation on cognitive function and inflammatory factors in elderly patients with hypertensive intracerebral hemorrhage undergoing minimally invasive puncture hematoma removal. *Chin. J. Gerontol.* 41, 3920–3923.

Yantis, S., Schwarzbach, J., Serences, J. T., Carlson, R. L., Steinmetz, M. A., Pekar, J. J., et al. (2002). Transient neural activity in human parietal cortex during spatial attention shifts. *Nat. Neurosci.* 5, 995–1002. doi: 10.1038/nn921

Yin, M. Y., Luo, J., Hu, X. Q., Xian, Q. L., Huang, L., Zhang, S. X., et al. (2018). Effects of high frequency repetitive transcranial magnetic stimulation on post-stroke cognitive impairment. *Chin. J. Rehabil. Med.* 33, 763–769.

Yin, Z. H., Huang, X. T., Li, D., and Zhang, Y. (2008). Neural mechanism about scalar timing model. *Adv. Psychol. Sci.* 16, 59–64.

Zhou, T., Gong, Z. F., Wang, S. Y., Wang, M., and Wang, Y. (2017). Impact of repetitive transcranial magnetic stimulation on executive dysfunction after stroke. *J. Pract. Med.* 33, 1036–1039.

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Effects of additive sensory noise on cognition

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Background: Adding noise to a system to improve a weak signal's throughput is known as stochastic resonance (SR). SR has been shown to improve sensory perception. Some limited research shows noise can also improve higher order processing, such as working memory, but it is unknown whether SR can broadly improve cognition.

Objective: We investigated cognitive performance while applying auditory white noise (AWN) and/or noisy galvanic vestibular stimulation (nGVS).

Methods: We measured cognitive performance (n = 13 subjects) while completing seven tasks in the cognition test battery (CTB). Cognition was assessed with and without the influence of AWN, nGVS, and both simultaneously. Performance in speed, accuracy, and efficiency was observed. A subjective questionnaire regarding preference for working in noisy environments was collected.

Results: We did not find broad cognitive performance improvement under the influence of noise ($p > 0.1$). However, a significant interaction was found between subject and noise condition for accuracy (p = 0.023), indicating that some subjects exhibited cognitive changes with the addition of noise. Across all metrics, noisy environment preference may trend to be a potential indicator of whether subjects will exhibit SR cognitive benefits with a significant predictor in efficiency (p = 0.048).

Conclusion: This study investigated using additive sensory noise to induce SR in overall cognition. Our results suggest that using noise to improve cognition is not applicable for a broad population; however, the effect of noise differs across individuals. Further, subjective questionnaires may be a means to identify which individuals are sensitive to SR cognitive benefits, but further investigation is needed.

KEYWORDS

stochastic resonance (SR), auditory white noise, noisy galvanic vestibular stimulation, cognition test battery for spaceflight, sensory cognition

Highlights

- Additive sensory white noise does not broadly affect human cognitive performance.
- Influence of additive sensory noise on cognitive performance varies by individual.
- Cognitive effects of noise may be associated with a person's noisy environment preference and warrants further investigation.

Introduction

Stochastic resonance (SR) is a phenomenon where additive noise can improve the throughput of a signal in non-linear systems (Moss et al., 2004). Conceptually, SR may occur by applying an ideal level of noise, such that it resonates with the sensory signal. Therefore, it is believed that an "optimal" level of noise is required to achieve throughput enhancement (Galvan-Garza, 2018). Psychophysical experimentation suggests that SR can improve perceptual performance, such as lowering auditory thresholds, both within the same sensory modality [e.g., using auditory white noise (AWN) to improve hearing (Zeng et al., 2000)] and across separate sensory modalities [e.g., using noisy galvanic vestibular stimulation (nGVS) to improve visual perception (Voros et al., 2021)]. While perception has been shown to be affected by additive noise, there is limited research on whether higher order cognitive processes is subject to SR.

Noise-enhanced sensory information could be utilized by the whole central nervous system (Hidaka et al., 2000), suggesting that SR could affect higher order information processing. In human subject experiments, background AWN (~78 dB SPL) improved verbal recall, visuo-spatial working memory, and motor response in inattentive school children (Söderlund et al., 2010; Helps et al., 2014). For a neurotypical population, AWN has been shown to improve elements of attention and visual/auditory working memory (Othman et al., 2019; Awada et al., 2022). Cognitive SR benefits extend to modalities other than auditory though. This is supported by studies showing that nGVS improves visual working memory in healthy adults (Wilkinson et al., 2008). Aside from enhanced processing in healthy adults, SR could also offset reduced perceptual abilities that may negatively affect cognition.

Bigelow and Agrawal (2014) summarized the link between vestibular and cognitive functions, noting that visuospatial ability and attention are negatively impacted in subjects with vestibular impairments. Pineault et al. (2020) also suggested that impairments to the saccule and semi-circular canals of the vestibular system affects various aspects of cognition. It has been shown that nGVS improves vestibular self-motion perception (Galvan-Garza, 2018; Keywan et al., 2019), suggesting enhanced vestibular function. Therefore, improved vestibular function from nGVS could potentially offset cognitive decrements due to perceptual impairment.

Existing studies that suggest adding sensory noise can enhance cognition are limited as they focus on specific cognitive domains and do not investigate cognitive effects more broadly. Cognitive domains are individual cognitive processes, like working memory, which are employed when synthesizing information for decision making and behavior control (Harvey, 2019). Certain cognitive domains recruit different regions of the brain (Basner et al., 2015) and additive noise influences regional activity within the cerebral cortex (Mendez-Balbuena et al., 2018; Huidobro, 2020). This regional influence may correspond to specific cognitive domains. For example, the temporal lobe houses auditory and other multisensory association areas in addition to cognitive centers that are attributed to memory (Kandel et al., 2000); thus, surrounding regions may see neuronal influence by AWN which could affect memory. Supporting this, Kim et al. (2013) reports that nGVS leads to gamma wave suppression in the frontal region which is associated with several cognitive abilities. However, literature investigating cognitive benefits of adding sensory noise has focused on working memory and motor response, neglecting other domains, such as vigilance and visual search. This presents a substantial gap in our knowledge of sensory noise influence on overall cognition as a thorough analysis across multiple cognitive domains has yet to be investigated.

Often, these studies also fail to consider the potential confounding effect of arousal induced by sensory stimulation as the mechanism of cognitive improvement, as opposed to the presumed mechanism of stochastic resonance. Arousal resulting from periodic visual and auditory stimuli have been shown to increase functional activity in frontal regions (Sturm and Willmes, 2001), potentially impacting cognitive abilities. Without the use of control conditions to assess the role of arousal from sensory stimulation, it is unclear whether SR is the dominant mechanism in any cognitive improvement.

Thus, our work aimed to explore the ability of enhancing broad cognitive performance using sensory noise. Our work evaluated cognition by using the validated cognition test battery (CTB) developed by Basner et al. (2015) which provides a sensitive evaluation of different cognitive domains using standardized techniques, such that when combined, the results provide a comprehensive insight on SR's influence on cognition. We hypothesized that single modality noise (AWN and nGVS) would enhance cognitive performance in human subjects when compared to performance without noise. Further, we hypothesized that stimulating both modalities simultaneously to induce multi-modal SR (MMSR) would enhance performance to a greater degree than single modality alone. This hypothesis is novel as, to our knowledge, no investigation exists evaluating the mental performance effects of compounding sensory noise across multiple modalities. To address the gap associated with improvement due to arousal, our work investigates the role of additive noise versus simple arousal stimulation in influencing cognition.

We also investigated the degree to which we could identify whether subjects may be sensitive to SR cognitive performance enhancement. SR perception studies have suggested that some individuals are susceptible to SR perception improvements, while others are not (Ries, 2007; Galvan-Garza, 2018). Thus, we hypothesized that only some subjects may receive SR cognitive benefits. Currently, there is no way to predict *a priori* whether an individual is likely to be sensitive to SR performance improvement. Therefore, we developed a subjective questionnaire for subjects to rate how well they could maintain focus in quiet and noisy environments. We hypothesized that there would be a positive correlation between noisy environment preference and cognitive enhancement under the influence of added sensory noise.

Materials and methods

Subjects

Thirteen subjects (7F/6M, range = 20–40 years, mean = 29.5 years, SD = 6.6 years) completed testing in the Bioastronautics Lab at the University of Colorado-Boulder. An *a priori* power analysis based on the results of Wilkinson et al. (2008) and Söderlund et al. (2010) suggested that we needed 8–12 subjects for our study design to find an effect size greater than 0.3, which was expected based on the former's findings. This research was approved by the University of Colorado-Boulder's Institutional Review Board (#20-0419) and written informed consent was obtained prior to participation. Subjects were pre-screened and excluded if they reported a history of health issues that could impact cognitive abilities, such as severe head trauma or disorders associated with thinking impairment. They were also excluded if they reported health issues that could impact auditory or vestibular processing, such as language impairment or vestibular dysfunction. Additionally, subjects underwent auditory screening to verify healthy and unobstructed ear canals (via otoscopy), normal tympanometry, and normal hearing (audiometric thresholds $<=$ 25 dB HL up to 8 kHz).

Protocol and study design

Broadband AWN was administered to subjects through ear buds (Essential Earphones HD) and a Samsung Tablet A; the auditory profiles were developed and calibrated by Creare LLC (Hanover, NH, United States). Broadband, unipolar, zero-mean white noise was bilaterally administered to subject mastoids through the Galvanic Vestibular Oscillating Stimulator (model 0810, Soterix Medical, Woodbridge, NJ, United States) using electrodes with a contact area of 2 cm^2. Tasks were completed using a Dell Latitude E6430 laptop, which is specifically calibrated to run the CTB, in a single walled sound booth (Whisperoom, Knoxville, TN, United States, MDL 4872).

A within-subject experimental design was implemented. Seven tasks in the CTB were chosen as they are associated with distinct cognitive domains and recruit different regions in the brain, allowing us to explore cognition and its sub-domains in a manner far more comprehensively than has been found in the literature. These seven tasks are presented in **Table 1** [recreated from Basner et al. (2015)], summarizing each task's cognitive domain and areas of the brain recruited to complete the task.

In their initial visit, subjects were trained in the standard manner on the CTB tasks by watching a 20-min tutorial video, after which they completed two practice trials of each CTB task. Next, testing occurred across two subsequent visits, where subjects completed all testing for each specific CTB task within a single session. MRT, MPT, and PVT were tested in one session and DSST, LOT, F2B, and VOLT were tested in the other session. The order of the tasks within the test day was randomized for each of the two test days.

In the CTB, cognitive performance is quantified in terms of speed and accuracy. However, the speed-accuracy tradeoff is confounding when evaluating improved performance (Wicklegren, 1977). The literature accounts for this through a post-hoc combination of the normalized speed and accuracy metrics, which is often referred to as efficiency (Scully et al., 2019; Basner et al., 2021). The dependent variables of accuracy, speed, and efficiency were used to assess performance in the cognitive tasks.

Recall, it is thought there is an optimal level of noise in terms of producing SR-benefits that depends on the subject, task, and sensory system (Moss et al., 2004). Thus, for each CTB task, a range of AWN and nGVS levels were assessed for each subject. Four nGVS levels [(0.2, 0.4, 0.6, and 0.8 mA)] and three AWN levels [(40, 55, and 70 dB SPL)] were tested in a randomized order, as has been done in our prior work (Voros et al., 2021). Speed and accuracy were corrected to account for trial-specific differences and learning effects, using corrections from Basner et al. (2020). From this initial set of measures, the SR level yielding the best score in feedback, another measure of combined performance in the CTB, was selected as the subject-specific best (or close to subject optimal) AWN and nGVS levels.

Once the subject-specific best SR levels were identified, six experimental conditions were investigated to understand the effects of additive noise on cognition. Subject-specific best levels of AWN, nGVS, and MMSR were tested, as determined from the initial suite of measures. To investigate the potentially confounding effect of arousal, subjects completed tasks under the stimulation of suprathreshold stimuli—an auditory pure tone signal at 55 dB SPL, as well as a direct current GVS (DC GVS) signal at 0.8 mA. These conditions stimulate the sensory modalities with a non-random signal in a manner that would not induce SR benefits, but would cause arousal. We hypothesized that these stimulation control conditions would not result in significant performance changes from sham, if indeed the mechanism for any benefit from added noise is due to SR. To summarize, the following six conditions were retained for statistical analysis: three control conditions; no stimulation sham, 55 dB pure tone auditory stimulation, and 0.8 mA DC GVS stimulation and three noise conditions; subject-specific best AWN, best nGVS, and MMSR. All conditions were

TABLE 1 Cognitive domains and brain regions associated with the seven CTB tasks (Basner et al., 2015).

Task	Cognitive domains	Recruited brain regions
Digit symbol substitution (DSST)	Visual search/Spatial memory/Paired associate learning	Temporal cortex/Prefrontal cortex/Motor cortex
Line orientation (LOT)	Spatial orientation	Right temporo-parietal cortex/Visual cortex
Matrix reasoning (MRT)	Abstract reasoning	Prefrontal cortex/Parietal cortex/Temporal cortex
Fractal 2-back (F2B)	Working memory	Dorsolateral prefrontal cortex/Cingulate/Hippocampus
Motor praxis (MPT)	Sensory-motor speed	Sensorimotor cortex
Psychomotor vigilance (PVT)	Vigilant attention	Prefrontal cortex/Motor cortex/Inferior parietal and visual cortex
Visual object learning (VOLT)	Spatial learning/Memory	Medial temporal cortex/Hippocampus

presented and tested in a randomized order for the cognitive tasks within each of the two test sessions. Short breaks were provided between tests to help mitigate subject mental fatigue, but as in other studies using nGVS (Goel et al., 2015; Mulavara et al., 2015; Galvan-Garza, 2018; Inukai et al., 2018; Keywan et al., 2018, 2019; Voros et al., 2021) we did not employ a more extensive break between nGVS applications, since the most rigorous studies using nGVS have not found carryover effects between nGVS stimulation levels (Nooristani et al., 2019; Keywan et al., 2020).

After completing all cognitive testing, subjects completed a subjective five-point Likert scale questionnaire that asked how well they felt they could maintain focus in quiet and noisy environments. Their noisy environment preference score was defined as the difference in subject ranking between quiet and noisy environments (i.e., a negative score means the subject prefers working in quiet places and a positive score means they prefer working in noisy places). This survey can be found in **Supplementary Data Sheet 1**.

Analysis

A within-subjects analysis was completed for the metrics of accuracy, speed, and efficiency. Two separate analyses were done by comparing sham to the noise conditions and to the stimulation control conditions. In each analysis, performance outcomes on each of the 7 CTB tasks were collapsed into one scale to create a comprehensive cognition metric. For this comprehensive metric, data was initially adjusted by subtracting the subject's specific average across the conditions of interest in that CTB task, to account for individual differences in performance. From there, the data was standardized for the task by calculating the z-score of each measurement with respect to all measurements across subjects within that CTB task as shown in Equation 1. Z_i represents the standardized cognition metric and P_i is the raw scores of that task datapoint. M_T and σ_T were the mean and standard deviation, respectively, of all raw data in the specific task. This process has been done for CTB data in prior work (Scully et al., 2019), yielding a normalized cognition outcome.

$$Z_i = \frac{P_i - M_T}{\sigma_T} \quad (1)$$

A repeated measures ANOVA (RMANOVA) with four levels (sham, AWN, nGVS, and MMSR) was conducted to investigate the effect of noise on cognition using this normalized cognition metric. This was applied to each of the metrics of speed and accuracy. Efficiency was calculated as the mean of these two normalized metrics. A separate RMANOVA was also completed for the three control conditions (sham, tone, DC GVS) to investigate the effect of arousal on cognition. Assumptions for homogeneity and residual normality were tested to ensure that parametric statistics were appropriate. Datapoints that created semi-studentized residuals greater than three were removed as outliers. If there was an outlier in one metric, say speed, the associated datapoint was also removed from the other two metrics, accuracy and efficiency. If the F-test results from the RMANOVAs were significant, Tukey HSD multiple pairwise comparisons were used to identify which conditions were different from another. If the F-test results from the RMANOVAs were insignificant, an equivalence test was completed to indicate whether the conditions were equivalent following the methods conducted by Rusticus and Lovato (2011).

To assess noise effects on overall cognition, as per our first hypothesis, subjects were treated as a random effect in our RMANOVAs, allowing us to posit on the broad utility of additive noise across all subjects in our sample. This analysis was done for the noise conditions (sham, nGVS, AWN, and MMSR) and control conditions (sham, pure tone auditory stimulation, DC GVS). For the second hypothesis analysis, subjects were included as an interaction term along with the noise conditions, allowing us to posit on whether noise effects are different across individuals.

Additionally, an exploratory analysis was conducted to see whether subjective noisy environment preference could be an indicator for individual differences in noise effects on cognition. Subjects' normalized cognition metric in the sham condition was subtracted from their normalized cognition metric in the additive noise conditions. The calculation of this metric is found in Equation 2. Linear models were fit to this entire dataset against their noisy environment preference scores.

$$\Delta Z_i = Z_{i,noise} - Z_{i,sham} \quad (2)$$

Results

For all models presented in these results, there were no observable violations of the residuals from our assumptions. **Figure 1** compares the normalized cognition metric scores for the noise conditions and the sham condition, for all subjects and tasks. This figure represents the difference in overall cognition, where higher scores in efficiency, accuracy, and inverted speed imply better performance. **Table 2** displays the RMANOVA results with subjects included as a random effect. Contradictory to our hypothesis that additive noise would improve cognition, no significant differences were found between sham and the noise conditions for all metrics. Separate to this main comprehensive analysis, we conducted an exploratory analysis of accuracy and speed in each CTB task individually and found no significant differences. These results are found in **Supplementary Table 1** and **Supplementary Figure 1** with figures and statistical findings. For all tables presented in these results, F(#, #) denotes the degrees of freedom (DOF) of our Omnibus tests, they are represented as F(DOF for treatment factor, DOF for error).

Five outliers were identified and removed within this first model, out of 364 total data points. When all of the data was included in the RMANOVA, the p-values increased. Thus, the conclusion that noise does not significantly affect cognition metric scores remains the same. No outliers were identified or removed in the other models presented.

To assess the effect of arousal, the same RMANOVA analysis was applied to the control conditions. These results are found in **Figure 2** and **Table 3**. In agreement with our hypothesis that arousal stimulation alone would not impact cognition, no significant differences between the control conditions were identified.

The lack of significant differences was further evaluated using a series of equivalence tests. First, leveraging the data from Wilkinson et al. (2008), a 90% equivalence interval of $\pm$ 0.793 was defined for the difference between noise conditions. When comparing

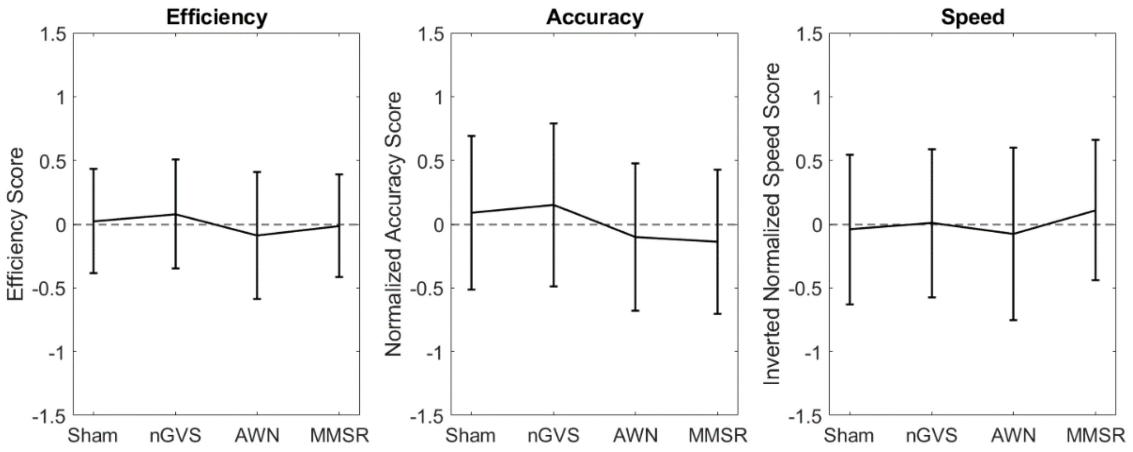

FIGURE 1
Scatter plots compiling normalized cognition metric scores combined across CTB tasks, for the noise conditions and sham. Error bars indicate the 95% confidence interval for score in that condition.

the noise conditions to sham, the largest 95% confidence interval for the multiple comparison was the mean difference ± 0.263 for efficiency, while for accuracy and speed it was ± 0.369. The small confidence intervals in our data suggest that the efficiency, accuracy, and speed were all equivalent between the noise treatments and sham. The largest 95% confidence interval for the control condition multiple comparison in our data (**Figure 2**) was only ± 0.348, suggesting the performance between the control conditions were equivalent.

To evaluate whether noise effects depend on subject (second hypothesis), we investigated the interaction of subject and condition. These results are presented in **Table 4**. In agreement with our hypothesis, significant interactions between subject and noise condition were identified for accuracy, but not speed and efficiency. This suggests that noise effects on cognition are inter-individually dependent. The efficiency results of four subjects are illustrated in **Figure 3**, where subject 2 appears to have cognitive benefits from applying noise, subject 5 was hindered, and subjects 8 and 10 have varied performance independent of noise. Four subjects are shown for legibility, plots containing all subjects can be found in **Supplementary Figure 2**.

Figure 4 explores the mental performance difference (normalized sham cognition metric subtracted from normalized noise cognition metric) as a function of noisy environment preference. These linear models use data from all noise conditions, independent of sensory modality, to assess trends of user susceptibility to noise given preference. The characteristics of these models are presented in **Table 5**. Positive slopes were identified for all three metrics (inverting speed so positive implies performance improvement). These trends, while consistent with the hypothesis, were not statistically significant for the metrics of accuracy and speed, but was statistically significant for efficiency. The slope of the regression line indicates a change in effect across the scale with an effect size of 0.44 for speed, 0.53 for accuracy, and 0.48 for efficiency.

TABLE 2 1×4 RMANOVA results for sham and noise conditions.

Metric	F(3, 343)	*P*-value	η_p^2
Efficiency	1.08	0.357	0.009
Accuracy	2.09	0.101	0.018
Speed	0.54	0.654	0.005

Subjects included as a random effect.

Discussion

This research aimed to understand the utility of using additive sensory noise to improve overall cognition. To our knowledge, this research represents the most comprehensive assessment of the effects of SR noise on cognition. We assessed performance across a broad range of cognitive domains. We also incorporated an expansive set of control conditions to investigate arousal effects. This investigation was similar to cross-modality perception studies which found noise, not arousal, was the mechanism of perceptual enhancements (Lugo et al., 2008). Further, we investigated mental performance effects of compounding sensory noise across multiple modalities.

This work observed subject performance in seven tasks of the CTB while under the influence of nGVS, AWN, and MMSR. Observing performance metrics of efficiency, accuracy, and speed for the cognitive tasks in our broad population, no significant level differences were found between any of the conditions. Additive sensory stimulation, whether noisy (aimed at inducing SR), multi-modal, or control stimulations (pure tone auditory or DC GVS), had no significant effect on broad cognitive performance, neither beneficial nor degrading. Visually though, there appears to be larger performance differences between the noise conditions and sham (**Figure 1**) than there were for the control conditions (**Figure 2**). This may suggest that random noisy sensory stimulation influences cognition to a greater degree than non-noisy stimulation.

While previous working memory studies using nGVS were able to find significant differences with small subject

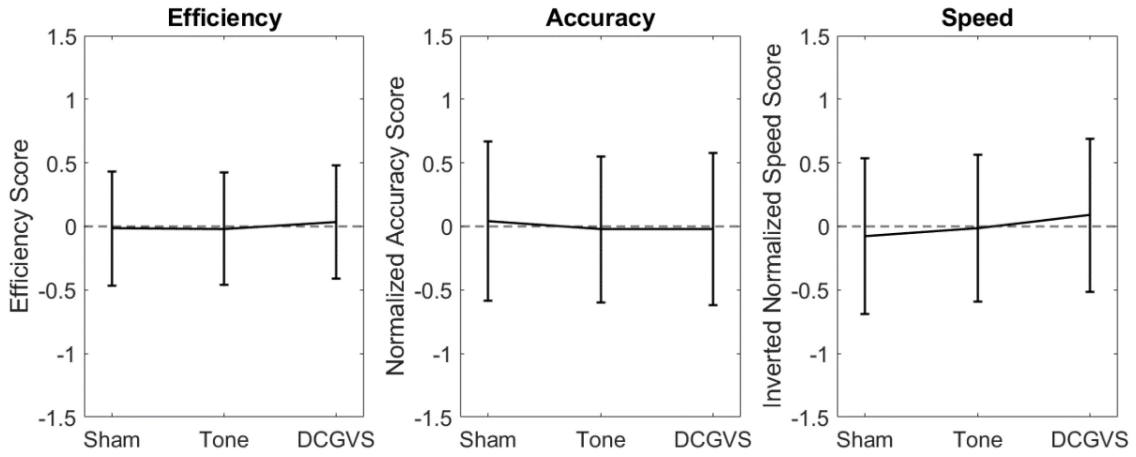

FIGURE 2
Scatter plots compiling normalized cognition metric scores combined across CTB tasks for the control conditions. Error bars indicate the 95% confidence interval for score in that condition.

numbers (Wilkinson et al., 2008), these studies, were limited in that they explored a singular aspect of cognition. While in this study we investigated 13 individuals, our methods comprehensively investigate seven tasks related to cognitive processing, which could allow us to understand broad effects of noise on cognition. Additionally, the repeated observations of our subjects in different tasks increased the statistical power of our models. Our results indicate via a retrospective power analysis that 12 subjects are sufficient to identify significant interaction differences, as shown in **Table 4**. However, based on the η^2 of the noise condition term alone (**Table 2**) it was found that 100 subjects are needed to reach significant effect. Thus, this suggests that individual differences may be the dominant effect of SR, rather than broad cognitive benefits across all individuals. Individualized responses to sensory noise to improve cognition may be consistent with the findings of Helps et al. (2014) which found that only children with low attention tendencies cognitively benefitted from loud auditory white noise ($\geq$ 65 dB). On the other hand, our results contrast those of Othman et al. (2019) and Awada et al. (2022) using AWN and Wilkinson et al. (2008) using nGVS to improve working memory, both in healthy adults. It could be possible that the benefits of additive sensory noise are limited to working memory (or other specific cognitive domains) and do not yield broad cognitive benefits, like we assessed here using seven tasks from the CTB. However, we conducted an exploratory RMANOVA of the adjusted scores for the fractal 2-back, a working memory task, and it still showed insignificance as well ($p > 0.3$). As such, our specific working memory task evaluation contradict findings in the literature. Referencing our exploratory analysis in **Supplementary Table 1** and **Supplementary Figure 1**, we found no significant differences in each of the individual tasks. It should be noted that our findings supplement mixed results within the literature when investigating the role of auditory noise in cognition for a neurotypical group. Awada et al. (2022) found evidence that certain noise levels improved aspects of attention and working memory; however, not all cognitive tests evaluated or noise levels administered yielded significant improvements from ambient noise. This could suggest

TABLE 3 1×3 RMANOVA results for the control conditions.

Metric	F(2, 258)	*P*-value	η_p^2
Efficiency	0.14	0.866	0.001
Accuracy	0.11	0.893	0.001
Speed	0.6	0.547	0.005

Subjects included as a random effect.

TABLE 4 1×4 RMANOVA results for the sham and noise conditions.

Metric	F(36, 312)	*P*-value	η_p^2
Efficiency	1.66	0.097	0.134
Accuracy*	1.58	0.023	0.154
Speed	1.07	0.364	0.110

Subjects included as an interaction term. Asterisks represent metrics that met a statistical significance below 0.05.

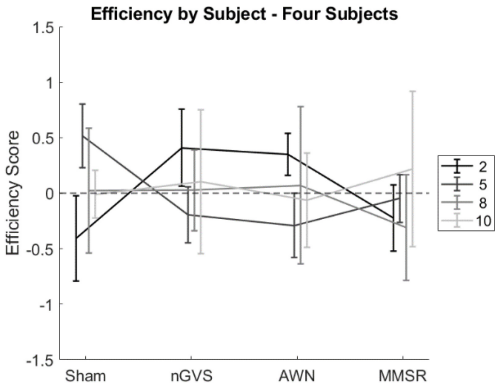

FIGURE 3
Scatter plots compiling efficiency scores across CTB tasks for four individual subjects for the noise conditions. Error bars indicate the 95% confidence interval for score in that condition.

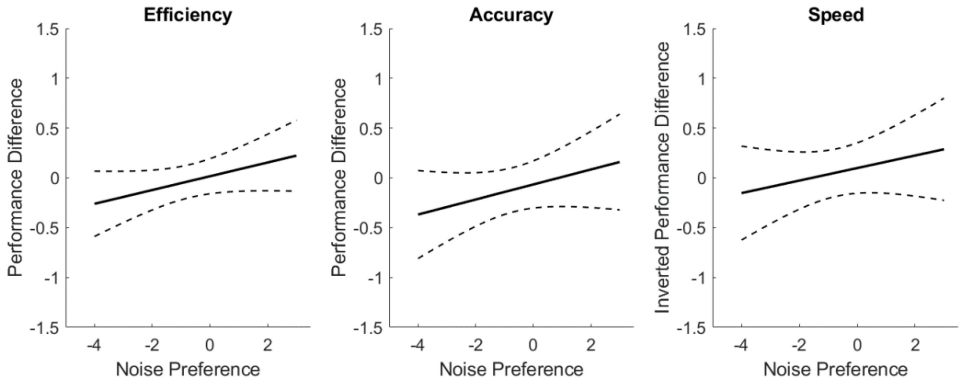

FIGURE 4
Linear regressions of cognitive performance improvement from sham as a function of noisy environment preference. Dashed lines indicate the 95% confidence interval of the modeled fit.

that noise does not influence neurotypical individuals to the degree it influences those with attentional disorders. While our results are not promising for generally using noise to enhance cognition, our results do indicate that individuals may be susceptible to benefits. Future work may move beyond inferential statistics used herein to analyze differences with Bayesian methods, which could provide further indications on the effect of noise on cognitive processes. Additionally, while we used the guidance of Basner et al. (2020) to correct for longitudinal effects that can stem from task learning or fatigue, it was of concern that these effects could still impact our results. Thus, we completed a regression analysis of accuracy and speed performance against number of times the task was completed to confirm this was not the case. We found no significant trends to indicate longitudinal effects skewed our data. These results can be found in **Supplementary Figures 3, 4**. Along with this sanity check, we believe our randomization procedures made us robust to this experimental concern.

The results of the linear models on preference for working in noisy environments shows novel promise for identifying users that may effectively use sensory noise for improved cognitive performance in an SR manner. Experimental literature suggests that some individuals are perceptual SR exhibitors, while others are not influenced by additive noise (Ries, 2007; Galvan-Garza, 2018). There has not been a way to identify, *a priori*, whether someone is susceptible though. This work identified trends in correlating cognitive performance improvement with subjective preference for working in noisy environments. A statistically significant, positive relationship was found between the efficiency metric and noise preference. The slopes of speed and accuracy trended toward significance, showing that additive sensory noise increases accuracy and reduces speed for subjects that prefer working in noisy environments. While there remains variability in response across the seven CTB tasks, these findings indicate that for some subjects, additive noise may yield improvements in cognitive performance, via the mechanism of SR. Further, those individuals were able to self-identify as performing better in noisy settings. To our knowledge, this is the first investigation exploring a means to independently identify which individuals may be susceptible to exhibiting SR benefits. This work's brief noise preference questionnaire points toward working environment affinity as a potential indicator for finding individuals that could see cognitive enhancement from additive noise. The role of individual differences in preference toward working in noisy environments and SR exhibition, particularly in cognitive performance, warrants further investigation.

TABLE 5 Statistical results for linear regressions of cognitive performance improvements as a function of noisy environment preference.

Metric	Slope	*P*-value
Efficiency	0.069	0.048
Accuracy	0.075	0.109
Speed	0.063	0.212

Models fit to all noise condition data.

We want to note two limitations to this study. First, while we utilized a power analysis to guide the number of subjects we tested, thirteen is still a small sample size. This could explain why we were able to find a significant trend for noisy environment preference in efficiency, while we were not able to find significant main effects in our other analyses. However, based upon the effect sizes we observed, the population-wide effects of applying auditory or vestibular white noise on cognition appear quite small and may not be practically relevant. Second, we also note that the repeated application of nGVS (or AWN, DC GVS, or pure tone auditory stimulation) potentially could have long-term effects on cognition. While the literature does not indicate these carryover effects are anticipated, it also has not been rigorously evaluated, as has been done for other neuromodulation techniques (Medeiros et al., 2012; Keywan et al., 2020). This should be investigated in the future to assess the degree to which carryover effect may be found in our study.

Conclusion

This investigation applied a comprehensive and rigorous evaluation of using sensory noise to improve cognition using

a suite of standard cognitive tests and performance comparisons with stimulation control conditions. We conclude that applying additive noise to the auditory and vestibular sensory modalities, as well as to both simultaneously, will not result in improved cognitive performance for a broad population. However, our results indicate that additive noise may have differing cognitive effects across individuals. We assessed a subjective survey's applicability to identify these individuals based on reporting of preference for working in a noisy environment and found a statistically significant, positive relationship. Thus, this type of subjective reporting may be a useful indicator, but further research into other identifying questions or techniques is needed.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the University of Colorado, Boulder's Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SS is the primary author and researcher on this manuscript. MG helped in the development and execution of this experiment. MB allowed us to use the cognition test battery and provided critical feedback. TC and AA were principal investigators on this project and provided critical feedback. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1092154/full#supplementary-material

References

Awada, M., Becerik-Gerber, B., Lucas, G., and Roll, S. (2022). Cognitive performance, creativity and stress levels of neurotypical young adults under different white noise levels. *Sci. Rep.* 12:14566. doi: 10.1038/s41598-022-18862-w

Basner, M., Dinges, D. F., Howard, K., Moore, T. M., Gur, R. C., Mühl, C., et al. (2021). Continuous and intermittent artificial gravity as a countermeasure to the cognitive effects of 60 days of head-down tilt bed rest. *Front. Physiol.* 12:643854. doi: 10.3389/fphys.2021.643854

Basner, M., Hermosillo, E., Nasrini, J., Saxena, S., Dinges, D. F., Moore, T. M., et al. (2020). Cognition test battery: adjusting for practice and stimulus set effects for varying administration intervals in high performing individuals. *J. Clin. Exp. Neuropsychol.* 42, 516–529. doi: 10.1080/13803395.2020.1773765

Basner, M., Savitt, A., Moore, T. M., Port, A. M., McGuire, S., Ecker, A. J., et al. (2015). Development and validation of the cognition test battery for spaceflight. *Aerospace Med. Hum. Perform.* 86, 942–952. doi: 10.3357/AMHP.4343.2015

Bigelow, R. T., and Agrawal, Y. (2014). Vestibular involvement in cognition: visuospatial ability, attention, executive function, and memory. *J. Vestib. Res.* 25, 73–89. doi: 10.3233/VES-150544

Galvan-Garza, R. C. (2018). Exhibition of stochastic resonance in vestibular tilt motion perception. *Brain Stimul.* 7, 716–722. doi: 10.1016/j.brs.2018.03.017

Goel, R., Kofman, I., Jeevarajan, J., De Dios, Y., Cohen, H. S., Bloomberg, J. J., et al. (2015). Using low levels of stochastic vestibular stimulation to improve balance function. *PLoS One* 10:e0136335. doi: 10.1371/journal.pone.0136335

Harvey, P. (2019). Domains of cognition and their assessment. *Dialogues Clin. Neurosci.* 21, 227–237. doi: 10.31887/DCNS.2019.21.3/pharvey

Helps, S. K., Bamford, S., Sonuga-Barke, E. J. S., and Söderlund, G. B. W. (2014). Different effects of adding white noise on cognitive performance of sub-, normal and super-attentive school children. *PLoS One* 9:e112768. doi: 10.1371/journal.pone.0112768

Hidaka, I., Nozaki, D., and Yamamoto, Y. (2000). Functional stochastic resonance in the human brain: noise induced sensitization of baroreflex system. *Phys. Rev. Lett.* 85, 3740–3743. doi: 10.1103/PhysRevLett.85.3740

Huidobro, N. (2020). Augmenting global coherence in EEG signals with binaural or monaural noises. *Brain Topogr.* 33, 461–476.

Inukai, Y., Otsuru, N., Masaki, M., Saito, K., Miyaguchi, S., Kojima, S., et al. (2018). Effect of noisy galvanic vestibular stimulation on center of pressure sway of static standing posture. *Brain Stimul.* 11, 85–93. doi: 10.1016/j.brs.2017.10.007

Kandel, E. R., Schwartz, J. H., and Jessell, T. M. (eds) (2000). *Principles of neural science*, 4th Edn. New York, NY: McGraw-Hill, Health Professions Division.

Keywan, A., Badarna, H., Jahn, K., and Wuehr, M. (2020). No evidence for after-effects of noisy galvanic vestibular stimulation on motion perception. *Sci. Rep.* 10:2545. doi: 10.1038/s41598-020-59374-9

Keywan, A., Jahn, K., and Wuehr, M. (2019). Noisy galvanic vestibular stimulation primarily affects otolith-mediated motion perception. *Neuroscience* 399, 161–166. doi: 10.1016/j.neuroscience.2018.12.031

Keywan, A., Wuehr, M., Pradhan, C., and Jahn, K. (2018). Noisy galvanic stimulation improves roll-tilt vestibular perception in healthy subjects. *Front. Neurol.* 9:83. doi: 10.3389/fneur.2018.00083

Kim, D. J., Yogendrakumar, V., Chiang, J., Ty, E., Wang, Z. J., and McKeown, M. J. (2013). Noisy galvanic vestibular stimulation modulates the amplitude of EEG synchrony patterns. *PLoS One* 8:e69055. doi: 10.1371/journal.pone.0069055

Lugo, E., Doti, R., and Faubert, J. (2008). Ubiquitous crossmodal stochastic resonance in humans: auditory noise facilitates tactile, visual and proprioceptive sensations. *PLoS One* 3:e2860. doi: 10.1371/journal.pone.0002860

Medeiros, L. F., de Souza, I. C. C., Vidor, L. P., de Souza, A., Deitos, A., Volz, M. S., et al. (2012). Neurobiological effects of transcranial direct current stimulation: a review. *Front. Psychiatry* 3:110. doi: 10.3389/fpsyt.2012.00110

Mendez-Balbuena, I., Arrieta, P., Huidobro, N., Flores, A., Lemuz-Lopez, R., Trenado, C., et al. (2018). Augmenting EEG-global-coherence with auditory and visual noise: multisensory internal stochastic resonance. *Medicine* 97:e12008. doi: 10.1097/MD.0000000000012008

Moss, F., Ward, L. M., and Sannita, W. G. (2004). Stochastic resonance and sensory information processing: a tutorial and review of application. *Clin. Neurophysiol.* 115, 267–281. doi: 10.1016/j.clinph.2003.09.014

Mulavara, A. P., Kofman, I. S., De Dios, Y. E., Miller, C., Peters, B. T., Goel, R., et al. (2015). Using low levels of stochastic vestibular stimulation to improve locomotor stability. *Front. Syst. Neurosci.* 9:117. doi: 10.3389/fnsys.2015.00117

Nooristani, M., Maheu, M., Houde, M.-S., Bacon, B.-A., and Champoux, F. (2019). Questioning the lasting effect of galvanic vestibular stimulation on postural control. *PLoS One* 14:e0224619. doi: 10.1371/journal.pone.0224619

Othman, E., Yusoff, A. N., Mohamad, M., Abdul Manan, H., Giampietro, V., Abd Hamid, A. I., et al. (2019). Low intensity white noise improves performance in auditory working memory task: an fMRI study. *Heliyon* 5:e02444. doi: 10.1016/j.heliyon.2019.e02444

Pineault, K., Pearson, D., Wei, E., Kamil, R., Klatt, B., and Agrawal, Y. (2020). Association between saccule and semicircular canal impairments and cognitive performance among vestibular patients. *Ear Hear.* 41, 686–692. doi: 10.1097/AUD.0000000000000795

Ries, D. T. (2007). The influence of noise type and level upon stochastic resonance in human audition. *Hear. Res.* 228, 136–143. doi: 10.1016/j.heares.2007.01.027

Rusticus, S. A., and Lovato, C. Y. (2011). Applying tests of equivalence for multiple group comparisons: demonstration of the confidence interval approach. *Pract. Assess. Res. Eval.* 16:7. doi: 10.7275/D5WF-5P77

Scully, R. R., Basner, M., Nasrini, J., Lam, C., Hermosillo, E., Gur, R. C., et al. (2019). Effects of acute exposures to carbon dioxide on decision making and cognition in astronaut-like subjects. *NPJ Microgravity* 5:17. doi: 10.1038/s41526-019-0071-6

Söderlund, G. B., Sikström, S., Loftesnes, J. M., and Sonuga-Barke, E. J. (2010). The effects of background white noise on memory performance in inattentive school children. *Behav. Brain Funct.* 6:55.

Sturm, W., and Willmes, K. (2001). On the functional neuroanatomy of intrinsic and phasic alertness. *Neuroimage* 14, S76–S84. doi: 10.1006/nimg.2001.0839

Voros, J. L., Sherman, S. O., Rise, R., Kryuchkov, A., Stine, P., Anderson, A. P., et al. (2021). Galvanic vestibular stimulation produces cross-modal improvements in visual thresholds. *Front. Neurosci.* 15:640984. doi: 10.3389/fnins.2021.640984

Wicklegren, W. (1977). Speed-accuracy tradeoff and information processing dynamics. *Acta Psychol.* 41, 67–85.

Wilkinson, D., Nicholls, S., Pattenden, C., Kildu, P., and Milberg, W. (2008). Galvanic vestibular stimulation speeds visual memory recall. *Exp. Brain Res.* 189, 243–248. doi: 10.1007/s00221-008-1463-0

Zeng, F.-G., Fu, Q.-J., and Morse, R. (2000). Human hearing enhanced by noiseq. *Brain Res.* 5, 251–255.

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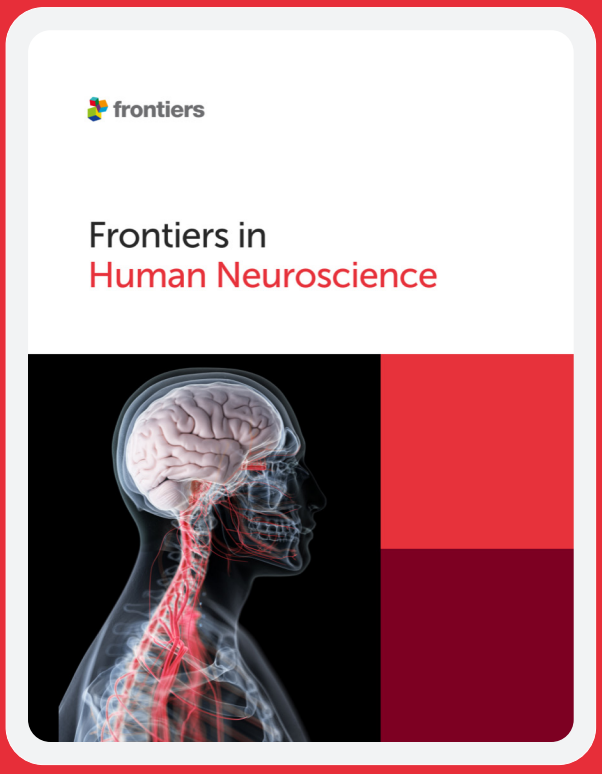

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