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# Impaired emotional response inhibition among adolescents with bipolar depression: evidence from event-related potentials and behavioral performance

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## Abstract

**Background** Impaired inhibition of inappropriate responses in the emotional context is a core feature in patients with bipolar disorder. However, there has been little research exploring the underlying mechanism of impaired response inhibition for emotional stimuli in adolescents with bipolar depression. To explore this issue, we employed event-related potentials (ERPs) to investigate the underlying neuroelectrophysiological mechanisms of inhibition of inappropriate emotional stimuli in adolescents with bipolar depression.

**Methods** Twenty-five adolescents with bipolar depression and nineteen healthy controls completed an emotional Go/No-Go task during electroencephalography recording. Reaction time (RT), reaction time variability (RTV), discriminability, and response bias were measured as behavioral performance indicators. ERP components, theta-band oscillation and inter-trial coherence (ITC) were compared between the two groups.

**Results** Behavioral performance analysis found that adolescents with bipolar depression showed smaller d' values, and larger RT and RTV, than healthy controls. Nogo-P3 amplitude was decreased in adolescents with bipolar depression in comparison with healthy controls. Theta-band oscillation and ITC for emotional stimuli were also reduced in adolescents with bipolar depression. Pearson correlation analysis showed there was a negative correlation between the Nogo-P3 amplitude induced by negative trials and RTV in adolescents with bipolar depression.

**Conclusion** Our findings suggest that adolescents with bipolar depression exhibit abnormal response inhibition in the emotional context. Impaired attentional function and discrimination of emotional information are related to the failure of behavioral inhibition in negative emotional contexts, and attenuated P3 amplitude and theta-band oscillation could be an electrophysiological indicator for this impairment.

**Keywords** Bipolar depression, Adolescents, Response inhibition, ERPs

## Introduction

Bipolar disorder (BD) is a mental illness characterized by episodes of mania or hypomania and depression; depressive episodes have been found to account for a high proportion of time spent ill in individuals with bipolar disorder [28, 39]. Research has shown that individuals with BD manifest depressive symptoms approximately 72% of the time for which they are ill [27]. Furthermore,

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it is estimated that at least half of individuals with BD initially present with a depressive episode. Additionally, bipolar depression has maintained a high incidence of disease on the bipolar spectrum [6, 45]. This has led to an increasing focus on the clinical significance of bipolar depression in recent decades [5]. Moreover, some studies have indicated that depression is associated with excess mortality and disability, particularly among adolescents [18, 40]. Adolescents with bipolar depression, compared with adults, had more severe and longer depressive episodes [35]. The evidence suggests that bipolar depression is associated with greater functional impairments than unipolar depression among adolescents [63]. Consequently, it is of paramount importance that future intervention and management strategies are based on the pathological mechanisms and physiological indicators of bipolar depression in adolescents.

Emotional disturbance is a distinctive clinical feature of bipolar disorder from remission to mood states [12, 52, 53]. Studies have shown that emotional dysregulation in individuals with bipolar disorder may be due to inhibitory control deficits [34]. Response inhibition, which refers the ability to suppress a habitual or proponent response that was inappropriate in a given context, is an important component of the inhibitory control system [46]. The Go/No-Go task is a traditional measurement used to explore response inhibition, in which participants are instructed to respond as quickly as possible to frequent target stimuli and inhibit their response when shown infrequent non-target stimuli [55]. Due the Go/No-Go task may reflect various cognitive functions, there has been ongoing debate among researchers regarding how to report and interpreted behavioral measurements [43]. Reaction time (RT) and accuracy (ACC) are the most commonly explored behavioral indicators, which identified as an "attention and/or response bias" or "an approach to target stimuli", and an index of inhibitory control [44]. Several prior studies have demonstrated that individuals with BD show longer RT and increased ACC of failure for executive responses on Go trials and for response inhibition on No-Go trials in non-emotional and emotional Go/No-Go tasks [52, 53, 64]. Recently, signal detection theory (SDT) was applied to analyze the response accuracy results. It can measure sensitivity (d' value) and response bias (β) information from both the rate of correct response execution (Go accuracy) and the rate of failure to inhibit [59]. Reaction time variability (RTV) is quantified as the standard deviation of reaction time for all "Go" trials from the task. Its increases are an indicator of the reduced cognitive control efficiency and also an indicator of attentional fluctuations when participants need sustained attention to complete the task [14]. Individuals with bipolar disorder exhibit reduced discrimination and larger RTV than controls [42, 61]. Furthermore, some neuroimaging differences have been found. Compared with a bipolar euthymic group, a group with bipolar depression and mania showed lower insula activity when asked to inhibit happy faces and greater putamen, insula and lateral prefrontal cortex activity when asked to inhibit sad faces [33]. A recent study found that adolescents with BD in the manic state showed greater left superior frontal gyrus activation when inhibiting emotional versus neutral distracters, when compared with adolescents with BD in a euthymic state [66]. Adolescence is a sensitive period of emotional instability. However, there is insufficient evidence from studies on emotional response inhibition in adolescents with bipolar depression, despite its importance in the clinical setting. Thus, examining response inhibition processing in the emotional context can advance our understanding of the underlying mechanisms of bipolar depression and guide future intervention among adolescents.

Event-related potentials (ERPs), with high temporal resolution in milliseconds, allow recording of the time course of neural activity associated with emotional response inhibition [32, 69]. Two main components, N2 and P3amplitudes, are thought to be related to response inhibition [56]. Amplitudes induced by No-Go trials are larger than those for Go trials. Prior studies have indicated that the N2 and P3 components reflect different sub-processes of response inhibition: N2 is considered to be associated with conflict detection and monitoring processing, whereas P3 is suggested to be related to conflict resolution and behavioral inhibition [23, 36]. Individuals with BD exhibited delayed inhibitory control process for emotional information, which was indexed by longer latencies of emotional stimuli [19]. Moreover, numerous researchers posit that the No-Go-P3 is indicative of the inhibitory process itself [1, 58]. There are evidence that individuals with BD exhibit reduced P3 amplitude in response to emotional faces when compared with healthy controls [42]. Neural oscillations, which are thought to be more fundamental physiological mechanisms involved in various aspects of neural functioning, are also studied broadly in the field of neuroscience [57]. Theta-band oscillation over midline fronto-central scalp sites is becoming increasingly established as a direct neural index of certain aspects of cognitive control [11]. Some studies have suggested that individuals with bipolar disorder exhibit reduced theta-band power and inter-trial coherence during auditory processing and visual face processing [4, 37]. A study has also revealed that theta-band power and inter-trial coherence are reduced in adults with bipolar disorder during an emotional Go/No-Go task [2]. However, there are few published studies investigating oscillatory activity, which is related to the

inhibitory response in an emotional context in adolescents with bipolar depression.

Use of happy and sad faces may provide information regarding positive and negative biases, and are often used to investigate emotional inhibitory control processing. Murphy et al. reported biases consistent with mood: patients with mania were biased toward positive stimuli and depressed patients were biased toward negative stimuli [47]. Psychosocial models of BD suggest that individuals with BD in remission episodes self-report a heightened and persistent positive affect in response to emotional stimuli [51]. Given that bipolar depression in adolescents is common and difficult to distinguish from unipolar depression, it is necessary to explore the processing of emotional stimuli in adolescents with bipolar depression [9]. Therefore, the main goal of the present study was to explore the neural substrates of response inhibition to negative and positive faces in adolescents with bipolar depression, based on ERP recordings. We hypothesized that adolescents with bipolar depression would show deficits in response inhibition for both negative and positive faces, and would therefore show larger RT and RTV as well as a reduced discrimination of emotional faces relative to healthy controls. The frontal-parietal network, particularly nodes such as the inferior frontal gyrus (IFG) and posterior parietal cortex (PPC), is critical for top-down inhibitory control [3]. Theta-band oscillation over midline fronto-central scalp sites have been regarded as a direct neural index of certain aspects of cognitive control, while P3 amplitude over parietal cortex was associated with successful motor inhibition [11, 58]. Thus, For the ERP components, we also expected reduced parietal Nogo-P3 amplitude was reduced among adolescents with bipolar depression and frontal theta-band oscillation was also reduced among adolescents with bipolar depression.

## Methods

### Participants

Adolescent patients with bipolar depression were recruited from the children and adolescents outpatient clinic and ward at the Fourth People's Hospital of Wuhu City. G*power 3.1 software was used to estimate sample size before data collection to allow reliable detection of an effect [26]. Based on prior methodological reporting guideline for studies of ERPs, at least 30 participants were needed to detect a medium effect (Cohen d' = 0.35,$\alpha = 0.05$, 1-$\beta = 0.95$, Repeated ANOVA interaction effects) [16, 25]. A total of 44 participants were enrolled in the present study, and a sensitivity analysis showing that the conclusion hold even if the true effect size is smaller than assumed (Cohen d' = 0.28). All patients were diagnosed by at least one associate chief psychiatrist, who had received rigorous and standard training of the 10th version of the International Classification of Diseases (ICD-10). They met the diagnostic criteria for bipolar and its related disorders after a semi-structured interview and assessment by psychiatrist and in the present period of depressive episodes. Hamilton Depression Rating Scale (HAMD-17) and Young Manic Rating Scale (YMRS) were used to assess the depressive and manic symptoms, respectively. Thus, the inclusion criteria for adolescents with bipolar depression were: (a) meet the diagnostic criteria of bipolar and its related disorders after being evaluated by at least 1 chief psychiatrist; (b) currently in the depressive episode and scored > 7 on the Hamilton Depression Rating Scale (HAMD-17); (c) boys or girls between the ages of 12 and 18; (d) all adolescents with bipolar depression were treated with oral sertraline hydrochloride plus valproate or only valproate, with treatment unchanged for 4 weeks prior to enrollment; (e) right handed and normal or corrected vision. Closely matched healthy adolescents were recruited through advertisements published on social media and offline, and the psychiatric illnesses of healthy controls also evaluated by a attending psychiatrist. The inclusion criteria for healthy adolescents were: (a) adolescents who had no known mental disorder currently or in the past;(b) no history of psychiatric illnesses in a first-degree relative, (c) scored < 7 on the HAMD-17;(d) no medical diseases or neurological illnesses; and(d) no substance abuse. In addition, adolescents who could not cooperate to complete the experiment were excluded. We recruited a total of 25 adolescents with bipolar depression ($Mean_{age} = 15.00 \pm 1.53$, male/female: 3/22) and 19 healthy adolescents ($Mean_{age} = 15.25 \pm 1.89$, male/female: 4/15). Two adolescents with bipolar depression and one healthy adolescent were excluded owing to poor EEG data quality. The experimental procedure was in accordance with the ethical principles of the Declaration of Helsinki, and approved by the Ethics Committee of Wuhu Fourth People's Hospital (Number: 2019008). All participants and their guardians voluntarily participated and signed the informed consent form.

### Stimuli and procedure

In this study, we used to a modified version of the emotional Go/No-Go paradigm, which was applied using E-prime 2.0 software [60]. The stimuli presented during the emotional Go/No-Go task comprised 32 (16 male, 16 female) pictures of positive and negative emotional faces, which were selected from the native Chinese Facial Affective Picture System (CFAPS). Similar to the traditional Go/No-Go task, participants were asked to respond as rapidly as possible to "Go" emotional facial

trials and to inhibit their responses to the "No-Go" emotional facial trials.

The emotional Go/No-Go task included two blocks (Go positive and Go negative). In the Go positive block, participants were required to press the "J" key to positive faces and inhibit responses to negative faces, whereas they should do the opposite in the Go negative block. The order of the emotional blocks was counterbalanced, with a relaxation period between the two blocks. Each trial was initiated by a small white cross that was presented for 150 ms on the black screen, followed by a 300 ms face presentation at the center of the screen. The inter-stimulus interval, which means the time interval from stimulus offset to stimulus onset, was 1200–1400 ms. A practice session consisting of 32 trials was administered before the start of the formal experiment to ensure that participants understood the experimental process. The experiment comprised 512 trials, which consisted of 192 (75%) Go trials and 64 (25%) No-Go trials in each block, lasting for approximately 18 min. The task procedure is outlined in Fig. 1.

#### EEG recording and analysis

An elastic cap with 64 channels, placed according to the international 10/20 system using a Brainproduct recording system (Brain Products GmbH, actiCHamp, Germany), was used to collect EEG data when participants had completed the effective Go/No-Go task. The system was grounded with a forehead electrode. The EEG signals were recorded using the FCz electrode as the online reference. The raw EEG data were amplified with a 0.01–80 Hz band-pass filter and continuously sampled at the 500 Hz/channel. All electrode impedances were maintained below 10 kΩ.

The EEGLAB toolbox running in the MATLAB environment was used to process and analyze the offline EEG data [20]. The collected EEG data were re-referenced off-line to the average of the left and right mastoids and subjected to a high-pass filter at 1 Hz (finite impulse response filter conducted with pop_eegnewfilt with the default parameters, cutoff frequency of 0.5 Hz, and 26 dB) to remove baseline drift, thereby ensuring reliable results for independent component analysis [21]. Continuous data were filtered and segmented from 1000 ms before the Go or No-Go stimulus was presented after 2000 ms. All epochs were baseline corrected from 1000 ms pre-stimulus to improve the reliability of the independent components. In addition, artifactual epochs were identified and removed based on: 1) abnormal spectral characteristics of high frequency noise (rejspec; 20–40; $< -35$ or $> 35$ dB); 2) abnormal trends (rejtrend; slope $> 200$ μV with $R2 > 0.3$); 3) abnormal amplitude (threshold $-500$ μV or $+500$ μV); 4) improbable data using joint probability [jointprob, 8 standard deviations

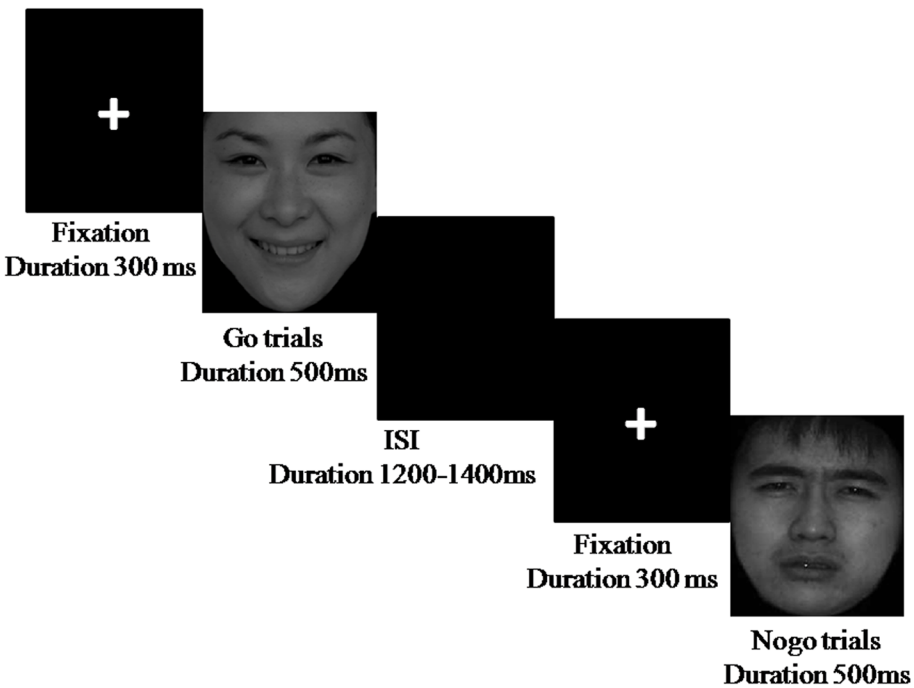


**Fig. 1** Illustration of emotional Go/No-Go task. The emotional Go/No-Go task was presented in two blocks. In the negative Go/positive No-Go trials, participants were required to press the "J" key for negative faces and inhibit responses to positive faces. They were instructed to respond vice in the opposite way in the positive Go/negative No-Go trials

(SD) for single channel and 4 SD for all channels]; or 5) abnormal distributions (rejkurt; 8 SD for single channel and 4 SD for all channels). Data from electrodes responsible for more than 10% of rejected epochs were rejected. Subsequently, epoched data were decomposed into maximally independent components using an extended infomax algorithm implemented by the runica() function with default parameters. Artifactual components from the electrooculogram and electromyogram were identified and removed by the EEG_SASICA plugin in EEGLAB [13]. On average, 46.8 (95% CI, [45.07, 48.44]) components remained in the group of adolescents with bipolar depression and 48.11 (95% CI, [46.66, 49.64]) in the healthy controls. In total, 178.4 (95% CI, [170.76, 184.96]) trials were left in the positive Go condition and 59.28 (95% CI, [56.68, 61.44]) trials were left in the negative No-Go condition in the bipolar depression group; 178.05 (95% CI, [168.88, 185.36]) trials were left in the positive Go condition and 58.95 (95% CI, [55.16, 61.87]) trials were left in the negative No-Go condition in the healthy control group; 174.56 (95% CI, [164.29, 183.06]) trials were left in the negative Go condition and 57.88 (95% CI, [54.19, 60.95]) trials were left in the positive No-Go condition in the bipolar depression group; and 184.11 (95% CI, [178.47, 188.55]) trials were left in the negative Go condition and 60.79 (95% CI, [58.94, 62.25]) trials were left in the positive No-Go condition in the healthy control group.

The time–frequency analysis was obtained using Morlet wavelet decomposition operated with the EEGLAB newtimef function. Spectral power was calculated with 50 log-spaced center frequencies ranging from 3 to 50 Hz, and 200 linearly spaced time bins across the epoch. Given the balance between frequency and temporal resolution, the wavelets were built on the parameter [3, 0.8] specifically for three cycles at the lowest frequency (3 Hz) and 10 cycles at the highest frequency (50 Hz). The normalized power employed a dB transform [dB power = 10*log10 (power/baseline)].

The cleaned ERP waveforms were time-locked to stimulus onset and epoched to 200 ms pre-stimulus and 1,000 ms post-stimulus. The ERPs were averaged separately for Go trials and No-Go trials under positive and negative emotional conditions. Although N2 and P3 components are the most commonly analyzed, because they are thought to be related to response inhibition processing, the present study did not show a significant N2 component in the waveform diagram. According to previous research, the P3 component, compared with the N2, is a more direct indicator of response inhibition [42]. Furthermore, RTV was analyzed in the present study to explore top-down attention allocation and executive control ability. Grand-average P3 amplitudes were measured within the time window from 400 to 600 ms. The event-related spectral perturbations (ERSPs) and inter-trial coherence (ITC) of the theta-band frequency measurements (4–6 Hz, 300–500 ms) for Go and No-Go trials in negative and positive conditions were calculated and averaged across participants. Consistent with the established role of frontal-parietal region in inhibitory control, the ERP and ERSP data frontal (FC3, FC4, FCz, C3, C4, Cz) and parietal (CP3, CP4, CPz) electrode clusters based on the previous studies [2, 67, 68].

### Statistical analysis

All data were analyzed using IBM SPSS 16.0 (IBM Corp., Armonk, NY, USA). The chi-square test was used to assess the difference in sex ratio between the groups. Independent samples t-tests were performed to assess group differences in age, years of education, and HAMD scores. Independent samples t-tests were used to analyze the differences in the reaction times for Go positive and Go negative trails between the two groups. Two-way mixed design ANOVA was conducted to analysis the RTV between the two groups, with different emotional valence (positive VS negative) and block types (block one VS block two) as within-subject factors. Mixed design ANOVA was conducted to analyze the average amplitude of P3 and theta-band oscillation power with different emotional valence (positive VS negative), response types (Go VS Nogo), and electrodes (FC3, FC4, FCz, C3, C4, Cz, CP3, CP4, and CPz) as within-subjects factors, and group (bipolar depression group VS healthy controls group) as a between-subject factor. Given medications also influence event-related potentials and event-related oscillation, repeated-ANOVA analysis conducted to analysis the medication effect of antidepressants on P3 amplitude and theta-band oscillations on the basis of controlling the dose of mood stabilizers. Logistical binary regression analysis was performed for the behavioral performance and neuroelectrophysiological factors of group status outcomes. Bivariate Pearson's correlation coefficients were calculated to examine the strengths of the associations among HAMD scores, behavioral performance, P3 amplitude, and theta-band power oscillation to assess the association between clinical symptoms and response inhibition impairment. To examine the reliability of the behavioral and neural measurements, the internal consistency values (e.g. Cronbach's Alpha) were also reported in the current study. A two-tailed $P < 0.05$ was considered to indicate a significant difference in all tests. The Bonferroni method was used to correct for multiple comparisons in post hoc tests. The Greenhouse–Geisser correction was used to adjust the degrees of freedom. Partial eta squared ($\eta p^2$) values were obtained to examine the sizes of effects in the ANOVA models, where 0.05

indicated a small effect, 0.1 indicated a medium effect, and 0.2 indicated a large effect.

## Results

### Demographic and clinical characteristics

Compared to the healthy controls, adolescents with bipolar depression showed lower MoCa and higher HAMD scores, as shown in Table 1.

### Behavioral performance

Behavioral performance results as shown in Table 2. D' values and β were analyzed in the present study. The Cronbach's Alpha of D' was 0.913 in the present study. Repeated-measures ANOVA of d' values showed that the main effect of valence ($F_{1,42}=45.56$, $P<0.001$, $\eta_p^2=0.52$) and group ($F_{1,42}=32.75$, $P<0.001$, $\eta_p^2=0.44$) were significant. Compared to healthy controls, adolescents with bipolar depression showed smaller d' values when they were instructed to inhibited inappropriate responses in the negative and positive emotional context. The interaction effect of group and valence was also significant ($F_{1,42}=14.71$, $P<0.001$, $\eta_p^2=0.26$). Compared to healthy controls, adolescents with bipolar depression showed smaller difference between d' values in the two conditions, which indicated that their impaired ability to suppress negative and positive emotions. However, analysis of response bias showed the main effect of valence and group, the interaction effect of valence and group were not significant ($Fs \leq 1.99$, $Ps \geq 0.494$).

Repeated-measures ANOVA of the reaction time showed that the main effect of valence factor was significant ($F_{1,42}=6.01$, $P=0.018$, $\eta_p^2=0.13$). Although the main effect of group was not significant, the reaction

**Table 1** Sample demographic and clinical characteristic of adolescents with bipolar depression and healthy controls

| | Healthy Control | Bipolar Depression | $t/\lambda^2$ | *P* |
|---|---|---|---|---|
| **Demographic** | | | | |
| Age | 15.25 ± 1.88 | 15.00 ± 1.53 | −0.491 | 0.626 |
| Sex(male:female) | 4/15 | 3/22 | $\lambda^2=0.661$ | 0.416 |
| Education(yrs) | 10.05 ± 2.26 | 10.20 ± 1.76 | 0.239 | 0.803 |
| MoCa | 29.55 ± 0.83 | 27.88 ± 2.07 | −3.395 | 0.001 |
| **Clinical** | | | | |
| HAMD | 2.12 ± 1.27 | 16.44 ± 5.78 | 10.603 | < 0.001 |
| YMRS | - | 2.12 ± 1.26 | - | - |
| Years since Illness Onset | - | 2.32 ± 1.29 | - | - |

*MoCA* Montreal Cognitive Assessment, *HAMD* Hamilton Depression Scale, *YMRS* Young Manic Rating Scale

**Table 2** Means and standard deviations of sensitivity, response bias, RT, RTV and ACC by group and task condition

| | Healthy Controls(HC) | Bipolar Depression(BD) | *t* values | *P* values |
|---|---|---|---|---|
| **Reaction Time(RT)** | | | | |
| Positive Go | 414.05 ± 55.77 | 450.78 ± 109.23 | 1.337 | 0.188 |
| Negative Go | 449.85 ± 61.09 | 461.37 ± 102.33 | 0.775 | 0.443 |
| **Reaction Time Variability(RTV)** | | | | |
| Positive Go | 103.32 ± 32.85 | 179.92 ± 62.10 | 4.874 | < 0.001 |
| Negative Go | 109.93 ± 29.14 | 172.85 ± 48.43 | 5.007 | < 0.001 |
| **Accuracy Rates(ACC)** | | | | |
| Positive Go | 0.91 ± 0.11 | 0.76 ± 0.25 | −2.424 | 0.020 |
| Negative Go | 0.91 ± 0.05 | 0.78 ± 0.21 | −2.810 | 0.007 |
| Positive Nogo | 0.71 ± 0.16 | 0.52 ± 0.16 | −4.104 | < 0.001 |
| Negative Nogo | 0.91 ± 0.05 | 0.60 ± 0.16 | −8.177 | < 0.001 |
| **Sensitivity(D' value)** | | | | |
| Positive Go/Negative Nogo | 3.02 ± 0.84 | 1.19 ± 1.01 | −6.360 | < 0.001 |
| Negative Go/Positive Nogo | 2.09 ± 0.61 | 0.94 ± 1.00 | −4.401 | < 0.001 |
| **Response Bias (β)** | | | | |
| Positive Go/Negative Nogo | 1.99 ± 1.97 | 2.79 ± 2.50 | 1.153 | 0.255 |
| Negative Go/Positive Nogo | 3.06 ± 3.22 | 2.43 ± 2.79 | −0.694 | 0.492 |

time of the group with bipolar depression was longer than the group of health control [(456.08 ± 17.02)μV vs (427.45 ± 19.52)μV]. The interaction effect between the response and group was not significant ($F_{1,42}=1.13$, $P=0.294$, $\eta_p^2=0.03$). The Cronbach's Alpha was 0.913 in the present study.

Repeated-measures ANOVA of the accuracy rates (ACC) showed that the main effect of group was significant ($F_{1,42}=33.81$, $P<0.001$, $\eta_p^2=0.45$). The main effect of block was significant ($F_{1,42}=26.35$, $P<0.001$, $\eta_p^2=0.39$). The main effect of valence was significant ($F_{1,42}=28.93$, $P<0.001$, $\eta_p^2=0.33$). The interaction effect between group and block was critical significant ($F_{1,42}=3.45$, $P=0.070$, $\eta_p^2=0.08$). Compared to healthy controls, adolescents with bipolar depression showed decreased ACC both in Go and Nogo blocks.

Repeated-measures ANOVA of the RTV showed that the main effect of group was significant ($F_{1,42}=28.93$, $P<0.001$, $\eta_p^2=0.41$). The interaction effect between group and block was critical significant ($F_{1,42}=3,92$, $P=0.054$, $\eta_p^2=0.09$), and further simple analysis of the interaction effect showed that adolescents with bipolar depression exhibited significant larger RTV in block one than block two [(166.56 ± 8.90) ms vs (186.20 ± 10.36) ms]. The interaction effect between valence and block was significant ($F_{1,42}=3.92$, $P=0.039$, $\eta_p^2=0.09$). The main effect of valence was not significant ($F_{1,42}=0.001$, $P=0.97$, $\eta_p^2<0.001$). The main effect of block was not significant ($F_{1,42}=0.75$, $P=0.39$, $\eta_p^2=0.018$). The Cronbach's Alpha was 0.864 in the present study.

**Event-related potentials and event-related oscillation data**

Table 3. shows the means and standard deviations of P3 amplitude, theta-band oscillations and inter-trial coherence in each condition for each group.

***P3 amplitude***

Repeated-measure ANOVA of P3 amplitude showed that the main effect of group was significant ($F_{1,42}=24.00$, $P<0.001$, $\eta_p^2=0.36$). Adolescents with bipolar depression exhibited reduced P3 amplitude compared with controls [(0.05 ± 0.52)μV vs (3.96 ± 0.60)μV]. The main effect of valence was significant ($F_{1,42}=24.00$, $P<0.001$, $\eta_p^2=0.36$). Negative faces induced larger P3 amplitude than happy faces [(2.23 ± 0.46)μV vs (1.78 ± 0.37)μV]. The main effect of response was significant ($F_{1,42}=26.97$, $P<0.001$, $\eta_p^2=0.39$). Nogo trials induced more positive P3 amplitude than Go trials [(2.74 ± 0.47)μV vs (1.27 ± 0.37)μV]. The interaction effect of response and group was significant ($F_{1,42}=8.46$, $P=0.006$, $\eta_p^2=0.17$). Compared with healthy controls, adolescents with bipolar depression showed indistinctive difference between Go trials and Nogo trials [(−0.27 ± 0.49)μV vs (0.38 ± 0.62)μV]. The main effect of electrode was significant ($F_{1,42}=35.32$, $P<0.001$, $\eta_p^2=0.46$), where the P3 amplitude was largest with the CPz electrode [(3.60 ± 2.51)μV]. The interaction effect of valence and group was not significant ($F_{1,42}=1.70$, $P=0.20$, $\eta_p^2=0.04$). The interaction effect of valence, response and group was not significant ($F_{1,42}=0.52$, $P=0.48$, $\eta_p^2=0.01$). The Cronbach's Alpha of P3 amplitude were 0.983 and 0.984 in Go and Nogo trials in the present study. Shown in Fig. 2.

**Table 3** Means and standard deviations of P3 amplitude, theta-band oscillations and ITC by group and conditions

| | Healthy Controls(HC) | Bipolar Depression(BD) | *F* values | *P* values | 95%CI[lower upper] |
|---|---|---|---|---|---|
| **P3 amplitude (μV)** | | | | | |
| Positive Go | 2.57 ± 0.56 | 0.39 ± 0.49 | 15.847 | < 0.001 | [1.463 4.473] |
| Negative Go | 3.06 ± 0.61 | −0.15 ± 0.53 | 15.701 | < 0.001 | [1.571 4.831] |
| Positive Nogo | 4.63 ± 0.61 | 0.33 ± 0.53 | 28.004 | < 0.001 | [2.656 5.930] |
| Negative Nogo | 5.59 ± 0.88 | 0.42 ± 0.77 | 19.275 | < 0.001 | [2.796 7.555] |
| **Theta-band oscillations (dB)** | | | | | |
| Positive Go | 0.96 ± 0.30 | −0.23 ± 0.26 | 9.050 | 0.004 | [0.393 1.996] |
| Negative Go | 1.87 ± 0.31 | 0.002 ± 0.27 | 20.621 | < 0.001 | [1.037 2.696] |
| Positive Nogo | 1.37 ± 0.34 | 0.53 ± 0.30 | 3.449 | 0.070 | [−0.073 1.767] |
| Negative Nogo | 2.45 ± 0.35 | 0.57 ± 0.30 | 15.805 | < 0.001 | [0.906 2.774] |
| **ITC (dB)** | | | | | |
| Positive Go | 0.21 ± 0.01 | 0.17 ± 0.01 | 4.404 | 0.042 | [−0.077 −0.002] |
| Negative Go | 0.22 ± 0.02 | 0.18 ± 0.02 | 2.457 | 0.125 | [−0.092 0.012] |
| Positive Nogo | 0.26 ± 0.02 | 0.21 ± 0.02 | 3.427 | 0.071 | [−0.106 0.005] |
| Negative Nogo | 0.30 ± 0.02 | 0.22 ± 0.01 | 14.130 | 0.001 | [−0.125 0.038] |

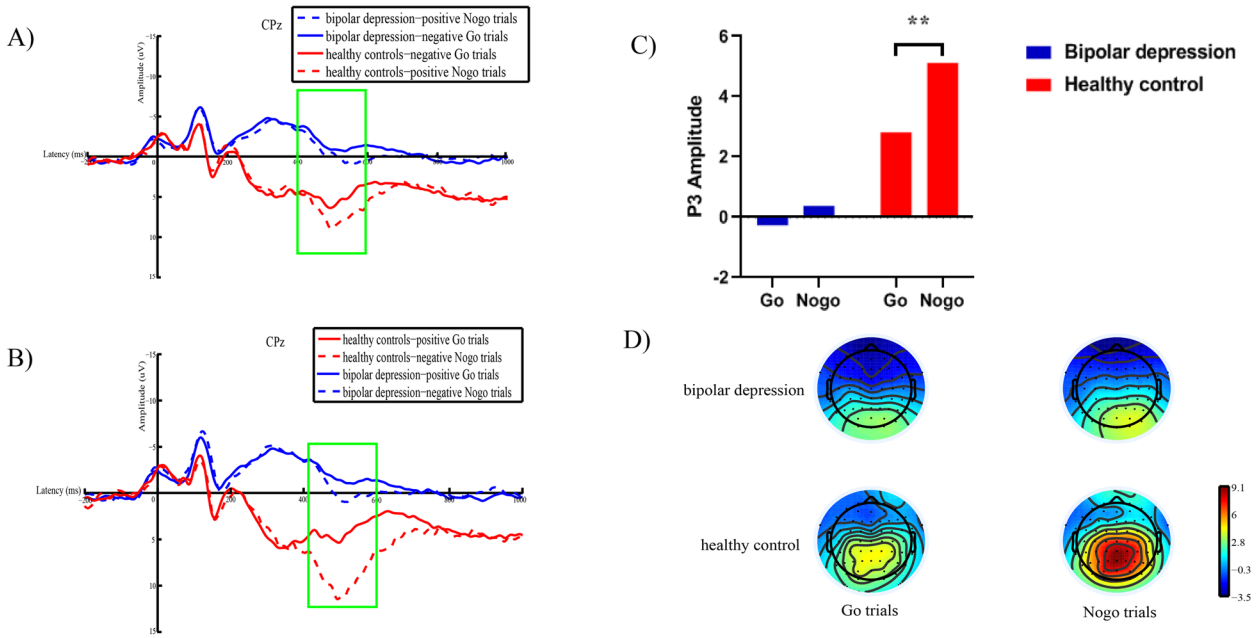


**Fig. 2** Grand-averaged P3 amplitude in the negative Go/positive Nogo trials (**A**) and positive Go/negative Nogo trials (**B**) across adolescents with bipolar depression and healthy controls. There was significant interaction effect between response types and groups. The interaction effect between group and response was shown in (**C**). Adolescents with bipolar depression showed indistinctive difference between Go trials and Nogo trials. Topographical maps assessed between 400 to 600 ms following stimulus onset cross all conditions for each group were shown in (**D**)

### *Theta-band oscillations*

All within-subjects factors included in the present study conformed to a normal distribution ($P>0.05$). Repeated ANOVA tests based on theta-band power activation showed that the main effect of valence was significant ($F_{1,42}=27.12$, $P<0.001$, $\eta_p^2=0.39$), where the theta oscillation power had a significantly larger effect with negative faces than positive faces [$(0.66\pm0.20)$ vs $(1.21\pm0.21)$]. The main effect of response was significant ($F_{1,42}=33.20$, $P<0.001$, $\eta_p^2=0.44$), where the effect of Nogo trials on theta-band oscillation was larger than that of Go trials ($0.65\pm0.19$ vs $1.22\pm0.22$). The main effect of group was significant ($F_{1,42}=13.05$, $P=0.001$, $\eta_p^2=0.24$). Adolescents with bipolar depression exhibited lower theta-band activation than controls [$(0.22\pm0.26)$ vs $(1.65\pm0.30)$]. The interaction effect of valence and group was significant ($F_{1,42}=15.27$, $P<0.001$, $\eta_p^2=0.27$). Simple analysis of the interaction effect of valence and group showed that the theta-band oscillation differed significantly between positive and negative faces within healthy control group. The main effect of electrode was significant ($F_{1,42}=24.55$, $P<0.001$, $\eta_p^2=0.37$), where the largest power was detected at the FCz electrode [$(1.47\pm0.21)$] Hz. The interaction effect of response and group was not significant ($F_{1,42}=0.90$, $P=0.35$, $\eta_p^2=0.02$). The Cronbach's Alpha of theta-band power were 0.987 and 0.986 in Go and Nogo trials in the present study. Shown in Fig. 3.

Repeated ANOVA tests based on ITC for Go trials and Nogo trials showed that the main effect of response was significant ($F_{1,42}=19.12$, $P<0.001$, $\eta_p^2=0.31$), where the effect of Nogo trials on ITC was larger than that of Go trials [$(0.26\pm0.01)$Hz vs $(0.23\pm0.01)$Hz]. The main effect of group was significant ($F_{1,42}=4.63$, $P=0.04$, $\eta_p^2=0.10$). Compared with health controls, adolescents with bipolar depression showed reduced ITC [$(0.26\pm0.01)$Hz vs $(0.23\pm0.01)$Hz]. The main effect of electrode was significant ($F_{1,42}=2.94$, $P=0.003$, $\eta_p^2=0.07$), where the largest ITC was detected at the CPz electrode ($0.27\pm0.01$) Hz. The main effect of valence was not significant ($F_{1,42}=1.17$, $P=0.29$, $\eta_p^2=0.03$). The interaction effect of valence and group was not significant ($F_{1,42}=1.24$, $P=0.27$, $\eta_p^2=0.03$). The interaction effect of valence, response and group was not significant ($F_{1,42}=2.17$, $P=0.15$, $\eta_p^2=0.05$). The Cronbach's Alpha of ITC were 0.967 and 0.854 in Go and Nogo trials in the present study. Shown in Fig. 4.

### Medication effect analysis

To investigate effects of antidepressants on event-related potentials and event-related oscillation results, Repeated-ANOVA was conducted to compare the differences among adolescents with bipolar depression who taking or not taking medications and healthy controls. The interaction effect between antidepressants and response

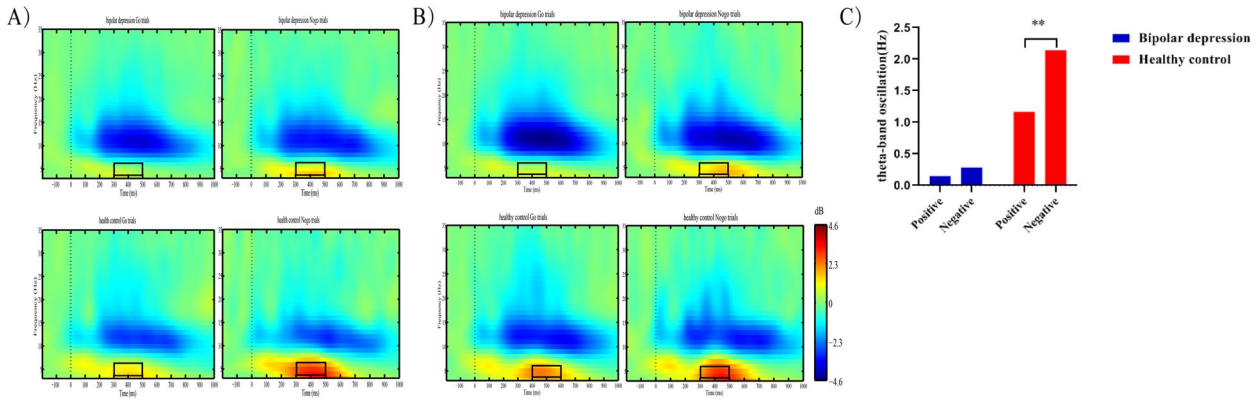


**Fig. 3** Grand-averaged theta-band oscillations in the negative Go/positive Nogo (**A**) and positive Go/negative Nogo trials (**B**) at FCz electrode in the bipolar depression adolescents group and healthy control group. Adolescents with bipolar depression showed lower theta-band oscillation than healthy controls (the black box is the time window of interest of theta-band frequency)

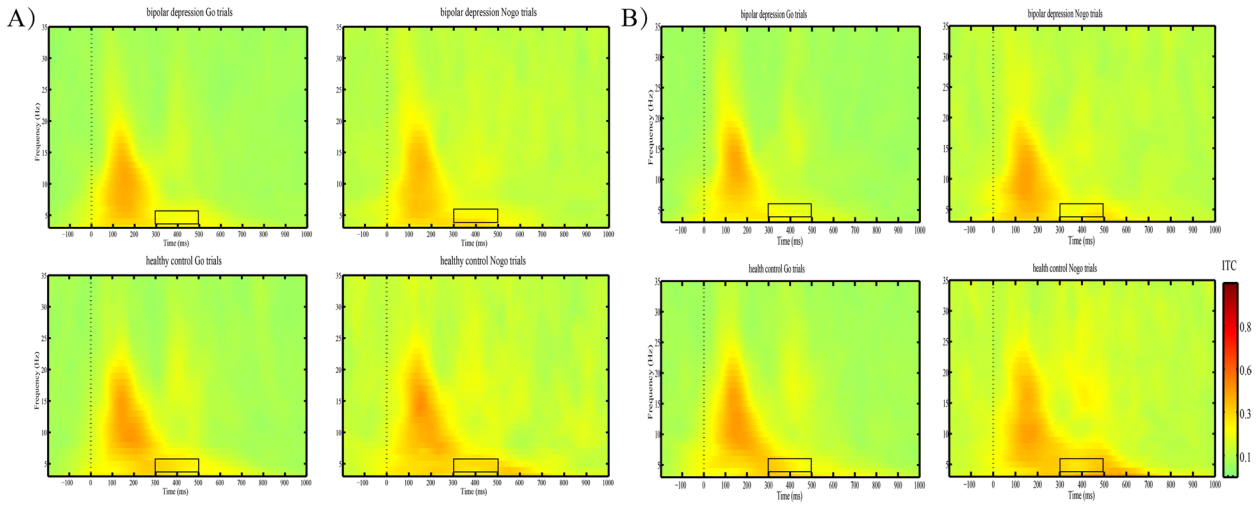


**Fig. 4** Inter-trial coherence (ITC) of theta-band frequency in the negative Go/positive Nogo (**A**) and positive Go/negative Nogo (**B**) trials at FCz electrode in the adolescents with bipolar depression group and healthy controls. Adolescents with bipolar depression showed lower theta-band oscillation than healthy controls (the black box is the time window of interest of theta-band frequency)

was significant on P3 amplitude ($F_{1,42}=3.31$, $P=0.047$, $\eta_p{}^2=0.142$). Further simple analysis showed that adolescents with bipolar depression who not taking medications exhibited lower P3 amplitude in Nogo trials than healthy controls [$(1.16\pm1.28)$vs$(7.08\pm1.36)$]. The interaction effect between antidepressants and valence was significant on theta-band oscillations ($F_{1,42}=4.13$, $P=0.024$, $\eta_p{}^2=0.171$). Further simple analysis showed that adolescents with bipolar depression who not taking antidepressants exhibited lower theta-band oscillations induced by negative stimuli than healthy controls [$(0.59\pm0.49)$ vs$(2.67\pm0.53)$].

### Correlation analysis

Pearson correlation analysis revealed that d' value under negative Go and positive Nogo trials exhibited positive correlation with P3 amplitude induced by negative faces ($r_{Go}=0.30$, $P=0.047$, $r_{Nogo}=0.37$, $P=0.013$). There is a positive correction between d' value under positive Go and negative Nogo trials and theta-band oscillation induced by negative Nogo trials ($r=0.30$, $P=0.046$). The d' value under negative Go and positive Nogo trials were corrected with theta-band oscillation induced by negative Go trials positively ($r=0.33$, $P=0.027$). Pearson's correlation analysis showed that P3 amplitude induced by negative Nogo trials exhibited negative association with the

RTV for negative Go trials ($r=-0.43$, $P=0.031$) among adolescents with bipolar depression. There are positive correlation between HAMD scores and theta-band oscillation induced by positive Nogo trials ($r=0.57$, $P=0.003$) within bipolar depression adolescents. No other significant relationship was found among P3 amplitude and depressive symptom or d' values within adolescents with bipolar depression.

Pearson correlation analysis also conducted to explore the relationship between the behavioral performance and neural indicators. The correlation analysis revealed that no significant relationship among P3 amplitude or theta-band oscillation and behavioral indicators ($Ps \geq 0.078$).

### Binary regression analysis

Binary regression analyses were conducted to explore the effect of behavioral performance and neural activity in group status. Analysis of P3 amplitude showed that P3 induced by negative Nogo trials was a protective factor for adolescents' bipolar depression. Analysis of theta-band oscillation showed that theta activity induced by negative Go trials was a protective factor and theta activity induced by positive Nogo trials was a risk factor for adolescents' bipolar depression. The results have shown in Table 4.

## Discussion

This study investigated the neural substrates of response inhibition deficits in negative and positive emotional contexts in adolescents with bipolar depression using an emotional Go/No-Go task with high time resolution ERP measurement. The behavioral and ERP data revealed that adolescents with bipolar depression showed impaired response inhibitory processing for both positive and negative facial stimuli. Adolescents with bipolar depression showed reduced P3 amplitude and theta-band oscillation for effective faces when compared with healthy controls, which confirmed that adolescents with bipolar depression exhibit deficits in response inhibition for both positive and negative effective information. In addition, reduced d' values were found in adolescents with bipolar depression when they were asked to respond to target effective faces stimuli and inhibit non-target effective faces stimuli. Theta-band oscillations and P3 amplitudes induced by positive No-Go trials showed significant positive correlation with depressive symptoms in adolescents with bipolar depression. In addition, the study also demonstrated that the P3 amplitude induced by negative No-Go trials was related to RTV for negative Go trials.

**Table 4** Binary regression analysis of neural activity in group status

| | B | Wald | OR(95% CL) | *P* |
|---|---|---|---|---|
| **P3 amplitude** | | | | |
| Positive Go | 0.079 | 0.098 | 1.082(0.659 1.777) | 0.754 |
| Negative Go | 0.101 | 0.248 | 1.106(0.744 1.645) | 0.619 |
| Positive Nogo | −0.295 | 1.286 | 0.745(0.447 1.240) | 0.257 |
| Negative Nogo | −0.546 | 4.052 | 0.580(0.341 0.986) | 0.044 |
| **Theta-band oscillation** | | | | |
| Positive Go | −0.369 | 0.289 | 0.691(0.180 2.656) | 0.591 |
| Negative Go | −2.253 | 0.513 | 0.105(0.019 0.591) | 0.011 |
| Positive Nogo | 1.862 | 6.445 | 6.436(1.529 27.092) | 0.011 |
| Negative Nogo | −0.441 | 6.534 | 0.105(0.019 0.591) | 0.474 |

As was hypothesized, adolescents with bipolar depression showed reduced P3 amplitude relative to healthy controls. Prior studies have suggested that P3 amplitude activation is associated with inhibitory control and conflict resolution in the response inhibition process [1]. In particular, Go-P3 amplitude reflects motivated attention, and No-Go-P3 amplitude reflects response inhibition, particularly motor inhibitory processes [24, 29]. The study found that adolescents with bipolar depression showed lower P3 amplitude than healthy controls on Nogo trials, but not on Go trials. Combined with the behavioral performance results, when compared with healthy controls, adolescents with bipolar depression exhibited larger RTV both in positive and in negative Go trials. RTV has been identified as a marker for impaired attention, and is associated with top-down attention control [38]. Immature cognitive function, which is due to the imbalance between the delayed maturation of the prefrontal "control" regions and the limbic system, may cause adolescents to have sufficient top-down attention resources to monitor conflict when they face effective stimuli [10, 17, 48].This may be one of the reasons why the N2 amplitude was not important in this study, which prolonged variability may result in adolescents with bipolar depression being unable to ensure sustained attention in completing tasks to monitor conflict. The negative association between RTV and P3 amplitude for negative effective stimuli also indicates that impaired attentional function to negative emotions is closely related to the failure of behavioral inhibition for them. In addition, fluctuations of emotion in adolescence also take up more attentional resources [30, 31]. Albert et al. found that there is an overlap of brain regions in the inhibitory processes of emotion and motor response, such as the anterior cingulate cortex, which are related to the interaction between emotional processing and motor-response inhibition [1, 7]. Moreover, the interaction is observed in the P3 component time window [1]. In addition, the present study also found that the d' value under negative Go and positive No-Go trials showed a positive correlation with the P3 amplitude induced by negative faces. The results

suggest that the fluctuation of P3 amplitude is affected by the ability of adolescents with bipolar depression to discriminate emotional stimuli. Thus, adolescents with bipolar depression exhibited weaker behavioral inhibition for negative information, which may lead them to experience more adverse emotions and problem behaviors.

Theta-band oscillation in the midline frontal region is another biomarker for investigating cognitive control abilities; it reflects a domain-general cognitive control mechanism of the prefrontal cortex [11]. This study revealed that adolescents with bipolar depression showed reduced theta-band power and inter-trial coherence for effective faces compared with healthy controls. Prior studies have revealed that theta-band oscillation is reduced in patients with bipolar disorder during cognitive control tasks, and provide initial evidence of attenuation during response inhibition in the emotional context [2, 4, 41]. It is worth noting that emotional information always captures people's attention rapidly and leads to different behavioral tendencies [50]. Previous studies have revealed that patients with depression exhibit attentional bias to negative cognition or information, and are unable to suppress the effects of negative emotions [8, 65]. Individuals with bipolar disorder have also been found to show cognitive–emotional interference in processing negative as well as positive stimuli [49, 66]. The present study found that adolescents with bipolar depression showed lower theta-band oscillation than healthy controls in response to negative faces, when compared with positive faces. This result reveals that adolescents with bipolar depression exhibit impaired response inhibition for effective faces, but especially for negative faces. In addition, theta-band oscillation over midline frontal sites is the best index of cognitive workload, which increases when processing unexpected information and signals the need for cognitive control [15]. Combined with the analysis of P3 amplitude, this finding suggests that adolescents with bipolar depression may be unable to suppress emotional information because they do not realize the need to inhibit their responses, especially to negative emotional stimuli.

The behavioral performance results revealed that adolescents with bipolar depression also showed poor behavioral discrimination of target emotional versus non-target emotional facial expressions (d' value) during the emotional Go/No-Go task. According to the analysis of signal detection metrics, the size of the d' values represents the ability of perceptual sensitivity to distinguish between target and non-target emotional stimuli, with larger d' indicating greater ability to distinguish stimuli [59]. Prior studies have demonstrated that patients with depression show smaller d' values when asked to withdraw negative facial expressions, which indicates diminished ability to suppress negative information [68]. Reduced discrimination of emotional stimuli (e.g. words, facial expression) is also found in individuals with bipolar disorder [2, 42]. A study conducted by Murphy et al. reported that individuals with bipolar disorder showed different emotional bias in different mood periods, with manic patients biased toward positive stimuli and depressed patients biased toward negative information [47]. The present study showed that adolescents with bipolar depression exhibited smaller d' values in inhibiting both positive and negative emotions, which is consistent with previous studies [2, 42]. Adolescents with bipolar depression showed larger RTV, which indicated the impaired attentional control and cognitive function in an emotional context among adolescents with bipolar depression. Thus, impaired attentional function and reduced discrimination of positive and negative emotional information may limit the opportunity to learn the task rules and establish the prepotent tendency.

Antidepressants also have reported influence P3 amplitudes and theta activity. P3 amplitude, which has been linked to both the motor and cognitive aspects of response inhibition, was a significant predictor of change in depressive symptoms following antidepressants treatment [22, 62]. The present study have revealed that adolescents with bipolar depression who not taking antidepressants exhibited lower P3 amplitude in Nogo trials than healthy controls, but not taking antidepressants. The results suggested antidepressants may relieve depressive symptoms by improving response inhibition in adolescents with bipolar depression. In addition, theta-band activity is also reported related to the activity of the anterior cingulated cortex (ACC), which plays an essential role in the processing of emotional information [54]. The present study showed that adolescents with bipolar depression who not taking antidepressants exhibited lower theta-band oscillations induced by negative stimuli than healthy controls, which suggested antidepressants could reduce the response to negative emotion in adolescents with bipolar depression.

The present study had some limitations. First, the sample size employed was relatively small, which may increase the likelihood of type II errors and then lead to an overestimate of actual effects. In addition, although the difference in prevalence of bipolar disorder between men and women is not significant, and the gender differences were not significant in the present study, most of participants recruited to the study were girls. Given that the clinical signs and symptoms of bipolar disorder differ between men and women, the present study may have provided only a limited understanding of adolescents with bipolar depression. Therefore, the future studies need to enroll a much larger and diverse samples or

meta-analysis in the field of psychophysiological studies in order to expand upon past findings. Second, this study only enrolled adolescents with bipolar disorder during depressive episodes, which prevented our studying emotional response inhibitory processing in other mood states. In addition, patients with depressive disorder also exhibit difficulty in inhibiting negative emotions. This makes it impossible to determine whether the results of the study have unique significance in bipolar disorder. Therefore, future studies need to enroll participants during different mood episodes, and individuals with bipolar and unipolar depressive disorder, to investigate the underlying neural mechanism of effective response inhibitory processing in adolescents with bipolar disorder. Thirdly, adolescence is a pivotal period for the development of response inhibitory ability. Previous studies have revealed that P3 component is a developmental endophenotype for disorder characterized by behavioral disinhibition, which amplitude increases across childhood. However, the cross-sectional study design may have limited our ability to study the influence of the adolescent development of response inhibition on the emotional deficits of bipolar disorder. Thus, longitudinal investigations are desperately needed to enhance our understanding as to the directionality of neural and mental health relationships as well as the etiology of bipolar disorders from childhood and adulthood. Finally, the present study conducted four-way ANOVA to capture the multi-dimensional interactions of neural mechanisms, but its complexity may limit the intuitiveness of the results. Future research could adopt computational modeling (e.g. reinforcement learning frameworks) or dynamic brain network analysis to more precisely dissect the neural mechanism underlying there interactions.

Despite the limitations stated above, our study indicates that adolescents with bipolar depression have difficulty inhibiting emotional information, especially in response to a negative stimulus. According to our results, adolescents with bipolar depression exhibited smaller d' values than healthy controls in response to negative and positive emotions. The Nogo-P3 amplitude and theta-band oscillation for negative emotion may be crucial indicators of emotional response inhibitory impairment in adolescents with bipolar depression. In addition, improved attentional monitoring for negative emotional stimuli may be able to reduce the failure of behavioral inhibition of negative emotions, and the Nogo-P3 amplitude induced by negative emotions may be an important electrophysiological indicator.

## Conclusion

The current study examined deficits of emotional response inhibition and the underlying dynamic mechanisms in adolescents with bipolar depression using ERPs. We found that adolescents with bipolar depression had reduced Nogo-P3 amplitude and theta-band oscillations in emotional contexts. Impaired attentional control function and reduced discrimination may result in deficits in response inhibition among adolescents with bipolar depression, and the No-Go-P3 amplitude induced by negative emotional stimuli may be an electrophysiological indicator of the impaired motor-response inhibition processing.

### Abbreviations

| | |
|---|---|
| BD | Bipolar Disorder |
| RT | Reaction time |
| RTV | Reaction Time Variability |
| ACC | Accuracy |
| ITC | Inter-trial coherence |
| SDT | Signal detection theory |

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### Authors' contributions

Fangfang Chen, Fengqiong Yu and Lianzi Wang designed the study and wrote the protocol. Lianzi Wang and Mingfei Wu enrolled the participants. Fangfang Chen and Cheng Chen conducted the data analysis. Bingqing Luo and Han Cai performance the data collection. Fangfang Chen wrote the manuscript. All authors contributed to and approved the final manuscript.

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### Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

## Declarations

### Ethics approval and consent to participate

The experimental procedure was in accordance with the ethical principles of the Declaration of Helsinki, and approved by the Ethics Committee of Wuhu Fourth People's Hospital (Number: 2019008). Written informed consent was obtained from all subjects and their guardians voluntarily before participation in this study.

### Consent for publication

Not applicable.

**Competing interests**
The authors declare no competing interests.

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