

Altered prefrontal late positive potential responses during neutral face processing are associated with negative interpretation bias in major depressive disorder

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Abstract

Background

Negative interpretation bias toward ambiguous social cues, particularly neutral faces, is an important cognitive feature of major depressive disorder (MDD), yet the spatiotemporal electrophysiological processes associated with this bias remain unclear. This study examined region- and time-specific late positive potential (LPP) responses during neutral face processing and their relationships with negative interpretation bias and social competence in MDD.

Methods

In this cross-sectional study, 120 individuals with MDD and 120 healthy controls (HCs) completed a facial emotion recognition task during electroencephalography recording. LPP mean amplitudes were examined across five scalp regions during early (400–600 ms) and late (600–800 ms) time windows using mixed-design analysis of variance with false discovery rate-adjusted post hoc comparisons. Within the MDD group, partial correlation analyses examined associations between LPP responses and behavioral measures while controlling for age, sex, body mass index, and years of education. Exploratory mediation analyses examined relationships among prefrontal LPP amplitudes, negative interpretation bias, and social competence.

Results

Compared with HCs, individuals with MDD showed lower neutral face recognition accuracy, longer reaction times, and a greater tendency to interpret non-negative facial expressions as negative. LPP analyses revealed region-specific alterations, including reduced right temporoparietal LPP mean amplitudes and less negative prefrontal LPP mean amplitudes during both time windows. Prefrontal LPP mean amplitudes were positively associated with negative interpretation bias during both the early ($r = .185, p = .046$) and late ($r = .209, p = .024$) windows. Exploratory mediation analyses further showed that the indirect association between late prefrontal LPP amplitude and social competence through negative interpretation bias was significant, whereas the corresponding indirect association for the early window was not.

Conclusions

MDD was characterized by region-specific alterations in LPP responses during neutral face processing. Prefrontal LPP amplitudes during both the early and late windows were associated with negative interpretation bias, while the late-window measure additionally showed a significant indirect association

with social competence through this bias. These findings link altered prefrontal processing of ambiguous facial information to negative interpretation bias and social-cognitive difficulties in MDD.

Background

Major depressive disorder (MDD) is a heterogeneous psychiatric condition[1, 2] characterized not only by mood symptoms but also by cognitive dysfunction and impaired social functioning[3, 4]. Social cognitive difficulties contribute substantially to interpersonal impairment, reduced quality of life, and unfavorable clinical outcomes in MDD[5–7]. Clarifying the neurocognitive mechanisms underlying these difficulties may inform clinical assessment and individualized psychosocial care for individuals with MDD.

Facial expressions provide essential social signals that guide interpersonal behavior[8, 9]. However, individuals with MDD exhibit abnormalities in facial emotion processing, including reduced recognition accuracy and biased interpretation of socio-emotional cues[10, 11]. Among these cognitive disturbances, negative interpretation bias has received particular attention. Negative interpretation bias refers to the tendency to assign negative meanings to ambiguous or non-negative social information[12, 13]. Previous studies have consistently shown that individuals with depression are more likely to interpret neutral facial expressions as negative, suggesting a maladaptive bias in evaluating ambiguous social cues[14–16]. According to Beck's cognitive theory, negative cognitive schemas may bias attention and interpretation of external information in depression[17]. Consequently, individuals with MDD may rely on negatively biased internal representations when evaluating ambiguous facial expressions[18–21], leading to increased negative interpretations of social cues[22–24].

Social competence reflects an individual's ability to establish and maintain interpersonal relationships[25]. Individuals with MDD frequently experience reduced social engagement and impaired interpersonal functioning, which are associated with symptom severity and prognosis[26–28]. Negative interpretation bias may further contribute to these difficulties by promoting maladaptive evaluations of social information[9, 29, 30]. Social isolation can erode social support networks, intensify feelings of loneliness and helplessness, and ultimately increase the risk of adverse clinical outcomes[31, 32]. However, the neurocognitive mechanisms linking negative interpretation bias with social functioning remain unclear.

Despite accumulating evidence of social cognitive biases and emotion processing abnormalities in MDD, the temporal neural mechanisms underlying negative interpretation bias remain poorly understood. Event-related potential (ERP) methods provide high temporal resolution for examining dynamic stages of information processing. The late positive potential (LPP) is a sustained ERP component associated with attentional engagement, emotional evaluation, and elaborative processing of motivationally relevant stimuli[33, 34]. Unlike early sensory components, the LPP reflects later-stage evaluative processes during which incoming information is integrated with contextual knowledge and internal expectations[35–37]. Therefore, altered LPP responses during neutral face processing may provide an electrophysiological correlate of biased interpretation of ambiguous social information in MDD.

In the present study, we combined a facial emotion recognition task with ERP recording to investigate late-stage neural responses during neutral face processing in individuals with MDD and healthy controls (HCs). We further examined whether LPP alterations were associated with individual differences in negative interpretation bias. We hypothesized that: (1) individuals with MDD would exhibit impaired behavioral performance and altered late-stage LPP responses during neutral face processing; and (2) individuals with MDD would show greater negative interpretation bias toward non-negative facial expressions, with LPP alterations associated with individual differences in this bias. In addition, we conducted exploratory analyses to examine the relationships among prefrontal LPP activity, negative interpretation bias, and social competence across the two LPP time windows.

Methods

Participants

This cross-sectional study was conducted at the Affiliated Mental Health Center of Jiangnan University, Wuxi, China, between August 2025 and May 2026. Sample size adequacy was evaluated using G*Power 3.1.9.7[38]. For a two-group comparison, assuming a conventional medium effect size (Cohen's $f = 0.25$) [39], an alpha level of .05, and statistical power of .95, the estimated minimum total sample size was 210 participants (105 per group). A total of 245 participants were initially recruited, including 122 individuals with MDD and 123 HCs. Following electroencephalography (EEG) and behavioral quality control, five participants were excluded because of excessive ocular or muscle artifacts resulting in insufficient artifact-free epochs ($n = 4$) or insufficient valid behavioral responses ($n = 1$), yielding a final sample of 240 participants (120 individuals with MDD and 120 HCs).

Individuals with MDD were consecutively recruited from the Department of Clinical Psychology at the Affiliated Mental Health Center of Jiangnan University during the study period, whereas HCs were recruited from the local community. All participants were Han Chinese. The study protocol was approved by the institutional ethics committee of the Affiliated Mental Health Center of Jiangnan University (Approval No. WXMHCIRB2025LLky105) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before participation.

Individuals with MDD were diagnosed independently by two experienced psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Inclusion criteria were: (1) age between 18 and 55 years; (2) absence of active suicidal intent, imminent suicide risk, or recent suicidal behavior; and (3) no history of electroconvulsive therapy within the previous 6 months. Participants were excluded if they had other psychiatric or neurological disorders, severe medical conditions, substance abuse, or conditions affecting cognitive function.

HCs were required to have no lifetime psychiatric disorders, psychiatric treatment history, or current use of medications affecting cognitive performance.

Clinical and Behavioral Assessments

Sociodemographic and clinical information was collected using a structured interview.

Depressive symptom severity was assessed using the Patient Health Questionnaire-9 (PHQ-9), a validated 9-item self-report scale measuring the severity of depressive symptoms over the previous two weeks. Higher scores indicate greater depressive symptom severity[40, 41].

Self-reported social competence was assessed using the 32-item Texas Social Behavior Inventory (TSBI), with higher scores indicating greater perceived social competence and self-esteem[42].

Facial Emotion Recognition Task (FERT)

Participants completed a facial emotion recognition task during EEG recording using 90 facial stimuli selected from the Chinese Facial Affective Picture System[43], comprising 30 negative, 30 neutral, and 30 positive faces. The task consisted of 400 trials (100 negative, 200 neutral, and 100 positive), with stimuli within each emotional category repeated approximately equally. A fixed pseudorandomized trial sequence was used for all participants.

The facial emotion recognition task was designed with reference to previously used paradigms[44]. Each trial consisted of a 1000-ms fixation cross followed by a facial stimulus presented for 2000 ms. Participants classified each face as negative, neutral, or positive during stimulus presentation. The next trial began immediately with the subsequent fixation cross. After a five-trial practice block, the task was completed in two experimental blocks separated by a brief self-paced rest period. The detailed experimental procedure is illustrated in Fig. 1.

Behavioral measures extracted from the task included neutral face recognition accuracy (ACC), neutral face recognition reaction time (RT) for correct responses, the Negative Bias Index (NBI), and the Neutral Misclassification Bias (NMB). Negative interpretation bias was assessed using the NBI, calculated as the proportion of non-negative facial expressions (neutral and positive) incorrectly classified as negative. Although ERP analyses focused on neutral faces, NBI was used as a behavioral index reflecting a broader tendency to assign negative meanings to non-negative facial cues. Following the log-ratio approach used to quantify misclassification bias in previous FERT research[45], NMB was calculated as $\ln [(H \text{ to } K + 0.01) / (H \text{ to } F + 0.01)]$, where H to K and H to F represent the proportions of neutral faces misclassified as positive and negative, respectively. Lower NMB values indicate a stronger tendency to interpret neutral faces negatively.

EEG Data Acquisition and ERP Analysis

Continuous EEG data were recorded using a 64-channel Ag/AgCl electrode system (EasyCap GmbH, Germany) based on the international 10–20 system. EEG signals were sampled at 500 Hz, and electrode

impedance was maintained below 10 k Ω .

Offline preprocessing was performed using MATLAB 2020b (MathWorks, USA) and EEGLAB 2024.2[46]. Data were re-referenced to the common average reference, band-pass filtered from 1 to 100 Hz, and notch filtered at 48–52 Hz. Noisy channels were identified and interpolated, followed by independent component analysis (ICA) to remove ocular and physiological artifacts[47, 48]. Continuous EEG data were segmented into epochs from – 1000 to 2000 ms relative to stimulus onset and baseline-corrected using the – 1000 to 0 ms prestimulus interval. Artifact-free epochs were averaged to generate participant-level ERP waveforms.

The present study focused on the late positive potential (LPP), which has been widely used to characterize sustained processing of emotionally salient information[9, 49]. Based on previous literature indicating that LPP typically emerges around 400 ms after stimulus onset[50], and considering the task characteristics and observed ERP topography, the analytical window was defined as 400–800 ms. To characterize temporal dynamics, this epoch was subdivided into early (400–600 ms) and late (600–800 ms) windows[51–53]. Activity within each temporal window was quantified using mean amplitude values.

Cluster-based permutation testing was conducted using FieldTrip[54] with 3,000 permutations to characterize the spatial distribution of LPP effects, with cluster-level significance set at $p < .05$. ROI definition was guided by previous ERP literature and established scalp topographies[55–58]. Five scalp regions of interest (ROIs) were defined: prefrontal (Fp1, Fpz, Fp2, AF3, AFz, and AF4), frontocentral (F3, F1, F2, F4, F6, F8, Fz, FC3, FC1, FC2, FC4, and FCz), left temporoparietal (TP7, P7, P5, and P3), right temporoparietal (CP2, CP4, CP6, TP8, P2, P4, P6, and P8), and occipital (PO3, PO4, O1, O2, and Oz) ROIs. Mean LPP amplitude was calculated by averaging across the electrodes within each ROI separately for the early (400–600 ms) and late (600–800 ms) windows.

Statistical Analyses

Demographic, clinical, and behavioral variables were compared between groups using Welch's two-sample t tests for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables, as appropriate.

ERP amplitudes were analyzed using a mixed-design ANOVA with group as the between-subjects factor and ROI and time window as within-subjects factors. When sphericity was violated, degrees of freedom were corrected using the Greenhouse–Geisser procedure. Post hoc between-group comparisons of ROI-level LPP mean amplitudes across time windows were performed using estimated marginal means, with the resulting p values adjusted for multiple comparisons using the false discovery rate (FDR) procedure. Cohen's d was calculated to quantify between-group effect sizes.

Exploratory partial Pearson correlation analyses were conducted within the MDD group to examine associations among LPP mean amplitudes, behavioral measures, negative interpretation bias, and TSBI

scores while controlling for age, sex, body mass index (BMI), and years of education. All tests were two-tailed; unadjusted p values $< .05$ were considered statistically significant. Additional exploratory item-level partial correlation analyses examined associations among late prefrontal LPP mean amplitude, NBI, TSBI scores, and individual PHQ-9 item scores while controlling for the same covariates.

To explore the statistical relationships among neural responses, negative interpretation bias, and social competence, exploratory mediation analyses were conducted using R software (version 4.2.2) with the mediation package. Based on the partial correlation findings, separate mediation models were examined for the early (400–600 ms) and late (600–800 ms) prefrontal LPP measures. In each model, prefrontal LPP mean amplitude was specified as the independent variable (X), NBI as the mediator (M), and total TSBI score as the dependent variable (Y). Indirect, direct, and total effects were estimated using the quasi-Bayesian Monte Carlo method with 3,000 simulations, and 95% confidence intervals (CIs) were calculated.

Use of artificial intelligence in manuscript preparation

ChatGPT (OpenAI) was used during manuscript preparation to assist with language editing. All scientific content, statistical analyses, interpretations, and references were reviewed and verified by the authors, who take full responsibility for the final manuscript.

Results

Demographic and Clinical Characteristics

The final sample consisted of 240 participants, including 120 individuals with MDD and 120 HCs (Table 1). The two groups did not differ significantly in sex distribution or annual household income distribution. Compared with HCs, individuals with MDD were older, had lower BMI and fewer years of education, and exhibited significantly higher PHQ-9 scores and lower TSBI scores (all $p < .01$). Age, sex, BMI, and years of education were included as covariates in subsequent partial correlation analyses.

Table 1
Demographic and clinical characteristics of participants

Variable	Group		Statistic	<i>p</i> -value
	HC N = 120	MDD N = 120		
Age, mean $\pm$ SD ^a	27 $\pm$ 8	31 $\pm$ 11	-3.60	< .001
Sex, n (%) ^b			0.29	.588
Male	44 (36.7%)	40 (33.3%)		
Female	76 (63.3%)	80 (66.7%)		
BMI, mean $\pm$ SD ^a	23.3 $\pm$ 4.1	21.9 $\pm$ 3.3	2.93	.004
Education, mean $\pm$ SD ^a	16.0 $\pm$ 2.4	14.1 $\pm$ 3.3	4.95	< .001
Annual household income, n (%) ^c				.673
< 100000 CNY	19 (15.8%)	25 (20.8%)		
100000–<300000 CNY	83 (69.2%)	80 (66.7%)		
300000–600000 CNY	14 (11.7%)	13 (10.8%)		
> 600000 CNY	4 (3.3%)	2 (1.7%)		
Illness duration, months, median (P25, P75)	–	24.0 (5.0, 48.0)	–	–
PHQ-9 scores, mean $\pm$ SD ^a	3 $\pm$ 3	16 $\pm$ 7	-18.51	< .001
TSBI scores, mean $\pm$ SD ^a	100.8 $\pm$ 18.4	79.4 $\pm$ 17.7	9.17	< .001

^a Welch's two-sample *t* test; ^b Pearson's χ^2 test; ^c Fisher's exact test. HC = healthy controls; MDD = major depressive disorder; BMI = body mass index; PHQ-9 = Patient Health Questionnaire-9; TSBI = Texas Social Behavior Inventory; CNY = Chinese yuan; P25 and P75 represent the 25th and 75th percentiles, respectively.

Behavioral performance on FERT

Compared with HCs, individuals with MDD showed poorer performance during neutral face recognition, characterized by reduced ACC and prolonged RT (both $p < .001$). They also demonstrated a stronger tendency to interpret neutral faces negatively, as indicated by a higher proportion of neutral faces misclassified as negative (H to F), higher NBI scores, and lower NMB scores (all $p < .05$). In contrast, no between-group difference was observed in the proportion of neutral faces misclassified as positive (H to

K). Detailed statistical results are presented in Table 2, while the corresponding distributions of behavioral measures are illustrated in Figs. 2 and 3.

Table 2
Behavioral measures derived from the Facial Emotion Recognition Task

Measure	Group		<i>t</i>	<i>p</i> -value
	HC	MDD		
ACC	0.87 ± 0.11	0.79 ± 0.20	3.92 ^a	< .001
RT	952.02 ± 138.48	1089.77 ± 225.51	-5.70 ^a	< .001
H to K	0.03 ± 0.05	0.03 ± 0.04	0.50 ^a	.620
H to F	0.07 ± 0.07	0.14 ± 0.18	-3.95 ^a	< .001
NBI	0.07 ± 0.06	0.10 ± 0.12	-3.15 ^a	.002
NMB	-0.69 ± 1.07	-1.09 ± 1.41	2.45 ^a	.015

^a Welch's two-sample *t* test. Values are presented as mean ± SD. HC = healthy controls; MDD = major depressive disorder; ACC = neutral face recognition accuracy; RT = neutral face recognition reaction time for correct responses; H to K = proportion of neutral faces misclassified as positive; H to F = proportion of neutral faces misclassified as negative; NBI = Negative Bias Index; NMB = Neutral Misclassification Bias.

ERP alterations in mean LPP amplitudes

The ERP data were analyzed using a mixed-design ANOVA, with group as a between-subjects factor and time window and ROI as within-subjects factors. The main effects of group, time window, and ROI were all significant (all $p < .05$, η^2 range = .026–.354). Significant Group × ROI ($F(1.29, 307.31) = 9.87$, $p < .001$, $\eta^2 = .040$) and Time window × ROI ($F(1.43, 340.91) = 24.75$, $p < .001$, $\eta^2 = .094$) interactions were observed. Neither the Group × Time window interaction nor the Group × Time window × ROI interaction reached significance (both $p > .05$). Detailed ANOVA results are provided in Supplementary Table S1 (Additional file 1).

Post hoc between-group comparisons based on estimated marginal means with FDR correction revealed significant differences in mean LPP amplitudes across all examined ROI and time-window combinations (all FDR-adjusted $p < .05$; Table 3). Compared with HCs, individuals with MDD exhibited reduced positive-going LPP mean amplitudes in the temporoparietal and occipital regions. In contrast, the prefrontal and frontocentral regions showed less negative LPP mean amplitudes, with values closer to the 0 μV baseline.

Given their relevance to subsequent behavioral association analyses, the right temporoparietal and prefrontal ROIs were highlighted in Fig. 4. Individuals with MDD showed reduced LPP mean amplitudes in the right temporoparietal ROI during both the early (400–600 ms) and late (600–800 ms) windows. In the prefrontal ROI, individuals with MDD exhibited less negative LPP mean amplitudes during both time windows. The grand-average ERP waveforms across all predefined ROIs are presented in Supplementary Figure S1 (Additional file 2).

Table 3
Between-group differences in LPP mean amplitudes across time windows and regions of interest

Time window / ROI	Group			
	HC (μV)	MDD (μV)	<i>p</i> -value	Cohen's <i>d</i>
400–600 ms				
Prefrontal	-1.29 ± 1.61	-0.72 ± 1.54	.008	-0.37
Frontocentral	-0.71 ± 0.84	-0.39 ± 0.77	.008	-0.40
Left temporoparietal	0.68 ± 1.05	0.27 ± 1.00	.008	0.40
Right temporoparietal	1.04 ± 1.01	0.61 ± 0.92	.008	0.44
Occipital	1.33 ± 1.43	0.83 ± 1.49	.011	0.34
600–800 ms				
Prefrontal	-1.06 ± 1.46	-0.62 ± 1.35	.018	-0.31
Frontocentral	-0.48 ± 0.81	-0.20 ± 0.66	.008	-0.37
Left temporoparietal	0.41 ± 0.82	0.12 ± 0.74	.008	0.38
Right temporoparietal	0.40 ± 0.95	0.08 ± 0.83	.009	0.36
Occipital	0.76 ± 1.16	0.43 ± 1.04	.019	0.31

Values are presented as mean ± SD. HC = healthy controls; MDD = major depressive disorder. Between-group comparisons were based on estimated marginal means, with *p* values adjusted for multiple comparisons using the false discovery rate (FDR) procedure. Cohen's *d* represents the standardized between-group effect size.

Partial Correlation Analysis Among Mean LPP Amplitudes, TSBI Scores, and Behavioral Measures

Partial correlation analyses were conducted within the MDD group to examine associations among mean LPP amplitudes, behavioral performance, negative interpretation bias, and social competence

while controlling for age, sex, BMI, and years of education (Table 4).

During the early window (400–600 ms), prefrontal LPP mean amplitude was negatively associated with neutral face recognition accuracy and positively associated with reaction time and NBI ($r = .185, p = .046$), whereas right temporoparietal LPP mean amplitude was positively associated with recognition accuracy and negatively associated with reaction time. During the late window (600–800 ms), prefrontal LPP mean amplitude was negatively associated with recognition accuracy and positively associated with both the proportion of neutral faces misclassified as negative (H to F) and NBI ($r = .209, p = .024$). Right temporoparietal LPP mean amplitude during the late window was also positively associated with recognition accuracy. Thus, prefrontal LPP mean amplitudes during both time windows were associated with negative interpretation bias, whereas associations with general recognition performance were observed across multiple LPP measures. Detailed correlation results are presented in Table 4 and Supplementary Table S2 (Additional file 3).

A significant negative correlation was observed between NBI scores and total TSBI scores in the MDD group ($r = -.208, p = .025$; Table 5). No other behavioral measures were significantly associated with TSBI scores.

Additional exploratory partial correlation analyses were performed to examine associations among neural activity, negative interpretation bias, social competence, and individual depressive symptom dimensions (Fig. 5). NBI scores were positively correlated with several PHQ-9 symptom dimensions, including anhedonia, depressed mood, sleep disturbance, and thoughts of death or self-harm. Mean LPP amplitude in the prefrontal ROI during the late window (600–800 ms) was positively correlated with NBI scores, whereas no significant associations were observed between this neural measure and individual PHQ-9 symptom dimensions. Total TSBI scores were negatively correlated with anhedonia, depressed mood, sleep disturbance, and feelings of worthlessness or guilt. For clarity, only PHQ-9 items significantly associated with NBI are displayed; complete item-level partial correlation results are provided in Supplementary Table S3 (Additional file 3).

Table 4
Selected partial correlations between LPP mean amplitudes and behavioral measures in MDD

Time Window / ROI	ACC	RT	H to K	H to F	NBI	NMB
400–600 ms						
Prefrontal	-0.218 *	0.300 **	–	–	0.185 *	–
Right temporoparietal	0.215 *	-0.198 *	–	–	–	–
600–800 ms						
Prefrontal	-0.261 **	–	–	0.217 *	0.209 *	–
Right temporoparietal	0.226 *	–	–	–	–	–

Partial Pearson correlation coefficients (r) are presented. Analyses were adjusted for age, sex, BMI, and years of education. The em dash (–) indicates non-significant correlations ($p \geq .05$). $*p < .05$, $**p < .01$ (two-tailed). ACC = neutral face recognition accuracy; RT = neutral face recognition reaction time for correct responses; H to K = proportion of neutral faces misclassified as positive; H to F = proportion of neutral faces misclassified as negative; NBI = Negative Bias Index; NMB = Neutral Misclassification Bias.

Table 5
Partial correlations between TSBI and behavioral measures in MDD

Measure	ACC	RT	H to K	H to F	NBI	NMB
TSBI	–	–	–	–	-0.208 *	–

Partial Pearson correlation coefficients (r) between TSBI scores and behavioral measures are presented for individuals with MDD. Analyses were adjusted for age, sex, BMI, and years of education. The em dash (–) indicates non-significant correlations ($p \geq .05$). $*p < .05$ (two-tailed). ACC = neutral face recognition accuracy; RT = neutral face recognition reaction time for correct responses; H to K = proportion of neutral faces misclassified as positive; H to F = proportion of neutral faces misclassified as negative; NBI = Negative Bias Index; NMB = Neutral Misclassification Bias; TSBI = Texas Social Behavior Inventory.

Mediation Analysis

Based on the partial correlation findings within the MDD group, separate exploratory mediation models were examined for the early and late prefrontal LPP measures. In both models, prefrontal LPP mean amplitude was entered as the independent variable (X), NBI as the mediator (M), and total TSBI score as the dependent variable (Y).

For the early window (400–600 ms), the estimated indirect effect through NBI did not reach statistical significance (estimate = -0.494, 95% CI [-1.246, 0.056], $p = .085$). Neither the direct effect (estimate = 1.362, 95% CI [-0.655, 3.453], $p = .182$) nor the total effect (estimate = 0.868, 95% CI [-1.236, 2.983], $p = .409$) was significant.

For the late window (600–800 ms), the total effect of prefrontal LPP amplitude on TSBI scores was not statistically significant (estimate = -1.490, 95% CI [-3.837, 0.912], $p = .216$), and the direct effect was also not significant (estimate = -0.750, 95% CI [-3.121, 1.672], $p = .523$). The estimated indirect effect through NBI was statistically significant (estimate = -0.740, 95% CI [-1.669, -0.071], $p = .023$; Fig. 6).

Discussion

In the current study, we investigated the temporal neural characteristics of neutral face processing in individuals with MDD using ERP measures combined with behavioral and clinical assessments. Three main findings emerged. First, individuals with MDD showed impaired recognition performance and an increased tendency to interpret non-negative facial expressions negatively, as reflected by higher NBI

scores. Second, ERP analyses revealed region-specific alterations in late-stage neural processing, including less negative prefrontal LPP mean amplitudes and reduced right temporoparietal LPP mean amplitudes across both the early (400–600 ms) and late (600–800 ms) windows. Third, prefrontal LPP mean amplitudes during both time windows were associated with negative interpretation bias. Exploratory mediation analyses further showed that the indirect association between late prefrontal LPP amplitude and social competence through negative interpretation bias was significant, whereas the corresponding indirect association for the early window was not.

At the behavioral level, individuals with MDD showed impaired neutral face recognition, characterized by reduced ACC and prolonged RT. These findings are consistent with previous studies demonstrating difficulties in interpreting ambiguous facial expressions in depression[24, 56]. Meta-analytic evidence further indicates that individuals with MDD exhibit altered facial emotion recognition, frequently accompanied by enhanced negative interpretation tendencies[11]. The prolonged RT in the MDD group is also consistent with previous reports[24, 59] and may reflect greater processing demands during ambiguous facial evaluation.

Beyond general recognition difficulties, individuals with MDD demonstrated a stronger negative interpretation tendency, reflected by higher NBI scores and increased misclassification of neutral faces as negative. This finding is consistent with previous evidence showing that depression is associated with a tendency to assign negative meanings to ambiguous social cues, particularly neutral facial expressions[24, 60]. Similar negative attribution patterns have also been reported across other emotional domains[61], suggesting that negative interpretation bias may represent a broader alteration in the evaluation of ambiguous information in MDD.

From a cognitive theoretical standpoint, these behavioral observations are consonant with prevailing cognitive models of depression, which posit that negative cognitive schemas and interpretive biases predispose individuals to preferentially attend to and process negatively valenced information[62]. Furthermore, this processing propensity may compromise interpersonal functioning by influencing the interpretation of social information, ultimately giving rise to difficulties in social adaptation[21, 63]. Our results further support previous meta-analytic evidence indicating that abnormalities in the processing of non-negative faces (especially neutral faces) in MDD involve both reduced recognition efficiency and enhanced negative interpretation tendencies[11].

To characterize the electrophysiological correlates of negative interpretation bias, we examined the spatiotemporal characteristics of LPP responses during neutral face processing. The LPP reflects sustained attention allocation and continued evaluation of emotionally relevant stimuli during later processing stages[34, 64]. Alterations in LPP responses have been reported in MDD and may reflect differences in emotional and cognitive processing[51, 65]. Compared with HCs, individuals with MDD exhibited less negative prefrontal LPP mean amplitudes and reduced right temporoparietal LPP mean amplitudes across both the early (400–600 ms) and late (600–800 ms) windows. These findings suggest altered late-stage evaluative processing during ambiguous facial evaluation in MDD. This

pattern is broadly consistent with previous ERP findings showing altered LPP responses in depression[56, 66].

Within the predictive processing framework, ambiguous facial information is evaluated through interactions between sensory inputs and prior expectations[67–69]. Therefore, altered prefrontal LPP responses may reflect differences in integrating external facial information with internally generated interpretations. Given the involvement of prefrontal systems in information integration, cognitive reappraisal, and emotion regulation[68, 70], the observed prefrontal scalp LPP differences may reflect altered higher-order evaluative processing associated with negative interpretation tendencies in MDD.

In contrast to the prefrontal ROI, reduced LPP amplitudes were observed over the right temporoparietal scalp region across both LPP time windows. The right temporoparietal region has been implicated in social perception, facial emotion processing, and the integration of socially relevant information[71–73]. Because LPP amplitude is sensitive to sustained attention toward emotionally meaningful stimuli[34, 74, 75], reduced LPP responses over the right temporoparietal scalp region may reflect altered maintenance and integration of facial information during sustained evaluation of neutral faces.

Our findings revealed associations of negative interpretation bias with depressive symptom dimensions and social competence. Higher NBI scores were associated with greater severity of anhedonia, depressed mood, sleep disturbance, and thoughts of death or self-harm, supporting previous evidence that negative interpretation bias represents an important cognitive feature associated with depressive symptomatology[16, 76–78]. In addition, higher NBI scores were associated with lower TSBI scores, indicating that a stronger tendency to interpret ambiguous social cues negatively was related to lower self-reported social competence. This association is consistent with cognitive models proposing that maladaptive cognitive biases shape the interpretation of social information and are linked to interpersonal and functional difficulties[18, 79–81].

We further examined whether LPP alterations were associated with individual differences in negative interpretation bias. Within the MDD group, prefrontal LPP mean amplitudes during both the early and late windows were positively associated with NBI scores and negatively associated with neutral face recognition accuracy. Together, these findings suggest that individual differences in negative interpretation tendencies toward ambiguous facial information are associated with variations in prefrontal LPP activity during both predefined LPP windows. Such associations may reflect differences in higher-order evaluative or top-down processing during ambiguous social evaluation[82]. Given the involvement of prefrontal systems in higher-order information integration, cognitive reappraisal, and emotion regulation[68, 70, 83], altered prefrontal LPP responses may reflect differences in neural processes supporting the evaluation and reinterpretation of facial information. These findings provide electrophysiological evidence linking negative interpretation bias in MDD with altered late-stage processing during ambiguous facial evaluation.

Exploratory mediation analyses further examined the relationships among prefrontal LPP activity, negative interpretation bias, and social competence. A significant indirect association through NBI was

observed for the late prefrontal LPP measure, whereas the corresponding indirect effect for the early-window measure was not statistically significant. This pattern suggests that negative interpretation bias may be particularly relevant to the statistical link between late prefrontal LPP activity and social competence in MDD.

From a psychiatric nursing perspective, negative interpretation bias may represent a clinically relevant cognitive dimension for understanding interpersonal difficulties in individuals with MDD. Incorporating attention to maladaptive interpretations of ambiguous social cues into psychosocial assessment may help inform individualized nursing care and support aimed at improving social functioning.

In summary, this study integrates behavioral assessments and spatiotemporal ERP analyses to characterize the neurocognitive correlates underlying altered neutral face processing in MDD. Our findings demonstrate region-specific alterations in LPP activity over the prefrontal and right temporoparietal scalp regions, with prefrontal LPP responses across both time windows associated with negative interpretation bias. The significant indirect association observed for the late-window prefrontal measure further links late-stage neural processing, negative interpretation bias, and social competence. These findings provide electrophysiological evidence consistent with cognitive models of depression, linking altered processing of ambiguous facial information with individual differences in negative interpretation tendencies.

Limitations

Several limitations should be considered. First, the cross-sectional design limits inference regarding the temporal relationships among neural activity, negative interpretation bias, and social competence; longitudinal studies could further clarify these associations. Second, medication exposure was not systematically characterized. Third, static facial stimuli may not fully capture the dynamic nature of real-world social interactions. Fourth, scalp-recorded ERPs provide limited spatial resolution for identifying the neural sources of the observed effects. Finally, the single-center and relatively homogeneous sample may constrain the generalizability of the findings.

Conclusions

In conclusion, individuals with MDD exhibited region-specific alterations in LPP responses during neutral face processing, including altered responses over the prefrontal and right temporoparietal scalp regions across both early and late LPP windows. Prefrontal LPP mean amplitudes during both time windows were associated with negative interpretation bias, supporting an electrophysiological link between late-stage prefrontal processing and biased interpretation of ambiguous facial information in MDD. Exploratory mediation analyses further showed that the indirect association between late prefrontal LPP amplitude and social competence through negative interpretation bias was significant, whereas the corresponding indirect association for the early window was not. Together, these findings suggest that altered late-stage neural processing and biased interpretation of ambiguous facial information may be

relevant to social-cognitive difficulties in MDD, providing a basis for further research on psychosocial assessment and individualized supportive care.

Abbreviations

ANOVA

analysis of variance

ACC

neutral face recognition accuracy

BMI

body mass index

CI

confidence interval

CNY

Chinese yuan

DSM-5

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

EEG

electroencephalography

ERP

event-related potential

FDR

false discovery rate

FERT

Facial Emotion Recognition Task

HC

healthy control

H to F

proportion of neutral faces misclassified as negative

H to K

proportion of neutral faces misclassified as positive

ICA

independent component analysis

LPP

late positive potential

MDD

major depressive disorder

NBI

Negative Bias Index

NMB

Neutral Misclassification Bias

PHQ-9

Patient Health Questionnaire-9

ROI

region of interest

RT

neutral face recognition reaction time for correct responses

SD

standard deviation

TSBI

Texas Social Behavior Inventory.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional ethics committee of the Affiliated Mental Health Center of Jiangnan University (Approval No. WXMHCIRB2025LLky105) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before participation in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HD: Conceptualization, Formal analysis, Investigation, Writing – original draft. YW: Methodology, Investigation, Writing – original draft. QL: Software, Data curation, Formal analysis. WW: Investigation, Writing – review & editing. XL: Investigation, Writing – review & editing. XW: Investigation. XG:

Investigation. ZZ: Supervision, Writing – review & editing. HZ: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. All authors read and approved the final manuscript.

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Figures

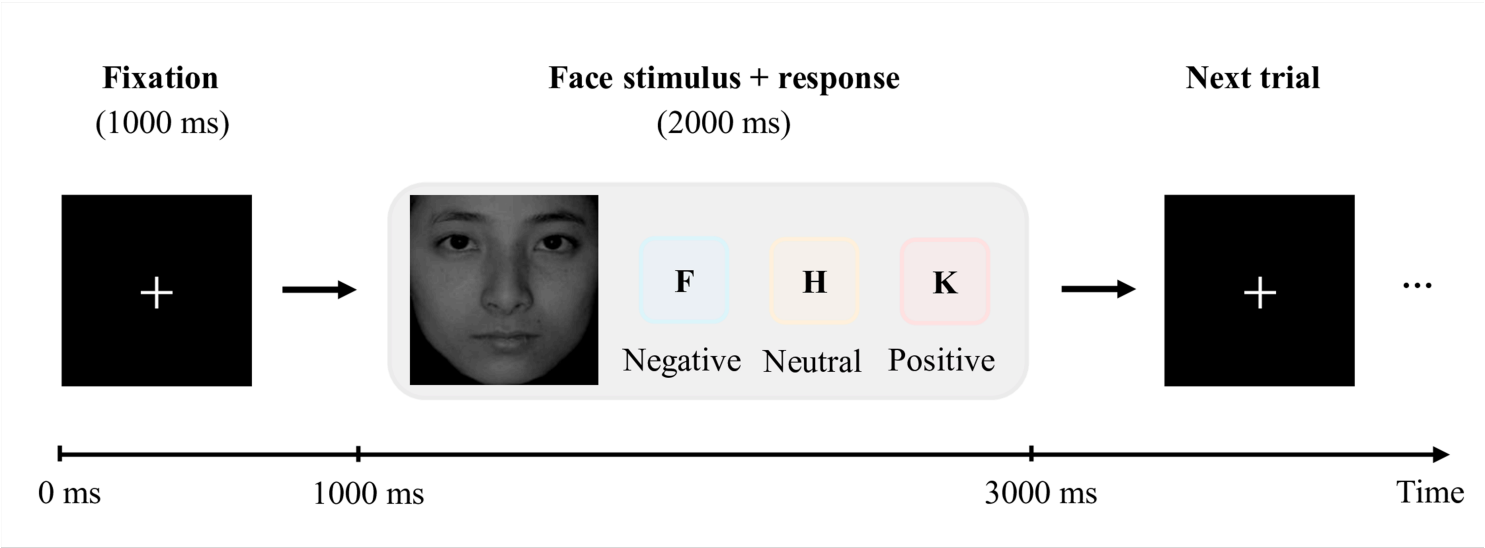


Figure 1

Experimental flow of the Facial Emotion Recognition Task. Each trial consisted of a 1000-ms fixation cross followed by a facial stimulus presented for 2000 ms, during which participants classified the face as negative, neutral, or positive. The next trial began immediately with the subsequent fixation cross. F = negative; H = neutral; K = positive.

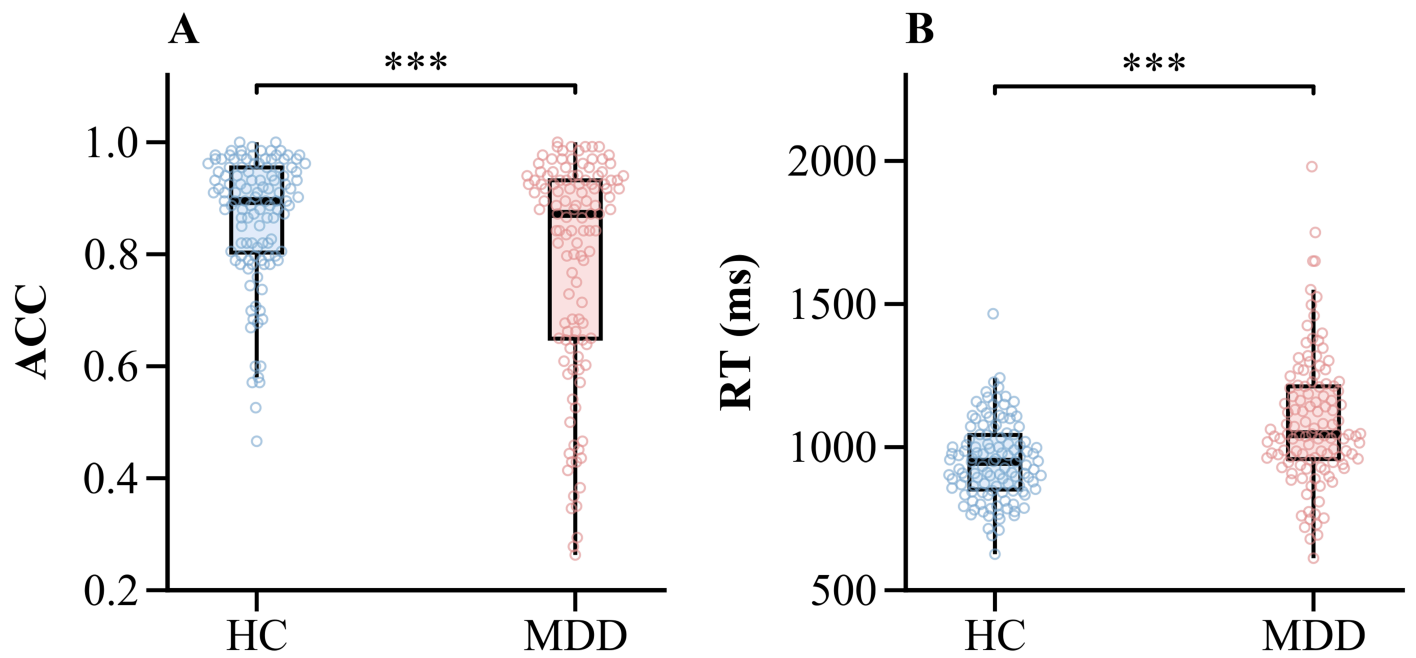


Figure 2

Behavioral performance during neutral face recognition in HCs and individuals with MDD. Boxplots with overlaid individual data points show (A) neutral face recognition accuracy (ACC) and (B) reaction time (RT) for correct neutral-face trials. Boxes indicate the interquartile range, horizontal lines indicate the median, and open circles represent individual participants. Between-group differences were analyzed using Welch's two-sample *t* test (***p* < .001). HC = healthy control; MDD = major depressive disorder.

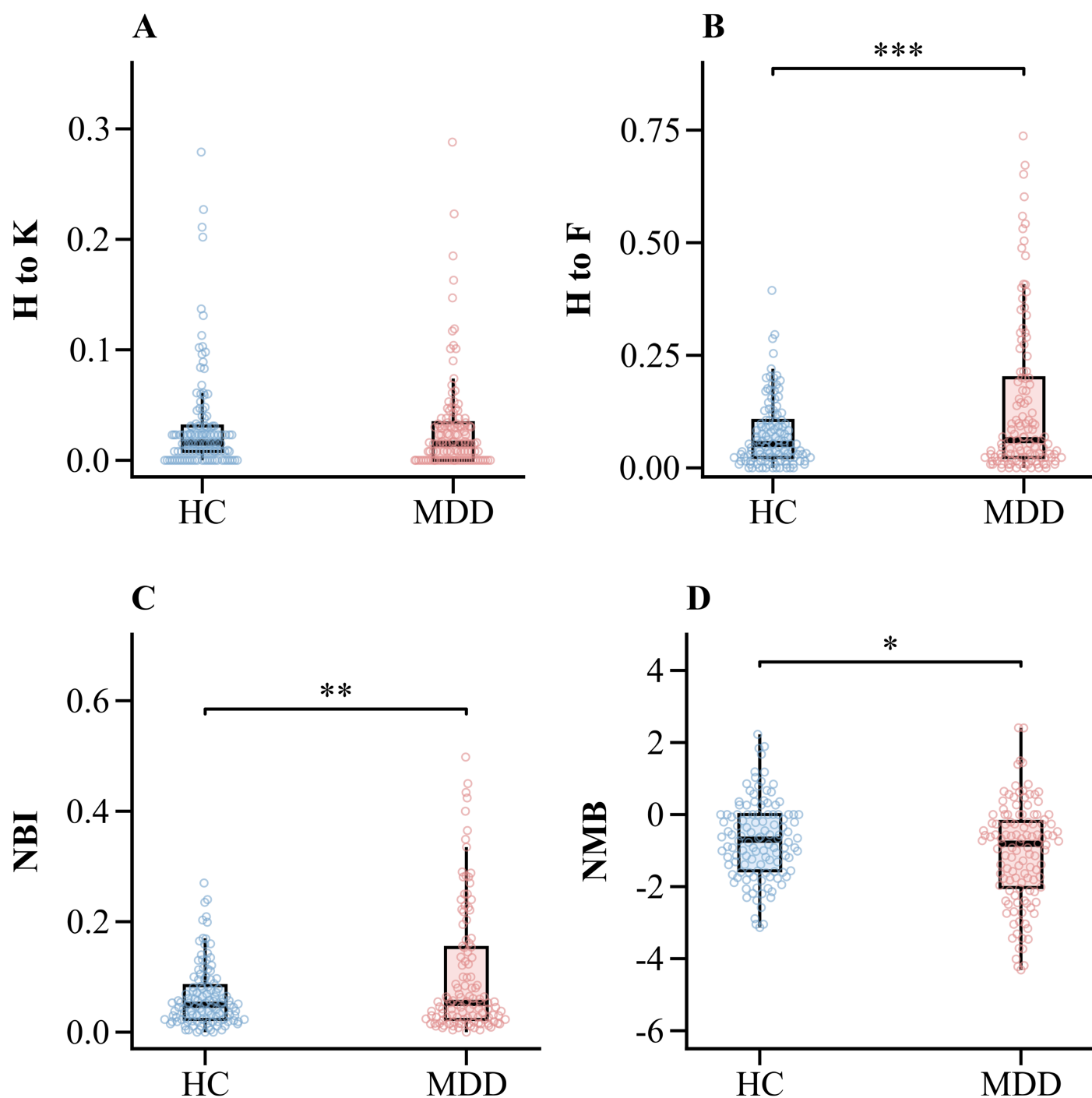


Figure 3

Group differences in interpretation-bias measures derived from the Facial Emotion Recognition Task.

Boxplots with overlaid individual data points compare HCs and individuals with MDD for (A) the proportion of neutral faces misclassified as positive (H to K), (B) the proportion of neutral faces misclassified as negative (H to F), (C) the Negative Bias Index (NBI), and (D) the Neutral Misclassification Bias (NMB). Boxes indicate the interquartile range, horizontal lines indicate the median, and open circles represent individual participants. Between-group differences were analyzed using

Welch's two-sample *t* test (**p* < .05, ***p* < .01, ****p* < .001). HC = healthy control; MDD = major depressive disorder.

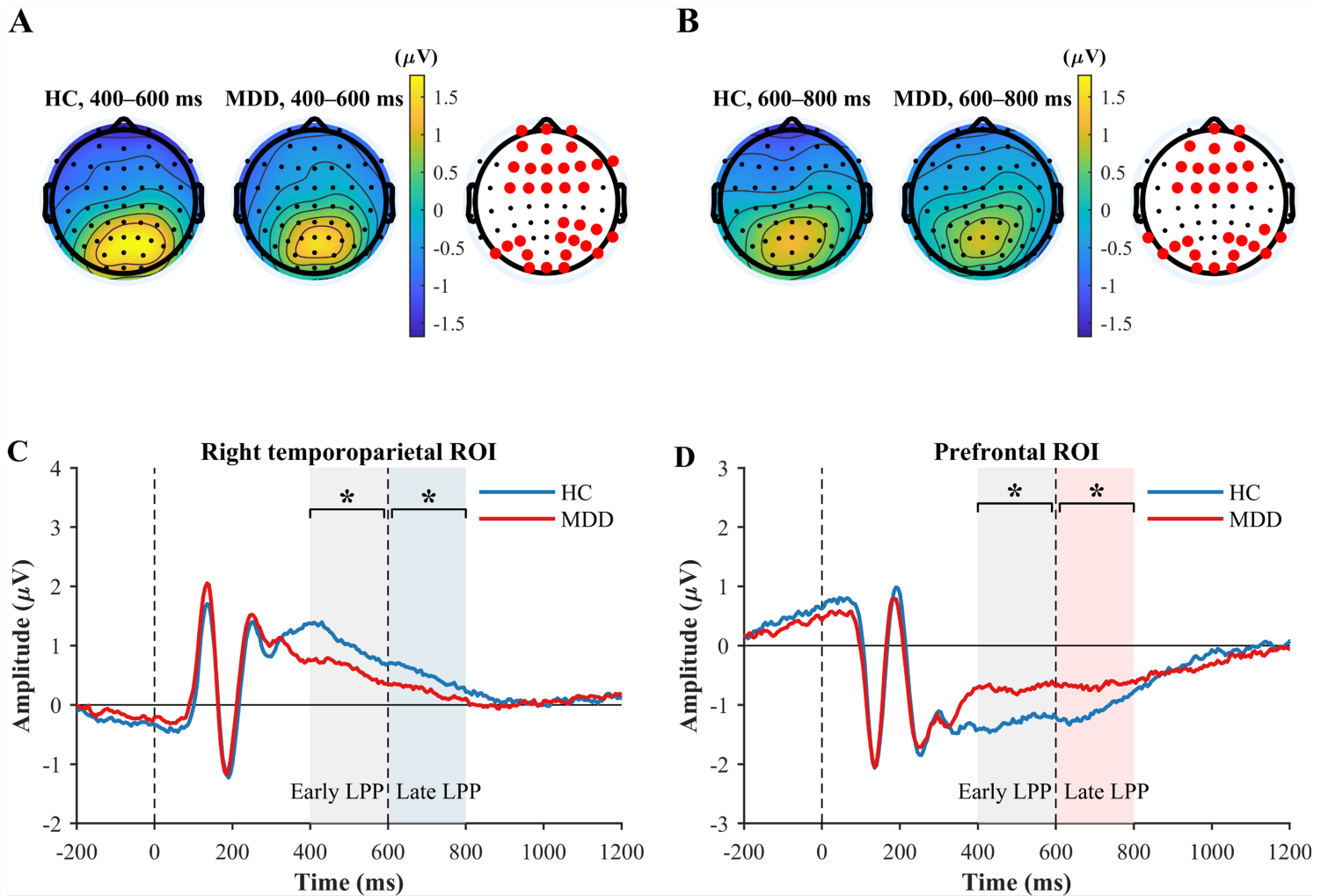


Figure 4

Spatiotemporal alterations in mean LPP amplitudes during neutral face processing. (A, B) LPP voltage topographies for HCs and individuals with MDD during the early (400–600 ms) and late (600–800 ms) windows. Red dots indicate electrodes belonging to significant clusters identified by cluster-based permutation testing (cluster-corrected $p < .05$). (C, D) Grand-average ERP waveforms for the right temporoparietal and prefrontal ROIs, respectively. Shaded areas indicate the analyzed LPP time windows, and asterisks denote FDR-adjusted between-group comparisons ($p < .05$). HC = healthy controls; MDD = major depressive disorder; LPP = late positive potential; ROI = region of interest.

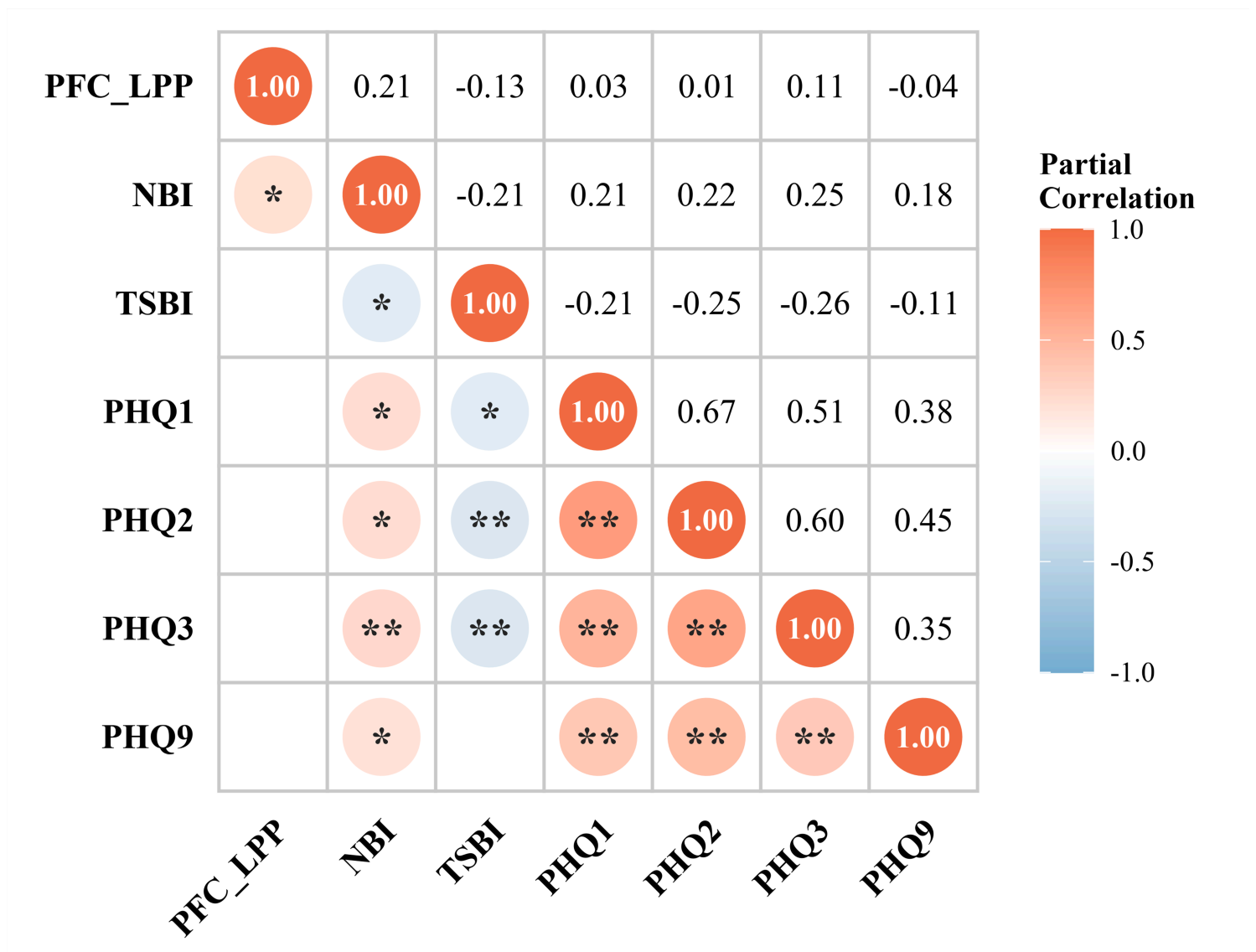


Figure 5

Associations among LPP amplitudes, negative interpretation bias, and clinical measures. For clarity, only PHQ-9 items significantly associated with NBI are displayed; complete item-level results are provided in Supplementary Table S3 (Additional file 3). The heatmap displays partial correlation coefficients (r) in the upper right triangle and corresponding significance levels in the lower left triangle. Color indicates the direction of the correlations (red, positive; blue, negative), whereas color intensity and circle size indicate their magnitude. PFC_LPP = mean LPP amplitude in the prefrontal ROI during the 600–800 ms time window; NBI = Negative Bias Index; TSBI = Texas Social Behavior Inventory; PHQ1 = PHQ-9 item 1 (anhedonia); PHQ2 = PHQ-9 item 2 (depressed mood); PHQ3 = PHQ-9 item 3 (sleep disturbance); PHQ9 = PHQ-9 item 9 (thoughts of death or self-harm). $*p < .05$, $**p < .01$.

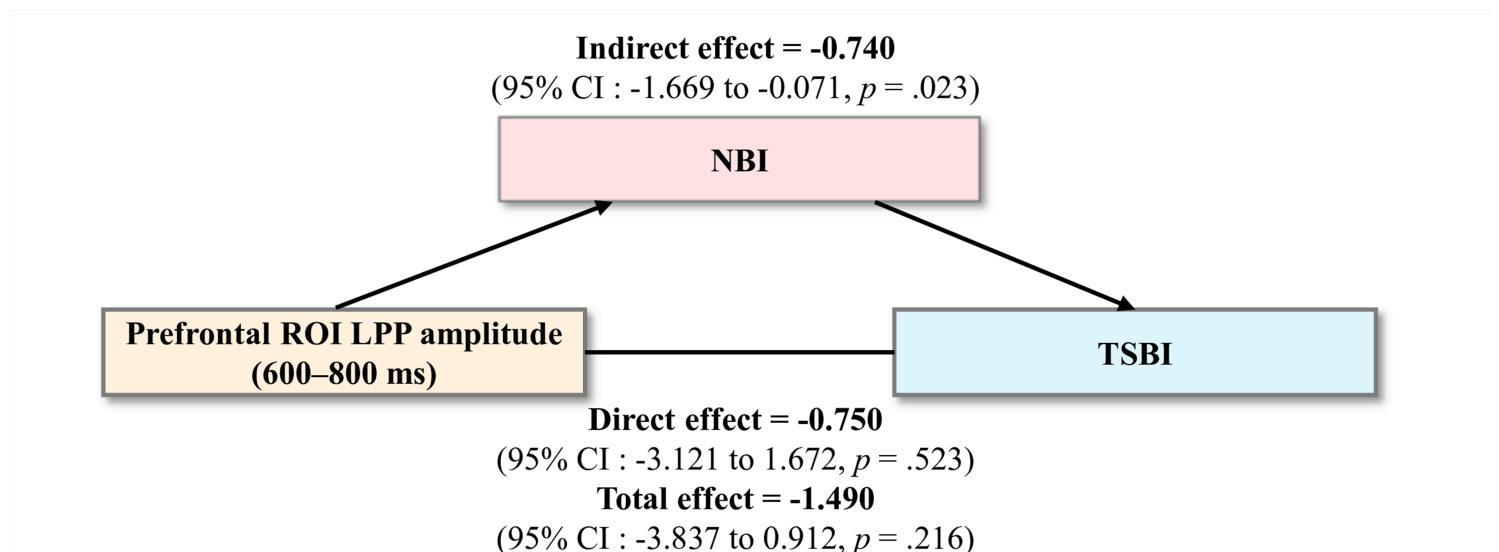


Figure 6

Exploratory mediation model of late prefrontal LPP amplitude, NBI, and TSBI scores in MDD. Estimates for the indirect, direct, and total effects and their 95% confidence intervals (CIs) were obtained using quasi-Bayesian estimation with 3,000 simulations in the R mediation package. MDD = major depressive disorder; NBI = Negative Bias Index; TSBI = Texas Social Behavior Inventory.

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