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Research paper

Biased minds, sensitive hearts: Divergent neural signatures of interpersonal sensitivity in atypical and non-atypical depression

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A R T I C L E I N F O

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A B S T R A C T

Background: Atypical depression (AD) is a distinct subtype of depression, with interpersonal sensitivity as one of its core characteristics. However, the electrophysiological mechanisms that underlie interpersonal sensitivity in AD remain insufficiently explored. Therefore, in the present study, we systematically investigated the neurophysiological differences in interpersonal sensitivity between individuals with AD and non-atypical depression (non-AD) using electroencephalography (EEG).

Methods: We assessed 93 patients (50 with AD and 43 with non-AD) using standardized scales, including the Rejection Sensitivity Questionnaire and the Symptom Checklist 90 (SCL-90) Interpersonal Sensitivity subscale. The Cyberball task combined with EEG recordings, followed by the Positive and Negative Affect Schedule, was used to evaluate electrophysiological and emotional responses. Exploratory analyses examined correlations between interpersonal sensitivity scores and behavioral/electrophysiological measures. In addition, a machine learning model was applied to identify key features for distinguishing between AD and non-AD.

Results: The AD group had significantly higher scores on the SCL-90 Interpersonal Sensitivity subscale compared with the non-AD group. Electrophysiological analyses detected distinct response patterns in the P3 amplitude and theta wave activity during both inclusion and exclusion blocks in the AD group compared with the non-AD group. Moreover, a random forest model developed by using features such as Interpersonal Sensitivity subscale scores achieved an accuracy of 83.3 % in distinguishing between AD and non-AD.

Conclusion: Thus, AD patients exhibited greater interpersonal sensitivity than non-AD patients, which was supported by cognitive and neurological evidence. Our findings provide critical insights for developing more precise diagnostic and therapeutic strategies for AD.

1. Introduction

Major depressive disorder (MDD) is a highly prevalent and heterogeneous psychiatric condition encompassing various subtypes with distinct clinical manifestations. In particular, atypical depression (AD) has emerged as a clinically significant variant that requires special attention (Lojko and Rybakowski, 2017). Epidemiological estimates indicate that AD affects 15.3 %–36.4 % of MDD patients (Matza et al., 2003; Xin et al., 2019). The definition of AD is still controversial in the academic community (Stewart et al., 2009) but according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), AD patients must simultaneously meet the diagnostic criteria for MDD and present the following characteristics: mood reactivity (characterized by a marked improvement in mood in response to positive events), increased appetite or significant weight gain, hypersomnia, or leaden paralysis (a sensation of heaviness in the limbs); and a

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persistent pattern of interpersonal sensitivity (American Psychiatric Association, 2013). Importantly, patients must not meet the diagnostic criteria for melancholic or catatonic depression.

A growing body of research has sought to delineate the distinctions between AD and non-AD to elucidate their distinct pathophysiological mechanisms. Clinically, AD patients typically exhibit an earlier age of onset, more prolonged disease course, more frequent depressive episodes, more severe symptoms, and different response to treatment compared with non-AD patients (Arathimos et al., 2021; Brailean et al., 2020; Cuijpers et al., 2017). Moreover, AD is associated with an increased risk of suicidal tendencies and higher prevalence of comorbid personality disorders (Gremaud-Heitz et al., 2014; Xin et al., 2019). Emerging evidence further highlights key pathophysiological differences. Patients with AD exhibit a higher prevalence of chronic inflammation (Bernier et al., 2024; Lasselin, 2020), lower hypothalamic–pituitary–adrenal axis activity (Juruena et al., 2018), and distinct gut microbiota profiles (Busch et al., 2024). In addition, a significant positive correlation has been observed between metabolic syndrome and AD, whereas no such association has been found for non-AD (Lamers et al., 2018; Onofre Ferriani et al., 2022; Takeuchi et al., 2013). Neurobiological investigations, particularly neuroimaging studies, have identified specific alterations in AD (Guo et al., 2024; Pagani et al., 2007). Furthermore, transcranial magnetic stimulation studies indicate that AD is characterized by a unique cortical excitability pattern marked by decreased cortical inhibition and increased cortical facilitation (Veronezi et al., 2016). Neuropsychological assessments also indicate that there are significant cognitive differences between AD and non-AD subtypes, where AD patients exhibit impairments in attention/vigilance and deficits in social cognition (Bosaipo et al., 2017; Lu et al., 2023). Collectively, these multifaceted distinctions encompassing clinical, inflammatory, microbiological, neurobiological, and cognitive domains highlight the need to recognize AD as a distinct diagnostic entity in clinical practice.

However, the diagnosis of AD is still affected by limitations in clinical practice. The DSM-5 specifies mood reactivity as the primary characteristic of AD, but many studies have raised concerns about the validity of this criterion (Seemuller et al., 2008; Stewart et al., 2009). In particular, operational convenience seems to lead many clinicians to rely primarily on reversed neurovegetative symptoms (hypersomnia and hyperphagia/weight gain) for identifying AD (Brailean et al., 2020). More importantly, studies by Parker et al. (2002, 2005) involving nearly 1000 patients with MDD consistently demonstrated that mood reactivity is insufficient as the primary diagnostic criterion for AD. Instead, they proposed that interpersonal/rejection sensitivity might represent a more distinctive feature of AD (Parker et al., 2002; Parker et al., 2005). In agreement with this perspective, Lyndon et al. proposed revising the DSM-5 to prioritize a long-standing pattern of interpersonal sensitivity as the primary diagnostic indicator, with mood reactivity as a secondary criterion (Lyndon et al., 2017). Furthermore, clinical studies have identified a high incidence of interpersonal sensitivity in AD, which strongly correlates with the severity of clinical symptoms (Parker et al., 2002; Posternak and Zimmerman, 2001; Sachs-Ericsson et al., 2012). Consequently, some researchers advocate considering interpersonal sensitivity as the primary diagnostic feature in order to better reflect the patient's underlying personality vulnerability. However, few studies have investigated interpersonal sensitivity in AD, particularly regarding its neurobiological mechanisms.

Interpersonal sensitivity is a stable personality trait characterized by persistent concerns about negative social evaluation, social exclusion, and neglect, and it is consistently associated with interpersonal difficulties and impaired social functioning (Kwon et al., 2024; Marin and Miller, 2013). Previous studies have also demonstrated that individuals with AD score significantly higher on measures of interpersonal problems compared with those without AD (Gremaud-Heitz et al., 2014). Beyond traditional questionnaire-based assessments, such as Interpersonal Sensitivity Measure (Masillo et al., 2014), researchers have increasingly adopted experimental approaches to investigate interpersonal sensitivity. Standardized paradigms like the Cyberball task are commonly employed in laboratory settings to induce feelings of social exclusion and neglect, enabling systematic examination of interpersonal sensitivity through combined behavioral and electrophysiological measures (Vanhollebeke et al., 2023; Williams and Jarvis, 2006). The Cyberball paradigm consists of two primary conditions. In the inclusion condition, participants receive the ball equally with simulated allies (typically 33 % of throws in a three-player scenario). In the exclusion condition, participants receive the ball only occasionally (partial exclusion, 16 %–20 % of throws) or not at all (complete exclusion, 0 % of throws). The imaginary allies are computer-generated characters, so the number of throws is predetermined in each case, but participants believe they are playing a game with a real person, and thus experience a strong sense of rejection in the exclusion condition (Williams and Jarvis, 2006).

Previous studies using the Cyberball task have consistently shown that patients with depression display abnormal electrophysiological and neural responses during social interactions. For instance, depressed individuals exhibit atypical response patterns during social inclusion, suggesting lower expectations of social participation (Zhang et al., 2017), and similar findings in non-clinical samples indicate that depressive symptoms are linked to reduced social expectations (Groth and Rief, 2022). During social exclusion, individuals with MDD show heightened activation in emotion-related brain regions, such as the amygdala, insula, and ventrolateral prefrontal cortex, compared with healthy controls (Kumar et al., 2017). Moreover, higher levels of depressive symptoms are associated with stronger interpretative biases toward rejection (Bar-Sella et al., 2022). Importantly, different subtypes of depression also exhibit distinct patterns of response: patients with chronic depression, for example, display more intense feelings of rejection and aversion, as well as a stronger desire to withdraw, compared with those with episodic depression (Seidl et al., 2020). Taken together, these findings highlight that depression is characterized by abnormal behavioral and neural responses to both social inclusion and exclusion. However, little is known about the specific neurobehavioral features of atypical depression (AD) in this context. In particular, whether and how AD patients differ from non-AD patients during the Cyberball task remains largely unexplored. Addressing this gap is crucial for advancing our understanding of the interpersonal sensitivity that characterizes AD and for distinguishing its neural mechanisms from those of other depressive subtypes.

To investigate electrophysiological differences in response to social inclusion and exclusion between AD and non-AD, we employed the Cyberball task in combination with electroencephalography (EEG). Event-related potentials (ERPs) derived from EEG provide temporally precise indices of neural responses to social events, making them a widely used approach in Cyberball research (Vanhollebeke et al., 2023). Prior work has linked specific ERP components to different aspects of social information processing: the P3a is often associated with the induction of negative emotions, while the P3b reflects stimulus evaluation, classification, and violations of subjective beliefs and expectations (Fang et al., 2024; Vanhollebeke et al., 2023). The late positive potential (LPP) has been implicated in sustained emotional and motivational processing (Vanhollebeke et al., 2023). In addition, event-related spectral perturbation (ERSP) analysis complements ERP findings by capturing the spectral dynamics of EEG signals. Frontal theta oscillations, in particular, have been consistently linked to attentional engagement and cognitive control (Lavin et al., 2023; Tang et al., 2021), and heightened medial frontal theta activity during rejection has been associated with stronger experiences of rejection-related distress (van Noordt et al., 2015). Taken together, these neural signatures provide convergent indices of expectancy, emotional evaluation, and regulatory control in social interaction.

Recent neuroimaging studies have provided new evidence suggesting that individuals with AD exhibit structural and functional abnormalities in brain regions critically involved in social cognition and emotion processing, including the medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), and striatum (Guo et al., 2024; Wang et al., 2025; Zhang et al., 2025a; Zhang et al., 2025b). Specifically, the mPFC plays a key role in social cognitive processing, the OFC contributes to emotion regulation and adaptive decision-making, and the striatum is crucial for reward processing and motivational control. These neural abnormalities indicate that electrophysiological indices such as P3, late positive potential (LPP), and frontal theta oscillations may capture the neural correlates of altered social information processing in AD. Building on this, the present study aimed to examine whether AD patients exhibit distinct patterns of P3, LPP, and frontal theta responses during social inclusion and exclusion compared with non-AD patients. We hypothesized that AD would be associated with atypical neural response patterns, reflecting alterations in expectancy, emotional evaluation, and cognitive control during social interactions. Furthermore, we utilized machine learning techniques to explore whether indicators related to interpersonal sensitivity could serve as reliable markers for distinguishing AD from non-AD.

2. Methods

2.1. Participants

In total, 93 patients who met the criteria for MDD as defined in the DSM-5 participated in clinical symptom assessments, where all were recruited from the outpatient department of the Second Affiliated Hospital of Anhui Medical University. All patients were first-time visitors who had never received psychotropic medication and were diagnosed by qualified psychiatrists. All patients were Chinese nationals of East Asian background. Among these patients, 50 comprising seven males and 43 females exhibited atypical features of DSM-5 (including mood reactivity and two or more others: hyperphagia, leaden paralysis, hypersomnia, and interpersonal rejection sensitivity) and were classified as having AD (Lu et al., 2023), with an average age of 22.28 ± 4.45 years. The remaining 43 patients comprising 10 males and 33 females were classified as having non-AD, with an average age of 24.56 ± 6.12 years. Additional demographic information is presented in Table 1 and Supplementary Materials.

In the AD group, 20 patients declined to proceed with the EEG data collection task due to practical considerations (e.g., time constraints related to medical visits, scheduling conflicts, or concerns/unfamiliarity with the EEG procedure). An additional four patients were excluded due to missing EEG data, resulting in a final analysis cohort of 26 patients (4 males and 22 females; mean age = 21.81 ± 3.87 years). In the non-AD group, 20 patients similarly declined to participate in EEG recording for the above reasons, and two were excluded due to missing EEG data, yielding a final analysis cohort of 21 patients (5 males and 16 females; mean age = 24.86 ± 5.71 years). Additional demographic information is presented in Supplementary Materials. Each participant provided written informed consent prior to the experiment, and for minors, additional written consent was obtained from their legal guardians. The study was approved by the Ethics Committee of Anhui Medical University (83220005). This study was not preregistered.

Inclusion criteria included: (1) aged 16 to 45 years; (2) meeting the DSM-5 diagnostic criteria for MDD at enrollment; (3) a score of 17 or higher on the Hamilton Depression Scale−17 items (HAMD-17); and (4) the ability to understand and cooperate with data collection. Exclusion criteria included: (1) current manic or hypomanic episodes; (2) pregnancy, lactation, or plans for pregnancy; (3) a suicide attempt within the last 2 weeks; (4) receiving electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation in the past 6 months; and (5) a history of substance dependence, comorbid psychiatric disorders (e.g., anxiety disorder or personality disorders), organic mental disorders, neurodevelopmental disorders, neurodegenerative diseases, traumatic brain injury, or cerebrovascular disease.

Table 1
Demographic and clinical characteristics of groups (mean ± standard deviation).

	Depression group		t/χ^2	p
	Atypical ($N = 50$)	Non-atypical ($N = 43$)		
Age (years)	22.28 ± 4.45	24.56 ± 6.12	−2.072	0.041*
Gender (male/female)	7/43	10/33	1.326[a]	0.250
Years of education	13.72 ± 2.26	14.37 ± 2.05	−1.449	0.151
family history (yes/no)	8/42	4/39	0.923[a]	0.337
Bodily Pain (yes/no)	34/16	28/15	0.087[a]	0.769
Depression subtypes (bipolar/unipolar)	4/46	2/41	0.430[a]	0.683
Age of onset (years)	18.10 ± 4.20	22.49 ± 6.41	−3.824	0.000***
duration of disease (month)	50.65 ± 42.78	30.03 ± 32.75	2.441	0.017*
suicidal behavior (time)	1.88 ± 7.54	0.91 ± 3.45	0.779	0.438
HAMD	22.62 ± 3.48	21.67 ± 6.39	0.903	0.369
TERS	70.26 ± 8.45	67.16 ± 9.20	1.692	0.094
Interpersonal sensitivity subscale of SCL-90	30.86 ± 5.72	26.95 ± 6.47	3.091	0.003**
SSI	32.56 ± 9.09	27.10 ± 13.00	2.334	0.022*
TEPS	60.50 ± 12.32	58.20 ± 16.07	0.729	0.468

[a] Chi-square test; *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$; HAMD: Hamilton Depression Scale; TERS: Tendency to Expect Rejection Scale; SCL-90: Symptom Checklist 90; SSI: Scale for Suicide Ideation; TEPS: Temporal Experience of Pleasure Scale.

2.2. Clinical assessments

We used the following scales to collect clinical data: self-administered questionnaires on general demographic and clinical characteristics, HAMD-17, the Tendency to Expect Rejection Scale (TERS) (Rebecca, 2003), Interpersonal Sensitivity subscale of Symptom Checklist 90 (SCL-90) (Bech et al., 2014), Scale for Suicide Ideation (SSI) (Beck et al., 1979), and the Chinese version of the Temporal Experience of Pleasure Scale (CV-TEPS) (Chan et al., 2012).

2.3. Cyberball task and ratings

Cyberball is a computerized ball tossing game where participants are told that they will play a game involving throwing balls at two other players connected via the Internet, but they are actually two virtual players (Themanson et al., 2013). In the present study, each participant's neuroelectrical activity was recorded during the Cyberball game. The Cyberball game was programmed and presented using MATLAB 2011 (MathWorks, Natick, MA). Stimuli were displayed on a 24-inch LCD monitor with a refresh rate of 60 Hz and brightness set to 120 cd/m^2. Participants were seated approximately 70 cm from the screen, resulting in a visual angle of approximately 3.5° × 3.5° for the stimulus.

The experimental paradigm comprised two distinct phases: an inclusion block followed by an exclusion block, with each involving 80 trials. In the inclusion block, participants had a 50 % chance of receiving the ball in each throw included in the block, resulting in each participant receiving ~33 % of the throws. Accordingly, the trials in the inclusion block were categorized into two events based on whether the participant received the ball: "my turn" when the virtual player passed the ball to the participant, and "not my turn" when the two virtual players passed the ball to each other without involving the participant. When the subject received the ball, he/she could press the F key if they wanted to throw the ball to the player on their left and the J key for the player on their right. Every trial lasted 2.5 s, with a 1.5 s period of ball movement, and 0.5 s before and after throwing the ball period. Random intervals between 0.5 and 3.0 s were set to create a sense that the two computerized players were making a choice about throwing to a player. In the exclusion block, after receiving approximately 10 passes, participants were no longer included in the game as the virtual players exclusively passed the ball to each other, leading to nearly 60 rejection events. EEG analysis included only rejection events from the exclusion block and "my turn" and "not my turn" events from the inclusion block. Event markers were inserted at the times when the computerized players decided to throw the ball. During the experiment, participants were seated comfortably in a quiet room and were continuously monitored by the experimenter to ensure wakefulness. Participants were instructed to maintain focus on the task, and short breaks were provided between blocks to minimize fatigue.

The Chinese version of the Positive and Negative Affect Schedule (PANAS) was used to assess the emotional responses of participants. The PANAS was administered before the Cyberball task to establish a baseline measurement, and again after both the inclusion and exclusion blocks to evaluate changes in emotion throughout the experiment.

2.4. EEG recording and analysis

During the Cyberball task, 64-channel EEG signals were continuously recorded using a Neuroscan recording system. Electrodes were positioned on the scalp according to the international 10/20 system, with the left mastoid electrode serving as the online reference, and the data were re-referenced offline to the average of the left and right mastoids. A forehead electrode was used as ground. Vertical and horizontal bipolar electrooculography (EOG) activity was recorded to monitor eye movements. Electrode impedance was maintained below 10 kΩ. Continuous sampling was performed at 500 Hz/channel, and the recording standard of the filter broadband was 0.1–30 Hz. The EEGLAB toolbox (an open source MATLAB package for EEG analysis) was used for offline analysis. Time–frequency information was extracted using Morlet wavelet decomposition and the EEGLAB NewTimef function. ERP data were segmented within a time window of −500 ms to 2000 ms, where the zero point corresponded to the moment when the player was about to throw the ball. Baseline correction was applied using a 200-ms pre-stimulus period. Bad channels were identified and interpolated using signals from adjacent electrodes. After visual inspection of the EEG waveforms, independent component analysis (ICA) was performed to identify and remove components related to scalp muscle activity and ocular artifacts. Finally, trials with EEG voltages exceeding ±150 μV were excluded from further analysis.

Based on previous studies using the Cyberball task (Tang et al., 2021; Vanhollebeke et al., 2023), ERP analysis primarily focused on the P3 and LPP components. The P3 component was analyzed using the average amplitude within a 400–500 ms time window at five electrode sites (FCz, CPz, Cz, C1, and C2). The LPP component was examined within a 500–1000 ms time window at five electrode sites (P2, P4, P6, PO4, and PO6). In addition, mean ERSP values were extracted for the theta (4–7 Hz) frequency band within a 200–400 ms time window at the F3 electrode position (Tang et al., 2019). To address the concern of relying on a single electrode, we conducted additional analyses using surrounding electrode clusters. Specifically, we examined three electrodes (F3, F1, F5) and an extended cluster of five electrodes (F3, F1, F5, AF3, FC3). The results of the additional analysis can be found in the supplementary materials.

2.5. Classification analysis

A suitable machine learning method for small sample analysis was used to explore the predictive values of interpersonal sensitivity related indicators for differentiating between AD and non-AD subtypes. In particular, using Python's computational environment (version 3.12), the data were divided into a training set (76 %) and independent test set (24 %) according to the random sampling principle. Feature selection was based on 15 predictors across two domains: (1) behavioral measures comprising scores obtained from interpersonal sensitivity scales and PANAS scores; and (2) neurophysiological measures, including ERP components (P3 and LPP amplitudes) and theta band oscillatory energy extracted from the Cyberball task. The modeling phase utilized RandomForestClassifier in Scikit-learn, which is an ensemble method that constructs multiple decision trees through bootstrap aggregation. Classification outcomes were determined by majority voting, combining computational efficiency with robust generalization capabilities. To optimize the model's performance, we implemented the Optuna framework for hyperparameter tuning, employing Bayesian optimization to systematically adjust critical parameters including the maximum tree depth, feature subset size, and leaf node minimum sample thresholds.

To assess the robustness of the model, we additionally conducted 5-fold and 10-fold cross-validation within the training set. In each procedure, the data were partitioned into K subsets, with one subset used for validation and the others for training, and performance metrics were averaged across folds before final evaluation on the independent test set.

2.6. Statistical analyses

All data were analyzed using SPSS 24.0. Demographic and clinical data analyses were conducted based on a total of 93 patients, and PANAS and EEG data analyses involved 47 patients. Inter-group differences in demographic and clinical characteristics between the AD and non-AD groups were assessed using independent-samples *t*-tests or chi-square tests. Statistical analysis of the Cyberball task was performed using two different approaches across experimental phases: (a) repeated-measures analysis of variance (ANOVA) was conducted with event type ("my turn" vs. "not my turn") as the within-subject factor and group (AD vs. non-AD) as the between-subject factor to examine group differences in behavioral and electrophysiological measures during the inclusion block, with LSD tests applied for post-hoc multiple comparisons; and (b) independent-samples *t*-tests were used to compare group differences in the exclusion block. The primary dependent variables were self-reported emotional responses (PANAS scores), ERP components (P3 and LPP), and theta-band spectral power. Subsequently, Pearson's correlation coefficients were calculated, and age and HAMD scale score were used as control variables to explore the relationships among PANAS scores, P3 and LPP amplitudes, theta wave power, and rejection sensitivity scale scores in depressed patients. To control for type I error, *p*-values of the correlation analyses were further corrected using the false discovery rate (FDR) method. Numerical variables were expressed as means (M) ± standard deviations. $p < 0.05$ was considered to indicate a statistically significant difference.

3. Results

3.1. Demographic and clinical characteristics

The two groups had comparable baseline characteristics in terms of gender distribution, years of education, and family history of mental disorders (Table 1). Regarding clinical presentations, no statistically significant differences were observed between groups in terms of bodily pain, depression subtypes, severity of depressive symptoms, times of suicide behavior, or degree of anhedonia. However, critical differences were found in three clinical parameters: the AD group exhibited a significantly earlier age of onset ($p < 0.001$), longer duration of disease ($p = 0.017$), and greater suicidal ideation ($p = 0.022$) compared with the non-AD group. In particular, the results indicated a marginally significant difference in the TERS scores ($p = 0.094$) and statistically significant variations in the interpersonal sensitivity subscale of the SCL-90 (*p*

= 0.003), suggesting potential differences in rejection sensitivity between the two groups of depressed patients.

3.2. PANAS results

At baseline, no significant between-group differences were observed in self-reported positive affect ($t = 1.684$, $p = 0.099$) or negative affect ($t = 0.755$, $p = 0.454$). Two-factor repeated measures ANOVA detected a significant block main effect for positive affect ($F_{(1,44)} = 11.850$, $p = 0.001$, $\eta_p^2 = 0.212$), with lower scores following exclusion (M = 15.24 ± 5.14) than inclusion blocks (M = 18.26 ± 5.48). The group main effect ($F_{(1,44)} = 0.712$, $p = 0.403$, $\eta_p^2 = 0.016$) and block × group interaction ($F_{(1,44)} = 2.331$, $p = 0.134$, $\eta_p^2 = 0.050$) were not significant for positive affect.

For negative affect, no significant block main effect ($F_{(1,44)} = 0.603$, $p = 0.442$, $\eta_p^2 = 0.014$) or block × group interaction ($F_{(2,43)} = 0.005$, $p = 0.946$, $\eta_p^2 = 0.000$) was observed. However, a significant group main effect was found ($F_{(1,44)} = 4.839$, $p = 0.033$, $\eta_p^2 = 0.099$), where the AD group reported higher negative affect (M = 23.89 ± 1.10) than the non-AD group (M = 20.70 ± 1.20).

3.3. ERP component results

3.3.1. P3

In the inclusion block, repeated-measures ANOVA was conducted to examine the effects of event types ("my turn" vs. "not my turn") and depression groups (AD vs. non-AD) on P3 amplitude. The results indicated a significant main effect of event type ($F_{(1,45)} = 6.462$, $p = 0.015$, $\eta_p^2 = 0.126$). The main effect of group ($F_{(1,45)} = 1.483$, $p = 0.230$, $\eta_p^2 = 0.032$) was not significant, but the event type × group interaction approached significance ($F_{(1,45)} = 2.940$, $p = 0.093$, $\eta_p^2 = 0.061$). Post-hoc analysis with LSD correction detected significant event type differences in the AD group ($F_{(1,45)} = 10.139$, $p = 0.003$, $\eta_p^2 = 0.184$), but not in the non-AD group ($F_{(1,45)} = 0.309$, $p = 0.581$, $\eta_p^2 = 0.007$). The results are presented in Fig. 1.

In the exclusion block, an independent *t*-test conducted to compare P3 amplitudes between depression groups found no significant group differences ($t_{(1,45)} = 0.030$, $p = 0.977$).

3.3.2. LPP

In the inclusion block, repeated-measures ANOVA was conducted to examine the effects of event types ("my turn" vs. "not my turn") and depression groups (AD vs. non-AD) on LPP amplitude. The results indicated a significant main effect of event type ($F_{(1,45)} = 31.238$, $p < 0.001$, $\eta_p^2 = 0.410$). However, the main effect of group ($F_{(1,45)} = 0.016$, $p = 0.899$, $\eta_p^2 < 0.001$) and the event type × group interaction ($F_{(1,45)} = 0.548$, $p = 0.463$, $\eta_p^2 = 0.012$) were not significant.

In the exclusion block, an independent *t*-test was performed to compare the LPP amplitudes between the two depression groups. The results indicated a marginally significant group difference ($t_{(1,45)} = 1.696$, $p = 0.097$). The results are presented in Fig. 1.

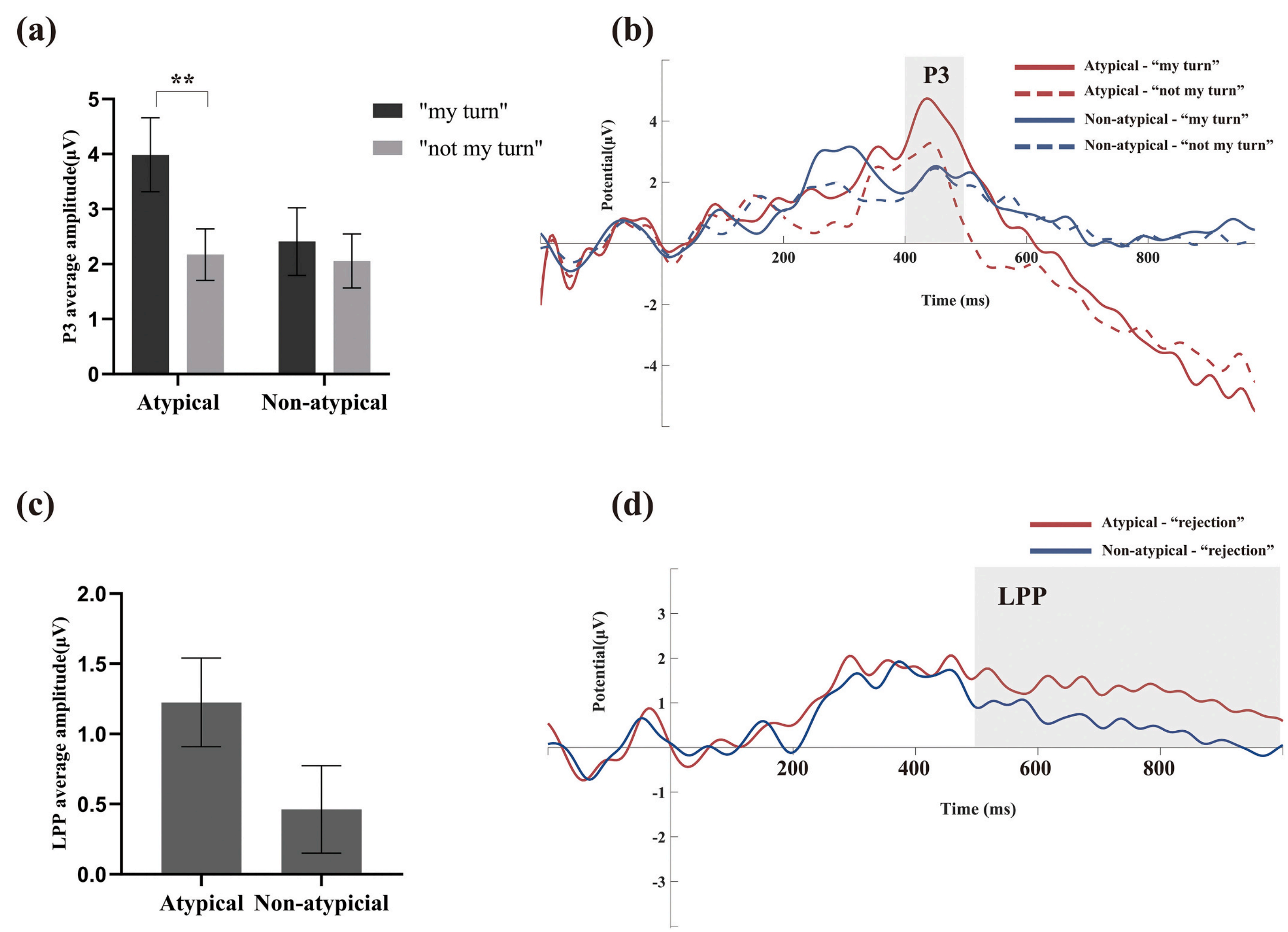

Fig. 1. Results for P3 and LPP components. (a) Bar graph showing average P3 amplitudes in the inclusion block. (b) Average P3 amplitudes in the inclusion block. (c) Bar graph showing average LPP amplitudes in the exclusion block. (d) Average LPP amplitudes in the exclusion block.

3.4. ERSP component results

In the inclusion block, repeated-measures ANOVA was conducted to examine the effects of event type ("my turn" vs. "not my turn") and depression group (AD vs. non-AD) on theta waves. The results indicated a significant main effect of event type ($F_{(1,45)} = 13.485$, $p = 0.001$, $\eta_p^2 = 0.231$). However, the main effect of group was not significant ($F_{(1,45)} = 0.508$, $p = 0.480$, $\eta_p^2 = 0.011$). In particular, a significant interaction effect was found between event type and group ($F_{(1,45)} = 4.708$, $p = 0.035$, $\eta_p^2 = 0.095$). Post-hoc analysis with LSD correction detected significant differences in event type for the non-AD group ($F_{(1,45)} = 15.424$, $p < 0.001$, $\eta_p^2 = 0.255$), but not for the AD group ($F_{(1,45)} = 1.263$, $p = 0.267$, $\eta_p^2 = 0.027$). Furthermore, no significant difference was found between groups for the "my turn" event ($F_{(1,45)} = 0.730$, $p = 0.397$, $\eta_p^2 = 0.016$), although a trend toward significance was observed for the "not my turn" event ($F_{(1,45)} = 3.360$, $p = 0.073$, $\eta_p^2 = 0.069$). The results are presented in Fig. 2.

In the exclusion block, an independent *t*-test was performed to compare theta waves between the two depression groups. The results indicated a significant difference between groups ($t_{(1,45)} = -2.116$, $p = 0.040$). The results are presented in Fig. 3.

3.5. Correlation analysis results

Correlation analysis detected the following significant associations. The TERS scale score had positive correlations with the LPP amplitude ($r = 0.451$, $p = 0.020$) in response to "rejection" events. Moreover, the Interpersonal Sensitivity subscale score of the SCL-90 had significant positive correlations with the negative affect score ($r = 0.446$, $p = 0.020$) and LPP amplitude ($r = 0.377$, $p = 0.037$) for "not my turn" events, as well as with the negative affect score ($r = 0.391$, $p = 0.037$) for "rejection" events. Further details of the correlations are presented in Table 2.

3.6. Classification results

Based on the behavioral and neuroelectrophysiological features associated with interpersonal sensitivity, a random forest classifier was constructed to identify depression subtypes. The supplementary 5-fold and 10-fold cross-validation analyses within the training set indicated stable classification performance. In 5-fold cross-validation, the model achieved an average accuracy of 72.0 % (±0.21), sensitivity of 83.0 % (±0.24), specificity of 64.4 % (±0.22), and F1 score of 71.1 % (±0.24). In 10-fold cross-validation, the model achieved an average accuracy of 72.5 % (±0.19), sensitivity of 72.5 % (±0.33), specificity of 77.5 % (±0.20), and F1 score of 73.9 % (±0.17). Importantly, evaluation on the independent test set confirmed that the model was effective at distinguishing AD from non-AD, achieving an accuracy of 83.3 %, sensitivity of 80.0 %, and specificity of 85.7 %.

4. Discussion

In the present study, we combined cognitive psychological assessments with EEG recordings to explore the differences between AD and non-AD in terms of clinical symptoms, cognitive psychological mechanisms, and neural processes in social interactions. Our main findings showed that individuals with AD had significantly higher interpersonal sensitivity scores compared with those with non-AD. Electrophysiological evidence also confirmed that AD patients exhibited abnormal neural reactivity in both social inclusion and social exclusion scenarios, suggesting greater sensitivity to interpersonal interactions at the neural level. Moreover, further analysis using machine learning methods indicated that interpersonal sensitivity-related features could effectively distinguish AD from non-AD, supporting the idea that interpersonal sensitivity is a key feature of AD.

4.1. Differences in clinical characteristics between groups

In the present study, we identified significant demographic and clinical differences between AD and non-AD. AD is associated with an earlier onset, longer illness duration, and higher incidence of suicidal ideation. Our findings align with previous research (Brailean et al., 2020; Ross et al., 2010; Xin et al., 2019), reinforcing the notion that AD represents a distinct depressive subtype with unique clinical and pathophysiological features (Juruena et al., 2018). In addition, AD patients obtained significantly higher scores on the Interpersonal Sensitivity subscale of SCL-90 compared with those with non-AD. Similarly, previous studies used validated interpersonal sensitivity assessments, such as the Interpersonal Sensitivity Measure, and also found elevated sensitivity scores in AD (Luty et al., 2002). These findings support the view that AD is a non-depressive syndrome primarily influenced by personality factors (Parker, 2007), thereby highlighting the important role of interpersonal sensitivity in its clinical profile.

4.2. AD patients exhibited increased negative emotions following Cyberball task

In this study, the Cyberball task was combined with the PANAS to examine the emotional responses of individuals with AD in social interactions. PANAS analysis revealed that the negative affect scores were significantly higher in the AD group than the non-AD group, regardless of whether they were included or excluded. Similarly, previous research

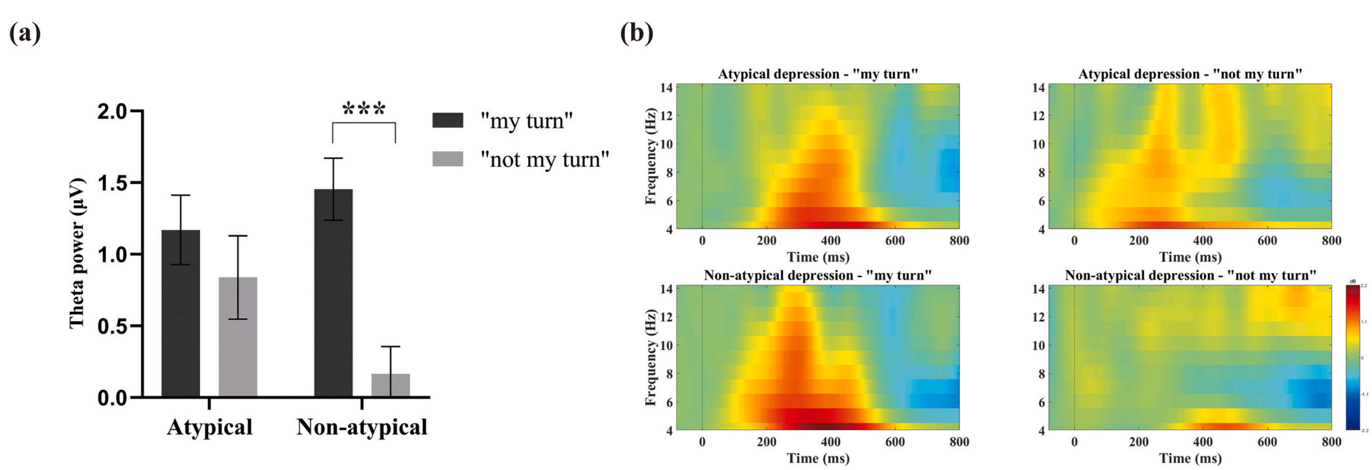

Fig. 2. Theta wave results in the inclusion block. (a) Bar graph showing theta power in the inclusion block. (b) Time–frequency diagrams showing theta signal in the inclusion block.

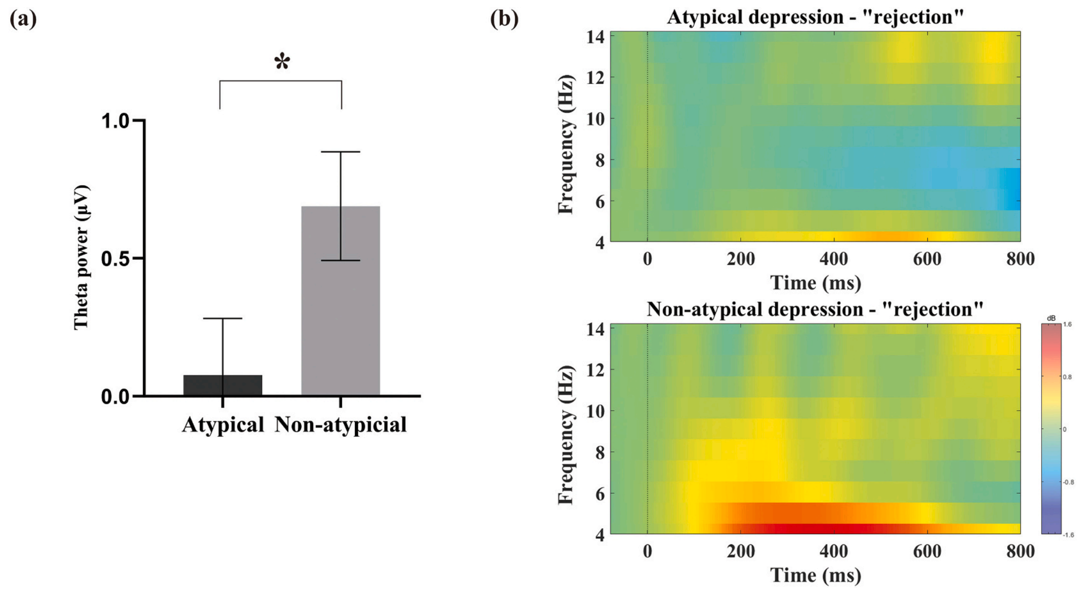

Fig. 3. Theta activity results in the exclusion block. (a) Bar graph showing theta power in the inclusion block. (b) Time–frequency diagrams showing theta signal in the exclusion block.

Table 2
Correlations between rejection sensitivity scale scores, and behavior and electrophysiological indicators in the Cyberball task.

Indicators	Event types	TERS		Interpersonal sensitivity subscale of SCL-90	
		r	p[a]	r	p[a]
Positive affect	"Not my turn"	0.073	0.746	0.281	0.136
	"Rejection"	0.066	0.746	0.126	0.487
Negative affect	"Not my turn"	0.228	0.296	**0.446**	**0.020**
	"Rejection"	0.299	0.163	**0.391**	**0.037**
P3 amplitude	"Not my turn"	0.181	0.392	0.118	0.487
	"Rejection"	0.313	0.163	0.085	0.577
LPP amplitude	"Not my turn"	0.219	0.296	**0.377**	**0.037**
	"Rejection"	**0.451**	**0.020**	0.274	0.136
Theta wave	"Not my turn"	−0.134	0.546	0.131	0.487
	"Rejection"	−0.010	0.946	0.193	0.342

[a] FDR-adjusted p-values; LPP: Late positive potential; TERS: Tendency to Expect Rejection Scale; SCL-90: Symptom Checklist 90. Bold denotes significance ($p < 0.05$).

showed that social exclusion elicits strong negative emotions, including in individuals with depression (Barzilai et al., 2024; Seidl et al., 2020), because it threatens fundamental psychological needs such as belonging and self-esteem (Williams and Nida, 2022). Even mild exclusion can trigger negative emotional experiences, and AD individuals, who are particularly sensitive to social rejection, are more likely to perceive exclusion and experience intensified negative emotions. Furthermore, their heightened interpersonal sensitivity may lead them to misinterpret neutral social interactions as rejection even in inclusive settings, further amplifying negative emotional responses. This pattern is consistent with findings obtained in Cyberball task studies of borderline personality disorder, a condition also characterized by interpersonal sensitivity, where individuals with high interpersonal sensitivity tend to perceive rejection even in objectively inclusive situations, resulting in pronounced negative emotional experiences (De Panfilis et al., 2015; Kulakova et al., 2024; Weinbrecht et al., 2018). Our results obtained by correlation analysis also indicated a significant positive correlation between interpersonal sensitivity scale score and negative affect score, supporting the explanation that AD may be more likely to produce negative emotions in interpersonal interactions due to higher interpersonal sensitivity.

4.3. AD patients exhibited distinct neural response patterns during the Cyberball task

Based on ERPs, we found distinct neural response patterns to interpersonal interaction in AD than typical depression at the electrophysiological level. First, analysis of the P3 components showed that the average amplitudes of the "my turn" and "not my turn" conditions were significantly different in the AD group, where the neural response pattern was inconsistent with that in the non-AD group. Previous studies showed that the P3 amplitude increased when catching a ball violated an individual's inherent expectation of exclusion (Harrewijn et al., 2018; Kulakova et al., 2024; Vanhollebeke et al., 2023). In the present study, the higher P3 amplitude in the "my turn" condition may indicate that AD patients tended to expect exclusion, even in a friendly social interaction context. Receiving the ball might therefore have violated this expectation, suggesting a reduced anticipation of social acceptance in AD. This phenomenon may further elucidate the characteristics of AD: a persistent cognitive bias where individuals perceive social rejection despite existing within an objectively accepting environment, thereby generating the need for an extreme situation of acceptance (De Panfilis et al., 2015). In addition, the increased P3 amplitude may also indicate that AD patients invest more cognitive resources in evaluating and classifying the interaction invitations of others (Vanhollebeke et al., 2023). This heightened processing could reflect a hypervigilance toward social signals, consistent with the elevated interpersonal sensitivity often observed in AD. Furthermore, analysis of the LPP component during the exclusion block revealed a trend toward higher amplitudes in individuals with AD compared with those with non-AD, suggesting a tendency for stronger negative emotional responses to social exclusion. Social exclusion significantly activates neural circuits involved in emotional processing, where the intensities of neural responses in the anterior cingulate cortex and prefrontal cortex are positively correlated with individuals' subjective experience of exclusion (Groschwitz et al., 2016; McIver et al., 2019). Notably, AD and non-AD patients exhibit distinct patterns of neural activity and functional connectivity in the prefrontal region (Guo et al., 2024), which may contribute to the heightened emotional reactivity to social exclusion observed in AD. A previous clinical study also indicated that AD patients struggle with emotion regulation (Fornaro et al., 2025), potentially impairing their ability to manage the negative emotions triggered by social exclusion. In the present study, correlation analysis further demonstrated a significant positive association between interpersonal sensitivity scores and LPP amplitude, suggesting that individuals with higher interpersonal sensitivity were more prone to experiencing negative emotions in response to social exclusion. Moreover, previous research has shown that heightened rejection sensitivity is associated with structural abnormalities in brain regions involved in emotion and anxiety processing (Bach et al., 2019). These findings consistently suggest that due to their higher interpersonal sensitivity, individuals with AD are more likely to experience negative emotions in social interactions, which may further lead to adverse outcomes such as internalizing symptoms (Rudolph et al., 2016).

Time–frequency analysis further demonstrated that AD and non-AD individuals exhibited distinct neural response patterns during interpersonal interactions. In particular, under the inclusion condition, non-AD individuals exhibited significant differences in theta activity between the "my turn" event and the "not my turn" event, whereas no significant differences were found in theta activity between these two events in AD individuals. Theta activity is associated with attention engagement and cognitive control (Tan et al., 2024). Our findings indicate that individuals with AD allocated more attentional resources even during "not my turn" events, which did not require a response. Thus, they may have remained highly vigilant even in neutral social interactions, reflecting a cognitive negativity bias in their perception of social situations (Renneberg et al., 2012). In addition, the frontal theta activity is related to cognitive control and self-inhibition in the process of social participation (Lavin et al., 2023). Therefore, individuals with AD may rely on cognitive control to regulate their expectations and negative cognitions while waiting to interact with others. Under the rejection condition, the theta activity was significantly lower in the AD group than the non-AD group. The prefrontal cortex serves as a crucial node in the emotion regulation network (Zhang et al., 2023). The observed reduction in theta activity in the left frontal cortex in AD patients may reflect altered prefrontal engagement during processing of rejection stimuli (Guo et al., 2024), potentially indicating difficulties in sustaining or enhancing neural resources for emotion regulation (Fertuck et al., 2023). This abnormality may contribute to heightened experiences of social pain in individuals with AD (Cristofori et al., 2013; Tang et al., 2019; van Noordt et al., 2015).

4.4. Indicators of interpersonal sensitivity effectively distinguished AD from non-AD

Machine learning analysis using the random forest method demonstrated that interpersonal sensitivity-related indicators, including the interpersonal sensitivity scale scores (TERS and Interpersonal sensitivity subscale of SCL-90), as well as behavioral and electrophysiological measures obtained from the Cyberball task, could distinguish AD from non-AD with an accuracy of up to 83.3 %. Despite the small sample size in the present study, the results still provide some degree of support for the view that interpersonal sensitivity is the primary feature for AD diagnosis (Lojko and Rybakowski, 2017; Parker et al., 2002).

This study has several limitations. First, although we classified depression patients into AD and non-AD groups, we did not further subdivide the non-AD group into melancholic and non-melancholic subtypes, which limits more precise investigations of depression subtypes and their underlying mechanisms. Second, the relatively small sample size constrained the interpretation of the results, and the absence of a healthy control group made it difficult to accurately assess the degree of neural processing abnormalities related to interpersonal sensitivity in AD patients. Additionally, mismatches in demographic characteristics between groups—such as differences in age, age at onset, and sex distribution—as well as the inclusion of participants from a single ethnic background may further limit the generalizability of the findings. Third, although we employed a random forest classifier, which is suitable for small-sample analysis, future studies should use larger samples to validate the findings and assess the robustness of the machine learning model. Fourth, the study relied primarily on cross-sectional data collected in a laboratory setting, and the Cyberball task induces only acute, transient social inclusion or exclusion, which does not fully capture the chronic, trait-like interpersonal sensitivity characteristic of AD patients. Nevertheless, neural responses elicited during the task may serve as measurable indicators of interpersonal sensitivity–related neural processes. To address these limitations, future studies should employ larger and more diverse cohorts, subdivide depression subtypes for finer-grained analyses, and incorporate more ecologically valid paradigms, such as interactive social tasks or near-infrared spectroscopy, to more accurately capture the neural mechanisms underlying interpersonal sensitivity in real-world contexts. Importantly, research could also focus on social sensitivity to develop targeted neuromodulation or other intervention strategies. These approaches could provide guidance for personalized interventions aimed at improving social functioning and quality of life in AD patients.

Overall, the findings obtained in this study suggest that AD represents a distinct depressive subtype characterized by clinical symptoms and cognitive–neural mechanisms that differ significantly from those of non-AD. Electrophysiological evidence indicated that individuals with AD exhibited distinct neural response patterns to interpersonal interactions compared with non-AD patients, which may reflect a tendency toward negative cognitive appraisal of positive or neutral social acceptance scenarios and relatively stronger negative emotional responses to social exclusion. Moreover, random forest analysis suggested that interpersonal sensitivity may be a core feature for distinguishing AD from non-AD. These findings enhance our understanding of the neurocognitive mechanisms that underlie interpersonal sensitivity in AD, as well as highlighting the importance of incorporating interpersonal relationship assessments and interventions in the diagnosis and treatment of this specific depressive subtype.

CRediT authorship contribution statement

Qingqing Zhang: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Fangchen Chen:** Writing – original draft, Validation, Project administration, Methodology. **Yanting Lin:** Validation, Investigation, Data curation. **Lei Huang:** Project administration, Methodology. **Yi Jiang:** Writing – review & editing, Conceptualization. **Chunyan Zhu:** Writing – review & editing, Funding acquisition.

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Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.120519.

Data availability

Due to reasons of data protection, the preprocessed data is available only upon reasonable request to the corresponding author.

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