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Research paper

Atypical subcortical involvement in emotional face processing in major depressive disorder with and without comorbid social anxiety

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ABSTRACT

Previous research on major depressive disorder (MDD) has largely focused on cognitive biases and abnormalities in cortico-limbic circuitry during emotional face processing. However, it remains unclear whether these abnormalities start at early perceptual stages via subcortical pathways and how comorbid social anxiety influences this process. Here, we investigated subcortical mechanisms in emotional face processing using a psychophysical method that measures monocular advantage (i.e., superior discrimination performance when two stimuli are presented to the same eye than to different eyes). Participants included clinical patients diagnosed with MDD (n = 32), patients with MDD comorbid with social anxiety (comorbid MDD-SAD, n = 32), and a control group of healthy participants (HC, n = 32). We assessed monocular advantage across different emotions (neutral, sad, angry) and among groups. Results indicated that individuals with MDD showed a stronger monocular advantage for sad expressions compared to neutral and angry expressions. In contrast, HC and comorbid MDD-SAD groups showed a greater monocular advantage for neural over negative expressions. Cross-group comparisons revealed that MDD group had a stronger monocular advantage for sad expressions than both HC and comorbid MDD-SAD groups. Additionally, self-reported depressive symptoms were positively correlated with monocular advantage for sad expressions, while social anxiety symptoms were negatively correlated with monocular advantage for negative expressions. These findings suggest atypical early perceptual processing of sadness in individuals with MDD via subcortical mechanisms, with comorbid social anxiety potentially counteracting this effect. This study may inform novel interventions targeting sensory processing and expand beyond cognitive bias modification.

1. Introduction

Major depressive disorder (MDD) is a widespread mental health condition characterized by persistent feeling of low mood and diminished interests in activities (Otte et al., 2016). Cross-national epidemiological studies indicate a lifetime prevalence of MDD among screen-positives exceeding 19 % (Kessler and Bromet, 2013), with a rising trend of early-onset depressive symptoms in childhood and adolescence (Daly, 2022). MDD not only affects emotional experience but also alters information processing mechanisms. Specifically, individuals with depression demonstrate aberrant processing of negative stimuli (Gotlib and Joormann, 2010; Bourke et al., 2010), characterized by enhanced vigilance and biased attention towards sadness-related expressions (Gotlib et al., 2004). They also tend to interpret neutral or ambiguous faces as more negative (Leppänen et al., 2004). While extensive research has examined cognitive biases of emotional faces in MDD, few studies have explored whether these abnormalities occur at early perceptual stages.

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To investigate whether MDD affects early face perception, one approach is to examine subcortical contributions to face perception. Theories of face perception suggest that subcortical structures lay the foundation for the cortical face-processing network (Johnson, 2005; Johnson et al., 2015). In newborns, face preference is primarily mediated by subcortical pathways due to the immaturity of cortical areas; these pathways continue to play a role in early face detection over development (Garvert et al., 2014; Johnson et al., 2015). However, assessing face processing in subcortical structures is challenging due to their small size, deep location and low signal-to-noise ratio (Jia et al., 2023). To address this, we used monocular segregation – a technique that presents visual information separately to each eye – to examine subcortical involvement in face perception. This approach is effective because subcortical areas are primarily composed of monocular neurons (Palmer, 1999). In particular, signals from retinal ganglion cells project primarily to the lateral geniculate nucleus (LGN) (Casagrande and Boyd, 1996), where neurons respond exclusively to input from one eye (Wiesel and Hubel, 1966). This monocular segregation persists up to Layer IV of the primary visual cortex (Baker et al., 1974; Menon et al., 1997). When stimuli are presented sequentially to the same eye, compared to different eyes, behavioral benefits in the same-eye condition reflect the activations of the same set of monocular neurons (i.e., monocular advantage). Previous studies have used this approach and demonstrated a monocular advantage for face stimuli in healthy individuals (Gabay et al., 2014; Almasi and Behrmann, 2021).

While studies comparing individuals with depression to healthy controls provide insights into disorder-specific mechanisms, MDD is highly comorbid with social anxiety disorder (SAD) in clinical settings (Kessler et al., 2005; Ter Meulen et al., 2021). This comorbidity is associated with higher psychiatric severity and greater impairments in social functioning (Adams et al., 2016; Kessler et al., 2015). Therefore, comparing MDD and MDD-SAD groups can help clarify the effects of comorbid SAD on depression, potentially providing diagnostic markers for distinguishing "pure" depression from comorbid MDD-SAD. Previous research on cognitive biases has produced mixed findings regarding how comorbid MDD-SAD might affect depression (Kircanski et al., 2017). For instance, some evidence suggests that attentional processing of emotional information is predominantly influenced by one of the disorders (Kircanski et al., 2015), while other studies show that individuals with comorbid MDD and SAD exhibit either additive (Wilson and Rapee, 2005; LeMoult and Joormann, 2012; Ottenbreit et al., 2014) or counteracting responses to negative emotions, compared to those with pure disorders (Musa et al., 2003; Grant and Beck, 2006). The considerable variability may be partly due to the focus on cognitive processes, which can be influenced by task-related factors. Examining early face perception may provide more reliable evidence to resolve this inconsistency. This is particularly true for the measured monocular difference in our study, as participants were unaware of which eye the visual stimulus was projected to, minimizing the impact of task strategies. Moreover, since the neural mechanisms of perceptual processing are well-understood in healthy individuals, investigating these abnormalities could provide insights into the neurobiological basis of depression (Heeger et al., 2017) and inform the development of intervention strategies targeting perceptual systems.

The present study aimed to examine whether depression affects early perceptual processing of emotional faces and how comorbid social anxiety influences this process. Using a stereoscope for monocular segregation of visual inputs (Gabay et al., 2014; Almasi and Behrmann, 2021), we compared the monocular advantage in processing emotional faces between individuals with MDD, comorbid MDD-SAD, and a matched group of healthy controls (HC). We hypothesized that depressed individuals would show larger monocular advantage, particularly for sad expressions. The specific patterns in comorbid MDD-SAD group need further exploration. If MDD predominantly affects early face processing or if MDD and SAD have additive effects, MDD and comorbid MDD-SAD groups would exhibit similar monocular patterns. Conversely, if MDD and SAD influence early face processing in distinct ways, MDD and comorbid MDD-SAD groups would show differential monocular patterns.

2. Materials and methods

2.1. Participants

To determine the sample size, we ran a Power analysis using MorePower 6.04 (Campbell and Thompson, 2012). A sensitivity analysis suggested that 32 participants per group (a total number of 96 participants) is sufficient to detect a medium-sized effect ($\eta_p^2 = 0.08$) for our primary effect of interest of a four-way interaction in a 2 (Stimulus Presentation) × 2 (Image Match) × 3 (Facial Expression) × 3 (Group) mixed repeated-measures analysis of variance (ANOVA) with a power of 0.9 ($\alpha = 0.05$). Therefore, we recruited a total of 96 participants for this study (Table 1).

The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-5; Silverman et al., 2015) was used by clinical psychiatrists to determine the diagnostic status of treatment-seeking patients. We recruited patients diagnosed with principal MDD with or without comorbid SAD symptoms from the clinic of the Department of Psychiatry at the Second Affiliated Hospital of Zhejiang University School of Medicine. These patients also completed subjective ratings on the Beck Depression Inventory (BDI-II) (Beck et al., 1996) and Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987). Based on clinical assessment and self-reported scales, thirty-two patients (19 females; age: M = 25.06 years) were classified into MDD group (BDI ≥16 and LSAS <38). Thirty-two patients (22 females; age: M = 27.87 years) were classified into comorbid MDD-SAD group (BDI-II ≥16 and LSAS ≥38). This LSAS cutoff value was suggested particularly for Chinese samples (He and Zhang, 2004). Twenty-six patients (40.6 %) received pharmacological treatment before participating our experiment: nineteen were prescribed selective serotonin-reuptake inhibitors (SSRIs), three were prescribed serotonin–norepinephrine reuptake inhibitors (SNRIs), four were prescribed both SSRIs and SNRIs. The remaining patients (N = 38, 59.4 %) did not use medications. None of these patients underwent psychological interventions. As a control group, we recruited thirty-two healthy participants (20 females; age: M = 26.34 years) from Zhejiang University and local communities to match the patient groups in demographic characteristics. None of the participants in HC group reported a history of psychological or psychiatric treatment.

Table 1
Demographic information for healthy control, individuals with major depressive disorder, and those with co-occurring social anxiety (Values are mean ± SD).

Measure	HC (N = 32)	MDD (N = 32)	Comorbid MDD-SAD (N = 32)	Group Effect
Female (%)	65.6 %	71.9 %	75.0 %	$\chi^2(2) = 0.71$, $p = 0.703$
Age (years)	25.09 (7.71)	27.87 (6.80)	26.53 (7.75)	$F(2,93) = 1.12$, $p = 0.330$
College graduate (%)	71.8 %	68.7 %	68.7 %	$\chi^2(2) = 0.10$, $p = 0.952$
BDI	3.37 (2.91)	24.16 (8.21)	30.41 (8.47)	$F(2,93) = 128.55$, $p < 0.001$
LSAS	22.41 (8.13)	21.41 (10.31)	77.28 (22.45)	$F(2,93) = 146.13$, $p < 0.001$

Note. HC = Healthy Controls; MDD = Major Depressive Disorder; SAD = Social Anxiety Disorder; BDI-II = Beck Depression Inventory – II; LSAS = Liebowitz Social Anxiety Scale – Self Report Version.

They scored below the cutoff on BDI-II and LSAS scales (BDI-II <16 and LSAS <38). All participants had normal or corrected-to-normal vision and were right-handed. They provided written informed consent approved by the Institutional Review Board at Department of Behavioral Sciences and Psychology, Zhejiang University (protocol number: 2022–06-063).

2.2. Stimuli and apparatus

30 male and 30 female face images obtained from the Chinese Facial Affective Picture System (Gong et al., 2011) were used in the experiment. All images displayed front views of faces with neutral, angry or sad expressions. The face images were cropped to remove hair cues and were displayed in grayscale against a black background. Face stimuli were 8° in height and 6° in width. Two images were presented in two separate squares on the left and right side of the same screen (10° in height and 10° in width 5° to the left and right of the center). The images were presented in the front view on a 23.8-in. LCD monitor (resolution: 1024 × 768, refresh rate: 60 Hz). Participants viewed the images at an approximate distance of 60 cm.

The stimuli were viewed with a mirror stereoscope placed in front of the participants. Two mirrors were positioned separately near one eye at a 45° angle to that eye's line of viewing (Fig. 1A). Another two mirrors were placed on either side of each of the first two mirrors, facing the stimuli at a 45° angle. To block the line of vision to the other eye's stimulus, a sheet of cardboard divider was placed between the participants' eyes, extending from the midline of the stereoscope towards the center of the display. This arrangement could enable eye-specific stimulus presentation. The mirrors can be rotated to enhance the adjustability to each participant's eyes, inducing a single, fused image. Participants were not aware of the eye to which the visual image was presented in either the same-eye or different-eye condition.

2.3. Procedure and tasks

At the beginning of each trial (Fig. 1B), two squares with white fixation were shown on the left and right side of the screen (5° from the center) for 1 s. Participants were instructed to maintain fixation throughout the experiment. Two face images were shown sequentially, either to the same eye (monocular) or to different eyes (dichoptic). Each image was shown for 1 s and separated by an interstimulus interval of 1 s. Participants were asked to respond whether the identity of two faces were same or different after the second image appeared. Half of the trials contained two identical images, whereas the remaining half containing two different images. Each trial consisted of two face images with one of the three expressions (neutral, sad and angry). We included both sad and angry expressions because individuals with depression are presumably more biased towards sadness-related stimuli, and those with social anxiety are presumably more biased towards threat-related stimuli (Joormann and Gotlib, 2006; Hankin et al., 2010). The facial expression was irrelevant to the discrimination of face identity. Based on the data of the image bank (28), the selected facial expression has high identification rate (neutral: 82.4 %; sad: 84.6 %; angry: 81.0 %), which was comparable across three expressions (One-way ANOVA: F(2,38) =

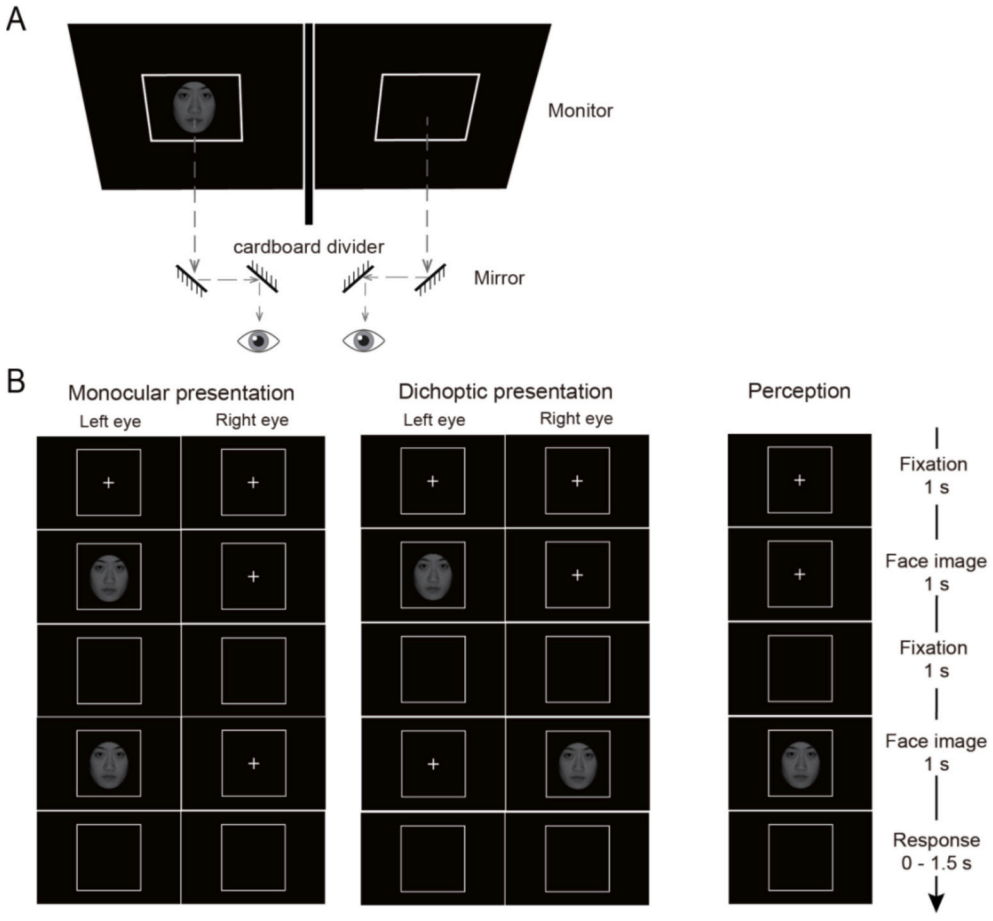

Fig. 1. Experimental setup and task procedure. (A) Participants viewed stimuli through a mirror stereoscope. Two mirrors were positioned at a 45° angle in front of each eye, with another two mirrors on either side, also at a 45° angle. A cardboard divider between the eyes blocked vision to the other eye's stimulus. (B) An example trial with neutral expressions presented to same-eye (monocular presentation) and to different eyes (dichoptic presentation). The right panel represents participants' perception of the fused images. Participants were not aware of the eye-of-origin.

0.545, $p = 0.584$, $\eta_p^2 = 0.028$). All trial types were of equal probability and randomly interleaved across trials. Each participant completed 20 practice trials and 5 blocks of trials (72 trials per block).

2.4. Statistical analysis

Because the mean percentage of correct identification of faces were high across groups (HC: 96.9 %; MDD: 95.34 %; comorbid MDD-SAD: 95.29 %), we primarily focused our analyses on measured RT. For each participant, trials with reaction time (RT) outside the specified response window (0.2–1.5 s) or exceeding three standard deviations away from each individual's mean were excluded. RT from incorrect trials were also excluded. To examine potential difference in face perception across experimental conditions, a four-way mixed ANOVA was applied on RT, with Group (HC, MDD, comorbid MDD-SAD) as the between-subject factor, Stimulus Presentation (same vs. different eye), Image Match (same vs. different image), and Facial Expression (neutral, angry vs. sad) as within-subject factors. To examine the relationships between the monocular differences and self-reported symptoms, we computed partial correlations between these indices. Bivariate outliers were excluded using the Robust Correlation Toolbox (Pernet et al., 2013) and the outliers were not shown in the data figures. Excluding outliers in RTs is a standardized method, as outliers can significantly distort the data distribution when RT is the dependent variable (Ratcliff, 1993). However, we observed that even without excluding outliers, the patterns of results remained qualitatively similar across all the analyses mentioned above (see Supplementary Materials for details).

2.5. Transparency and openness

All data, analyses, and task codes have been made publicly available via the Open Science Framework at https://osf.io/9ew8t/. Data were analyzed using MATLAB, Version 2020b (The MathWorks, Natick, MA) and JASP Version 0.16.3 (JASP Team, 2022). This study was not pre-registered.

3. Results

3.1. Participant characteristics

Demographic details for each group of participants were presented in Table 1. The three groups of participants did not differ significantly in age, gender and education level (*ps* > 0.330). As expected, the three groups differed significantly in their BDI scores ($F(2,93) = 128.55$, $p < 0.001$; $\eta_p^2 = 0.734$). BDI scores increased from HC to MDD group ($p < 0.001$), and from MDD to comorbid MDD-SAD group ($p < 0.001$). The three groups differed significantly in their LSAS scores ($F(2,93) = 146.13$, $p < 0.001$; $\eta_p^2 = 0.759$). The comorbid MDD-SAD group had higher LSAS scores than both the MDD and HC groups (*ps* < 0.001), while MDD and HC groups did not differ significantly from each other ($p = 0.868$). These findings support the valid classification of depressed individuals into groups with and without social anxiety.

3.2. Cross-group differences of monocular advantages

The mean RT in the face identification task across experimental conditions and groups are presented in Fig. 2. To examine whether the

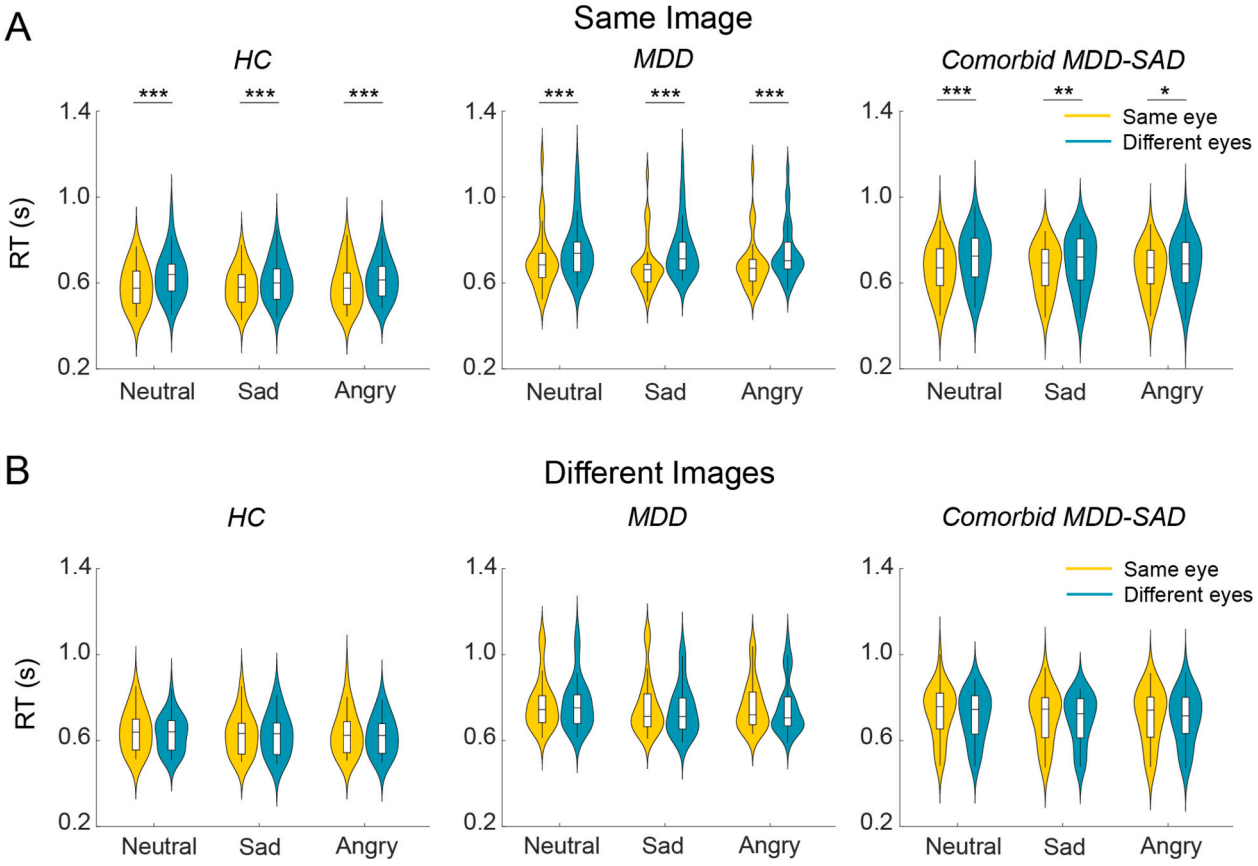

Fig. 2. Results across conditions and groups. (A) RTs for the same image (top row) and (B) different images (bottom row) conditions. Yellow and green colors represent the same-eye and different-eye condition, respectively. Each subplot represents each Group (HC, MDD, comorbid MDD-SAD). The data table is provided in Supplementary Materials (Table S1). The asterisks represent the significance level. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

monocular processing of different facial expressions varies across groups, we conducted a four-way mixed ANOVA (Stimulus Presentation × Image Match × Facial Expression × Group) on measured RT. The analysis revealed significant main effects of Stimulus Presentation ($F(1,93) = 27.98$, $p < 0.001$, $\eta_p^2 = 0.231$), Image Match ($F(1,93) = 64.20$, $p < 0.001$, $\eta_p^2 = 0.408$). The Stimulus Presentation × Image Match interaction was also significant ($F(1,93) = 126.02$, $p < 0.001$, $\eta_p^2 = 0.575$), showing that participants responded faster in the same-eye condition compared to the different-eyes condition when the two images were the same than when they were different, replicating previous findings of monocular advantage for face perception (Gabay et al., 2014; Almasi and Behrmann, 2021; Gong et al., 2024). We also observed a significant main effect of Facial Expression ($F(2,186) = 31.97$, $p < 0.001$, $\eta_p^2 = 0.256$), demonstrating faster identification for emotional faces compared to neutral faces ($ps < 0.001$), but not between the sad and angry faces ($p = 0.407$).

Particularly relevant to our interest in group-level differences, we observed a main effect of Group ($F(2,93) = 10.68$, $p < 0.001$, $\eta_p^2 = 0.187$), demonstrating that MDD and comorbid MDD-SAD groups responded significantly slower than did the HC group ($ps < 0.005$), without significant difference between MDD and comorbid MDD-SAD group ($p = 0.099$). More importantly, we observed a significant four-way interaction ($F(4,186) = 4.65$, $p = 0.001$, $\eta_p^2 = 0.091$), indicating that participants from different groups exhibited distinct patterns of response to emotional faces via monocular and binocular processing. To further elucidate the four-way interaction effect, we analyzed the patterns of RTs separately for each group. To emphasize the extent of monocular face processing, we subtracted RTs in the same-eye condition from the different-eye condition (i.e., *RT difference*), separately for each facial expression and match type. A greater difference between monocular and binocular conditions would suggest a stronger reliance on subcortical pathways for face processing.

3.2.1. Healthy control

To establish a baseline for monocular processing of facial emotions, we analyzed data from HC group using a two-way repeated-measures ANOVA (Facial Expression × Image Match) on RT difference (Fig. 3, left). This analysis revealed a significant main effect of Image Match ($F(1,31) = 51.16$, $p < 0.001$, $\eta_p^2 = 0.623$) and a two-way interaction effect ($F(2,62) = 4.76$, $p = 0.012$, $\eta_p^2 = 0.133$). Simple effect analysis showed significant modulations of facial emotions in the same-image condition ($F(2,62) = 4.33$, $p = 0.017$, $\eta_p^2 = 0.123$), but not in the different-image condition ($F(2,62) = 2.45$, $p = 0.095$, $\eta_p^2 = 0.073$). Follow-up planned *t*-tests for the same-image condition revealed greater monocular advantage for neutral expression than sad expression ($t(31) = 2.25$, $p = 0.032$, Cohen's $d = 0.398$, 95 % CI = [0.035, 0.755]) and angry expression ($t(31) = 2.46$, $p = 0.020$, Cohen's $d = 0.434$, 95 % CI = [0.068, 0.794]). No significant difference was observed between angry and sad expressions ($t(31) = 0.70$, $p = 0.488$, Cohen's $d = 0.124$, 95 % CI = [−0.225, 0.471]).

3.2.2. Major depressive disorder

The same two-way repeated-measures ANOVA (Facial Expression × Image Match) was applied on the RT difference in MDD group (Fig. 3,

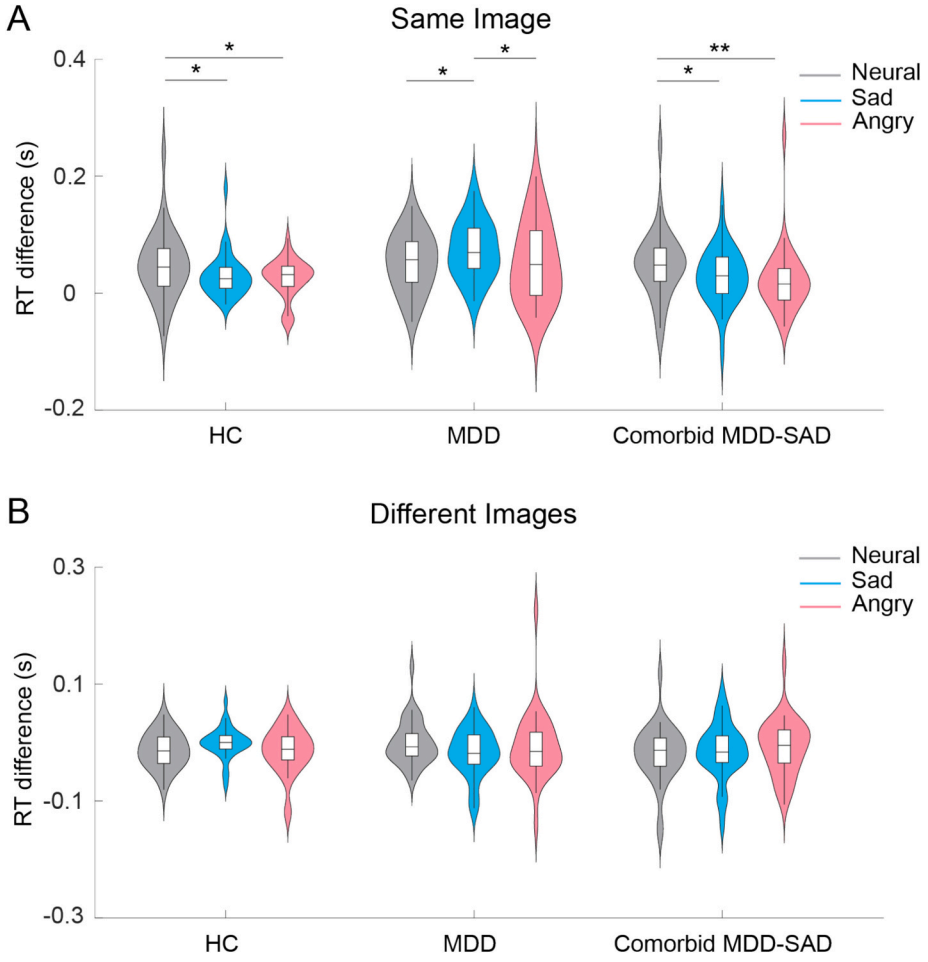

Fig. 3. Cross-group comparisons of the monocular difference (as indexed by RT difference: different-eye *minus* same-eye condition) as a function of Facial Expressions for the same image (upper panel) and different images (bottom panel). The data table is provided in Supplementary Materials (Table S2). The asterisks represent the significance level. *$p < 0.05$, **$p < 0.01$.

middle). Similar to the results observed in HC group, the analysis revealed a significant main effect of Image Match ($F(1,31) = 53.25$, $p < 0.001$, $\eta_p^2 = 0.632$) and a two-way interaction effect ($F(2,62) = 3.35$, $p = 0.042$, $\eta_p^2 = 0.097$). Simple effect analysis showed a significant modulation of facial emotions in the same-image condition ($F(2,62) = 3.19$, $p = 0.048$, $\eta_p^2 = 0.093$), but not in the different-image condition ($F(2,62) = 1.12$, $p = 0.333$, $\eta_p^2 = 0.035$). Despite these similarities with HC group, planned *t*-tests for the same-image condition showed significantly greater monocular advantage for sad expression compared to neutral ($t(31) = 2.41$, $p = 0.022$, Cohen's d = 0.426, 95 % CI = [0.061, 0.785]) and angry expressions ($t(31) = 2.30$, $p = 0.028$, Cohen's d = 0.406, 95 % CI = [0.043, 0.764]). The monocular advantage did not differ between neutral and angry expressions ($t(31) = 0.066$, $p = 0.948$, Cohen's d = 0.012, 95 % CI = [−0.335, 0.358]). These results suggest emotional specificity for sad expression in depressed individuals.

3.2.3. Comorbid MDD-SAD

The same analysis applied on RT difference in comorbid MDD-SAD group revealed similar results as those observed in HC group (Fig. 3, right). In brief, we found a significant main effect of Image Match ($F(1,31) = 29.30$, $p < 0.001$, $\eta_p^2 = 0.486$) and an interaction effect ($F(2,62) = 4.79$, $p = 0.012$, $\eta_p^2 = 0.134$), demonstrating emotional modulations in the same-image condition ($F(2,62) = 6.00$, $p = 0.004$, $\eta_p^2 = 0.162$), but not in the different-image condition ($F(2,62) = 0.68$, $p = 0.508$, $\eta_p^2 = 0.022$). Planned t-tests revealed significantly greater monocular advantages for neutral expression compared to sad ($t(31) = 2.28$, $p = 0.030$, Cohen's d = 0.403, 95 % CI = [0.039, 0.761]) and angry expressions ($t(31) = 3.64$, $p < 0.001$, Cohen's d = 0.644, 95 % CI = [0.258, 1.021]), but not between sad and angry expressions ($t(31) = 0.75$, $p = 0.461$, Cohen's d = 0.132, 95 % CI = [−0.217 0.479]). The similarity observed between comorbid MDD-SAD and HC, in contrast to the differential patterns observed between comorbid MDD-SAD and MDD, was somewhat unexpected, given that all clinical patients exhibited depressive symptoms. These findings might suggest opposing influences when MDD and SAD co-occur, as proposed by prior studies (Grant and Beck, 2006; Musa et al., 2003), leading to counteracting effects.

3.2.4. Cross-group comparison of monocular advantage

We conducted a cross-group comparison to assess diagnostic specificity using the monocular advantage. Because modulation of facial emotions was specifically observed in the same-image condition, consistent with previous studies (Gabay et al., 2014; Almasi and Behrmann, 2021; Gong et al., 2024), we restricted our analyses on RT difference from the same-image condition.

Using a two-way mixed ANOVA (Facial Expression × Group) on RT difference, we observed significant main effects of Facial Expression ($F(2,186) = 5.61$, $p = 0.004$, $\eta_p^2 = 0.057$), Group ($F(2,93) = 3.58$, $p = 0.032$, $\eta_p^2 = 0.071$) and an interaction effect ($F(4,186) = 3.68$, $p = 0.007$, $\eta_p^2 = 0.073$). Simple effect analysis revealed a Group effect for the sad expression ($F(2,93) = 10.58$, $p < 0.001$, $\eta_p^2 = 0.185$). In particular, individuals with MDD showed a greater monocular advantage for sad expression than did both the HC ($t(62) = 3.89$, $p < 0.001$, Cohen's d = 0.973, 95 % CI = [0.339 1.607]) and comorbid MDD-SAD group ($t(62) = 4.07$, $p < 0.001$, Cohen's d = 1.018, 95 % CI = [0.382 1.654]), while no significant difference was observed between HC and comorbid MDD-SAD groups ($t(62) = 0.18$, $p = 0.857$, Cohen's d = 0.045, 95 % CI = [−0.564 0.655]). The effect of Group was not significant for neutral ($F(2,93) = 0.05$, $p = 0.949$, $\eta_p^2 = 0.001$) and angry expressions ($F(2,93) = 2.81$, $p = 0.066$, $\eta_p^2 = 0.057$).

Although the RT difference accounted for mean response difference across HC, MDD and comorbid MDD-SAD groups, a more rigorous approach to control for potential difference in individual response speed involves using normalized RT. Specifically, for each participant and each condition, we divided the RT difference by the sum of the RT for the same-eye and different-eye condition using the following formula: $(RT_{different} - RT_{same})/(RT_{different} + RT_{same})$. The patterns of results remained qualitatively unchanged when applying the same ANOVA analysis (Facial Expression × Group interaction: $F(4,186) = 3.89$, $p = 0.005$, $\eta_p^2 = 0.077$), revealing a cross-group difference for the sad expression (MDD vs. HC: $p < 0.001$; MDD vs. comorbid MDD-SAD: $p < 0.001$; HC vs. comorbid MDD-SAD: $p = 0.502$), but not for other expressions ($ps > 0.097$).

3.3. Self-reported depression and social anxiety levels predicts the monocular advantage

One potential explanation for the group-level difference in monocular advantage is that the comorbid social anxiety counteracted the enhanced monocular advantage for sad expression in depressed individuals. To test this possibility, we concatenated data across three groups and conducted following correlation analyses to assess how the magnitude of monocular advantage covaried with self-reported severity of depression and social anxiety symptoms (Fig. 4).

Pearson correlation analyses showed a significant positive relationship between BDI scores and RT difference for sad expression ($r_{partial} = 0.350$, $p < 0.001$) after partialling out LSAS scores. By contrast, the analyses revealed significant negative relationships between LSAS scores and RT difference for both sad ($r_{partial} = -0.285$, $p = 0.006$) and angry expressions ($r_{partial} = -0.236$, $p = 0.024$) after partialling out BDI scores. None of the other analyses reached significance levels ($ps > 0.205$). These findings indicate that depressive symptom predicted enhanced monocular advantage in processing sad expressions, while social anxiety symptom predicted diminished monocular advantage in processing negative expressions. The contrasting correlations provide evidence of potential counteracting effects between co-occurring depression and social anxiety on early processing of sad faces.

4. Discussion

The aim of this study was to investigate the influence of depression, with and without comorbid social anxiety, on the early perceptual processing of facial emotions. Using a stereoscopic presentation of stimuli in a face discrimination task, we utilized the difference in behavioral responses between monocular and dichoptic presentation of emotional faces as indicators of early subcortical processing (Gabay et al., 2014; Almasi and Behrmann, 2021). We observed that MDD group exhibited a stronger monocular advantage for sad expression compared to neutral and angry expressions, whereas HC and comorbid MDD-SAD groups showed a stronger monocular advantage for neutral expression over negative expressions. This specificity for sad expression in MDD group was more pronounced compared to both HC and comorbid MDD-SAD groups, which could not be explained by mean response difference across groups. Furthermore, the self-reported depressive symptom was positively corrected with the monocular advantage for sad expressions, whereas social anxiety symptom was negatively correlated with this advantage for negative expressions. The increased monocular advantage in MDD group indicates stronger reliance on subcortical pathways for processing sadness-related information, while the coexistence of SAD may exert an opposing influence on this mechanism. Our findings underscore the importance to investigate abnormalities in the sensory mechanisms underlying depression, as the atypical response at early perceptual stage likely contributes to a variety of cognitive and emotional biases observed in depression.

To our knowledge, this study is the first to use monocular advantage to investigate atypical perceptual processing of emotional faces in depressed individuals. Research in the past few decades has primarily focused on cognitive bias towards emotional faces in MDD, such as attention, memory and interpretation biases (Gotlib and Joormann, 2010; Bourke et al., 2010; Gotlib et al., 2004; Leppänen et al., 2004; Suslow et al., 2020). Our findings expand the scope by highlighting atypical processing at early perceptual stage, likely originating from subcortical visual pathways. These pathways are thought to enable rapid face perception

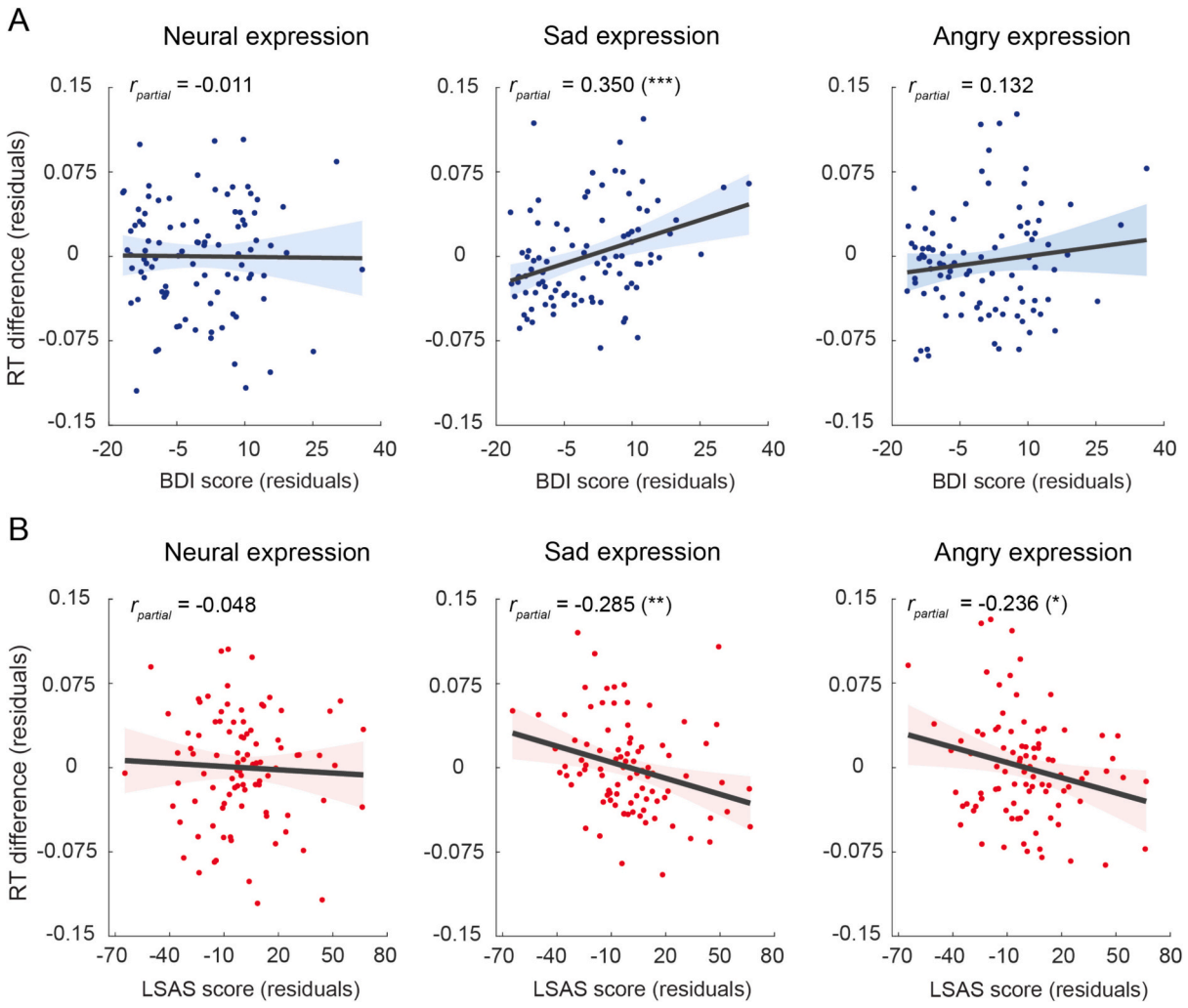

Fig. 4. (A) Partial correlation between the monocular advantage (RT difference for the same image) and BDI scores across groups (HC, MDD, comorbid MDD-SAD) for different Facial Expressions. (B) Partial correlation between the monocular advantage and LSAS scores across groups for different Facial Expressions. Each dot represents one subject's data. The asterisks represent the significance level * $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$.

during early processing (Garvert et al., 2014; Kragel et al., 2021), providing an alternative route for processing facial expressions, even when lesions are present in the primary visual cortex (Weiskrantz et al., 1974) and face-selective regions (Striemer et al., 2019). Subcortical structure in these pathways, such as pulvinar, is not only connected with many other subcortical sites but also exhibit reciprocal connections throughout the cortical areas. Thus, they could contribute to emotional face processing in emotional circuits (e.g., amygdala, insula), fusiform face gyrus, and frontal areas (Stuhrmann et al., 2011). Consistent with this account, the cognitive bias towards sadness-related information, as reported in previous studies (Gotlib and Joormann, 2010; Bourke et al., 2010; Gotlib et al., 2004; Leppänen et al., 2004; Suslow et al., 2020), may reflect early sensory changes as indexed by the heightened monocular advantage for sad expressions in MDD group.

Despite numerous studies on emotional face processing in individuals with depression (Stuhrmann et al., 2011) or social anxiety (Horley et al., 2003; Rozen and Aderka, 2023), few studies have directly compared the influences of depression with and without comorbid social anxiety. Our findings reveal differential patterns of monocular advantage between MDD and comorbid MDD-SAD group. Moreover, while BDI scores were positively correlated with monocular advantage for sad expression, LSAS scores were negatively correlated with both negative expressions. These results suggest that these two disorders may exert opposing influences on subcortical face processing when they co-occur, despite their similarities in causing social impairments in facial emotion processing (Joormann and Gotlib, 2006). This may seem counterintuitive; however, previous findings have implicated the opposing influences when MDD and SAD co-occur. For instance, cognitive bias towards specific emotions observed in individuals with SAD was absent in those with comorbid SAD and MDD (Grant and Beck, 2006). Comorbid MDD attenuates emotional startle responses in SAD (McTeague et al., 2009). Under certain conditions, the comorbid MDD-SAD group behaved similarly to healthy individuals (Musa et al., 2003), similar to our findings between HC and comorbid MDD-SAD groups. Electrophysiological and fMRI studies have demonstrated these opposite effects on neural activity (Bauer and MacNamara, 2021; Chen et al., 2023). Specifically, activation in dorsolateral frontal cortex (dlPFC), a crucial node for emotion processing and regulation (Ray and Zald, 2012), was positively associated with depression symptoms but negatively associated with anxiety symptoms (Chen et al., 2023). The increased dlPFC activity and decreased connectivity with amygdala in MDD may indicate impaired control of negativity processing (Jamieson et al., 2024), leading to an enhanced reliance on subcortical pathways for processing sad expressions. In contrast, the impact of SAD on dlPFC recruitment is inconsistent (Bruehl et al., 2014). While extensive studies demonstrated abnormalities of cortico-limbic circuitry in MDD and SAD (Stuhrmann et al., 2011; Bruehl et al., 2014), we speculate that comorbid MDD and SAD may exert more pronounced influence on cortical face processing

and potentially diminish reliance on subcortical pathways.

The task in our study offers a more implicit assessment of atypical processing of facial emotions compared to tasks requiring explicit judgment of emotional contents. Importantly, our analytic approach focused on the monocular difference (same eye vs. different eyes), of which participants were unaware. This ensured that the obtained results were not influenced by specific strategies or motivations during the task (e.g., attempts to conceal symptoms on self-reported scales). However, there are several limitations in the present study. First, our selection of emotional expressions was limited due to the constrained time available for clinical patients. Future studies should test a broader range of emotional expressions, including both positive and negative expressions, to more precisely characterize the patterns of monocular advantage across different types of emotions. Second, while the monocular advantage serves as an index for atypical subcortical involvement in face perception, we are unable to specify the exact structure in subcortical pathway. To our knowledge, a few fMRI studies have demonstrated eye-specific effects in the human LGN (Haynes et al., 2005; Qian et al., 2020), but neither study measured the monocular advantage. This may be due to the methodological challenges involved in measuring neural activities in these subcortical areas. Future studies should take advantage of the higher signal-to-noise ratio afforded by high resolution 7 T fMRI (Jia et al., 2021; Jia et al., 2024) to detect signals changes in candidate subcortical structures (e.g., superior colliculus, pulvinar and amygdala), in order to identify potential target regions for treatment.

Our findings have important clinical implications for real-world applications. First, the monocular advantage for emotional face processing may serve as an early indicator for diagnosing MDD and distinguishing between MDD with and without comorbid SAD. The mirror stereoscope is a portable and convenient device ideal for clinical assessments in hospitals. Even outside the clinical environments, red/green glasses – a common tool used for patients with amblyopia or strabismus – can simulate the effect of a mirror stereoscope. In this setup, the eye behind the green lens sees only the green stimuli, and the eye behind red lens sees only the red stimuli. Presenting paired faces in the same or different colors can create same-eye and different-eye conditions, as demonstrated in this study. By integrating this approach with an electronic application and red/green glasses, it could serve as a convenient test for broader populations. Second, investigating sensory mechanisms in MDD could pave the way for novel interventions targeting perceptual systems, expanding upon the limited clinical effects of cognitive bias modification in MDD (Koster and Hoorelbeke, 2015). For instance, MDD is associated with changes in gamma-aminobutyric acid (GABA) concentrations and/or ratio of excitatory-inhibitory neurotransmitter levels in occipital cortex (Petty, 1995; Sanacora et al., 2004). Behavioral tools like perceptual learning can induce changes in neurochemical processing (i.e., glutamate, GABA) within sensory areas (Frangou et al., 2019; Jia et al., 2022). Additionally, direct brain stimulation (i.e., tDCS) of the primary visual cortex, or indirect stimulation using cortical-subcortical functional connectivity to target subcortical structures, may alter GABA concentrations and/or the ratio of excitatory-inhibitory neurotransmitter levels (Bachtiar et al., 2015), potentially alleviating depressive symptoms.

In conclusion, this study demonstrated an enhanced monocular advantage for sad expressions in individuals with MDD, suggesting abnormalities in the sensory mechanisms underlying depression, likely involving subcortical visual pathways. The reduced monocular advantage in individuals with comorbid MDD and SAD suggests potentially counteracting mechanisms between these two disorders in the subcortical processing of facial emotions. Our findings point to the importance of the perceptual system in atypical facial emotion processing in depression.

CRediT authorship contribution statement

Qiaozhen Chen: Writing – review & editing, Resources, Project administration, Funding acquisition. **Chaoya Pan:** Software, Methodology, Investigation, Formal analysis. **Yuze Shen:** Resources, Investigation. **Qi Pan:** Resources, Investigation. **Qing Zhang:** Resources, Investigation. **Jun Wang:** Writing – review & editing. **Yuzheng Hu:** Writing – review & editing. **Han Xu:** Writing – review & editing, Funding acquisition. **Mengyuan Gong:** Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition, Formal analysis. **Ke Jia:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Funding acquisition.

Ethical statement

Ethical approval for this study was obtained from the Institutional Review Board at Department of Behavioral Sciences and Psychology, Zhejiang University (protocol number: 2022–06-063).

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Declaration of competing interest

All authors declare no conflict 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.2025.01.081.

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