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Reward processing disruption in anxiety: fMRI evidence of vulnerability to frustration non-reward

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Original Article

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Abstract

Background. Anxiety is a persistent trait that disrupts functioning and increases the risk of severe consequences, while reward processing has garnered attention in anxiety research. Here, we report a critical concern in reward processing among individuals with anxiety: although anxious individuals may show similar reward processing abilities as non-anxious individuals in typical environments, they are more vulnerable to disruptions in positive emotions caused by frustrative non-reward, leading to maladaptive reward processing patterns.

Methods. The functional magnetic resonance imaging (fMRI) was used in this study. A total of 66 participants were recruited for the experiment, with 33 in the high anxiety (HA) group and 33 in the low anxiety (LA) group. The simulation of frustrative non-reward was conducted during fMRI scanning.

Results. Under the low frustration condition, the HA group exhibited task accuracy comparable to the LA group and showed greater activation in visual processing regions (inferior occipital gyrus, superior occipital gyrus, angular gyrus) and cognitive control areas (precuneus, precentral gyrus) during attentional reorienting following frustration. However, in the high frustration condition, the HA group displayed significantly lower accuracy, with maladaptive information processing patterns observed in several brain regions associated with the cognitive-emotional control system (cuneus-precuneus, anterior cingulate cortex, precentral gyrus, inferior frontal gyrus, superior frontal gyrus, orbitofrontal cortex, and amygdala).

Conclusions. This demonstration of two contrasting processing patterns deepens the current understanding of reward processing in anxiety. It also holds significance for a broader understanding of the risk factors in cognitive processing among individuals with anxiety.

Introduction

Anxiety refers to an individual's tendency to experience negative emotional responses, such as feelings of tension and worry, in response to perceived threats or adverse environments (Elwood, Wolitzky-Taylor, & Olatunji, 2012). Anxiety, as a personality trait, is a relatively enduring tendency (Johnson & Spielberger, 1968) that may negatively impact daily functioning and occupational efforts (Eysenck, Moser, Derakshan, Hepsomali, & Allen, 2023) and, in severe cases, can lead to an increased risk of suicide (Niu et al., 2024). Therefore, a better understanding of the pathophysiology of anxiety is necessary to guide the development of new mechanism-based treatments for this common and debilitating problem.

Reward information serves as feedback that can enhance individuals' motivation or understanding of their performance (Lei et al., 2019; Lin et al., 2020). Previous research has established that deficits in reward processing are a key marker of depressive affective disorders characterized by anhedonia (Admon & Pizzagalli, 2015). However, although individuals with anxiety disorders exhibit motivational deficits and anhedonia similar to those observed in depression (Craske, Dunn, Meuret, Rizvi, & Taylor, 2024), they do not show marked maladaptive patterns in reward processing. Neumann, Glue, and Linscott (2021) found that individuals with anxiety demonstrate reward processing abilities comparable to those without anxiety during reward-related tasks. Additionally, studies using neural indicators suggest that, compared to non-anxious individuals, those with anxiety may exhibit greater activation in cognitive-related brain regions, such as the inferior orbitofrontal cortex (OFC) (Forbes et al., 2006), medial prefrontal cortex (mPFC) (Sequeira et al., 2021), right middle frontal gyrus (MFG) (Mikita et al., 2016), as well as heightened activation in emotion-related regions, such as the left amygdala (Forbes et al., 2006). These findings indicate that individuals with anxiety may experience rewards similarly or even more intensely than non-anxious individuals in typical environments.

However, some studies suggest that individuals with anxiety are prone to interruptions and reductions in positive emotions (Dias Lopes et al., 2020), which may further lead to abnormal cognitive processing (Frewen, Dozois, Joanisse, & Neufeld, 2008; Ouimet, Gawronski, & Dozois,

2009). Frustrative non-reward constitutes a prototypical affective disruption within reward processing mechanisms, defined as an aversive motivational property elicited by detected discrepancies between obtained and anticipated rewards (whether qualitative or quantitative in nature) (Papini et al., 2024). Davey, Yücel, and Allen (2008) pointed out that repeated failure or frustration in obtaining rewards may inhibit the brain's prefrontal reward system, a finding supported by Deveney (2019), who observed that such frustration leads to declines in task performance during reward processing. Silk, Davis, McMakin, Dahl, and Forbes (2012) proposed a theoretical model highlighting specific alterations in reward processing relevant to anxiety. Crucially, they argue that while anxious youth may possess an intact capacity for reward processing in non-threatening contexts, their reward seeking and responsiveness can be inhibited or disrupted, particularly in the face of frustrative non-reward or the anticipation of potential negative outcomes. This disruption manifests as maladaptive patterns, such as blunted responsiveness to actual reward receipt and/or altered sensitivity during reward anticipation (e.g. heightened monitoring of contingencies or outcomes). Collectively, these findings suggest a significant concern in reward processing among individuals with anxiety: while anxious individuals may show similar reward processing abilities as non-anxious individuals in typical environments, they may be more vulnerable to disruptions in positive emotions caused by frustrative non-reward, leading to maladaptive reward processing patterns. Should this concern be substantiated, it would not only advance our understanding of how anxiety as a negative emotional trait contributes to risk-related cognitive processes and shapes developmental trajectories of risk susceptibility, but also provide novel insights for anxiety interventions targeting reward processing. The aim of this study is to test this prediction.

In what follows, we employ functional magnetic resonance imaging (fMRI) to investigate neural mechanisms by using real-time frustration induction to simulate different levels of frustrative non-reward (i.e. low frustration and high frustration). This approach enables us to explore how frustrative non-reward, the specific disruption of positive affect caused by the omission of expected rewards, affects reward processing at the level of brain activity (Perlman et al., 2015). In the formal experiment, we utilize the affective Posner 2 paradigm (Lugo-Candelas, Flegenheimer, Harvey, & McDermott, 2017; Tseng et al., 2017) to simultaneously examine both the direct neural response to reward and the impact of reward on subsequent attentional orienting during tasks during the frustration task. These two cognitive processes have been shown to be distinct in fMRI studies (Ross et al., 2021; Tseng et al., 2019), allowing for a more comprehensive understanding of reward processing in individuals with anxiety.

Overall, our study used fMRI and simulated different levels of frustrative non-reward, systematically examining potential disruptions in reward processing in anxiety. Our research focuses on several key objectives: First, we aim to examine whether there are task performance differences in reward processing between high and low anxiety groups under frustrative conditions, using a high-low grouping method. Second, we investigate the neural mechanisms of reward processing under frustration in individuals with anxiety, specifically exploring the differences between high (HA) and low anxiety (LA) groups in (1) the direct neural response to reward and (2) the neural response to task-related attention following reward. Furthermore, previous research has indicated that individuals with anxiety may exhibit dissociable neural activity in response to different reward valences (Mikita et al., 2016). Therefore, we also examine the interaction between reward valence (gain/loss) and anxiety group.

Methods

Participants

This study was conducted in accordance with the principles outlined in the Helsinki Declaration and approved by the Sichuan Normal University's ethics committee. The Chinese version of the Self-Rating Anxiety Scale (SAS) was used to screen anxiety. This scale is widely used to assess anxiety symptoms in adults and serves as an effective and simple tool for both anxiety screening and evaluating the severity of anxiety (Zung, 1971). A total of 561 college students from Sichuan Normal University were screened, with participants scoring in the top 10% of the anxiety distribution assigned to the HA group, while those scoring in the bottom 10% were assigned to the LA group. The final experiment included 66 participants: 33 in the HA group (9 males, 24 females; mean age 19.70 ± 1.59 years) and 33 in the LA group (7 males, 26 females; mean age 20.18 ± 1.74 years). The SAS score for the HA group was 51 ± 5.71, and for the LA group, it was 24.97 ± 2.48. An independent samples t-test revealed a significant difference between the groups (t = 24.01, p < 0.001). All participants were right-handed, had normal vision or corrected vision, and none had a history of neurological disease. Additionally, we assessed participants' depression scores using the Beck Depression Inventory to facilitate subsequent covariate analysis related to depression. Informed consent was obtained from all participants before partaking in the experiment.

fMRI paradigm

Participants completed the modified Affective Posner 2 task (Ross et al., 2021; Tseng et al., 2019), which has been demonstrated to reliably and consistently induce frustrative non-reward (Tseng et al., 2017). During the experiment, each trial began with a fixation cross (1,000–5,000 ms), followed by the appearance of two white squares on the screen (each 4 cm × 4 cm, spaced 8 cm apart). Then, a blue square (cue, 3.2 cm × 3.2 cm) appeared randomly in one of the two white squares for 200 ms. Simultaneously with the disappearance of the white squares, a black square (target, 1.5 cm × 1.5 cm) appeared within one of the white squares for 1,260 ms. Participants were asked to identify the target by button press (left or right). After the button press, a blank screen appeared for 1,000–3,000 ms, followed by 2,000 ms of reward feedback: 'YOU WIN!', 'WRONG!', or 'TOO SLOW!' (Figure 1).

The blue square functioned as a cue, indicating the likely location of the upcoming target. The experiment included two types of trials: valid trials (75% of the trials, where the blue cue and black square appeared in the same position) and invalid trials (25% of the trials, where the cue and square appeared in opposite positions). This design aimed to encourage participants to strategically balance speed and accuracy: responding quickly based on the cue could enhance speed but increase errors on invalid trials, whereas waiting for the target could improve accuracy at the expense of slower reaction times (Ross et al., 2021; Tseng et al., 2019). The blue box in Figure 1 highlights the feedback phase of the 'N' portion, which was used to assess neural activity during processing of rigged feedback versus positive feedback. The red box denotes the attentional phase of the subsequent 'N + 1' portion, aimed at assessing

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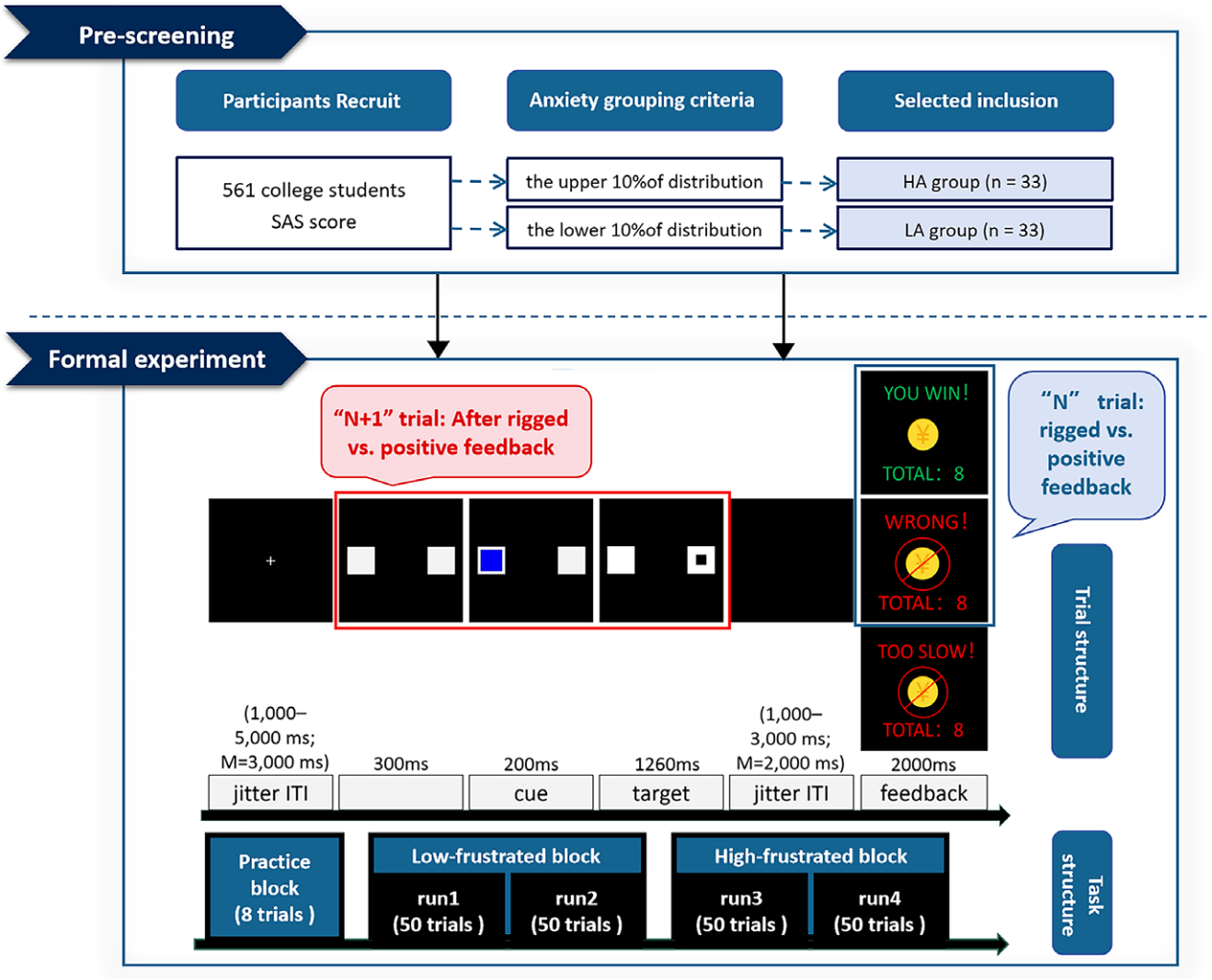

Figure 1. Experimental structure included pre-screening and formal experiment. In low-frustrated runs, 10% of correct responses were followed by rigged feedback ('TOO SLOW!'), and 90% of correct responses were followed by gain feedback ('YOU WIN!'). In high-frustrated runs, 60% of correct responses were followed by rigged feedback ('TOO SLOW!'), and 40% of correct responses were followed by gain feedback ('YOU WIN!'). All incorrect responses were followed by wrong feedback ('WRONG!'). Imaging analysis focused on the 'N' portion of the task (i.e. reward feedback, including gain feedback and rigged feedback) and the 'N + 1' portion (post-feedback attention events). Note: HA, high anxiety group; LA, low anxiety group; ITI, intertrial interval; SAS, Self-Rating Anxiety Scale.

neural responses during attentional processing following rigged feedback versus positive feedback.

The experiment consisted of a practice block (eight trials) and two formal experimental blocks (100 trials for each block) (Figure 1). During the practice block, participants were informed that they needed to respond correctly and would receive accurate feedback about their performance, that is 'YOU WIN!' or 'WRONG!'. Following the practice block, participants were instructed that the difficulty of the formal experiment would increase, necessitating both increased rapid and accurate responses to earn bonuses. Failure to respond within the system-specified timeframe was considered too slow, resulting in the loss of bonuses (inducing frustration, as participants were given the feedback 'TOO SLOW!' and lost bonuses regardless of their actual response speed). Participants then completed a low frustration block and a high frustration block (each consisting of two runs). In the low frustration block, they received gain feedback for 90% of correct trials and rigged feedback for 10% of correct trials. In the high frustration block, they received gain feedback for 40% of correct trials and rigged feedback for 60% of correct trials.

Procedure

Participants were remotely recruited by graduate/doctoral students from Chinese universities. Recruitment personnel posted study information online, and interested participants left their contact details. The research team then contacted the participants to screen their SAS scores. Eligible participants were subsequently invited to join the formal experiment.

Upon arriving at the laboratory, participants were briefly introduced to the basic information and rules of the experiment to ensure their understanding and informed consent. Subsequently, participants completed a magnetic resonance imaging (MRI) safety screening form and provided basic demographic information, including gender, age, handedness, and vision/health status. They then proceeded into the MRI scanner room to join the experiment.

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In the MRI scanner room, participants first completed the practice block, and once they achieved 100% accuracy on the practice block (to ensure they fully understood the task instructions), they proceeded to the formal experiment. After completing the practice block and each formal task block, participants were asked to rate their experience level of frustration on a 9-point Likert scale as a measure of self-reported frustration, where 1 represented 'no frustrating', 5 represented 'middle', and 9 represented 'extremely frustrating.'

Imaging acquisition

Neuroimaging data were acquired on a 3-T MRI scanner (Tim Trio, Siemens). Anatomical images were acquired using a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence, repetition time (TR) = 2530 ms; echo time (TE) = 2.98 ms, resolution matrix = 64 × 64, axial slices = 192, slice thickness = 1.0 mm, flip angle = 7°, field of view (FOV) = 256 mm × 256 mm, and voxel size = 0.5 × 0.5 × 1 mm^3. Functional images were acquired by T2∗-weighted gradient-echo echo-planar imaging, TR = 2,000 ms, TE = 30 ms, axial slices = 62, slices thickness = 2 mm, resolution matrix = 64 × 64, flip angle = 90°, FOV = 224 mm × 224 mm, and voxel size = 2.0 × 2.0 × 2.0 mm^3.

Data analyses

Neuroimaging preprocessing was conducted using the Data Processing & Analysis of Brain Imaging (DPABI_V8.0_231111; http://restfmri.net/forum/DPABI) toolbox (Yan, Wang, Zuo, & Zang, 2016), which is based on Statistical Parametric Mapping (SPM12, Welcome Department of Imaging Neuroscience, London, UK; http://www.fl.ion.ucl.ac.uk/spm). Imaging data were converted to NIFTI format and then were slice timing corrected by shifting the signal measured in each slice relative to the acquisition of the slice at the mid-point of each TR. Next, realignment correction was performed, with the maximum head translation was −3 to 3 mm, and the head rotation was −3 to 3°. After realignment, each participant's T1 structural image was used as a reference to segment their functional images into gray matter, white matter, and cerebral effusion. The functional images were then registered to the Montreal Neurological Institute (MNI) standard space (bounding box = [−90–126 -72; 90 90 108], voxel size = 3.0 × 3.0 × 3.0 mm^3). Finally, all the standard MNI space functional images were smoothed using a 6-mm full-width at half-maximum Gaussian kernel. Preprocessed data were saved in the NIFTI format, with a total of 192 volumes for the T1 structural image and 225 volumes for each run of the functional images (450 volumes for each block).

To investigate the specific neural mechanisms involved, each trial of the frustrative non-reward task was segmented into the reward feedback portion ('N' portion, 2,000 ms throughout the feedback) and the attention portion following the reward ('N + 1' portion, 1,760 ms, from the appearance of the two white squares until the target disappearance) to explore the direct neural response to frustration and the effects of reward on attentional orientation in anxiety. Only valid, correct trials were included in imaging analyses, excluding all wrong/invalid trials due to their insufficient numbers. Therefore, the imaging results for the 'N' portion reflect a direct comparison between different types of feedback – expected positive feedback versus unexpected rigged feedback – based solely on valid and correct trials. Similarly, the imaging results for the 'N + 1' attentional portion were derived from valid and correct trials that followed either expected positive feedback or unexpected rigged feedback. This approach was intended to minimize variability arising from processes unrelated to frustration, thereby isolating neural correlations of frustration while minimizing confounding effects from task performance or cue validity.

We conducted whole-brain analyses at the group level. To address the fundamental difference in baseline frustration levels between conditions (where the high frustration baseline may already be saturated with frustrative non-reward, as noted by Tseng et al., 2019), we followed the approach established by Tseng et al. (2019). Specifically, we refrained from direct comparisons between the low and high frustration blocks and instead, mirroring their analytical strategy, conducted separate whole-brain analyses for the 'N' portion and 'N + 1' portion within each frustration block (low and high). Additionally, to ensure that our results were not driven by inconsistencies in baseline activity, we also compared group-level baseline conditions under each block. No significant group differences were observed in any brain region. In the formal analysis, we first used the Flexible factorial F test to examine the interaction effect. For the 'N' portion, a 2 (group: HA/LA) × 2 (feedback: gain/rigged) mixed analysis was conducted. For the 'N + 1' portion, a 2 (group: HA/LA) × 2 (attention: post-gain attention orientation/post-rigged attention orientation) mixed analysis was performed. Then we used 2-sample t-tests to examine the main group effect, that is average feedback portion contrast for the 'N' portion in the low frustration block and high frustration block, average attention portion contrast for the 'N + 1' portion in the low frustration block and high frustration block. The resulting clusters were considered statistically significant if they exceeded a false discovery rate corrected (FDR-corrected) $p < 0.05$ at peak level ($k > 10$).

Additionally, given the strong association between anxiety and amygdala activation (Anand & Shekhar, 2003; Rauch, Shin, & Wright, 2003; Zugman, Jett, Antonacci, Winkler, & Pine, 2023), we conducted regions-of-interest (ROI) analysis of the bilateral amygdala in each condition. The bilateral amygdala ROI was defined using the Automated Anatomical Labeling regions (Lancaster et al., 1997) provided in the Wake Forest U PickAtlas Toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003) extension in SPM12. Each of the ROI area signals changed value (% signal change) was calculated by Marsbar.

E-Prime 2.0 was used to collect participant responses in the experiment. SPSS 25.0 (IBM, New York, NY) was used for statistical analyses. Self-reported frustration results were analyzed using a 2 (group: HA, LA) × 3 (frustrating condition: baseline after practice, low frustration, high frustration) mixed-design ANOVA. Accuracy and reaction time results were analyzed using a 2 (group: HA, LA) × 2 (frustrating condition: low frustration, high frustration) mixed-design ANOVA. Reaction times were analyzed only for the correct trial. To further investigate whether feedback ('N') or attention portion ('N + 1') activations between groups were associated with affective rating or task performance (reaction time and accuracy), we conducted Pearson correlation analyses between neural signal change values across all imaging results and participants' self-reported frustration/reaction time/accuracy. Additionally, to rule out the potential confounding effects of task performance and depression (an affective disorder associated with abnormal reward processing) on neural activation patterns, we performed covariate analyses using reaction time, accuracy, and depression scores as covariates. The Greenhouse–Geisser correction was used to correct for degrees of freedom when the Mauchly test indicated a violation of the spherical hypothesis. Bonferroni correction was used for multiple comparisons.

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Results

Behavior data

Self-reported frustration

Figure 2A presents the results of the self-reported frustration. A Group × Condition ANOVA for self-reported frustration revealed main effects of the Group [$F(1, 64) = 25.44$, $p < 0.001$, $\eta_p^2 = 0.28$] and the Condition [$F(2, 119.25) = 235.84$, $p < 0.001$, $\eta_p^2 = 0.79$], as well as Group × Condition interaction [$F(2, 119.25) = 8.68$, $p < 0.001$, $\eta_p^2 = 0.12$]. Follow-up analyses of the interaction showed that there was no significant difference in self-reported frustration between HA and LA groups at baseline after practice ($p = 0.286$). However, the HA group reported significantly higher frustration compared to the LA group under low frustration ($p < 0.001$) and high frustration conditions ($p < 0.001$).

Accuracy

Figure 2B presents the results of the accuracy. A Group × Condition ANOVA for accuracy showed the main effect of the Condition [$F(1, 64) = 166.80$, $p < 0.001$, $\eta_p^2 = 0.72$] and Group × Condition interaction [$F(1, 64) = 4.17$, $p = 0.045$, $\eta_p^2 = 0.06$]. Follow-up analyses of the interaction indicated that in the low frustration condition, there was no significant difference in accuracy between HA and LA groups ($p = 0.283$). However, under the high frustration condition, the HA group showed significantly lower accuracy compared to the LA group ($p = 0.041$). The main effect of the group was not significant [$F(1, 64) = 3.68$, $p = 0.060$, $\eta_p^2 = 0.05$].

Reaction time

Figure 2C presents the results of the reaction time. A Group × Condition ANOVA revealed the main effect of the Condition [$F(1, 64) = 140.86$, $p < 0.001$, $\eta_p^2 = 0.69$], showing that reaction time under the high frustration condition was significantly shorter than under the low frustration condition. The main effect of the Group [$F(1, 64) = 1.24$, $p = 0.271$, $\eta_p^2 = 0.02$] and Group × Condition interaction [$F(1, 64) = 0.58$, $p = 0.450$, $\eta_p^2 = 0.01$] were not significant.

Imaging data

Whole-brain activation in 'N + 1' portion

During the low frustration phase, the results of the whole brain analysis showed significant main effects of Group in 'N + 1' portion (Table 1). Compared to the LA group, the HA group exhibited higher activation levels in the bilateral lingual gyrus (LG), right superior occipital gyrus (SOG), right precuneus, right cerebellar, and right precentral gyrus (PG) (Figure 3). No significant Group × Attention interaction effects were found.

Pearson correlation analyses revealed that activation in the right precuneus-rigged ($r = -0.28$, $p = 0.025$) was significantly correlated with participants' self-reported frustration. No significant associations between activation levels and reaction time or accuracy ($ps > 0.05$, Supplementary Table S1). The covariate analysis controlling for depression, reaction time and accuracy revealed that only the right precuneus showed a change from significance to non-significance ($p = 0.067$), whereas all other brain regions remained statistically significant ($ps < 0.05$).

During the high frustration phase, no significant main effect of Group or Group × Attention interaction was found in 'N + 1' portion.

Whole-brain activation in 'N' portion

During the low frustration phase, no significant main effect of Group or Group × Feedback interaction was found in 'N' portion.

During the high frustration phase, we found significant Group × Feedback interaction effects in left cuneus, right precuneus, right posterior orbitofrontal cortex (OFCpost), left inferior frontal gyrus (IFG), left superior frontal gyrus (SFG), bilateral middle occipital gyrus (MOG), left middle temporal gyrus (MTG), right superior temporal gyrus (STG), left rolandic operculum (RO), right anterior cingulate cortex (ACC), right cerebellar, and right PG (Table 2; Figure 4A). To further observe the trend of the interactions, the blood-oxygen-level-dependent percent signal change for these clusters were extracted for each participant and plotted (Figure 4B). It was found that compared to the LA group, the HA group showed lower activation in these brain regions when processing gain feedback; conversely, the HA group showered higher activation in these regions when processing rigged feedback.

Pearson correlation analyses for the interaction effects revealed that activation in the left cuneus-rigged ($r = 0.28$, $p = 0.023$), right precuneus-rigged ($r = 0.41$, $p = 0.001$), right OFCpost-rigged ($r = 0.27$, $p = 0.026$), left IFG-rigged ($r = 0.32$, $p = 0.008$), left SFG-rigged ($r = 0.24$, $p = 0.048$), left MOG-rigged ($r = 0.31$, $p = 0.011$), left MTG-rigged ($r = 0.34$, $p = 0.006$), right STG-rigged ($r = 0.35$, $p = 0.005$), right ACC-rigged ($r = 0.34$, $p = 0.006$), right cerebellar ($r = 0.37$, $p = 0.002$), right PG-rigged ($r = 0.28$, $p = 0.021$) was significantly correlated with participants' self-reported frustration. Activation in the left cuneus-gain ($r = 0.25$, $p = 0.044$), left MOG-rigged ($r = -0.28$, $p = 0.23$), right cerebellar-rigged ($r = -0.28$, $p = 0.021$), right PG-rigged ($r = -0.27$, $p = 0.028$) was significantly correlated with participants' accuracy. Activation in the left MOG-rigged ($r = -0.31$, p = 0.011) and right PG-rigged ($r = -0.27$, $p = 0.031$) was significantly correlated with participants'

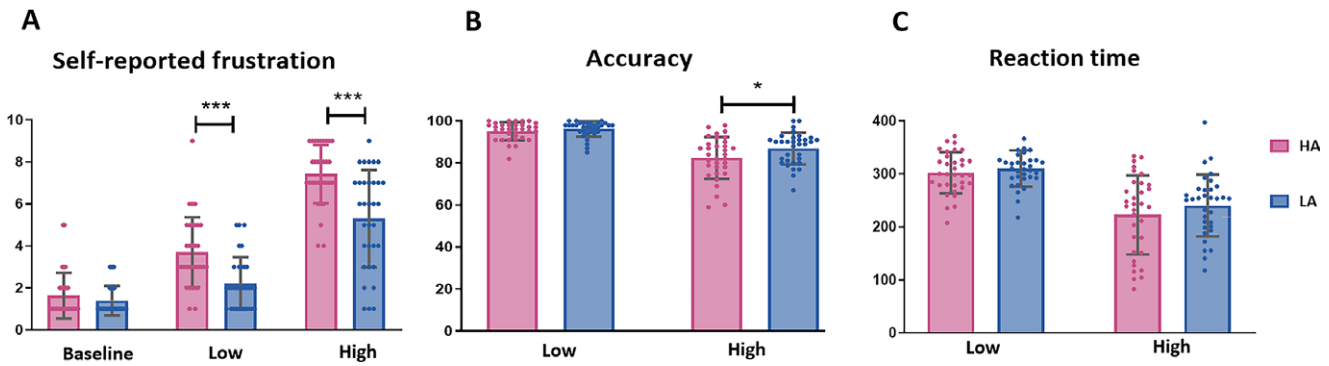

Figure 2. Results of self-reported frustration, accuracy, and reaction time, including individual data. The error bars represent SDs. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Note: Baseline, baseline after practice; HA, high anxiety group; High, high frustration; Low, low frustration; LA, low anxiety group.

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Table 1. 'N + 1' portion during the low frustration phase: The main effects of Group (HA versus LA) from whole-brain activation analysis

Region	Cerebral hemisphere	*k*	Peak MNI coordinates			*t*	$p_{FDR\text{-}corr}$
			X	*Y*	*Z*		
Lingual gyrus	R	124	18	−90	−18	4.24	0.008
Lingual gyrus	L	1,064	9	−54	−6	5.36	0.004
Superior occipital gyrus	R	13	21	−93	3	3.47	0.026
Superior occipital gyrus	R	42	21	−75	15	3.89	0.013
Precuneus	R	81	6	−63	54	3.96	0.012
Cerebellar	R	44	3	−57	−57	4.07	0.010
Precentral gyrus	R	18	15	−27	72	3.71	0.018

Note: L, left hemisphere; R, right hemisphere; *t*, t-test. false discovery rate corrected (FDR-corrected) $p < 0.05$ at the peak level ($k > 10$).

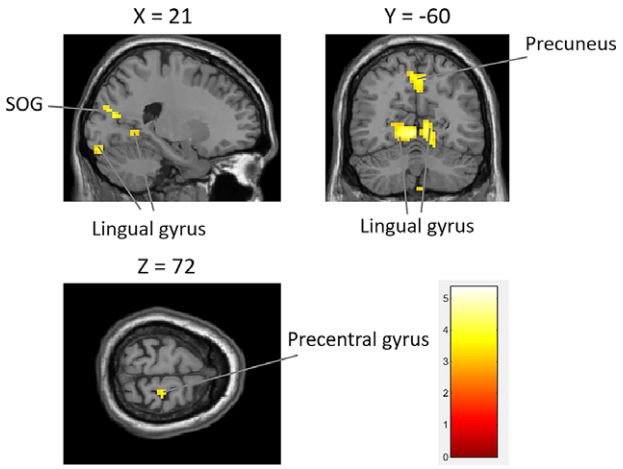

Figure 3. Partial main effects of Group in whole-brain activation. Significant between-group differences (HA > LA) are observed in brain region-related activities during the 'N + 1' portion of the low frustration phase. Note: SOG, superior occipital gyrus.

reaction time (Supplementary Table S2). Covariate analyses controlling for depression, reaction time, and accuracy revealed that all previously significant brain activations remained statistically significant ($ps < 0.05$).

ROI activation

The ROI analysis of the bilateral amygdala reveals a significant Group × Feedback interaction during the high frustration phase in the 'N' portion [$F(1, 64) = 4.36$, $p = 0.041$, $\eta_p^2 = 0.06$]. Follow-up analyses of the interaction indicated that there was no significant difference in activation levels between the HA and LA groups for gain feedback; however, the HA group showed significantly higher activation levels for rigged feedback compared to the LA group (Figure 5). The main effect of the Group is not significant [$F(1, 64) = 2.13$, $p = 0.150$, $\eta_p^2 = 0.03$].

Pearson correlation analyses revealed that activation in bilateral amygdala-rigged was significantly correlated with participants' self-reported frustration ($r = 0.25$, $p = 0.042$). No significant associations between signal changes in the bilateral amygdala and reaction time or accuracy ($ps > 0.05$, Supplementary Table S3). Covariate analyses controlling for depression, reaction time and accuracy showed that the interaction in the bilateral amygdala remained statistically significant ($p = 0.004$).

During the 'N + 1' portion of the high frustration phase, as well as in the 'N' and 'N + 1' portions of the low frustration phase, both the main effect of the Group and the Group × Feedback interaction was not significant ($ps > 0.05$).

Discussion

Anxiety, as a persistent negative emotional disorder, has garnered significant attention regarding its underlying cognitive mechanisms (Lisk, Vaswani, Linetzky, Bar-Haim, & Lau, 2020; Moran, 2016). Abnormal reward processing is closely linked to various affective disorders, such as anhedonia and depression (Admon & Pizzagalli, 2015), and has also been widely studied within anxious populations (Craske et al., 2024). Our study reveals a critical concern in reward processing among individuals with anxiety: they tend to be more susceptible to frustrative non-reward, leading to disrupted reward processing, with contrasting behavioral and neural processing mechanisms observed under low and high frustration conditions. Further discussion will focus on the research objectives outlined in the introduction.

Behavioral data from the condition results indicate that as frustration level increases, participants' self-reported frustration rises, accuracy declines, and reaction times speed up, confirming the effectiveness of the frustration manipulation. Nevertheless, interpretations of these results should be made with caution. According to Amsel and Roussel (1952), frustration can serve as a motivational state that significantly enhances subsequent behavioral responses. Thus, the observed differences between low and high frustration conditions may not solely reflect an 'emotional frustration' effect but could also be attributed to a 'response invigoration' effect triggered by reward omission. Future studies are necessary to dissociate these mechanistic interpretations.

Further between-group analyses reveal that, compared to low anxiety participants, high anxiety participants report greater frustration in frustrative non-reward situations, experimentally demonstrating that highly anxious individuals are more prone to experiencing negative emotions due to interruptions in positive emotions (Carl, Fairholme, Gallagher, Thompson-Hollands, & Barlow, 2014; Young, Sandman, & Craske, 2019). In addition, as frustration levels escalate (i.e. during the high-frustration condition), this maladaptation extends to their behavior, with a significant decline in task performance (evidenced by lower accuracy). This finding supports concerns about reward processing in anxiety from a behavioral perspective: although HA individuals may exhibit reward processing abilities comparable to those of LA individuals in relatively gentle environments, they may struggle to maintain coordinated brain cognitive function in more challenging

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Table 2. 'N' portion during the high frustration phase: The Group × Feedback interaction effects from whole-brain activation analysis

Region	Cerebral hemisphere	*k*	Peak MNI coordinates			*F*	$p_{FDR\text{-}corr}$
			X	*Y*	*Z*		
Cuneus	L	1647	−6	−78	24	55.36	< 0.001
Precuneus	R	83	9	−39	51	18.01	0.004
Posterior orbitofrontal cortex	R	12	36	21	−15	15.71	0.008
Inferior frontal gyrus	L	42	−45	18	−12	16.58	0.006
Inferior frontal gyrus	L	26	−42	24	6	18.89	0.003
Superior frontal gyrus	L	17	−6	57	−9	14.92	0.011
Superior frontal gyrus	L	31	0	51	21	14.33	0.013
Middle occipital gyrus	L	138	−42	−75	6	29.81	< 0.001
Middle occipital gyrus	R	11	33	−78	12	15.56	0.009
Middle temporal gyrus	L	33	−54	12	−30	17.66	0.005
Middle temporal gyrus	L	63	−45	−27	−3	27.26	< 0.001
Superior temporal gyrus	R	43	51	−21	−3	21.60	0.002
Rolandic operculum	L	22	−36	−33	15	16.72	0.006
Anterior cingulate cortex	R	22	3	21	21	15.07	0.010
Cerebellar	R	16	27	−57	−33	15.50	0.009
Precentral gyrus	R	12	42	−9	48	15.78	0.008

Note: L, left hemisphere; R, right hemisphere; *F*, F-test. False Discovery Rate corrected (FDR-corrected) $p < 0.05$ at the peak level ($k > 10$).

settings with positive emotional interruptions (Chen, Duan, Kan, Qi, & Hu, 2020; Li et al., 2020; Liu et al., 2022), thereby impairing their performance. No significant group differences were found in reaction times. This may be attributable to two factors: (1) the high-frustration condition was relatively challenge, possibly leading to a ceiling effect in reaction times that masked group differences; and (2) the task was performed inside the MRI scanner, where participants responded while lying down using button boxes – a response mode that differs from typical keyboard-based responses at a computer (Koten, Langner, Wood, & Willmes, 2013). Individual differences in adapting to this posture and response format may have further obscured any group-level differences in reaction times.

The imaging results reveal that, compared to LA participants, HA participants exhibit greater activation during the low-frustrated attentional orientation portion ('N + 1') in visual processing regions (the LG and the SOG) (Ceh et al., 2021; Iidaka, Yamashita, Kashikura, & Yonekura, 2004; Yang, Deng, Xing, Xia, & Li, 2015) as well as in cognitive integration and control areas, including the precuneus (Cavanna & Trimble, 2006; Dadario & Sughrue, 2023) and the PG (Jin et al., 2022). Hahn, Ross, and Stein (2006) suggested that this occipital lobe-precuneus-PG activation network constituted a top-down system for controlling spatial selective attention. Thus, our findings confirm previous research on reward processing in anxiety for relatively gentle conditions (Morris & Rottenberg, 2015; Reilly et al., 2020), indicating that high anxiety individuals exhibit heightened sensitivity, with greater activation in the top-down attentional control system to allocate selective attentional resources more effectively.

However, in the subsequent high-frustration phase, an intriguing opposite pattern emerged: a significant Group × Feedback interaction was observed in the 'N' portion, involving sensory processing areas (occipital and temporal lobes) (Jagiellowicz et al., 2011), higher cognitive processing areas (SFG, IFG, cuneus-precuneus, and PG) (Dadario & Sughrue, 2023; Tagliaferri, Giampiccolo, Parmigiani, Avesani, & Cattaneo, 2023; Yousry, 1997), reward-sensitive region like the ACC (Sallet et al., 2007; Yu, Zhou, & Zhou, 2011), and reward-emotional control region OFC (Rolls, Cheng, & Feng, 2020). HA participants displayed maladaptive responses to gain–loss reward information, characterized by reduced activation in these brain areas during gain feedback processing, indicating insufficient engagement. Conversely, during loss-feedback processing, these areas showed heightened activation, suggesting overprocessing of lost information. Further ROI results revealed that this cognitive processing was also closely related to amygdala activity, which is also responsible for emotional regulation (Barreiros, Almeida, Baía, & Castelo-Branco, 2019). Collectively, these results, from a neuroimaging perspective, highlight the impact of frustrative non-reward on reward processing in anxiety, driven by the coordinated involvement of an emotional-cognitive control network (Ferri, Schmidt, Hajcak, & Canli, 2016; Morawetz, Bode, Baudewig, & Heekeren, 2017). Notably, amygdala activation was significant only during the high-frustration phase, indicating that high anxiety individuals may experience maladaptive information processing when positive emotions are disrupted, potentially due to abnormal emotion regulation (Cho, White, Yang, & Soto, 2019; Young et al., 2019). Under challenging high-frustration conditions, HA individuals may struggle to adopt appropriate emotion regulation strategies (Pan, Wang, & Li, 2019), impairing their ability to integrate and coordinate cognitive resources (Cisler & Koster, 2010). This difficulty in shifting cognitive resources from loss information to gain information might lead to maladaptive reward processing. Additionally, we observed that the brain regions exhibiting interaction effects overlapped with areas within the default mode network (DMN) active during resting-state (including the visual cortex, precuneus, and prefrontal cortex) (Fair et al., 2008; Raichle et al., 2001), suggesting potential similarities in neural mechanisms. Notably, Raichle et al. (2001) have emphasized

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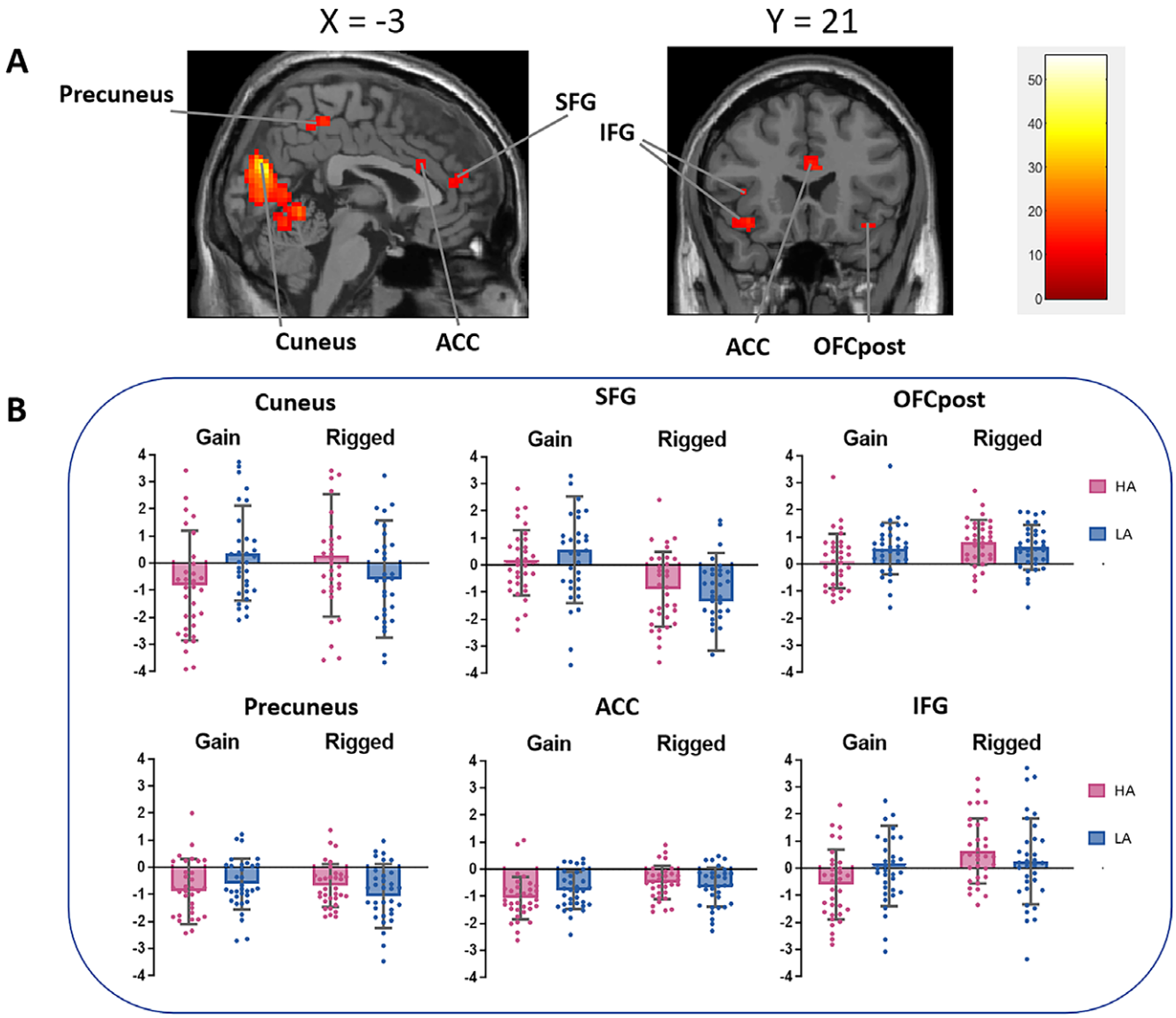

Figure 4. (A) Partial Group × Feedback interaction effects in whole-brain activation. Significant Group × Feedback interaction effects are found in brain region-related activities during the 'N' portion of the high frustration phase. (B) To further observe the trends of the interactions, the blood-oxygen-level-dependent percent signal change for these clusters were extracted for each participant. The differences in these values between the HA group and LA group for gain and rigged feedback were plotted. The error bars represent SDs. To avoid overstating significance, as these values were computed based on extracted signal change from voxels that survived whole-brain correction, we did no conducted the further statistical analysis. Note: ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; OFCpost, posterior orbitofrontal cortex; SFG, superior frontal gyrus.

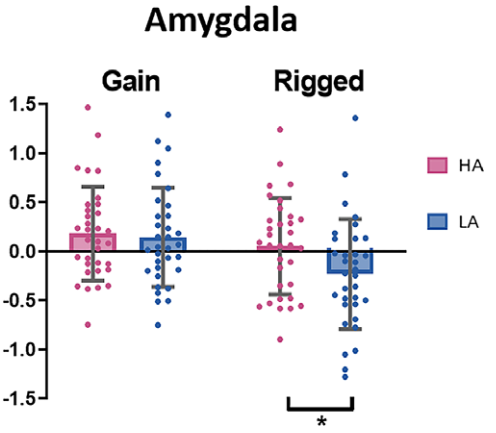

Figure 5. The ROI results for the bilateral amygdala during the high frustration phase 'N' portion. The error bars represent SDs. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Note: HA, high anxiety group; LA, low anxiety group.

that such DMN activity is typically suspended during the specific goal-directed task. This implies that the Group × Feedback interaction under the high-frustration condition might be associated with DMN disinhibition. To further investigate this, we compared our task-induced activation patterns with previous findings of anxiety-related DMN regions (Coutinho et al., 2016), revealing spatial overlap solely in the left middle temporal gyrus. This dissociation demonstrates that the differential activation patterns associated with the anxiety-related Group × Feedback interaction are indeed driven by task manipulation rather than pre-existing resting-state DMN configurations. Collectively, these findings delineate a promising research direction for future research – linking task-state anxiety effects with DMN disinhibition, which warrants further exploration.

Pearson correlation analysis between imaging results and self-reported frustration levels revealed that during the low-frustrated 'N + 1' portion, a significant correlation with participants' subjective reports was observed only in the right precuneus for the rigged condition. In contrast, during the high-frustrated 'N' portion, the

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vast majority of activated brain regions (only except for the right middle occipital gyrus and the left Rolandic operculum) for the rigged condition exhibited significant positive correlations with self-reported frustration. These findings not only validate the effectiveness of the frustration induction manipulation but also demonstrate consistency between subjective reports and neural activity, indicating that higher levels of self-reported frustration were associated with stronger activation across multiple brain regions. Pearson correlation analyses between imaging results and task performance revealed no significant associations of activated brain regions (identified through whole-brain analysis) with either accuracy rates or reaction times in the low-frustrated 'N + 1' portion. These findings suggest that the observed group differences in neural activation were unlikely to be driven by performance variability. In the high-frustrated 'N' portion, correlations within regions exhibiting a significant Group × Feedback interaction revealed that only areas involved in visual information processing (precuneus–visual cortex–cerebellum) (Vanni, Tanskanen, Seppä, Uutela, & Hari, 2001; Wei et al., 2023) and motor control (PG) (Banker & Tadi, 2019) related to button-press responses were significantly linked to task performance. Activation in regions subserving emotional and reward processing (amygdala, OFC, and ACC) and other higher cognitive processing areas (SFG and IFG) showed no relationship with performance, suggesting that these activations were more directly driven by anxiety rather than by task behavior.

The covariate analyses further supported this conclusion: after controlling for reaction time, accuracy, and depression scores, the group difference in the low-frustration 'N + 1' portion became non-significant only in the precuneus (a region previously established in Zhang, Chang, Guo, Zhang, & Wang, 2013 as being associated with abnormal monetary reward processing in depression), demonstrating that the anxiety-related effects observed in this study are distinct from depression. Previous studies have identified dysfunction in reward circuitry (primarily involving the ventromedial prefrontal cortex and striatum) (Pujara, Philippi, Motzkin, Baskaya, & Koenigs, 2016) during frustrative non-reward processing in depression (Harlé, Ho, Connolly, Simmons, & Yang, 2023). In contrast, the reward-anxiety circuitry revealed in our study incorporates critical affective circuitry components, specifically the amygdala-prefrontal-OFC. Converging with these findings, He et al. (2019) demonstrated that functional connectivity between the amygdala and prefrontal, temporal, and orbitofrontal cortices partially mediates the effect of anxiety on depression severity. Integrative analysis of these results suggests that aberrant amygdala activity during reward processing may serve as a key neurobiological marker differentiating anxiety-related disorders from depression, which provides novel insights into the potential developmental trajectory from anxiety to depression.

Aberrant neural activation during frustrative non-reward paradigms has been established as a critical biomarker in emotional dysregulation disorders such as irritability and bipolar disorder (Deveney, 2019; Rich et al., 2005). Previous investigations revealed neural signatures across these populations: (1) under the high-frustration 'N' portion-rigged condition, bipolar disorder patients exhibited heightened activation in the SFG but reduced insular engagement compared to controls (Rich et al., 2011), whereas irritable individuals showed diminished activation in affect-processing regions (amygdala and striatum) and attention-related networks (parietal cortex and posterior cingulate cortex) (Deveney et al., 2013). (2) In high-frustration 'N + 1' attentional portion, bipolar disorder patients displayed more negative amygdala-cerebellar functional connectivity compared to controls (Ross et al., 2021), while irritability correlated positively with frontal-striatal activation patterns, particularly in the dorsolateral prefrontal cortex, IFG, and caudate (Tseng et al., 2019). In contrast, our anxiety-focused study identified: (1) a significant anxiety × feedback valence interaction during high-frustration 'N' portion, highlighting deficient positive feedback processing in anxious individuals. (2) Anxiety-related group differences localized to low-frustration conditions during 'N + 1' portion, with no significant effects under high frustration. Collectively, these results reveal anxiety's unique neural signature in frustrative non-reward: insufficient reward feedback processing ('N + 1' portion) during high frustration rather than attentional dysregulation ('N + 1' portion). This suggests that the core pathophysiology of anxiety centers on maladaptive responses triggered by distorted reward expectation, rather than the prefrontal-limbic regulatory dysfunction seen in bipolar disorder or the attentional resource allocation deficits characteristic of irritability. This provides important neurobiological evidence for the differential diagnosis of emotional disorders.

Overall, our study confirms concerns about disrupted reward processing in anxiety, identifying two contrasting behavioral and neural patterns in reward processing under low- and high-frustrated non-reward conditions. However, several limitations should be noted. First, although HA participants reported significantly more negative emotional experiences in the low-frustrated condition compared to LA participants, no significant amygdala activation differences were observed in the imaging data. This may be due to the amygdala's heightened sensitivity to loss aversion (De Martino, Camerer, & Adolphs, 2010; Sokol-Hessner, Camerer, & Phelps, 2013), and the few loss trials under the low-frustrated condition may not have been sufficient to detect this activation. Future studies should consider incorporating more trials to better assess amygdala involvement. Second, our study only investigated reward processing in anxiety under low- and high-frustrated conditions, which may not capture the full range of frustrative non-reward scenarios. Third, the covariate analyses were limited to depressive symptoms and did not include scores from other potential emotional disorders. Finally, although our experiment included incorrect and invalid trials, their limited number led to their exclusion from analysis. We encourage future research to further investigate the underlying mechanisms of these trial types.

Despite these limitations, our study is the first to utilize fMRI technology to simulate frustrative non-reward, providing a thorough examination of reward processing in anxious individuals, and offering critical behavioral and neural evidence for their patterns of risk perception. To extend our findings and generalize to broader populations, we recommend several avenues for future research. First, future studies could consider frustrative non-reward as a key variable or intervention target in anxiety research. Second, an increased number of trials can be employed (e.g. graded frustration levels, post-high-frustration low-frustration conditions) to simulate a broader range of frustrative non-reward conditions and to explore the neural mechanisms underlying different trial types (e.g. invalid or incorrect trials). Third, incorporate multi-dimensional emotional disorder assessments to disentangle disorder-specific neural activation patterns. Fourth, we recommend further exploration of the impact of other forms of positive emotion disruption on this cognitive process to achieve a more comprehensive understanding of disrupted reward processing in anxiety. Additionally, future studies could expand the sample size (e.g. to include adolescent or older adult populations) and incorporate additional reward-processing-related factors, such as intelligence assessments, processing speed, and perfectionism, to achieve a more comprehensive understanding of this cognitive process in anxious populations.

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Conclusions

Our study confirmed concerns about disrupted reward processing in anxiety, identifying two contrasting patterns of behavioral and neural mechanisms. Under the low frustrative non-reward condition, the HA group exhibited task performance comparable to the LA group and even showed greater activation in visual and cognitive-related brain regions during the attentional processing phase of the task. However, under the high frustrative non-reward condition, the HA group demonstrated significantly poorer task performance, with a range of brain regions involved in the emotion-cognitive control system showing maladaptive information processing. These results deepen our understanding of the risk factors in cognitive processes among individuals with anxiety. Future research could further explore cognitive interventions targeting frustrative non-reward in anxious individuals to enhance our understanding of their manifestations, preventions, and interventions.

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Competing interests. The authors declare no competing financial or academic interest.

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