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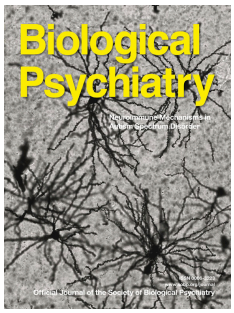

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Anxiety and stress alter decision-making dynamics and causal amygdala-dorsolateral prefrontal cortex circuits during emotion regulation in children

Short title: Anxiety and stress alter emotion dynamics and circuits

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Abstract

Background: Anxiety and stress reactivity are risk factors for the development of affective disorders. However, the behavioral and neurocircuit mechanisms that potentiate maladaptive emotion regulation are poorly understood. Neuroimaging studies have implicated the amygdala and dorsolateral prefrontal cortex (DLPFC) in emotion regulation, but how anxiety and stress alter their context-specific causal circuit interactions are not known. Here we use computational modeling to inform affective pathophysiology, etiology, and neurocircuit targets for early intervention.

Methods: Forty-five children (ages 10-11; 25 male) reappraised aversive stimuli during fMRI scanning. Clinical measures of anxiety and stress were acquired for each child. Drift-diffusion modeling of behavioral data and causal circuit analysis of fMRI data, with an NIMH Research Domain Criteria approach, were used to characterize latent behavioral and neurocircuit decision-making dynamics driving emotion regulation.

Results: Children successfully reappraised negative responses to aversive stimuli. Drift-diffusion modeling revealed that, emotion regulation was characterized by increased initial bias towards positive reactivity during viewing of aversive stimuli, and increased drift rate which captured evidence accumulation during emotion evaluation. Crucially, anxiety and stress reactivity impaired latent behavioral dynamics associated with reappraisal and decision-making. Anxiety and stress increased dynamic casual influences from the right amygdala to DLPFC, but not the reverse. In contrast, DLPFC, but not amygdala, reactivity was correlated with evidence accumulation and decision-making during emotion reappraisal.

Conclusions: Our findings provide new insights into how anxiety and stress in children impact decision-making and amygdala-DLPFC signaling during emotion regulation, and uncover latent behavioral and neurocircuit mechanisms of early risk for psychopathology.

Introduction

Childhood is a vulnerable period for the development of symptoms and syndromes of anxiety ranging from typical developmental experiences to pathological (1). Nearly all affective disorders have an onset in childhood and are the most frequent mental disorders in children and adolescents (1, 2). Cognitive and neural models of anxiety have implicated impaired emotion regulation in the etiology and maintenance of anxiety disorders (3-5). Few studies have investigated the cognitive and neural dynamics of emotion regulation in children, and how these processes are altered by anxiety and stress reactivity, which is important for the development of clinically useful biomarkers for early diagnosis and treatment implementation. Here, we investigate how anxiety and stress reactivity affect latent behavioral emotion regulation processes and dynamic causal neural circuits in a developmentally homogenous group of children.

Reappraisal is a widely used strategy for altering emotional reactivity to aversive stimuli and events by reinterpreting the meaning or significance of the experience (6). Reappraisal relies on a frontoparietal network linking amygdala with prefrontal cortex (PFC) regions involved in cognitive control including the dorsolateral PFC (DLPFC), ventrolateral, and medial prefrontal cortices (7-11). The amygdala detects and encodes emotionally salient stimuli and mediates threat learning and vigilance (12), while adaptive responses to emotionally negative stimuli are thought to be regulated by the DLPFC along with coordinated interactions among other PFC regions, attenuating or heightening affective response (13-17). The DLPFC is of particular interest because it plays a critical role in supporting mental representations of affective states and their manipulation in working memory, processes essential for emotion regulation (8, 18). Brain

imaging studies of emotion regulation have also identified the DLPFC as a locus of deficits in clinical populations (22). The DLPFC also has an outsized role as an intervention target in brain stimulation studies designed to alleviate treatment-resistant anxiety and mood disorders in adults (19-21, 23). Thus, convergent lines of evidence indicate that DLPFC dysfunction plays a prominent role in anxiety- and stress-related emotion dysregulation. Understanding the effects of anxiety and stress reactivity on causal amygdala-DLPFC circuits during emotion regulation in children may provide new insights into pathophysiological mechanisms of vulnerability to affective disorders.

Attentional Control Theory posits that excessive anxiety biases bottom-up signals from the amygdala, disrupting cognitive functions associated with the DLPFC, limiting attentional resources necessary for emotion regulation (24). This theory has not been empirically tested within a causal circuit analysis framework. As anxiety is associated with a bias towards negative interpretations, anxious individuals may not have the prerequisite abilities to alter distorted perceptions (25). However, extant behavioral studies suggest that anxious individuals perform similarly to non-anxious individuals on emotion reappraisal tasks (26, 27). Thus, observed behavioral measures (reaction time, accuracy) may not be adequate to uncover dynamic processes driving reappraisal and its modulation by anxiety and stress (28). Computational modeling approaches are needed to uncover latent behavioral and neuronal processes and their links to emotional reappraisal and reactivity in children (6, 29-31).

Here, we use computational modeling to determine how individual differences in anxiety and stress reactivity influence latent behavioral dynamics and causal bottom-up and top-down neural

signaling between the amygdala and DLPFC during emotion regulation. A developmentally homogenous (ages 10-11) group of children performed an emotion reappraisal task in which they downregulated their emotional experience of aversive visual images (6, 31). Trait-like measures of anxiety (worry) and stress reactivity (temperament), which are associated with appraising situations as more stressful and threatening and are risk factors for developing anxiety disorders (32, 33) were assessed in each child. Drift diffusion modeling (DDM) (34) was used to dissociate observed behavior into latent dynamic processes representing distinct cognitive-affective components, including initial bias during viewing of aversive stimuli and a subsequent decision-making process during evaluation of emotional reaction. We tested the hypothesis that anxiety and stress reactivity negatively impact both these latent emotion regulation processes. As worry is cognitively demanding, we anticipated that anxiety would have broad effects on latent emotion regulation decision-making processes.

To investigate the role of causal amygdala-DLPFC circuits in emotion regulation, we used a state-space multivariate dynamical systems (MDS) model (35) to compute directional (bottom-up and top-down) causal interactions between amygdala and DLPFC in (latent) quasi-neuronal space, unconfounded by regional variations in hemodynamic response. We hypothesized that anxiety and stress in children would be associated with greater bottom-up causal interactions from the amygdala, reflecting maladaptive influence on DLPFC cognitive control mechanisms. Alternatively, greater top-down causal interactions from the DLPFC might reflect an adaptive role in ameliorating the effects of anxiety and stress. Finally, we hypothesized that the DLPFC would be sensitive to decision-making and evaluation of reactivity to aversive stimuli during emotion regulation.

Methods and Materials

Participants

76 children were recruited from a suburban public-school district in northern California for a larger study examining health and wellness in a historically low socioeconomic status and high adversity community. Participants were excluded from the present study if they demonstrated excessive motion during fMRI acquisition (n = 12), failed to engage in the task, experienced equipment failure (n = 8), or did not complete clinical measures (n = 11). Our final sample size included 45 participants (**Figure 1A; Supplementary Materials**). Participant demographics are summarized in **Table S1**.

Clinical measures of anxiety and stress reactivity

The anxiety subscale from the Behavioral Assessment System for Children, Second Edition (BASC) (36) was used to evaluate predominately worry-related anxiety symptoms. The involuntary response to stress subscale from the Response to Stress Questionnaire (RSQ) (37) was used to assess physiological and/or temperamental reactions to stressors (stress reactivity).

fMRI experimental design and emotion regulation task

Consistent with well-validated procedures (31), participants were trained on the experimental paradigm prior to scanning. Participants were told that they would see an instructional cue followed by an image. For 'LOOK' cues, participants were asked to notice their feelings towards the picture. For 'LESS' cues, participants were asked to reappraise aversive images by telling

themselves a story to make the pictures seem less negative, or more positive (**Supplementary Materials**).

During fMRI acquisition, participants completed two scanning runs, each consisting of 30 experimental trials. Each trial began with a 2-second instructional cue word ('LOOK' or 'LESS'), followed by an aversive or neutral image appearing for 7.5-seconds, followed by a rating scale appearing for 2-seconds (**Figure 2A**). Participants rated their emotional state for the following conditions: looking at neutral images and responding naturally ('LOOK'; Neutral Condition), looking at aversive images and responding naturally ('LOOK'; Aversive Condition), and reappraising aversive images ('LESS'; Reappraisal Condition). There were 20 trials in each of the three task conditions: Neutral, Aversive, and Reappraisal. The rating scale consisted of numbers 1 "Okay" through 4 "Very Bad". Participant ratings served as a behavioral index of reappraisal effectiveness. Reappraisal success was computed using the following equation: (($^{\mu}$aversive - $^{\mu}$reappraisal)/$^{\mu}$aversive))*100, with higher scores indicating better reappraisal ability.

fMRI data acquisition and pre-processing

Images were pre-processed using a standard SPM12 pipeline. For each participant, contrast images corresponding to Aversive vs. Neutral, Reappraisal vs. Neutral, and Reappraisal vs. Aversive task conditions were generated using a GLM. An omnibus F-test was used to identify brain regions showing significant group-level responses to Reappraisal vs Neutral or Aversive vs Neutral task conditions, with a height threshold $p < 0.005$ and FWE corrections for multiple comparisons at $p < 0.01$ (minimum cluster size = 87 voxels or 696 mm^3). Activation peaks in bilateral amygdala, DLPFC and other PFC regions were identified and used to construct 6mm

sphere ROIs for subsequent dynamic causal and latent brain-behavior analyses (**Figures 1B, 5, S2; Supplementary Materials**).

Computational modeling of latent behavioral dynamics during emotion regulation

The emotion evaluation process was modeled as a drift diffusion process, in which evidence accumulates over time resulting in a decision when a decision threshold is reached. The evaluations were coded as positive (ratings of 1 or 2) or negative (ratings of 3 or 4) (**Figure 3A**). The initial bias represented the starting point for the drift diffusion process, and captures the initial reaction during image viewing, prior to the decision window. The drift rate parameter (δ) characterizes evidence accumulation, with higher values indicating a greater proportion of positive responses, and higher absolute values of the drift rate characterizing faster responses. For this task, drift rate indexes not only evidence accumulation, but also the decision to make an evaluative response ("Ok" to "Very Bad") when presented with an image. The decision threshold parameter (α) captures response caution, or the degree of confidence required to conclusively evaluate the emotion, with higher values characterizing slower and more consistent responses. The decision threshold for an individual was allowed to vary by instruction – viewing (Look) versus reappraisal (Less). The drift rate and initial bias could vary by instruction (Look, Less) and stimulus type (Neutral, Aversive, and Reappraisal). The non-decision time, reflecting perceptual processes prior to evidence accumulation, for each individual was fixed across instructions and stimulus types. The initial bias for aversive reappraisal condition was constrained to lie between viewing neutral and aversive conditions. The DDM was implemented within a Bayesian inference framework using JAGS (38). Model fit was validated by comparing

the posterior predictive model emotion evaluations and response times under the three different conditions to the actual values (**Supplementary Materials**).

Computational modeling of dynamic causal interactions between amygdala and DLPFC

We used multivariate dynamical systems (MDS), a state-space model for estimating context-dependent causal interactions between multiple brain regions while accounting for regional variation in hemodynamic responses (35). MDS has been validated using extensive simulations (35, 39, 40). See **Supplementary Materials** for details of the computational model and Variational Bayes solution used to infer model parameters.

Results

Behavioral performance and emotion regulation abilities

Children rated their emotional reaction to negative stimuli during Reappraisal and Aversive task conditions, and to stimuli in a Neutral task condition. Stimuli were rated as less unpleasant during the Reappraisal condition than the Aversive condition ($t(44) = -3.57$, $p = 0.001$) (**Figure 2B**). Stimuli were rated as more unpleasant during the Aversive ($t(44) = 13.66$, $p < 0.001$) and Reappraisal ($t(44) = 8.55$, $p < 0.001$) conditions compared to the Neutral condition. Results demonstrate that children are able to modulate their negative affective ratings of aversive stimuli, with more positive evaluations reflecting a higher degree of reappraisal success.

Latent behavioral dynamics during emotion regulation

A novel implementation of DDM was used to determine initial bias, which captures the initial reaction during viewing of aversive images, prior to the decision window and the drift rate, which captures the ability to regulate emotion evaluation during the response (decision) window, and a decision threshold, which measures response caution (**Figure 3A**). Children showed a greater initial bias during the Reappraisal (0.51 ± 0.11) than the Aversive (0.48 ± 0.14) condition ($t(44) = 3.62$, $p < 0.001$) (**Figure 3B**). Children also showed higher drift rates during Reappraisal (0.22 ± 0.88) than the Aversive conditions (-0.12 ± 0.79) ($t(44) = 2.67$, $p = 0.011$) (**Figure 3C**). Children did not show a significant difference in the decision threshold parameter under Reappraisal (2.83 ± 1.1) than Aversive (2.83 ± 1.08), or Neutral (2.83 ± 1.08) conditions. Results show that emotion regulation is characterized by increased positivity bias while viewing images under the reappraisal condition and higher drift rate during the decision period when evaluating their emotional reaction.

Latent behavioral dynamics during decision-making are correlated with reappraisal scores

We determined whether DDM-derived latent cognitive parameters are related to reappraisal success. Individual reappraisal scores were correlated with change in drift rate between the Reappraisal and Aversive conditions ($t(42) = 12.96$, $r = 0.89$, $p < 0.001$) (**Figure S1**). Hierarchical linear regressions with reappraisal success as the dependent variable and changes in initial bias, drift rate, and decision threshold under Reappraisal vs. Aversive conditions as the independent variables revealed an excellent model fit (adjusted $R^2 = 0.78$, $F(3, 41) = 53.64$, $p < 0.001$). Change in drift rate from the Aversive to Reappraisal conditions was the only independent variable that contributed unique variance and thus emerged as the dominant predictor ($t(41) = 11.36$, $\beta = 0.99$, $p < 0.001$; See **Supplementary Results**). Results suggest that

success in emotion regulation is characterized by decision-making during the post-viewing, response period and not initial bias during reappraisal.

Anxiety and stress impair latent behavioral dynamics during viewing and evaluation

Anxiety scores were negatively correlated with initial bias ($t(43) = -2.18$, $r = -0.32$, $p = 0.035$), drift rate ($t(43) = -2.36$, $r = -0.34$, $p = 0.023$), and decision threshold ($t(43) = -2.28$, $r = -0.33$, $p = 0.028$) during Reappraisal (**Figure 4A-C**). Stress reactivity was negatively correlated with the decision threshold during Reappraisal ($t(43) = -2.34$, $r = -0.34$, $p = 0.024$; **Figure 4D**). Anxiety and stress reactivity were not correlated with reappraisal success ($ps > 0.4$). Results demonstrate that anxiety and stress impair latent behavioral dynamics of emotion regulation and that DDM captures their influence on behavior in ways that traditional response selection and reaction time measures by themselves do not.

Brain areas activated during Reappraisal and Aversive emotion processing

An omnibus F-test contrasting Reappraisal vs. Neutral or Aversive vs. Neutral conditions revealed significant activation in bilateral amygdala, DLPFC, DMPFC, VLPFC, posterior parietal cortex, posterior cingulate cortex, and occipital cortex (**Figures 5, S2; Tables S2-S5**), consistent with previous reports (7-10, 41) (**Supplementary Results**).

Anxiety increases causal interactions between amygdala and DLPFC during emotion regulation

To identify amygdala and DLPFC regions of interest (ROIs) for causal circuit and latent brain-behavior analyses, we used task-related activation identified by the F-test, as described above,

thereby avoiding biases associated with selection of regions specific to either task condition. We also conducted additional control analysis using multiple PFC regions (DLPFC, VLPFC, DMPFC, and anterior insula) identified by the F-test (**Table S5**), with FDR-corrections for multiple comparisons.

We then used MDS to compute task condition-specific causal circuit interactions between amygdala and DLPFC ROIs in each hemisphere. A contrast of the strength of causal interactions between the Reappraisal and Aversive conditions was used to probe how anxiety influences causal circuit interactions during emotion regulation. Both forward (amygdala → DLPFC) and backward (DLPFC → amygdala) links in both hemispheres were tested, with FDR corrections ($p < 0.05$) for multiple comparisons.

The strength of causal influence from right amygdala to right DLPFC (**Figure 6A**) during emotion regulation (Reappraisal vs. Aversive conditions) was positively correlated with BASC anxiety ($t(42) = 3.28$, $r = 0.45$, *p FDR-corrected* = 0.008) (**Figure 6B**). No such effects were observed in the reverse connectivity pattern (DLPFC → amygdala). Post-hoc analysis of left amygdala → DLPFC link with anxiety showed a marginally significant effect ($t(42) = 1.84$, $r = 0.27$, *uncorrected p* = 0.074).

We conducted additional analysis using bilateral VLPFC, DMPFC, and anterior insula regions that also showed significant activation associated with emotion processing (**Table S6**). Again, only the right amygdala → DLPFC link was significantly correlated with anxiety (*p FDR-corrected* = 0.033).

Stress reactivity increases causal interactions between amygdala and DLPFC during emotion regulation

Next, we examined whether the strength of causal influence from the right amygdala → DLPFC was also correlated with stress reactivity. We found that right amygdala → DLPFC was positively correlated with stress reactivity ($t(42) = 3.04$, $r = 0.42$, $p\ FDR\text{-}corrected = 0.016$) (**Figure 6C**). No such effects were observed for the reverse direction (DLPFC → amygdala).

Amygdala-DLPFC causal circuit is a common pathway for anxiety and stress during emotion regulation

To disentangle the roles of anxiety and stress in their relation to amygdala → DLPFC causal interaction during emotion regulation, we conducted additional analyses using residualized anxiety, derived by regressing stress out from anxiety, and residualized stress, derived by regressing anxiety out from stress. The strength of causal influence from the right amygdala to right DLPFC was not correlated with residualized anxiety ($t(42) = 1.54$, $r = 0.23$, $p = 0.13$) or residualized stress ($t(42) = 1.06$, $r = 0.16$, $p = 0.30$). Formal structural equation modelling revealed a significant relationship between the strength of right amygdala → DLPFC causal interactions and a latent factor underlying anxiety and stress (**Figure 6D**). These results suggest that shared variance between anxiety and stress reactivity drives bottom-up amygdala → DLPFC signaling during emotion regulation (**Supplementary Results**).

Right DLPFC reactivity is correlated with latent behavioral dynamics

Finally, we investigated the role of the DLPFC in decision-making during emotion regulation. Activation in right DLPFC was correlated with difference in drift rate between Reappraisal vs Aversive conditions ($t(42) = 2.48$, $r = 0.36$, $p = 0.017$) (**Figure 7**). No such relation was observed with amygdala response or causal interactions between amygdala and right DLPFC ($ps > 0.05$). Results demonstrate that right DLPFC, rather than amygdala, reactivity underlies evidence accumulation and decision-making during emotion regulation.

Discussion

Although anxiety and stress are known risk factors for the development of affective disorders, the behavioral and neurocircuit mechanisms that potentiate maladaptive emotion regulation behaviors are poorly understood. We used computational tools to investigate how anxiety and stress impact latent decision-making processes and dynamic causal amygdala-PFC interactions during emotion regulation in children. An NIMH Research Domain Criteria (RDoC) approach (42, 43) allowed us to capture dimensional and shared representations of childhood anxiety and stress reactivity. We found that emotion regulation in children is characterized by increased initial bias during viewing of aversive stimuli and a more positive evaluation of their emotional reaction to negative stimuli during reappraisal. Anxiety impaired multiple latent behavioral dynamic measures, including initial bias and decision-making during evaluation, and stress reactivity resulted in less confident, more impulsive decision-making. State-space circuit modeling revealed that directed causal influences from amygdala to DLPFC, but not the reverse, were exacerbated by anxiety and stress reactivity during reappraisal. Furthermore, DLPFC, but not amygdala, reactivity was correlated with weak evidence accumulation during emotion reappraisal. Control analyses confirmed the specificity of our findings with respect to the

amygdala, DLPFC, and their functional circuit interactions. Our findings reveal latent dynamic behavioral and neurocircuit mechanisms of early pathophysiology during childhood.

Anxiety and stress impair latent behavioral dynamics during emotion regulation

We devised a novel DDM to disentangle three latent components supporting emotion regulation: (i) initial reaction while viewing aversive stimuli, captured by changes in initial bias, (ii) decision-making during emotion evaluation, captured by changes in drift rate, and (iii) response caution, captured by changes in decision threshold (44) (**Figure 3A**).

DDM revealed that children with higher anxiety demonstrated lower positivity bias (initial reaction), lower drift rate (lower ability to regulate), and lower decision threshold (less consistent and controlled evaluation) during reappraisal. These results point to lower and less consistent positivity ratings under reappraisal for higher anxiety scores and highlight latent mechanisms by which anxiety impacts the reappraisal process (**Figure 4**). Stress reactivity effects were only observed in relation to decision threshold, indicating that reappraisal is associated with less cautious, and more impulsive decision-making in children with higher reactive stress responses. These effects were specific to latent behavioral dynamic measures as overt ratings of reappraisal were not correlated with clinical measures of anxiety or stress reactivity. Thus, DDM provided a more sensitive measure of anxiety and stress reactivity effects on behavior than traditional response times and accuracy measures (28). Our findings provide new insights into the mechanisms by which anxiety and stress impair emotion regulation in children, and suggest that

anxiety and stress may not manifest overtly in behavioral performance measures of emotion regulation (45).

Anxiety and stress are correlated with causal right-hemisphere amygdala → DLPFC interactions during emotion regulation

We focused on dissociations between bottom-up and top-down causal interactions between the amygdala and DLPFC as this pathway has been theorized to be critical for regulating reactivity to negative emotions (8, 18, 46). Our causal circuit analysis addressed an important gap in the literature as the effects of anxiety and stress on this core pathway have been poorly understood. Our analysis revealed that the strength of dynamic causal interaction from amygdala to DLPFC was enhanced by both anxiety and stress reactivity during emotion regulation. Crucially, top down influences from DLPFC to amygdala were not correlated with anxiety or stress, highlighting the specificity of directional signaling from amygdala to DLPFC. These effects were specific to the DLPFC, as amygdala interactions with insula, VMPFC, and DMPFC were not correlated with anxiety and specific to right hemisphere amygdala-DLPFC interactions. We also found that variance shared between anxiety and stress reactivity drives right amygdala to DLPFC signaling, suggesting that these interactions reflect a transdiagnostic circuit in childhood. Furthermore, asymmetric involvement of right amygdala-DLPFC circuits is consistent with right-hemispheric dominance for anxiety and anxiety-related processes observed in adults (47-51).

Our findings that both anxiety and stress are associated with bottom-up, context-dependent functional signaling from the amygdala are consistent with the Attentional Control Theory which posits that excessive anxiety biases bottom-up signals from the amygdala (24). Our findings add important developmental dimensions to emerging neurobiological models of anxiety and stress close to the age at which these symptoms manifest, suggesting that early adverse experiences are associated with modulation of causal dynamics in amygdala-DLPFC circuitry rather than amygdala reactivity itself.

Right DLPFC reactivity drives evidence accumulation and decision-making during emotion regulation

We next investigated DLPFC involvement in decision-making during emotion regulation in children, given its central role in cognitive and affective control (8). Right DLPFC activity was modulated by drift rate, reflecting the efficiency of evidence accumulation and decision-making process during emotion regulation. These effects were specific to DLPFC activation as drift rate did not modulate amygdala activation or causal interactions between the amygdala and DLPFC. Furthermore, reaction time and response selection, were not associated with DLPFC activity demonstrating that latent behavioral dynamic measures provide new insights into the role of the DLPFC that cannot be obtained from overt behavioral measures. While DDM has been widely used to investigate perceptual decision-making, to our knowledge no previous studies have examined decision-making processes associated with emotion regulation. It is noteworthy that aversive stimuli remained perceptually unchanged while the child reappraised its negative content, revealing a novel aspect of DLPFC function based on internally generated cognitive

control processes engaged during reappraisal. These findings further highlight the role of the DLPFC in children's decision-making during emotion regulation.

Integrative view of findings

Increased right amygdala → DLPFC connectivity with anxiety and stress raises the question of whether such signaling reflects adaptive or maladaptive function. Our findings suggest that enhanced signaling in this pathway represents "hijacking" a key cortical circuit involved in cognitive control. If it were primarily adaptive function signaling the need for more top-down control, we would expect that DLPFC → amygdala would be negatively correlated with anxiety and stress, which we did not find evidence for. More likely, this signaling is not effectual in increasing top-down control and, in the context of latent behavioral findings that anxiety and stress reactivity impair emotion regulation decision-making dynamics, enhanced anxiety- and stress-related causal amygdala-DLPFC signaling points to ineffective engagement of cognitive control.

Clinical implications

Our findings may represent a promising target for understanding early pathophysiology in line with the recent focus on identifying early psychological and biological factors that cut across diagnoses to explain mental illness (57). As trait-like aspects of negative emotional reactivity, including cognitive (worry) and temperamental (stress reactivity) are present in some form across all anxiety disorders and related psychopathologies (58, 59), bottom-up causal amygdala-

DLPFC effects may represent a critical transdiagnostic circuit. Anxiety disorders are generally chronic and persist into adulthood, and childhood is a critical period for their development. Characterizing the neurobiological effects of trait-like anxiety and stress reactivity in the developing brain on a circumscribed functional circuit may provide a fruitful approach for understanding the emergence and course of early pathological anxiety and related disorders.

Conclusions

Our study provides new insights into how anxiety and stress reactivity in children impact latent decision-making processes, dynamic causal interactions between the amygdala and DLPFC, and DLPFC reactivity during emotion regulation. Over time, it is likely these dynamics would impoverish cognitive control processes anchored in the right DLPFC, rendering it a node of vulnerability and a target for intervention. Our identification of a common circuit that impacts cognitive-emotional function as children enter adolescence may contribute to improved early treatment of anxiety disorders and related psychopathology.

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Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

Figure Captions

Figure 1. Schematic view of participant selection procedure and data analysis pipeline. (A) Children (ages 10-11) were excluded if they failed to engage with the task, demonstrated excessive motion during fMRI acquisition (n = 12), did not complete clinical measures (n = 11), or their behavioral data could not be acquired due to equipment failure (n = 8), yielding a final sample size of 45 participants. (B) Reappraisal success and latent behavioral dynamics were computed using behavioral data. BASC anxiety and stress reactivity were the clinical measures of interest. Brain response to task conditions were estimated using a general linear model (GLM) and an omnibus F-test to identify amygdala and prefrontal cortex regions of interest (ROIs). Time-series were extracted from each ROI and were used to estimate causal interactions between amygdala and prefrontal cortex ROIs using a multivariate dynamical state space model. Finally, the relation between latent behavioral dynamics, anxiety/stress, and casual brain circuit measures were examined.

Figure 2. fMRI experimental design, behavioral performance and emotion regulation abilities. (A) Children ages 10-11 were presented with cues (LOOK or LESS) followed by neutral or aversive images. They were asked to notice their feelings towards the picture when LOOK was presented, and to reappraise aversive images by telling themselves a story to make the pictures seem less negative or more positive when LESS was presented. Neutral condition consisted of viewing a neutral picture, Aversive condition consisted of viewing an aversive picture, and Reappraisal condition consisted of reframing an aversive picture as less negative. Following the presentation of a neutral or aversive image, a rating scale consisting of numbers 1 (“Okay”) through 4 (“Very Bad”) was shown for children to indicate their emotional evaluation. (B) Children reported neutral stimuli to be significantly less unpleasant than the aversive images, regardless of the instructional cue, and reported the aversive stimuli to be significantly less unpleasant during the Reappraisal condition.

Figure 3. Drift diffusion model of latent behavioral dynamics. (A) Illustration of a single trial of the drift diffusion process, where the random walk represents noisy evidence accumulation over time for a positive versus negative evaluation of the stimulus. When the evidence accumulation process hits either decision boundary (separated by the decision threshold) a response is made. The initial bias captures the bias towards positivity or negativity that is built up over the 7500ms stimulus window and acts as a starting point for the random walk. The drift rate captures the rate of evidence accumulation during the 2000ms response window. (B) Children showed significantly greater initial bias under Reappraisal than the Aversive condition. Initial bias is highest in the Neutral condition. (C) Children showed significantly higher drift rates under Reappraisal than Aversive conditions. Drift rate is the highest in the Neutral condition.

Figure 4. Relationship between latent behavioral dynamics and anxiety and stress. BASC anxiety scores were negatively correlated with (A) initial bias, (B) drift rate, and (C) decision threshold during Reappraisal. (D) Stress reactivity was negatively correlated with the decision threshold during Reappraisal.

Figure 5. ROI identification. (A) An omnibus F-test was conducted to identify brain regions showing greater responses in either Aversive and Reappraisal vs Neutral conditions. Significant

activation ($p < 0.005$, minimum cluster size = 87 voxels or 696 mm^3) was detected in bilateral amygdala, bilateral DLPFC, bilateral insula, bilateral caudate, bilateral DMPFC, left VLPFC, right supramarginal gyrus, bilateral precuneus, and bilateral occipital cortices. (B) ROIs were centered (6mm radii) around activation peaks in amygdala (MNI coordinates: (-24, -6, -14) and (22, -6, -14)) and DLPFC (MNI coordinates: (-42, 12, 44) and (40, 8, 38)). (C) Comparison of DLPFC ROIs from the present study with those identified in previous meta-analysis studies of emotion regulation (7-10, 41). Our DLPFC ROIs were localized to the middle frontal gyrus/inferior frontal junction (60).

Figure 6. Anxiety and stress increase causal interactions between amygdala and DLPFC during emotion regulation. (A) The strength of causal influence from right amygdala to right DLPFC during emotion regulation was positively correlated with (B) BASC anxiety and (C) Stress reactivity. (D) Structural equation modeling revealed that shared variance between anxiety and stress drives right amygdala → DLPFC interactions during emotion regulation.

Figure 7. Right DLPFC reactivity increases with evidence accumulation during emotion regulation. Increased activation in right DLPFC (Reappraisal vs. Aversive conditions) was correlated with evidence accumulation during evaluation of emotional reaction, as assessed by change in drift rate between the conditions.

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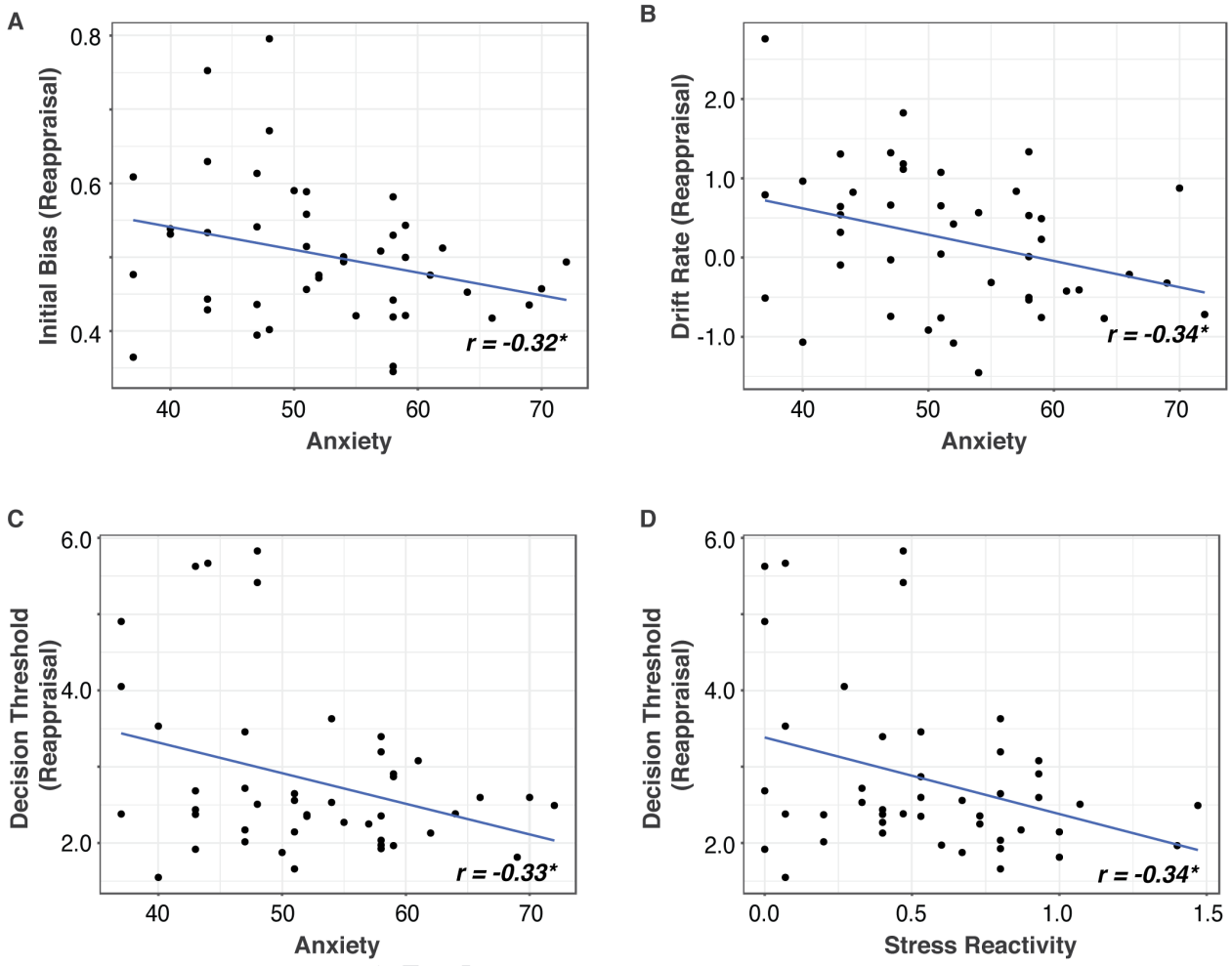
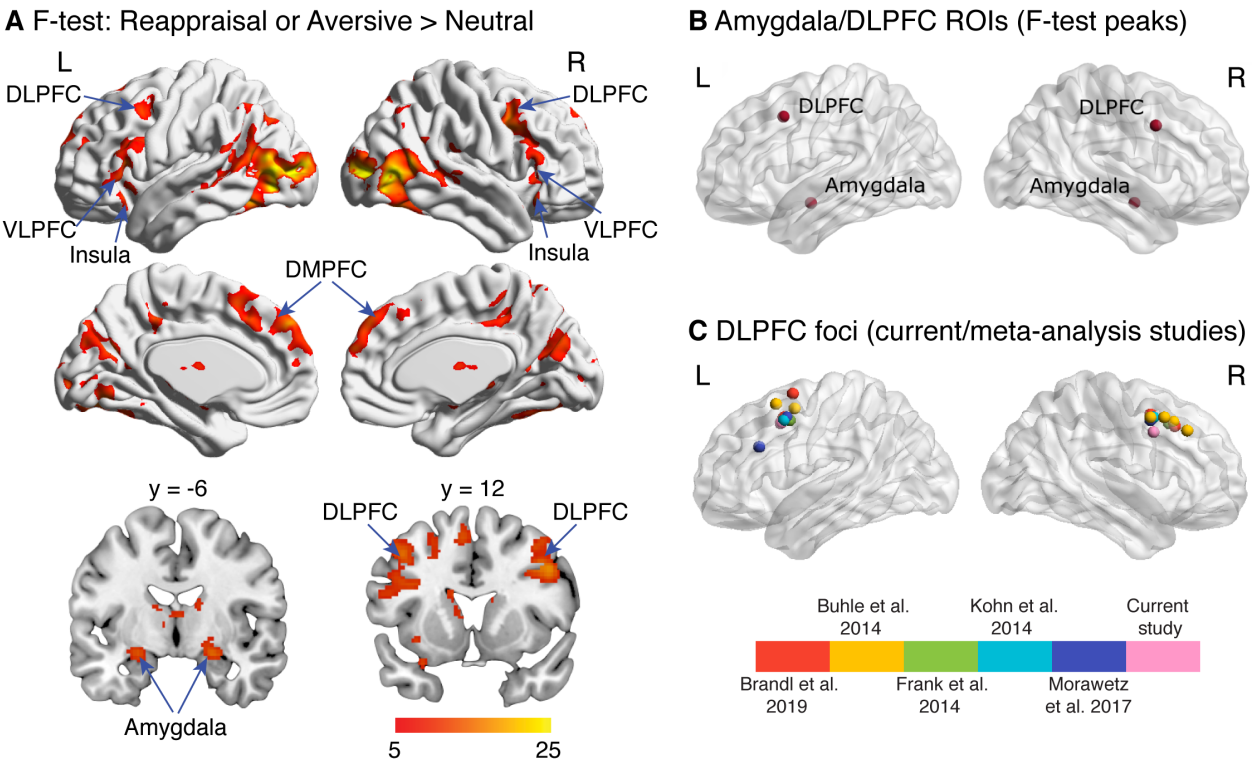
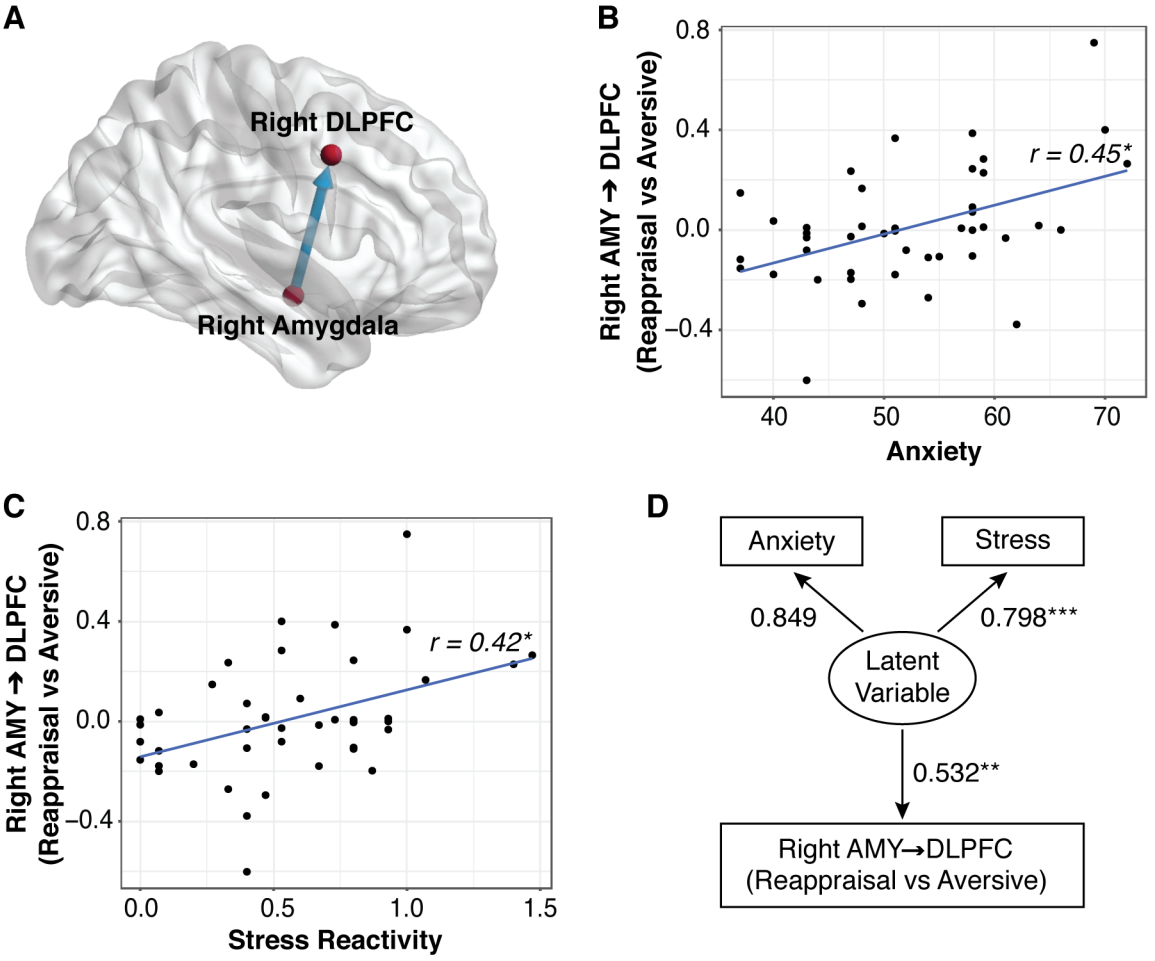
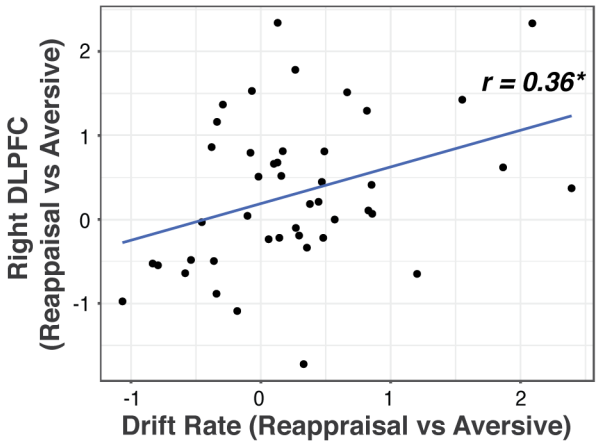
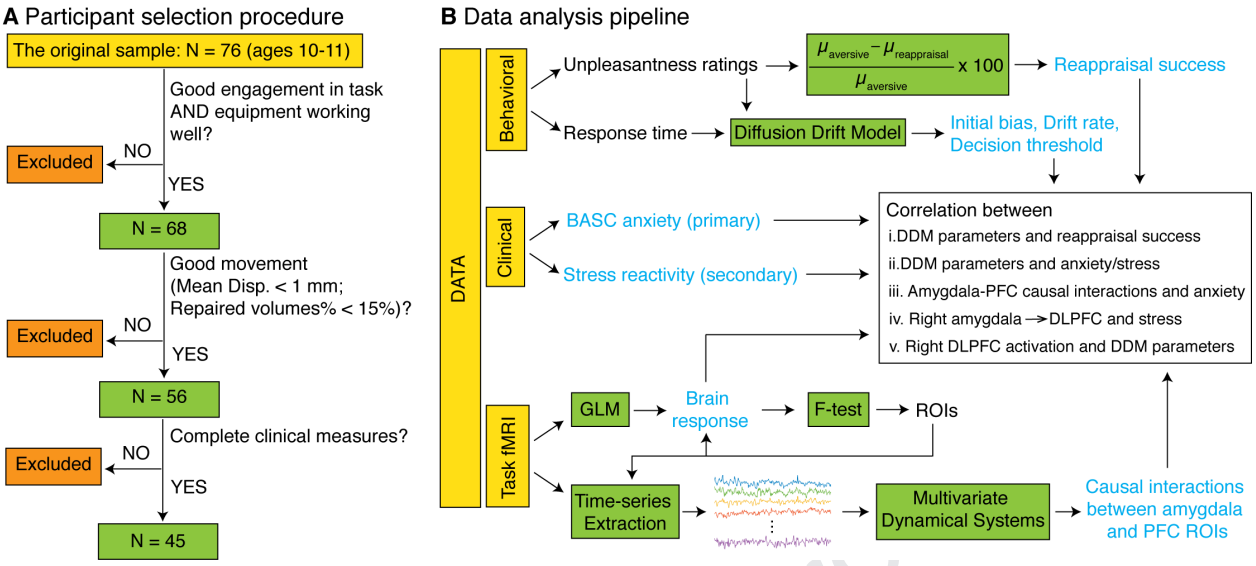
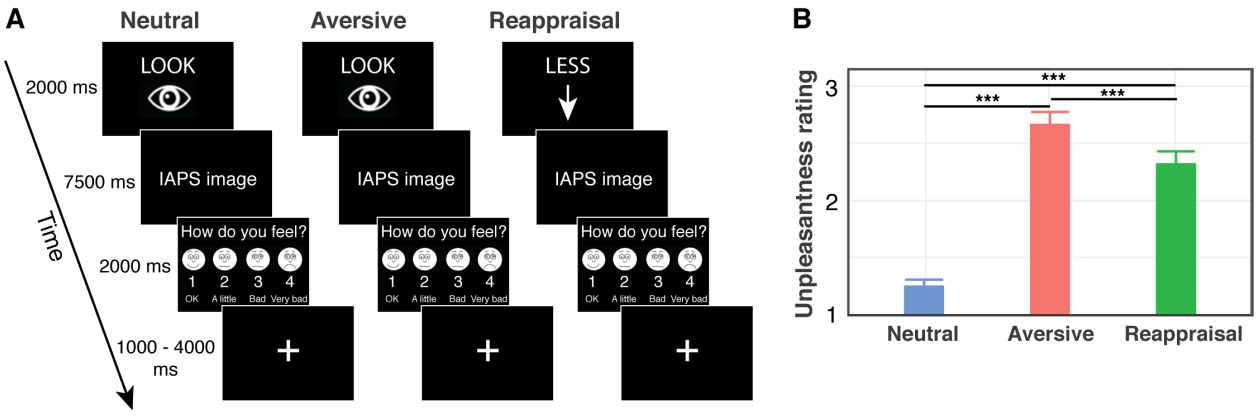

A
Initial Bias (Reappraisal)
0.8
0.6
0.4
40
50
60
70
Anxiety
r = -0.32*
B
Drift Rate (Reappraisal)
2.0
1.0
0.0
-1.0
40
50
60
70
Anxiety
r = -0.34*
C
Decision Threshold (Reappraisal)
6.0
4.0
2.0
40
50
60
70
Anxiety
r = -0.33*
D
Decision Threshold (Reappraisal)
6.0
4.0
2.0
0.0
0.5
1.0
1.5
Stress Reactivity
r = -0.34*

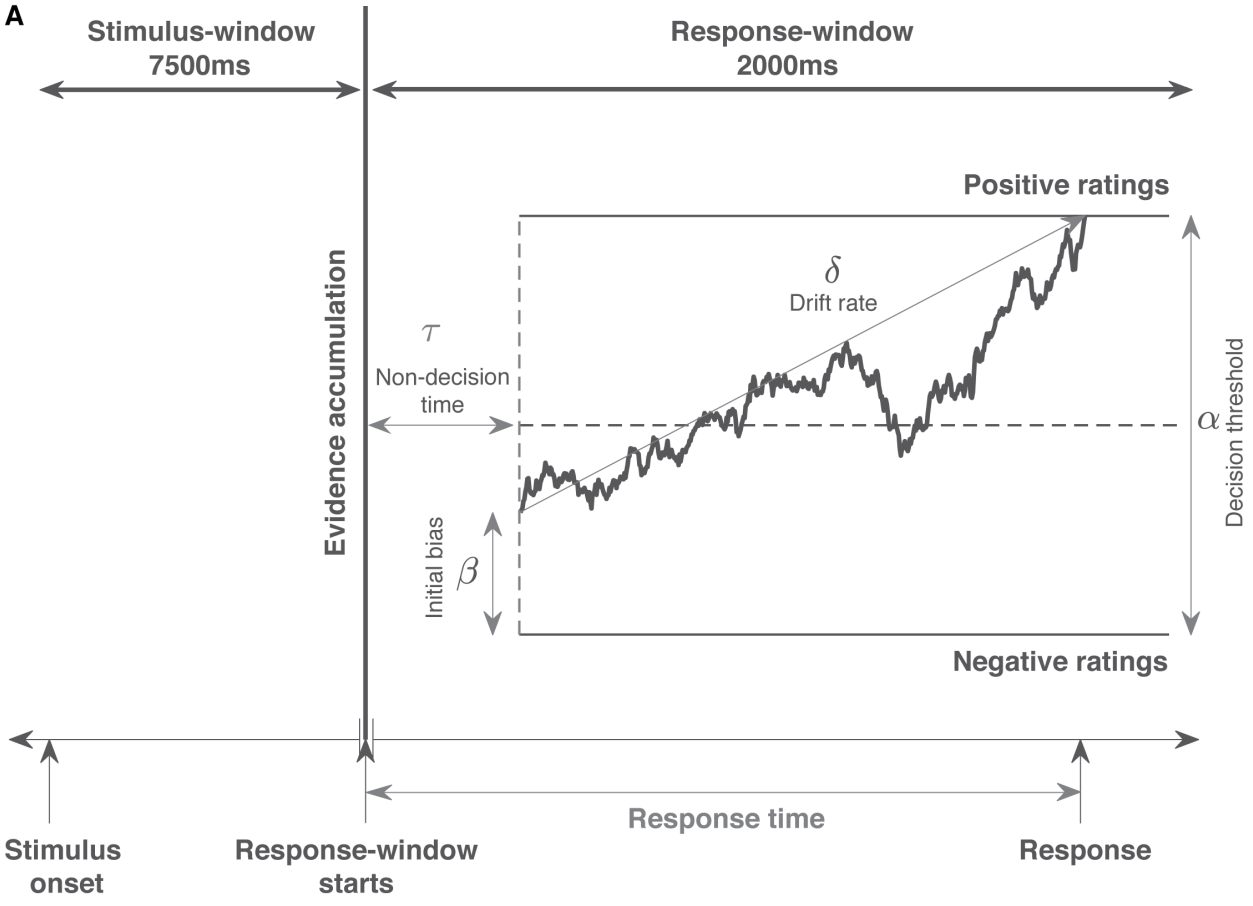


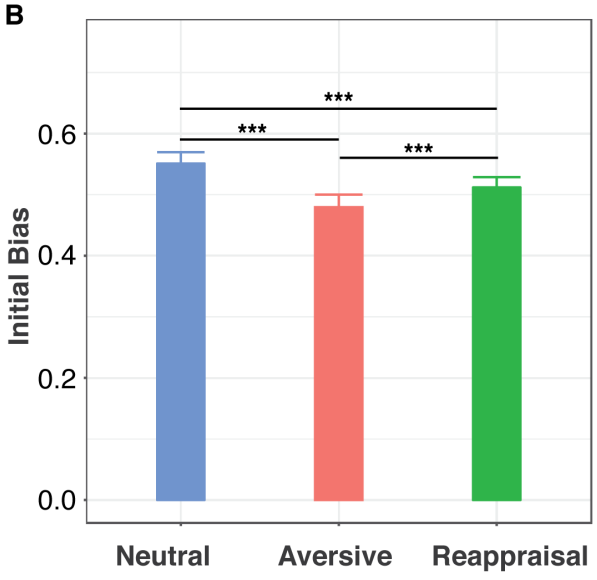

A
Right DLPFC
Right Amygdala
B
Right AMY → DLPFC
(Reappraisal vs Aversive)
0.8
0.4
0.0
−0.4
r = 0.45*
40
50
60
70
Anxiety
C
Right AMY → DLPFC
(Reappraisal vs Aversive)
0.8
0.4
0.0
−0.4
r = 0.42*
0.0
0.5
1.0
1.5
Stress Reactivity
D
Anxiety
Stress
0.849
0.798***
Latent
Variable
0.532**
Right AMY→DLPFC
(Reappraisal vs Aversive)

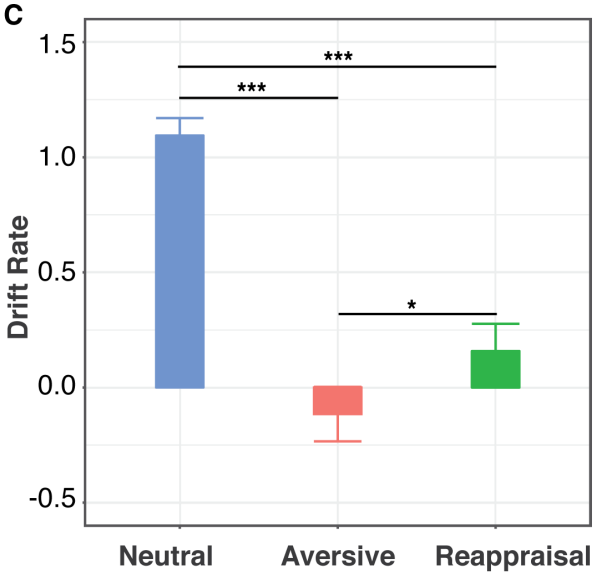







A
Stimulus-window
7500ms
Response-window
2000ms
Positive ratings
Evidence accumulation
δ
Drift rate
τ
Non-decision
time
α
Decision threshold
Initial bias
β
Negative ratings
Response time
Stimulus
onset
Response-window
starts
Response


B
Initial Bias
0.0
0.2
0.4
0.6
***
***
***
Neutral
Aversive
Reappraisal


C
Drift Rate
-0.5
0.0
0.5
1.0
1.5
***
***
*
Neutral
Aversive
Reappraisal