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# Stress and reward: A multimodal assessment of childhood sexual abuse

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ABSTRACT

*Background:* Childhood adversity has been found to impact stress and brain reward systems but it is unclear whether interactions between these systems might explain resilient vs. non-resilient trajectories following childhood sexual abuse (CSA). To address this gap, we adopted a multimodal approach in which cortisol reactivity to an acute stressor was assessed in conjunction with behavioral and neural measures of reward responsiveness in females with major depressive disorder (MDD) or no psychiatric disorders (i.e., resilient) who experienced CSA compared to females with and without MDD who did not experience abuse.

*Methods:* Latent Class Mixed Modelling (LCMM) identified classes of adults ($n = 62$; $M_{Age} = 26.48$, SD = 5.68) characterized by distinct cortisol trajectories in response to a combined social evaluative cold pressor task. Classes were examined for their history of CSA and resilience as well as behavioral and neural measures of reward responsiveness using 128-channel electroencephalography (event-related potentials and source localization analysis).

*Results:* LCMM analysis identified two distinct classes of individuals with increased (*Responders*) or blunted (*Non-Responders*) cortisol reactivity to an acute stressor. Unlike Responders, Non-Responders did not modulate reward responses throughout the stress manipulation. No differences emerged between Responders and Non-Responders in terms of CSA or resilience. However, exploratory results showed that blunted cortisol response and non-modulation of reward responses emerged for those who experienced CSA at a younger age.

*Conclusions:* Co-occurring blunted stress and reward reactivity emerged irrespective of adults' experience of CSA or resilience. However, preliminary findings showed that CSA ending during peripubertal development was associated with blunted cortisol and reward responsiveness. Future research needs to replicate findings in larger samples and could investigate if increasing reward responsiveness during critical times of neurodevelopment could normalize stress reactivity to future stressors and thus promote resilience.

## 1. Introduction

Based on the US Department of Health and Human Services (Child Welfare Information Gateway, 2021), about 9.3% of children experienced childhood sexual abuse (CSA) in 2019. Early adversity accounts for 26–32% of adult psychiatric illnesses (Green et al., 2010), with over 60% of adults who experienced early adversity meeting criteria for major depressive disorder (MDD) (Teicher et al., 2009). The estimated lifetime economic burden resulting from childhood adversity is approximately $124 billion, surpassing combined economic costs of other major pediatric health problems (Fang et al., 2012; Heim et al., 2019). Yet not all individuals exposed to adversity develop psychopathology, with some showing remarkable resilience (for reviews see Dutcher and Creswell, 2018; Yoon et al., 2021). Such variability in the

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sequelae of adversity makes it imperative to understand mechanisms underlying and/or promoting resilience. Despite ongoing debates, resilience is generally understood as behavioral, psychosocial and neurobiological factors that interact to enable adaptive functioning following adversity (Rakesh et al., 2019; Southwick et al., 2014). Critically, although resilience is often operationalized as the absence of a pathological response, it likely comprises an active underlying process that enables individuals to adapt to past and future stressors (Charney, 2004; Feder et al., 2019; Cathomas et al., 2019). Our research aims to investigate if stress and reward responsiveness could serve as such mechanisms associated with resilience after CSA.

An organism's survival depends on its ability to engage with rewards and cope with stressors. While these neurobiological systems are well-characterized, their putative interactions in shaping resilience have received far less attention (Dutcher and Creswell, 2018). To address this, we used a multi-modal approach to examine the relationship of self-report, behavioral, physiological, and neural correlates of acute stress and reward responsiveness in a sample of females with MDD or no psychopathology (i.e., resilient) who experienced CSA compared to females with and without MDD who did not experience abuse. In line with other research on resilience [e.g., (Dutcher and Creswell, 2018)], we operationalized resilience as the absence of lifetime psychiatric disorder following childhood adversity. The term *acute stress* will be used to refer to individual's cortisol reactivity to a lab-based stressor to distinguish it from early life stress.

***Stress Responsiveness***. Childhood adversity increases vulnerability to psychopathology in the context of subsequent life stressors (McLaughlin et al., 2010). Such vulnerability likely stems from neurodevelopmental disruptions during sensitive periods of brain maturation. Childhood adversity has been linked with the excessive release of glucocorticoids from the hypothalamic-pituitary-adrenal (HPA) axis (Andersen and Teicher, 2008; Lupien et al., 2009; Tarullo and Gunnar, 2006), which can impact the development of critical neural circuitries such as the amygdala and prefrontal cortex (PFC) (Lupien et al., 2009; Teicher et al., 2016).

Consistent with these theories, in early studies, Heim (2000) found increased pituitary-adrenal and autonomic responses to lab-based stressors in adults who experienced abuse, particularly in those who also reported current depression. Different results emerged in adults without psychiatric disorders who experienced childhood adversity (i.e., resilient) who showed lower cortisol responses to psychosocial stress (Carpenter et al., 2007, 2011; Elzinga et al., 2008). Initial findings therefore suggested that cortisol reactivity may be lower in those who remained well in adulthood following childhood adversity, but elevated reactivity may develop in adults with later depression. This led us to hypothesize that adults with history of CSA develop distinct cortisol profiles depending on whether they experience psychopathology or not.

However, Suzuki and colleagues (2014) recently examined cortisol responses to an acute stressor in abused and non-abused adults with and without depression. Adults who experienced abuse showed reduced cortisol reactivity to acute stress *irrespective* of their depressive diagnosis. Yet, cortisol stress reactivity was elevated in adults with depression who did not experience abuse relative to adults without depression or abuse histories. Blunted cortisol reactivity to acute stress might therefore be a long-standing effect of childhood trauma that overrides depression-like cortisol responses and thereby limits any harmful impact on brain development (Gold and Chrousos, 2002). In support of this attenuation hypothesis, longitudinal studies have shown that following a period of HPA hyperactivity in childhood, cortisol activity to acute stress starts to diminish in adolescence with significant lower levels in young adults who experienced CSA (Trickett et al., 2010). Critically, unlike some early reports [e.g., (Heim, 2000)], recent meta-analytic evidence points to an association between early life adversity and *blunted* cortisol response to acute stress (Bunea et al., 2017; Brindle et al., 2022).

***Reward Responsiveness***. A rich literature has delineated the role of the cortico-striatal circuitry encompassing the striatum, orbitofrontal cortex (OFC), and medial prefrontal cortex (mPFC) in reward encoding, reward value computation, and reward-related decision making [for reviews, see Haber and Knutson, 2010, Rolls et al., 2020]. While reward-related neural circuitries have been implicated in neurobiological changes associated with early adversity (Teicher et al., 2016; Hanson et al., 2021), a responsive reward system may serve as a resilience factor that protects during acute stress (Dutcher and Creswell, 2018).

Following adversity, children (Mehta et al., 2010; Takiguchi et al., 2015), adolescents (Hanson et al., 2015) and adults (Dillon et al., 2009; Hanson et al., 2016) showed blunted striatal responses to reward. Conversely, individuals with high behavioral and neural reward responsiveness were less likely to experience depression, concurrently or prospectively, following childhood trauma (Dennison et al., 2016). Similar evidence has emerged from event-related potential (ERP) studies probing the reward positivity (RewP), a positive deflection occurring at frontocentral electrodes approximately 250–350 ms after reward presentation (Proudfit, 2015), which has been found to correlate with ventral striatum activation [(Becker et al., 2014; Foti et al., 2014; but see also Cohen et al., 2011)]. A blunted or average RewP predicted greater depressive symptoms among young people who experienced stressful life events (Goldstein et al., 2020; Kujawa et al., 2019).

In sum, blunted reward responsiveness might represent a vulnerability to depression linked to exposure to life stress. Heightened reward responsiveness, however, may buffer against risk to develop negative sequalae after childhood adversity (McLaughlin and Lambert, 2017), although more research is needed. As such, we hypothesized that reduced behavioral and neural measures of reward responsiveness would be observed in adults with CSA and depression but not individuals with CSA without lifetime psychopathology (i.e., resilient) or individuals without experiences of abuse or psychopathology.

***Relationship of Stress and Reward Responsiveness.*** During acute stress, individuals without psychiatric disorders or abuse histories show reduced behavioral reward responsiveness (Bogdan and Pizzagalli, 2006), RewP amplitude (Burani et al., 2021), and striatal and OFC activation (Lincoln et al., 2019; Kumar et al., 2014; Porcelli et al., 2012) during reward delivery and reduced mPFC when anticipating rewards (Ossewaarde et al., 2011). However, a promising line of research shows that intact reward processing may *buffer* responses to acute stress (Dutcher and Creswell, 2018), although this is underexplored in individuals with childhood adversity. For example, greater positive affect and greater trait resilience were found in adults who showed increased reward responsiveness to acute stress (Corral-Frías et al., 2016). Although stress and reward systems are both vulnerable to the impact of adversity, few studies have investigated their relationship under conditions of acute stress to differentiate resilient vs. non-resilient trajectories after CSA. To fill this gap, we adopted a multi-modal approach in which behavioral and neural measures of reward responsiveness (RewP amplitude, mPFC and OFC activation) were assessed in conjunction with cortisol responsiveness to an acute stressor in adults with MDD and a history of CSA, in adults without psychiatric disorders after CSA (i.e., resilient), in adults with MDD but no history of abuse, and in adults without lifetime psychiatric disorders or abuse.

Initially, we intended to use a between-group design to investigate differences in stress and reward responsiveness (National Institute of Mental Health, grant R01 MH095809). However, the reduced sample size of participants with EEG data prevented such analysis. Instead, we adopted a data-driven approach that relied on latent class mixed modelling (LCMM) focused on cortisol responsiveness to stress. LCMM analysis allowed us to identify distinct classes of participants presenting similar trajectories of cortisol response, which were then evaluated for their relationship to behavioral and neural measures of reward responsiveness, CSA, and resilience. Critically, LCMM empirically estimates the number of distinct trajectories of cortisol response that best capture variability in the data without requiring *a priori* assumptions regarding the number, size, or pattern of change of these trajectories. We expected

to identify distinct classes characterized by cortisol responses trajectories that would correspond to: (1) a history of CSA and (2) resilient functioning after CSA. Moreover, we hypothesized that (3) blunted cortisol trajectories would be associated with reduced behavioral and neural measures of reward responsiveness (reduced RewP, blunted OFC and mPFC activation to reward) in adults with CSA and MDD but not in individuals showing resilience after CSA or controls (i.e., no history of abuse or psychopathology).

## 2. Methods and materials

### 2.1. Participants

Data were derived from a larger study of right-handed, unmedicated females ($n = 153$; aged 20–45) enrolled in one of four groups: a) adults without CSA and no past or current DSM-IV diagnosis (healthy controls; HC); b) resilient individuals with CSA operationalized as having no lifetime history of any psychiatric disorders (CSA + Res); c) individuals with MDD, but no abuse (MDD); and d) individuals with MDD and CSA (CSA + MDD). Females with CSA reported at least one incident of contact sexual abuse between the ages of 5–14. This age period was selected based on hypotheses that the brain reward system (specifically, striatal regions) would be especially vulnerable to the effects of CSA occurring between 5 and 14 years old (Teicher et al., 2016). Females in the MDD groups met DSM-IV criteria of current MDD. Only secondary anxiety disorders were allowed in the MDD groups, with all other diagnosis leading to exclusion. Females in the HC or resilient group were free of any past or current DSM-IV diagnoses and did not have first degree relatives with a history of MDD, bipolar disorder, or psychosis.

Our final sample included 62 individuals[1] (17 HC, 15 CSA + Res, 18 CSA + MDD, 12 MDD) who met study inclusion criteria and completed the clinical assessments, stress manipulation, and behavioral reward paradigm. EEG data were available for 44 females (14 HC, 13 CSA + Res, 12 CSA + MDD, 5 MDD) who were representative of the final sample ($n = 62$) in key demographics and clinical characteristics (see *Supplement*).

### 2.2. Procedure and measures

This study was approved by the Mass General Brigham Institutional Review Board, and participants provided written informed consent. As part of a larger study, participants completed three sessions: (1) Clinical diagnostic and trauma history interviews, (2) Pharmacological manipulation and MRI scan (unrelated to the current analyses; see Kaiser et al., 2018), (3) Exposure to an acute stressor and EEG recordings during a behavioral reward paradigm. Only data from Session 1 and 3 are included here and have not been published elsewhere.

***Clinical Assessment.*** The Structured Clinical Interview for the DSM-IV-TR Non-Patient Edition (First et al., 2002) and Trauma Antecedents Questionnaire [TAQ; Herman and van der Kolk, 1990] were administered by doctoral and masters level clinicians to determine lifetime history of psychiatric disorders and childhood trauma. CSA severity was recorded using a single TAQ item (0 (not at all) to 5 (extreme)). Overall CSA severity in the sample was moderate to high severity ($M = 3.61$, $SD = 1.25$). The Beck Depression Inventory-II [BDI-II; Beck et al., 1996] assessed depressive symptom severity.

***Stress Manipulation.*** Participants underwent the Maastricht Acute Stress Test [MAST; Smeets et al., 2012] between 12 and 1 p.m. to control for diurnal cortisol fluctuations (see *Supplement*). The MAST is a physically and social-evaluative laboratory stress test combining the Trier Social Stress Test (Kirschbaum et al., 1993) and the Cold Pressure Test (Mitchell et al., 2004; Fig. 1).

***Cortisol.*** Saliva samples were collected for cortisol assessment at five time points, on average: (1) T = −102 min before the MAST (with T = 0 as ***Stress Onset***); (2) T = +12 min post-MAST; (3) T = +28 min post-MAST onset; (4) T = +38 min post-MAST onset; and (5) T = +80 min post-MAST onset (Fig. 1). Approximately 40 min after stress onset (T = +40 min post-MAST onset), participants were told that they do not need to repeat the MAST procedure (i.e., Relief).

***Self-Reported Affect.*** Affective responses to the MAST were assessed using the Visual Analog Mood Scales [VAMS; Folstein and Luria, 1973] at five time points (Fig. 1). VAMS consisted of three 100-mm horizontal lines, each representing a bipolar dimensional mood state (friendly-hostile, relaxed-tense, happy-sad). Lower VAMS scores reflected greater negative affect. Self-report measures of positive (PANAS-P) and negative affect [PANAS-N; Watson et al., 1988] and state anxiety [STAI-S; Spielberger et al., 1983] were completed immediately before and after the stress manipulation and following the stress relief (Fig. 1).

***Probabilistic Reward Task (PRT).*** Participants completed two blocks of the PRT (Pizzagalli et al., 2005, 2007a, 2008) both before and after the MAST (Fig. 1). Rooted in signal detection theory, the PRT uses an asymmetric reinforcement schedule to assess a person's propensity to modulate behavior based on prior reinforcements as an index of reward responsiveness (see *Supplement*).

***Electroencephalography (EEG).*** During the PRT, 128-channel EEG data were recorded using a Hydrocel Geodesic Sensory Net system (Electrical Geodesics, Inc, Eugene, Oregon) in an electrically shielded room. Data were sampled at 250 Hz (bandwidth, 0.1–100 Hz, impedances <100 kΩ) and referenced to the vertex electrode (Cz) ($n = 44$; see *Supplement*).

*Scalp-recorded ERP*. Epochs were extracted from −250 to 1050 ms around the presentation of the reward feedback for the RICH stimulus (i.e., the stimulus associated with 3x more frequent reward) (no LEAN stimulus trials were used due to low number of useable segments). Epochs were visually inspected, remaining artifacts were removed, baseline-corrected (−250 to 0 ms), and averaged. The Rew P was assessed using the time-window averages (252–324 ms after RICH feedback) at midline electrodes (Fz, FCz, Cz, CPz).

*Source Localization.* Standardized Low Resolution Electromagnetic Tomography [sLORETA; Pascual-Marqui, 2002] was used to estimate intracerebral current density after RICH feedback. As outlined in Whitton et al. (2016), ROIs were defined based on two independent meta-analyses of fMRI studies specifying the left posterior OFC, middle vmPFC, and right vmPFC as core neural regions of reward activity [Bartra et al., 2013; Sescousse et al., 2013; see *Supplement*]. ROI activation derived from fMRI coordinates of these meta-analyses (Bartra et al., 2013; Sescousse et al., 2013) and all voxels in a 10 mm radius to ensure greater representativeness of the reward literature. Data were intensity-normalized (to unity), log-transformed and averaged across voxels within a given ROI.

### 2.3. Analyses

Incomplete data on key variables were missing at complete random (MCAR Little's Test: $x^2(68) = 48.75$, $p = .96$) and imputed using Expectation Maximization algorithms using model and key demographic parameters (i.e., age, ethnicity). Cortisol responses were log-transformed to reduce skewness. A response threshold was calculated using a standardized criterion identifying those who increased ≥2.5 nmol/L after stress induction as $\text{Responders}_{\geq 2.5\ \text{nmol/L}}$ (Admon et al., 2017; Foley and Kirschbaum, 2010). Repeated-measure ANOVA assessed cortisol responses for main effect of *Time*. Either Greenhouse-Geisser or Huynh-Feldt corrections were used as appropriate to correct for sphericity violations. Significant findings ($\alpha = 0.05$) were followed-up with Bonferroni-corrected simple tests in SPSS.

***Latent Class Mixed Modelling (LCMM).*** We tested whether a 2-, 3- or 4-class model of distinct trajectories best fit the cortisol data. Bayesian information criterion (BIC) was used to compare different models to determine the optimal number of classes based on variability in the data

[1] Analyses based on the original group assignments are included in the *Supplement*.

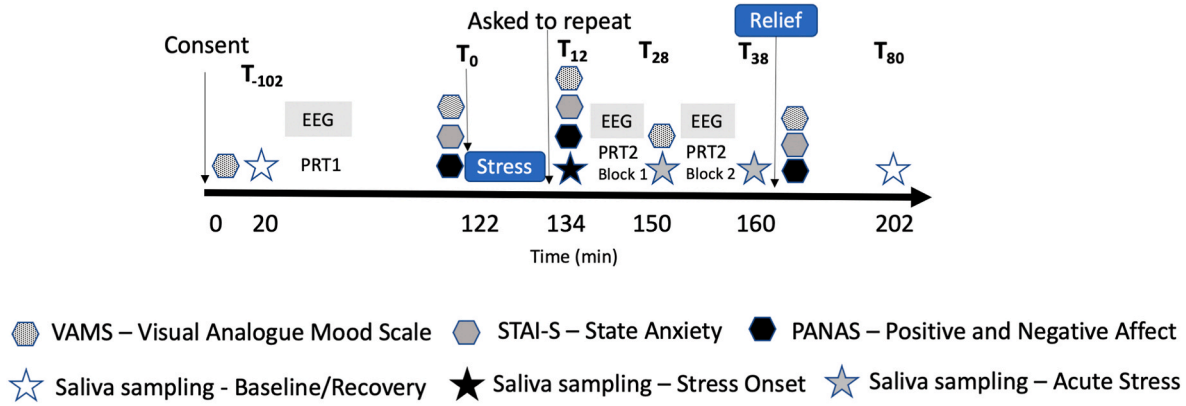


**Fig. 1.** Schematic diagram illustrating the timeline and design of the session. Participants provided written consent before completing the baseline saliva sample and baseline affect measures followed by the pre-stress Probabilistic Reward Task (PRT 1) and additional pre-stress affect measures. Then, the MAST (stress manipulation) was administered followed by stress onset saliva sampling, affect measures and the acute stress probabilistic reward task (PRT2 Block 1). Another acute stress saliva sample and affect measures were collected before transitioning to PRT2 Block 2 and the final acute saliva sample after completion of PRT Block 2. To prolong the acute stress effect, participants were initially told that their performance was 'not good enough' and that the MAST had to be repeated after the remaining tasks. Relief (i.e., being told not needing to repeat procedure) occurred after the last PRT block and the acute saliva sample. This was followed by PostRelief affect measures and finally a PostRelief saliva sample. 128-channel EEG data were collected during the PRT tasks, from which ERPs (Reward Positivity) and source-localization (standardized Low Resolution Electromagentic Tomography; sLORETA) data were computed.

(Nylund et al., 2007). Low BIC values indicate a better fit of the model to the data. Analyses were performed in R Studio (4.0.2 Version) using the lcmm package (Proust-Lima et al., 2017). To avoid endogenous variation in cortisol levels, only the three stress-related cortisol responses were included in the LCMM (Admon et al., 2017). However, to ensure reliability of findings, we also conducted analyses including a fourth time point (PostRelief: T = +80 min post-MAST onset) which yielded a similar two-class distinction (see *Supplement*).

***Cortisol.*** Repeated-measure ANOVA with three cortisol sampling points (*Time*) as within-subject factor and *Class* as between subject-factor were conducted. Cortisol response to stress was also examined by computing the area under the curve (AUC) with respect to ground ($AUC_g$) and increase ($AUC_i$). Data were analyzed separately using one-way ANOVAs with LCMM *Class* as between-subject factor (Pruessner et al., 2003).

***Demographics and Clinical Assessment.*** Chi-Square tests, Fisher's Exact tests and independent sample t-tests evaluated demographic variables and relationships between class and clinical variables (i.e., cortisol response criterion, CSA, resilience) to empirically characterize cortisol trajectories.

***Self-Reported Affect.*** Repeated-measure ANOVA included five sampling time points and three VAMS scales (within-factors) and *Class* (between-subject factor). Repeated-measure ANOVAs separately examined STAI-S, PANAS-N and PANAS-P with sampling *Time* (n = 3) as within-subject factor and *Class* as between-subject factors.

***PRT***. PRT data were subjected to quality control following prior procedures (see *Supplement*). Response bias (i.e., tendency to bias responding toward the more frequently rewarded RICH stimulus) and discriminability (i.e., the ability to distinguish between the two stimuli) were separately analyzed using ANOVAs with *Stress* (Pre-Stress, Acute-Stress) x *Block* (1, 2) x *Class*.

***Scalp-Recorded ERP.*** Mixed ANOVAs were used to examine *Stress* (Pre-Stress, Acute-Stress) x *Electrodes* (Fz, FCz, Cz, CPz) *x Class* for RewP amplitude following RICH feedback.

***Source Localization.*** A mixed ANOVA with *Stress* (Pre-stress, Acute-Stress) and *ROI* (left posterior OFC, middle vmPFC, right vmPFC) as within-subject factor and *Class* as between-subject factor determined differences in reward-related neural PFC activity associated with stress.

## 3. Results

### 3.1. Stress manipulation

An ANOVA assessing cortisol response in the overall sample revealed a main effect of *Time* ($F(1.77, 107.67) = 10.81$, $p < .001$) with quadratic ($F(1, 61) = 6.06$, $p = .02$) and cubic effect ($F(1, 61) = 42.18$, $p > .001$). Post-hoc analysis showed significant increases in mean cortisol level from directly after the stress onset ($T_{12min}$) to the two consecutive acute stress assessments ($T_{28min}$; $p < .001$ and $T_{38min}$; $p = .02$). Upon arrival, baseline cortisol was elevated thus showing no significant increases to onset of stress ($T_{12min}$, $T_{28min}$, $T_{38min}$: all $p$'s $> 0.12$) but a reduction in post relief cortisol levels ($T_{80min}$; $p < .02$).

### 3.2. LCMM

The LCMM analysis was conducted across stress-related time points ($T_{12min}$, $T_{28min}$, $T_{38min}$). BIC criteria comparing the different LCMM models ($BIC_2 = 231$, $BIC_3 = 245$, $BIC_4 = 238$; Table 1) indicated that two classes were optimal. The estimated mean trajectories of the two classes showed good discrimination, with <11% of participants *a posteriori* classified in another class than initially assigned.

**Cortisol**. The two classes were labeled based on their distinct trajectories as '*Non-Responders*' ($n = 44$; 71%) and '*Responders*' ($n = 18$; 29%) and independently confirmed when comparing classes based on cortisol responder criterion (i.e., $Responders_{\geq 2.5\ nmol/L}$ vs. $Non\text{-}Responders_{\geq 2.5\ nmol/L}$; Fisher's Exact Test: $p < .001$) (Admon et al., 2017; Foley and Kirschbaum, 2010). Significant differences in class emerged for $AUC_i$ ($F(1, 61) = 86.02$, $p < .001$) but not $AUC_g$ ($F(1, 61) = 0.002$, $p = .96$). Negative values emerged for cortisol responsiveness for Non-Responders ($M = -1.71$, $SD = 5.86$) but not Responders ($M = 16.03$, $SD = 8.82$) serving as an index of cortisol decrease for Non-Responders over time (Pruessner et al., 2003).

As shown in Table 2, Responders and Non-Responders classes did not differ in their experience of CSA (occurrence, duration or severity; all $p$'s $> 0.20$) or resilience ($p = .78$; Table 2). Yet, exploratory analysis showed that compared to Responders, Non-Responders experienced CSA at a younger age ending during the peripubertal period ($p = .02$). Interestingly, when splitting the sample based on the $Responders_{\geq 2.5\ nmol/L}$ Vs. $Non\text{-}Responders_{\geq 2.5\ nmol/L}$ criterion (Admon et al., 2017; Foley and Kirschbaum, 2010), $Non\text{-}Responders_{\geq 2.5\ nmol/L}$ primarily consisted of individuals with a history of CSA (67.6%; Fisher's Exact Test; $p = .02$)

**Table 1**
LCMM model statistics.

| *Between-model comparison* | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Log likelihood | NMP [a] | BIC | Class 1 [b] | Class 2 [b] | Class 3 [b] | Class 4 [b] |
| 2 Classes | −95.02 | 10 | 231.31 | 70.97% | 29.03% | | |
| 3 Classes | −93.78 | 14 | 245.34 | 67.74% | 3.23% | 29.03% | |
| 4 Classes | −82.16 | 18 | 238.61 | 61.29% | 33.87% | 3.23% | 1.61% |

| *Within the two-class model: Fixed effects allowing for quadratic time (t) trends* | | | | | | |
|---|---|---|---|---|---|---|
| | *n* (%) | | Coefficient | *SE* | Wald | *P* |
| Non-Responders | 44 (70.97%) | *t* | −0.36 | 2.38 | −0.15 | 0.88016 |
| | | $t^2$ | −6.14 | 1.39 | −4.42 | 0.00001 |
| Responders | 18 (29.03%) | *t* | 31.79 | 4.83 | 6.59 | <0.0001 |
| | | $t^2$ | −19.32 | 2.87 | −6.73 | <0.0001 |

| *Within the two-class model: mean of posterior probabilities (%) in each class* | | |
|---|---|---|
| | Class 1 | Class 2 |
| Non-Responders ($n = 44$) | 97 | 3 |
| Responders ($n = 18$) | 11 | 89 |

[a] Number of model parameters.
[b] Posterior proportion for each class.

**Table 2**
Sample Demographics and Clinical Characteristics between LCMM classes.

| | Non-Responders $n = 44$ | Responders $n = 18$ | test value | *p* values |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age in Years, Mean (SD) | 25.73 (5.01) | 28.33 (6.87) | −1.66 | .10 |
| No. Caucasian (%) | 28 (63.60) | 10 (55.60) | | .38[a] |
| Education in Years, Mean (SD) | 15.36 (2.39) | 17.17 (2.75) | −2.58 | **.01** |
| No. Income > $50,000 (%) | 13 (29.50) | 8 (44.40) | | .20[a] |
| **Clinical Characteristics** | | | | |
| No. Cortisol Non-Responders[b] (%) | 31 (70.5) | 3 (16.7) | | **<.001**[a] |
| BDI-II Mean score (SD) | 13.95(15.81) | 12.78 (13.21) | 0.28 | .78 |
| No. Current MDE (%) | 21 (47.70) | 7 (38.90) | | .36[a] |
| No. Current Anxiety Dx (%) | 11 (25.00) | 3 (16.70) | | .36[a] |
| No. Past Anxiety Dx (%) | 12 (27.30) | 5 (27.80) | | .60[a] |
| No. Individuals reporting CSA (%) | 25 (56.80) | 8 (44.4) | | .27[a] |
| CSA Severity, Mean (SD) | 3.52 (1.23) | 3.88 (1.36) | | .49 |
| CSA Onset in Years, Mean (SD) | 7.80 (3.37) | 9.38 (4.10) | −1.09 | .28 |
| CSA Ending in Years, Mean (SD) | 11.16 (3.21) | 14.38 (3.50) | −2.41 | **.02** |
| CSA Duration in Years, Mean (SD) | 3.56 (2.82) | 5.25 (4.13) | −1.32 | .20 |
| Time since CSA Years, Mean (SD) | 15.80 (6.83) | 12.38 (7.96) | 1.19 | .24 |

MDE = major depressive episode, Dx = diagnosis, CSA = child sexual abuse.
[a] Fisher's Exact Test, one-sided.
[b] Indicating <2.5 nmol/L from stress onset to any subsequent time-point (Admon et al., 2017; Foley and Kirschbaum, 2010).

irrespective of their reported resilience (Fisher's Exact Test; $p = .61$).

### 3.3. Demographics and Clinical Assessment

Classes did not differ in age, ethnicity, or income (Table 2). Despite Non-Responders reporting fewer years in education, this did not correlate with variables of interest (reward responsiveness: *all p's* > 0.43; cortisol: *all p's* > 0.22; self-reported affect: *all p's* > 0.24).

### 3.4. Self-reported affect

VAMS results showed a main effect of *Time* ($F(2.71, 162.49) = 55.77$, $p < .001$), *Scales* ($F(2, 120) = 12.80$, $p < .001$) and a *Time x Scale* interaction ($F(6.71, 402.32) = 8.24$, $p < .001$). No class effect or interactions emerged (all *p's* > 0.09; Fig. 2).

STAI results revealed a main effect of *Time* ($F(1.76, 105.93) = 75.44$, $p < .001$). Individuals showed an increase of negative affect after stress onset and a reduction post-relief (all *p's* < 0.001). No class effect or interaction emerged (all *p's* > 0.22; Fig. 3).

PANAS-P was characterized by a main effect of *Time* ($F(1.75, 105.05) = 9.14$, $p < .001$) with all individuals showing a positive mood reduction after stress onset ($p = .003$). No class effect or interaction emerged (all *p's* > 0.05). PANAS-N featured a main effect of *Time* ($F(1.34, 80.12) = 60.24$, $p < .001$) due to negative affect increasing with stress and decreasing post-relief (all *p's* < 0.002). No class or interaction emerged (all *p's* > *0.61*; Fig. 3).

### 3.5. PRT

*Response Bias.* A main effect of *Block* ($F(1, 60) = 12.27$, $p = .01$; partial $eta^2 = 0.17$) emerged with response bias increasing from Block 1 to 2 for all groups irrespective of stress. A significant *Class x Stress* interaction ($F(1, 60) = 4.60$, $p = .04$; partial $et\ a^2 = 0.07$) was driven by differences in response bias between Non-Responders and Responders at pre-stress ($p = .05$) but not at post-stress ($p = .14$). Critically, only Responders increased their response bias from pre-to post-stress ($p = .04$); the change for Non-Responders was not significant ($p = .53$; Fig. 3). No other effects or interactions emerged (all *p's* > 0.15).

*Discriminability.* No effects emerged (all *p's* > 0.10), indicating that response bias effects were not confounded by task difficulty or order effects.

### 3.6. Scalp-recorded ERP

A significant main effect of *Electrode* ($F(1.51; 63.51) = 12.83$, $p < .001$) emerged. Post-hoc tests showed varying RewP amplitudes between electrodes (all *p's* < 0.03) except between FCz and CPz ($p = 1.0$) and Cz and CPz ($p = .52$). No other effects or interactions emerged (all *p's* > 0.21).

### 3.7. Source localization

A *Stress* x *ROI* x *Class* ANOVA showed a main effect of ROI ($F(1.43, 59.85) = 25.49$, $p < .001$). Post-hoc tests showed no difference between

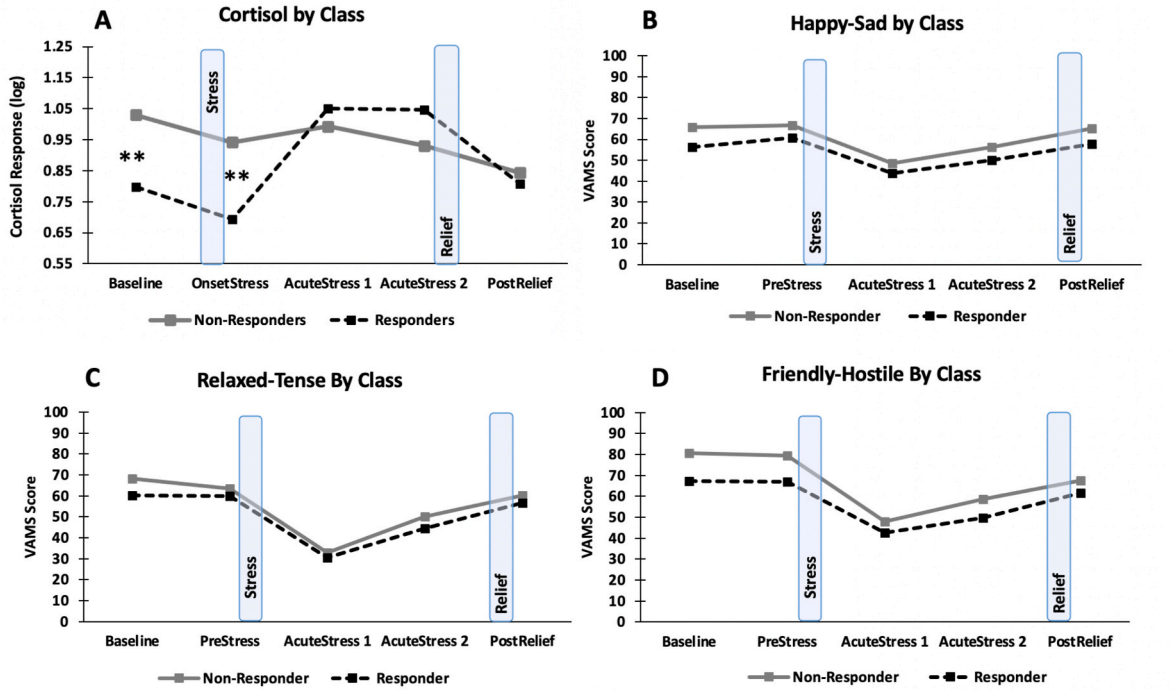


**Fig. 2.** Trajectories of cortisol responses and self-reported affect during stress manipulation. **(A)** Applying LCMM to cortisol data revealed that the model with the best fit included two latent classes, labeled based on their distinct trajectories of cortisol response to stress as Non-Responders (n = 44) and Responders (n = 18). Note that Non-Responders did not vary in their cortisol responses to the stressor over time and entered the study with significantly higher levels of cortisol compared to Responders. $^{**}p < .01$. **(B–D)** Self-reported affect during the session with Visual Analog Manual Scale (VAMS) ratings by class. Lower VAMS scores reflect greater negative affect.

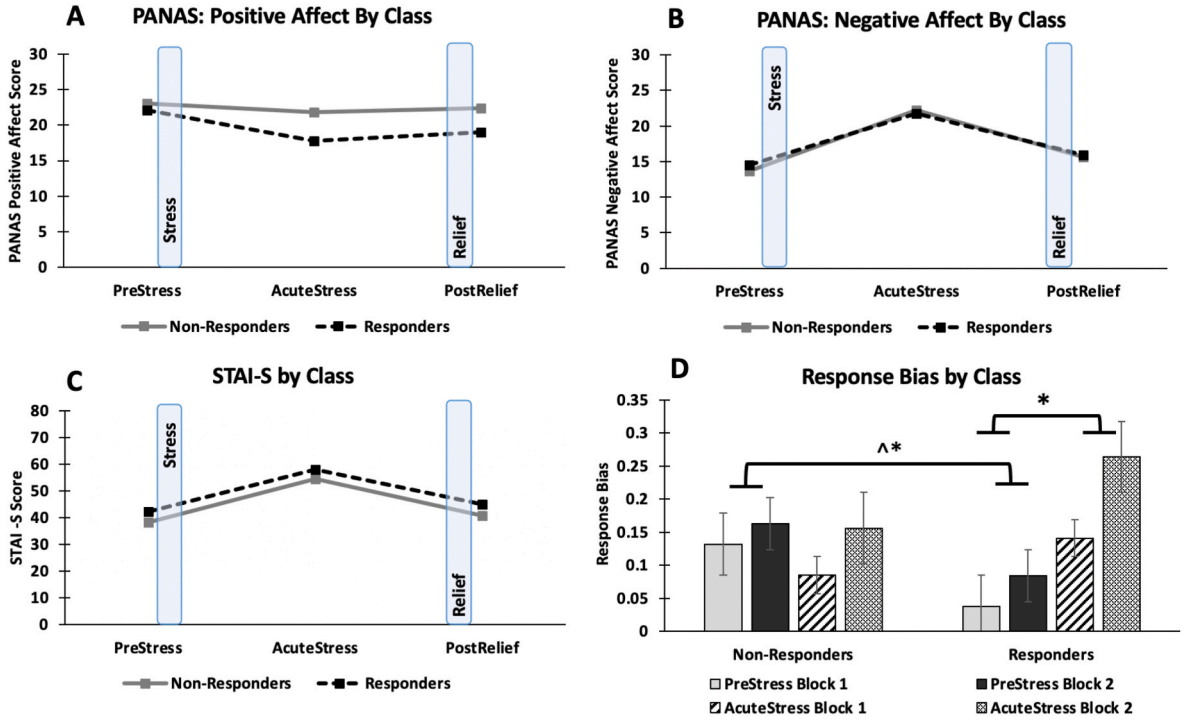


**Fig. 3.** Changes in positive and negative affect and reward responsiveness during stress manipulation. Changes in **(A–B)** positive and negative affect measured using the Positive and Negative Affect Schedule (PANAS) and **(C)** state anxiety measured using Spielberger State Anxiety Inventory (STAI-S) across Responders and Non-Responders classes. **(D)** Response bias by class in the Probabilistic Reward Task ($n = 62$) before and during stress manipulation (Non-Responders = 44; Responders = 18). Significant differences in response bias emerged between Non-Responders and Responders at pre-stress but not at post-stress. Critically, only Responders increased their response bias from pre- to post-stress, with no significant change for Non-Responders. Error bars represent standard errors. $^{*}p < .05$, $^{\wedge *}p = .05$.

left and middle vmPFC activations ($p > 1.0$) but greater negative current density in vmPFC regions compared to left posterior OFC (all $p's < 0.001$).

## 4. Discussion

Using a data-driven approach, we identified two distinct classes: adults with blunted (*Non-Responders*) and increased (*Responders*) cortisol reactivity to a combined social-evaluative cold pressor task. Contrary to our first and second hypotheses, neither Responders nor Non-Responders were primarily represented by adults who reported CSA or resilience. Partly supporting our third hypothesis, unlike Responders, Non-Responders fail to modulate their reward responses as a function of stress on a behavioral task. Exploratory analysis showed that Non-Responders experienced CSA at a younger age than Responders possibly pointing to a window of opportunity for intervention.

During acute stress, Non-Responders showed blunted stress responsiveness compared to Responders which was confirmed by two independent measures: the cortisol responder criterion (≥2.5 nmol/L; (Admon et al., 2017; Foley and Kirschbaum, 2010) and a negative index for cortisol increase (AUCi; -(Pruessner et al., 2003). However, blunted cortisol reactivity to acute stress was not directly associated with CSA, thus findings do not support the cortisol attenuation hypothesis after childhood adversity (Brindle et al., 2022; Bunea et al., 2017; Suzuki et al., 2014). Results may be partially explained by our data-driven LCCM approach as most studies showing blunted cortisol response after childhood adversity use a pre-determined group design [e.g., Suzuki et al., 2014]. LCMM estimates distinct trajectories of cortisol reactivity aimed to capture multifaceted variability in the data without prior assumptions. Although the post-hoc characterization of classes can be complex to disentangle, it can also provide novel insights potentially missed by pre-determined groups designs. For example, follow-up analyses showed that, when splitting our sample based on the cortisol responder criterion (≥2.5 nmol/L), females with a history of CSA showed blunted cortisol response. These findings replicate previous research showing blunted responsiveness to acute stress after adversity possibly due to downregulation of the adrenocortical function to limit disruption to neurodevelopment (Teicher et al., 2016; Trickett et al., 2010). However, only our data-driven LCMM approach highlighted that the timing of CSA forms an important component for understanding differences in stress responsiveness (irrespective of severity, duration, or years since CSA). For Non-Responders, CSA occurred from middle childhood to the peripubertal period ($M = 11.2$ years) while Responders experienced CSA from late childhood to adolescence ($M = 14.38$). Recent research by Gunnar and colleagues (2019) highlights the importance of early life and puberty during which the social environment can have a substantial impact on the development of HPA axis and other stress-mediating system [see also Pechtel et al., 2014]. Interestingly, they identified the peripubertal developmental period as a window of opportunity during which improvements in a person's supportive environments can help to recalibrate HPA axis (Gunnar et al., 2019). Further research is needed to understand the differential impact of stress responsiveness for those who experienced CSA into later adolescence as shown by our Responders. Beyond any association with CSA, attenuated cortisol levels as shown in our sample have been linked to serious diseases (Pruessner et al., 2013; Raison and Miller, 2003; Schalinski et al., 2019) and suicide risk (O'Connor et al., 2020). Prospective research could explore opportunities to re-establish moderate stress reactivity that do not overload the system but allows a person's interaction with their environment.

In terms of reward responsiveness, Responders started with a lower response bias before continuously increasing their reward responsiveness throughout the stress manipulation (Fig. 3). This pattern has previously been found in PRT studies with *participants without psychopathology* (Pizzagalli et al., 2005, 2007b) even under conditions of stress (Bogdan and Pizzagalli, 2006). Non-Responders, however, started with a greater response bias but then failed to adjust behavior to increase reward throughout the stress manipulation. At first sight, greater initial response bias in the Non-Responders class might appear surprising. Yet, this pattern has been observed in PRT studies in *remitted and clinical samples* who also reported greater initial response biases than controls followed by a lack of increasing reward responses over time (Pechtel et al., 2013; Vrieze et al., 2013). In our sample, Non-Responders showed both elevated cortisol and reward responsiveness at baseline which then remained unchanged throughout the manipulation. One could speculate that Non-Responders operate at 'ceiling level' which diminishes their interactions with both stress and reward environments. Although reduced interactions could serve a protective role in limiting overload of the stress response system, it may also hinder Non--Responders' ability to optimize responses to gain reward and foster resilience.

Overall, we did not find support that resilience was associated with higher reward responsiveness (Dennison et al., 2016). Unlike our data-driven approach that probed reward responsiveness in the context of stress, studies linking reward processing to resilience often use a group design *without* stress manipulations (Dennison et al., 2016). As such our results are not necessarily contrary to findings of intact reward function buffering against psychopathology but rather represent a specific subgroup of individuals characterized by a *co-occurrence* of reduced stress and reward responsiveness. Future research could investigate a potential bidirectional relationship of stress and reward by recruiting a large sample of adults who maintain their ability to modulate reward responses in the context of blunted stress reactivity to investigate a possible relationship with resilience.

Interestingly, altered behavioral reward responsiveness by Non-Responders did not translate into neural differences (i.e., RewP or PFC activation). Animal studies have found that dopamine receptor expression in the striatum and PFC peak in the peripubertal period/onset of puberty before undergoing rapid pruning in adolescence (Andersen et al., 2000; Teicher et al., 1995). Hanson et al. (2021) suggested that, depending on the timing of the adversity, there may be differential implications for behavioral and neurobiological measures of reward. Indeed, Non-Responders who did not adjust their reward responses over time experienced CSA starting in childhood ($M = 7.8$ years) and ending during the peripubertal period ($M = 11.2$ years) before neural pruning begins in adolescence. Future research could explore if adversity during the maturational processes of overproduction vs. pruning may differentially affect behavioral and/or neural differences in reward processing.

Finally, our findings of co-occurring altered stress and reward responsiveness may help to guide treatment development. Dutcher and Creswell (2018) highlighted that increasing reward can buffer responses to subsequent stressors. For example, giving and receiving social support activates reward-related regions (Eisenberger et al., 2011; Inagaki and Eisenberger, 2012; Younger et al., 2010) and buffers against acute stress (Kirschbaum et al., 1995; Thorsteinsson et al., 1998). Our current findings further highlight that the timing of such interventions may be critical. Randomized controls trials could explore if creating a highly rewarding environment (e.g., supportive social connections) during critical phases of neurodevelopment (i.e., peripubertal) might help to recalibrate HPA axis activity to allow a mild-moderate stress interaction to promote resilience.

### 4.1. Limitations

Our study used a multi-method approach to address important and underexplored relationships between stress, reward, and CSA. However, several limitations should be noted. First, although there is no consensus regarding the minimum required sample size for latent class analysis, given our smaller sample size, our findings require replication in a larger sample. Second, despite our full and EEG sample did not differ in critical characteristics and showed a similar Responder/Non-Responder ratio

(see *Supplement*), the sample size for the ERP analyses may have been underpowered. In line with recent guidance for latent class analyses [e.g., Weller et al., 2020], several follow-up tests needed to be conducted to help interpret each class. All key analyses were adjusted for multiple comparisons (e.g., stress manipulation, PRT, scalp-recorded ERP, source localization). When we applied a conservative Bonferroni-corrected significance threshold (.05/5 = 0.01) to assess CSA clinical characteristics of each class, our finding that Non-Responders experienced CSA at a younger age remained significant ($p = .01$) for one-sided tests but not two-sided tests ($p = .02$). Accordingly, results will need to be confirmed in a larger sample. Third, like other relevant research [e.g., Suzuki et al., 2014], we defined resilience as the absence of psychopathology which may not have captured the complexity of resilience [i.e., ratio of adversity to well-being; Van Harmelen et al., 2017]. Consequently, future research adopting this definition of resilience may want to consider using a terminology to reflect this (e.g., CSA-noDiagnosis). Despite research suggesting different types of abuse are associated with stress and reward-related outcomes, studies commonly use a broader definition encompassing various forms of adversity. Here, we integrated CSA-specific research wherever possible but had to refer to non-specific abuse literature when needed.

## 5. Conclusion

The stress and reward systems are vulnerable to early life adversity (Brindle et al., 2022; Teicher et al., 2016). The current study utilized an empirical approach to identify two distinct cortisol trajectories (*Responders* and *Non-Responders*) to an acute stressor which were examined in the context of CSA history, resilience, and behavioral and neural measures of reward responsiveness. Non-Responders showed blunted cortisol reactivity to acute stress combined with a lack of modulating reward responsiveness on behavioral but not neural measures. While blunted cortisol was not directly related to a history of CSA or resilience, Non-Responders experienced CSA at an earlier age compared to Responders. Future research needs to replicate preliminary findings in larger samples and evaluate whether targeting reward responsiveness during critical times of development (i.e., peripubertal) can adjust stress reactivity to future stressors to promote resilience.

## Disclosure

Over the past 3 years, Dr. Pizzagalli has received consulting fees from Albright Stonebridge Group, Boehringer Ingelheim, Compass Pathways, Concert Pharmaceuticals, Engrail Therapeutics, Neurocrine Biosciences, Neuroscience Software, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; honoraria from the Psychonomic Society (for editorial work) and Alkermes, and research funding from NIMH, Dana Foundation, Brain and Behavior Research Foundation, Millennium Pharmaceuticals. In addition, he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (former BlackThorn Therapeutics), and Neuroscience Software. Dr. Pizzagalli has a financial interest in Neumora Therapeutics (former BlackThorn Therapeutics), which has licensed the copyright to the Probabilistic Reward Task through Harvard University. Dr. Pizzagalli's interests were reviewed and are managed by McLean Hospital and Massachusetts General Brigham in accordance with their conflict-of-interest policies. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. All other authors report no financial relationships with commercial interest.

## CRediT authorship contribution statement

**Pia Pechtel:** Conceptualization, Project administration, Data curation, Formal analysis, Writing – original draft. **Emily L. Belleau:** Project administration, Data curation, Writing – review & editing. **Roselinde H. Kaiser:** Project administration, Data curation, Supervision, Writing – review & editing. **Alexis E. Whitton:** Data curation, Writing – review & editing. **Miranda Beltzer:** Data collection, Data curation, Writing – review & editing. **Rachel Clegg:** Data collection, Data curation, Writing – review & editing. **Franziska Goer:** Data collection, Data curation, Writing – review & editing. **Gordana Vitaliano:** Writing – review & editing. **Martin H. Teicher:** Writing – review & editing. **Diego A. Pizzagalli:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

## Declaration of competing interest

Over the past 3 years, Dr. Pizzagalli has received consulting fees from Albright Stonebridge Group, Boehringer Ingelheim, Compass Pathways, Concert Pharmaceuticals, Engrail Therapeutics, Neurocrine Biosciences, Neuroscience Software, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; honoraria from the Psychonomic Society and American Psychological Society (for editorial work) and Alkermes, and research funding from NIMH, Dana Foundation, Brain and Behavior Research Foundation, Millennium Pharmaceuticals. In addition, he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (former BlackThorn Therapeutics), and Neuroscience Software. Dr. Pizzagalli has a financial interest in Neumora Therapeutics (former BlackThorn Therapeutics), which has licensed the copyright to the Probabilistic Reward Task through Harvard University. Dr. Pizzagalli's interests were reviewed and are managed by McLean Hospital and Massachusetts General Brigham in accordance with their conflict-of-interest policies. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. All other authors report no financial relationships with commercial 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.ynstr.2022.100498.

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