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Neural, behavioural and neuroendocrine responses to psychosocial stress in healthy women with adverse childhood experiences: an fMRI study

Claudio Peñafiel-Poblete
University of Chile
Francisco Zamorano
Clínica Alemana
Josué Luiz Dalboni Da Rocha
St. Jude Children's Research Hospital
Maria Jesus Vera
University of Chile
Rodrigo Valenzuela
University of Chile
Claudio Silva
Clínica Alemana
César Salinas
Clínica Alemana
Ximena Stecher
Universidad del Desarrollo
Ranganatha Sitaram
St. Jude Children's Research Hospital
Sergio Ruiz
sruiz@uc.cl

Pontificia Universidad Católica de Chile

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Abstract

Adverse childhood experiences (ACEs) are associated with an altered stress response, yet their neural, behavioural and neuroendocrine signatures in adults without psychopathology remain incompletely understood. We assessed responses to acute psychosocial stress in 79 healthy adult women with extreme scores on the Childhood Maltreatment Index (high ACE, n = 39; low ACE, n = 40), who completed a modified Montreal Imaging Stress Task (MIST) during functional magnetic resonance imaging, while subjective distress (SUD) and salivary cortisol were measured at four time points. Whole-brain analysis showed greater stress-related activation in the high-ACE group in the medial prefrontal cortex, bilateral superior frontal and angular gyri, supramarginal gyrus and posterior cingulate. The groups differed in reaction times during the no-stress condition ($p = .034$), whereas anxiety independently predicted reaction time under stress beyond maltreatment severity ($\beta = 0.28$, $p = .011$). The high-ACE group reported greater baseline distress (SUD1: 3.87 vs. 2.59; $p = .008$) and elevated cortisol 20 min post-task ($p < .01$), indicating delayed HPA-axis recovery rather than hyperreactivity. Resilience moderated the maltreatment–cortisol association at peak stress ($\beta = -0.337$, $p = .040$). These findings suggest that early adversity contributes to a latent, multimodal profile of stress vulnerability, detectable without psychopathology.

INTRODUCTION

Adverse childhood experiences (ACEs)—encompassing various forms of abuse (physical, emotional, sexual), neglect and family-related adversity—are among the most consistent risk factors for physical and mental health. When experienced during critical developmental periods, these adversities may exert long-lasting effects that persist into adulthood [1, 2]. Although a substantial body of evidence links ACEs to alterations in the adult stress response, the underlying pathophysiological mechanisms remains incompletely understood. Notably,reviews of cortisol response to acute social stressors in adolescents and adults with early adversity have yielded mixed findings, with inconsistent associations across studies [3]. Clarifying these mechanisms has been recognized as a research priority, given the high global prevalence of childhood adversity and its substantial public-health burden. Accordingly, numerous studies have shown that ACEs are associated with functional and structural alterations in brain regions critical for emotion regulation and the stress response, such as the hippocampus, amygdala and prefrontal cortex [4, 5].

Part of the heterogeneity in these findings may be explained by factors that modulate the impact of adversity. The intensity and duration of ACEs may translate into differential neurological effects [6], and chronic adversity may cause deeper alterations when it occurs in periods of heightened brain plasticity [5]. Moreover, not everyone exposed to ACEs develops emotional or health problems: resilience—the capacity to maintain or recover equilibrium after adversity [7]—has been linked to factors ranging from genetic and neurobiological substrates to social support and emotional self-regulation [8, 9].

Studies using standardized social-stress paradigms, such as the Montreal Imaging Stress Task (MIST) or the Trier Social Stress Test (TSST), have documented differential behavioral and neural responses among individuals exposed to childhood maltreatment. Reported neural differences involve regions implicated in stress regulation and socioemotional processing, including the ventromedial prefrontal cortex, rostral anterior cingulate and parietal regions, although the specific regions implicated vary across studies [10, 11]. This variability may partly reflect the fact that most studies were conducted in clinical populations with post-traumatic stress disorder PTSD or major depression, leaving unresolved how these differences manifest in adults without overt psychopathology. Studying psychiatrically healthy adult women with an history of severe ACE llows the neurobiological signature of early adversity to be examined independently of the confounding effects of active psychiatric illness. Moreover, the inclusion of both men and women i may have contributed to inconsistent findings, given the well-established sex differencesex differences in hypothalamic-pituitary-adrenal (HPA) axis reactivity to psychosocial stress [12], and the higher prevalence among women of certain forms of childhood maltreatment, particularly sexual abuse [13]. Focusing exclusively on women may therefore help reduce a potentially important source of biological and experiential heterogeneity.

Importantly, characterizing the stress response in ACEs requires going beyond brain activation to incorporate the principal neuroendocrine stress axis. Early adversity can dysregulate cortisol production, giving rise to both heightened reactivity [14] and a blunted response [15]. A recent meta-analysis of 129 studies confirmed that childhood adversity is associated with higher evening cortisol, a flatter diurnal slope and, notably, blunted cortisol reactivity, with a pattern dependent on the stage at which the adversity occurred [16]. Consistent with these findings, healthy adults without psychopathology who report childhood maltreatment show decreased cortisol and ACTH responses on the TSST [17], and individuals with childhood trauma exhibit altered emotional and cortisol responses to acute social stress [18]. Accordingly, assessing salivary cortisol at multiple time points provide a valuable approach for characterizing whether HPA-axis responses in these women exhibit acute hyperreactivity, blunted responsivity, or delayed recovery—patterns that cannot be differentiated using neuroimaging measures alone.

Naturally, stress responses extend beyond neuroendocrine and neural processes to include a subjective dimension, which may be dissociated from physiological indices. Quantifying perceived distress with the Subjective Units of Distress (SUD) scale concurrently with cortisol levels can help understand if the subjective experience of stress coincides with—or decouples from—HPA-axis activation. The potential dissociation between subjective and physiological stress responses is of particular interest, as individuals with childhood trauma have been shown to exhibit a decoupling between the emotional/subjective response and the cortisol response to social stress [18]. Furthermore, emotion-regulation capacity seems to moderate the relationship between maltreatment and cortisol reactivity [19]. Integrating subjective (SUD), neuroendocrine (cortisol), behavioral (reaction time) and neural (BOLD) indices within a single protocol offers a multilevel characterization of latent stress vulnerability in ACEs.

A less explored aspect concerns the factors that may modulate this latent vulnerability to stress. Most prior studies on brain responses to stress following childhood adversity did not systematically control for depressive symptoms, anxiety or resilience, making it difficult to determine whether observed differences are directly attributable to early adversity itself or are instead shaped by these co-occurring factors. While resilience was introduced above as a construct linked to neurobiological and psychosocial protective factors, its role—together with that of anxiety and depressive symptoms—in modulating the acute stress response remains poorly characterized. Resilience, in particular, might buffer the impact of adversity on the stress response [7, 19], whereas anxiety and depressive symptoms might intensify it. The present study addresses this gap by incorporating these three variables into the analyses, in order to evaluate their modulating role on the neural, behavioural and neuroendocrine stress responses.

We hypothesized that, in adult women without active psychopathology, adverse childhood experiences would be associated with altered patterns of brain activity—measured by the blood oxygenation-level dependent (BOLD) signal via fMRI—during psychosocial stress- We further hypothesized that these neural alterations would be accompanied by a distinct profile of behavioural, subjective and neuroendocrine stress responses, and that the magnitude of these responses would be modulated by psychological variables (resilience, anxiety and depressive symptoms).

H1 A greater burden of adverse childhood experiences would be associated with a greater stress-related BOLD signal during the psychosocial-stress task.

H2 The burden of adverse childhood experiences would be associated with differences in reaction time under psychosocial stress.

H3 A greater burden of adverse childhood experiences would be associated with an altered profile of subjective (SUD) and salivary-cortisol responses across the protocol, including patterns of hyperreactivity, blunted responsivity, or delayed recovery.

H4 Resilience, anxiety and depressive symptoms would modulate these responses; in particular, resilience would attenuate the association between maltreatment burden and stress reactivity, whereas anxiety and depressive symptoms would intensify it based on this rationale,

The present study examined whether adverse childhood experiences (ACEs) are associated with distinct neural, behavioural, subjective, and neuroendocrine responses in response to social-stress, in adult women without active psychopathology. The specific objectives were: (1) to compare brain activations under psychosocial stress in adult women with and without an ACE history; (2) to compare behavioural responses (reaction time) under psychosocial stress across groups; (3) to compare subjective (SUD) and neuroendocrine (salivary cortisol) responses across groups throughout the protocol; and (4) to evaluate whether resilience, depressive symptoms or anxiety modulate these responses.

RESULTS

Participant characteristics

The final sample comprised 79 adult women (low MACE, n = 40; high MACE, n = 39), aged 18 to 40 years. All had absent or mild psychological symptoms and were not undergoing psychological or psychiatric treatment. The groups differed significantly ($p < .01$) on all clinical scales except the CD-RISC (resilience), where there was no significant difference (Table 1). Age did not differ between groups.

Table 1
Participant characteristics by group.

Variable	High MACE (M ± SD, median)	Low MACE (M ± SD, median)	p
Age (years)	24.32 ± 4.82 (23.00)	24.48 ± 4.80 (23.00)	n.s.
Total MACE	19.71 ± 6.61 (19.71)	2.13 ± 1.79 (2.00)	< .01
CMI (z-score)	1.77 ± 0.95 (1.73)	−1.77 ± 0.89 (− 1.74)	< .01
PHQ-9 (depression)	9.59 ± 7.04 (9.00)	3.90 ± 3.31 (3.00)	< .01
GAD-7 (anxiety)	7.10 ± 6.34 (6.00)	3.21 ± 2.97 (3.00)	< .01
CD-RISC (resilience)	62.97 ± 13.08 (66.00)	64.60 ± 13.66 (64.50)	n.s.
Psychiatric treatment (years)	2.58	1.75	—
Psychotherapy episodes (n)	0.83	0.65	—

Note. High MACE, n = 39; Low MACE, n = 40. The second value in each cell is the median. CMI = Childhood Maltreatment Index (standardized Rasch z-score). n.s. = non-significant ($p > .05$).

Behavioural results: reaction times

Figure 3. Behavioural results. (A) Reaction time by group and condition (mean ± SEM); Low MACE (blue) and High MACE (orange); **$p < .01$ under the no-stress condition. (B) Intragroup Spearman correlation between the Childhood Maltreatment Index (CMI) and stress reaction times; no correlation reached significance (all $p > .10$).

A mixed-design ANOVA (group × condition) revealed a significant main effect of condition, $F(1,77) = 49.17$, $p < .001$, and a significant group × condition interaction, $F(1,77) = 4.67$, $p = .034$ (Fig. 3A). Post-hoc analyses with Bonferroni correction showed that the low-MACE group had significantly longer reaction times than the high-MACE group in the no-stress condition ($p = .004$), with no between-group differences under stress ($p > .05$). As accuracy data were not available, these differences cannot be directly interpreted in terms of cognitive efficiency.

Maltreatment–reaction-time correlation

Because the CMI was used as the criterion for selecting the extreme groups, a global correlation over the whole sample was avoided so as not to artificially inflate the coefficient. Spearman correlations were computed independently within each group (Fig. 3B). No within-group correlation reached significance: under no-stress, low MACE ρ = −0.007 (p = .966) and high MACE ρ = 0.182 (p = .295); under stress, low MACE ρ = −0.255 (p = .112) and high MACE ρ = 0.187 (p = .281).

Hierarchical regression of reaction time under stress

To examine how resilience, anxiety and depressive symptoms influenced the CMI–behavioural-performance relationship, a hierarchical regression was performed with mean stress reaction time as the dependent variable (Table 2). In Step 1, CMI showed a significant effect (β = 0.25, p = .027; R^2 = .06). In Step 2, adding resilience (CD-RISC) slightly reduced the effect of CMI (β = 0.22, p = .041). In Step 3, incorporating GAD-7 and PHQ-9, CMI was no longer significant (β = 0.13, p = .132), whereas anxiety emerged as a significant predictor (β = 0.28, p = .011); resilience (β = −0.20, p = .062) and depressive symptoms (β = 0.09, p = .335) were not significant. The final model explained more variance (adjusted R^2 = .18) than CMI alone, indicating that anxiety is a substantial predictor of behavioural stress reactivity beyond the direct effect of maltreatment.

Table 2
Hierarchical regression of reaction time under stress.

Step	Predictor	β	p	R^2 / adj. R^2
1	CMI	0,25	.027	R^2 = .06
2	CMI	0,22	.041	—
	CD-RISC (resilience)	n.s.	n.s.	—
3	CMI	0,13	.132	adj. R^2 = .18
	CD-RISC (resilience)	−0,20	.062	
	GAD-7 (anxiety)	0,28	.011	
	PHQ-9 (depression)	0,09	.335	

Note. Dependent variable: mean reaction time in the stress condition. β = standardized coefficients.

Neuroimaging results: main contrast

Figure 4. fMRI results for the high MACE > low MACE contrast (stress > no-stress), overlaid on a standard MNI brain (axial and sagittal sections and a superior glass-brain view); the colour bar indicates the Z-value. Images follow radiological convention (L = left, R = right); on the sagittal section, S = superior and P = posterior. (A) Baseline model, without covariates. (B) Model including all psychological covariates

(PHQ-9, GAD-7, CD-RISC). The similarity between the two models reflects that the covariates did not substantially alter the activation pattern.

The main contrast (high MACE > low MACE, stress > no-stress, without covariates) identified six clusters with significantly greater activation in the high-MACE group, surviving cluster-size correction (Z > 2.3; FWE-corrected p < .05) (Fig. 4A; Table 3). These clusters comprised the medial frontal cortex, bilateral superior frontal gyrus, bilateral angular gyrus, supramarginal gyrus, posterior cingulate, and left superior temporal gyrus.

Table 3
Significant clusters of the main contrast (high MACE > low MACE, stress > no-stress).

Cluster	Peak Z	x	y	z	Area (Harvard-Oxford Atlas)	Hem.
6	4,55	66	−52	14	Angular gyrus	R
	4,46	68	−40	18	Supramarginal gyrus, posterior division	R
5	4,74	4	40	52	Superior frontal gyrus	R
	4,66	−16	22	58	Superior frontal gyrus	L
4	3,96	−4	−46	20	Posterior cingulate	L
	3,61	8	−50	26	Posterior cingulate	R
3	5,02	0	54	−14	Medial frontal cortex	R
	4,36	8	68	8	Frontal pole	R
2	3,75	−66	−18	−2	Superior temporal gyrus	L
	3,70	−56	−4	−10	Superior temporal gyrus	L
1	4,35	−58	−56	38	Angular gyrus	L
	4,16	−54	−60	40	Lateral occipital cortex	L

Note. Coordinates in MNI space (mm), corresponding to the peak voxel of each cluster. Threshold Z > 2.3 with cluster-size correction (FWE, p < .05). Hem. = hemisphere (R = right, L = left).

Hierarchical model comparison. To examine whether psychological variables contributed to the observed neural differences, a series of hierarchical second-level models was fitted in SPM12, comparing the baseline model (high MACE > low MACE; stress > no-stress) against versions including PHQ-9, GAD-7 and CD-RISC scores as covariates, individually and in combination, with otherwise identical design matrices. No covariate model produced suprathreshold clusters after family-wise error correction at the cluster level (p < .05). Voxelwise F-statistic maps showed no improvement in model sensitivity: maximum F-values ranged from 9.89 to 11.23, all with corrected p-values above .08, and no voxels exceeded uncorrected thresholds (p < .05, .01 or .001) in any model. Compared with the baseline analysis in FSL (six clusters), the inclusion of covariates produced a slight reduction (five clusters)

(Fig. 4B), suggesting that these psychological traits did not add meaningful explanatory power in this context.

Subjective distress results (SUD)

Figure 5. Subjective and neuroendocrine responses. (A) Subjective Units of Distress (SUD) by group and time point (mean ± SEM); **p < .01 at baseline (SUD1). (B) Salivary cortisol by group and time point (geometric mean ± SEM, log10 scale); **p < .01 at time point 4 (20 min post-task). Low MACE (blue), High MACE (orange).

Subjective distress rose markedly from baseline to the time point following the no-stress phase in both groups (within-subject SUD1→SUD2: high MACE d = 0.90, low MACE d = 1.37, both p < .001) and then declined across the remaining time points (Fig. 5A). The high-MACE group reported significantly greater baseline distress than the low-MACE group (SUD1: 3.87 vs. 2.59; U = 950, p = .008, Mann-Whitney U). At the subsequent time points, no significant between-group differences were observed (SUD2: 5.79 vs. 5.43, p = .561; SUD3: 3.37 vs. 3.14, p = .805; SUD4: 2.25 vs. 1.77, p = .406).

Cortisol results

No significant cortisol differences were observed between groups at time points 1, 2 or 3 (p > .05 in all cases). At time point 4 (20 minutes post-task), the high-MACE group showed significantly higher cortisol than the low-MACE group (geometric mean: 0.2586 vs. 0.0968; p < .01, Welch's t-test on log10 values) (Fig. 5B). This pattern—no differences during acute stress but elevated cortisol in the recovery phase—suggests delayed HPA-axis recovery in the group with greater early adversity.

Moderation of the maltreatment–cortisol relationship by resilience

To examine whether resilience moderated the maltreatment–cortisol association, hierarchical regression models with the CMI × CD-RISC interaction term were fitted at each time point. Models at time points 2 and 4 were not significant (R^2 = .021, p = .707 and R^2 = .018, p = .852, respectively). At time point 3 (peak stress), the CMI × CD-RISC interaction was significant (β = −0.337, SE = 0.159, t = − 2.117, p = .040; R^2 = .129). Simple-slopes analysis revealed a positive maltreatment–cortisol relationship in participants with low resilience (− 1 SD; β = +0.339) and an inverted relationship in those with high resilience (+ 1 SD; β = −0.335), indicating that resilience selectively attenuates the neuroendocrine impact of maltreatment under maximal psychosocial demand.

DISCUSSION

This study examined the behavioural, neural, subjective and neuroendocrine responses to psychosocial stress in healthy adult women with high versus low ACE histories, and exploratorily evaluated the moderating role of anxiety, resilience and depressive symptoms. To our knowledge, this is the first study

to integrate neural (fMRI), behavioural (reaction time), subjective (SUD) and neuroendocrine (salivary cortisol) stress measures within a single protocol exclusively in women with childhood adversity but without active psychopathology.

It is important to clarify the scope of the term "healthy" used to describe the sample. Although both groups were free of active psychiatric diagnosis and no participant was undergoing psychological or psychiatric treatment at the time of the study, the high-MACE group displayed elevated subclinical scores on depressive symptomatology (PHQ-9: 9.59 ± 5.81) and anxiety (GAD-7: 7.10 ± 4.41), significantly higher than those of the low-MACE group ($p < .01$). Participants with severe depressive symptoms (PHQ-9 ≥ 20) were excluded and referred to specialized care. Thus, the sample does not represent psychologically asymptomatic women, but rather women without active psychopathology—a distinction that, far from constituting a limitation, is precisely what allows examining the imprint of early adversity within a subclinical range, free of the confound of current diagnosis or treatment. The findings converge on a latent, multimodal vulnerability profile associated with early adversity, detectable even in the absence of overt psychopathology.

Overall, our general hypothesis was supported: in women without active psychopathology, childhood adversity was associated with a distinct multimodal stress profile spanning neural, behavioural, subjective and neuroendocrine levels, with psychological traits playing a partial modulating role.

Behavioural findings

Consistent with H2, The observed reaction-time pattern—longer times in the low-MACE group under the no-stress condition, with no differences under stress—is consistent with the hypothesis that early adversity alters baseline behavioural-processing patterns. As accuracy data were not available, this interpretation remains conservative. Hierarchical regression analyses revealed that anxiety was the most robust predictor of reaction times under stress, explaining significant variance beyond CMI. This finding aligns with evidence that state anxiety predicts cognitive performance under acute psychosocial stress independently of cortisol reactivity [20], and with models proposing that anxiety constitutes a proximal mechanism through which distal childhood adversity influences adult stress-related functioning [21]. In the present sample, the attenuation of the CMI effect upon inclusion of anxiety in the model suggests that current anxiety symptoms may partially account for the behavioural differences initially attributed to maltreatment severity alone.

Neuroimaging findings

In line with H1 the main contrast identified greater activation in the high-MACE group across a distributed network comprising the medial frontal cortex, bilateral superior frontal gyrus, bilateral angular gyrus, supramarginal gyrus, posterior cingulate, and left superior temporal gyrus. These regions have been implicated in emotion regulation, error monitoring and cognitive control [4, 10, 11].

Tangentially, part of this topography—medial prefrontal cortex, posterior cingulate and angular gyrus—overlaps with regions described in social- and self-referential-processing networks [22, 23]. However, this remains speculative, as these processes were not examined directly in this study.

The hierarchical model comparison revealed no significant contribution of the psychological variables (resilience, anxiety, depressive symptoms) to the neural differences: no covariate model survived correction for multiple comparisons, and the inclusion of covariates only slightly reduced the number of clusters relative to the baseline model. This suggests that the activation pattern associated with early adversity is relatively robust and independent of these psychological traits.

Subjective (SUD) and cortisol responses

As predicted in H3 the high-MACE group showed significantly greater baseline subjective distress (SUD_1: 3.87 vs. 2.59; $p = .008$), with no between-group differences at later time points, consistent with chronic stress sensitization rather than differential acute reactivity [14, 18].

Taken together, the SUD and cortisol findings suggest a differentiated response profile at the subjective and neuroendocrine levels. At the subjective level, greater baseline distress without differences in task reactivity points to chronic activation rather than acute hypersensitivity. At the neuroendocrine level, the absence of differences during acute stress but elevated cortisol at time point 4 (20 min post-task; geometric mean 0.2586 vs. 0.0968; $p < .01$) suggests delayed HPA-axis recovery. This dissociation between elevated baseline subjective distress and a delayed—rather than immediate—cortisol rise is congruent with stress-sensitization models and with evidence of blunted or altered cortisol reactivity following early adversity [15, 16, 17]. These multimodal data reinforce the notion of a latent vulnerability profile operating at the neural, behavioural, subjective and neuroendocrine levels, observable even without clinical psychopathology.

Moderation by resilience

H4 was partially supported. Resilience moderated the maltreatment–cortisol relationship specifically at peak stress ($\beta = -0.337$, $p = .040$): high resilience inverted the positive maltreatment–cortisol slope observed in low-resilience individuals. This pattern suggests that resilience does not operate as a tonic buffer against HPA-axis activation but rather exerts a phasic protective effect precisely when the system is under maximal demand, in line with context-dependent models of resilient neuroendocrine functioning [19, 24]. The clinical implication is that resilience could constitute a modifiable target for reducing the neuroendocrine burden of early adversity under acute stress. Nevertheless, because the overall model at time point 3 did not reach significance ($R^2 = .129$, $p = .111$), this finding should be interpreted with caution. Contrary to our hypothesis, depressive symptoms did not emerge as a significant modulator of the stress response at any level—behavioural, neural or neuroendocrine. This may reflect the restricted range of depressive symptomatology in a sample without active psychopathology, or suggest that anxiety, rather than depression, is the more proximal affective correlate of stress reactivity in this population.

A methodological aspect relevant for future research is that, although the MIST is one of the most widely used psychosocial-stress paradigms in neuroimaging, the behavioural performance of the task—particularly response times—is rarely reported, since the MIST is used predominantly as a stress inducer for studying neural activation and the cortisol response. The present study suggests that the behavioural parameters of the MIST could provide complementary information about stress processing in populations with early adversity, and that their systematic reporting in future studies could be informative.

Limitations

The present study has some limitations. First, the sample size (n = 79) limits statistical power, particularly for the hierarchical comparison of neuroimaging models. Second, the cross-sectional design precludes causal inference. Third, the absence of accuracy data during the MIST task limits the interpretation of reaction-time differences in terms of cognitive efficiency. Fourth, because the CMI was used as the grouping criterion—selecting participants with extreme scores to maximize between-group contrast—unbiased global CMI–reaction-time correlations could not be computed, and the within-group analyses are therefore exploratory. Fifth, no slice-timing correction was applied; given the block design, the impact of this omission on the present results is considered limited.

CONCLUSIONS

This study found significant behavioural, neural, subjective and neuroendocrine differences between healthy adult women with high versus low ACE histories during a psychosocial-stress task. The high-ACE group showed shorter reaction times under neutral conditions, greater activation in emotion-regulation and cognitive-control regions, elevated baseline subjective distress consistent with chronic sensitization, and a delayed cortisol rise suggesting compromised HPA-axis recovery. Anxiety emerged as a significant predictor of behavioural stress reactivity beyond maltreatment, and resilience moderated the maltreatment–cortisol relationship at peak stress. These findings highlight a latent, multimodal vulnerability arising from early adversity and underscore both anxiety and resilience as clinically relevant targets for stress-regulation interventions.

METHODS

Participants

Initially, 700 women from the general population were recruited through social media and snowball sampling. Of these, 435 completed the screening questionnaires and 79 met the inclusion criteria, constituting the final sample.

Inclusion criteria: women aged 18 to 40 years, right-handed, with at least completed primary education and no contraindications for magnetic resonance imaging. Participants were selected on the basis of extreme scores on the Childhood Maltreatment Index (CMI) of the MACE questionnaire [6] to maximize

between-group differentiation. Two groups were defined: high MACE (high ACE, n = 39), with high childhood-maltreatment severity (more than 20 episodes before age 18, each lasting 3 or more years); and low MACE (low ACE, n = 40), with minimal maltreatment (fewer than 10 episodes before age 18, each lasting no more than 1 year).

Exclusion criteria: documented head trauma, brain damage, severe chronic medical or psychiatric illness, problematic substance use, and psychiatric medication that could not be discontinued. Women with severe depressive symptoms (PHQ-9 ≥ 20) were excluded and referred to specialized care. The Scientific Ethics Committee for Health Sciences of the Pontificia Universidad Católica de Chile approved the study protocol (protocol ID 200618005; approved 20 May 2021). All participants provided written informed consent before enrolment. All methods were carried out in accordance with the Declaration of Helsinki and with the relevant guidelines and regulations.

Measurement instruments

Maltreatment and Abuse Chronology of Exposure (MACE). A questionnaire that retrospectively assesses exposure to various forms of childhood maltreatment and generates the Childhood Maltreatment Index (CMI), a cumulative severity-and-frequency score derived from a Rasch-model-based analysis [6].

Patient Health Questionnaire-9 (PHQ-9). A 9-item self-report instrument assessing the severity of depressive symptoms over the previous two weeks [25], validated in the Chilean population [26].

Generalized Anxiety Disorder-7 (GAD-7). A 7-item self-report instrument assessing the severity of generalized anxiety symptoms [27], validated in Chile [28].

Connor-Davidson Resilience Scale (CD-RISC). A scale assessing individual resilience characteristics, defined as the capacity to adapt to and recover from adversity [29], validated in Chilean samples [30].

Subjective Units of Distress (SUD). A single-item self-report scale quantifying perceived distress from 0 (no stress) to 10 (maximum imaginable stress), administered at four time points.

Salivary cortisol. Four saliva samples were collected using Salivette devices (Sarstedt, Nümbrecht, Germany) at the same four time points as the SUD scale. After collection, samples were stored at 2–8°C until processing. Cortisol concentration was determined by a competitive enzyme immunoassay (Cortisol Parameter Assay Kit, catalogue KGE008B; R&D Systems, Minneapolis, MN, USA), with a sample volume of 20 µL and a nominal sensitivity of 0.111 ng/mL. Samples were analysed across several runs. Cortisol values (ng/mL) were log-transformed (log10) for analyses, given their skewed distribution.

Psychosocial stress-induction task (MIST)

Figure 1. Montreal Imaging Stress Task (MIST) paradigm. The task comprises three phases: practice (outside the scanner, no time limit), no-stress (inside the scanner, no time pressure or negative feedback) and stress (inside the scanner, with adaptive time pressure and negative feedback).

The Montreal Imaging Stress Task (MIST [31]) (Fig. 1) was used to induce psychosocial stress in a controlled manner inside the scanner. The MIST consists of arithmetic problems of varying complexity presented visually; responses are provided via a joystick-controlled dial. The paradigm contrasts high-difficulty blocks (which, together with time pressure and negative feedback, constitute the stress condition) against low-difficulty blocks (no-stress condition). The task comprises three phases: a practice phase (outside the scanner) for familiarization and individual difficulty calibration; a no-stress phase (inside the scanner) of five 50-s blocks without time limits or negative feedback, each followed by 30 s of rest; and a stress phase (inside the scanner) with identical structure but adaptive time limits (0.5–5 s) and continuous negative feedback ensuring the perception of failure.

The protocol consisted of five consecutive phases, with subjective distress (SUD) recording and cortisol collection at four time points: (1) baseline, before the task; (2) after the no-stress phase; (3) after the stress phase; and (4) 20 minutes after task completion, to assess recovery (Fig. 2).

Figure 2. Schematic representation of the experimental protocol. The Montreal Imaging Stress Task (MIST) comprises three phases: practice (outside the scanner), no-stress (inside the scanner, no time pressure or negative feedback) and stress (inside the scanner, with adaptive time pressure and negative feedback). Subjective distress (SUD) and salivary cortisol were collected at four time points: (1) baseline, before the task; (2) after the no-stress phase; (3) after the stress phase; and (4) 20 minutes after task completion, to assess recovery.

Image acquisition

Images were acquired at Clínica Alemana de Santiago (Santiago, Chile) on a 3 T Siemens Magnetom Skyra scanner (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil.

T1 anatomical sequence. Sagittal MPRAGE with parallel acceleration (iPAT/GRAPPA, factor 2): TR = 2530 ms; TE = 2.21 ms; isotropic voxel of 1 × 1 × 1 mm; matrix 256 × 256; 176 slices.

BOLD functional sequence (EPI). Single-shot gradient-echo EPI: TR = 2210 ms; TE = 30 ms; flip angle = 80°; 38 slices; slice thickness = 3 mm; slice separation = 4.02 mm (gap ≈ 1.02 mm); acquisition matrix 74 × 74; in-plane resolution ≈ 3 mm; interleaved acquisition order; parallel acceleration (iPAT/GRAPPA, factor 2); 412 volumes (duration ≈ 15.2 min).

fMRI preprocessing and analysis

Preprocessing and analysis of the main contrast were performed with FSL 6.0.5 (FMRIB Software Library, Oxford, UK). Brain extraction of the T1 image was performed using the SIENA brain-extraction (BET) routine, first cropping the head-neck field of view; the extracted T1 served as the structural reference for registration.

Functional preprocessing. No initial volumes were removed. Motion correction with MCFLIRT, brain extraction with BET, spatial smoothing with a 5-mm FWHM Gaussian kernel and high-pass temporal

filtering with a 100-s cutoff were applied. No slice-timing correction or B0 field unwarping was applied. Prewhitening was applied in the statistical model.

Motion handling. The six rigid-body motion parameters (three translations and three rotations) estimated by MCFLIRT were included as nuisance regressors in the first-level model. An exclusion threshold for excessive motion was applied; no participant exceeded it, so there were no exclusions on this basis.

Registration. Functional images were registered to the individual T1 with 6 degrees of freedom and, from there, to MNI152 standard space (2-mm MNI152_T1 template) with 12 degrees of freedom followed by nonlinear registration (FNIRT, 10-mm warp resolution).

First-level model (GLM). Two explanatory variables (EVs) were modelled, corresponding to high-difficulty blocks (hard, stress condition) and low-difficulty blocks (easy, no-stress condition), in three-column format and convolved with the canonical double-gamma hemodynamic response function; the temporal derivative of each regressor was included. The first-level contrast of interest was stress > no-stress (hard > easy).

Second-level model (main contrast). The between-group comparison (high MACE > low MACE) was performed with a mixed-effects model (FLAME 1). Clusters were identified at $Z > 2.3$ with cluster-size correction controlling the family-wise error rate (FWE) at $p < 0.05$. Regions were labelled using the Harvard-Oxford Cortical Structural Atlas.

To assess whether psychological variables contributed to the observed neural differences, a series of hierarchical second-level models was fitted in SPM12 (Wellcome Centre for Human Neuroimaging, London, UK). Starting from the baseline model (high MACE > low MACE; stress > no-stress), versions including CD-RISC, PHQ-9 and GAD-7 scores as covariates were generated, individually and in combination, with otherwise identical design matrices. Because each model yields differences at the cluster and BOLD-signal levels, the models were formally compared with one another to determine whether these differences were significant—a procedure not directly performed by FSL's mixed-effects contrast. The main group contrast was therefore conducted in FSL and the hierarchical model comparison in SPM12; the two packages were used for complementary purposes.

Behavioural and neuroendocrine statistical analysis. The normality of distributions was assessed with the Shapiro-Wilk test. Reaction times were analysed with a mixed-design ANOVA (group × condition). For SUD measures, a t-test was used for SUD2 (normal distribution) and Mann-Whitney U tests for SUD1, SUD3 and SUD4. Between-group cortisol comparisons used Welch's t-test on log10-transformed values. Moderation of the maltreatment–cortisol relationship by resilience was assessed with hierarchical regressions including the interaction term (CMI × CD-RISC) at each time point. For the CMI–reaction-time relationship, Spearman correlations were computed independently within each group, to avoid the artificial inflation arising from extreme-group selection [32, 33]. Age was not included as a covariate, as it did not differ significantly between groups.

Declarations

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Author contributions

C.P.-P.: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. F.Z.: Methodology (fMRI protocol setup), Formal analysis, Investigation, Writing – review & editing. J.D.R.: Software, Formal analysis (neuroimaging pipeline), Writing – review & editing. M.J.V.: Investigation (saliva sample collection and cortisol determination). R.V.: Investigation (saliva sample collection and cortisol determination), Resources. C.Si.: Investigation (MRI acquisition). C.Sa.: Investigation (MRI acquisition). X.S.: Investigation (MRI acquisition). R.S.S.: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. S.R.: Conceptualization, Supervision, Funding acquisition, Project administration, Writing – original draft, Writing – review & editing.

Competing interests

The authors declare no conflicts of interest.

Data availability

The data supporting the findings of this study are available upon request from the corresponding author, SR (sruiz@uc.cl). The data are not publicly available due to privacy restrictions.

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Figures

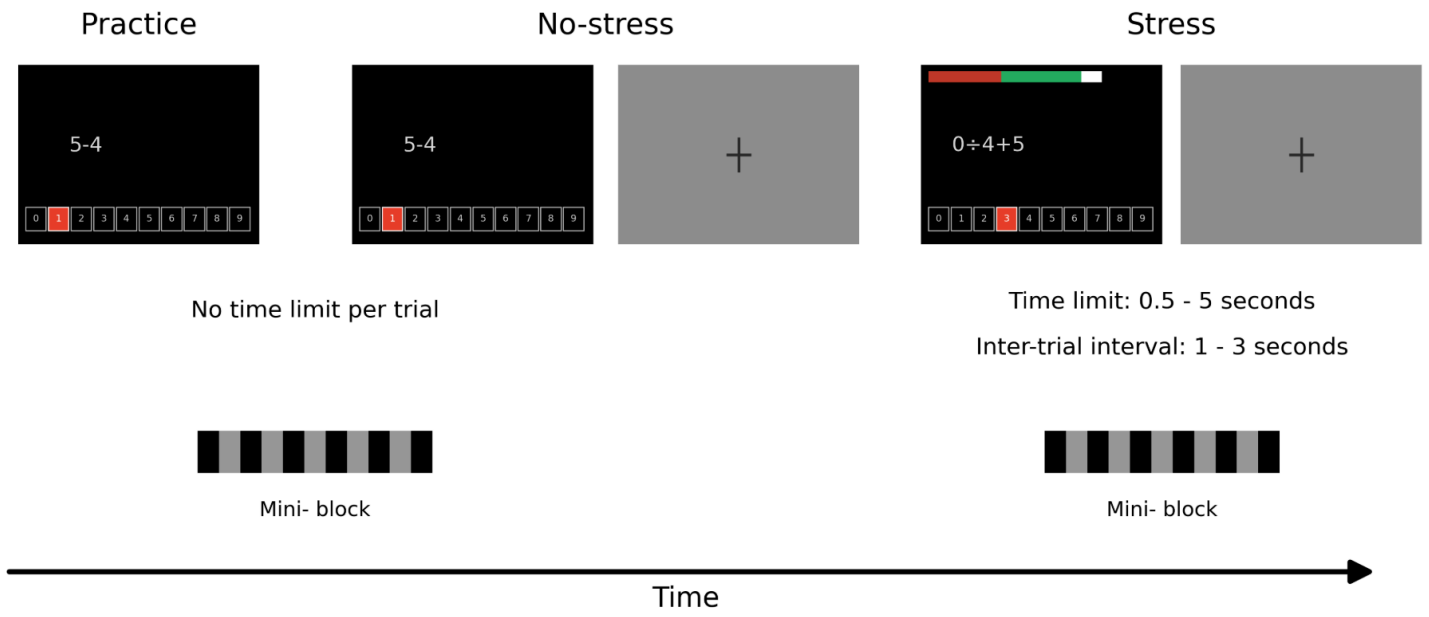


Figure 1

Montreal Imaging Stress Task (MIST) paradigm. The task comprises three phases: practice (outside the scanner, no time limit), no-stress (inside the scanner, no time pressure or negative feedback) and stress (inside the scanner, with adaptive time pressure and negative feedback).

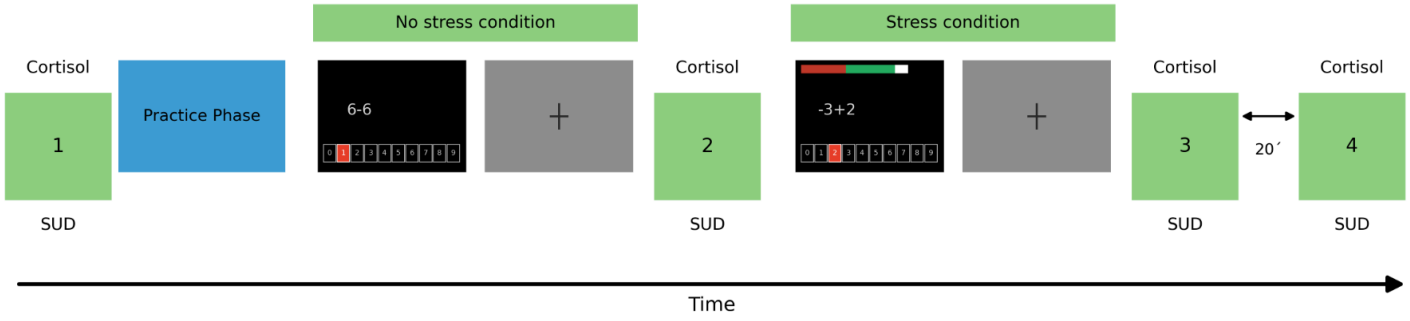


Figure 2

Schematic representation of the experimental protocol. The Montreal Imaging Stress Task (MIST) comprises three phases: practice (outside the scanner), no-stress (inside the scanner, no time pressure or negative feedback) and stress (inside the scanner, with adaptive time pressure and negative feedback). Subjective distress (SUD) and salivary cortisol were collected at four time points: (1) baseline, before the task; (2) after the no-stress phase; (3) after the stress phase; and (4) 20 minutes after task completion, to assess recovery.

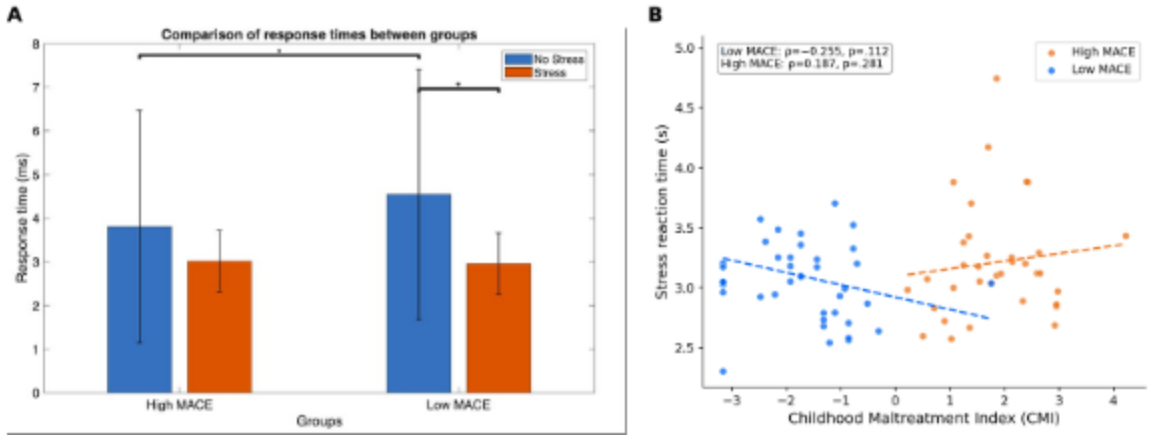


Figure 3

Behavioural results. (A) Reaction time by group and condition (mean ± SEM); low MACE (blue) and high MACE (orange); **p < .01 under the no-stress condition. (B) Intragroup Spearman correlation between the Childhood Maltreatment Index (CMI) and stress reaction times; no correlation reached significance (all p > .10).

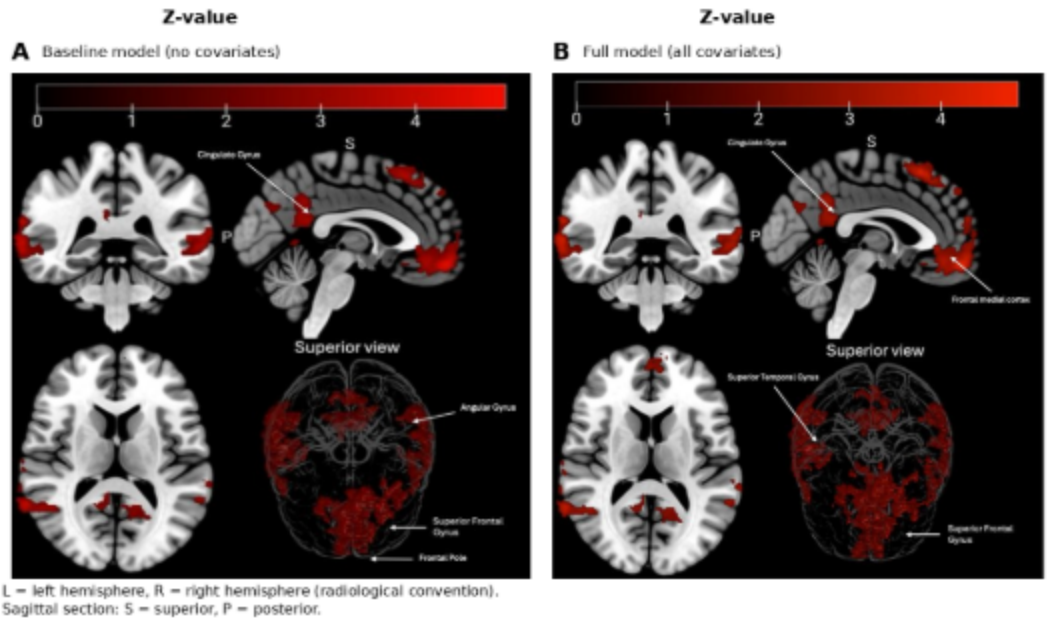


Figure 4

RI results for the high MACE > low MACE contrast (stress > no-stress), overlaid on a standard MNI brain (axial and sagittal sections and a superior glass-brain view); the colour bar indicates the Z-value. Images follow radiological convention (L = left, R = right); on the sagittal section, S = superior and P = posterior. (A) Baseline model, without covariates. (B) Model including all psychological covariates (PHQ-9, GAD-7, CD-RISC). The similarity between the two models reflects that the covariates did not substantially alter the activation pattern.

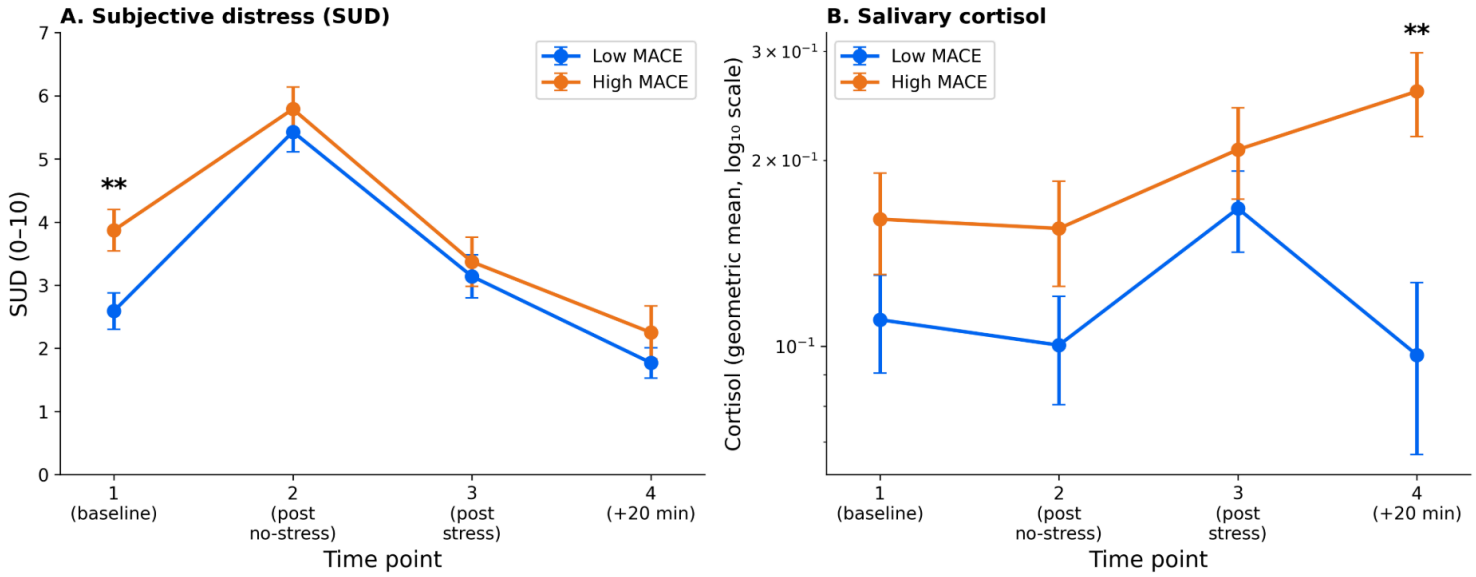


Figure 5

Subjective and neuroendocrine responses. (A) Subjective Units of Distress (SUD) by group and time point (mean ± SEM); **p < .01 at baseline (SUD1). (B) Salivary cortisol by group and time point (geometric mean ± SEM, log10 scale); **p < .01 at time point 4 (20 min post-task). Low MACE (blue), high MACE (orange).

Supplementary Files

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