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Effects of Exposure to Life Stressors, Perceived Stress, and Psychopathological Symptoms on Cortisol Awakening Response: Individual Differences in Resilience

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ABSTRACT

Cortisol awakening response (CAR) has been proposed as a viable biomarker for assessing the function of the hypothalamic-pituitary-adrenal axis. However, there are inconsistencies within the literature on the relationship between CAR and psychopathology. This study examined the unique effects of psychopathological symptoms on hypothalamic-pituitary-adrenal axis functioning (indexed through CAR) while considering the effects of exposure to major life stressors and self-reported perceived stress. The sample consisted of 71 participants, aged 25–37 years old. The Life Stress Index, Perceived Stress Scale, and Symptom Checklist-90 were administered. Salivary cortisol samples were collected across five time points (1 pre-bedtime and 4 upon awakening). A generalised additive model revealed a non-linear effect of time on cortisol concentration upon awakening, characterising CAR's prototypical inverted U-shaped pattern. The analysis also revealed a unique linear relationship between major life stressors and cortisol concentration. That is, greater exposure to major life stressors over the past 5 years was associated with elevated CAR. By contrast, there was also a unique linear relationship between psychopathological symptoms and cortisol concentration in the opposite direction. Contrary to expectations, our findings suggest that exposure to major life stressors, but not perceived stress, may increase cortisol awakening response, which may have implications for negative mental health outcomes (i.e., potential protective factor). These results highlight the importance of considering the complex interplay between stressors and psychopathological symptoms in understanding resilience.

1 | Introduction

We live in a dynamic environment, facing a myriad of stressors every day, which have a significant impact on our lives. The adaptive response of resilience is imperative to negotiate such a challenging environment, which is the capacity to preserve an individual's direction towards existential purpose in spite of adverse, traumatic, or stressful life experiences (Sisto et al. 2019). At the biological level, the hypothalamic-pituitary-adrenal axis has been purported to play an important role in this protective response through the secretion of cortisol as part of the adaptation process to environmental stressors (Feder et al. 2009). Consistent with this notion, an atypical hypothalamic-pituitary-adrenal axis has been demonstrated to have significant negative mental health outcomes (McEwen 2003). Hence, to better understand the neurobiological underpinnings of resilience, it is imperative to investigate how major life stressors, perception of

stress, and psychopathology may influence hypothalamic-pituitary-adrenal axis functioning.

The hypothalamic-pituitary-adrenal axis is thought to be central to our stress response system, releasing cortisol as a physiological response to the onset of stressors (Russell and Lightman 2019). An increase in cortisol in the bloodstream facilitates the mobilisation of energy and increases cardiovascular functioning, which are crucial functions for an individual to cope with the current demands of the situation (Herman et al. 2016). Notably, the hypothalamic-pituitary-adrenal axis has a non-linear diurnal pattern of basal activity, characterised by a spike in cortisol levels in the initial 30 min after waking up, followed by a gradual decline in cortisol throughout the day (Koss and Gunnar 2018; Lupien et al. 2009). This initial spike is known as cortisol awakening response (CAR), a distinctive feature of the hypothalamic-pituitary-adrenal axis (Fries et al. 2009; Wilhelm et al. 2007). One proposed functional significance of CAR has been purported to be an adaptive response to prepare an individual for the anticipated demands and challenges of the day (Contreras and Gutierrez-Garcia 2018; Fries et al. 2009; Seizer 2024; Stalder et al. 2025). Another proposed functional significance of CAR is its role as a counter-regulatory mechanism, helping the body return to homoeostasis following prior day negative emotional experiences (Adam et al. 2006; Doane and Adam 2010; Law et al. 2013; Stalder et al. 2025). In addition, individual differences in CAR have been found to vary as a function of multiple factors, including circadian and environmental factors, as well as affective and cognitive processes (Adam et al. 2010; Anderson et al. 2025; Bowles et al. 2022; Stalder et al. 2025). Overall, it appears that CAR is sensitive to hypothalamic-pituitary-adrenal axis activity, which can be measured reliably through the sampling of salivary cortisol concentration (Chida and Steptoe 2009).

While stress promotes adaptation, prolonged exposure to stress has been linked to alterations in the hypothalamic-pituitary-adrenal axis, which in turn can lead to an increased risk of negative mental health outcomes (Guidi et al. 2021). This long-term cumulative effect is more commonly known as allostatic load, in which chronic overloading may lead to an aberrant hypothalamic-pituitary-adrenal axis response (McEwen 1998, 2003, 2007; McEwen and Stellar 1993). Consistent with the notion of CAR as a biomarker of hypothalamic-pituitary-adrenal axis functioning, previous research has found attenuated CAR in individuals who have been exposed to chronic stress (Barker et al. 2012; Duan et al. 2013) and adversity during the early stages of puberty (Quevedo et al. 2012). Furthermore, within the psychopathology literature, attenuated CAR was observed in individuals with posttraumatic stress disorder (C. S. de Kloet et al. 2007), clinical depression (Rhebergen et al. 2015; Stetler and Miller 2005), atypical depression, and chronic fatigue syndrome (Herane-Vives et al. 2020). Healthy individuals who reported higher levels of trait anxiety, mild-to-moderate depression, and maladaptive eating behaviour were also found to have greater attenuation in CAR (Therrien et al. 2008; Walker et al. 2011). By contrast, other independent studies have also shown findings in the opposite direction. That is, elevated CAR was also observed in individuals with major depressive disorder (Bhagwagar et al. 2005; Vreeburg et al. 2009), panic disorder with agoraphobia, and various anxiety disorders with comorbid depressive disorder (Vreeburg et al. 2010). Furthermore, elevated CAR has been observed in healthy individuals with high levels of internalising symptoms, such as anxiety and depressive symptoms (Chong et al. 2017; M. Pruessner et al. 2003). While the findings remain inconsistent within the literature, hypothalamic-pituitary-adrenal axis functioning, indexed by CAR, appears to be implicated in various psychopathologies, suggesting an underlying stress-related vulnerability shared across these disorders rather than a disorder-specific phenomenon.

In contrast to allostatic load, perceived stress refers to an individual's subjective experience and perception of stressful situations (Cohen et al. 1983). Notably, perceived stress is one of many factors that influence allostatic load (McEwen 1998, 2003, 2007; McEwen and Stellar 1993). Like most psychological states, however, the perception of stress requires a certain level of introspection and self-awareness for appraisal (Haeffel and Howard 2010). This is particularly difficult given that the onset, intensity, and duration of stress can come in various forms, which may affect the perception of stress (Dunn et al. 2021). Interestingly, previous research has also demonstrated that one's perception of stress is not directly linked to physiological reactivity to stressors (Rith-Najarian et al. 2014). Given that allostatic load and perceived stress are closely related but distinct constructs, the heterogeneity in previous findings may be related to the lack of consideration of individual differences in these psychosocial factors, influencing variability in CAR (see Boggero et al. 2017 for a review). Hence, the present study aimed to investigate the role of hypothalamic-pituitary-adrenal axis functioning (i.e., indexed through CAR) as a potential transdiagnostic marker for the phenotypic expression of psychopathology. In addition, this study furthered previous research by taking into consideration the effects of both perceived stress and allostatic load (i.e., exposure to major life stressors). Given that stress response is purported to be one of the main functions of the hypothalamic-pituitary-adrenal axis, it is predicted that greater levels of perceived stress would be uniquely associated with greater levels of CAR. Exposure to major life stressors would also be uniquely and positively associated with greater levels of CAR. However, the existing literature pertaining to the relationship between CAR and psychopathology remains equivocal, which we hypothesise may be due to the lack of consideration of individual differences in allostatic load and perceived stress. Hence, if an aberrant hypothalamic-pituitary-adrenal axis is indeed involved in negative mental health outcomes, we predict that greater levels of self-reported psychopathological symptoms would also be uniquely associated with CAR but in the opposite direction, after controlling for the effects of perceived stress and exposure to major life stressors.

2 | Method

2.1 | Participants

Ethics approval was obtained from the Human Research Ethics Committee of the University of Hong Kong. Recruitment avenues included printed and social media advertisements and

directly from the FAMILY Cohort—a participant registry of Hong Kong residents (Leung et al. 2017). Given that data collection was conducted during the Coronavirus Disease 2019 (COVID-19) pandemic, individuals who were vaccinated (including any other form of vaccine), recently tested positive for COVID-19, had symptoms of COVID-19, or had a close contact (e.g., family member) that was diagnosed with COVID-19, were reinvited to join the study after 1 month. In addition, those who have travelled internationally were reinvited to join the study after 1 month.

Inclusion criteria included (1) healthy adults between ages 25–45 years old, (2) normal or corrected-to-normal vision and hearing, (3) at least grade 2 level literacy, (4) no history of major physical/psychiatric disorders, substance use, or heavy smoking (i.e., > 20 cigarettes per day), (5) not pregnant, breastfeeding, or taking oral contraceptives, and (6) not taking any medication or receiving any treatment within 2 weeks prior to the study that may affect the body's endocrinological system. The Structured Clinical Interview for DSM-5 Disorders—Clinician Version (First et al. 2016) was administered online or in person. Those meeting the diagnostic criteria for psychiatric disorders, such as mood disorders, anxiety disorders, substance-related and addictive disorders, feeding and eating disorders, or posttraumatic stress disorder, were excluded from this study. A total of 74 participants joined this study. Three participants did not adhere to the stipulated cortisol awakening sampling protocol and were omitted from the study. The final sample consisted of 71 participants, of which 41 were males, with ages ranging from 25 to 37 (M = 30.52, SD = 2.83). In terms of monthly household income, 2.82% reported less than $15,000, 21.13% reported between $15,000 and $29,999, 21.13% reported between $30,000 and $44,999, 15.49% reported between $45,000 and $59,999, 26.76% reported between $60,000 and $100,000, and 12.68% reported greater than $100,000 (Hong Kong Dollars; HKD). For context, the median monthly household income in Hong Kong is $30,000 (Department Census and Statistics 2024). Informed consent was obtained from all participants.

2.2 | Instruments

2.2.1 | Perceived Stress Scale (PSS)

The PSS is a 10-item self-report measure used to assess an individual's feelings and perception of stress over the past 3 months (Cohen et al. 1983). Items were rated on a 5-point Likert Scale. Possible range of responses include, '0—never', '1—almost never', '2—sometimes', '3—fairly often', or '4—very often'. Negatively keyed items were reverse-scored. The total score was derived by summing the scores on all items. Higher scores indicated greater levels of perceived stress. Previous research using a Chinese version of the PSS has demonstrated good internal consistency reliability (Cronbach's α = 0.86) and moderate temporal stability (r = 0.68) in the Chinese population (Wang et al. 2011), which we adopted for this study. Our sample achieved good internal consistency reliability (Cronbach's α = 0.87).

2.2.2 | Life Stress Index (LSI)

The LSI is an 18-item self-report measure used to assess major stressful life events that an individual has experienced or witnessed over the past 5 years. The inventory includes items such as 'Natural disaster', 'Sexual assault', and 'Death of family member or close friend'. Possible responses include (a) it happened to you personally or (b) you witnessed it happening to someone else. No response to a particular item indicated that the item does not apply to the participant. Each occurrence of a particular type of event was given a score of 1 for option (a) or 0.5 for option (b) and summed to derive the respective item scores. A total score for each participant was derived by summing all items. Higher scores indicated greater exposure to potentially traumatic events. Notably, we designed this inventory by referencing the Life Events Checklist for Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (Weathers et al. 2013), which has been demonstrated to have good 7-day test-retest reliability (r = 0.82) and moderate 12-week agreement (ICC = 0.54) (Gray et al. 2004; Pugach et al. 2021), and the Life Stress Assessment, which has been developed in Hong Kong's context (Nan et al. 2012).

2.2.3 | Symptom Checklist-90 (SCL-90)

The SCL-90 is a 90-item self-report checklist designed to assess the severity of a broad range of psychopathological symptoms over the past week (Derogatis 1994), which has been revised and translated for the Chinese population. The range of symptomatic dimensions spans 10 categories, namely somatisation, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, and additional items. The inventory includes items, such as 'Nervousness or shakiness inside', 'Feeling that most people cannot be trusted', and 'Worrying too much about things'. Each item was rated on a 5-point Likert scale ('NOT AT ALL', 'A LITTLE BIT', 'MODERATELY', 'QUITE A BIT', 'EXTREMELY'). Each subscale score is derived from summing the respective items. The total score (i.e., Global Severity Index) is derived from summing all items. Higher scores indicated greater severity of psychopathological symptoms. Our sample achieved excellent internal consistency reliability (Cronbach's α = 0.98).

2.3 | Salivary Cortisol Assay

Salivary samples were collected using the Salivette Cortisol tubes (Sarstedt, Art. No. 51.1534.500). The inter- and intra-assay coefficients of variation were 3.44% and 2.35%, respectively (Dubberke et al. n.d.). Prior to any sampling, participants were instructed to read the user manual provided by the manufacturer. Thereafter, participants were required to collect salivary samples at 5 time points—prior to sleeping, immediately after waking, 15 min after waking, 30 min after waking, and 60 min after waking. Participants had to (1) avoid caffeine (e.g., coffee) and alcohol intake within 24 h of the first salivary sampling, (2) avoid any food or beverage intake within 1 hour of each sampling, and (3) avoid toothbrushing, chewing gum, smoking,

flossing, or any other mint flavoured products within 1 hour of each sampling. At each time point, participants had to chew on a cotton swab for 45 s and, thereafter, allow the cotton swab to absorb their saliva under the tongue for 15 s. Thereafter, the swab had to be transferred to the Salivette Cortisol tubes. Participants were instructed to keep the tube tightly sealed, place the tubes in a zipper bag, and store the bag in the fridge at a recommended temperature of 4°C.

Participants were tasked to bring the samples to the site of the experiment using the provided isothermal bag with the provided ice pack. Participants were tasked to fill the ice pack with water and place it in the freezer overnight before usage. The collected samples were then preliminarily processed at an on-site laboratory. The salivary samples were extracted from the tube by centrifugation at 3000 × *g* for 5 min. The extracted samples were sent to the Centre for PanorOmic Sciences—Proteomics and Metabolomics Core, Li Ka Shing Faculty of Medicine, University of Hong Kong for further processing. Specifically, the centre performed liquid chromatography-tandem mass spectrometry analysis to quantify the level of cortisol concentration in the salivary samples (Raff and Phillips 2019).

2.4 | Procedure

After signing up for the study, a package containing five Salivette Cortisol tubes, an isothermal bag, a COVID-19 rapid antigen test kit, an ice pack, a zipper bag, a printed consent form, and an instruction sheet, was sent to each participant's homes via express courier services. Participants were invited to sign the informed consent. Thereafter, participants were instructed to read through the instructions carefully. On the day before the experiment (within 24 h of the first cortisol sampling time point), participants were first instructed to self-administer the rapid antigen test and send the results to the research team via email or instant messenger. Salivary sample collection would only begin after the confirmation of a negative rapid antigen test by the research team. At each cortisol sampling time point, participants were tasked to record and send the exact time of each sample collection to the research team via email or instant messenger. If participants had to take any medication during the cortisol sampling, they were required to inform the research team.

On the day of the experiment, participants were required to bring the samples to the laboratory using the provided zipper bags and ice packs to ensure that the samples were under cooled conditions during transport. Once on-site, participants had to hand over the samples to the research team. The self-report questionnaires were collected as part of a larger research project, and some of the works have been published (e.g., Shao et al. 2023). At the end of the experiment, participants were debriefed regarding the nature of the study.

2.5 | Statistical Analysis

The MGCV: Mixed GAM Computation Vehicle with Automatic Smoothness Estimation package in *R* was used to build the generalised additive model (Wood 2017). The generalised additive model is a flexible statistical framework used for modelling complex linear and non-linear fixed and random effects (Hastie and Tibshirani 1990). The dynamic changes in cortisol concentration over time upon awakening can be represented in the model more accurately by using a smooth function of time as compared to a single aggregated metric (e.g., area under the curve). Notably, deviations in the time of sampling are known to influence the estimation of CAR using traditional metrics (Smyth et al. 2013). This is a significant concern given that our study was a home-based experiment and, consequentially, greater deviations in sampling compliance were to be expected. Using the aforementioned approach can account for variations in sampling times as well as unequal numbers of observations across subjects or groups (Mundo et al. 2022) and, coupled with restricted maximum likelihood estimation, provides more reliable and less biased estimates of underlying variance components (Patterson and Thompson 1971). Consistent with previous research, the distribution of cortisol concentration is positively skewed; thus, gamma distribution with log link function was used (D'Elia et al. 2021; Kroll et al. 2019; Rudolph et al. 2016). Hence, to investigate the linear effects of perceived stress, major life stressors, and psychopathological symptoms, as well as the non-linear effect of time, on cortisol concentration upon awakening, a generalised additive model was employed. Given that previous research has demonstrated that the length of the previous night's sleep (Anderson et al. 2021) as well as pre-bedtime cortisol levels of the previous night (Proulx et al. 2017) may modulate CAR, the effects of sleep duration and pre-bedtime cortisol were included as covariates. Age and gender were identified as potential biological covariates previously (Almeida et al. 2009) and, thus, included in the model. Additionally, household income was used as a proxy measure for socioeconomic status, which has been found to be a psychosocial covariate (Wright and Steptoe 2005; Zhu et al. 2019). Lastly, subject was added to the model as a random effect. Four observations were excluded from the analysis due to incomplete data. Given the complexity of the generalised additive model, power analysis was conducted through a simulation-based approach (Kumle et al. 2021). The simulation included one polynomial term, three linear predictors, five linear covariates, and a random intercept. The outcome variable was simulated with a gamma distribution and a log link function. With an alpha level of 0.05 and a power of 0.80, the estimated sample size to detect small effect sizes for this study was 67.

3 | Results

The descriptive statistics of the predictors, covariates, and outcome used in subsequent analyses are reported in Table 1. The correlation matrix of the main predictors in the generalised additive model is reported in Supporting Information S1.

As reported in Table 2, time was a significant non-linear predictor of cortisol concentration, independent of the effects of perceived stress, major life stressors, psychopathological symptoms, sleep duration, pre-bedtime cortisol concentration, gender, age, and income. As can be seen in Figure 1, there was a non-linear pattern of change over time in cortisol upon

awakening, such that there was an increase in cortisol concentration approximately during the first 20 min of awakening, followed by a plateau for around the next 10 min, and then a decrease in cortisol concentration. The analysis also revealed a significant unique linear relationship between major life stressors and cortisol concentration. That is, greater exposure to major life stressors over the past 5 years was associated with elevated salivary cortisol concentration upon awakening (see Figure 2), even after controlling for the effects of time, perceived stress, psychopathological symptoms, sleep duration, pre-bedtime cortisol concentration, gender, age, and income. By contrast, the analysis revealed that psychopathological symptoms were a significant linear predictor of cortisol concentration (see Figure 2), but in the opposite direction. That is, greater severity of self-reported psychopathological symptoms was associated with attenuated levels of salivary cortisol concentration upon awakening. As can be seen in Supporting Information S1, the random effect of subject was also significant, capturing the intra-individual clustering effect of repeated sampling of cortisol after awakening. Overall, the model explained 68.9% of the variance of cortisol concentration upon awakening. The diagnostics plots of the non-linear model are illustrated in Supporting Information S1. In addition, another generalised additive model was conducted with the inclusion of the interaction terms between the main predictors (i.e., perceived stress, major life stressors, psychopathological symptoms). No interaction effect was observed in this model (see Supporting Information S1). Results using the traditional approach (i.e., AUC_{ground} and $AUC_{increase}$; J. C. Pruessner et al. 2003) are reported in Supporting Information S1 for comparison.

TABLE 1 | Descriptive statistics of the perceived stress scale, life stress index, global severity index of the symptom checklist-90, and sleep duration, with cortisol concentration measured at 5 time points.

			Range	
	M	**SD**	**Min**	**Max**
Perceived stress scale	17.24	6.14	2	33
Life stress index	0.92	1.13	0	5.5
Global severity index	33.32	37.77	1	191
Sleep duration (min)	472.93	86.35	242	652
Salivatory cortisol (ng/mL)				
Pre-bedtime	0.19	0.37	0.00	1.97
Immediately after waking	2.69	1.81	0.61	8.05
15 min after waking	3.96	2.39	0.60	11.45
30 min after waking	3.87	2.08	0.52	11.47
60 min after waking	2.40	1.22	0.33	6.27

4 | Discussion

The present study investigated the role of hypothalamic-pituitary-adrenal axis functioning, indexed through cortisol awakening response, in relation to the phenotypic expression of psychopathology, while accounting for perceived stress and allostatic load. Our findings reveal that the cortisol awakening

TABLE 2 | Generalised additive model with salivary cortisol concentration as the outcome variable, perceived stress scale, life stress index, global severity index of the symptom checklist-90, salivary cortisol assay time, sleep duration, pre-bedtime cortisol concentration, gender, age, and income as predictors.

	Estimate	**SE**	***T***	***p***
Parametric terms				
Intercept	1.59e+00	0.78	2.03	0.043*
Perceived stress scale	3.18e−03	0.01	0.26	0.794
Life stress index	1.39e−01	0.06	2.47	0.014*
Global severity index	−4.92e−03	0.00	−2.44	0.016*
Sleep duration (min)	−1.44e−03	0.00	−1.93	0.055
Pre-bedtime salivatory cortisol (ng/mL)	2.73e−01	0.17	1.62	0.106
Gender	1.56e−01	0.12	1.28	0.203
Age	2.75e−03	0.02	0.12	0.902
Income	−3.39e−02	0.04	−0.79	0.430
	edf	***rdf***	***F***	***p***
Smooth terms				
Time (min)	3.60	4.27	24.94	< 0.001*
Random term				
Subject	54.29	62.00	7.22	< 0.001*
$R^2_{adjusted}$	0.689			
Deviance explained	0.762			

Note: Gamma distribution with log link function was used. Time refers to the salivary cortisol assay time. All predictors were entered simultaneously.
Abbreviations: *edf* = effective degrees of freedom; *rdf* = reference degrees of freedom.

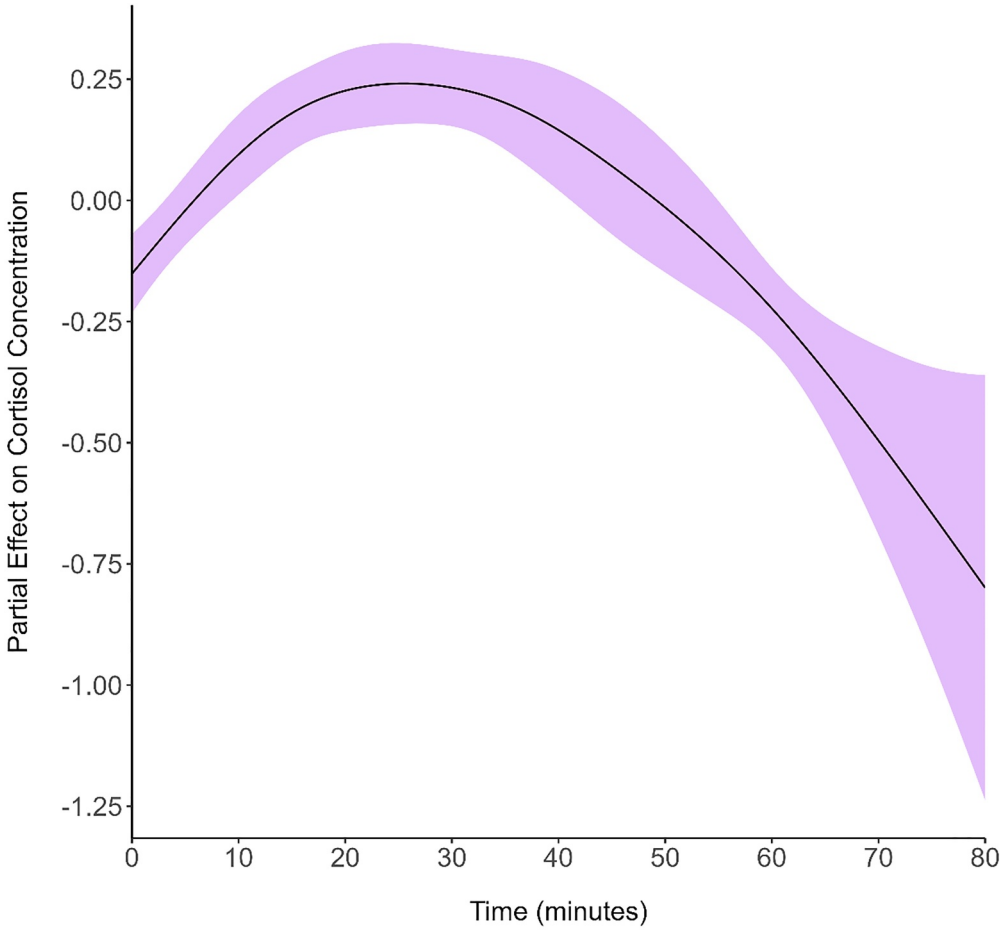

FIGURE 1 | Zero-centred smooth term of salivary cortisol assay time on cortisol concentration upon awakening. The solid line represents the partial effect of time on cortisol concentration and the pink shaded area represents the upper and lower bounds of an approximated 95% confidence interval.

response is linked to both higher stress exposure and lower psychopathological symptoms. Specifically, we demonstrated that greater exposure to major life stressors over the last 5 years was uniquely associated with higher levels of salivary cortisol after controlling for the linear effects of perceived stress, psychopathological symptoms, sleep duration, pre-bedtime cortisol levels, gender, age, income, and the non-linear effect of sampling time. Considering that the hypothalamic-pituitary-adrenal axis is viewed as our stress response system, which releases cortisol as a physiological response to the onset of stressors (Russell and Lightman 2019), the elevated cortisol levels reported in our study corroborated the purported functional significance of CAR as an adaptive response to prepare an individual for the anticipated demands upon awakening (Contreras and Gutierrez-Garcia 2018; Fries et al. 2009). This finding also indicates that the allostatic load due to previous major life stressors may not be sufficiently high and enduring to result in a compromised hypothalamic-pituitary-adrenal axis (McEwen 1998, 2003, 2007; McEwen and Stellar 1993). A recent review also purported that the increase in circulatory cortisol due to hypothalamic-pituitary-adrenal axis activation is responsible for regulating stress recovery, which helps promote resilience (E. R. de Kloet and Joëls 2023). While previous research has suggested that prolonged exposure to adversity has a negative impact on mental health (Guidi et al. 2021), other studies have shown that exposure to moderate levels of life stressors predicted better mental health outcomes (Dooley et al. 2017; Seery et al. 2010). Indeed, our variability in scores on life stressors appears to be on the lower end of the spectrum of severity, suggesting that our sample had only low to moderate levels of major life stressors. In combination with our findings, we argue that this enhanced CAR may be due to the development of a higher stress response in individuals who had been exposed to major life stressors. Future research should ascertain this notion by examining the non-linear effect across low, moderate, and high levels of adversity on CAR, through a larger sample of participants with greater variability in life stressors scores, and their effects longitudinally on future mental health outcomes.

Our study, however, did not find that perceived stress was a unique predictor of salivary cortisol upon awakening. This is inconsistent with previous research by Duan et al. (2013) finding that perceived stress was negatively correlated with CAR. A key difference between our study and previous research (e.g., Duan et al. 2013) is that we assessed stress exposure in addition to perceived stress. One plausible explanation for this inconsistency may be due to the distinction between exposure to stressors and perception of stressors. Notably, previous research found that stress exposure and perceived stress are only weakly associated (Vasunilashorn et al. 2015). Drawing from a recently introduced neurobiological theoretical framework for sensory processing in

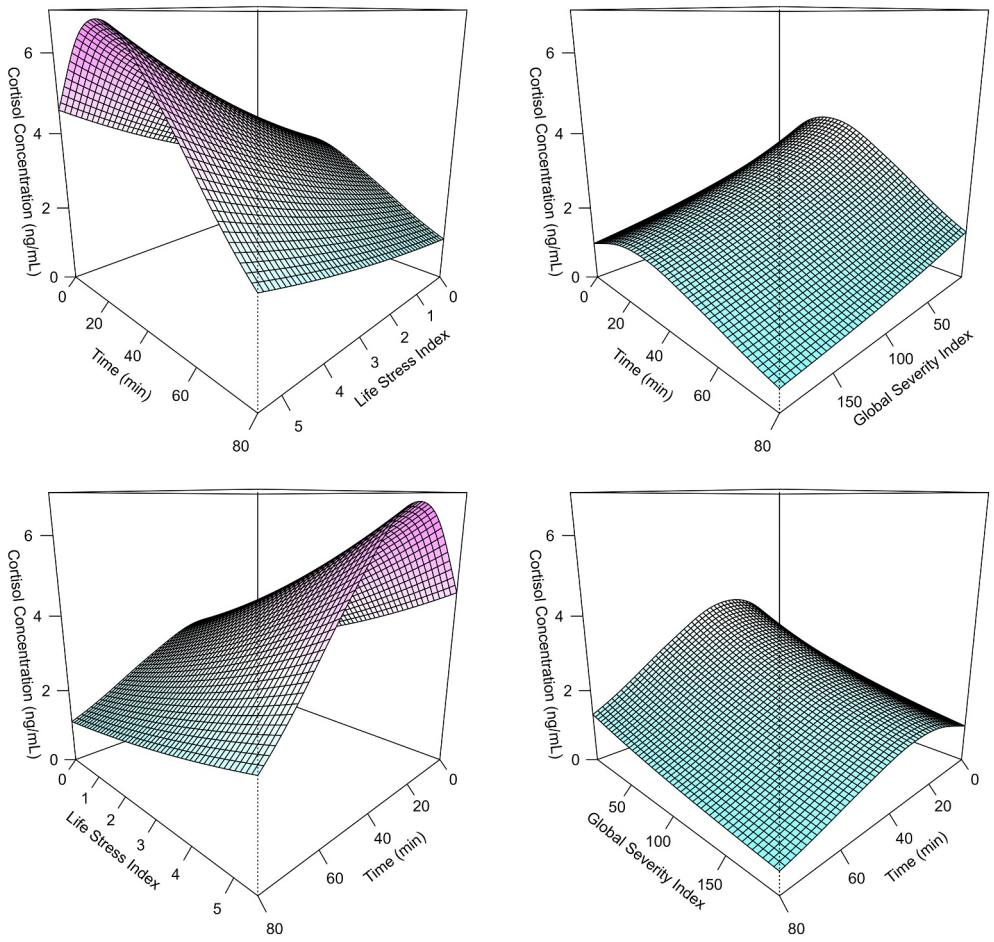

FIGURE 2 | The partial effects of recent major life stressors (on the left) and psychopathological symptoms (on the right) on cortisol awakening response with two different viewing angles.

posttraumatic stress disorder (Harricharan et al. 2021), the brain is hierarchically organised, such that the brainstem is involved in the phenomenon of sensory experience, the insula is implicated in the awareness of such experience, and the prefrontal cortex puts the context of such experience into perspective. Arguably, exposure and perception of stress may differentially modulate different regions of the brain, which in turn may lead to different patterns of cortisol response upon awakening. As compared to exposure, the perception of stress is a more dynamic process, which requires some level of higher-order cognitive evaluation (Lazarus and Folkman 1984). Future research should consider incorporating neuroimaging to investigate how differential neural activation may potentially moderate the relationship between perceived stress, stress exposure, and CAR.

Our results also revealed that greater severity of psychopathological symptoms was uniquely associated with attenuated CAR, corroborating studies that have reported that attenuated CAR was associated with various psychopathology and underlying symptoms (C. S. de Kloet et al. 2007; Herane-Vives et al. 2020; Rhebergen et al. 2015; Stetler and Miller 2005; Therrien et al. 2008; Walker et al. 2011). However, other studies have also demonstrated the relationship in the opposite direction (Bhagwagar et al. 2005; Chong et al. 2017; J. C. Pruessner et al. 2003; Vreeburg et al. 2009, 2010). That is, elevated CAR was associated with greater severity of psychopathology. The inconsistency in previous findings could potentially be due to the lack of consideration of individual differences in recent life stressors. As reported in our model, life stressors, alongside psychopathological symptoms, are both unique predictors of CAR. Building on previous research, our study provided some empirical evidence to support the notion that an aberrant hypothalamic-pituitary-adrenal axis may play a key role in the development of negative psychopathological outcomes. Specifically, the blunted cortisol awakening response associated with psychopathology may be indicative of a compromised hypothalamic-pituitary-adrenal axis. By contrast, the elevated response due to previous major life stressors may be indicative of resilience-building, where the system adapts to better deal with stressors. In any case, it appears that varying levels of psychopathological symptoms, as well as recent life stress events, may have their own distinct and unique influences on cortisol awakening response, highlighting the importance of considering these psychosocial factors when investigating the hypothalamic-pituitary-adrenal axis function in future studies.

It should be noted that the effect sizes reported in this study, while expected within this area of research, were relatively small. This might largely be due to the lack of variability at the higher end of the scale on both the psychopathological symptoms as well as major life stressors. Without diminishing the contribution of our findings to a healthy adult population, we also acknowledge that

there may be limitations in terms of generalisability to the clinical population. The limited variability at the top end is partly due to the exclusion of the clinical population from this study and the diversity of life stressors considered in the study. Hence, future researchers should consider stratified sampling across the range of possible scores of psychopathological symptoms as well as major life stressors. This would involve recruiting from both clinical and non-clinical populations, thereby allowing for more in-depth subgroup analysis across varying types, levels of severity, and durations of stressors and psychopathology. While our study only sampled cortisol on a single day, future researchers examining cortisol awakening response should be reminded that a minimum of 2 days is recommended to achieve greater reliability in CAR estimates (Stalder et al. 2016, 2022). Furthermore, given the complex relationship between the hypothalamic-pituitary-adrenal axis and individual differences in stress perception and exposure, future research should explore combining other neurobiological markers, as well as other clinical assessments, to create multivariate models to better characterise the different phenotypic expressions, risk, and neurobiological underpinnings of psychopathology.

5 | Conclusion

Consistent with the Research Domain Criteria framework (Cuthbert and Insel, 2013; Insel et al. 2010), our study examined the degree to which cortisol concentration upon awakening, which is a robust index of hypothalamic-pituitary-adrenal axis functioning, may be explained by individual differences in stress exposure and psychopathology amongst healthy adults. The findings of this study demonstrated that greater levels of cortisol awakening response varied uniquely as a function of greater levels of major life stressors, whereas greater levels of cortisol awakening response varied uniquely as a function of lower levels of psychopathological symptoms, providing endocrinological evidence that hypothalamic-pituitary-adrenal axis functioning may be differentially influenced by the aforementioned resilience-related psychosocial factors. In sum, while it may appear counterintuitive, life stressors should not be viewed as inherently detrimental to our lives. At moderate levels, each and every challenging experience could help build and fortify our resilience, through the adaptive response of our hypothalamic-pituitary-adrenal axis, preparing us for the next hurdle.

Author Contributions

Conceptualisation and design of the study (K.F.A. Lee and T.M.C. Lee). Acqusition and preprocessing of data (H. Tong and R.R. Jin). Analysis and interpretation of data (K.F.A. Lee). Drafting of initial manuscript (K.F.A. Lee). Revising of manuscript (K.F.A. Lee, H. Tong, R.R. Jin, and T.M.C. Lee). Final Approval (K.F.A. Lee, H. Tong, R.R. Jin, and T.M.C. Lee).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data will be available upon reasonable request.

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Supporting Information

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