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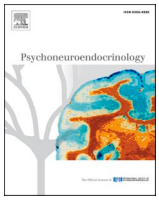

Stress arousal reappraisal and worked example effects on the neuroendocrine stress response during breaking bad news in medical education

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ABSTRACT

Breaking bad news (BBN; i.e., the disclosure of a serious diagnosis) is a necessary but challenging task in the medical field, often raising stress levels among physicians. According to the biopsychosocial model of challenge and threat, stress responses can manifest as adaptive challenge states or maladaptive threat states. Prior research has proposed that specific patterns in neuroendocrine responses may signal challenge and threat. In this study, we employed a 2 × 2 design to examine the effects of stress arousal reappraisal (SAR; i.e., reframing bodily arousal as a functional response) and worked example (WE; i.e., stepwise demonstration of BBN) interventions on salivary cortisol, dehydroepiandrosterone, and alpha-amylase responses. A total of 229 third-year medical students participated in a BBN simulation. While significant activation (rise) and regulation (decline) of neuroendocrine markers were observed in response to the BBN encounter, neither the SAR nor the WE intervention affected their peak levels or the magnitude (area under the curve) of the response. Only the WE intervention decelerated the rise and decline in dehydroepiandrosterone levels around individual peaks, potentially indicating an attenuated stress response. These findings suggest that neither of the interventions induced the expected challenge pattern in neuroendocrine activity. However, due to the low temporal resolution of salivary measurements and the dynamic process of challenge and threat orientations, we propose that the neuroendocrine responses may have limitations in distinguishing between challenge and threat.

1. Introduction

1.1. Neuroendocrine markers of challenge and threat

Stress is an inherent aspect of daily life, often perceived negatively despite being essential for human functioning, growth, and performance (Dhabhar, 2014). The biopsychosocial model (BPSM) of challenge and threat (Blascovich, 2008) considers both the positive and negative aspects of stress, specifically in motivated performance situations (i.e., personally relevant situations requiring an active response). According to this model, appraisals of coping resources relative to situational demands result in stress responses that are either challenge-oriented (when resources meet or exceed demands) or threat-oriented (when demands exceed resources). These responses are embodied in distinct cardiovascular activity patterns, which have been validated within the BPSM framework (e.g., Mendes and Park, 2014; Seery, 2011). Furthermore, researchers have shown sustained interest in establishing potential neuroendocrine markers of challenge and threat (e.g., Gaab et al., 2005; Guyon et al., 2020; Mendes and Park, 2014). It is theorized that sympathetic-adrenal-medullary (SAM) axis activation is similar during both challenge and threat, whereas heightened hypothalamic-pituitary-adrenal (HPA) axis responsiveness in anticipation of failure or harm may inhibit the beneficial effects of the SAM response during threat (Blascovich, 2008; Blascovich and Mendes,

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2010). However, empirical research on neuroendocrine markers differentiating between challenge and threat remains limited and inconclusive (e.g., Jamieson et al., 2010; Mendes et al., 2007; Schickel et al., 2023; Sicorello et al., 2021).

During stress exposure, activation of the HPA axis triggers the release of the catabolic hormone cortisol and the anabolic hormone dehydroepiandrosterone (DHEA; Izawa et al., 2008). Cortisol and DHEA regulate each other and together control vital processes such as the immune system and glucose metabolism, preparing the organism to cope with stressors (Buford and Willoughby, 2008). During psychosocial stress, elevated cortisol reactivity has been associated with reduced cardiac efficiency, impaired decision making and performance, whereas DHEA may act as a protective factor, enhancing similar processes (Hidalgo et al., 2020; Jamieson et al., 2012; Schickel et al., 2023; Shields et al., 2016). Given the interaction between DHEA and cortisol, the anabolic balance represented by the DHEA/cortisol ratio—an indicator of resilience and thriving under stress (Epel et al., 1998)—may be particularly sensitive to challenge and threat (Mendes et al., 2007; Mendes and Park, 2014). The HPA axis responds to stress exposure with peak salivary DHEA (sDHEA) levels immediately after the stressor and a progressive decline to baseline levels within 60 min (Dutheil et al., 2021). Observable changes in salivary cortisol (sC) peak approximately 20 min after stress offset and return to baseline after more than 30 min (Dickerson and Kemeny, 2004).

Regulation of the SAM axis predominantly occurs via the locus coeruleus-norepinephrine system in the brainstem (Kaltsas and Chrousos, 2007). In response to a stressor, the synthesis and release of epinephrine and norepinephrine from the adrenal medulla rise, both of which are crucial in regulating cardiovascular adaptations (Berntson et al., 2016). Salivary alpha-amylase (sAA) has emerged as a valuable non-invasive proxy for peripheral SAM axis activity (Nater et al., 2013). Within the BPSM, increases in sAA co-occurred with adaptive psychological and performance responses (Beltzer et al., 2014; Jamieson et al., 2010; but see Sicorello et al., 2021), indicative of challenge-oriented stress responses. The SAM axis allows for an instant response, with sAA peaking immediately after stress offset and a return to baseline after approximately 10 min (Jones et al., 2020).

In summary, lower reactivity in sC, higher reactivity in sDHEA and sAA, along with a more favorable anabolic balance between sDHEA and sC, may represent a more adaptive stress response and are more likely to manifest during challenge, whereas the opposite pattern may occur during threat.

1.2. Current study

In this study, we applied the BPSM of challenge and threat to investigate the neuroendocrine response of medical students engaged in simulated breaking bad news (BBN) encounters. BBN refers to the disclosure of serious diagnoses, which is recognized as one of the most distressing and difficult communication tasks in medicine (Baile et al., 2000). Simulation is an integral part of healthcare training, providing guided experiences that replicate key aspects of real clinical settings in a fully interactive manner (Gaba, 2007). It allows students to practice handling stressful encounters in a safe environment without jeopardizing patient well-being. Research has observed elevated psychophysiological stress during BBN, including in simulated settings (Studer et al., 2017). Notably, simulation-based training is often just as stressful as real clinical settings (Bong et al., 2016), although different stressors may shape challenge and threat appraisals in distinct ways (Peek et al., 2023). BBN is a frequent task in clinical practice, and even experienced healthcare professionals report considerable distress during these interactions (Francis and Robertson, 2023). Understanding how to promote adaptive stress responses during these interactions is crucial, as repeated exposure to high-stress situations without effective coping mechanisms may contribute to long-term psychological and physiological strain. Over time, fostering challenge-oriented neuroendocrine responses could help strengthen healthcare providers' resilience to BBN (Mendes et al., 2007). To foster challenge-oriented neuroendocrine responses, we implemented two interventions: stress arousal reappraisal (SAR) and worked example (WE)-based learning.

SAR emphasizes the adaptive function of short-term stress responses and encourages individuals to view stress arousal as beneficial for task performance (Jamieson et al., 2018). For instance, an accelerated heartbeat can be reappraised as the body preparing for difficult situations by delivering additional oxygen. Research suggests that SAR may reduce sC reactivity (Jamieson et al., 2022) and enhance sAA reactivity (Beltzer et al., 2014; Jamieson et al., 2010) in motivated performance situations.

WEs decompose complex tasks into stepwise solutions, facilitating skill acquisition (Sweller et al., 1998). This method is particularly effective for novice learners, as it helps them build schemas that organize task-related elements—an advantage in stressful situations where cognitive resources are limited. While the effects of WEs on sC, sDHEA, and sAA remain unexplored, research highlights their potential for stress regulation during simulated clinical training (Bong et al., 2016).

According to the BPSM of challenge and threat, both SAR and WE interventions could induce challenge-oriented stress responses. SAR achieves this by leveraging the adaptive resources mobilized during stress, while WE promote skill acquisition. This theoretical foundation is supported by previous analyses of cardiovascular and psychological indicators of challenge and threat within the same sample (see Bosshard et al., 2025). Based on these premises, we hypothesized that medical students trained in BBN using the SAR or WE interventions would exhibit higher reactivity in sAA and sDHEA, and lower reactivity in sC (in terms of both magnitude and peak), and a higher anabolic balance compared to students not receiving these interventions. Additionally, we explored the trajectory of these neuroendocrine markers to gain additional insights into the adaptiveness of the responses (Blascovich and Mendes, 2010). To further evaluate the SAR intervention, we assessed participants' stress mindset (i.e., beliefs about the nature of stress; Crum et al., 2013) and their use of stress reappraisal versus stress suppression strategies during the BBN encounter. This allowed us to determine whether SAR induced the intended cognitive and emotional adaptations, particularly among medical students who already possess a foundational understanding of stress mechanisms.

2. Methods

The current article focuses on neuroendocrine outcomes. Cardiovascular and psychological parameters have also been assessed as part of the project and are reported elsewhere (Bosshard et al., 2025; see Bosshard et al., 2023 for the study protocol).

2.1. Sample size calculation

The sample size was determined in advance using the G*Power 3 software (Faul et al., 2007). Upon reviewing research on the interventions' effects on psychophysiology, we deemed an effect size of $d = 0.4$ both reasonable and practically significant for the main effects of the SAR and WE interventions. To achieve a statistical power of 0.80 with a two-tailed alpha level of 0.05, it was calculated that 50 participants per group (total $N = 200$) would be required to adequately test our hypotheses.

2.2. Participants

To participate in the study, medical students were required to be in their third year at a Swiss university and fluent in German. Third-year students are ideal candidates as they have completed basic communication courses but lack specialized knowledge in BBN. A total of 229 medical students were recruited via circular email from the universities of Bern ($n = 127$), Basel ($n = 44$), Fribourg ($n = 39$), and Zurich ($n = 19$).

The participants had a mean age of 22.42 years ($SD = 1.83$) and a mean BMI of 22.32 ($SD = 2.79$). Sixty-nine percent were female ($n = 158$), with half of them ($n = 79$) reporting the use of hormonal contraceptives. Additionally, 26 % of participants ($n = 59$) worked night shifts. Students were excluded from the study if they reported cardiovascular or neuroendocrine conditions, were taking medications or psychoactive drugs known to affect study's outcomes, or had a pacemaker. Female participants were required not to be pregnant or lactating, and, whenever possible, were tested during the first week following menstruation to control for the potential effects of fluctuating sex hormones on neuroendocrine stress responses (Symonds et al., 2004).

2.3. Study design

We employed a 2 (SAR vs. No-SAR) by 2 (WE vs. No-WE) between-subjects design, resulting in four groups: 1) SAR-only, 2) WE-only, 3) SAR & WE, 4) No-intervention. Group assignment was stratified by sex and randomized within blocks of 4 or 8 participants. Experimenters were not blinded, as they were required to manually set up the learning modules. Participants were unaware of the different conditions, and the simulated patients receiving the bad news were also blinded to group assignment.

2.4. Study procedure

To control for the effects of circadian rhythm on endocrine levels and reactivity, all experimental sessions began at 2 pm. Participants were instructed to refrain from consuming alcohol and engaging in intense physical activity for 24 h before the experiment, avoid heavy meals and caffeine for 2 h prior, and abstain from tobacco and food 1 h before the experiment.

At the start of the session, the experimenter explained the procedure and obtained written consent. Participants were then given detailed instructions on saliva collection, and a first sample (S1) was taken. Next, participants were briefed on the general setting of the BBN encounter (a prenatal diagnosis). A second saliva sample (S2) was collected before participants engaged in a 40-min BBN learning module. This module followed the well-established SPIKES protocol (Baile et al., 2000) and was accompanied by the assigned interventions (SAR, WE, SAR & WE, or No-intervention). Afterwards, a third saliva sample (S3) was collected, and participants received specific information about a diagnosis (Trisomy 21). They were given 5 min to prepare before delivering the diagnosis to a simulated patient (an actress), during an encounter lasting up to 12 min. Three additional saliva samples were collected after the encounter approximately 10 min apart (S4-S6), with participants completing questionnaires between each sample (see Bosshard et al., 2023 for more details on the study procedure). Stress mindset, stress reappraisal, and stress suppression were assessed between S4 and S5. The timing of the saliva samples with respect to the BBN encounter is illustrated in Fig. 1.

2.5. BBN task

Participants were required to assume the role of a junior doctor tasked with delivering a Trisomy 21 diagnosis to a simulated pregnant patient. The students were instructed to follow the SPIKES protocol (Baile et al., 2000). To ensure consistency across the large number of participants, 11 simulated patients were trained to adhere to a detailed script, which described specific behaviors (e.g., emotional shock after the diagnosis), thereby providing all participants with a standardized stress stimulus.

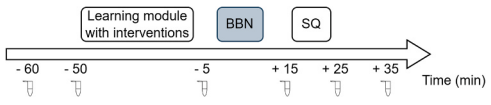

Fig. 1. Timing of saliva samples with respect to breaking bad news (BBN) onset. SQ = Stress questionnaires: including stress mindset measure, stress reappraisal, and stress suppression.

2.6. Measurements

2.6.1. Eligibility criteria and potential control variables

Inclusion and exclusion criteria were assessed via an online entry questionnaire, which also gathered potential control variables known to affect the neuroendocrine stress response, i.e., age (Otte et al., 2005), sex (Kirschbaum et al., 1999), and shift work (Niu et al., 2011). Female participants reported the date of their last menstrual cycle and whether they were pregnant, lactating, or using hormonal contraceptives at the time of the experiment. Other potential control variables included the body mass index (Peterson Hugh et al., 1988), depression (Hamer et al., 2007), anxiety (Shirotsuki et al., 2009), and life stress (Pike et al., 1997), measured using the DASS-21 (Lovibond and Lovibond, 1996), and BBN-related practical and theoretical experience, perceived skills in BBN, general interest in BBN, and motivation to perform well during the BBN encounter. These scales are provided in the Supplementary Material.

2.6.2. Saliva sampling

Participants were instructed to swallow any saliva in their mouth, then passively accumulate saliva for 2 min before transferring it into low-bind polypropylene 2 mL cryovials (Salicap, IBL International, Hamburg, Germany). To prevent dilution, participants were only permitted to drink water immediately after providing a sample. Samples were stored at −30°C. SC (in nmol/L) and sDHEA (in pg/mL) levels were measured using Saliva Luminescence Immunoassay kits (IBL-Tecan, Hamburg Germany). SAA activity (in U/mL) was assessed using reagents from DiaSys Diagnostic Systems (Holzheim, Germany). Ten percent of samples were analyzed in duplicate. Intra-assay variation coefficients were 3.67 % for sC, 5.46 % for sDHEA, and 4.51 % for sAA. Inter-assay variation coefficients were 5.29 % for sC, 9.22 % for sDHEA, and 4.30 % for sAA.

2.6.3. Stress mindset measure, stress reappraisal, stress suppression

Participants' stress mindset was assessed using a short version of the Stress Mindset Measure (SMM; Crum et al., 2013), with two items each gauging the enhancing and debilitating aspects of stress (e.g., "Experiencing stress enhances performance and productivity.", "Experiencing stress inhibits learning and growth."). Responses ranged from 0 *Strongly Disagree* to 4 *Strongly Agree*. The two debilitating items were reverse-scored, and the final score was calculated as the mean of all four items, with higher scores indicating a stress-is-enhancing mindset. In this study, the scale achieved a reliability of McDonald's $\omega = .61$.

We assessed participants' engagement in stress reappraisal with the question "How much did you try to interpret unpleasant feelings (nervousness, stress…) as positive and functional during the delivery of the bad news?" and in stress suppression with the question "How much did you try to suppress unpleasant feelings (nervousness, stress…) while delivering the bad news?". Both items were answered on a scale from 1 *not at all* to 6 *very much*.

2.7. Interventions

The learning module included the SPIKES protocol (Baile et al., 2000) and the assigned intervention materials.

2.7.1. Stress arousal reappraisal (SAR)

The content of the SAR intervention was structured according to previously used SAR materials (Beltzer et al., 2014; Jamieson et al., 2022, 2012). Participants watched a 7-min screencast explaining the functionality of bodily stress responses (e.g., faster breathing as a sign of

additional oxygen intake) and their evolutionary purpose. They were encouraged to view stress arousal during the BBN task as performance-enhancing. Finally, they were asked to reflect on past and future stressful experiences and how arousal might help them perform well in these situations. The control screencast was a 7-min video on neurocognitive aspects of memory. Both screencasts are available in the OSF repository (https://osf.io/9aqwn/).

2.7.2. Worked example (WE)

The WE intervention consisted of a 10-min video in which a physician disclosed bad news to a simulated patient according to the SPIKES protocol (Baile et al., 2000). For each step, the physician provided applied examples, accompanied by textual hints (i.e., the specific behavior characterizing a certain step). For instance, during the "Perception" step, the physician inquired about the current state of knowledge ("What were the reasons for you to undergo a medical examination?"). The groups not receiving the WE interventions had an extra 10 min to review the SPIKES protocol.

2.8. Data reduction

Saliva samples were assayed in the following sequence: sC, sAA, and sDHEA. Five samples lacked sufficient saliva for sDHEA analysis, and in two samples from the same participant, sAA levels were below the detection limit. In total, 99.5 % of the samples were available for statistical analysis.

2.9. Statistical analysis

Statistical analysis was performed using R (version 4.3.1), with packages *lme4* (version 1.1.33) and *lmerTest* (version 3.1.3). For all linear models, the assumptions of linearity, residual homoscedasticity, and normality were sufficiently met, as determined by visual inspections of residuals versus fitted value plots, QQ-plots of the residuals, and random effect plots. An alpha level of .05 was applied for significance testing. Significant interactions between the interventions were analyzed with post-hoc pairwise comparisons of the estimated marginal means, with *p*-values not being adjusted.

2.9.1. Neuroendocrine markers

For the analysis of the neuroendocrine markers, the saliva sample taken at −50 min (S2) was treated as the baseline value, because it was collected after participants had acclimated to the experimental setting and immediately before the interventions. S1 is not presented in any analysis. Natural log transformation was applied to normalize the right-skewed distributions of sC, sDHEA, and sAA. All observed values were biologically plausible; however, one extreme sDHEA value (i.e., 15 times higher) was winsorized to the next highest value recorded for that participant. This adjustment did not affect the significance of the results.

To comprehensively evaluate the stress response, we employed a multi-faceted analytical approach, providing a robust assessment of both the magnitude and the temporal characteristics of the stress response. First, the area under the curve with respect to increase (AUC_I) was calculated to quantify the overall reactivity (magnitude) of the stress response, integrating all measurements relative to the baseline. Second, a two-piece growth curve model (GCM) with landmark registration was utilized to examine individual peaks and the temporal dynamics of the response. Preliminary analyses were conducted for both approaches to identify which potential control variables to include in specific models, based on the significance of their predictive value (see Supplementary Tables S1 and S2).

The AUC_I was calculated by subtracting the area under the baseline level (S2) from the total area under the curve, using the trapezoidal rule based on the individual endocrine levels (S3 to S6) and the corresponding time intervals (in minutes) between each measurement (Pruessner et al., 2003). Additionally, the AUC_I for sDHEA was divided by the AUC_I for sC to represent the anabolic balance between the two hormones. The AUC_I values and the anabolic balance were analyzed using separate linear regression models.

The two-piece GCM with landmark registration aligned the growth curves around individual peaks, allowing for identification of potential differences in the activation and regulation of neuroendocrine responses while accounting for individual variations in the timing of peak occurrence (same approach as Lopez-Duran et al., 2014). Individual peaks were identified when subsequent measurements did not exceed the peak value by more than 10 %. Two time variables were created: one for the time (in minutes) before the individual peak (activation slope) and one for the time after the peak (regulation slope). The repeated endocrine measurements (S3-S6) were included as outcomes in the GCM, with the intercept representing the individual peak values when both time variables are 0. Random intercepts for participants and random slopes for the two time variables were incorporated to account for individual differences in the response and the rate of change before and after the peak, respectively.

First, to assess the significance of the increase to (activation slope) and subsequent decline from (regulation slope) individual peaks across all participants, unconditional models were employed, including only the variables TimeBeforePeak and TimeAfterPeak. Next, the unconditional model was expanded to include fixed effects for the SAR and WE interventions, the SAR × WE interaction, selected control variables, and baseline levels of the neuroendocrine marker (S2). Interactions between these predictors and the two time variables were added to assess their effects on the activation and regulation slopes (e.g., SAR × TimeBeforePeak represented the influence of SAR on the activation slope). The main effects were interpreted as the effects on the neuroendocrine peak levels.

2.9.2. Stress mindset, stress reappraisal, stress suppression

The SMM score and the engagement in reappraisal and suppression strategies were analyzed in separate linear regression models, with fixed effects for SAR and WE, and the SAR × WE interaction.

3. Results

3.1. Sociodemographic and BBN-related variables

The effects of potential control variables on neuroendocrine stress responses are presented in Supplementary Tables S1 and S2, including sex, age, night shift work, BMI, depression, anxiety, life stress, and BBN-related factors. Female participants exhibited significantly lower sC AUC_I values than males, characterized by more gradual increases before reaching peak levels and lower peak concentrations. Higher anxiety was associated with lower sC AUC_I, whereas longer BBN duration was linked to an increase in sC AUC_I. Similarly, sDHEA AUC_I was lower in females and in individuals with higher anxiety and life stress, while longer BBN duration was linked to a steeper decline after peak levels. Prior theoretical BBN experience was associated with lower sAA AUC_I, whereas students with higher motivation demonstrated a steeper increase in sAA before peak levels, and older participants exhibited a steeper decline post-peak. Variables that significantly influenced the outcomes were included as control variables in the respective analyses. No other significant effects were observed. Group-specific values for the sociodemographic and BBN-related variables are presented in Supplementary Table S3. The only significant difference among experimental groups was in motivation to perform well on the BBN task, with the SAR group being significantly more motivated than the WE group ($p = .005$).

3.2. Neuroendocrine markers

The descriptive statistics for the neuroendocrine outcomes are reported in Supplementary Table S4 and illustrated in Fig. 2. The unconditional GCMs revealed significant activation before and significant

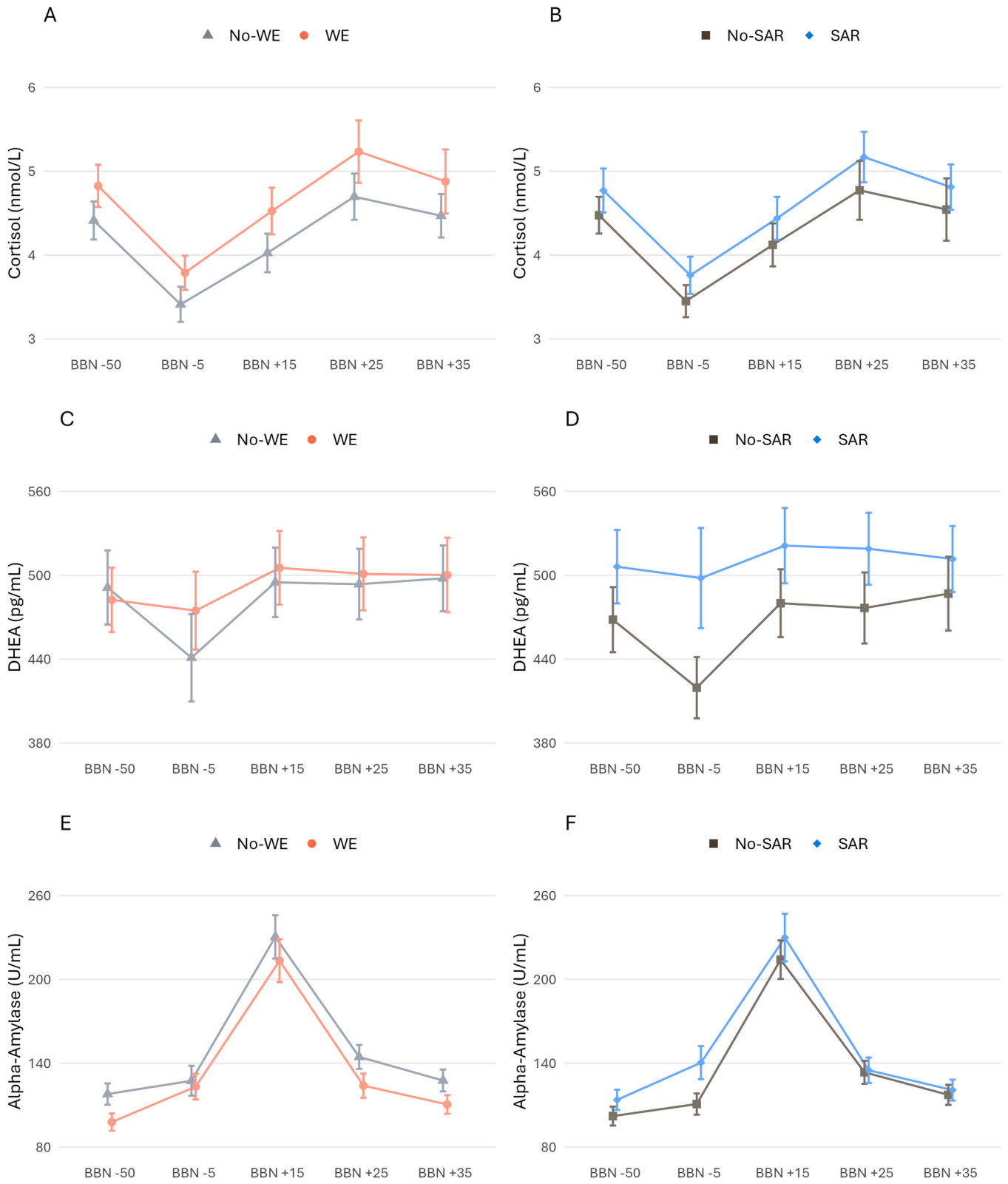

Fig. 2. Raw mean salivary cortisol (A & B), salivary dehydroepiandrosterone (DHEA; C & D), and salivary alpha-amylase (E & F) for the stress arousal reappraisal (SAR) and worked example (WE) groups, from S2 to S6 (min respective to breaking bad news encounter). The error bar represents the standard error.

regulation after the individual peaks in sC, sDHEA, and sAA in response to the BBN encounter (see Table 1).

3.2.1. Cortisol

Neither the SAR nor the WE intervention had a significant effect on sC AUC_I. The SAR × WE interaction was also not significant (see Table 2).

The GCM showed no significant effect of the interventions nor their interaction on the individual peak sC levels. The activation and regulation slopes were also unaffected by the interventions and their

Table 1
Unconditional growth curve models.

	Fixed Effect	Beta	*SE*	*p*
Salivary Cortisol	Intercept	1.4740	0.0454	< .001
	TimeBeforePeak	**0.0182**	**0.0011**	**< .001**
	TimeAfterPeak	**−0.0068**	**0.0005**	**< .001**
Salivary Dehydroepiandrosterone	Intercept	6.1900	0.0371	< .001
	TimeBeforePeak	**0.0122**	**0.0007**	**< .001**
	TimeAfterPeak	**−0.0071**	**0.0006**	**< .001**
Salivary Alpha-Amylase	Intercept	5.0644	0.0515	< .001
	TimeBeforePeak	**0.0275**	**0.0014**	**< .001**
	TimeAfterPeak	**−0.0243**	**0.0013**	**< .001**

Note. Significant effects (p < .05) are presented in bold. Time before and after individual peaks in minutes (i.e., Beta = increase/decrease per minute).

Table 2
Individual linear models for the areas under the curve with respect to increase of the neuroendocrine markers.

Outcome	Fixed effect	Beta	*SE*	*p*
Salivary Cortisol (nmol/L)	Intercept	−1.27	2.60	.63
	SAR[a]	2.99	2.77	.28
	WE[a]	0.09	2.76	.97
	Sex[b]	**−9.74**	**3.12**	**.002**
	Anxiety	−0.80	0.54	.14
	BBN duration	1.28	0.75	.087
	SAR × WE	−2.39	5.52	.66
Salivary Dehydroepiandrosterone (pg/mL)	Intercept	4.38	2.39	.069
	SAR[a]	1.50	2.41	.53
	WE[a]	1.94	2.43	.43
	Sex[b]	−4.98	2.71	.068
	Anxiety	−0.42	0.61	.49
	Life stress	−0.46	0.45	.31
	SAR × WE	**10.32**	**4.80**	**.033**
Salivary Alpha-Amylase (U/mL)	Intercept	17.47	2.12	< .001
	SAR[a]	−2.23	4.01	.58
	WE[a]	3.87	4.02	.34
	Theoretical Experience[c]	**−15.07**	**6.70**	**.026**
	SAR × WE	1.56	8.04	.85
Anabolic Balance (sDHEA/sC)	Intercept	0.67	0.87	.44
	SAR[a]	0.59	1.73	.74
	WE[a]	−2.32	1.73	.18
	SAR × WE	−5.28	3.47	.13

Note. SAR = stress arousal reappraisal. WE = worked example. Significant effects ($p < .05$) are presented in bold. [a] Both interventions were effect-coded (SAR = 0.5, No-SAR = −0.5; WE = 0.5, No-WE = −0.5) to ensure that the main effects remained interpretable even in the presence of the SAR × WE interaction. [b] Male = 0, Female = 1. [c] 0 = no previous theoretical experience, 1 = previous experience.

interaction (see Supplementary Table S5).

3.2.2. Dehydroepiandrosterone

Neither the SAR nor the WE intervention significantly influenced sDHEA AUC_I. In contrast, the SAR × WE interaction was significant (see Table 2). Post-hoc pairwise contrasts of the estimated marginal means revealed that participants receiving SAR and WE in combination, exhibited higher sDHEA AUC_I than participants only receiving either the SAR or the WE intervention, but not compared to participants receiving no intervention (see Table 3).

The GCM indicated no significant main effects of the interventions nor their interaction on peak sDHEA levels. However, both the increase in sDHEA levels before individual peaks (WE × TimeBeforePeak) and the decrease after individual peaks (WE × TimeAfterPeak) were significantly decelerated in the WE groups compared to the No-WE groups. The SAR intervention and the SAR × WE interaction had no significant effects on the activation or the regulation slopes. Detailed GCM statistics regarding sDHEA can be found in Supplementary Table S6.

Table 3
Post-hoc analysis of the significant SAR × WE interaction for dehydroepiandrosterone AUC_I.

Contrast	Beta	*SE*	*p*
SAR-only vs. No-intervention	−3.65	3.42	.29
WE-only vs. No-intervention	−3.22	3.39	.34
SAR & WE vs. No-intervention	3.44	3.40	.31
SAR-only vs. WE-only	−0.43	3.44	.90
SAR & WE vs. SAR-only	**7.09**	**3.45**	**.040**
SAR & WE vs. WE-only	**6.66**	**3.37**	**.049**

Note. SAR = stress arousal reappraisal. WE = worked example. Significant effects ($p < .05$) are presented in bold. Pairwise contrasts based on the estimated marginal means of the area under the curve with respect to increase.

3.2.3. Alpha-amylase

Neither the SAR nor the WE intervention significantly affected sAA AUC_I. The SAR × WE interaction was also non-significant (see Table 2).

The GCM revealed that neither the interventions nor their interaction affected peak sAA levels, activation slope, or regulation slope (see Supplementary Table S7 for GCM specifics regarding sAA).

3.2.4. Anabolic balance

Anabolic balance (AUC_I sDHEA/AUC_I sC) did not differ significantly between the intervention groups and their respective control groups. There was no significant SAR × WE interaction (see Table 2).

3.3. Stress mindset, stress reappraisal, and stress suppression

Compared to participants who did not receive the SAR intervention, participants receiving the SAR intervention reported a significantly more positive stress mindset ($B = 0.59$, $SE = 0.07$, $p < .001$), used stress reappraisal more ($B = 1.40$, $SE = 0.16$, $p < .001$) and used stress suppression less ($B = -0.87$, $SE = 0.18$, $p < .001$). The WE intervention had no significant impact on stress mindset ($B = 0.06$, $SE = 0.07$, $p = .36$), stress reappraisal ($B = 0.03$, $SE = 0.16$, $p = .83$), or stress suppression ($B = -0.10$, $SE = 0.18$, $p = .59$). The SAR × WE interaction was not significant for any of these parameters (stress mindset $B = 0.21$, $SE = 0.14$, $p = .12$; stress reappraisal $B = -0.28$, $SE = 0.33$, $p = .39$; stress suppression $B = 0.05$, $SE = 0.36$, $p = .88$). The descriptive statistics are presented in Supplementary Table S8.

4. Discussion

Using the BPSM of challenge and threat as the theoretical framework, the present study investigated the effects of SAR and WE interventions on sC, sDHEA, sAA during a simulated BBN encounter. We hypothesized that both interventions would lead to a decreased sC response, an increased sDHEA and sAA response, and a more favorable anabolic balance. Although significant activation and regulation in neuroendocrine responses were present, there were no significant main effects of the SAR and WE intervention on the AUC_I nor on the individual peak levels (indicated by GCM), which contradicts our hypotheses. Only the WE intervention was found to significantly reduce the rate of increase in sDHEA levels before individual peaks and decelerate the decrease after individual peaks. No other significant effects on the trajectories of sC, sDHEA, and sAA were found.

The slower rise in sDHEA prior to reaching its peak among WE participants may suggest that these individuals experienced the BBN encounter as less stressful, whereas the slower decline in sDHEA following the peak may reflect a more favorable recovery phase, allowing DHEA to exert protective effects by modulating lingering cortisol levels. However, these findings are difficult to interpret in light of missing significant effects on the sDHEA response magnitude (AUC_I) and peak levels, as well as the absence of similar effects on sC and sAA. The significant SAR × WE interaction on the sDHEA AUC_I seems negligible, as the combined effect of SAR and WE led to higher values than

either intervention alone but did not differ significantly from the No-intervention condition.

Apart from these specific findings, the absence of the hypothesized decreased sC response and increased sDHEA and sAA responses among intervention participants warrants thorough consideration. From the perspective of the BPSM of challenge and threat, the BBN encounter met the criteria of motivated performance situations, and the results demonstrated general response trajectories aligned with the literature, showing immediate increases in sDHEA and sAA levels following stress offset, with a delayed peak in sC levels. Notably, the absence of SAR and WE effects contrasts with prior findings from the same sample, which demonstrated the interventions' effectiveness in promoting challenge-oriented cardiovascular and/or psychological stress responses (Bosshard et al., 2025). Additionally, the SAR intervention resulted in a more positive stress mindset, coupled with greater use of reappraisal strategies and less use of suppression, suggesting that the intervention fostered beneficial adaptations for stress management in this study.

Based on these results, and limited and inconsistent findings of previous research, it is possible that the neuroendocrine responses did not effectively differentiate between challenge and threat. The idea that distinct activation patterns of the SAM and HPA axes are responsible for challenge and threat responses (Blascovich, 2008; Seery, 2011) has faced criticism before (Wright and Kirby, 2003). Specifically, the BPSM's derivation of the established cardiovascular indices of challenge and threat from SAM and HPA activity is contradictory and neglects important physiological considerations. For instance, the BPSM assumes that the SAM axis exerts vasodilatory effects during challenge, despite the vasoconstrictive properties of norepinephrine and epinephrine, particularly at high concentrations (Ebert, 2019).

Further, previous studies have shown an inconsistent relationship between neuroendocrine and psychological evaluations of challenge and threat. For instance, while DHEA and the anabolic balance have been found to correlate with resource evaluations, they did not align as expected with the conceptually more relevant resources-demands differential (Mendes et al., 2007). Other studies have struggled to establish consistent links between cortisol, alpha-amylase, and challenge and threat states (Mendes et al., 2007; Schickel et al., 2023; Sicorello et al., 2021).

Another potential issue with using neuroendocrine responses as indicators of challenge and threat relates to the temporal resolution of the assessment. Challenge and threat states are dynamic processes that can fluctuate throughout the course of a situation (Blascovich, 2008). For instance, the simulated patient in the BBN encounter portrayed an emotional state of shock and became detached after receiving the bad news, which would likely contribute to a perceived lack of control among the participants and a shift away from challenge states (Schickel et al., 2023). The time lag between these event dynamics, saliva sampling, and the endocrine response means that the measured endocrine levels may represent an aggregation of varying states rather than nuanced adaptations, complicating their interpretation in relation to the stressor (King and Liberzon, 2009). This also suggests that neuroendocrine markers may be more appropriate in situations characterized by relatively stable appraisals, as real-time assessment during the task is hardly feasible.

4.1. Strengths, limitations, and outlook

In a controlled simulated environment, we explored SAR and WE interventions in a BBN scenario without compromising the well-being of real patients. For the first time, we found that the WE intervention can have subtle effects on the trajectory of the sDHEA response. Further, whereas previous research within the BPSM has mostly relied on a single biomarker, our study simultaneously assessed sC, sDHEA, and sAA. This approach not only advances the BPSM but also deepens our understanding of stress responses during simulated training scenarios. The applied statistical approaches (AUC_I and GCM) allowed for a thorough understanding of the overall stress response and the nuanced temporal patterns around individual peaks.

However, the findings should be interpreted in light of the limitations of the current study. First, although a 12-min time limit was set, participants were allowed to conclude the conversation earlier if desired. It is important to note that the variability in the duration of the stressor could have influenced endocrine levels and the timing of saliva samples. However, the groups did not differ significantly in the duration of the BBN encounter or the timing of saliva sampling, and the effects of BBN duration were statistically controlled for in the analyses. Moreover, a more fine-grained saliva sampling in the 20–30 min following the end of the stressor would have captured the trajectories and peak neuroendocrine activity more accurately (Labuschagne et al., 2019). Additionally, compared to other studies applying GCM in similar contexts (Laferton et al., 2023; Lopez-Duran et al., 2014), we only collected saliva for up to 35 min after the stressor, which resulted in limited information after individual peaks. Thus, findings related to the GCMs should be interpreted with caution. Finally, while overall stress levels in simulation and real clinical settings appear comparable, simulation scenarios may be perceived as more threatening due to their social-evaluative context. As a result, neuroendocrine responses during simulation may not fully mirror those in real-world clinical encounters (Peek et al., 2023).

Future studies may employ longer and more frequent saliva sampling to yield more accurate information about the trajectory of the stress response. More broadly, future research could clarify if neuroendocrine markers might be more reliably applied in situations characterized by relatively stable appraisals. In this context, it would be valuable to investigate the impact of varying patient feedback on challenge and threat states in social evaluative tasks (similar to Crum et al., 2017), and to align the physiological assessments more precisely with certain event dynamics (Studer et al., 2017). Lastly, our findings indicate that the SAR and WE interventions, in their current form, do not significantly improve neuroendocrine stress responses. While this suggests that their application in real clinical settings may not yield meaningful improvements, further research is needed to compare stress management in simulated environments with real-world clinical interactions. Such investigations are essential for clarifying the broader implications of simulation-based training. Nonetheless, these findings contribute valuable insights by identifying approaches that may be ineffective, which is a crucial step in refining future stress management strategies.

4.2. Conclusions

In conclusion, both the SAR and WE intervention failed to induce the proposed challenge pattern in neuroendocrine stress responses and thus could not be related to distinct SAM and HPA axis activity. We argue that the lack of effect may be attributed to the inability of neuroendocrine markers to accurately indicate challenge and threat in this study. Instead, the observed elevated endocrine levels possibly reflected a general stress response or an accumulation of challenge and threat states. We perceive neuroendocrine markers, with their low temporal resolution, as suboptimal for capturing dynamic challenge and threat states within the BPSM. Considering the contradicting results in prior research, it may be advisable to rely on well-established psychological and cardiovascular markers of challenge and threat with clearer implications, or at the very least to consider them alongside neuroendocrine markers. However, future research is needed before drawing conclusive statements about the situational appropriateness of neuroendocrine markers for assessing challenge and threat.

Ethics statement

Informed consent was obtained from all participants prior to the experimental procedure. The study has been approved by the ethics committee of the canton of Bern (2021–02098). The study was

conducted according to the World Medical Association Declaration of Helsinki, the ICH-Good Clinical Practice Guidelines, and the Swiss Federal Human Research Act.

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CRediT authorship contribution statement

Berendonk Christoph: Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Gomez Patrick:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Schmitz Felix:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Guttormsen Sissel:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Nater Urs Markus:** Writing – review & editing, Resources, Methodology, Funding acquisition, Conceptualization. **Bosshard Michel:** Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT to edit the manuscript. After using ChatGPT, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2025.107439.

Data Availability

The data and statistical analysis code are available on the OSF repository (https://osf.io/9aqwn/).

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