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Psychobiological Stress Response Profiles in Current and Remitted Depression: A Person-Centered, Multisystem Approach

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ABSTRACT

BACKGROUND: A dysregulated stress response, including exaggerated affective reactivity and abnormal hypothalamic-pituitary-adrenal axis responsivity, has been implicated in the etiology, maintenance, and relapse of major depressive disorder (MDD). Among adolescents, discordant affective and physiological stress response profiles have been linked to negative affective outcomes and increased risk for psychopathology. Whether these findings extend to adults with varying degree of MDD risk is unclear, as are possible links to various risk factors.

METHODS: We used a person-centered, multisystem approach in a sample of 119 unmedicated adults with current or remitted MDD and individuals without past MDD to evaluate psychobiological stress response profiles. Multitrajectory modeling was applied to positive affect, negative affect, and salivary cortisol (CORT) levels in response to the Maastricht Acute Stress Test.

RESULTS: Analyses identified 4 within-person profiles, 1 typical, termed normative (n = 32, 26.9%) and 3 atypical: CORT hyperreactivity affective stability (n = 17, 14.3%), CORT hyporeactivity affective reactivity 1 (n = 45, 37.8%), and CORT hyporeactivity affective reactivity 2 (n = 25, 21.0%). While validating the assumption of a normative profile and increased risk for psychopathology in non-normative stress response profiles, coherent associations emerged between stress response profiles and clinical status, depression severity, anhedonia, perceived stress, childhood adversity, and reports of well-being, suggesting increased risk for psychopathology for individuals with a hyperreactive or discordant hyporeactive stress response profile.

CONCLUSIONS: This work advances our understanding of stress response mechanisms in MDD and underscores the potential of targeted interventions to enhance resilience and reduce psychopathology based on individual stress response profiles.

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Stress has long been implicated in the etiology of major depressive disorder (MDD) (1–3). Both prospective and retrospective studies have suggested that up to 70% to 80% of first major depressive episodes (MDEs) are preceded by severe life stressors (4), and stress has generally been linked to both maintenance of MDD and poor disease course (1). With recurrences, neurobiological sequelae triggered by MDD and stress have been hypothesized to sensitize individuals, that is, increase risk for future MDEs even in the absence of stressors (5–7). Collectively, these findings point to dysregulated stress response function in MDD, including abnormal hypothalamic-pituitary-adrenal (HPA) axis responsivity.

A well-regulated HPA axis is essential for responding adaptively to stressors, maintaining homeostasis, and preserving mental and physical health. Thus, when facing an acute stressor, humans show a rapid release of cortisol (CORT), which mobilizes neuroendocrine resources required to cope with the stressor. Thanks to various negative feedback loops, the release of CORT is then terminated after successful coping (8,9). Therefore, the CORT response presents a downstream measure of HPA reactivity. In MDD, repeated activation of the HPA axis due to chronic stress may initially lead to prolonged exposure to high levels of CORT, eventually leading to habituation of HPA responses (i.e., blunted HPA reactivity to acute stress). While habituation to familiar stressors may be beneficial, a blunted HPA response to a heterotypic stressor may increase risk for future MDEs (8,10). Consistent with these theories, MDD has been linked to dysregulated HPA function, although the patterns are complex, likely sex specific, and often inconsistent (11,12). For example, meta-analytic evidence points to reduced and potentiated CORT in current MDD in response to acute psychosocial stressors in women and men, respectively (12). These findings were largely replicated and extended by a recent meta-analysis that evaluated various HPA variables in MDD, including basal CORT, hair CORT, CORT awakening response, or CORT stress reactivity (11). Specifically, relative to healthy women, women with MDD were characterized by elevated evening basal CORT and a

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higher CORT awakening response but lower CORT stress reactivity. Relative to healthy males, males with MDD showed higher overall, morning, and evening basal CORT but no differences in hair CORT, CORT awakening response, or CORT stress reactivity. Finally, relative to males with MDD, females with MDD showed higher hair CORT and CORT awakening response but lower CORT stress reactivity (11). In general, reduced negative feedback regulation of the HPA axis (due to reduced affinity of CORT on the glucocorticoid receptor) has been implicated in the pathophysiology of MDD (13) and would explain findings of higher basal CORT levels but lower CORT stress reactivity.

Notably, recent evidence indicates that MDD and MDD risk are associated with discordance across the experience of, expression of, and physiological responses to stress (14). For example, using multitrajectory modeling (MTM) (15) to identify profiles of concordance or discordance across stress variables, Bendezú *et al.* (16) recently reported that adolescents who were characterized by high negative affective responses (experience) and high behavioral expression but low physiological (CORT) stress reactivity (i.e., low stress correspondence) reported higher levels of depressive symptoms and higher rates of lifetime nonsuicidal self-injury and suicidal ideation than adolescents who were in one of 3 subgroups that showed high stress correspondence (low, moderate, or high responses across all variables) [for a replication, see (17)]. These findings were further extended by the same group, which reported that concordant stress response profiles (e.g., low-low-low or high-high-high) predicted more resilience and well-being over time, whereas blunted physiological (CORT) responses coupled with high perceived and expressed stress was associated with poorer clinical outcomes over time (14). Collectively, these findings highlight that focusing on a single level of analysis (e.g., CORT stress reactivity or affective responses) may yield an incomplete (and at times inadequate) understanding of stress dysregulation in MDD.

In the current study, we sought to extend these findings in various ways. First, although evidence of stress discordance has been linked to more depressive symptoms and lower well-being among adolescents, it is unclear whether such relationships exist among adults with MDD. Second, it is unclear whether stress discordance especially characterizes individuals in a current MDE rather than euthymic individuals with a history of MDD. Third, previous studies have not incorporated positive affect responses in their characterization of stress discordance among adults with MDD, which is an important construct in depression (18). Finally, previous studies did not evaluate the putative associations between stress discordance and various clinical variables associated with increased risk for depression, including anhedonia, early-life adversity, and well-being. Based on recent literature (14,16,17), we hypothesized that discordance across stress variables (physiological: CORT stress reactivity; affective: positive and negative affect) would be associated with higher severity of depression and anhedonia, higher prevalence of early-life adversity, and lower well-being.

METHODS AND MATERIALS

Participants

Data were obtained from a larger neuroimaging study (N = 142; mean age = 26.15 years, SD = 6.22; female n = 108, male n = 34) with a focus on stress in MDD. Participants were between ages 18 and 45 years, fluent in English, and right-handed, with normal or corrected-to-normal vision and hearing. Participants were excluded for current recreational drug use or pregnancy (assessed via a urine test at both the screening and imaging visits), current medication use, or for any history of serious or unstable physical or mental illness, seizures, dopaminergic drug use, thyroid disorder, thermoregulatory illness, or electroconvulsive therapy.

Eligible participants attended a baseline visit, during which they completed a series of questionnaires, a functional magnetic resonance imaging (fMRI) visit (Figure S1), a positron emission tomography visit, and 6- and 12-month follow-up visits. All participants gave written informed consent to undergo procedures approved by the Mass General Brigham Institutional Review Board. The fMRI was scheduled within 1 month of the screening visit (including baseline questionnaire measures), or participants were reassessed before the fMRI visit. Among the 142 participants, 119 (female n = 90, male n = 29; MDD: n = 42, mean age [SD] = 26.60 [6.51], 79% female; remitted MDD: n = 33, mean age [SD] = 26.58 [5.96], 67% female; and demographically matched healthy control participants [HCs]: n = 44, mean age [SD] = 26.16 [6.35], 80% female) had self-report and physiological stress data at the fMRI visit for the MTM analyses (15).

Stress Procedure

As part of the fMRI visit (Figure S1), participants underwent the Maastricht Acute Stress Test (MAST), which is a validated laboratory stressor paradigm that elicits robust psychological and physiological stress responses (19,20). As in our previous work, we included a sustained stress manipulation. For a detailed description, see the Supplement.

Measures

Psychiatric Diagnoses. To confirm diagnostic group (i.e., MDD, remitted MDD, or HC) and assess exclusionary psychiatric history, participants were interviewed at baseline by a masters- or doctoral-level clinician using the Structured Clinical Interview for DSM-5 (21).

Subjective and Physiological Stress. Self-reported affective experience levels were captured at 3 time points, relative to MAST onset, using the positive affect and negative affect composite scores from the Positive and Negative Affect Schedule-State (22). As a physiological marker of stress response, salivary CORT was assessed relative to MAST onset (for details, see the Supplement).

Psychopathology, Stress, Early-Life Adversity, and Quality-of-Life Correlates. To evaluate whether subgroups with different latent trajectory profiles differed in various theory-driven clinical domains (i.e., to validate the profiles), several questionnaires were administered. Depression severity was assessed using the self-reported 16-item Quick Inventory of Depression Symptomatology (QIDS) (23) and the clinician-administered 17-item Hamilton Rating Scale for Depression (HAMD-17) (24); self-reported anhedonia was assessed using the 14-item Snaith-Hamilton Pleasure Scale

(25); self-reported childhood maltreatment was assessed using the 28-item Childhood Trauma Questionnaire-Short Form (26); self-reported perceived stress in the past month was assessed using the 14-item Perceived Stress Scale (27); self-reported general quality of life was assessed using the total score from the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (28); and self-report of health-related quality of life was assessed using the 36-item Short-Form Health Survey (29). We analyzed the 36-item Short-Form Health Survey mental component score and physical component score, which represent orthogonal indices of psychosocial and physical quality of life, respectively.

Overview of Analyses

Aim 1: Psychobiological Stress Response Profiles. MTM (15) was used to identify subgroups of participants who exhibited similar trajectory profiles in their salivary CORT, positive affect, and negative affect responses to the MAST. As described elsewhere (14), the PROC TRAJ procedure in SAS version 9.4 with the MULTGROUPS option employed was utilized. Little's missing completely at random test (30) was nonsignificant (χ^2_{91} = 54.109 $p > .25$). Thus, we proceeded to use full-information-maximum likelihood to handle missing stress response data (4.2%). Quadratic polynomial functions were estimated for all response trajectories, a decision informed by visual inspection of the data as well as the expected reactivity patterns to the MAST[a]. At each step of model specification (e.g., 1-group, 2-group), nonsignificant highest-order polynomial functions for each stress index were systematically eliminated until a solution containing only significant highest-order polynomial parameter estimates was obtained. The log Bayes factor approximation ($\approx [2\log_e(B_{10})]$) was utilized at each step as a conservative fit index (31), with a ($2\log_e[B_{10}]$) value >10 favoring the more complex solution. Given our sample size (n = 119) and recommendations from the procedure developers ($n > 100$) (31), we limited model specification to 4 groups. Following specification, we evaluated MTM adequacy via average posterior probability > 0.70, odds of correct classification > 5.00, and the ratio of the probability of profile assignment to the proportion of participants that were assigned to a profile ($[prob_j/prop_j] \approx 1$) (15). After adequacy evaluation, Wald tests helped distinguish the groups, delineating how intercept and polynomial functions for each trajectory were relatively higher or lower (e.g., baseline) or more pronounced or less pronounced (e.g., response patterns) across groups.

Aim 2: Correlates of Psychobiological Stress Response Profiles. A series of multinomial logistic regression analyses were used to examine profile membership-correlate associations[b]. Specifically, 9 models were run in total, each examining one of 6 focal correlates (no missing correlate data): depression status (assessed by the Structured Clinical Interview for DSM-5); depression severity (QIDS, HAMD-17); anhedonia severity (Snaith-Hamilton Pleasure Scale); maltreatment exposure (Childhood Trauma Questionnaire); perceived stress (Perceived Stress Scale); and overall quality of life (Quality of Life Enjoyment and Satisfaction Questionnaire, Short-Form Health Survey psychosocial and physical quality of life). Age and sex were included as covariates in correlation analyses.

[a]Models including cubic polynomial parameter estimates for cortisol trajectories were considered in an effort to keep with the exploratory nature of our investigation. No significant cubic parameter estimates emerged, supporting our use of quadratic functions.

[b]To account for conceptual multiple comparisons within each focal correlate domains, Bonferroni correction was applied (i.e., depression severity: 2 variables, overall quality of life: 3 variables), and we clarified in both the Results section and Table 2 whether a parameter became insignificant.

RESULTS

Aim 1: Psychobiological Stress Response Profiles

MTM parameter estimates, adequacy indices, and trajectory distinction analysis results are summarized in Table 1. MTM specification revealed 4 profiles as the final model (Figure 1): 2-to-1-profile comparison ($2\log_e[B_{10}]$ = 214.38), 3-to-2 profile comparison ($2\log_e[B_{10}]$ = 94.72), and 4-to-3 profile comparison ($2\log_e[B_{10}]$ = 111.40). Following recommendations (31), examination of average posterior probability, odds of correct classification, and $prob_j/prop_j$ model adequacy indices suggested that the final 4-profile model fit the data well (15).

One profile reflected typical psychobiological stress response function across systems (normative; n = 32, 26.9%), while 3 profiles emerged whose trajectories potentially reflected varying degrees of atypical psychobiological stress responsivity across systems (32–34): CORT hyperreactivity affective stability (n = 17, 14.3%), CORT hyporeactivity affective reactivity 1 (n = 45, 37.8%), and CORT hyporeactivity affective reactivity 2 (n = 25, 21.0%). Next, we outline significant trajectory differences to characterize the profiles in detail (see Figure 1).

The normative profile was characterized by relatively low baseline salivary CORT levels and moderately pronounced salivary CORT reactivity, the highest baseline positive affect levels in the sample, and stable positive affect across the experiment, as well as the lowest negative affect baseline levels in the sample and less pronounced negative affect reactivity. The CORT hyperreactivity affective stability profile was characterized by the highest baseline salivary CORT levels and the most pronounced salivary CORT reactivity in the sample, relatively moderate baseline levels of positive affect and stable positive affect across the experiment, as well as relatively low levels of baseline negative affect and less pronounced negative affect reactivity. The CORT hyporeactivity affective reactivity 1 profile was characterized by relatively high salivary CORT levels at baseline and CORT nonreactivity (i.e., linear declining levels), relatively low baseline positive affect levels and more pronounced positive affect reactivity (i.e., a positive affect decrease that failed to return to baseline), as well as relatively high levels of negative affect at baseline and more pronounced negative affect reactivity (i.e., a negative affect increase that failed to return to baseline). Finally, the CORT hyporeactivity affective reactivity 2 profile was characterized by the lowest baseline salivary CORT levels in the sample and CORT nonreactivity (i.e., linear declining levels), relatively low levels of positive affect at baseline, and more pronounced positive affect reactivity (i.e., a decrease in positive affect that failed to return to baseline), as well as relatively high baseline negative affect levels and more pronounced

Table 1. Parameter Estimates (Standard Errors) and Model Adequacy Indices for Final Multitrajectory Modeling 4-Group Solution

	Salivary Cortisol	Positive Affect	Negative Affect	$AvePP_j$	OCC_j	$Prob_j$	$Prop_j$	Ratio
Normative, *n* = 32, 59% Female								
Intercept	0.425[a] (0.010)[A]	34.759[a] (0.948)[A]	1.057[a] (0.026)[A]	0.924	36.349	0.258	0.269	0.959
Linear	0.001[a] (0.001)		0.003[a] (0.001)					
Quadratic	−0.001[a] (0.001)[a]		−0.001[a] (0.001)[a]					
CORT Hyperreactivity Affective Stability, *n* = 17, 88% Female								
Intercept	0.508[a] (0.014)[B]	24.540[a] (1.261)[B]	1.117[a] (0.032)[A,B]	0.992	353.13	0.154	0.143	1.077
Linear	0.003[a] (0.001)		0.004[a] (0.002)					
Quadratic	−0.001[a] (0.001)[b]		−0.001[a] (0.001)[a]					
CORT Hyporeactivity Affective Reactivity 1, *n* = 45, 78% Female								
Intercept	0.478[a] (0.007)[C]	21.052[a] (1.095)[C]	1.162[a] (0.021)[B]	0.928	38.533	0.369	0.378	0.976
Linear	−0.001[a] (0.001)[c]	−0.152[a] (0.066)	0.006[a] (0.001)					
Quadratic		0.001[a] (0.001)[a,PR]	−0.001[a] (0.001)[b]					
CORT Hyporeactivity Affective Reactivity 2, *n* = 25, 84% Female								
Intercept	0.387[a] (0.009)[D]	22.300[a] (1.375)[C]	1.181[a] (0.027)[B]	0.957	66.882	0.219	0.210	1.043
Linear	−0.001[a] (0.001)[c]	−0.162[a] (0.086)	0.006[a] (0.002)					
Quadratic		0.001[b] (0.001)[a,PR]	−0.001[a] (0.001)[b]					

Following recommendations (31), examination of $AvePP_j$, OCC_j, and $prob_j$/$prop_j$ model adequacy indices suggested that the final 4-profile model fit the data well (15). Uppercase superscripts (^{A,B,C,D}) denote significant differences in intercept parameter estimates within the same MAST response index (e.g., salivary cortisol, positive affect, negative affect). Lowercase superscripts (^{a,b,c,d}) denote significant differences in polynomial parameter estimates within the same MAST response index. PR indicates protracted recovery (i.e., failure to return to baseline). Ratio indicates the ratio of $prob_j$ to $prop_j$.

$AvePP_j$, average posterior probability; CORT, cortisol; MAST, Maastricht Acute Stress Test; OCC_j, odds of correct classification; $prob_j$, probability of group assignment; $prop_j$, proportion of participants in each group.

[a]$p < .05$.

[b]$p = .07$.

negative affect reactivity (i.e., an increase in negative affect that failed to return to baseline). Notably, lower baseline CORT levels differentiated the CORT hyporeactivity affective reactivity 1 and 2 profiles.

Aim 2: Correlates of Psychobiological Stress Response Profiles

Because the normative profile was thought to reflect typical psychobiological stress responsivity, it was used as the reference profile in multinomial logistic regression analyses. Parameter estimates for our multinomial logistic regression models are summarized in Table 2, and log odds ratios are shown in Figure 2.

Covariates. With respect to covariates, relative to participants with the normative profile, participants with the CORT hyperreactivity affective stability, CORT hyporeactivity affective reactivity 1, and CORT hyporeactivity affective reactivity 2 profiles were significantly more likely to be female in most models (Table 2). Age had an inconsistent effect, and only a few models showed an association between higher age and increased likelihood of non-normative group assignment (Table 2).

Depression Status. The current and remitted depression model was significant. Figure 3 depicts the number and percentage of HCs and participants with current MDD and remitted MDD within each psychobiological stress response profile. Relative to the normative profile, a diagnosis of current

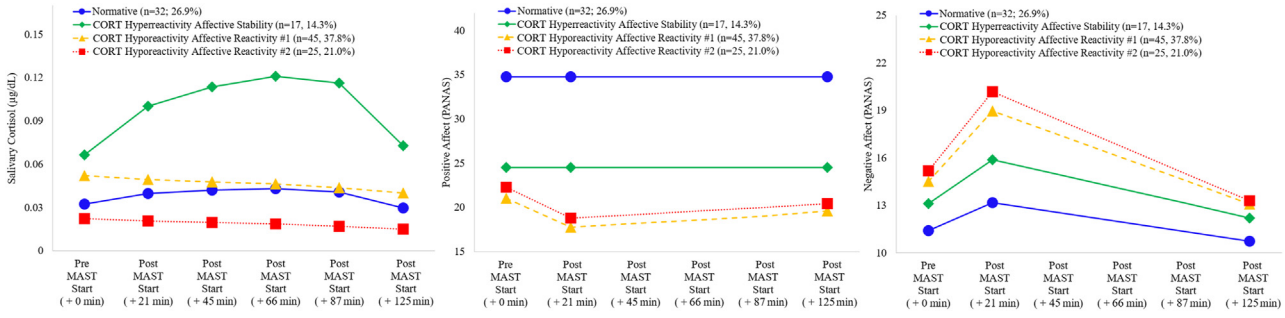

Figure 1. Cortisol (CORT) and affective response trajectories for the final 4-profile solution. Reverse-transformed salivary CORT and affect values are displayed here for ease of interpretation and cross-study communication. MAST, Maastricht Acute Stress Test; PANAS, Positive and Negative Affect Schedule.

Table 2. Parameter Estimates (Standard Errors) for Cross-Sectional MLRs Predicting Multitrajectory Modeling Profile Membership

Model	Current and Remitted Depression			QIDS Depression Severity			HAMD-17 Depression Severity		
Comparison Profile	CORT Hyperreactivity Affective Stability	CORT Hyporeactivity Affective Reactivity 1	CORT Hyporeactivity Affective Reactivity 2	CORT Hyperreactivity Affective Stability	CORT Hyporeactivity Affective Reactivity 1	CORT Hyporeactivity Affective Reactivity 2	CORT Hyperreactivity Affective Stability	CORT Hyporeactivity Affective Reactivity 1	CORT Hyporeactivity Affective Reactivity 2
Sex	−2.136[a] (0.908)	−1.339[a] (0.647)	−1.885[a] (0.778)	−1.648[b] (0.857)	−1.436[a] (0.725)	−1.034 (0.607)	−1.632[b] (0.865)	−1.412[b] (0.730)	−1.017 (0.617)
Age	0.003 (0.058)	−0.005 (0.048)	0.090[b] (0.049)	0.002 (0.056)	0.086[b] (0.047)	−0.017 (0.047)	0.000 (0.057)	0.084 (0.048)	−0.018 (0.048)
Predictor	1.677[a,c] (0.767)	1.233[b] (0.634)	1.246 (0.764)	0.167[a,d] (0.077)	0.231[a] (0.073)	0.242[a] (0.070)	0.193[a] (0.080)	0.233[a] (0.077)	0.245[a] (0.075)
	3.432[a,e] (1.243)	4.089[a] (1.120)	4.136[a] (1.183)						
χ^2		$\chi^2_{12} = 48.436^a$			$\chi^2_9 = 40.652^a$			$\chi^2_9 = 43.693^a$	
Nagelkerke's R^2		0.360			0.313			0.333	

Model	SHAPS Anhedonia Severity			CTQ-SF			PSS Stress Appraisal		
Comparison Profile	CORT Hyperreactivity Affective Stability	CORT Hyporeactivity Affective Reactivity 1	CORT Hyporeactivity Affective Reactivity 2	CORT Hyperreactivity Affective Stability	CORT Hyporeactivity Affective Reactivity 1	CORT Hyporeactivity Affective Reactivity 2	CORT Hypereactivity Affective Stability	CORT Hyporeactivity Affective Reactivity 1	CORT Hyporeactivity Affective Reactivity 2
Sex	−1.737[a] (0.854)	−1.673[a] (0.729)	−1.085[b] (0.574)	−1.861[a] (0.866)	−1.702[a] (0.708)	−1.114[a] (0.557)	−1.864[a] (0.872)	−1.784[a] (0.762)	−1.267[a] (0.611)
Age	0.001 (0.055)	0.084 (0.046)	−0.013 (0.044)	0.002 (0.055)	0.089[a] (0.045)	−0.009 (0.043)	0.031 (0.057)	0.138[a] (0.052)	0.037 (0.048)
Predictor	0.045 (0.043)	0.138[a] (0.039)	0.127[a] (0.035)	0.064[a] (0.029)	0.066[a] (0.028)	0.072[a] (0.025)	0.073[b] (0.038)	0.144[a] (0.035)	0.125[a] (0.033)
χ^2		$\chi^2_9 = 37.210^a$			$\chi^2_9 = 25.382^a$			$\chi^2_9 = 45.724^a$	
Nagelkerke's R^2		0.289			0.207			0.343	

Model	SF-36 Mental Health (MCS)			SF-36 Physical Health (PCS)			Q-LES-Q Quality of Life		
Comparison Profile	CORT Hyperreactivity Affective Stability	CORT Hyporeactivity Affective Reactivity 1	CORT Hyporeactivity Affective Reactivity 2	CORT Hyperreactivity Affective Stability	CORT Hyporeactivity Affective Reactivity 1	CORT Hyporeactivity Affective Reactivity 2	CORT Hyperreactivity Affective Stability	CORT Hyporeactivity Affective Reactivity 1	CORT Hyporeactivity Affective Reactivity 2
Sex	−1.887[a] (0.873)	−1.728[a] (0.766)	−1.180[a] (0.873)	−1.548[b] (0.849)	−1.491[a] (0.685)	−0.874 (0.519)	−2.300[a] (0.933)	−2.199[a] (0.869)	−1.690[a] (0.720)
Age	0.017 (0.056)	0.105[a] (0.050)	0.009 (0.048)	−0.006 (0.055)	0.083[b] (0.043)	−0.016 (0.041)	0.039 (0.059)	0.136[a] (0.056)	0.038 (0.052)
Predictor	−0.085[a,d] (0.037)	−0.122[a] (0.036)	−0.116[a] (0.035)	−0.039 (0.052)	0.009 (0.048)	0.023 (0.045)	−9.124[a] (2.842)	−13.592[a] (2.881)	−12.140[a] (2.736)
χ^2		$\chi^2_9 = 49.167^a$			$\chi^2_9 = 15.489^a$			$\chi^2_9 = 69.186^a$	
Nagelkerke's R^2		0.364			0.131			0.474	

Sex coded as 0 for males and 1 for females. For a visual representation of predictor estimates, see Figure 2. χ^2 values identify the MLR model as being significant, allowing us to assess a significant prediction of group assignment by the group/clinical variable.

CORT, cortisol; CTQ, Childhood Trauma Questionnaire; HAMD-17, Hamilton Depression Rating Scale; MCS, mental component score; MLR, multiple linear regression; PCS, physical component score; PSS, Perceived Stress Scale; QIDS, Quick Inventory of Depressive Symptomatology; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; SF-36, 36-item Short-Form Health Survey.

[a] $p < .05$.

[b] $p < .07$.

[c] Healthy control (0) vs. remitted depression (1).

[d] Parameter becomes insignificant after Bonferroni correction for multiple comparisons.

[e] Healthy control (0) vs. current depression (1). Normative served as the reference profile.

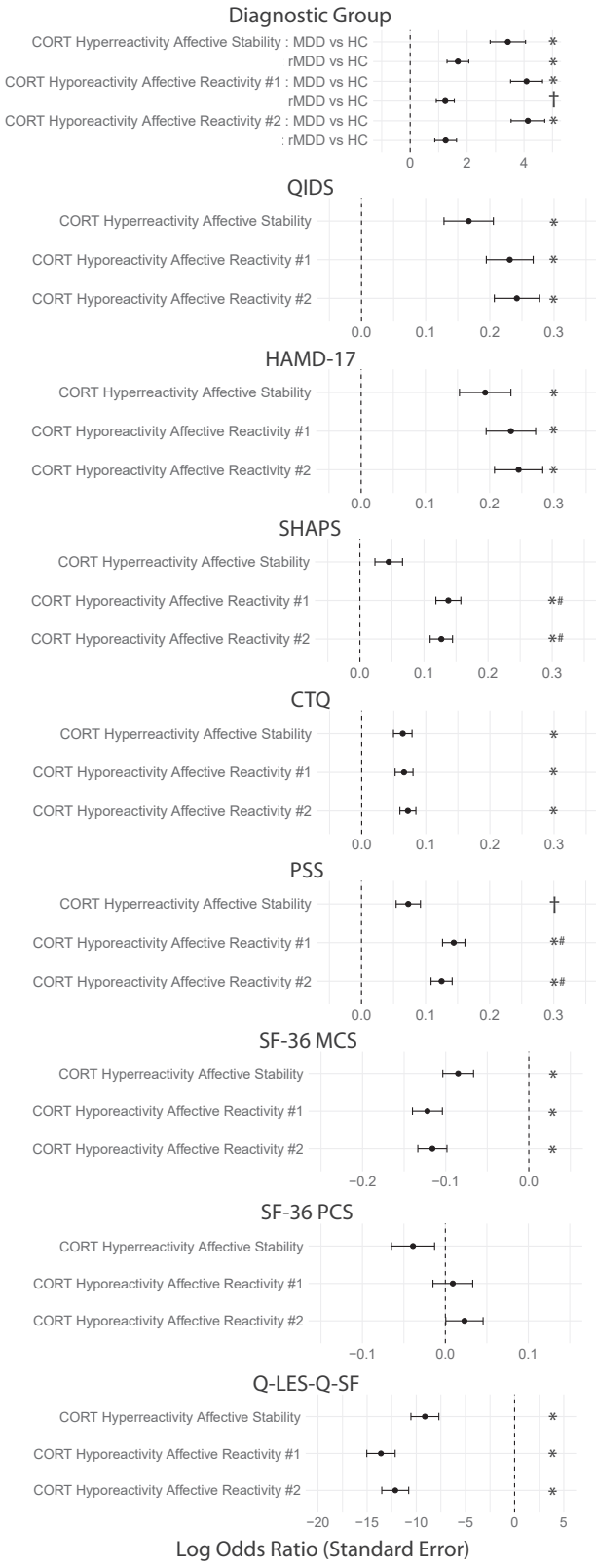

Figure 2. Log odds ratios (standard error) for multinomial logistic regressions, using normative as the reference group. †$p < .07$, *$p < .05$.

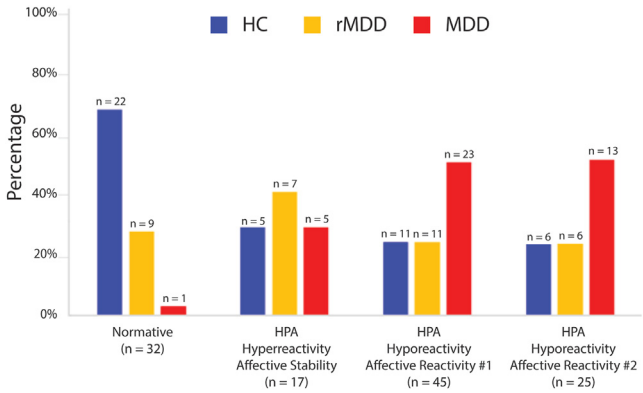

Figure 3. Bar chart illustrating the percentage of participants assigned to the healthy control participant (HC), remitted depression (remitted major depressive disorder [rMDD]), and current depression (MDD) groups within each psychobiological stress response profile. Accompanying statistics of increased likelihood for participants belonging to either the hypo- or hyperreactive groups based on patient group status can be found in Table 2.

or remitted MDD increased the likelihood of membership in the CORT hyperreactivity affective stability profile group rather than the HC group. However, relative to the normative profile, increased likelihood of membership in the CORT hyporeactivity affective reactivity 1 and CORT hyporeactivity affective reactivity 2 profile groups was more likely only for participants with current depression, but not remitted depression, compared with HCs.

Depression Severity. Both depression severity models were significant. Depression severity across measures (i.e., HAMD-17, QIDS) was significantly associated with a greater probability of membership in the CORT hyperreactivity affective stability (HAMD-17: $p < .05$, QIDS: not significant when correcting for multiple comparisons), CORT hyporeactivity affective reactivity 1, and CORT hyporeactivity affective reactivity 2 profile groups than the normative profile group.

Anhedonia Severity. The anhedonia severity model was significant. Anhedonia severity was significantly associated with an increased likelihood of belonging to the CORT hyporeactivity affective reactivity 1 and CORT hyporeactivity affective reactivity 2 profile groups relative to the normative profile group. Anhedonia severity was not significantly predictive of membership in the CORT hyperreactivity affective stability profile group relative to the normative profile group.

Follow-up analyses were performed for measures showing potential differences by nonoverlapping standard error bars between non-normative group profiles (i.e., for Snaith-Hamilton Pleasure Scale [SHAPS], Perceived Stress Scale [PSS]). #denotes significant log odds ratios for both cortisol (CORT) hyporeactivity affective reactivity groups, using the CORT hyperreactivity affective stability profile as reference. CTQ, Childhood Trauma Questionnaire; HAMD-17, Hamilton Depression Rating Scale; HC, healthy control participant; MDD, major depressive disorder; rMDD, remitted MDD; MCS, mental component score; PCS, physical component score; QIDS, Quick Inventory of Depressive Symptomatology; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; SF-36, 36-item Short-Form Health Survey.

Maltreatment Exposure. The maltreatment exposure model was significant. Maltreatment exposure was associated with a significantly greater probability of membership in the CORT hyporeactivity affective reactivity 1, CORT hyporeactivity affective reactivity 2, and CORT hyperreactivity affective stability profile groups than the normative profile group.

Perceived Stress. The perceived stress model was significant. Perceived stress was significantly associated with a greater probability of belonging to the CORT hyporeactivity affective reactivity 1 and CORT hyporeactivity affective reactivity 2 profile groups than the normative profile group. Perceived stress was not significantly associated with membership in the CORT hyperreactivity affective stability profile group relative to the normative profile group.

Quality of Life. All 3 quality-of-life models were significant. Psychosocial quality of life was significantly associated with a lower probability of belonging to the CORT hyperreactivity affective stability, CORT hyporeactivity affective reactivity 1 (Quality of Life Enjoyment and Satisfaction Questionnaire: $p < .05$, physical component score: $p < .05$, mental component score: not significant when correcting for multiple comparisons), and CORT hyporeactivity affective reactivity 2 profile groups relative to the normative profile group. Likewise, overall quality of life was significantly associated with a lower probability of belonging to the CORT hyperreactivity affective stability, CORT hyporeactivity affective reactivity 1, and CORT hyporeactivity affective reactivity 2 profile groups than the normative profile group. Physical quality of life was not significantly associated with MTM profile membership.

DISCUSSION

Discordant affective and physiological stress response profiles have been linked to negative affective outcomes and increased risk for psychopathology in adolescents (14,16,17). Using a person-centered, multisystem approach in a sample of unmedicated individuals with current or remitted MDD, as well as HCs, the current study extends these observations to adults by identifying 4 within-person profiles of psychobiological stress reactivity based on an integration of self-reported positive and negative affect as well as salivary CORT levels in response to an acute laboratory stressor. Notably, coherent associations emerged between stress response profiles and clinical status as well as indices of depressive symptoms, anhedonia, (early) life stress, and well-being, all factors that may contribute to increased risk for psychopathology for individuals with a hyperreactive or discordant hyporeactive stress response profile.

Among the 4 data-driven stress responsivity profiles identified, a normative profile emerged, consistent with the hypothesis that an adaptive and resilient stress response is characterized by a well-regulated HPA axis response coupled with flexible affective responding. This profile featured relatively low baseline levels of salivary CORT and moderately pronounced salivary CORT reactivity, relatively high and stable levels of positive affect, low baseline levels of negative affect and less pronounced negative affect reactivity. Consistent with the conceptualization of stress correspondence (14,16,17), the normative group demonstrated overall concordance across different levels of the stress response, decreased risk of psychopathology, and high levels of quality of life. In turn, non-normative profiles with increased stress response reactivity (i.e., heightened CORT or emotional responding) and/or more discordant stress response profiles (i.e., mismatch between CORT HPA and emotional responding) were associated with an increased risk of psychopathology (clinical status of current or past MDD).

Participants with a current MDD diagnosis were more likely to exhibit 1 of the 3 non-normative psychobiological stress response profiles, with only 1 individual with current MDD assigned the normative profile (see Figure 3). In turn, those with remitted MDD were more likely to exhibit the CORT hyperreactivity affective stability pattern, but not the CORT hyporeactivity affective reactivity 1 or 2 profiles. We speculate that, relative to the CORT hyporeactivity affective reactivity 1 and 2 profiles, the CORT hyperreactivity affective stability profile reflects a less pathological state of psychobiological dysregulation; thus, an overreactive but still responsive CORT system and overall concordant stress response may confer some protection and thereby decrease the risk of current MDD. This interpretation is corroborated by findings that perceived stress and anhedonia severity (2 well-established vulnerability factors for MDD) positively predicted membership in both the CORT hyporeactivity affective reactivity 1 and 2 profiles but did not differentiate participants in the CORT hyperreactivity affective stability group from those in the normative group. Collectively, our findings suggest that remitted, nonanhedonic MDD may be characterized by neuroendocrine hyperreactivity and moderately elevated positive affect levels in the face of psychosocial stress, while current, anhedonic MDD is associated with neuroendocrine hyporeactivity, a decrease in low positive affect levels, and delayed stress relief following acute stress exposure. Future prospective studies are required to test whether the CORT hyperreactivity affective stability profile is associated with a lower likelihood of relapse.

Notably, although some inconsistencies exist, previous literature points to blunted stress responsivity in more chronic depression, whereas recent-onset depressive symptoms have been linked to elevated CORT reactivity (35). This may suggest a gradual shift from hyper- to hyporeactivity of the HPA axis to stress in MDD, which may stem from the perception of chronic stress, leading to downregulation of stress-related HPA axis responsivity (36). Accordingly, we speculate that a higher likelihood of being in the hyporeactive physiological stress profile for individuals with current MDD reflects a gradation of risk. Thus, whereas increased vulnerability to MDD early in the course of the disease is linked to a hyperresponsive neuroendocrine response to acute stressors, the ongoing allostatic load caused by chronic hyperresponsivity of the HPA axis may eventually culminate in a hyporeactive HPA axis, which may foster the maintenance of MDD. Supporting this hypothesis, on a dimensional level, individuals with more severe depression symptomatology had a greater likelihood of belonging to any of the 3 non-normative groups, but such relative probability increased from the hyperreactive groups to the hyporeactive group (see Figure 2). More fundamentally, the current person-centered analysis offers a more fine-grained picture of how stress reactivity across units of analysis is associated with MDD, depression severity, and various risk factors. Future

studies focused on characterizing depression phenotypes would benefit from incorporating measurements of cytokines as an indicator of sickness syndrome (10).

While these observations are intriguing, the causal effects that link altered stress response profiles with MDD and various risk factors remain unclear. One approach to inform this discussion would entail longitudinal studies, including those focusing on early-life adversity, which is a known risk factor for MDD. However, inconsistent results have plagued this literature, with meta-analytical evidence pointing to blunted CORT reactivity in individuals with childhood adversity (37), while others have reported potentiated stress-related reactivity (38–40). A potential reason for these inconsistencies may stem from the focus on variable-centered, rather than person-centered, approaches for examining CORT reactivity. In our study, compared with the normative profile, assignment to all non-normative profiles was equally associated with increased levels of reported childhood adversity. This is consistent with several prominent developmental models of life stress and HPA dysregulation, including the biological embedding model (41) and the stress sensitization model (42), with both allowing for either hyper- or hyporeactivity as a maladaptive outcome of early-life stress.

Finally, whether altered stress responsivity has an impact on daily functioning and quality of life is generally unexplored. In our analyses, low psychosocial (but not physical) functioning and quality-of-life scores were associated with a significantly increased likelihood of belonging to any of the 3 non-normative stress response profile groups. These findings are consistent with previous evidence that reduced quality of life was linked to maladaptive acute stress response patterns among patients being treated for hypercortisolism or hypocortisolism (43). Similarly, health-related quality of life was low for patients with HPA axis dysregulation who did not respond to endocrinological treatments (44). Notably, however, these previous results were limited to a single-variable approach solely focusing on CORT whereas our observations offer new insights by clarifying links between psychobiological stress profiles and quality of life.

Despite several strengths, including the relatively large and well-characterized sample of unmedicated individuals with varying degrees of MDD risk, the current study has some limitations. First, biological variables were restricted to CORT, and including adrenocorticotropic hormone measurements would have more precisely captured HPA axis reactivity. In addition, it would be interesting in future studies to consider additional markers sensitive to acute stressors (e.g., interleukin 6). Second, group-averaged CORT responses for some groups were comparatively lower than CORT responses in the original MAST procedure (19), which might have been caused by the extended procedure that included imaging and an adapted version of the MAST. Third, although we included both men and women, we were likely underpowered to test for possible sex-specific effects. Fourth, several factors such as metabolic state and circadian or sleep-wake activity rhythm can affect CORT responses. While participants were instructed to arrive well rested and fasted to the visit, these factors were not systematically assessed and cannot be evaluated for potential differences among groups. Fifth, given the available sample size, this study aimed at a theory-driven exploration of discordance patterns in stress reactivity, building on our previous work with adolescents. Future large databases of physiological and affective responses to an acute stressor will be needed for data-driven approaches, which would allow division of the data into discovery and validation cohorts and ultimately to testing the generalizability of these findings. Lastly, the cross-sectional nature of the current study limits our ability to establish causality and leaves open the possibility of reverse directionality (where a clinical variable may influence stress reactivity, although the strength of our study stems from a convergence across a set of different variables) and residual confounding (where unmeasured variables could have potentially affected the observed associations). Despite these limitations, the current person-centered analytical approach to stress trajectories yielded a nuanced understanding of stress response profiles and their links to mental health, risk factors, and psychosocial functioning. Future studies with a longitudinal design are warranted to test several hypotheses generated by the current results, including that the CORT hyperreactivity affective stability profile is associated with a lower likelihood of relapse, and CORT hyporeactivity affective reactivity profiles are associated with more disease severity and chronicity. Ultimately, it is hoped that a better understanding of stress response mechanisms in MDD will point to targeted and personalized interventions to enhance resilience and reduce MDD risk and recurrences.

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SUPPLEMENTARY INFORMATION

Psychobiological Stress Response Profiles in Current and Remitted Depression: A Person-Centered, Multisystem Approach

Kuhn *et al.*

Subjective and Physiological Stress Assessments

Self-reported affective experience levels were captured at three timepoints, relative to MAST onset (on average, 0 min, +21 min, +125 min), using the Positive Affect (PA) and Negative Affect (NA) composite scores of the Positive and Negative Affect Schedule-State (PANAS-S; 22). As a physiological marker of stress response, salivary cortisol was assessed at eight timepoints, relative to MAST onset (on average, -93 min, -54 min, 0 min, +21 min, +45 min, +66 min, +87 min, +125 min). The third salivary cortisol collection took place just before stress onset and therefore represented an optimal baseline pre-stress marker of physiological arousal because participants had ample time to get used to the MRI environment and for differences in metabolic states to reach an equilibrium (e.g., due to differences in food consumption or exercise prior to the experiment). Thus, the first two salivary cortisol collections were excluded from the analyses. Salivary cortisol was collected using Salivettes (Salivette®, Sarstedt, Nümbrecht, Germany), and participants were instructed to keep the cotton swabs in their mouth for approximately 2 minutes. Salivettes were stored in a -80 degree Celsius freezer, before being assayed for salivary-free cortisol. Inter-assay and intra-assay coefficients of variation were < 9%, and < 5%, respectively. To control for diurnal cortisol fluctuations, the fMRI visit took place between 1:00pm and 5:00pm, and all female participants attended this visit during the follicular phase of their menstrual cycle (i.e., days 1-12 of first day of last menstrual period, which was verbally confirmed with participants prior to the visit).

Data Preparation and Preprocessing

Seventeen cortisol values were > 3 SDs from the grand mean: Pre MAST Start + 0 min (n=5), Post MAST Start + 21 min (n=2), Post MAST Start + 45 min (n=1), Post MAST Start + 66 min (n=3), Post MAST Start + 87 min (n=3), Post MAST Start + 125 min (n=3). Five negative affect values were > 3 SDs from the grand mean: Pre MAST Start + 0 min (n=2), Post MAST Start + 21 min (n=1), Post MAST Start + 125 min (n=2). As in prior studies (1,2), these outliers were included to better understand whether theoretically meaningful profile trajectories might exist at the tail end of the salivary cortisol and negative affect distributions. Salivary cortisol and negative affect values were 4^{th} root (3) and $\log_{10}$ transformed, respectively, which normalized the observed positive skew.

Stress Procedure

After an initial scan, the scanner table was brought out and the participant was asked to complete a 12-minute MAST protocol whilst lying on the scanner table: two experimenters (whom the participant had not met yet) acting as “doctors” entered the scanner suite and gave instructions for the MAST task, which involved interleaving blocks of mental arithmetic (counting backward from a four-digit number out loud in steps of 17) and immersing their hand in ice-cold (0-2° Celsius) water. As part of the stress manipulation, participants were informed that they were ostensibly being videotaped so that study staff could analyze their facial expressions of pain; in reality, no recordings took place. Additionally, after completing the task, all participants were told by the evaluators that, due to below-average performance, they had to repeat the task at a

later time. This marked the start of the *Sustained Stress* period, which lasted until the end of the scan period, at which point experimenters informed the participant that they would not be repeating the MAST (i.e., *Stress-Relief* timepoint). After stress relief, participants completed additional computer tasks and surveys, and were then fully debriefed and compensated.

Supplementary References

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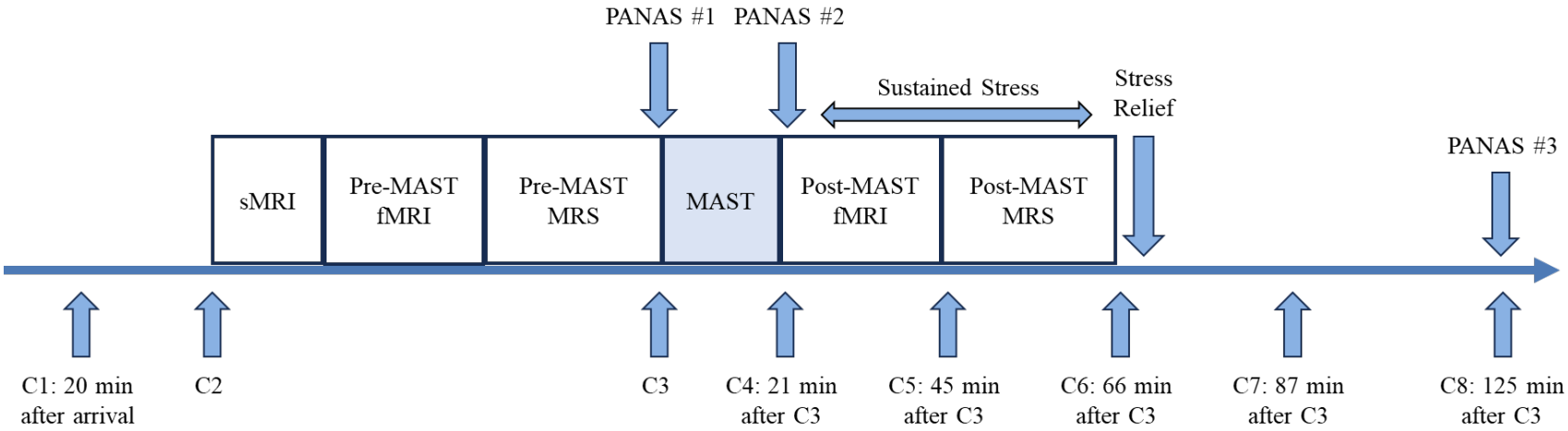

Figure S1. Procedural details of the fMRI session. At arrival to the session, participants provided an initial cortisol sample (C1) and underwent drug and, if applicable, pregnancy screening. Before entering the MRI scanner, participants provided another cortisol sample (C2). Next, participants underwent structural MRI (sMRI), functional MRI (pre-MAST) and MRS (pre-MAST MRS) scans. Before onset of the MAST stress procedure, another cortisol sample was collected (C3) and affective ratings (PANAS #1) administered. Next, the participants underwent the MAST stress induction procedure including a sustained stress induction (for details see Methods section of the main text). Directly following the MAST procedure, another cortisol sample was collected (C4) and affective ratings were administered (PANAS #2). Next, post-MAST fMRI and Post-MAST MRS scans were performed including an interleaved cortisol sample acquisition (C5). After the fMRI scans were completed, another cortisol sample was collected (C6) and stress relief provided. Over the rest of the study procedure, two further cortisol samples were collected (C7 and C8), concluding with a final administration of affective ratings (PANAS #3).