

The Ups and Downs of Brain Stress: Extending the Triple Network Hypothesis

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ABSTRACT

BACKGROUND: This preregistered functional magnetic resonance imaging study aimed to test and possibly extend the triple network hypothesis of psychosocial stress processing, positing that responses in the salience network (SN) and the default mode network (DMN) dominate at the expense of the central executive network (CEN). Furthermore, we tested the hypothesis that stress-related responses in SN and DMN structures are associated with hormonal, cardiovascular, and affective stress responses, while CEN and DMN structures are associated with task performance. We also examined sex-specific associations between neural and stress-induced cortisol, heart rate, and negative affect responses as well as task performance.

METHODS: We reviewed all psychosocial stress studies and conducted a mega-analysis of ScanSTRESS datasets ($n = 459$; 222 female) with harmonized preprocessing.

RESULTS: Our findings advanced the original hypothesis, revealing activations and deactivations across all 3 networks, related in a complex way to cortisol, heart rate, negative affect, and performance parameters. Additionally, we identified a novel age effect of increasing DMN activation with age, replicated an exposure-time effect of decreasing activation with duration, showed sex-specific patterns, and confirmed the involvement of all networks by task-based connectivity analyses.

CONCLUSIONS: Based on our findings we suggest a new, differentiated triple network hypothesis of psychosocial stress processing. Reactivity in SN and DMN structures is associated with hormonal, cardiovascular, and affective stress responses, whereas CEN and DMN structures process the stress-eliciting tasks. Moreover, the age effect may indicate that the ability to downregulate the DMN is reduced with age. Finally, we suggest that the exposure-time effect (decreasing signal within ScanSTRESS) may be a promising resilience biomarker.

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Stress has become a constant in daily life triggering both adaptive and maladaptive reactions. While acute stress mobilizes resources in the short term, chronic stress can severely impact mental and physical health (1). Neuroscientific research has increasingly illuminated the brain networks involved in stress coping (2). The triple network hypothesis, initially developed to model large-scale brain dysfunctions in psychiatric disorders (3,4), provides a useful framework to understand how psychosocial stress affects neural functioning. It proposes that under stress, the salience network (SN) facilitates dynamic switching between the internally oriented default mode network (DMN) and the externally focused central executive network (CEN). In the context of psychosocial stress, a prioritization of the SN and DMN over the CEN has been suggested, although the evidence is inconclusive (2,4): It has been speculated that negative social feedback, an emotionally significant component of psychosocial stress (5), intensifies SN and DMN responses during emotional

processing (2,6,7), while CEN reactivity decreases. This shift is reflected in both increased regional reactivity and altered network connectivity (4).

Each network contributes uniquely to stress processing: The SN detects and prioritizes salient stimuli, the DMN is associated with internal mentation and self-referential thought, and the CEN enables goal-directed behavior and cognitive regulation (2,4). While mostly activation-based studies are reviewed here, the triple network hypothesis is rooted in connectivity-based resting-state literature (3). Furthermore, individual differences related to sex, age, specific context (i.e., site), and repeated exposure may influence stress-related network patterns but remain underexamined. Consequently, in this preregistered mega-analysis (i.e., pooling raw data across studies), we investigated if acute psychosocial stress amplifies SN and DMN responses at the expense of the CEN. We further examined neural association patterns with endocrine, cardiovascular, affective, and

behavioral stress markers and explored moderating effects of sex, age, and site as well as the impact of stress exposure time.

Reviews of task-based functional magnetic resonance imaging (fMRI) studies on (psychosocial) stress demonstrate inconsistency across studies for both networks and individual structures (8–10). To contextualize our findings, we reviewed and summarized all published whole-brain fMRI studies on acute psychosocial stress using ScanSTRESS (11) and the Montreal Imaging Stress Task (MIST) (12) (Table 1), focusing on their relevance to the triple network hypothesis. These paradigms, similar to the Trier Social Stress Test (13), manipulate social evaluation, forced failure, and negative feedback by having participants perform cognitive tasks (subtraction, mental rotation) under third-party evaluation (8,9,11,12). For additional region of interest-based and non-neuroimaging studies as well as hormonal, affective, and cardiovascular responses, see Table S1.

Table 1 suggests that the triple network hypothesis of stress processing remains inconclusive: Regarding SN structures, the frontoinsula cortex (FIC) and dorsal anterior cingulate cortex (dACC) were predominantly activated in ScanSTRESS and MIST studies. However, amygdala (AMY) and temporal pole (TP) responses were less consistently reported, with the AMY often deactivated in ScanSTRESS studies and not mentioned in MIST studies. For DMN structures, the medial prefrontal cortex (mPFC), precuneus (PCU), and posterior cingulate cortex (PCC) were consistently deactivated in ScanSTRESS studies, though effects for the (para) hippocampus [(p)HIP] and inferior parietal lobule (IPL) were inconsistent, especially in MIST studies. CEN structures, such as dorsolateral PFC (dlPFC), posterior parietal cortex (PPC), and dorsomedial PFC (dmPFC), were generally less frequently mentioned, which may reflect a reporting bias due to specific research questions or broad anatomical labels. Study designs and analysis strategies also likely contributed to these variations (8,14).

In addition to neural responses, stress studies often measure hormonal, cardiovascular, affective, and behavioral variables to confirm successful stress induction (8). Most studies have focused on cortisol as a marker of hypothalamic-pituitary-adrenal axis reactivity (1,7,15,16). A few ScanSTRESS studies have reported positive associations between cortisol levels and activation in structures such as the FIC, dACC, AMY, mPFC, PCC, and HIP (17–20), with some of these effects found only in male participants (18). Also MIST studies showed associations with similar structures, although often with an inverse pattern, in which higher cortisol responses correlated with less activation in SN and DMN structures (21–26), including one region of interest-based study (26) not listed in Table 1. Additionally, a few studies have indicated sex-specific differences in neural stress responses in these same structures, but without a clear pattern (23,27,28). This may have resulted from variations in menstrual cycle phases, hormonal contraceptive use, or overall reproductive status, as these factors are often not controlled (29,30). One ScanSTRESS study nonetheless found sex-specific associations between neural and cortisol responses in SN and DMN structures, comparing males with females taking oral contraceptives (19,30). Regarding affective

responses, only 1 ScanSTRESS study found SN and DMN activations to predict negative affect (19), while MIST studies showed mixed results (31–33). No ScanSTRESS or MIST study to our knowledge has yet explored links between neural responses and cardiovascular reactivity or task performance in healthy adults.

To rigorously test and extend the triple network hypothesis in the context of acute psychosocial stress, we conducted a preregistered mega-analysis on ScanSTRESS datasets with 459 participants from 8 studies using a harmonized analysis pipeline (34). We assumed that all 3 networks—SN, DMN, and CEN—are engaged during stress processing, but contribute in functionally distinct ways rather than exhibiting uniform increases or decreases in activity. We examined general responses in both task-based activations/deactivations and task-based connectivity using generalized psychophysiological interactions (gPPI) (35). Associations with individual stress responses—cortisol, heart rate, negative affect, and task performance—were analyzed for task-based activations and deactivations. Specifically, we hypothesized that SN and DMN would be involved in affective, interoceptive, and self-referential components of stress and therefore correlate with hormonal, cardiac, and emotional responses. In contrast, the CEN was expected to support goal-directed control and task regulation and to be associated with task performance under stress—potentially overlapping with prefrontal DMN areas (3,36). While the task performance analysis was not preregistered, it was theoretically and empirically motivated by proposed network functions and the lack of prior evidence in healthy participants under ScanSTRESS and MIST conditions.

We further explored moderating effects of sex, age, and site. Sex was considered in terms of both main effects and sex-specific associations with stress response systems. Age was included given evidence for age-related variation in triple network responsivity and the inclusion of one of the few older ScanSTRESS samples in this mega-analysis (37–41). Site differences were examined to account for methodological variations [e.g., implementation of a shortened ScanSTRESS version (8)]. Finally, as preregistered, we investigated if repeated exposure to psychosocial stress modulates neural reactivity. While healthy individuals tended to show neural habituation of triple network structures, depressed female participants and participants with burnout symptoms exhibited neural sensitization—potentially indicating maladaptive stress processing (18,19,41,42).

METHODS AND MATERIALS

Participants

The present mega-analysis is based on data from 4 sites: Regensburg, Mannheim, Berlin 1, and Berlin 2. Regensburg contributed 5 studies with identical protocol, scanner, and cortisol assay (19,41,43–45); only healthy participants (41,46) and those exposed to the original ScanSTRESS version (45) were included. Mannheim provided the first published ScanSTRESS study (11), while 2 Berlin studies, differing in protocols, scanners, and cortisol assays, were included as Berlin 1 (18) and Berlin 2 (47,48). Of available datasets with a total $N = 537$ (Table 2), 482 were considered for the mega-analysis. After quantitative movement and visual quality control of fMRI data,

Table 1. Overview of Studies That Report on Task-Related Whole-Brain Responses in Structures of the Triple Network

Studies	N ^a (F/M)	SN				DMN					CEN		
		FIC	dACC	TP	AMY	mPFC	PCU	PCC	IPL	(p)HIP	dIPFC	PPC	dmPFC
ScanSTRESS Studies													
Akdeniz <i>et al.</i> (17)	80 (41/39)	act	act	–	act	deact	–	deact	–	act	–	–	–
Bärthel <i>et al.</i> (41) ^b	106 (56/50)	act	act	–	–	deact	deact	–	–	deact	–	–	–
Dahm <i>et al.</i> (18)	86 (50/36)	act	act	–	deact	deact	–	deact	–	both	–	–	–
Dimitrov-Discher <i>et al.</i> (47)	42 (0/42)	act	–	–	act	deact	–	deact	–	act	–	–	–
Giglbberger <i>et al.</i> (43)	111 (70/41)	act	–	–	deact	deact	deact	deact	deact	deact	act	–	deact
Henze <i>et al.</i> (19)	67 (31/36)	act	act	deact	–	deact	deact	deact	–	–	–	–	–
Herrmann <i>et al.</i> (72)	36 (0/36)	act	–	deact	–	deact	–	deact	act	deact	–	–	act
Hu <i>et al.</i> (73)	70 (31/39)	both	both	both	deact	–	both	deact	both	deact	both	act	act
Konzok <i>et al.</i> (44)	61 (30/31)	both	–	deact	–	deact	deact	deact	–	–	both	–	–
Kuhn <i>et al.</i> (27)	140 (67/73)	both	–	deact	deact	deact	deact	deact	both	deact	both	both	act
Lederbogen <i>et al.</i> (74)	57 (25/32)	act	act	–	–	–	–	act	–	act	–	–	–
Liu <i>et al.</i> (75)	72 (32/40)	both	both	both	deact	–	both	deact	act	both	both	–	both
Sandner <i>et al.</i> (20)	40 (12/28)	act	act	both	deact	deact	–	deact	both	–	act	–	deact
Streit <i>et al.</i> (11)	42 (20/22)	act	act	both	act	deact	both	deact	act	act	act	both	both
Wang <i>et al.</i> (76)	62 (39/23)	–	–	both	act	–	both	both	–	both	both	–	both
MIST Studies													
Albert <i>et al.</i> (31)	28 (28/0)	–	–	deact	–	deact	–	deact	both	deact	–	–	–
Allenby <i>et al.</i> (77)	75 (35/40)	–	act	act	–	–	–	–	–	–	act	–	act
Alpheis <i>et al.</i> (78) ^b	79 (28/51)	–	–	act	–	–	act	act	–	–	act	–	–
Ashare <i>et al.</i> (79)	39 (17/22)	act	act	–	–	act	act	act	act	–	–	act	–
Boehringer <i>et al.</i> (80)	25 (14/11)	–	–	–	act	act	–	–	–	act	–	–	–
Chung <i>et al.</i> (81)	31 (31/0)	–	–	act	–	–	act	–	–	–	act	–	–
Corr <i>et al.</i> (23)	101 (44/57)	act	act	act	–	deact	both	deact	act	deact	act	act	deact
Dagher <i>et al.</i> (82)	15 (7/8)	–	–	deact	deact	deact	deact	deact	–	deact	–	–	–
Dedovic <i>et al.</i> (83)	28 (0/28)	act	act	–	–	deact	deact	deact	act	both	deact	–	–
Dedovic <i>et al.</i> (84) ^b	49 (25/24)	act	act	act	–	deact	act	act	–	–	–	–	–
Edebol Carlman <i>et al.</i> (85)	22 (16/6)	–	act	act	–	act	act	act	act	–	–	–	–
Goodman <i>et al.</i> (86) ^b	72 (55/17)	–	–	act	–	–	–	–	–	act	–	–	act
Goodman <i>et al.</i> (87)	15 (6/9)	act	act	–	–	act	–	–	–	act	act	–	–
Grimm <i>et al.</i> (24)	32 (0/32)	act	–	act	–	–	act	–	–	act	–	–	–
Grodin <i>et al.</i> (88) ^b	25 (10/15)	act	–	act	–	act	act	act	act	–	–	–	–
Khalili-Mahani <i>et al.</i> (21)	19 (0/19)	–	–	deact	–	deact	–	–	–	–	–	–	–
Kogler <i>et al.</i> (28)	80 (40/40)	deact	–	both	–	–	act	–	both	–	both	–	–
König <i>et al.</i> (89)	62 (na/na)	act	–	–	–	act	–	–	–	act	–	–	–
Lederbogen <i>et al.</i> (25)	32 (16/16)	act	act	act	–	–	act	act	–	–	–	–	–
Lord <i>et al.</i> (90)	39 (39/0)	deact	act	–	–	both	act	–	–	deact	–	–	–
Luo <i>et al.</i> (91)	44 (23/21)	act	act	both	act	act	act	act	both	both	act	act	–
Ming <i>et al.</i> (92)	105 (54/51)	act	deact	both	–	deact	–	–	deact	deact	act	–	–

Studies	N ^a (F/M)	SN				DMN					CEN		
		FIC	dACC	TP	AMY	mPFC	PCU	PCC	IPL	(p)HIP	dIPFC	PPC	dmPFC
Orem <i>et al.</i> (32)	239 (113/126)	act	act	–	act	–	–	–	–	deact	act	–	act
Pruessner <i>et al.</i> (22)	40 (20/20)	–	act	–	deact	act	–	–	–	deact	–	–	–
Raufelder <i>et al.</i> (93)	41 (22/19)	act	act	act	–	–	–	–	act	–	–	–	–
Ren <i>et al.</i> (94)	44 (23/11)	act	act	both	–	deact	act	act	both	act	act	act	both
Soliman <i>et al.</i> (95)	40 (27/13)	act	both	deact	–	deact	both	deact	deact	deact	act	act	deact
Sun <i>et al.</i> (96)	307 (153/154)	act	act	deact	–	deact	–	–	deact	deact	–	–	deact
Sun <i>et al.</i> (97)	101 (0/101)	act	act	deact	–	deact	–	–	deact	deact	–	–	deact
Vaessen <i>et al.</i> (98) ^b	29 (13/16)	act	–	act	–	–	act	–	–	–	act	act	–
Voges <i>et al.</i> (99)	65 (39/26)	act	act	act	act	act	–	act	deact	–	–	deact	act
Wheelock <i>et al.</i> (33)	53 (23/30)	act	act	act	act	–	act	–	act	act	act	act	act
Zhang <i>et al.</i> (100)	115 (62/53)	act	–	–	–	deact	–	–	both	–	act	–	–
Zhao <i>et al.</i> (101)	51 (0/51)	act	–	–	–	–	act	act	–	–	act	–	act
Zhong <i>et al.</i> (26)	96 (57/39)	act	–	–	–	deact	–	–	–	–	act	–	–
Zschucke <i>et al.</i> (102)	36 (0/36)	act	act	both	deact	–	–	–	both	–	deact	–	–

AMY, amygdala; CEN, central executive network; dACC, dorsal anterior cingulate cortex; DMN, default mode network; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial PFC; F, female; FIC, frontoinsular cortex; IPL, inferior parietal lobule; M, male; MIST, Montreal Imaging Stress Task; MNI, Montreal Neurological Institute; mPFC, medial PFC; na, not available; PCC, posterior cingulate cortex; PCU, precuneus; (p)HIP, (para)hippocampus; PPC, posterior parietal cortex; SN, salience network; TP, temporal pole.

^bStudies including preclinical or clinical samples.

Table 2. Descriptives for Included Study Samples, Study-Specific Scanner Parameters, and Descriptives for Present Mega-Analysis

Site	Original Study	Descriptives for Study Samples					Scanner Parameters					Descriptives for Mega-Analysis		
		<i>N</i>	Age, Years, Mean $\pm$ SD	Sex Ratio, F/M, <i>n</i>	Scan- STRESS Version	Immunoassay	Siemens System 3T	TR/TE, ms	FoV, mm	Flip Angle, °	No. of Slices (Size/Gap, mm)	<i>N</i>	Age, Years, Mean $\pm$ SD	Sex Ratio, F/M, <i>n</i>
Regensburg	Bärthl <i>et al.</i> (41)	116	41.24 $\pm$ 10.73	56/60	Original	DELFIA	Magnetom Prisma	2000/30	192	90°	37 (3/1)	56	40.09 $\pm$ 10.74	27/29
	Giglberger <i>et al.</i> (43)	111	21.96 $\pm$ 1.83	70/41	Original	DELFIA	Magnetom Prisma	2000/30	192	90°	37 (3/1)	117	21.91 $\pm$ 2.01	75/42
	Henze <i>et al.</i> (19) ^a	67	23.06 $\pm$ 3.14	31/36	Original	DELFIA	Magnetom Prisma	2000/30	192	90°	37 (3/1)	67	23.06 $\pm$ 3.14	31/36
	Konzok <i>et al.</i> (44) ^a	61	23.69 $\pm$ 3.82	30/31	Original	DELFIA	Magnetom Prisma	2000/30	192	90°	37 (3/1)	61	23.69 $\pm$ 3.82	30/31
	Speicher <i>et al.</i> (45)	40	23.85 $\pm$ 4.41	0/40	Original	DELFIA	Magnetom Prisma	2000/30	192	90°	37 (3/1)	20	23.70 $\pm$ 4.74	0/20
Mannheim	Streit <i>et al.</i> (11)	42	28.00 $\pm$ 6.00	20/22	Original	DELFIA	Trio	2000/30	192	80°	32 (3/1)	38	27.74 $\pm$ 5.91	18/20
Berlin 1	Dahm <i>et al.</i> (18)	86	27.70 $\pm$ 6.02	50/36	Original	IBL	Tim Trio	1960/25	192	80°	36 (2.40/0.60)	93	27.90 $\pm$ 6.29	54/39
Berlin 2	Nowak <i>et al.</i> (48)	50	30.23 $\pm$ 5.39	0/50	Short Version	ECLIA	Magnetom Trio	1560/25	192	64°	28 (3/0.75)	43	30.30 $\pm$ 5.43	0/43
Total		537	27.46 $\pm$ 5.17	257/316								459	26.97 $\pm$ 7.98	222/237

DELFIA, dissociation-enhanced lanthanide fluorescent immunoassay; ECLIA, electrochemiluminescence immunoassay; F, female; FoV, field of view; M, male; TE, echo time; TR, repetition time.

^aFor Henze *et al.* (19) and Konzok *et al.* (44), 36 participants (13 female) overlapped, which is why the total number of participants was reduced by this number.

459 participants (222 female; age, mean $\pm$ SD 26.97 $\pm$ 7.98 years; range, 18–62 years) were included in our study (23 datasets with either mean framewise displacement > 0.5 mm or poor image quality were excluded). For cortisol, 446 participants (217 female) with available data were included; for heart rate, 317 (136 female) were included; for negative affect, 457 (221 female) were included; and for task performance, 367 (169 female) were included. All participants gave written informed consent, and studies were approved by local ethics committees.

General Procedure and Determination of Cortisol, Heart Rate, Negative Affect, and Task Performance Data

As this preregistered mega-analysis (<https://osf.io/yc64p/>) is based on previously published data, we refer to the original studies for detailed descriptions of data collection. All studies used ScanSTRESS to induce psychosocial stress and measured blood oxygenation level-dependent (BOLD) signal changes. Originally, ScanSTRESS was conceived as a block design with alternating 60-second stress and control blocks over 16 epochs, split into 2 runs. Berlin 2 used a shortened version, omitting 2 blocks per condition in run 1; BOLD was not measured during these blocks (Figure 1A).

Salivary cortisol was collected in the afternoon at all sites; 10 (Regensburg), 8 (Mannheim), and 7 (Berlin) samples were collected. To assess the stress response, cortisol increase (peak – pre-stress) and total cortisol output (area under the curve with respect to the ground [AUCg] and AUC with respect to increase [AUCi]) (49) were calculated (Figure 1B). For heart rate, mean values during stress induction were available for Regensburg, Mannheim, and Berlin 2; no data were recorded during stress in Berlin 1. Negative affect was assessed at all sites with varying items and scales. We mapped site-specific items (Regensburg: irritated, scale 1–5; Mannheim: tense, scale 0–3; Berlin 1: stressed, scale 0–3; Berlin 2: stressed, scale 1–10) to a common factor termed

negative affect (factor loading = 1, comparative fit index = 1, Tucker-Lewis index = 1, root mean square error of approximation = 0, $R^2 = 1$) after applying linear transformations for Regensburg and Berlin 2. Task performance was measured as error rates (i.e., ratio of incorrect tasks to total tasks) during stress blocks. Descriptive statistics are in [Table S2](#).

fMRI Data Analysis

In line with our preregistration, we processed the fMRI data as follows: Skull-stripping of anatomical images was done using the convolutional neural network SynthSeg with robust segmentation performance independent of changes in contrast and resolution (50). Functional images were preprocessed via ENIGMA HALFPipe (34) applying motion correction, distortion correction, coregistration, and spatial normalization via fMRI-Prep (51), followed by spatial smoothing (6 mm), grand mean scaling, motion correction, and temporal filtering (high-pass: 125 seconds). Neural stress reactivity was modeled in HALFPipe (FSL), with BOLD signal changes for each condition (stress, control, announcements) analyzed using a hierarchical approach (19): For each participant, a general linear model was fitted at the first level, and responses from the 2 Scan-STRESS runs were aggregated (fixed effects, second level). Group-level mixed-effects analyses (third level) contrasted activations (stress > control) and deactivations (control > stress) as neural stress response measures. All voxelwise analyses were performed using false discovery rate (FDR) corrections ($p_{FDR} < .05$, calculated using the FSL tool *fdr*) to account for the number of comparisons typical for exploratory, whole-brain designs (52). For gPPI analyses, familywise error (FSL default setting) correction was applied with additional verification via *fdr*, yielding identical thresholds.

A group-level mixed-effects analysis was performed using 1-sample *t* tests, adjusting for age, sex (female, male), and site (Regensburg, Mannheim, Berlin 1, Berlin 2). Aggregated contrast images from both ScanSTRESS runs were used for

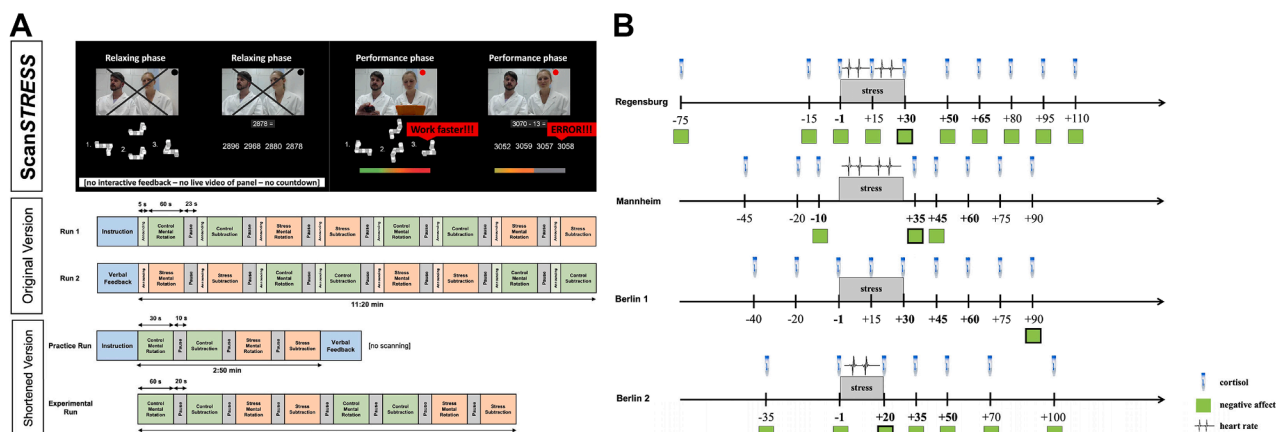


Figure 1. Psychosocial stress induction paradigm ScanSTRESS and site-specific experimental protocols. Depiction of the implemented ScanSTRESS versions **(A)** and site-specific protocols for cortisol, heart rate, and negative affect assessments with stress onset (i.e., start of ScanSTRESS) as common reference point **(B)**. For the determination of individual cortisol increases, the site-specific sampling point before ScanSTRESS as well as the respective post-stress sampling points of each site are highlighted in bold in panel **(B)** to quantify the difference between the individual cortisol peak and the pre-stress level. Likewise, the respective time point for the considered negative affect rating is marked by a black box around the affect symbol for each site.

all sites except Berlin 2, where only 1 run was available. To check if use of the shortened version of ScanSTRESS at Berlin 2 affected results, a second analysis excluded this site. Additionally, we explored main effects of sex and (not pre-registered) age and site, as these are relevant to the interpretation of effects. Hence, separate 1-sample t tests were conducted for each site to confirm findings. Furthermore, as preregistered, gPPI analyses were conducted using FSL (53) to quantify task-based connectivity. Seed regions were based on prior triple network literature (54) defined as 6-mm spheres around Montreal Neurological Institute (MNI) coordinates of left/right FIC (SN: 232, 26, 214/38, 22, 210), PCU/PCC (DMN: 1, 255, 17), and left/right dlPFC (CEN: 242, 34, 20/44, 36, 20). First-level gPPIs were computed per run using FEAT, with psychological (stress > control) as well as physiological (seed time-series) regressors, and their interaction (PPI+/PPI-). Additional regressors captured control > stress and announcements. Subject-level fixed-effects analyses combined runs with Berlin 2 data including only 1 run. Group-level mixed-effects models (1-sample t tests) adjusting for age, sex, and site were performed for each seed (further information is in the Supplement).

To examine associations between neural and (sex-specific) cortisol responses to stress, we conducted a group-level analysis adjusted for age, sex, and site. We tested the effect of cortisol (1-sample t test with covariate: separate models for cortisol increase, AUCg, AUCi) and the interaction between cortisol and sex (2-group analysis with covariate interaction) on neural stress responses. To account for menstrual cycle, hormonal contraception, and reproductive status (29,30,55,56), we reran this model using the variable cycle ($N = 427$, 4 levels: $n = 229$ males, $n = 104$ females in luteal phase, $n = 83$ females using hormonal contraceptives, $n = 11$ postmenopausal females). Additionally, we explored associations between neural responses and heart rate, negative affect, and (not pre-registered) task performance, adjusting for age, sex, and site, while also testing sex-specific interactions for these variables.

Labeled as exploratory in the preregistration, we tested for exposure-time effects—an increasing deactivation (i.e., less activation over time) of prefrontal structures over the 2 ScanSTRESS runs (18,19)—previously linked to stress-related psychopathology (41,42). We analyzed neural response differences between runs using the sandwich estimator (57), correcting for age, sex, and site (excluding Berlin 2).

RESULTS

We report only on triple network responses, excluding results for visual, auditory, and motor structures (Supplemental Results).

Activations and Deactivations in Response to Stress

The whole-brain analysis revealed activations and deactivations in all triple network structures across the total sample ($z_{FDR} > 3.76$) (Figure 2B) and in each site-specific analysis (Regensburg: $z_{FDR} > 3.45$, Mannheim: $z_{FDR} > 3.53$, Berlin 1: $z_{FDR} > 3.50$, Berlin 2: $z_{FDR} > 3.85$ [Figure 2C]; peak

voxels [Tables S3–S7]). Site effects showed response differences primarily in cluster extent with only one qualitative difference in Berlin 2 (male-only sample) showing deactivations in the AMY instead of activations. Excluding Berlin 2, results remained unchanged (Figure S1).

Sex differences ($z_{FDR} > 3.44$) (Figure S2 and Table S8) revealed stronger activations in males compared with females in the right angular gyrus (AG) (DMN) and stronger deactivations in SN (bilateral opercular cortex [OC], right orbitofrontal cortex [OFC]), DMN (right supramarginal gyrus [SMG], PCC), and CEN (left frontal pole [FP], right middle frontal gyrus [MFG]) structures.

Generalized Psychophysiological Interactions

Task-based connectivity analysis confirmed involvement of all 3 networks (Figure 3 and Tables S9 and S10). The FIC seeds (SN) showed increased connectivity (PPI+) within the SN and to the FP (CEN); decreased connectivity (PPI-) occurred within the SN and to DMN and CEN structures. The PCU/PCC seed (DMN) showed PPI+ to SN, CEN, and SMG (DMN), and PPI- to CEN, MTG (SN), and mPFC (DMN). The dlPFC seeds (CEN) exhibited PPI+ to SN, DMN, and FP (CEN) and PPI- to SN, DMN, and within the CEN.

Associations With Cortisol, Heart Rate, Negative Affect, and Task Performance

Positive associations between cortisol increase and activations emerged, peaking in the right AMY, extending to the insular cortex (IC) and DMN structures [AG, (p)HIP] ($z_{FDR} > 2.54$) (Figure 4A and Table S11). These effects persisted when controlling for cycle and could be confirmed for both AUC measures, although with a smaller cluster extent (Figure S3). Sex-specific analyses showed that males exhibited negative associations between cortisol increases and activations, while females displayed positive associations, peaking in the right IC ($z_{FDR} > 2.94$) (Figure 4F and Table S12) and further comprising other SN (left IC, nucleus caudatus, dACC, thalamus, right AMY) and DMN [left (p)HIP, PCC, and right mPFC] structures. Again, these effects persisted when correcting for cycle and were confirmed for AUC measures, again to a smaller cluster extent (Figure S4).

Heart rate was negatively associated with activations in DMN structures, peaking in the left PCC ($z_{FDR} > 3.10$) (Figure 4B and Table S13), including left SMG, paracingulate gyrus (PCG), and (p)HIP. Negative affect was positively associated with activations peaking in the right IC, extending to the right dACC (SN) and SMG (DMN) ($z_{FDR} > 2.77$) (Figure 4C and Table S14). Moreover, a sex-specific effect for negative affect was significant for right dACC activation, with males exhibiting negative associations and females exhibiting positive associations ($z_{FDR} > 3.10$) (Figure 4G and Table S15). Task performance correlated positively with activations in the right subgenual ACC (sACC) (DMN) (Figure 4D) and FP (CEN) ($z_{FDR} > 3.10$) (Figure 4E and Table S16). Additionally, the effect in the right FP was sex specific ($z_{FDR} > 3.10$) (Figure 4H and Table S17) with females showing a more positive association compared with males.

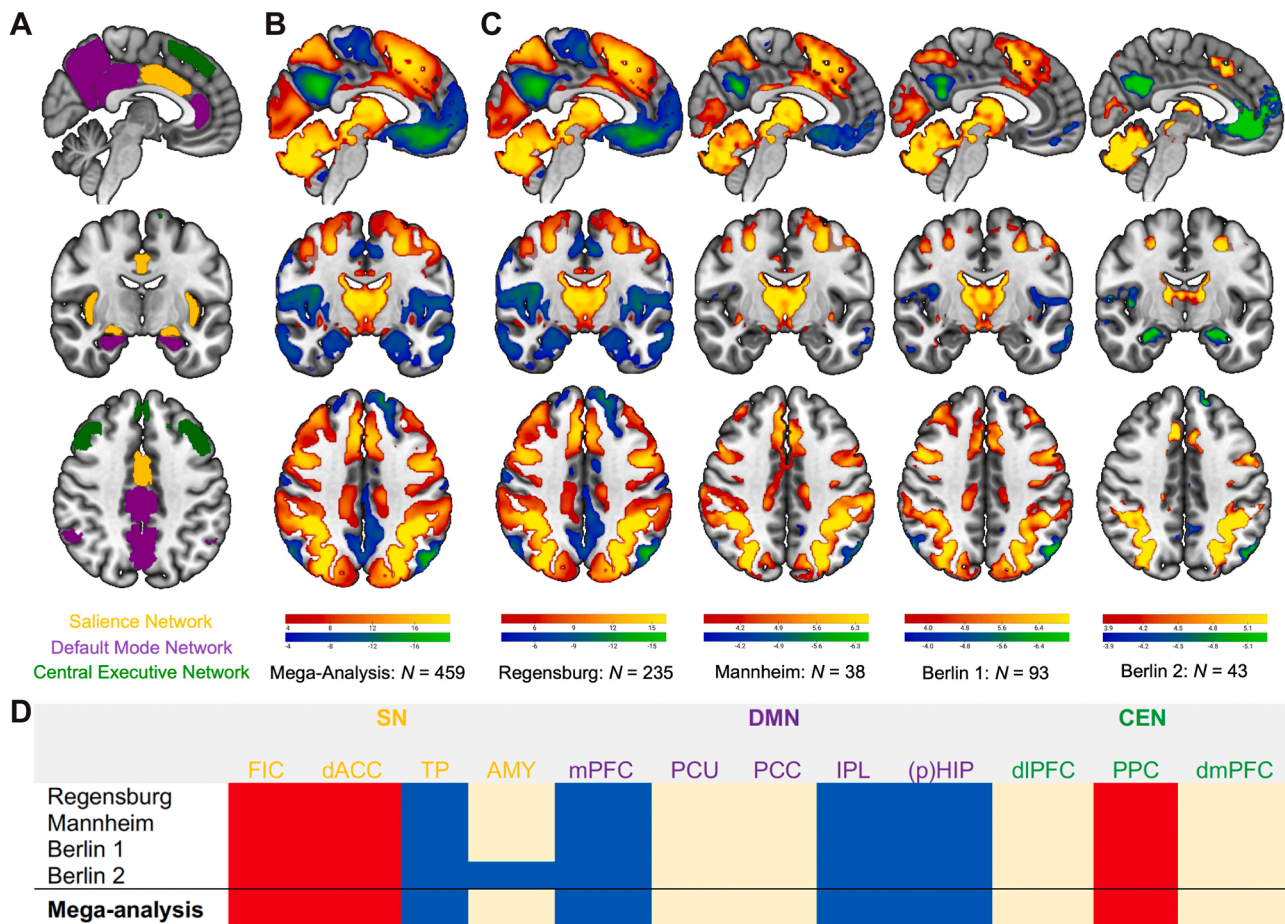


Figure 2. Triple network responses. Depiction of triple network structures color coded with structures of the salience network (SN) in orange, default mode network (DMN) structures in purple, and central executive network (CEN) structures in green (A), along with whole-brain results for the total sample (B), site-specific whole-brain results (C), and a color-coded tabulation of responses (D) whereby red indicates activations, blue indicates deactivations, and beige indicates the presence of both reaction qualities. AMY, amygdala; dACC, dorsal anterior cingulate cortex; dIPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial PFC; FIC, frontoinsula cortex; IPL, inferior parietal lobule; mPFC, medial PFC; PCC, posterior cingulate cortex; PCU, precuneus; (p)HIP, (para) hippocampus; PPC, posterior parietal cortex; TP, temporal pole.

When excluding the outlier (error rate > 0.8), these effects remained.

Age and Exposure-Time Effect

Age was positively associated with activations in DMN [left PCU, bilateral mPFC, (p)HIP] structures, indicating increased activation with advancing age ($z_{FDR} > 3.76$) (Figure 5A and Table S18). Similar patterns were found in SN (left middle temporal gyrus, dACC, bilateral OC, putamen, OFC) and CEN (bilateral superior frontal gyrus, FP) structures, but to a lesser extent. To rule out the influence of older participants from Regensburg (41), the analysis was repeated omitting this subsample. The effects in DMN structures persisted with reduced cluster extent ($z_{FDR} > 3.10$) (Figure S5). We also found an exposure-time effect, i.e., smaller signal in run 2 compared with run 1, in all structures of the triple network except for the dACC (SN) and PPC (CEN) ($z_{FDR} > 4.95$) (Figure 5B and Table S19). Increasing signal strength over runs was not detected.

DISCUSSION

The main research question of this study was to test and possibly extend the triple network hypothesis for psychosocial stress, postulating that SN and DMN responses predominate at the expense of the CEN. To this end, we reviewed all psychosocial stress induction studies and performed a mega-analysis of ScanSTRESS datasets with 459 participants from 8 studies with harmonized pre-processing and data analysis. We found that the triple network hypothesis for psychosocial stress should be differentiated and extended: There were activations and deactivations in all 3 networks, which were related to endocrine, cardiac, affective, and performance parameters. Furthermore, we found an unexpected age-related increase in DMN activation, replicated an exposure-time effect of decreasing activation over time, and demonstrated several sex-specific effects. Based on our findings, we suggest a modified and extended triple network hypothesis of psychosocial stress processing.

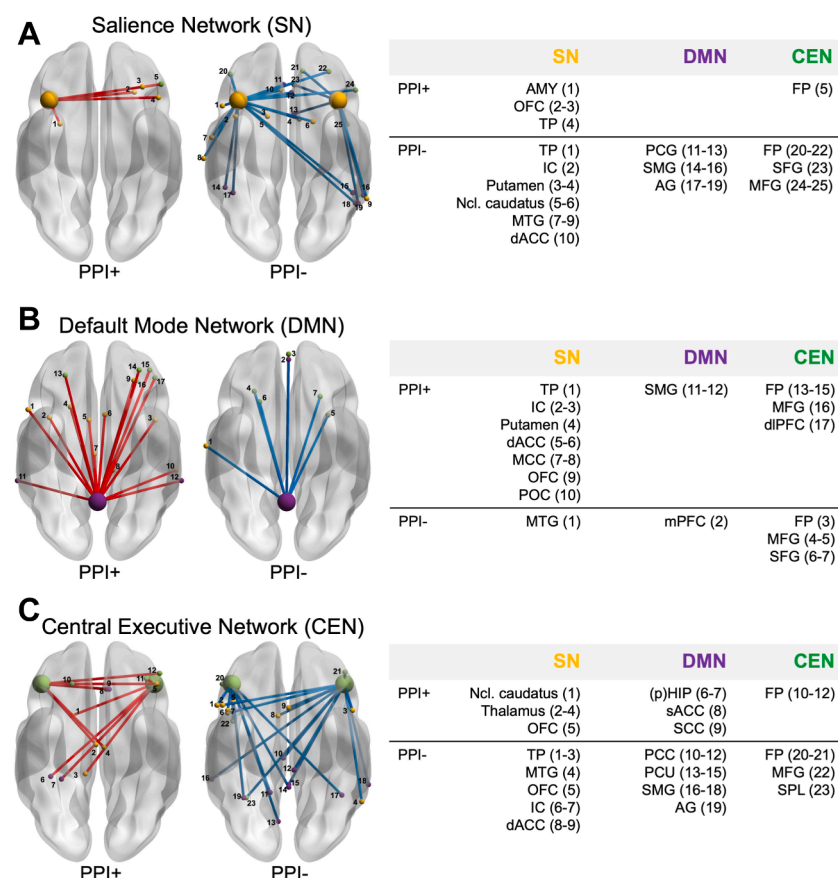


Figure 3. Functional connectivity during psychosocial stress. Increased/positive connectivity (PPI+), in red, and decreased/negative connectivity (PPI-), in blue, during psychosocial stress of the **(A)** salience network (SN), **(B)** default mode network (DMN), and **(C)** central executive network (CEN). AG, angular gyrus; AMY, amygdala; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; FP, frontal pole; IC, insular cortex; MCC, middle cingulate cortex; MFG, middle frontal gyrus; mPFC, medial PFC; MTG, middle temporal gyrus; Ncl., nucleus; OFC, orbitofrontal cortex; PCG, posterior cingulate cortex; PCU, precuneus; (p)HIP, (para) hippocampus; POC, parietal opercular cortex; PPI, psychophysiological interaction; sACC, subgenual ACC; SCC, subcallosal cortex; SFG, superior frontal gyrus; SMG, supramarginal gyrus; SPL, superior parietal lobule; TP, temporal pole.

Activations and Deactivations in All 3 Networks

Contrary to the hypothesis of Van Oort *et al.* (4), we could not demonstrate generally increased SN and DMN responses at the expense of CEN reactivity. Instead, we observed activations and deactivations across all 3 networks, replicated within each site. Our results emphasize that stress responses cannot be consistently categorized within a network or structure (58). For example, SN structures such as the FIC and dACC showed activation, while the TP was deactivated, and the AMY exhibited both. In the male-only Berlin 2 sample, the AMY showed exclusive deactivations confirming that the sample composition per se may lead to deviating correlates. Similarly, DMN structures (mPFC, IPL, (p)HIP) were mostly deactivated, while PCU and PCC showed both responses. CEN structures such as dlPFC and dmPFC also exhibited both activations and deactivations. These findings challenge the simplified notion of consistent network responses in stress processing and emphasize that the broad anatomical designations, which summarize many smaller yet functionally relevant subregions within each network (e.g., TP for the SN, mPFC and IPL for the DMN, or dlPFC, PPC, and dmPFC for the CEN), are not very informative, especially in the context of stress. Furthermore, our connectivity findings confirm the involvement of all 3 networks. Carefully interpreted, our gPPI results suggest that the FIC as an SN seed may act as initiator, processing stressors and shifting between DMN and CEN

structures (3,4,58,59). Increased connectivity within the SN (from FIC to other SN structures) was paired with reduced connectivity to DMN and CEN structures, aligning with previous reports (54). Moreover, the SN showed increased connectivity solely to the FP in the CEN, likely steering cognitive resources toward coping with stress, as this structure exhibited associations with task performance. However, reduced connectivity within certain SN structures hints at a hierarchical network ordering, warranting further investigation. Moreover, the DMN and CEN proved involvement, with the DMN seed interacting with both SN and CEN structures and the CEN seed connecting to SN and DMN structures that we found to be linked to physiological and behavioral stress responses.

Relevance of Harmonized Preprocessing and Data Analysis

Our mega-analysis demonstrated that consistent effect patterns can be established when data are processed in a standardized way (34). Discrepancies between original study findings and our site-specific results likely arise from differences in analysis strategies. We recommend standardizing analysis for stress paradigms such as ScanSTRESS, considering subject- and run-specific analyses at the first level, fixed effects at the second level, and mixed effects at the group level (19). This standardization could explain inconsistencies in

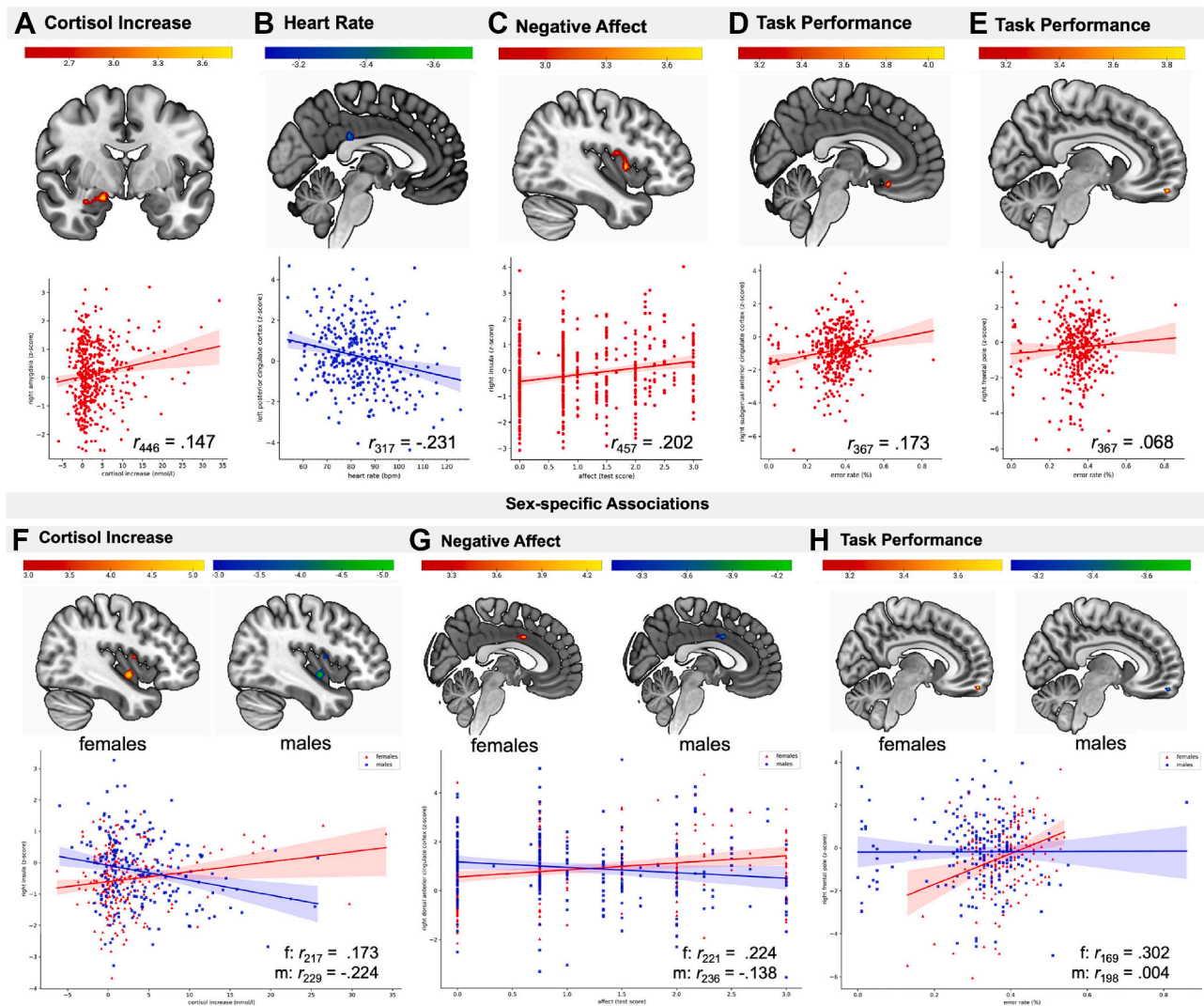


Figure 4. Associations between responses of the triple network and physiological as well as behavioral stress reactions. Associations between neural responses and (A) cortisol increases, (B) heart rate elevations, (C) negative affect ratings, and (D, E) task performance quantified by error rates during the task as well as sex-specific associations between neural responses and (F) cortisol increases, (G) negative affect ratings, and (H) task performance. F, female; M, male.

previous reviews (8–10,16); for instance, associations such as AMY activation with stress-induced cortisol or dACC activation with negative affect response may have been missed in individual studies. Accordingly, when applying the same stress-inducing components and analysis standards, consistent neural stress responses are to be expected. The shortened version of ScanSTRESS, used in Berlin 2, still produced comparable results, suggesting that it can be effective when scanning time is limited or when focusing on processes following rather than during acute stress.

Association of Brain Response With Physiology and Behavior

Our mega-analysis explored which neural structures are associated with other components of the stress response, namely, the hypothalamic-pituitary-adrenal axis, sympathetic nervous system, subjective-emotional experience, and

performance. Cortisol increase and total cortisol release (AUCg, AUCi) were positively associated with activation in SN and DMN structures, particularly in the AMY, IC, AG, and (p)HIP, confirming previous findings (17–20). Interestingly, DMN structures, showing deactivations during stress, exhibited more activation when cortisol was considered. Hence, DMN structures exhibited the opposite response quality when the influence of an additional variable was taken into account, possibly illustrating the central role of DMN structures in stress processing (4,58,60). Additionally, heart rate was associated with DMN deactivations [PCC, SMG, PCG, (p)HIP], and negative affect responses were correlated positively with activations in SN and DMN regions (IC, dACC, SMG), confirming our hypothesis. Lastly, both DMN and CEN activations were positively related to task performance, especially in the FP and sACC, further supporting our hypothesis.

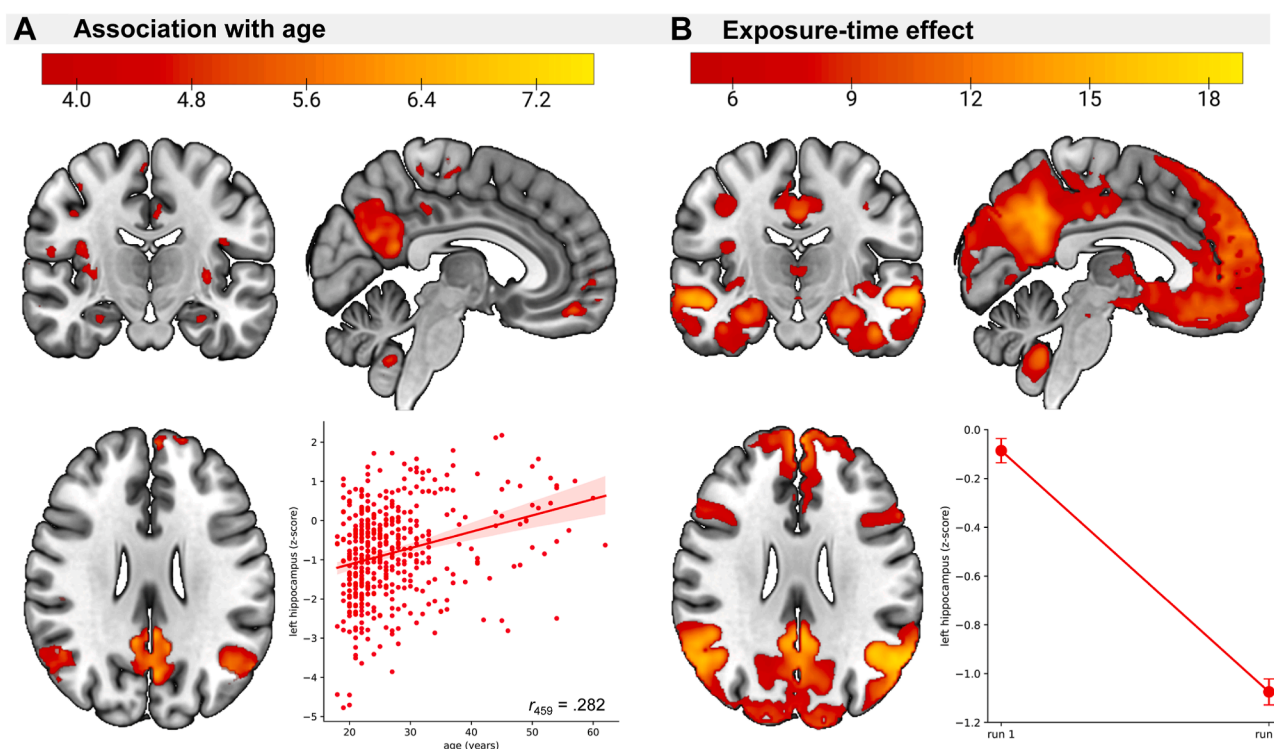


Figure 5. Age and exposure-time effect. Illustration of the positive association between age and neural stress response (stress > control), including a descriptive visualization of the effect for the left hippocampus (A) and depiction of structures demonstrating an exposure-time effect with higher signal in the first compared with the second run of ScanSTRESS (exposure-time effect: run 1 > run 2), as well as a descriptive visualization for the left hippocampus including standard error of the mean (B).

Extended Triple Network Hypothesis of Psychosocial Stress Processing

Based on our findings, we propose an extended triple network hypothesis for psychosocial stress processing (Figure 6), emphasizing the central role of the DMN. We suggest that the SN and DMN are differentially associated with distinct stress responses, while the CEN and DMN reflect responses to stress-inducing tasks. This model, based on ScanSTRESS data, highlights that triple network activations are linked to cortisol, heart rate, negative affect, and task performance. Associations may vary for other stress paradigms such as the MIST (19,21–26,31–33). Our extended model fills a research gap by providing a framework to study healthy stress processing and stress-related disorders, linking neural reactivity with distinct stress response systems and resilience factors (58). Furthermore, it provides a basis for more accurate research into stress-related conditions.

Sex Effects

Our mega-analysis revealed sex-specific whole-brain effects, highlighting that males compared with females showed, apart from stronger activations in AG, particularly stronger deactivations in SMG, PCC (DMN), OC, OFC (SN), FP, and MFG (CEN). This suggests that males under psychosocial stress do downregulate emotional and cognitive control structures more than females, while relying on internal processes. However, our sample included females in

the luteal phase, females using hormonal contraceptives, and postmenopausal females, limiting interpretations due to known cycle-related stress processing effects (55,61–63). Few studies have explored neural sex differences in ScanSTRESS or MIST studies (23,27,28), and there is a need to consider not only biological sex, but also psychosocial factors such as gender (64). Nevertheless, our findings support that although the same structures are involved in stress processing for both sexes, the response quality or direction do differ (30,65,66). For cortisol, we found that higher cortisol increases were linked to activations in females (independent of cycle), while one study in our mega-analysis showed deactivations in females using oral contraceptives compared with males (30). This highlights the significant impact of sample composition on effect patterns and underscores the importance of thoroughly investigating the role of menstrual cycle, hormonal contraception, and reproductive status on stress processing. Besides, striatal differences, crucial for reward processing and resilience (58), suggest sex-based differences in stress response and cognitive task performance, with females exhibiting more activations linked to negative affect and worse task performance (17,30,67,68). These findings emphasize again that while the same neural structures are involved in stress processing for both sexes, their associations with certain stress responses differ. Interestingly, females and males do not need to differ in these stress responses to detect

The Extended Triple Network Hypothesis

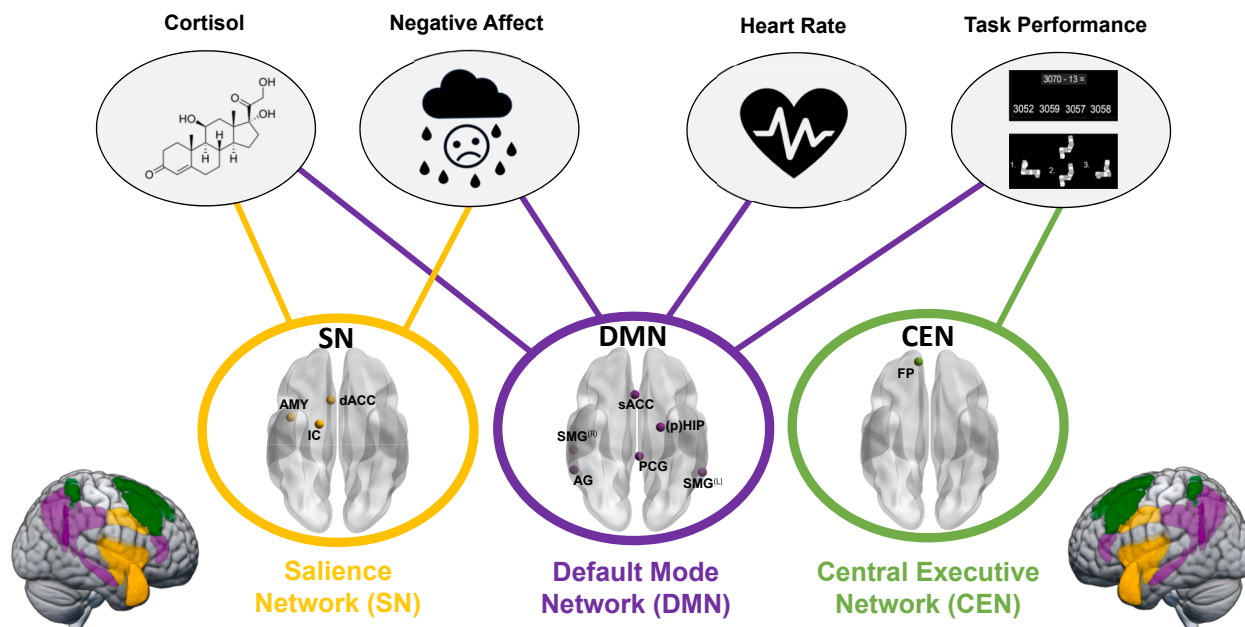


Figure 6. Extended triple network hypothesis. Shown are structures of the salience network (SN), default mode network (DMN), and central executive network (CEN), exhibiting associations with cortisol, negative affect, and heart rate responses to psychosocial stress as well as associations with task performance. While the SN and DMN are associated with distinct stress reactions, the CEN (together with the DMN) is engaged in processing the stress-inducing tasks. AG, angular gyrus; AMY, amygdala; dACC, dorsal anterior cingulate cortex; FP, frontal pole; IC, insular cortex; L, left; PCG, paracingulate gyrus; (p)HIP, (para)hippocampus; R, right; sACC, subgenual ACC; SMG, supramarginal gyrus.

differences in association with neural responses. For example, we found sex differences in cortisol, heart rate, and task performance, but not in negative affect (Table S2) (29,69).

Surprising Age Effect

Interestingly and unexpectedly, we found a positive association between age and activations, particularly in DMN structures, i.e., activations increase with advancing age. Although all DMN structures showed deactivations during stress, this shifted to activations when considering age, suggesting that older individuals may have a reduced ability to efficiently switch between resting and task-related states, which may also reflect age-related changes in cognitive control, attention, or self-referential processing (70,71).

Replication of Exposure-Time Effect

Notably, we replicated the exposure-time effect for all triple network structures except for the dACC and PPC. Activation in all networks decreased from run 1 to run 2, consistent with a neural habituation pattern. Such decreases have previously been associated with adaptive stress processing and greater resilience, whereas the absence or reversal of this effect may indicate vulnerability to chronic stress (18,19,41,42). Remarkably, this exposure-time effect was reported to be altered in individuals with burnout symptoms compared with

healthy control individuals in the dACC, suggesting that certain structures—particularly within the SN—may fail to downregulate under repeated stress exposure, potentially reflecting maladaptive stress responses (41).

Limitations and Outlook

Our mega-analysis has several limitations, primarily due to inconsistencies in the included study protocols. While we standardized key variables (e.g., onset of stress, analysis strategy), some inconsistencies could not be fully corrected. For heart rate, Berlin 2 provided only mean responses, lacking dynamics between stress and control blocks. Negative affect was assessed differently across sites, and error rates may not be the best task performance indicator due to variations in task presentation. Additionally, site-specific sample sizes varied substantially, with Regensburg contributing the largest subsample, which may have disproportionately influenced group-level effects. Further mega-analyses are needed to evaluate the extended triple network model across different stress induction paradigms and to address issues such as menstrual cycle, hormonal contraception, reproductive status, gender, and diversity. When integrating more heterogeneous paradigms or study designs, future analyses may also benefit from modeling site as a random effect within mixed-effects frameworks. Combining existing data could enhance future studies, especially on resilience and stress-related factors.

Brain Stress: Extending the Triple Network Hypothesis

We think that our more nuanced and extended triple network model could be valuable in clinical settings, providing insight into the identification of biomarkers that shed light on the effects of stress in vulnerable populations. In addition, the application of this model to clinical samples could provide important information, particularly when focusing on variables such as age and duration of stress exposure (i.e., chronic stress), which may help to explain individual differences in stress processing. Building on our findings, this could be achieved by focusing on individual neural structures. Specifically, regions of the DMN and the dACC appear to hold promise for identifying neural biomarkers of coping mechanisms and resilience.

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G-IH, PK, and HW were responsible for conceptualization. G-IH, PK, TEN, SE, and HW were responsible for methodology. G-IH, ES, LW, LK, and TEN were responsible for software. G-IH, MG, MN, and TK were responsible for validation. G-IH, TK, ES, and LW were responsible for formal analysis. G-IH, MG, CB, JK, HLP, NS, FS, and IMV were responsible for investigation. G-IH, FS, IMV, BMK, SW, SE, and HW were responsible for resources. G-IH, MG, CB, and JK were responsible for data curation. G-IH and MN were responsible for visualization. G-IH was responsible for project administration and writing—original draft. G-IH, BMK, SW, SE, and HW were responsible for funding acquisition. SE and HW were responsible for supervision. G-IH, MG, CB, JK, MN, TK, ES, LW, HLP, LK, NS, FS, IMV, PK, TEN, BMK, SW, SE, and HW were responsible for writing—review and editing.

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The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request. A repository of studies that have already used and published the Regensburg data is available at <https://osf.io/echja/>.

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ARTICLE INFORMATION

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