RESILIENCE: LIFE EVENTS, TRAJECTORIES AND THE BRAIN

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RESILIENCE: LIFE EVENTS, TRAJECTORIES AND THE BRAIN

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EDITORIAL
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Editorial: Resilience: Life Events, Trajectories and the Brain

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Keywords: resilience, life events, trauma, trajectories, gender, neurobiology, longitudinal studies

Editorial on the Research Topic

Resilience: Life Events, Trajectories and the Brain

Given the prevalence of stressful events and their impact on individuals, families, communities and societies, promoting and supporting resilience is a global societal need and challenge at the same time. There is considerable variation in the way resilience is currently being understood, defined, and measured both within animal and human studies. Resilience has been defined as either characteristic of the individual or as a dynamic cultural pluralistic interactional process. Based on evolving research the concept of resilience has significantly changed from a trait-oriented to a dynamic outcome, which draws on concepts of life-course epidemiology, trans-diagnostic psychiatry, developmental psychology, emotion research, and cognitive neuroscience. We initiated this Research Topic by proposing that resilience is dynamic interactional process, which includes distal and proximal protective and risk factors/mechanisms. In parallel with articles published in this Research Topic, recent research has advanced our knowledge of resilience highlighting that resilience is an interactive multidimensional process. In light of this contemporary research, the present Research Topic on "Resilience: Life Events, Trajectories and the Brain" in Frontiers in Psychiatry makes a contribution with articles comprising original research, reviews, and theoretical insights.

Three articles considered resilience in the context of early life events. Up to half of children and adolescents in Western societies experience at least one type of early life adversity. Accordingly, these children and youth might be at risk of developing stress-related psychopathologies. In a systematic review, Fritz et al. found empirical evidence for 20 resilience factors (individual level, family resilience factors, and community factors). This highlights the importance of considering resilience factors on different levels of analyses and suggests that resilience factors systems rather than single resilience factors should be studied (Fritz et al.). Another insightful review by Agorastos et al. adds knowledge on human stress system modifications due to early life stress. This review discusses evidence from mainly human research on the 10 most acknowledged neurobiological allostatic pathways exerting enduring adverse effects of early life adversity decades later (hypothalamic-pituitary-adrenal axis, autonomic nervous system, immune system and inflammation, oxidative stress, cardiovascular system, gut microbiome, sleep and circadian system, genetics, epigenetics, structural, and functional brain correlates). Understanding the effects of dysregulated interconnection between all neural systems involved provides new insights into the pathophysiologic trajectories that link early life stress during developmental stages of childhood and adolescence to adult psychopathology. The third study in the context of early life stressors investigates resilience, well-being, and mental health behaviors in migrant and non-migrant adolescents tested across six countries (Australia, New Zealand, UK, China, South Africa, and Canada). Authors explore the impact of country-specific factors, migrancy itself, and trauma exposure on resilience,

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well-being, and mental health among migrant and non-migrant adolescents aged 10–17 showing that migrant adolescents exhibited greater resilience resources than non-migrants despite a higher trauma load (Gatt et al.).

Another group of articles discuss resilience mechanisms in the brain. In the study by Dimitrov et al. resting state fMRI data were acquired before and immediately after stress induction inside the MRI scanner to determine amygdala RSFC. Changes in resting state connectivity from pre- to post-stress were compared between cortisol responders and non-responders. Only non-responding males showed an increased functional connectivity between the posterior cingulate cortex and bilateral amygdala, potentially indicating an increased engagement of the amygdala within the DMN directly after stress in cortisol non-responders. In a review Escamilla et al. discuss the current literature on lifespan-related reorganization processes in the brain that can be related to protective mechanisms that help coping with age-related situations and reduce the burden for brain alterations linked to mental disorders. The authors conclude that correct adaptation of brain connectivity patterns could be the key to healthy aging and diminish the risk for developing neurological and neuropsychiatric disease at different stages across the lifespan. Another review by Bolsinger et al. comprehensively synthesized the literature neuroimaging correlates of resilience to traumatic events, especially focusing on functional connectivity (connectivity of the amygdala, the anterior cingulate cortex, and the prefrontal cortex). Increased prefrontal cortex activity came up to be a protective factor in this study. Finally, increased amygdala and anterior cingulate cortex activities and decreased prefrontal cortex activity as a response to external stimuli were also associated with higher vulnerability, while increased prefrontal cortex activity was associated with lower vulnerability.

Two other studies summarize and evaluate the current state of scientific affairs on the biological basis of resilience and potential interventions. Snijders et al. provide an overview of the literature on animal and human studies of resilience in order to promote resilience. In this review a variety of interventions to promote resilience are proposed such as installing positive emotions and improving cognitive abilities, social interactions, and feelings of purpose and meaning of life along with physical health. Another study by Ben-Zion et al. provides insights into the effects of traumatic events and the mediating factors of cognitive flexibility based on two empirical studies. Cognitive flexibility, shortly after trauma exposure, emerged as a significant predictor of PTSD symptom severity. The findings of these studies shed light on the underlying neurocognitive mechanisms of PTSD symptoms, and demonstrate the effectiveness of an early neurocognitive intervention in relieving PTSD symptoms. Such findings may help develop early mechanism-driven, stage-specific interventions for PTSD, thus improving life resilience.

A crucial novel perspective, which has emerged in resilience studies, is that resilient animals have active adaptive mechanisms that are distinct from actions that reverse deleterious effects in susceptible animals. Therefore, the research aimed in this Research Topic investigates both, the relationship and essential distinction of reversing deleterious effects and ways to cultivate active adaptive mechanisms. An integrated combination of studies from different fields including a wide array of disciplines such as epidemiology, psychiatry, and neurobiology studies will be essential for generating a clearer picture of resilience. Additionally, further studies should focus not only on the resilience of individuals or small human/animal populations, but also communities and societies, which are under considerable pressure at the moment due to the COVID-19 pandemic.

Finally all authors suggest that longitudinal studies are recommended as a pathway to elucidating the factors, and mechanisms and of resilience. Understanding resilient individuals better is a key precursor to the development of interventions and strategies to enhance resilience in the wider population. Taken as a whole, two key messages resonated from the articles included in this Research Topic. Firstly, resilience is a dynamic trajectory, which needs interdisciplinary longitudinal research designs. Secondly, resilience research can contribute to develop neurobehavioral based and justified interventions.

This Research Topic has contributed to the extant literature, not just bringing together most recent research but researchers from different fields of expertise by posing new questions to advance the research conceptually, methodologically, and finally in terms of practice impact. Beyond the intra-individual level, the other levels of resilience (i.e., family, community, and societies) and their interactions need much more dedicated research.

AUTHOR CONTRIBUTIONS

JL and OT co-wrote the editorial. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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A Systematic Review of Amenable Resilience Factors That Moderate and/or Mediate the Relationship Between Childhood Adversity and Mental Health in Young People

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Background: Up to half of Western children and adolescents experience at least one type of childhood adversity. Individuals with a history of childhood adversity have an increased risk of psychopathology. Resilience enhancing factors reduce the risk of psychopathology following childhood adversity. A comprehensive overview of empirically supported resilience factors is critically important for interventions aimed to increase resilience in young people. Moreover, such an overview may aid the development of novel resilience theories. Therefore, we conducted the first systematic review of social, emotional, cognitive and/or behavioral resilience factors after childhood adversity.

Methods: We systematically searched Web of Science, PsycINFO, and Scopus (e.g., including MEDLINE) for English, Dutch, and German literature. We included cohort studies that examined whether a resilience factor was a moderator and/or a mediator for the relationship between childhood adversity and psychopathology in young people (mean age 13–24). Therefore, studies were included if the resilience factor was assessed prior to psychopathology, and childhood adversity was assessed no later than the resilience factor. Study data extraction was based on the STROBE report and study quality was assessed with an adapted version of Downs and Black's scale. The preregistered protocol can be found at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016051978.

Results: The search identified 1969 studies, of which 22 were included (eight nationalities, study sample *n* range: 59–6780). We found empirical support for 13 of 25 individual-level (e.g., high self-esteem, low rumination), six of 12 family-level (e.g., high family cohesion, high parental involvement), and one of five community-level resilience factors (i.e., high social support), to benefit mental health in young people exposed to childhood adversity. Single vs. multiple resilience factor models supported the notion that resilience factors should not be studied in isolation, and that interrelations between resilience factors should be taken into account when predicting psychopathology after childhood adversity.

Conclusions: Interventions that improve individual, family, and/or social support resilience factors may reduce the risk of psychopathology following childhood adversity. Future research should scrutinize whether resilience factors function as a complex interrelated system that benefits mental health resilience after childhood adversity.

Keywords: resilience factors, protective factors, childhood adversity, psychopathology, mental health disorders

INTRODUCTION

Up to half of Western children and adolescents suffer from at least one type of childhood adversity [CA (1)]. CAs span a wide range of traumatic and stressful experiences, and are associated with an increased risk for subsequent psychopathology (1, 2). Recently, a World Health Organization study, based on data from 21 countries ($N = 51945$), showed that approximately 30% of all mental health problems are attributable to CA (2). Fortunately, not all individuals who have experienced CA develop psychopathology (1, 2). Some remain mentally healthy, succumb shortly but recover quickly, recover in the longer term, or even grow mentally after CA (3–7). These individuals may possess or acquire skills and resources that help them to adapt effectively after CA, a phenomenon known as resilience (3, 5, 8, 9). A better understanding of what sets these individuals apart is critically important for interventions aimed to increase resilience in those with a history of CA.

Resilience is an adaptive process following adversity, and can only be scrutinized when risk has been present (4, 5, 7, 10–14). Moreover, resilience should be considered as a dynamic and changing concept, not as a static trait (3, 5, 7, 8, 11, 13–21). Finally, given that resilient functioning waxes and wanes, it can be improved by resilience enhancing factors [RFs (3, 5, 11, 16, 22, 23)].

RFs have a promotive impact on the adjustment process following CA and thus help individuals to adapt and recover from the sequelae of CA (5, 22, 23). Statistically, RFs operate as a moderator (11, 23), and/or as a positive mediator (13, 24) for the relationship between CA and psychopathology. A moderating RF will operate by lowering the level of psychopathology more in adolescents with CA, compared to adolescents without CA. A mediating RF will mitigate the relationship between CA and psychopathology; if the relationship between CA and the RF has the same directionality as the relationship between the RF and psychopathology, improving the level of the RF would lower the level of psychopathology. To date, some reviews provided overviews of potential RFs (16, 25–27). Yet, these reviews were not specific to adversity in childhood (26), examined one type of CA [e.g., childhood sexual abuse (16, 25, 28)], examined one type of psychopathology [e.g., posttraumatic stress disorder (26, 28)], and/ or were not conducted systematically (27). Therefore, this is the first systematic RF review that incorporates various forms of CA and various types of psychopathology. Given that adolescence and young adulthood are characterized by a heightened risk for psychopathology (29), we focus our review specifically on those RFs that benefit mental health in young people.

Abbreviations: CA, Childhood Adversity; RF(s), Resilience Factor(s); DSM, Diagnostic and Statistical Manual of Mental Disorders; SES, Socio-Economic Status; MRA(s), Multiple Regression Analysis(es); SEM(s), Structural Equation Model(s).

Rationale

This preregistered systematic review offers health care providers a comprehensive overview of RFs that improve resilience to psychopathology in young people after CA. The results of our review potentially advance personalized therapy plans (14, 16), as well as preventative and public health interventions aimed at young people with a history of CA. Finally, this review aids the development of novel resilience theories and may therefore enhance our understanding of the complex concept of resilience factors.

Objective

We aimed to identify empirically-supported RFs that reduce the risk of psychopathology in young people subsequent to CA. We focused on social, emotional, cognitive and behavioral RFs, as these factors are amenable to modification, and can be targeted in therapeutic and preventative interventions (16, 20).

METHODS

Protocol and Registration

On the 30th of November 2016 we preregistered our review protocol (30) at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016051978, to enable the reader to compare the suggested with the eventually conducted reviewing procedure.

Information Sources and Search Strategy

We searched English, Dutch and German literature in Web of Science, PsycINFO, and Scopus (e.g., including MEDLINE), for all years until November 2016. Search terms, searched documents and database specific search strategies can be found in **Table 1**.

Study Selection

Duplicates were filtered out using the Mendeley reference manager. Three reviewers (AdG, HC, & JF) pilot-screened 300 titles and abstracts in November 2016. The remaining articles were screened by two of the three reviewers with an approximately equal number of articles per pair. All articles were screened based on the PI(C)OS concept (31): Population (P), intervention (I; i.e., RF), outcome (O), and study design (S). When P, I, and O were met and the design was unknown, the full-text articles were screened for design. Incongruent ratings were solved through discussion, if necessary including a third author (PW).

TABLE 1 | Used search strategy for the databases: Web of Science, Scopus, and PsycINFO.

SEARCH TERMS	
Search category: title, abstract, & keywords	
	(resilien* OR advers*)
AND	(child* OR infan* OR adolescen* OR teen* OR youth* OR pediatr* OR paediatr*)
AND	("self harm*" OR *suicid* OR psychopatholog* OR psycholog* OR psychiatr* OR emotion* OR affect* OR mental* OR disorder*)
Search category: title	
AND	(resilien* OR protect* OR support* OR adapt* OR promot* OR moderat* OR mediat* OR predict*)
AND	(advers* OR "at risk" OR hardship* OR loss* OR "family discord" OR parent* OR trauma* OR traged* OR "chronic* *stress*" OR "life *stress*" OR abus* OR maltreat* OR mistreat* OR assault* OR violen* OR molest* OR neglect*)
SEARCHED DOCUMENTS	
Types*[a]	(in press) articles, proceedings, conference papers, editorial materials, and electronic collections
DATABASE SPECIFIC STRATEGIES	
Scopus	We searched the subject areas "Health Sciences" (covering MEDLINE) and 'Social Sciences & Humanities'
PsycINFO	We additionally utilized subject headings for the two superordinate concepts: 'resilience' and 'childhood adversity': ("Resilience (Psychological)" OR "Protective Factors" OR "Adaptability (Personality)" OR "Adjustment" OR "Coping Behavior" OR "Emotional Adjustment" OR "Adaptive Behavior") AND ("At Risk Populations" OR "Risk Factors" OR "Dysfunctional Family" OR "Emotional Trauma" OR "Trauma" OR "Chronic Stress" OR "Emotional Abuse" OR "Child Neglect" OR "Verbal Abuse" OR "Child Abuse" OR "Sexual Abuse" OR "Physical Abuse" OR "Violence" OR "Domestic Violence" OR "Exposure to Violence" OR "Social Deprivation").

*[a] *We included all of the mentioned document types available for the three databases.*

Study Selection Screening: Eligibility Criteria I

CA

CA, prior to age 18, was defined as one or multiple adversities (1, 2, 32), including: Loss of a significant other, discord within the family, poor parenting, traumatic life events/tragedy, chronic or life stress, hardship, at-risk environment, childhood abuse/maltreatment/mistreatment, and/ or childhood neglect. As we expect financial adversity to be indirectly related to psychopathology, via emotional adversity, we did not include financial adversity as CA (33, 34).

RFs

Inclusion criteria: The RF (a) is a direct effect, moderator, and/or a mediator for the relationship between CA and psychopathology, (b) belongs either to the individual-, family-, or community-level category, and (c) belongs to the cognitive, behavioral, social, and/or emotional functioning domain. Exclusion criteria: The RF is defined (a) as financial advantage, (b) as no re-victimization, (c) as inverse of CA, (d) as inverse of psychopathology, or is (e) not amenable.

Psychopathology

Psychopathology was defined as general mental distress, as self-harm behavior, as suicidal ideation, or as categorical diagnosis or continuous symptoms of any disorder included in the Diagnostic and Statistical Manual of Mental Disorders IV Text Revision [DSM-IV-TR, (35)] .

Design

We included all longitudinal studies in which the RF was assessed before psychopathology, and CA was measured no later than the RF (i.e., cohort designs). Additionally, we excluded experimental designs which involved intervention on the RF.

Study Selection Rescreening: Eligibility Criteria II

The first screening led to more than 200 eligible articles. Therefore, we applied two additional selection criteria outlined below. AdG and JF rescreened the eligible articles in full-text, including the two additional selection criteria (see **Figure 1**; eligibility stage), which reduced the number of studies to a manageable number of 22 studies.

RFs

RFs should operate as moderator and/or mediator for the relationship between CA and psychopathology, as this indicates that the RF is specific to CA. When the RF is a direct effect, the RF may not be specific to CA and may operate the same for the whole population. We believe that this criterion is crucial, as it ensures that our "resilience factor" definition precisely matches our "resilience" definition, i.e., good mental health despite a history of adversity. In the case of mediation, if CA predicts a potential RF *positively* (e.g., high rumination), then a high level of this potential RF would have to predict psychopathology *positively* (e.g., high rumination leads to higher psychopathology). This means that a *low* level of this factor (e.g., low rumination) would be referred to as RF. Similarly, if CA predicts a potential RF *negatively* (e.g., low cognitive reappraisal), then a high level of this potential RF would have to predict psychopathology *negatively* (e.g., high cognitive reappraisal leads to lower psychopathology). Hence, a *high* level of this factor (e.g., high cognitive reappraisal) would then be referred to as RF. Thus, especially for adolescents with CA it would be advantageous to *reduce* the levels of *low* RFs (e.g., rumination) and to *enhance* the levels of *high* RFs (e.g., cognitive reappraisal), to subsequently lower psychopathology levels. In the case of moderation, lower levels of *low* and higher levels of *high* RFs reduce psychopathology levels more in adolescents with CA, compared to adolescents without CA. Hence, according to this criterion all RFs are especially crucial for adolescents with a history of CA.

Psychopathology

Psychopathology had to be assessed at a mean age of 13–24 years. This criterion is important to enable the systematic selection of more homogeneous studies, to ease and enhance the comparability of findings across studies. We chose this

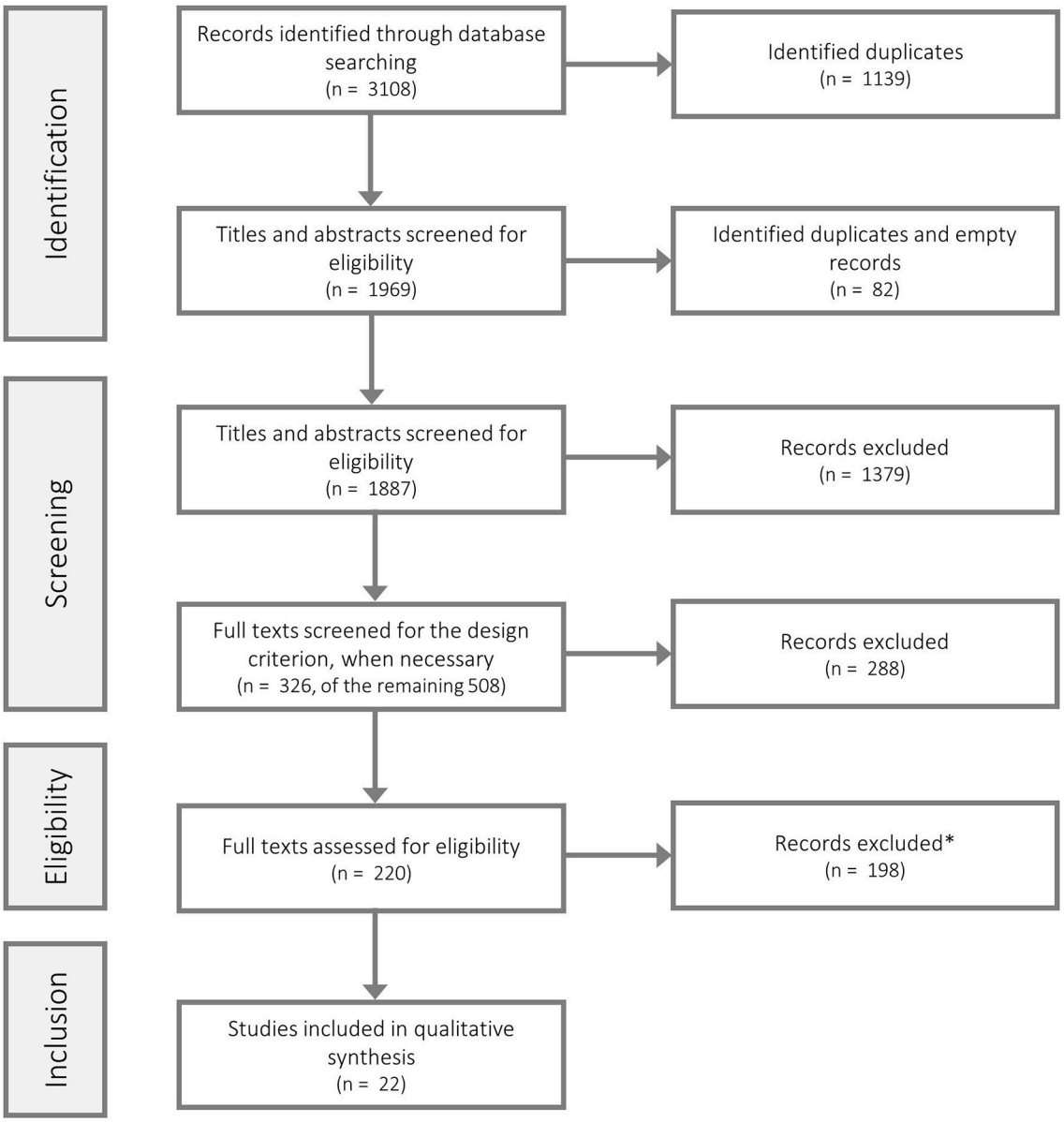

FIGURE 1 | Study selection flow chart. We identified 878 potentially eligible studies in Web of Science, 1050 in Scopus and 1180 in PsycINFO. *Of the 198 excluded articles of the eligibility review stage, one study was identified as duplicate and three studies were excluded due to insufficient information. The flow chart was modelled along the PRISMA recommendations (being under a Creative Commons Attribution License; see e.g. Liberati et al. (31), PLoS Med, can be retrieved from: https://doi.org/10.1371/journal.pmed.1000100).

age range, because it is characterized by a heightened risk for psychopathology and thus allows for relevant and insightful conclusions (29).

Mediation Effects

The "eligibility criteria II" state that the RF must function as moderator and/or mediator for the relationship between CA and psychopathology. Yet, when referring to mediation effect we mean "positive mediation" effects, as "negative mediation" effects do not function as RFs. More specifically, when we refer to RFs that have been supported by mediation analyses, we exclusively refer to factors that operated as "positive mediators" —i.e., their relationships with both CA and psychopathology are in the same direction (i.e., either both are negative, or both are positive, as described in section RFs). A "negative mediator" would have opposite relationship directionalities with CA and psychopathology (i.e., one positive and one negative relationship), and therefore cannot function as an RF. Moreover, when we refer to a supported mediation effect, we expect that the association between CA and psychopathology is not significantly negative, as the mediator otherwise can also not function as an RF.

Data Extraction and Quality Assessment

The data extraction form was based on the STROBE report (36) and an adapted version of Downs and Black's (37) validated scale was used for the study quality ratings (see item templates in Supplement 2 and 3). AdG and JF conducted the data extraction pilot (3 studies: *M* Byrt's kappa = 0.56, *SD* = 0.29, range: 0.29–0.86; see Supplement 1A), the final data extraction (*M* Byrt's kappa = 0.74, *SD* = 0.17, range: 0.43–0.96; see Supplement 1A), and the study quality ratings (*M* Byrt's kappa = 0.61, *SD* = 0.19, range: 0.30–1.00; see Supplement 1A). Incongruent ratings were solved through consensus, if necessary including a third author (PW). When articles lacked relevant information, we emailed the corresponding authors. Moreover, to be able to systematically judge the quality of the reviewed moderation and mediation analyses, PW and JF additionally applied quality criteria to the analysis methods (i.e., adequacy of sample size, single vs. multiple RF model, quality of moderation/mediation analysis; see Supplement 4). Incongruent ratings were solved through consensus. Notably, the ratings of the analysis methods were not part of the pre-registered protocol and should therefore be considered as *post hoc* evaluation.

Data Synthesis Method

Given that we conjectured to find a heterogeneous set of eligible studies (i.e., in terms of CA, RFs, and psychopathology) a quantitative meta-analysis would not be appropriate. Therefore, a narrative synthesis was conducted.

Narrative Description of Moderating and Mediating RFs

We shall describe moderation effects as follows: "the association between CA and psychopathology is weaker for adolescents with a higher (or lower) level of the RF." We shall describe positive mediation effects as "a *high level of x* mediates the effect between CA and PP." This means that a high level of CA is associated with a high level of x and a high level of x is in turn associated with a high level of psychopathology. Hence, a *low level of x* is the RF. On the other hand, if a *low level of x* mediates the effect between CA and PP, a *high level of x* is the RF (as a high level of CA is associated with a low level of x and a low level of x is in turn associated with a high level of psychopathology).

RESULTS

Study Selection

After electronically removing duplicates (1139 of the initial 3108 studies, see **Figure 1**), all 1969 remaining studies were screened based on title and abstract screening, according to the criteria of the study selection *screening* stage (Eligibility Criteria I). Of the 1969 studies we identified 82 as additional duplicates or empty records (which have not been identified electronically), resulting in 1887 potential studies. Of those 1887 studies 1379 did not meet the screening criteria (Eligibility Criteria I). The exclusion of these 1379 studies, resulted in 508 remaining potential studies. Of those 508 studies 182 met the eligibility criteria of stage 1. Yet, the remaining 326 studies (508–182) had to be screened in full-text, as for those studies we could not assess the design criterion only based on the title and the abstract. Of those 326 we could exclude 288 studies, resulting in 38 potentially eligible studies. Therefore, after initial screening we revealed 182 (508–326) potential studies which did not have to be screened in full text for the design criterion, plus 38 (326–288) potential studies that had to be screened in full text for the design criterion, resulting in total in 220 potentially eligible studies. Accordingly, those 220 studies were then rescreened in full text according to both the criteria of the study selection *screening* (Eligibility Criteria I) and the study selection *rescreening* (Eligibility Criteria II) stages. Of those 220, 198 studies could be excluded and 22 studies were thus eligible for data abstraction (**Table 2**).

Study Characteristics

All 22 studies were published in English, which is representative as only a negligible number of the screened articles were written in German or Dutch. Twenty-one of the studies included both genders (*M* male = 47.95%, *SD* = 8.27, range: 32–69%; see Supplement 1B). Walter et al. (54) included females only. The studies had a mean of 3.41 time points (*SD* = 1.65, range: 2–9), with a time frame ranging from 10 weeks to 16 years (*M* years = 4.55, *SD* = 4.37; see Supplement 1B). Sample sizes ranged from 59 to 6780 participants (*M* = 1052, *SD* = 1436; see Supplement 1B). As shown in **Figure 2**, 27.27% of the studies investigated more than 1,500 participants, 9.09% more than 1,000 participants, 13.64 percent more than 500 participants, and 50% fewer than 500 participants. Importantly, one of the 13 studies that conducted moderation analyses had a sample size below 77, which may be insufficient in terms of power. We used a sample size of 77 as guideline, as this is the sample size that is required for moderation analyses to detect a moderate effect ($f^2 = 0.15$, power = 0.80, $\alpha = 0.05$; see Supplement 5). However, all 12 studies that performed mediation analyses had sample sizes higher than 150, which we assume to be sufficient in terms of power. We used a sample size of 150 as guideline, as MacKinnon, Fairchild and Fritz (59) report that a sample size of 100 to 200 was sufficient even for multiple mediator models. At the CA assessment, the participants' mean age was 14.75 years (*SD* = 3.25, range: 11–22; see Supplement 1B). Four studies utilized a low, three a medium and two a high socio-economic status (SES) sample. Thirteen studies lacked information or did not provide an interpretation for SES. Twelve studies were performed in the United States or Canada, three in Europe, three in Israel and/ or Palestine, two in Australia, one in Korea, and one lacked information.

In total, 15 types of CAs were assessed (Supplement 6): Five types of childhood maltreatment (nine studies), seven types of intra-family adversity (seven studies), two types of community adversity (four studies) and one clustered type of adverse life experiences (two studies). Moreover, five types of disorders and four clustered types of psychopathology have been assessed (Supplement 6), with a mean of 1.59 assessed types of psychopathology per study (*SD* = 0.80, range: 1–3). Overall, 46 RFs were examined (**Table 3**), with a mean of 2.09 RFs per study (*SD* = 1.23, range: 1–6).

Individual-Level RFs

We report findings of individual-level RFs (**Table 3**) within four clusters. In total we found 13 supported individual-level RFs

TABLE 2 | Methodological and sample characteristics of the analyzed studies.

S	Gender	Analysis *N*	*M*[*a] age	T for gender	% male	SES level	Nationality	CA[*b]	CA measure	RF[*b]	RF measure	PP[*b]	PP measure
(38)	Both	244	12	T2 (baseline)	54.5	-	US	Emotional abuse	Quest.	Distress tolerance	Task	Anxiety symptoms	Quest.
(39)	Both	1973	14	T1	32	High	Australia	Adverse life experiences	Quest.	Expressive Suppression Cognitive reappraisal Rumination	Quest. Quest. Quest.	Psychological distress	Quest.
(40)	Both	451	–	T1	47.67	–	US	Marital distress/conflict	Quest. + task[*c]	Positive parenting	Quest. + task[*c]	Poor emotional well-being Externalizing Internalizing	Quest. Quest. Quest.
(41)	Both	59	17	T1	39	–	US	Physical, sexual abuse	Quest. + interview	Behav. reward reactivity Emotion. reward reactivity	Task Task[*e]	Depressive symptoms	Interview
(42)	Both	1501	-	T1	49.24	–	Palestine & Israel	Ethnic-political conflict	Quest.	Academic grades Self-esteem Positive parenting	Interview Interview Interview	PTS symptoms	Interview
(43)	Both	492	16	T1	47.5	–	US	Parental problem drinking	Quest.	Family cohesion Adolescent-mother com. Adolescent-father com.	Quest. Quest. Quest.	Externalizing	Quest.
(44)	Both	163	12	T2	50	–	Australia	Aggressive parenting	Task	Rumination	Quest.	Depressive symptoms	Quest.
(45)	Both	652	19	T2	32.2	–	–	Emotional, sexual, physical abuse	Quest.	Negative cognitive style Insecure attachment	Quest. Quest.	Depression symptoms Anxiety symptoms	Quest. Quest.
(46)	Both	312	14	i-sample	50	Low	US	Community violence	Quest.	Extended family support Parental involvement	Quest. Quest.	Internalizing Externalizing	Quest. Quest.
(47)	Both	6780	-	T1	42.2	–	Canada	Sexual abuse	Quest.	Maternal support	Quest.	Mental health problems	Quest.
(48)	Both	1064	-	T1	69	–	US	Parental violence	Quest.	Coping expectancy Enhancement expectancy	Quest. Quest.	Peak alcohol use Heavy episodic drinking	Quest. Quest.
(49)	Both	1643	14	T1 (i-sample)	49.4	Medium	Germany	Parental mental health problems	Quest.	Self-efficacy Family climate Social support	Quest. Quest. Quest.	Depressive symptoms	Quest.
(50)	Both	585	-	T1	52	-	US	Physical abuse	Interview	Proactive parenting	Interview	Internalizing Externalizing	Quest. Quest.
(51)	Both	400	-	T1	59.25	Low	US	Emotional, sexual, physical abuse, neglect	Objective	Ego under vs. over-control Over-control vs. resilient Under-control vs. resilient	Quest.[*f] Quest.[*f] Quest.[*f]	Subtance use: cannabis Subtance use: alcohol Internalizing Externalizing	Interview Interview Quest. Quest.
(52)	Both	83	11	T2	48.8	Low	Palestine	Ethnic-political conflict	Quest.	Mental flexibility	Task	Emotional disorders[*g] Emotional disorders[*h] PTS symptoms	Quest. Quest. Interview
(53)	Both	332	-	T1 (i-sample)	45	-	Israel	Ethnic-political conflict (i.e., rocket attacks)	Quest.	School personnel support Friend support Immediate family support	Quest. Quest. Quest.	Violence commission Anxiety symptoms Depressive symptoms	Quest. Quest. Quest.
(24)	Both	771	-	i-sample	41.8	High	UK	Accumulated family adversity	Interview	Immediate family support Friendship support	Quest. Quest.	Depressive symptoms	Quest.

(Continued)

TABLE 2 | Continued

S	Gender	Analysis N	M*a age	T for gender	% male	SES level	Nationality	CA*b	CA measure	RF*b	RF measure	PP*b	PP measure
(54)	Female	360	22	T1	0	Low	US	Emotional, sexual, physical abuse	Quest.	Protective self-cognitions*d	Quest.	PTS symptoms	Interview
(55)	Both	189	-	i-sample	43.4	Medium	US	Adverse life experiences	Quest. + interview	Parenting quality	Quest.*f	Conduct	Quest. + interview
(56)	Both	1052	14	i-sample	52.6	Medium	Spain	Emotional abuse	Quest.	Disconnection/ rejection Impaired autonomy Other-directedness	Quest. Quest. Quest.	Social anxiety symptoms Depressive symptoms	Quest. Quest.
(57)	Both	2021	12	T1	49	-	US	Stressful family-level life events	Interview	Socialization Boldness Prosocial peers Academic engagement Parent-child relationship Antisocial peers	Quest. Quest. Quest. Quest. Quest. Quest.	Substance abuse	Interview
(58)	Both	2013	-	i-sample	52.4	-	Korea	Emotional, physical abuse, emotional, physical neglect	Quest.	Aggression	Quest.	Violent delinquency Non-violent delinquency	Quest. Quest.

*CA, childhood adversity; RF, resilience enhancing factor; PP, psychopathology; S, study; T, assessment time point; i-sample, investigated sample; quest, questionnaire; behav., behavioral; emotion., emotional; com., communication; PTS, posttraumatic stress; *a for CA assessment; *b information regarding the assessment instruments can be requested from the author; *c observer ratings on task performance; *d this study contained interventions, but given that we did not expect the interventions to have an effect on the RF, we included the study; *e subjective ratings integrated in task; *f questionnaires completed by counselors/ interviewers; *g self report; *h multiple reporters.*

including three cognitive, four emotion regulation, three social interaction/attachment and three personality/self-concept RFs:

Cognition and Academic Performance

Qouta et al. (52) found that the positive relationship between traumatic events (i.e., ethnic-political conflict) and emotional disorders (i.e., internalizing and externalizing symptoms) was stronger for adolescents with lower levels of mental flexibility (moderation). Yet, mental flexibility did not moderate the relationship between traumatic events and posttraumatic stress symptoms (52). In the study of Boyes et al. (39) the association between a history of adverse life events and psychological distress was weaker for adolescents who reported more cognitive reappraisal (moderation). Low cognitive reappraisal also mediated the association between a history of adverse life events and psychological distress (39). Similarly, Boyes et al. (39) revealed that high rumination mediates the association between a history of adverse life events and psychological distress. However, no moderation effect was found for rumination (39). Gaté et al. (44) found that rumination does not mediate the association between aggressive parenting and depressive symptoms. Moreover, Hankin (45) reported that a negative cognitive style no longer mediates the relationship between emotional abuse and subsequent depressive symptoms, when controlling for negative life events and an insecure attachment style. Hankin (45) did not investigate mediation effects for other combinations of CA (i.e., sexual, physical, and/or emotional abuse) and psychopathology (depressive or anxiety symptoms), as pairwise associations between variables were lacking. For the same reason, Hicks et al. (57) did not analyse the mediation effect of academic engagement along the relationship between stressful life events and substance abuse. Finally, Dubow et al. (42) found that academic grades do not moderate the association between ethnic-political conflict (e.g., violence) and posttraumatic stress symptoms. In sum, we found support for high mental flexibility, high cognitive reappraisal, and low rumination as RFs.

Emotion Regulation

Banducci et al. (38) found that adolescents with less distress tolerance and more emotional abuse experienced the most anxiety symptoms in the long term (moderation). Along these lines, Boyes et al. (39) revealed that high expressive suppression mediates the association between a history of adverse life events and psychological distress, however, no moderation effect was found. In the study of You and Lim (58), high aggression mediated the association between abuse (emotional and physical) and violent as well as non-violent delinquency. High aggression also mediated the association between emotional neglect and violent delinquency, as well as between physical neglect and non-violent delinquency. However, aggression did not mediate the association between emotional neglect and non-violent delinquency, as well as between physical neglect and violent delinquency (58). Jester et al. (48) showed that high alcohol coping expectancy, i.e., consuming alcohol to handle stress, mediates the association between inter-parent violence and both peak alcohol use and heavy episodic drinking (when taking distress as intermediate predictor into account). In contrast,

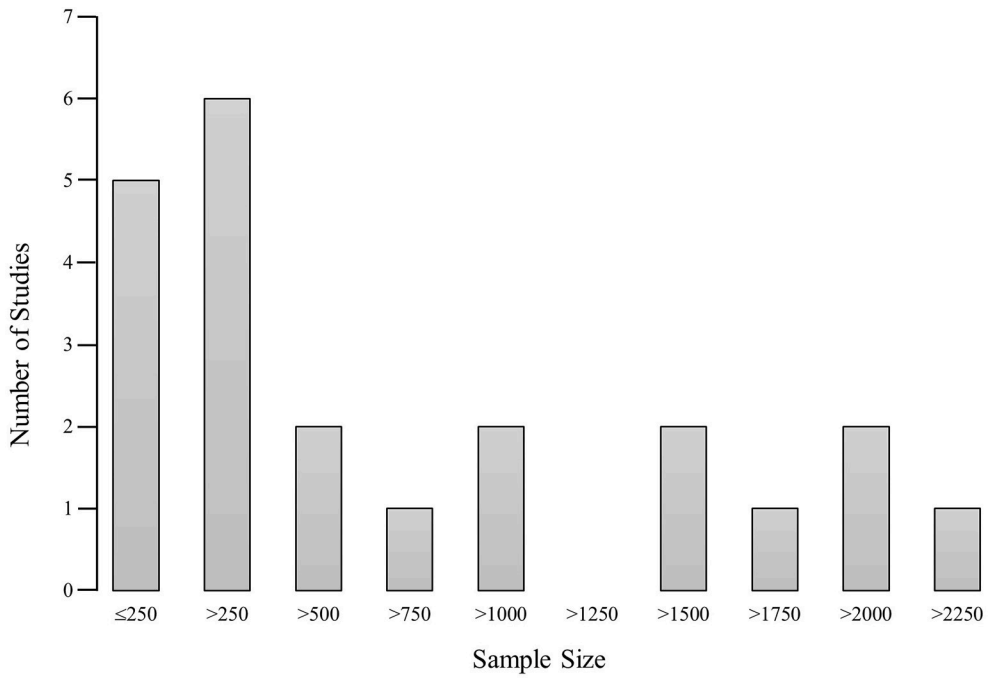

FIGURE 2 | Sample size histogram. The histogram depicts the frequency of the studied sample sizes. The x-axis indicates the size of the studied sample in steps of 250 participants. The y-axis indicates the frequency of studies that investigated the belonging sample size.

no mediation effects were found for alcohol enhancement expectancy, i.e., consuming alcohol to improve mood (48). Finally, Dennison et al. (41) found that emotional and behavioral reward reactivity did not moderate the relationship between childhood maltreatment (physical and/or sexual abuse) and subsequent depressive symptoms. Hence, high distress tolerance, low expressive suppression, low aggression, and low alcohol coping expectancy were supported as RFs.

Attachment and Social Interactions

Hankin (45) found that high insecure attachment mediates the relationship between emotional abuse and depressive symptoms. No mediation effects were analyzed for other combinations of CA (i.e., sexual, physical, and/ or emotional abuse) and psychopathology (i.e., depressive or anxiety symptoms), due to the lack of pairwise associations (45). Calvete (56) investigated disconnection/rejection, other-directedness and impaired autonomy factors along the relationship between two CAs (i.e., abuse by parents and peers) and two psychopathology variables (i.e., depressive and social anxiety symptoms). High disconnection/rejection mediated the relationship between abuse by peers and depressive symptoms. High other-directedness mediated the relationship between abuse by peers and social anxiety. Due to the absence of pairwise associations, no mediation effects were analyzed for other combinations of CA and psychopathology, or for impaired autonomy (56). Finally, Hicks et al. (57) found that socialization (e.g., obeying rules and committing to ethical values) does not mediate the relationship between stressful life events and substance abuse. Additionally, due to the absence of pairwise associations, no mediation effect was analyzed for boldness [e.g., social confidence, adaptability to distress, and sensation seeking (57)]. Therefore, low insecure attachment, low disconnection/rejection and low other-directedness were supported as RFs.

Personality and Self-Concept

Oshri et al. (51) studied the putative RF ego control, which was split into: (a) ego over-control vs. ego resilience, (b) ego under-control vs. ego resilience and (c) ego under-control vs. ego over-control. High ego over-control vs. resilience mediated the association between early child maltreatment and internalizing, but not between early child maltreatment and cannabis use, alcohol use (see Supplement 1C), or externalizing behaviors. High ego under-control vs. resilience mediated the association between early child maltreatment and cannabis use, internalizing and externalizing behaviors, but not between early child maltreatment and alcohol use. For ego under-control vs. ego over-control no mediation effects were found (51). Dubow et al. (42) found that the association between ethnic-political conflict (e.g., violence) and posttraumatic stress symptoms was only significant for adolescents with a low amount of self-esteem (moderation). In contrast, in the study of Klasen et al. (49) self-efficacy did not moderate the association between parental psychopathological problems and the development of depressive symptoms in the adolescent offspring. Similarly, in the study of Walter et al. (54), protective self-cognitions (i.e., self-esteem and self-efficacy) did not mediate the association between child abuse and posttraumatic stress symptoms (taking

TABLE 3 | Resilience factors tested in the analyzed studies, split into individual, family, and community level.

Individual		Family		Community	
Supported	**Not supported**	**Supported**	**Not supported**	**Supported**	**Not supported**
High distress tolerance [MO (38)]	–	High positive parenting [ME (40)]+[MO (42)]	Positive parenting [MO (40)]	High social support [MO (49)]*a	-
High cognitive reappraisal (MO + ME (39)]	-	High family cohesion [ME (43)]	Family cohesion [ME (43)]	-	Friend support [MO (53)]+[ME (24)]
Low expressive suppression [ME (39)]	Expressive suppression [MO (39)]	–	Adolescent-father communication [ME (43)]	–	School support [MO (53)]
Low rumination [ME (39)]	Rumination [MO (39)]+[ME (44)]	–	Adolescent-mother communication [ME (43)]	–	Prosocial peers [ME (57)]*c
–	Behavioral reward reactivity [MO (41)]	High extended family support [MO (46)]	Extended family support [MO (46)]	–	Antisocial peers [ME (57)]*c
–	Emotional reward reactivity [MO (41)]	High parental involvement [MO (46)]	Parental involvement [MO (46)]		
–	Academic grades [MO (42)]	-	Maternal support [MO (47)]		
High self-esteem [MO (42)]	-	Positive family climate [MO (49)]	-		
Low insecure attachment [ME (45)]	Insecure attachment [ME (45)]	-	Proactive parenting [MO (50)]		
-	Negative cognitive style [ME (45)]	High immediate family support [MO (53)]+[ME (24)]	Immediate family support [MO (24, 53)]		
Low coping expectancy[def1] [ME (48)]	-	-	Parenting quality [MO (55)]*b		
-	Enhancement expectancy[def2] [ME (48)]	-	Parent-child relationship [ME (57)]*c		
-	Self-efficacy [MO (49)]				
Low ego over-control [ME (51)]	Ego over-control [ME (51)]				
Low ego under-control [ME (51)]	Ego under-control [ME (51)]				
-	Ego under- vs. over-control [ME (51)]				
High mental flexibility [MO (52)]	Mental flexibility [MO (52)]				
-	Protective self-cognitions [ME (54)]				
Low disconnection/rejection [ME (56)]*c	Disconnection/rejection [ME (56)]*c				
Low other-directedness [ME (56)]*c	Other-directedness [ME (56)]*c				
-	Impaired autonomy [ME (56)]*c				
-	Socialization [ME (57)]*c				
-	Boldness [ME (57)]*c				
-	Academic engagement [ME (57)]*c				
Low aggression [ME (58)]*c	Aggression [ME (58)]*c				

MO, moderation analysis; ME, mediation analysis. *a *The social support measure could potentially also include family support and should therefore also belong to the family domain.* *b *The CA timeline requirements might not be fully met.* *c *The analysis did not include the direct path between CA and psychopathology when calculating the indirect mediation effect of the RF.* def1 *Definition, Consuming alcohol to handle stress;* def2 *Definition, Consuming alcohol to improve mood.*

resource loss as intermediate mediator into account). Thus, in the personality/self-concept cluster we found support for low ego over-control, low ego under-control, and high self-esteem.

Family RFs

We split family-level RFs (**Table 3**) into two clusters and found empirical support for four family support and two parenting RFs:

Family Support

Hardaway et al. (46) found that the effect of community violence on externalizing behaviors was only significant for adolescents with a small amount of extended family support (moderation). No effect was found for the relationship between community violence and internalizing behaviors (46). Van Harmelen et al. (24) showed that low immediate family support mediates the relationship between accumulated family adversity and depressive symptoms. No moderation effect was found (24). Similarly, Shahar and Henrich (53) revealed that immediate family support significantly attenuates the relationship between exposure to rocket attacks and both subsequent depressive symptoms and severe commission of violence (moderation). Yet, immediate family support did not moderate the relationship between exposure to rocket attacks and anxiety (53). Moreover, Finan et al. (43) found that low family cohesion mediates the association between paternal alcohol abuse problems and both violation of rules (boys and girls) and aggressive conduct (girls only). No mediation effect was found for any other combination of CA (i.e., maternal or paternal alcohol abuse problems) and psychopathology [i.e., alcohol use, drug use, or binge drinking (43)]. Similarly, in the study of Klasen et al. (49), the positive relationship between parental psychopathological problems and the development of depressive symptoms in the adolescent offspring was mitigated for adolescents who experienced a better family climate (moderation). Hence, we found support for high extended family support, immediate family support, family cohesion, and a positive family climate as RFs.

Parental Support

Hardaway et al. (46) found that the effect of community violence on externalizing behaviors was only significant for adolescents with a small amount of parental involvement (moderation). Yet, parental involvement did not moderate the relationship between community violence and internalizing behaviors (46). Similarly, Dubow et al. (42) found that the association between ethnic-political conflict (e.g., violence) and posttraumatic stress symptoms was only significant for adolescents with a low amount of positive parenting (moderation). Cui and Conger (40) found that low positive parenting (i.e., high positive parenting includes low negative parenting) mediates the association between marital problems and poor emotional well-being, internalizing, as well as externalizing symptoms. Moderation effects for positive parenting were mostly not supported, as only one out of 12 effects was significant [i.e., for the association between marital distress and poor emotional well-being (40)]. Due to the absence of direct associations, Hicks et al. (57) did not analyse the mediation effect of the parent-child relationship for the association between stressful life events and substance abuse. Moreover, in the study of Masten et al. (55), parenting quality did not moderate the association between adverse life experiences and conduct symptoms. Similarly, Lansford et al. (50) found that proactive parenting does not moderate the relationship between physical abuse and change in both internalizing symptoms and externalizing behaviors.

Two studies focussed on RFs specific to one parent (43, 47). Finan et al. (43) found that adolescent-mother and adolescent-father communication (see Supplement 1D) do not mediate the association between parental alcohol abuse problems (i.e., maternal and paternal) and externalizing indicators (i.e., alcohol use, drug use, violation of rules, aggressive conduct, and binge drinking). Likewise, Hébert et al. (47) found that maternal support does not moderate the association between childhood sexual abuse and mental health problems. Thus, in sum, parental involvement and positive parenting were supported as RFs.

Community RFs

On the community level, Klasen et al. (49) found that the positive association between parental psychopathological problems and the development of depressive symptoms in the adolescent offspring is mitigated for adolescents who experienced more social support (moderation). In contrast, in the study of Shahar and Henrich (53) school and friendship support did not moderate the relationship between exposure to rocket attacks and depressive symptoms, anxiety symptoms, as well as severe violence commission. Due to the absence of pairwise associations, van Harmelen et al. (24) did not investigate the mediation effect of friendship support for the relationship between accumulated family adversity and depressive symptoms. For the same reason, Hicks et al. (57) did not analyse the mediation effects of prosocial and antisocial peers along the relationship between stressful life events and substance abuse. Therefore, on the community-level high social support was supported as RF.

Single vs. Multiple RFs

Of the 22 studies, only eight have tested indirect (i.e., mediation) and/ or interaction (i.e., moderation) effects, while correcting for at least one other RF. Calvete [other-directedness, disconnection/rejection, impaired autonomy (56)], Finan et al. [family cohesion, adolescent-mother communication, adolescent-father communication (43)], Hankin [insecure attachment, negative cognitive style (45)], Hicks et al. [socialization, boldness, prosocial peers, antisocial peers, academic engagement, parent-child relationship (57)], as well as Jester et al. [alcohol coping expectancy, alcohol enhancement expectancy (48)] tested mediation effects, while correcting for at least one other RF. Dubow [self-esteem, positive parenting, academic grades (42)] as well as Shahar and Henrich [immediate family support, school personnel support, friend support (53)] tested interaction effects in models containing more than one RF interaction. Boyes et al. (39) tested the indirect as well as the interaction effects of three RFs (expressive suppression, cognitive reappraisal, rumination). Yet, while the mediation analysis was corrected for the respective other two RFs, in the moderation model two RFs were only entered as main effects, not as interactions [expressive suppression, rumination (39)].

Hence, the current literature contains some effort to establish complex RF models that test mediation and moderation effects of RFs, while controlling for the impact of other RFs.

None of the eight mentioned studies included a model with more than six RFs. Jester et al. (48) as well as Hankin (45) first tested the indirect RF effects separately, before they performed a multiple RF model correcting for the respective other RFs. Jester et al. (48) showed that alcohol coping expectancy was a significant mediator in the single and the multiple RF model, whereas alcohol enhancement expectancy was neither significant in the multiple nor in the single RF model. In contrast, in Hankin's (45) study insecure attachment was a significant mediator in the single and the multiple RF model, whereas negative cognitive style was only a significant mediator in the single RF model. Hence, controlling for the interrelation between RFs is important as some RFs may only be significant when being tested in isolation, but not when being tested simultaneously with other individual, family, and community RFs. Along these lines, three studies found support for more than one RF in multiple RF models. This finding supports the notion that not one RF in isolation but complex interrelations of RFs affect the relationship between CA and psychopathology. In sum, such findings strongly underpin the need for a complex model that can account for various RFs following adversity, when predicting psychopathology.

Quantifying RF Effects

Comparing the effects of moderating and mediating effects statistically was not possible, as the reviewed RFs were studied following as many as 15 different forms of adversities, in the attempt to predict as many as five types of disorders (anxiety symptoms, depressive symptoms, posttraumatic stress symptoms, substance (ab)use symptoms, and conduct symptoms) and four clustered types of psychopathology (psychological distress, mental well-being, externalizing, and internalizing). Given such a variety of studied contexts, we believe that statistical comparison is not feasible. Some studies did report model related fit indices {moderation: e.g., R^2 (49, 52); mediation: e.g., Root Mean Square Error of Approximation [RMSEA; e.g. (24, 40, 54, 58)]} but the majority of the studies did not report RF related effect sizes. The manual calculation of the effect sizes for mediating RFs might theoretically have been possible, as the proportion mediated (indirect effect divided through the total effect) could be calculated (59). Yet, the interpretation of the proportion mediated is conditional on the total effect (i.e., a small proportion mediated of a large total mediation effect might with regard to actual effect still be strong, while a large proportion mediated of a small total mediation effect might with regard to the actual effect still be weak). Given that the total effects of the studies, being based on 15 different independent adversity variables and nine different dependent psychopathology variables, are so numerous, the proportion mediated would not have been comparable between studies. Moreover, the proportion mediated is only robust for sample sizes of 500 or larger (59), which would only have been the case in seven studies (24, 39, 45, 48, 56–58), of which three are statistically controversial as they lack the impact of the direct effect (56–58). Similarly, we considered the calculation of effect sizes for moderation RFs as not feasible. Firstly, standard effect sizes such as the incremental R^2, which indicates the contribution of an interaction to the moderation model, are difficult to interpret, as they merely designate the contribution of an interaction and not the magnitude of its effect (60). Moreover, for more advanced calculations of effect sizes the necessary information, such as the Mean Square Residuals [MSR (61)], was not provided.

Study Quality

Reporting, Internal and External Validity

Individual quality items were met by a mean of 16 studies (**Figure 3**; $SD = 6.97$, range: 2–22). The quality item "adjustment for variability in follow-up length between participants" [item 13 (37)] was the least frequently met item, being met by only two studies (41, 52). Similarly, the item assessing whether the researchers who measured psychopathology were in experimental terms blind (item 11), was only met by three studies (39, 51, 56). In contrast, as much as eight quality rating items (items 1, 2, 12, and 14–18) were met by all studies. Those eight

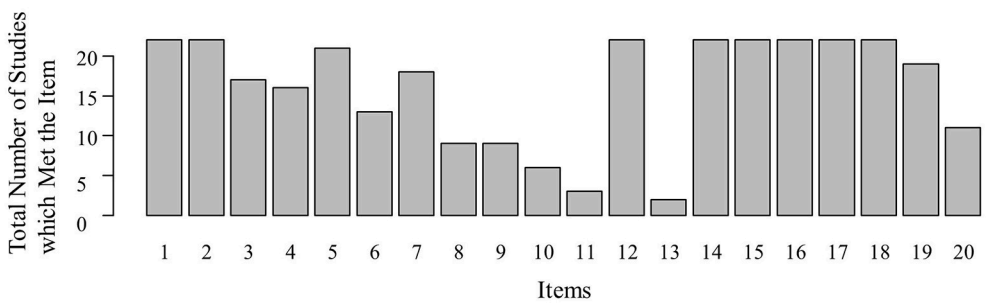

FIGURE 3 | Quality rating distribution. The number of studies (y) which met the respective item of the adapted version of Downs' and Black's (37) quality rating scale (x). 1, Clarity of study aim; 2, Sufficient description of outcome(s); 3, Sufficient description of participant characteristics; 4, Presence of description of confounders; 5, Appropriate description of findings; 6, Report of variability estimates; 7, Description lost to follow-up characteristics; 8, Report of exact *p*-values; 9, Representativeness of recruitment cohort; 10, Representativeness of participation cohort; 11, Blinding; 12, Clarity about data dredging; 13, Adjustment for variability in follow-up length between participants; 14, Adequacy of statistical tests; 15, Accurate CA measure(s); 16, Accurate RF measure(s); 17, Accurate psychopathology measure(s); 18, Recruitment of same population for participants of different CA groups; 19, Correction for confounding; 20, Loss to follow-up correction.

included for example the items "clarity of study aim" (item 1) or "sufficient description of the psychopathology variable" (item 2). Overall, all studies met more than half of the assessed quality items. Therefore, we concluded that all studies were of sufficient quality to be included ($M = 14.55$, $SD = 2.04$, range: 11–18).

Quality of the Analytic Methods

Ten studies performed moderation [five multiple regression analyses (MRAs), three growth models, two path models (38, 41, 42, 46, 47, 49, 50, 52, 53, 55)], nine mediation [one MRA, seven path models or structural equation models (SEMs), one SEM based on probit regression (43–45, 48, 51, 54, 56–58)] and three both types of analyses [four MRAs, two SEMs (24, 39, 40)]. Three studies (56–58) did not control for the direct effect between CA and psychopathology when calculating mediation effects, which violates Baron and Kenny's (62) traditional mediation approach. Moreover, in Masten and colleagues' (55) study, parts of the CA index may have been assessed later than the RF. Hence, these four studies should be interpreted with caution.

To be able to judge the qualitative value of the moderation and mediation analyses we additionally applied quality criteria to the analysis methods (i.e., this was not part of the pre-registered protocol and should therefore be considered as *post hoc* evaluation). Moderation analyses received (a) a "1" when lacking correlational and significance testing for the relationship between CA and psychopathology at different levels of the moderator variable, (b) a "2" for correlational *post hoc* probing of the relationship between CA and psychopathology at different levels of the moderator variable, and (c) a "3" for regression analytic *post hoc* probing of the relationship between CA and psychopathology at different levels of the moderator variable. Detailed descriptions of these analytic methods can be found in Holmbeck (63). Mediation analyses received (a) a "1" for either no calculation of the overall indirect effect or the usage of the "direct effect reduction to non-significance" criterion, (b) a "2" for the calculation of the Sobel test or comparable indirect effect tests, and (c) a "3" for the usage of bootstrap methods for the calculation of the indirect effect. Detailed descriptions of these analytic methods can be found in MacKinnon et al. (59). The quality ratings can be found in **Table 4**.

Of the 13 studies which analyzed moderation effects, one study could not be rated for its analytic quality, as it did not contain a description of whether *post hoc* probing would have been performed in case of significant interaction effects (24). Moreover, three of the 12 studies were rated with a "1" (see **Table 4**) and the remaining nine studies with a "3." Of the 12 studies that tested mediation, one study was rated with a "1," six studies were rated with a "2," and five studies were rated with a "3." In sum, we concluded that the majority (moderation: 75%; mediation: 91.67%; total 83.34%) of the analytic methods that were used by the studies to test RFs are in line with the general guidelines for testing moderation and mediation, and can be considered as qualitatively adequate.

Splitting the results into systemic levels (i.e., individual, family, and community levels) showed that for the individual level RFs 80% of the moderation analyses and 94.74% of the mediation analyses were qualitatively adequate (rating of "2" or higher). For the family level RFs 77.78% of the moderation analyses and 100% of the mediation analyses were qualitatively adequate. Similarly, for the community level RFs 66.67% of the moderation analyses and 100% of the mediation analyses were qualitatively adequate. The analytic quality was examined in percentages to control for the impact of the differing number of performed analyses on each systemic level. Overall, we did not identify any trend regarding analytic quality differences between individual, family, and/ or community RFs.

DISCUSSION

The aim of this systematic review was to identify empirically supported RFs that benefit mental health in young people following CA. We reviewed 22 studies, including 46 amenable RFs. Thirteen of 25 individual-level RFs, six of 12 family-level RFs, and one of five community-level RFs were confirmed to significantly reduce the risk of psychopathology following CA. The absolute number of supported RFs seems to indicate that individual- and family-level RFs are most effective. However, the seemingly lower relevance of community-level RFs may be artefactual due to the small number of community-level studies that we could include in this review.

The 13 supported individual-level RFs included three cognitive (high: cognitive reappraisal, mental flexibility; low: rumination), four emotion regulation (high: distress tolerance; low: alcohol coping expectancy, aggression, expressive suppression), three social interaction/attachment (low: insecure attachment, disconnection/rejection, other-directedness) and three personality/self-concept RFs (high: self-esteem; low: ego over-control, ego under-control). It is as yet unknown whether these RF dimensions have compensatory effects, in the sense that an individual who performs low on one of those dimensions might still be functioning resiliently through performing high on other dimensions. Moreover, for most of the RFs it is also unknown to what extent they overlap in their prediction of mental health resilience.

Supported family-level RFs consisted of four family support (high: family cohesion, positive family climate, immediate family support, extended family support) and two parenting RFs (high: positive parenting, parental involvement). Interestingly, all RFs that were specific to one parent, e.g., adolescent father communication or maternal support, were not supported as RFs. This may suggest that the totality of family support is more important for resilience, than the quality of support from individual family members. Yet, as for the individual-level RFs, it is unknown to what extent the RFs overlap in their prediction of mental health resilience.

The fact that on the community-level only high social support was revealed as RF might suggest that a general social network has a stronger resilience enhancing effect than specific types of social support. However, given the restricted number of included community-level studies this conclusion is rather preliminary and requires further investigation. For example, our lab recently found that friendship support predicts resilient functioning in young people (64). Thus, although only one RF was revealed on the community-level, this does not suggest that community-level RFs are less important for mental health resilience. Rather,

TABLE 4 | Quality ratings for the analysis methods that were used to analyse the resilience factors, split into individual, family, and community level.

Resilience factor	Study	Moderation quality rating	Moderation supported	Mediation quality rating	Mediation supported
INDIVIDUAL LEVEL					
Distress tolerance	(38)	3	Yes	NA	NA
Cognitive reappraisal	(39)	3	Yes	3	Yes
Expressive suppression	(39)	3	No	3	Yes
Rumination	(39)	3	No	3	Yes
Rumination	(44)	NA	NA	3	No
Behavioral reward reactivity	(41)	3	No	NA	NA
Emotional reward reactivity	(41)	3	No	NA	NA
Academic grades	(42)	3	No	NA	NA
Self-esteem	(42)	3	Yes	NA	NA
Insecure attachment	(45)	NA	NA	2	Yes
Negative cognitive style	(45)	NA	NA	2	No
Coping expectancy[def1]	(48)	NA	NA	2	Yes
Enhancement expectancy[def2]	(48)	NA	NA	2	No
Self-efficacy	(49)	1	No	NA	NA
Ego over-control	(51)	NA	NA	3	Yes
Ego under-control	(51)	NA	NA	3	Yes
Ego under- vs. over-control	(51)	NA	NA	3	No
Mental flexibility	(52)	1	Yes	NA	NA
Protective self-cognitions	(54)	NA	NA	1	No
Disconnection/rejection[*c]	(56)	NA	NA	3	Yes
Other-directedness[*c]	(56)	NA	NA	3	Yes
Impaired autonomy[*c]	(56)	NA	NA	3	No
Socialization[*c]	(57)	NA	NA	2	No
Boldness[*c]	(57)	NA	NA	2	No
Academic engagement[*c]	(57)	NA	NA	2	No
Aggression[*c]	(58)	NA	NA	3	Yes
FAMILY LEVEL					
Positive parenting	(40)	1	No	2	Yes
Positive parenting	(42)	3	Yes	NA	NA
Family cohesion	(43)	NA	NA	2	Yes
Adolescent-father communication	(43)	NA	NA	2	No
Adolescent-mother communication	(43)	NA	NA	2	No
Extended family support	(46)	3	Yes	NA	NA
Parental involvement	(46)	3	Yes	NA	NA
Maternal support	(47)	3	No	NA	NA
Positive family climate	(49)	1	Yes	NA	NA
Proactive parenting	(50)	3	No	NA	NA
Immediate family support	(53)	3	Yes	NA	NA
Immediate family support	(24)	Not rateable	No	2	Yes
Parenting quality[*b]	(55)	3	No	NA	NA
Parent-child relationship[*c]	(57)	NA	NA	2	No
COMMUNITY LEVEL					
Social support[*a]	(49)	1	Yes	NA	NA
Friend support	(53)	3	No	NA	NA
Friend support	(24)	NA	NA	2	No
School support	(53)	3	No	NA	NA
Prosocial peers[*c]	(57)	NA	NA	2	No
Antisocial peers[*c]	(57)	NA	NA	2	No

*NA, not performed; Not rateable, no significant effect and no information provided whether post hoc tests were applied in case of significant effects (i.e., in case of nonsignificant effects, follow up post hoc probing tests are not necessary for moderation). [*a]The social support measure could potentially also include family support and should therefore also belong to the family domain. [*b]The CA timeline requirements might not be fully met. [*c]The analysis did not include the direct path between CA and psychopathology when calculating the indirect mediation effect of the RF. [def1]Definition, Consuming alcohol to handle stress; [def2]Definition, Consuming alcohol to improve mood.*

community-level RFs have had less attention than individual- and family-level RFs and therefore require further investigation. A more thorough examination of community-level RFs may enhance our understanding of the overall picture of systemic levels that benefit mental health resilience. On the whole, our review found support for RFs on all studied systemic levels, i.e., individual-, family- and community-levels, which indicates a movement toward a more complete understanding of the resilience concept.

Despite the movement to a more systemic approach, only eight of the reviewed studies corrected for the impact of at least one other RF, when testing the indirect and/or interaction effect of an RF (i.e., multiple RF model). Findings of single vs. multiple RF models indicated that taking the interrelatedness of RFs into account is important, as some RFs may only be significant when being tested in isolation, but not when being tested simultaneously with other individual, family, and/or community RFs. Along these lines, three studies found support for more than one RF in multiple RF models. This supports the notion that not one RF in isolation but complex interrelations of RFs affect the relationship between CA and psychopathology. Such findings strongly underpin the need for a complex model that can account for various RFs following adversity that benefit mental health resilience.

It would have been advantageous if effect sizes could have been calculated for moderation and mediation effects. This would have allowed us to draw conclusions regarding the magnitude of specific RF effects. Knowing the magnitude of RFs is beneficial, as it gives an indication about which factors might be most efficient when being approached in therapy. In the future, open data sharing, as was for example done by van Harmelen et al. (24), may facilitate RF comparisons. Given that our findings suggest that RFs do not function in isolation but in complex interrelated systems, it would be advantageous to know effect sizes of isolated RF effects, yet it would perhaps be even more interesting to establish and examine the effects of several RFs being clustered in complex systems of unidirectional or directional interrelations.

For a systematic review it is of critical importance to carefully assess and investigate the (a) reporting, (b) internal, (c) external, and (d) the analytic quality of the studies. As all studies met more than half of the assessed quality items (i.e., for reporting, internal, and external validity), we decided that all studies were of sufficient quality to be included. However, the quality ratings were not without limitations. For example, Downs and Black's (37) quality criteria are not specific to cohort studies and some more recent statistical improvements, such as the match of the variable level and the analysis technique (e.g., categorical vs. continuous data analysis methods), are not directly covered. Critics might further argue that the impact of studies in a systematic review should be weighed according to the study quality. Given that the set of reviewed studies was highly disparate and fairly incomparable, weighing according to "reporting," "internal," or "external" validity criteria would not have been insightful. Yet, as the systematic review focussed on moderating and mediating RFs, we considered it most insightful to apply weights based on the quality of the applied moderation and mediation methods. Of the studies that (a) performed moderation analysis and (b) could be rated for the analytic quality, 75% applied qualitatively adequate analysis techniques. Of the studies that tested mediation, 91.67% applied adequate analysis techniques. Therefore, we concluded that the majority (83.34%) of the applied analytic methods could be considered as qualitatively adequate. Moreover, we did not identify any trend regarding analytic quality differences between individual, family and/ or community RFs. We believe that this finding supports our conclusion that RFs are not restricted to one systemic level but are found to function on all three investigated systemic levels. Therefore, we call future research to focus on a more systemic and complete understanding of the RF concept.

The reviewed studies were conducted in as many as eight different countries: United States [11 studies], Israel and/or Palestine [3 studies], Australia [2 studies], Canada [1 study], UK [1 study], Spain [1 study], Germany [1 study], and in Korea [1 study]. Moreover, all 22 reviewed studies were published in English and only a negligible number of the 1969 screened studies were published in German and Dutch. Hence, research scrutinizing resilience promoting factors seems to be an international imperative. Yet it needs to be noted, that despite the variety of studied nations, mainly Western populations were studied.

Even though the studies were highly disparate, 95.45% of the studies researched both genders with on average 47.95% males per sample. Therefore, we consider the review overall as gender balanced and on average gender representative. Nine studies provided a proper SES description, which covered a range from low to high SES (4 low, 3 medium, 2 high). However, we believe that not enough studies have provided sufficient information to draw a conclusion regarding the studies' representativeness of SES. Along these lines, no conclusion can be drawn whether RFs operate the same for adolescents with different SES levels. Similarly, as the studies varied strongly in the studied time frame, which ranged from 10 weeks to 16 years, and given that the CA assessment age ranged from age 11 to age 22, no conclusions are warranted regarding timing effects or critical developmental windows.

Whereas all studies that performed mediation analyses were considered to have a sufficiently large sample size, one of the 13 studies that conducted moderation analyses may have had an insufficient sample size. This moderation study failed to find significant moderation effects for the two tested RFs [emotional and behavioral reward reactivity (41)]. In sum, the majority of the reviewed studies seemed to be appropriate in terms of statistical power. However, shortcomings raising the possibility of type I errors are that: (a) not all studies were underpinned by resilience-focused hypotheses (11), (b) some RFs were secondary findings, (c) most RFs were only significant in one study, and (d) some positive findings were not replicated with different combinations of CA and psychopathology.

Regarding the studied designs, we only included cohort designs in which the RF was assessed before psychopathology and CA was measured no later than the RF. This design criterion was of major importance, as it ensured a causal timeline according to which psychopathology at the time of the outcome assessment would less likely have affected the RF and the RF would less likely have affected the CA experience. However, a more advanced design would have been to also assess the RFs

prior to the occurrence of CA, so that baseline levels of the RFs could have been taken into account. This would have allowed us to draw more stringent conclusions regarding which RFs are specific to mental health resilience after CA, and which RFs are time-independent and are predictive for mental health resilience regardless of being measured prior to or after CA. Similarly, if psychopathology would also have been measured prior to or together with CA, conclusions could have been drawn regarding the development of mental ill-health following CA, taking into account the baseline psychopathological level. Notably, some of the reviewed studies did control for baseline psychopathology levels. In sum, future research should investigate which of the RFs that predict mental health resilience are specific to the time period after the CA experience and which RFs are time-independent. Moreover, future research should not only examine the effectiveness of RFs in reducing the risk of psychopathology following CA, but should also examine the effectiveness of RFs in reducing the risk of the development of psychopathology following CA.

Critics might further raise the concern that our review does not capture resilience dynamics, given that most of the reported studies assessed the RFs at a single point in time. Yet, we believe that although the effectiveness of RFs may fluctuate, the RFs alter the relationship between CA and psychopathology irrespective of the time of their assessment, as long as they are measured after the occurrence of CA and prior to the assessment of psychopathology.

Overall, the review should be viewed in the light of the heterogeneity of the included studies (i.e., follow-up length, sample size, CA assessment age range, CA/ RF/ psychopathology assessment method, number of CA/ RF/ psychopathology types assessed per study, applied analysis techniques). Therefore, we do not claim that the supported RFs are protective following every type of CA, for every type of psychopathology, for individuals of all cultures, or at all developmental stages. In other words, it may potentially be the case that some of the reviewed RFs are supportive in one, but not in another context. For example, low levels of expressive suppression (i.e., low levels of suppressing emotions) may be protective in safe environments, but may be ineffective or perhaps even disadvantageous in highly dangerous and hazardous environments. As we reviewed 42 different RFs following 15 different forms of CA in an attempt to predict at least one out of nine different types of psychopathology, we ask the readers to be aware that our results are based on averages and may not generalize to all contexts, especially not when those are extreme and/ or exceptional. Yet, we conjecture that the supported RFs might be potential targets for alleviating the relationship between CA and psychopathology in young people. Nonetheless, replication research is critically needed to investigate the generalizability of RFs between people and across situations.

The fact that only two reviewed RFs were significant in more than one study, additionally highlights the crucial need of replication studies. In sum, future research should (a) replicate RF findings, (b) further examine community-level RFs, (c) study RF fluctuations as well as critical windows, and (d) scrutinize the therapeutic effectiveness of RF enhancement. Moreover, we advocate for more research along the lines of systemic resilience theories, to integrate individual-, family- and community-level RFs into one overall model. Along these lines, we believe that our review indicates that RFs do not function in isolation, but are connected via complex interrelations that eventually mediate and/ or moderate the relationship between CA and psychopathology.

In sum, this is the first preregistered systematic review on social, cognitive, emotional and behavioral RFs that attenuate psychopathology in young people after CA. The review revealed evidence for 20 amenable RFs. Interventions that improve the levels of these RFs may reduce the probability of psychopathology following CA. Clinicians could therefore look to improve these RFs as part of their focused intervention plans. The review provided support for a systemic framework of mental health resilience, as the identified RFs functioned on individual-, family- and community- levels. Moreover, our findings underpinned the notion that RFs function as complex interrelated systems. Therefore, we encourage resilience researchers to scrutinize RFs based on a systemic framework and to explore RFs as a complex interrelated system.

AUTHOR CONTRIBUTIONS

PW, A-LvH, and JF were responsible for the study conception and the development of the study protocol. The literature screening ($N = 1969$) was conducted by AdG, HC, and JF. The literature re-screening ($N = 220$) was conducted by AdG and JF. Data extraction and quality ratings were conducted by AdG and JF. In case of disagreement or uncertainty PW was included in the discussion. *Post hoc* quality ratings for statistical analyses were conducted by PW and JF. JF led the conduction process of the review under the supervision of PW and A-LvH. The writing up was performed by JF under the supervision of PW and A-LvH. All authors contributed to and approved the final manuscript. PW was responsible for the funding of the review.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00230/full#supplementary-material

REFERENCES

1. Greif Green J, McLaughlin KA, Berglund PA, Gruber MJ, Sampson NA, Zaslavsky AM, et al. Childhood adversities and adult psychopathology in the National Comorbidity Survey Replication (NCS-R) I: associations with first onset of DSM-IV disorders. *Arch Gen Psychiatry* (2010) 67:113–33. doi: 10.1001/archgenpsychiatry.2009.186.
2. Kessler RC, McLaughlin KA, Greif Green J, Gruber MJ, Sampson NA, Zaslavsky AM, et al. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *Br J Psychiatry* (2010) 197:378–85. doi: 10.1192/bjp.bp.110.080499
3. Masten AS. Resilience in children threatened by extreme adversity: frameworks for research, practice, and translational synergy. *Dev Psychopathol.* (2011) 23:493–506. doi: 10.1017/S0954579411000198
4. Mancini AD, Bonanno GA. Predictors and parameters of resilience to loss: toward an individual differences model. *J Pers.* (2009) 77:1805–32. doi: 10.1111/j.1467-6494.2009.00601.x
5. Rutter M. Annual research review: resilience – clinical implications. *J Child Psychol Psychiatry* (2013) 54:474–87. doi: 10.1111/j.1469-7610.2012.02615.x
6. Bonanno GA, Mancini AD, Horton JL, Powell TM, LeardMann CA, Boyko EJ, et al. Trajectories of trauma symptoms and resilience in deployed US military service members: prospective cohort study. *Br J Psychiatry* (2012) 200:317–23. doi: 10.1192/bjp.bp.111.096552
7. Rutter M. Implications of resilience concepts for scientific understanding. *Ann N Y Acad Sci* (2006) 1094:1–12. doi: 10.1196/annals.1376.002
8. American Psychological Association. The road to resilience. (2016) Available at: http://www.apa.org/helpcenter/road-resilience.aspx [Accessed October 20, 2016]
9. Kalisch R, Baker DG, Basten U, Boks MP, Bonanno GA, Brummelman E, et al. The resilience framework as a strategy to combat stress-related disorders. *Nat Hum Behav.* (2017) 1:784–90. doi: 10.1038/s41562-017-0200-8
10. Kalisch R, Müller MB, Tüscher O. A conceptual framework for the neurobiological study of resilience. *Behav Brain Sci.* (2015) 38:e92. doi: 10.1017/S0140525X1400082X
11. Fergus S, Zimmerman MA. Adolescent resilience: a framework for understanding healthy development in the face of risk. *Annu Rev Public Heal.* (2005) 26:399–419. doi: 10.1146/annurev.publhealth.26.021304.144357
12. World Health Organization. *Promoting Mental Health: Concepts, Emerging Evidence, Practice*. (2004) Available at: http://www.who.int/mental_health/evidence/en/promoting_mhh.pdf (Accessed March 18, 2017)
13. Masten AS. Ordinary magic: resilience processes in development. *Am Psychol.* (2001) 56:227–38. doi: 10.1037//0003-066X.56.3.227
14. Ungar M. Practitioner review: diagnosing childhood resilience – a systemic approach to the diagnosis of adaptation in adverse social and physical ecologies. *J Child Psychol Psychiatry* (2015) 56:4–17. doi: 10.1111/jcpp.12306
15. Luthar SS, Cicchetti D. The construct of resilience: implications for interventions and social policies. *Dev Psychopathol.* (2000) 12:857–885.
16. Afifi TO, MacMillan HL. Resilience following child maltreatment: a review of protective factors. *Can J Psychiatry* (2011) 56:266–272. doi: 10.1177/070674371105600505
17. Aburn G, Gott M, Hoare K. What is resilience? An integrative review of the empirical literature. *J Adv Nurs.* (2016) 72:980–1000. doi: 10.1111/jan.12888
18. Southwick SM, Bonanno GA, Masten AS, Panter-Brick C, Yehuda R. Resilience definitions, theory, and challenges: interdisciplinary perspectives. *Eur J Psychotraumatol.* (2014) 5:25338. doi: 10.3402/ejpt.v5.25338
19. Ungar M. Resilience, trauma, context, and culture. *Trauma Violence Abus.* (2013) 14:255–66. doi: 10.1177/1524838013487805
20. Kinard EM. Methodological issues in assessing resilience in maltreated children. *Child Abuse Negl.* (1998) 22:669–80.
21. Masten AS, Best KM, Garmezy N. Resilience and development: contributions from the study of children who overcome adversity. *Dev Psychopathol.* (1990) 2:425–44. doi: 10.1017/S0954579400005812
22. Zolkoski SM, Bullock LM. Resilience in children and youth: a review. *Child Youth Serv Rev.* (2012) 34:2295–303. doi: 10.1016/j.childyouth.2012.08.009
23. Rutter M. Resilience in the face of adversity: protective factors and resistance to psychiatric disoder. *Br J Psychiatry* (1985) 147:598–611.
24. van Harmelen A-L, Gibson JL, St Clair MC, Owens M, Brodbeck J, Dunn V, et al. Friendships and family support reduce subsequent depressive symptoms in at-risk adolescents. *PLoS ONE* (2016) 11:e0153715. doi: 10.1371/journal.pone.0153715
25. Marriott C, Hamilton-Giachritsis C, Harrop C. Factors promoting resilience following childhood sexual abuse: a structured, narrative review of the literature. *Child Abus Rev.* (2014) 23:17–34. doi: 10.1002/car.2258
26. Wright BK, Kelsall HL, Sim MR, Clarke DM, Creamer MC. Support mechanisms and vulnerabilities in relation to PTSD in veterans of the gulf war, iraq war, and afghanistan deployments: a systematic review. *J Trauma Stress* (2013) 26:310–8. doi: 10.1002/jts.21809
27. Traub F, Boynton-Jarrett R. Modifiable resilience factors to childhood adversity for clinical pediatric practice. *Pediatrics* (2017) 139:e20162569. doi: 10.1542/peds.2016-2569
28. Braithwaite EC, O'Connor RM, Degli-Esposti M, Luke N, Bowes L. Modifiable predictors of depression following childhood maltreatment: a systematic review and meta-analysis. *Transl Psychiatry* (2017) 7:e1162. doi: 10.1038/tp.2017.140
29. World Health Organization. *Risks to Mental Health: An Overview of Vulnerabilities and Risk Factors. Background Paper by WHO Secretariat for the Development of a Comprehensive Mental Health Action Plan*. (2012) Available online at: http://www.who.int/mental_health/mhgap/risks_to_mental_health_EN_27_08_12.pdf (Accessed November 17, 2016)
30. Fritz J, de Graaff A-M, Caisley H, van Harmelen A-L, Wilkinson P. Resilience following childhood adversity (CA): a systematic review of resilience factors which mitigate the risk of developing psychopathology after the exposure to CA. *Prospero* (2016) CRD4201605. Available online at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016051978
31. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* (2009) 6:e1000100. doi: 10.1371/journal.pmed.1000100
32. Dunn VJ, Abbott RA, Croudace TJ, Wilkinson PO, Jones PB, Herbert J, et al. Profiles of family-focused adverse experiences through childhood and early adolescence: the ROOTS project a community investigation of adolescent mental health. *BMC Psychiatry* (2011) 11:109. doi: 10.1186/1471-244X-11-109
33. World Health Organization. *Mental Health, Resilience and Inequalities*. (2009) Available online at: http://www.euro.who.int/__data/assets/pdf_file/0012/100821/E92227.pdf (Accessed November 17, 2016)
34. Martikainen P, Bartley M, Lahelma E. Psychosocial determinants of health in social epidemiology. *Int J Epidemiol.* (2002) 31:1091–3. doi: 10.1093/ije/31.6.1091
35. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders 4th edn.* Washington, DC: Author (2000).
36. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. STROBE initiative. strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Epidemiology* (2007) 18:805–35. doi: 10.1097/EDE.0b013e3181577511
37. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* (1998) 52:377–84. doi: 10.1136/jech.52.6.377
38. Banducci AN, Lejuez CW, Dougherty LR, MacPherson L. A prospective examination of the relations between emotional abuse and anxiety: moderation by distress tolerance. *Prev Sci.* (2017) 18:20–30. doi: 10.1007/s11121-016-0691-y
39. Boyes ME, Hasking PA, Martin G. Adverse life experience and psychological distress in adolescence: moderating and mediating effects of emotion regulation and rumination. *Stress Heal.* (2016) 32:402–10. doi: 10.1002/smi.2635
40. Cui M, Conger RD. Parenting behavior as mediator and moderator of the association between marital problems and adolescent maladjustment. *J Res Adolesc.* (2008) 18:261–84. doi: 10.1111/j.1532-7795.2008.00560.x
41. Dennison MJ, Sheridan MA, Busso DS, Jenness JL, Peverill M, Rosen ML, et al. Neurobehavioral markers of resilience to depression amongst adolescents exposed to child abuse. *J Abnorm Psychol.* (2016) 125:1201–12. doi: 10.1037/abn0000215

42. Dubow EF, Huesmann LR, Boxer P, Landau S, Dvir S, Shikaki K et al. Exposure to political conflict and violence and posttraumatic stress in middle east youth: protective factors. *J Clin Child Adolesc Psychol.* (2012) 41:402–16. doi: 10.1080/15374416.2012.684274
43. Finan LJ, Schulz J, Gordon MS, McCauley Ohannessian C. Parental problem drinking and adolescent externalizing behaviors: the mediating role of family functioning. *J Adolesc.* (2015) 43:100–10. doi: 10.1016/j.adolescence.2015.05.001
44. Gaté MA, Watkins ER, Simmons JG, Byrne ML, Schwartz OS, Whittle S, et al. Maternal parenting behaviors and adolescent depression: the mediating role of rumination. *J Clin Child Adolesc Psychol.* (2013) 42:348–57. doi: 10.1080/15374416.2012.755927
45. Hankin BL. Childhood maltreatment and psychopathology: prospective tests of attachment, cognitive vulnerability, and stress as mediating processes. *Cognit Ther Res.* (2005) 29:645–71. doi: 10.1007/s10608-005-9631-z
46. Hardaway CR, Sterrett-Hong E, Larkby CA, Cornelius MD. Family resources as protective factors for low-income youth exposed to community violence. *J Youth Adolesc.* (2016) 45:1309–22. doi: 10.1007/s10964-015-0410-1
47. Hébert M, Cénat JM, Blais M, Lavoie F, Guerrier M. Child sexual abuse, bullying, cyberbullying, and mental health problems among high schools students: a moderated mediated model. *Depress Anxiety* (2016) 33:623–9. doi: 10.1002/da.22504
48. Jester JM, Steinberg DB, Heitzeg MM, Zucker RA. Coping expectancies, not enhancement expectancies, mediate trauma experience effects on problem alcohol use: a prospective study from early childhood to adolescence. *J Stud Alcohol Drugs* (2015) 76:781–9. doi: 10.15288/jsad.2015.76.781
49. Klasen F, Otto C, Kriston L, Patalay P, Schlack R, Ravens-Sieberer U, The BELLA study group. Risk and protective factors for the development of depressive symptoms in children and adolescents: results of the longitudinal BELLA study. *Eur Child Adolesc Psychiatry* (2015) 24:695–703. doi: 10.1007/s00787-014-0637-5
50. Lansford JE, Malone PS, Stevens KI, Dodge KA, Bates JE, Pettit GS. Developmental trajectories of externalizing and internalizing behaviors: factors underlying resilience in physically abused children. *Dev Psychopathol.* (2006) 18:35–55. doi: 10.1017/S0954579406060032
51. Oshri A, Rogosch FA, Cicchetti D. Child maltreatment and mediating influences of childhood personality types on the development of adolescent psychopathology. *J Clin Child Adolesc Psychol.* (2013) 42:287–301. doi: 10.1080/15374416.2012.715366
52. Qouta S, El-Sarraj E, Punamäki R-L. Mental flexibility as resiliency factor among children exposed to political violence. *Int J Psychol* (2001) 36:1–7. doi: 10.1080/00207590042000010
53. Shahar G, Henrich CC. Perceived family social support buffers against the effects of exposure to rocket attacks on adolescent depression, aggression, and severe violence. *J Fam Psychol.* (2015) 30:163–8. doi: 10.1037/fam0000179
54. Walter KH, Horsey KJ, Palmieri PA, Hobfoll SE. The role of protective self-cognitions in the relationship between childhood trauma and later resource loss. *J Trauma Stress* (2010) 23:264–273. doi: 10.1002/jts.20504
55. Masten AS, Hubbard JJ, Gest SD, Tellegen A, Garmezy N, Ramirez M. Competence in the context of adversity: pathways to resilience and maladaptation from childhood to late adolescence. *Dev Psychopathol.* (1999) 11:143–69.
56. Calvete E. Emotional abuse as a predictor of early maladaptive schemas in adolescents: contributions to the development of depressive and social anxiety symptoms. *Child Abuse Negl.* (2014) 38:735–746. doi: 10.1016/j.chiabu.2013.10.014
57. Hicks BM, Johnson W, Durbin CE, Blonigen DM, Iacono WG, McGue M. Delineating selection and mediation effects among childhood personality and environmental risk factors in the development of adolescent substance abuse. *J Abnorm Child Psychol.* (2014) 42:845–59. doi: 10.1007/s10802-013-9831-z
58. You S, Lim SA. Development pathways from abusive parenting to delinquency: The mediating role of depression and aggression. *Child Abuse Negl.* (2015) 46:152–62. doi: 10.1016/j.chiabu.2015.05.009
59. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. *Annu Rev Psychol.* (2007) 58:593–614. doi: 10.1146/annurev.psych.58.110405.085542
60. Champoux JE, Peters WS. Form, effect size and power in moderated regression analysis. *J Occup Psychol.* (1987) 60:243–55. doi: 10.1111/j.2044-8325.1987.tb00257.x
61. Bodner TE. Standardized effect sizes for moderated conditional fixed effects with continuous moderator variables. *Front Psychol.* (2017) 8:562. doi: 10.3389/fpsyg.2017.00562
62. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol.* (1986) 51:1173–82. doi: 10.1037/0022-3514.51.6.1173
63. Holmbeck GN. Post-hoc probing of significant moderational and mediational effects in studies of pediatric populations. *J Pediatr Psychol.* (2002) 27:87–96. doi: 10.1093/jpepsy/27.1.87
64. van Harmelen A-L, Kievit RA, Ioannidis K, Neufeld S, Jones PB, Bullmore E, et al. Adolescent friendships predict later resilient functioning across psychosocial domains in a healthy community cohort. *Psychol Med.* (2017) 47:2312–22. doi: 10.1017/S0033291717000836

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Biological and Psychological Perspectives of Resilience: Is It Possible to Improve Stress Resistance?

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The term "resilience" refers to the ability to adapt successfully to stress, trauma and adversity, enabling individuals to avoid stress-induced mental disorders such as depression, posttraumatic stress disorder (PTSD) and anxiety. Here, we review evidence from both animal models and humans that is increasingly revealing the neurophysiological and neuropsychological mechanisms that underlie stress susceptibility, as well as active mechanisms underlying the resilience phenotype. Ultimately, this growing understanding of the neurobiological mechanisms of resilience should result in the development of novel interventions that specifically target neural circuitry and brain areas that enhance resilience and lead to more effective treatments for stress-induced disorders. Stress resilience can be improved, but the outcomes and effects depend on the type of intervention and the species treated.

Keywords: resilience, stress, depression, VTA, NAc, mPFC

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INTRODUCTION

Resilience means "the ability to withstand or recover quickly from difficult conditions" (Fletcher and Sarkar, 2013; Robertson et al., 2015). However, in the context of recent biological and psychological research, resilience has gained a more specific meaning. The idea of resilience as resistance to stress (**Figure 1**) originated in the 1970s when researchers began to study children capable of normal development despite a difficult upbringing (Masten, 2001). By the early 1990s, the emphasis of resilience research has shifted away from identifying protective factors, which involve positive emotions and the competence for self-regulation, to a study of how individuals overcome adversity and an examination of the psychosocial determinants of resilience in trauma-exposed adults (Luthar et al., 2000; Conger and Conger, 2002; Bonanno et al., 2015; Cai et al., 2017). Negative manifestations of resilience manifest as mood disorders, including major depressive disorder (MDD), fear, anxiety, posttraumatic stress disorder (PTSD) and other stress-associated negative emotions (Feder et al., 2009; Friedman, 2014; Alves et al., 2017).

Recent studies employing advanced technologies such as optogenetics have significantly deepened our understanding of the intrinsic biological mechanisms of resilience. This review article will first introduce the psychological and physiological perspectives of resilience, then describe the important neural circuits and neuroendocrine mechanisms involved in resilience, and finally discuss possible ways of improving resilience based on new insights provided by neurobiological studies.

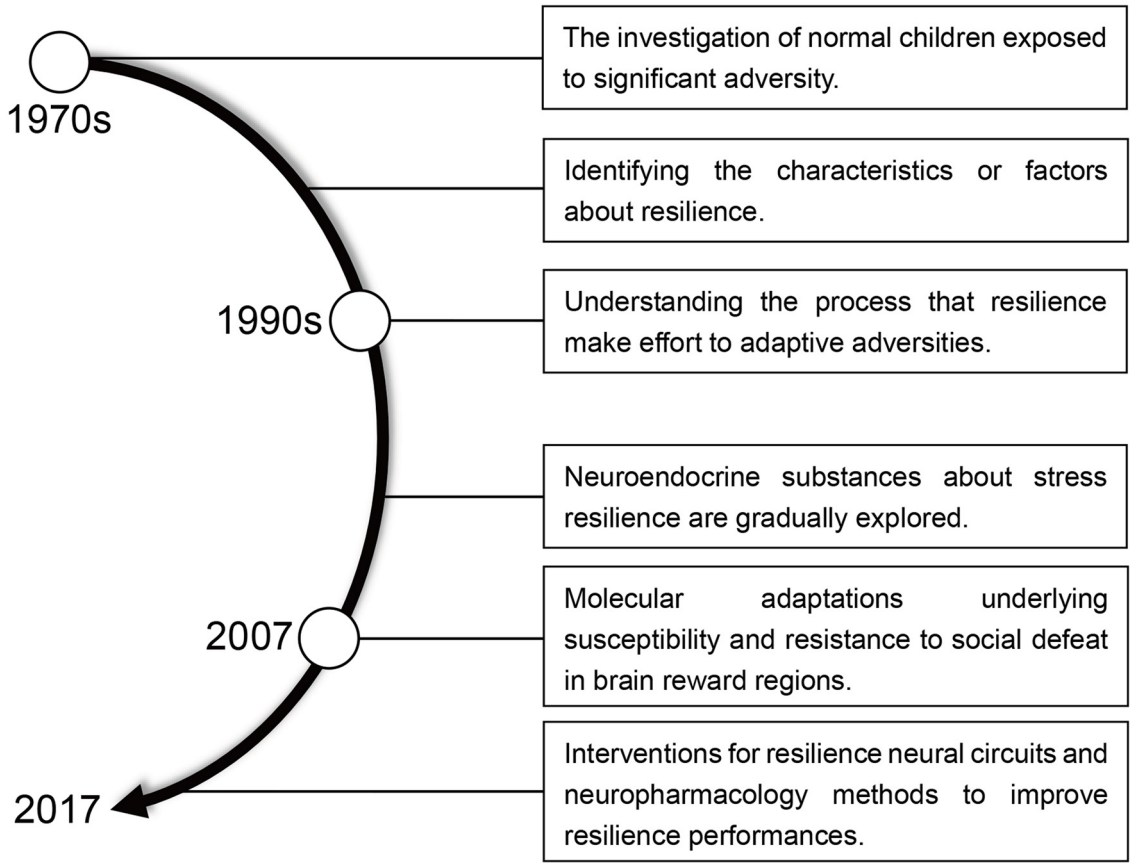

FIGURE 1 | A brief history of resilience research.

FUNDAMENTAL CONCEPTS AND FEATURES OF RESILIENCE RESEARCH

In the last 10 to 15 years, resilience has been examined in a range of contexts in both humans and animals. Animals that show fewer deleterious effects of stress are considered resilient (Steimer and Driscoll, 2005; Krishnan et al., 2007; Feder et al., 2009; Ergang et al., 2015). A number of animal models have been used to improve our understanding of stress resilience or susceptibility (**Table 1**), for example, chronic social defeat stress (CSDS; Golden et al., 2011), learned helplessness (LH; Berton et al., 2007; Fleshner et al., 2011), exposure to predator odor (Cohen et al., 2012) or chronic mild stress (CMS; Delgado y Palacios et al., 2011). Resilient and susceptible animals can be distinguished by their performance in specific behavioral tasks.

Whether resilience should be defined as a trait, process or outcome is frequently debated in human resilience studies. Connor and Davidson (2003) believe that resilience represents personal qualities that enable an individual to thrive in the face of adversity; therefore, in their opinion, resilience is a trait comprising a constellation of characteristics that enable individuals to adapt to the circumstances they encounter (Connor and Davidson, 2003). In contrast, the "process hypothesis" focuses on the interaction between the individual and adverse circumstance and emphasizes that changes over time are dynamic, encompassing positive adaptation within the context of significant adversity (Luthar et al., 2000). Finally, resilience can also be considered an outcome after experienced adversity (Masten, 2001). It is worth noting that all the above concepts of stress resilience have two elements in common, adversity and positive adaptation (Fletcher and Sarkar, 2013), which therefore must both be included in studies of resilience in human and animal models. In fact, most current psychological resilience studies involve four aspects: (a) baseline or pre-adversity; (b) the adversity itself; (c) post-adversity resilient outcomes; and (d) predictors of resilient outcomes; (Bonanno et al., 2015).

More cross-sectional studies that integrate different types of adverse stress are needed to clarify whether different stresses share common influential pathways. This is particularly important given that the term "adversity" covers a wide range of experiences. For example, in humans, adversity can encompass social rejection, failure in examinations, early life stress, depression and other chronic enduring stressful experiences, while in animals it can mean social defeat, forced swimming,

TABLE 1 | Research methods or models of stress resilience.

Stress model	Subject	Model overview	References
Chronic social defeat stress (CSDS)	Rodents	Experimental mice are exposed to an aggressive retired breeder CD1 mouse. After interaction the experimental mice are housed in the same cage with a perforated divider separating them from the CD1 mouse. This is a well-established protocol yielding stress-susceptible or resilient cohorts.	Krishnan et al. (2007) and Isingrini et al. (2016)
Chronic restraint stress	Rodents	The rodents are housed in a restrainer with no mobility for a short period daily and then are replaced in their home cage.	Nasca et al. (2015)
Early life stress	Rodents	Pups are separated from their parents during the first postnatal week. Paternal stress and gestational stress operate similarly, but with different separation periods.	Heim and Binder (2012) and Santarelli et al. (2017)
Chronic mild stress (CMS, unpredictable stress)	Rodents	Rodents are exposed to varying physical and psychosocial stresses, for example, shaking, cage tilting.	Suo et al. (2013) and Higuchi et al. (2016)
Learned helplessness (LH)	Rodents	A subset of animals exposed to unavoidable aversive stimuli (e.g., foot shock) develops learned helplessness, i.e., fails to escape when escape available.	Berton et al. (2007) and Brachman et al. (2016)
Use of predator odor	Rodents	Animals are exposed to predator-scent stress.	Cohen et al. (2012)
Acute stress models	Rodents	Breeding of rodent strains with markedly different responses in acute stress environments, such as the tail suspension test. These models are less directly applicable in resilience studies.	El Yacoubi et al. (2003)
Other animal models	Rodents	Comparisons across inbred lines of rats and mice, and selective breeding of rodent lines that display differential stress responses.	Crowley and Lucki (2005) and Overstreet et al. (2005)
Questionnaire investigation	Humans	Investigation of populations to uncover different resilience responses and resilience scale performances.	Hemington et al. (2017)
Psychotherapy or intervention	Humans	Exploration of suitable methods for improving adaptability using resilience interventions.	Langley et al. (2015)
Behavioral experiments and imaging technology	Humans	Evaluation and comparison of brain function while conducting various behavioral tasks relating to stress sensitivity in humans tusing non-invasive imaging technology (such as functional magnetic resonance imaging, fMRI).	Johnson et al. (2014) and Peterson et al. (2014)

foot shock and other types of acutely stressful stimulation (Janakiraman et al., 2016).

Depending on the specific stressful process, resilience might be understood as the ability: (1) to maintain natural functions and elude adversity; and (2) to deal with the stress positively and obtain some benefit from it. Neurobiological studies show that resilience is mediated by both the absence of certain key molecules that occur in susceptible animals and impair their coping ability, and the presence of distinct adaptation mechanisms seen in resilient individuals that promote normal behavior (Krishnan et al., 2007; Friedman et al., 2016). The former and latter are considered to be mechanisms of passive and active resilience, respectively (Russo et al., 2012).

REPRESENTATIVE ANIMAL MODELS OF RESILIENCE

CSDS (Golden et al., 2011) and CMS (Liu et al., 2018) are two of the most widely used resilient animal models and have been widely applied in the study of resilience and depression, although the more aggressive behavior of the outbred CD-1 mouse requires careful monitoring in the CSDS test (Albonetti and Farabollini, 1994). CMS consists of various random negative stressful stimuli, such as foot shock, swimming in cold water, light/dark succession and hunger (Chang and Grace, 2014), and may be more similar to the types of stress experienced by humans. Since female mice exposed to CMS are less stable than males (Franceschelli et al., 2014), gender differences should be taken into account when using this model.

Although such animal models have dramatically improved our understanding of the neural substrates underlying resilience, they have been less useful in defining the complex interactions between environmental stress, protective factors and individual personality. For example, increased self-criticism and decreased self-compassion enhance the risk of depression in humans (Ehret et al., 2015), but these effects are not represented (and arguably could not be represented) in animal models of resilience. On the other hand, techniques used to study regions of the brain involved in the regulation of human resilience, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) or deep brain stimulation (DBS), are limited by low spatio-temporal resolution and ethical considerations. Therefore, an appropriate combination of human and animal models is required to enable researchers to gain a precise understanding of resilience.

BEHAVIORAL CHARACTERISTICS OF RESILIENCE

A range of psychosocial factors that contribute to resilience have been identified. The factors include active coping (Snow-Turek et al., 1996; Hanton et al., 2013), optimism (Warner et al., 2012), cognitive reappraisal (Maren, 2008; Farchi and Gidron, 2010; Troy et al., 2010), prosocial behavior (Staub and Vollhardt, 2008), social support and others (Ozbay et al., 2008;

Cai et al., 2017). Social support is one of the main protective elements that influence family well-being, parenting quality and child resilience (Armstrong et al., 2005). A 10-year longitudinal study found that social support from partners promoted resilience in response to economic stress (Conger and Conger, 2002). In contrast, poor social support enhanced stress, leading to elevated heart rate (Stansfeld et al., 1997), depression (Oxman and Hull, 2001) and increased susceptibility to PTSD (Johnson et al., 1997).

Although the onset of psychiatric disorders such as PTSD and depression might be prevented by promoting adaptation to stress, the key to resilience and mental well-being lies in emotion regulation processes (Hu et al., 2014). For example, social support and resilience have multiple mediation effects on the regulation of cognitive emotion and acute stress in Chinese male soldiers (Cai et al., 2017). However, there are also studies that claim there are no relationships between resilience and social support, lifestyle factors or work-related factors (Corina and Adriana, 2013; Black et al., 2017), although it is generally acknowledged that resilience buffers against various types of stress. These inconsistent behavioral results might be attributed to the use of different resilience questionnaires, the sample size and type of human subjects, and non-standardization of the test procedure, suggesting that it is critical to identify the physiological substrates underlying the manipulation of resilience. Animal models and emerging technologies, such as optogenetics (Friedman et al., 2014, 2016), electrophysiological recording (Christoffel et al., 2015; Friedman et al., 2016) and animal imaging systems (Delgado y Palacios et al., 2011; Anacker et al., 2016), are generating a great deal of interest in the elucidation of the neural circuits and molecules involved in resilience.

A DYNAMIC FRAMEWORK OF RESILIENCE

In early studies, psychological models of resilience were established to describe the construction of active pathways of resilience. Garmezy et al. (1984) emphasized the interaction between adverse stimulation and the consequences of stress, while Rutter (1987) elaborated four pathways to elucidate how individuals process adversity, which involve reduction in risk impact and negative chain reactions, establishment and maintenance of self-esteem and self-efficacy, and the opening up of opportunities. These early theories had a great impact on psychological perspectives of resilience, and subsequently these and other contemporaneous researchers attempted to uncover how resilience interacts with environmental stress and other personal traits to influence the behavior of individuals.

The concept of "biopsychospiritual homeostasis" was introduced by Richardson (2002), whose model proposed that resilience was a dynamic equilibrium state in which physical, psychological and spiritual ingredients, as well as various adversity or protective factors reached a balance. However, Rutter (2012) was forthright in declaring that resilience "should not constitute a theory, nor should it be seen as equivalent to positive psychology or competence."

Although neurobiological research into resilience has less theoretical underpinning, new discoveries have emerged in recent years. For example, resilient individuals have been shown to have drastically different behavioral performances and neural substrates compared with, more susceptible individuals (Feder et al., 2009), while some recent study shows that a K^+ channel in ventral tegmental area (VTA) dopamine (DA) neurons differentially mediates neuronal activity in resilient, normal and susceptible mice (Friedman et al., 2016; Han and Nestler, 2017; Barrese et al., 2018).

NEURAL BASIS OF RESILIENCE

Researchers have demonstrated that various brain structures and pathways are involved in resilience (Franklin et al., 2012; Russo et al., 2012), and we review these below.

Medial Prefrontal Cortex

The medial prefrontal cortex (mPFC) exerts strong negative control over stress pathways, and maladaptive behavior in response to stress involves mPFC dysfunction (Wang et al., 2014). Inhibiting neuronal activity in the mPFC by DBS is effective at alleviating symptoms in depressed humans or rodent depression models (Covington et al., 2010; Warden et al., 2012), while enhanced mPFC excitation results in depression-like behavior (Wang et al., 2014). mPFC lesions augment the hypothalamic-pituitary-adrenal (HPA) axis in response to emotional stress, while, in contrast, intra-mPFC injection of corticosterone attenuates this response (Diorio et al., 1993). Neural activity and levels of immediate early gene expression are lower in the ventral mPFC following stressors such as CSDS, predator stress, or water submersion in susceptible rodents (Covington et al., 2010). Interestingly, depressive patients demonstrate decreased neuronal activity in the postmortem anterior cingulate cortex (ACC), a brain area with functional homology to the mPFC in rodents (Covington et al., 2010). Moreover, hypoactivity is corrected by optogenetic induction of cortical burst firing in animals and is accompanied by the reversal of CSDS-induced social anxiety and anhedonia (Covington et al., 2010; Adamec et al., 2012). In addition, the subgenual cingulate cortex, which is also homologous to the rodent mPFC, is hyperactive in mood disorders (Ressler and Mayberg, 2007; Drevets et al., 2008; Hamani et al., 2011).

The lateral prefrontal cortex often demonstrates hypoactivity in neuroimaging studies of depressed patients (Kinou et al., 2013; Rive et al., 2013). Selective activation of the mPFC–lateral habenula (LHb; Li et al., 2011; Warden et al., 2012) or the mPFC–amygdala pathway (Martinez et al., 2013; Moscarello and LeDoux, 2013) results in depression-like activity. However, stimulation of the mPFC–dorsal raphe nucleus (DRN) pathway promotes resilience (Warden et al., 2012). The precise mechanisms by which the mPFC interacts with its downstream targets and integrates different behavioral responses to stress, and in particular resilience to stress, deserve further investigation.

It should be noted that the results of research into the effect of early life stress on resilience remain inconsistent. Stress has extensively proven to be related to the emergence of diabetes (Marcovecchio and Chiarelli, 2012), child health issues (Charmandari et al., 2012), cardiovascular disease (Kivimäki and Steptoe, 2018) and depression (Pena et al., 2017). Adverse childhood experiences (ACEs), such as psychological or sexual abuse, violence against the mother and household dysfunction, are strongly correlated with a significantly increased risk of physical or psychological disease and unhealthy habits in subsequent life, for example, alcoholism, depression, smoking, severe obesity and illicit drug use (Felitti et al., 1998; Anda et al., 1999; Dube et al., 2001, 2003; Van Niel et al., 2014; Gilbert et al., 2015). Although it is well known that ACEs can result in serious longstanding consequences, mild exposure to stress at an early age, so-called stress inoculation (Meichenbaum and Cameron, 1989), might improve resilience. However, despite investigations into the mechanisms underlying the effects of stress inoculation, which have focused mainly on HPA axis-related variations (reviewed in Ashokan et al., 2016), the potential neural circuits and plasticity have remained elusive. A recent study demonstrated that learned-helplessness mice exposed to inescapable foot shocks for 6 days experienced spatial memory deficits and decreased basolateral amygdala-ventral hippocampus CA1 connection. However, under the same conditions learned-hopefulness mice showed enhanced spatial memory and neural activity (Yang et al., 2016), suggesting the existence of neural plasticity variations associated with a long period of negative stress.

Hippocampal Pathways

The hippocampus, which is modulated by stress hormones, is one of the main brain areas that exert regulatory control over the HPA axis. Stressors rapidly stimulate the parvocellular neurons of the paraventricular nucleus of the hypothalamus to secrete corticotropin-releasing factor and vasopressin, triggering the release of adrenocorticotropic hormone from the anterior pituitary; in turn the latter promotes the release of glucocorticoid stress hormones from the adrenal cortex into the circulation (Levone et al., 2015). There are both direct and indirect polysynaptic connections between the paraventricular nucleus and the hippocampus, which negatively influence the HPA axis via glucocorticoid-receptor- or mineralocorticoid-receptor-dependent feedback (Franklin et al., 2012; Levone et al., 2015). It has been shown, in both human and rodents, that stimulation of the hippocampus decreases glucocorticoid secretion, while, in contrast, hippocampal lesions increase basal glucocorticoid levels, especially during the stress recovery phase, the phase most reliant on negative feedback (Jankord and Herman, 2008).

The hippocampus is particularly vulnerable to the impact of stress. The glutamate hypothesis, of which impaired hippocampal function is a major component, has been widely accepted in the field of depression. Human studies show that, abnormal glutamatergic synaptic transmission, maladaptive structural and functional changes in hippocampal circuitry, and reduction in hippocampal volume, are associated with stress-induced conditions such as MDD (Franklin et al., 2012). Glutamatergic ventral hippocampus (vHIP) → nucleus accumbens (NAc) projections regulate susceptibility to CSDS. Reduced activity in the vHIP has been observed in mice resilient to CSDS (Bagot et al., 2015). Suppression of vHIP-NAc synaptic transmission by optogenetic induction of long-term depression is pro-resilient, while enhanced activity of this pathway is pro-susceptible. However, optogenetic activation of either mPFC or basolateral amygdala afferents to the NAc is pro-resilient (Bagot et al., 2015), highlighting an important circuit-specific mechanism in depression or stress resilience. Using magnetic resonance imaging, social avoidance in C57BL/6 mice with CSDS correlated positively with volume of the hippocampal CA3, accompanied by synchronized anatomic differences between hippocampus and several other areas, including the VTA, the cingulate cortex and the hypothalamus (Anacker et al., 2016).

Various postsynaptic receptors of the hippocampus, such as G-protein coupled gama-aminobutyric acid B ($GABA_B$) receptors, play important roles in stress regulation. Different isoforms of $GABA_B$ receptor subunits, such as $GABA_{B(1a)}$ and $GABA_{B(1b)}$, have been shown to differentially regulate stress resilience. Specifically, $GABA_{B(1a)}$ knockout mice are susceptible whereas $GABA_{B(1b)}$-deficient mice are resilient to stress-induced anhedonia and social withdrawal (O'Leary et al., 2014), suggesting that $GABA_B$ receptors may be novel therapeutic targets for regulation of stress. Hippocampal serotonin (5-HT) receptors are also important in stress regulation. Thus, knockdown of the hippocampal 5-HT receptor, $5\text{-}HT_{1A}$, significantly decreases the antidepressant-like effect induced by a nicotinic partial agonist, cytisine (Mineur et al., 2015).

VTA-NAc Pathways

A well-characterized reward circuit in the brain comprises dopaminergic neurons in the VTA that give projections to the NAc. This VTA–NAc circuit is crucial for reward motivation and the consumption of addictive substances (Skibicka et al., 2013; Juarez et al., 2017). However, increasing evidence in humans and animals suggests that VTA-NAc pathways also play an important role in mediating stress susceptibility.

DA neurons in the VTA mediate susceptibility and resilience in CSDS-induced behavioral abnormalities. VTA DA neurons exhibit low frequency tonic firing and high frequency phasic firing *in vivo* (Grace et al., 2003). Induction of phasic, but not tonic, firing by optogenetic stimulation in VTA DA neurons results in a susceptible phenotype in mice undergoing subthreshold CSDS, as indicated by social avoidance and decreased sucrose consumption.

Activation of VTA-NAc, but not VTA-mPFC, pathways leads to stress susceptibility to CSDS, highlighting a circuit-specific mechanism in stress resilience (Razzoli et al., 2011). In support of the above finding, VTA DA neurons of susceptible mice exhibit hyperactivity (Friedman et al., 2014). In contrast, mice resilient to CSDS exhibit stable normal firing of these neurons (Friedman et al., 2014, 2016). mTOR, which has been shown

to regulate cell growth, metabolism, proliferation and survival (Elghazi et al., 2017), shows elevated levels in the VTA 3 weeks after termination of CSDS in mice. Levels of phosphorylated AKT, an upstream regulator of mTOR, are also increased (Der-Avakian et al., 2014).

GABAergic medium spiny neurons (MSNs) are the principal neurons in the NAc. Recent studies suggest that impairment of GABAergic neurons in the NAc is linked to MDD. The NAc of stressed mice features a decrease in inhibitory synapses, leading to NAc dysfunction (Zhu et al., 2017). Mice in which the metabotropic glutamate receptor subunit 5 (mGluR5) is deleted display an increase in depression-like behavior compared to controls, while lentiviral transfection of mGluR5 in the NAc of these mutant mice counteracts their depression-like behavior (Shin et al., 2015).

TOWARDS IMPROVEMENT OF RESILIENCE

Both psychological and behavioral therapy have been used to improve resilience and thus reduce the symptoms of mental disorders and increase mental flexibility (Wolmer et al., 2011; Horn et al., 2016; Creswell, 2017). The drawback of psychological treatments is clear, as behavioral psychotherapy generally takes place over a long period of time, works slowly, and provides little improvement in our understanding of the internal mechanisms involved. Resilience is probably influenced largely by active adaptations, which occur specifically in resilient individuals. Genome-wide screening using the CSDS model has recognized numerous gene expression variations and chromatin alterations in the VTA and NAc that are observed only in resilience (Krishnan et al., 2007; Wilkinson et al., 2009). Thus, it seems possible to trigger natural mechanisms underlying resilience, which differ from the effects of existing antidepressants, in susceptible populations (Russo et al., 2012). We next discuss important research that has changed the understanding of resilience and indicates how new treatments of stress-related disorders might be developed.

Improving Resilience by Altering Neural Activity

Early studies showed that the degree of VTA DA neuronal activity is a crucial element determining behavioral susceptibility. Thus, *ex vivo* VTA neuronal firing increases in brain tissue of susceptible but not resilient mice (Krishnan et al., 2007; Feder et al., 2009), showing a negative correlation with social avoidance behavior (Cao et al., 2010). Either chronic, but not acute, administration of the antidepressant, fluoxetine, or optogenetic stimulation of VTA DA neurons, completely reverse these deleterious effects in susceptible mice (Cao et al., 2010; Chaudhury et al., 2013). Moreover, the hyperpolarization-activated cation current (I_h) increases in VTA DA neurons of susceptible mice, while chronic treatment with fluoxetine normalizes increased I_h (Cao et al., 2010). Local application or systemic administration of retigabine, a KCNQ-type K^+ channel opener, normalizes VTA DA neuron hyperactivity and depressive behavior (Friedman et al., 2016), identifying KCNQ as a target for conceptually novel antidepressants or methods of stress regulation. However, an even larger significant increase in I_h, in parallel with increased K^+ channel currents, is observed in resilient, compared to susceptible and control mice. Further experimental enhancement of I_h or an optogenetic activation of VTA DA neuron activity completely reverses depression-related behavior in susceptible mice (Friedman et al., 2014).

So we might ask, why don't we observe hyperactivity of VTA DA neurons in resilient mice? One possibility is that the upregulation of I_h in VTA DA neurons of resilient mice could drive neuronal firing to extremely high frequencies in parallel with activating a self-tuning K^+ current mechanism to normalize the excessive firing. The I_h potentiation could engender the overactivity that directly causes this K^+ current compensation (Friedman et al., 2014), a homeostatic plasticity mechanism established in the VTA-NAc, rather than in the VTA-mPFC pathway; these observations might lead to new therapeutic strategies for promoting natural resilience.

Increased activity in the NAc DA1-MSN pathway promotes resilience, while suppression of these MSNs leads to a depression-like phenotype after CSDS. Although bidirectionally modifying the NAc DA2-MSN pathway does not change behavioral outcomes in the CSDS model, repeatedly activating NAc DA2-MSNs evokes social avoidance in resilient mice after subthreshold CSDS (Francis et al., 2015). Therefore, the NAc DA1-MSN pathway may provide novel targets for the treatment of depression or other affective disorders.

Considering the direct anatomical and functional connections between the locus coeruleus (LC) noradrenergic neurons (NEs) and the VTA, the LC might be responsible for buffering the external stressors and stress response of VTA DA neurons (Guiard et al., 2008; Chandler et al., 2013). LC-VTA NE synaptic transmission is both necessary and sufficient for the promotion of resilience in response to social defeat. Furthermore, selective change in NE tone affects VTA DA-NAc projections (Isingrini et al., 2016). Chronic treatment with idazoxan, an α2 NE receptor antagonist, leads to reduction in VTA DA neuron excitability, which counteracts susceptibility (Chaudhury et al., 2013; Isingrini et al., 2016), but whether K^+ current compensation underlies the decreased neuronal excitability of the VTA DA system requires further investigation.

Improving Resilience Using Neuropharmacological Approaches

Various neurochemicals have been found to change resilience. The release of NPY, a 36 amino-acid peptide, is thought to help limit the negative consequences of stress and has anxiolytic-like effects (Cohen et al., 2012). Ketamine and a number of other neurochemicals likewise also bring about intense and enduring adaptations to stress (Sachs et al., 2015; Sciolino et al., 2015; Brachman et al., 2016).

NPY

Intranasal NPY administration provides neuronal protection when applied immediately prior, or following, exposure to traumatic stress in an animal model. Rats pretreated with intranasal NPY before single prolonged stress (SPS) exposure show less depressive-like and anxiety-like behavior (Serova et al., 2013). Traumatic stress-triggered dysregulation of the HPA axis can be prevented by intranasal NPY, which restores proper negative feedback inhibition within the HPA axis by changing the activity of glucocorticoid receptors (Laukova et al., 2014; Serova et al., 2014). Furthermore, 1 week after SPS exposure, when animals have developed symptoms of PTSD, treatment with intranasal NPY reduces anxiety-like and depressive-like behavior (Serova et al., 2014). These results suggest that NPY holds enormous promise for novel therapeutic approaches to the improvement of resilience, although the mechanism underlying NPY function remains unclear.

Ketamine

As an antagonist of the glutamatergic N-methyl-D-aspartate (NMDA) receptor, and an activator of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors, ketamine has rapid and sustained antidepressant effects (Berman et al., 2000; Zarate et al., 2006; Murrough et al., 2013; Price, 2016; McGowan et al., 2017). Ketamine infusion induces rapid reduction in the severity of PTSD and depressive symptoms, thereby improving the overall clinical presentation of PTSD patients (Murrough et al., 2013; Feder et al., 2014). Importantly, ketamine does not give rise, clinically, to significant persistent dissociative symptoms (Feder et al., 2014). A recent study showed that a single dose of ketamine prevents CSDS-induced depressive-like behavior. The effects of ketamine were also confirmed in LH and chronic corticosterone mouse models (Brachman et al., 2016), suggesting that ketamine strengthens resilience and thus might be useful in protecting against stress-induced disorders.

Importantly, ketamine may be clinically most useful if administered in a prophylactic manner, i.e., 1 week before a stressor. In mice undergoing the contextual fear conditioning (CFC) paradigm, administration of prophylactic ketamine for 1 week, but not 1 month or 1 h before CFC, prevents the animal from freezing behavior. However, ketamine treatment following CFC or during extinction does not change subsequent expression of fear (McGowan et al., 2017).

Recently, two Nature articles revealed the mechanism underlying the anti-depression effects of ketamine. Depressive rats were found to have increased bursting activity in the lateral habenula (LHb) due to upregulation of an astroglial potassium channel, Kir4.1 (Cui et al., 2018). Ketamine blocked NMDA-dependent bursting activity in the LHb and reversed depression-like symptoms (Yang et al., 2018), implicating the NMDA receptor and Kir4.1 in the LHb as potential targets for treatment of depression. It should be noted, however, that there is limited clinical use of ketamine due to its psychotogenic side effects and addictive liability. In the CSDS and LH models of depression, it was found that R-ketamine is more potent and shows a longer antidepressant effect than S-ketamine, while S-ketamine, but not R-ketamine, precipitates behavioral abnormalities (Yang et al., 2015). Therefore, unlike S-ketamine, R-ketamine could potentially be used to elicit a sustained and safe antidepressant effect. The antidepressant effect of ketamine requires metabolism of (R,S)-ketamine to (2S,6S; 2R,6R)-hydroxynorketamine (HNK). Moreover, the (2R,6R)-HNK enantiomer shows antidepressant actions in mice that is independent of NMDA receptor inhibition but involves early and persistent activation of AMPA receptors (Zanos et al., 2016). The cortical NMDA receptor complex is heteromultimeric, consisting of two GluN1 and two GluN2 subunits, the latter primarily of the GluN2A and GluN2B isotypes (Monyer et al., 1992). In addition to regulating depression-like behavior, the GluN2B-containing NMDA receptor plays a critical role in mediating the rapid antidepressant effect of ketamine (Miller et al., 2014). More work is required to reveal the details of how the NMDA receptor, the AMPA receptor and ketamine interact, and R-ketamine should be explored further as a potentially more effective and safe antidepressant medicine for improving resilience.

5-HT

5-HT is the neurotransmitter that is most relevant to resilience (Kim et al., 2013). Either 5-HT deficiency in the brain or exposure to psychosocial stress promotes the etiology of depression, anxiety, PTSD and other mood disorders (Sachs et al., 2015). Acute stress is associated with increased 5-HT turnover in the amygdala, NAc and PFC (Feder et al., 2009). Reduced levels of brain 5-HT result in enhanced vulnerability to psychosocial stress and thus reduce the antidepressant effects of fluoxetine following stress exposure in mice (Sachs et al., 2015).

The enteric nervous system, also called the gut brain, is intimately linked with 5-HT and resilience (Foster and McVey Neufeld, 2013). Some metabolites, derived from gut microbes, increase the production of 5-HT in the cells lining the colon (Yano et al., 2015). These cells account for 60% and more than 90% of peripheral 5-HT in mice and humans, respectively (Smith, 2015). In particular, germ-free mice, which lack an intestinal microbiome, have an increased turnover rate of key neurochemicals, including striatal 5-HT, which is associated with anxious behavior, but have significantly decreased levels of 5-HT in blood (Diaz Heijtz et al., 2011; Smith, 2015). Moreover, blood 5-HT levels in these mice can be restored by introducing spore-forming bacteria into the intestine (Diaz Heijtz et al., 2011; Smith, 2015), suggesting that gut microbes may directly or indirectly impact neurotransmitter levels, at least in rodents. However, it remains unclear whether these altered levels of 5-HT in the gut trigger a cascade of molecular events that consequently affect brain activity; the situation in humans requires further investigation.

Other Means of Improving Resilience

The neuropeptide galanin and a galanin receptor subtype, GalR1–3, are expressed throughout circuits that mediate stress responses, including the mPFC, DRN, LC, hypothalamus, hippocampus, VTA and amygdala (Hawes and Picciotto, 2004).

Exposure to stress decreases time spent in open arm exploration in sedentary rats, but not in those treated chronically with intracerebroventricular galanin or exercised rats which have increased galanin levels in the LC, implicating improved resilience in the latter groups. Increased DA overflow and loss of dendritic spines in the mPFC, observed after stress in sedentary rats, are prevented by both exercise and chronic, intracerebroventricular galanin. Moreover, chronic, but not acute, administration of galanin receptor antagonist M40 blocks the resilience-promoting effects of exercise (Sciolino et al., 2015). These results suggest that increased galanin levels promote resilience at both neural and behavioral levels, and galanin may thus improve stress resilience by regulation of mPFC neural plasticity. Phasic stimulation of VTA DA neurons leads to susceptibility and reverses resilience rapidly (Chaudhury et al., 2013), while midbrain DA activity and DA release can be inhibited by galanin (Sciolino et al., 2015; Weinshenker and Holmes, 2016).

Improving Resilience in Humans

Improvements in resilience in humans have been reported as a result of psychological and cognitive therapies, such as child caregiver advocacy resilience (Li et al., 2017), a life skills education-based program (Sarkar et al., 2017), the iNEAR programme (Tunariu et al., 2017), intensive mindfulness meditation training (Hwang et al., 2018) and stress inoculation training (Horn et al., 2016). Although all the above achieved good outcomes, the same method may have different therapeutic effects in different individuals. Therefore, the development of more general, stable, and faster effective interventions is likely to be a trend in the future.

DBS is now a well-established surgical option. More and more studies indicate that DBS has beneficial effects in many psychiatric disorders, such as PTSD (Koek et al., 2014), depression (Schlaepfer et al., 2008) and Parkinson's disease (Pellaprat et al., 2014). Early research identified another clinical tool, repetitive transcranial magnetic stimulation (rTMS), a non-invasive technique that normalizes activity of the HPA system and has an antidepressant effect (Czéh et al., 2002). It seems that rTMS induces alterations in neural networks and has an effect in some psychiatric disorders (Aleman, 2013). Since resilience is closely related to these diseases, it is possible that these technologies can be used to improve resilience, but this remains to be studied.

CONCLUDING REMARKS

The enormous impact of stress, trauma or other forms of adversity on humanity, together with limitations in available treatments, make it necessary to explore resilience mechanisms that might protect against PTSD, depression and other mental disorders. Most work in this discipline over the past decades has focused on the biological differences between resilience and susceptibility, and has explored, in animal models, means to reverse the deleterious effects of chronic stress. However, reversing these deleterious effects does not necessarily mean that resilience is enhanced and that the affected individuals have a better life. A crucial novel perspective, which has emerged in recent years, is that resilient animals have active adaptive mechanisms that are distinct from actions that reverse deleterious effects in susceptible animals. Therefore, current research aimed at improving stress resilience focuses on the relationship and essential distinction between reversing deleterious effects and cultivating active adaptive mechanisms. Finally, the development of "precision medicine" for improving stress resilience will require a clearer picture to emerge out of the messy realm of current resilience research. A dynamic and integrated combination of psychological and neurobiological studies will be essential for generating this clearer picture of resilience. Further studies should focus not only on the resilience of individuals or small human/animal populations, but also the wider human community, much of which is under pressure due to, for example, the global economic crisis. Given that social support, economic pressure and prosocial behaviors have a significant influence on an individual's response to stress, it will be necessary to uncover neuronal and psychological mechanisms of resilience at the level of different human communities.

Although mild exposure to stress at an early age (stress inoculation; Meichenbaum and Cameron, 1989), might improve resilience, it is worth noting that ACEs, at high score, have been proven to affect brain development, resulting in enormous, awful and long-term sequelae in adulthood (Felitti et al., 1998; Anda et al., 1999; Van Niel et al., 2014; Gilbert et al., 2015). Importantly, the consequence of ACEs is longstanding due, at least in part, to DNA methylation changes of BDNF gene (Kundakovic et al., 2015). Therefore, efforts toward reducing the childhood trauma that may require a public health campaign would have the greatest impact for the prevention of ACEs.

AUTHOR CONTRIBUTIONS

HL and LY designed the theme of the manuscript and wrote most sections. CZ and YJ together wrote one section. All authors approved the manuscript for submission and publication.

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REFERENCES

Adamec, R., Toth, M., Haller, J., Halasz, J., and Blundell, J. (2012). A comparison of activation patterns of cells in selected prefrontal cortical and amygdala areas of rats which are more or less anxious in response to predator exposure or submersion stress. *Physiol. Behav.* 105, 628–638. doi: 10.1016/j.physbeh.2011.09. 016

Albonetti, M. E., and Farabollini, F. (1994). Social stress by repeated defeat: effects on social behaviour and emotionality. *Behav. Brain Res.* 62, 187–193. doi: 10.1016/0166-4328(94)90027-2

Aleman, A. (2013). Use of repetitive transcranial magnetic stimulation for treatment in psychiatry. *Clin. Psychopharmacol. Neurosci.* 11, 53–59. doi: 10.9758/cpn.2013.11.2.53

Alves, N. D., Correia, J. S., Patrício, P., Mateus-Pinheiro, A., Machado-Santos, A. R., Loureiro-Campos, E., et al. (2017). Adult hippocampal neuroplasticity triggers susceptibility to recurrent depression. *Transl. Psychiatry* 7:e1058. doi: 10.1038/tp.2017.29

Anacker, C., Scholz, J., O'Donnell, K. J., Allemang-Grand, R., Diorio, J., Bagot, R. C., et al. (2016). Neuroanatomic differences associated with stress susceptibility and resilience. *Biol. Psychiatry* 79, 840–849. doi: 10.1016/j.biopsych.2015.08.009

Anda, R. F., Croft, J. B., Felitti, V. J., Nordenberg, D., Giles, W. H., Williamson, D. F., et al. (1999). Adverse childhood experiences and smoking during adolescence and adulthood. *JAMA* 282, 1652–1658. doi: 10.1001/jama.282.17.1652

Armstrong, M. I., Birnie-Lefcovitch, S., and Ungar, M. T. (2005). Pathways between social support, family well being, quality of parenting, and child resilience: what we know. *J. Child Fam. Stud.* 14, 269–281. doi: 10.1007/s10826-005-5054-4

Ashokan, A., Sivasubramanian, M., and Mitra, R. (2016). Seeding stress resilience through inoculation. *Neural Plast.* 2016:4928081. doi: 10.1155/2016/4928081

Bagot, R. C., Parise, E. M., Peña, C. J., Zhang, H. X., Maze, I., Chaudhury, D., et al. (2015). Corrigendum: ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression. *Nat. Commun.* 6:7626. doi: 10.1038/ncomms8626

Barrese, V., Stott, J. B., and Greenwood, I. A. (2018). "KCNQ-encoded potassium channels as therapeutic targets," in *Annual Review of Pharmacology and Toxicology* (Vol. 58) ed. P. A. Insel (Palo Alto, CA: Annual Reviews), 625–648.

Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., et al. (2000). Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry* 47, 351–354. doi: 10.1016/s0006-3223(99)00230-9

Berton, O., Covington, H. E. III., Ebner, K., Tsankova, N. M., Carle, T. L., Ulery, P., et al. (2007). Induction of ΔFosB in the periaqueductal gray by stress promotes active coping responses. *Neuron* 55, 289–300. doi: 10.1016/j.neuron.2007.06.033

Black, J. K., Balanos, G. M., and Whittaker, A. C. (2017). Resilience, work engagement and stress reactivity in a middle-aged manual worker population. *Int. J. Psychophysiol.* 116, 9–15. doi: 10.1016/j.ijpsycho.2017.02.013

Bonanno, G. A., Romero, S. A., and Klein, S. I. (2015). The temporal elements of psychological resilience: an integrative framework for the study of individuals, families, and communities. *Psychol. Inq.* 26, 139–169. doi: 10.1080/1047840x.2015.992677

Brachman, R. A., McGowan, J. C., Perusini, J. N., Lim, S. C., Pham, T. H., Faye, C., et al. (2016). Ketamine as a prophylactic against stress-induced depressive-like behavior. *Biol. Psychiatry* 79, 776–786. doi: 10.1016/j.biopsych.2015.04.022

Cai, W.-P., Pan, Y., Zhang, S.-M., Wei, C., Dong, W., and Deng, G.-H. (2017). Relationship between cognitive emotion regulation, social support, resilience and acute stress responses in Chinese soldiers: exploring multiple mediation model. *Psychiatry Res.* 256, 71–78. doi: 10.1016/j.psychres.2017.06.018

Cao, J.-L., Covington, H. E., Friedman, A. K., Wilkinson, M. B., Walsh, J. J., Cooper, D. C., et al. (2010). Mesolimbic dopamine neurons in the brain reward circuit mediate susceptibility to social defeat and antidepressant action. *J. Neurosci.* 30, 16453–16458. doi: 10.1523/jneurosci.3177-10.2010

Chandler, D. J., Lamperski, C. S., and Waterhouse, B. D. (2013). Identification and distribution of projections from monoaminergic and cholinergic nuclei to functionally differentiated subregions of prefrontal cortex. *Brain Res.* 1522, 38–58. doi: 10.1016/j.brainres.2013.04.057

Chang, C. H., and Grace, A. A. (2014). Amygdala-ventral pallidum pathway decreases dopamine activity after chronic mild stress in rats. *Biol. Psychiatry* 76, 223–230. doi: 10.1016/j.biopsych.2013.09.020

Charmandari, E., Achermann, J. C., Carel, J. C., Soder, O., and Chrousos, G. P. (2012). Stress response and child health. *Sci. Signal.* 5:mr1. doi: 10.1126/scisignal.2003595

Chaudhury, D., Walsh, J. J., Friedman, A. K., Juarez, B., Ku, S. M., Koo, J. W., et al. (2013). Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature* 493, 532–536. doi: 10.1038/nature11713

Christoffel, D. J., Golden, S. A., Walsh, J. J., Guise, K. G., Heshmati, M., Friedman, A. K., et al. (2015). Excitatory transmission at thalamo-striatal synapses mediates susceptibility to social stress. *Nat. Neurosci.* 18, 962–964. doi: 10.1038/nn.4034

Cohen, H., Liu, T., Kozlovsky, N., Kaplan, Z., Zohar, J., and Mathé, A. A. (2012). The neuropeptide Y (NPY)-ergic system is associated with behavioral resilience to stress exposure in an animal model of post-traumatic stress disorder. *Neuropsychopharmacology* 37, 350–363. doi: 10.1038/npp.2011.230

Conger, R. D., and Conger, K. J. (2002). Resilience in Midwestern families: selected findings from the first decade of a prospective, longitudinal study. *J. Marriage Fam.* 64, 361–373. doi: 10.1111/j.1741-3737.2002.00361.x

Connor, K. M., and Davidson, J. R. T. (2003). Development of a new resilience scale: The Connor-Davidson Resilience Scale (CD-RISC). *Depress. Anxiety* 18, 76–82. doi: 10.1002/da.10113

Corina, D., and Adriana, B. (2013). Impact of work related trauma on acute stress response in train drivers. *Procedia Soc. Behav. Sci.* 84, 190–195. doi: 10.1016/j.sbspro.2013.06.533

Covington, H. E. III., Lobo, M. K., Maze, I., Vialou, V., Hyman, J. M., Zaman, S., et al. (2010). Antidepressant effect of optogenetic stimulation of the medial prefrontal cortex. *J. Neurosci.* 30, 16082–16090. doi: 10.1523/JNEUROSCI.1731-10.2010

Creswell, J. D. (2017). Mindfulness interventions. *Annu. Rev. Psychol.* 68, 491–516. doi: 10.1146/annurev-psych-042716-051139

Crowley, J. J., and Lucki, I. (2005). Opportunities to discover genes regulating depression and antidepressant response from rodent behavioral genetics. *Curr. Pharm. Des.* 11, 157–169. doi: 10.2174/1381612053382278

Cui, Y. H., Yang, Y., Ni, Z. Y., Dong, Y. Y., Cai, G. H., Foncelle, A., et al. (2018). Astroglial Kir4.1 in the lateral habenula drives neuronal bursts in depression. *Nature* 554, 323–327. doi: 10.1038/nature25752

Czéh, B., Welt, T., Fischer, A. K., Erhardt, A., Schmitt, W., Müller, M. B., et al. (2002). Chronic psychosocial stress and concomitant repetitive transcranial magnetic stimulation: effects on stress hormone levels and adult hippocampal neurogenesis. *Biol. Psychiatry* 52, 1057–1065. doi: 10.1016/s0006-3223(02)01457-9

Delgado y Palacios, R., Campo, A., Henningsen, K., Verhoye, M., Poot, D., Dijkstra, J., et al. (2011). Magnetic resonance imaging and spectroscopy reveal differential hippocampal changes in anhedonic and resilient subtypes of the chronic mild stress rat model. *Biol. Psychiatry* 70, 449–457. doi: 10.1016/j.biopsych.2011.05.014

Der-Avakian, A., Mazei-Robison, M. S., Kesby, J. P., Nestler, E. J., and Markou, A. (2014). Enduring deficits in brain reward function after chronic social defeat in rats: susceptibility, resilience, and antidepressant response. *Biol. Psychiatry* 76, 542–549. doi: 10.1016/j.biopsych.2014.01.013

Diaz Heijtz, R., Wang, S., Anuar, F., Qian, Y., Björkholm, B., Samuelsson, A., et al. (2011). Normal gut microbiota modulates brain development and behavior. *Proc. Natl. Acad. Sci. U S A* 108, 3047–3052. doi: 10.1073/pnas.1005129108

Diorio, D., Viau, V., and Meaney, M. J. (1993). The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. *J. Neurosci.* 13, 3839–3847. doi: 10.1523/JNEUROSCI.13-09-03839.1993

Drevets, W. C., Savitz, J., and Trimble, M. (2008). The subgenual anterior cingulate cortex in mood disorders. *CNS Spectr.* 13, 663–681. doi: 10.1017/s1092852900013754

Dube, S. R., Anda, R. F., Felitti, V. J., Chapman, D. P., Williamson, D. F., and Giles, W. H. (2001). Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study. *JAMA* 286, 3089–3096. doi: 10.1001/jama.286.24.3089

Dube, S. R., Felitti, V. J., Dong, M., Chapman, D. P., Giles, W. H., and Anda, R. F. (2003). Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. *Pediatrics* 111, 564–572. doi: 10.1542/peds.111.3.564

Ehret, A. M., Joormann, J., and Berking, M. (2015). Examining risk and resilience factors for depression: the role of self-criticism and self-compassion. *Cogn. Emot.* 29, 1496–1504. doi: 10.1080/02699931.2014.992394

El Yacoubi, M., Bouali, S., Popa, D., Naudon, L., Leroux-Nicollet, I., Hamon, M., et al. (2003). Behavioral, neurochemical, and electrophysiological

characterization of a genetic mouse model of depression. *Proc. Natl. Acad. Sci. U S A* 100, 6227–6232. doi: 10.1073/pnas.1034823100

Elghazi, L., Blandino-Rosano, M., Alejandro, E., Cras-Méneur, C., and Bernal-Mizrachi, E. (2017). Role of nutrients and mTOR signaling in the regulation of pancreatic progenitors development. *Mol. Metab.* 6, 560–573. doi: 10.1016/j.molmet.2017.03.010

Ergang, P., Vodička, M., Soták, M., Klusoňová, P., Behuliak, M., Řeháková, L., et al. (2015). Differential impact of stress on hypothalamic-pituitary-adrenal axis: gene expression changes in Lewis and Fisher rats. *Psychoneuroendocrinology* 53, 49–59. doi: 10.1016/j.psyneuen.2014.12.013

Farchi, M., and Gidron, Y. (2010). The effects of "psychological inoculation" versus ventilation on the mental resilience of Israeli citizens under continuous war stress. *J. Nerv. Ment. Dis.* 198, 382–384. doi: 10.1097/NMD.0b013e3181da4b67

Feder, A., Nestler, E. J., and Charney, D. S. (2009). Psychobiology and molecular genetics of resilience. *Nat. Rev. Neurosci.* 10, 446–457. doi: 10.1038/nrn2649

Feder, A., Parides, M. K., Murrough, J. W., Perez, A. M., Morgan, J. E., Saxena, S., et al. (2014). Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry* 71, 681–688. doi: 10.1001/jamapsychiatry.2014.62

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., et al. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am. J. Prev. Med.* 14, 245–258. doi: 10.1016/s0749-3797(98)00017-8

Fleshner, M., Maier, S. F., Lyons, D. M., and Raskind, M. A. (2011). The neurobiology of the stress-resistant brain. *Stress* 14, 498–502. doi: 10.3109/10253890.2011.596865

Fletcher, D., and Sarkar, M. (2013). Psychological resilience: a review and critique of definitions, concepts, and theory. *Eur. Psychol.* 18, 12–23. doi: 10.1027/1016-9040/a000124

Foster, J. A., and McVey Neufeld, K.-A. (2013). Gut-brain axis: how the microbiome influences anxiety and depression. *Trends Neurosci.* 36, 305–312. doi: 10.1016/j.tins.2013.01.005

Franceschelli, A., Herchick, S., Thelen, C., Papadopoulou-Daifoti, Z., and Pitychoutis, P. M. (2014). Sex differences in the chronic mild stress model of depression. *Behav. Pharmacol.* 25, 372–383. doi: 10.1097/FBP.0000000000000062

Francis, T. C., Chandra, R., Friend, D. M., Finkel, E., Dayrit, G., Miranda, J., et al. (2015). Nucleus accumbens medium spiny neuron subtypes mediate depression-related outcomes to social defeat stress. *Biol. Psychiatry* 77, 212–222. doi: 10.1016/j.biopsych.2014.07.021

Franklin, T. B., Saab, B. J., and Mansuy, I. M. (2012). Neural mechanisms of stress resilience and vulnerability. *Neuron* 75, 747–761. doi: 10.1016/j.neuron.2012.08.016

Friedman, A. (2014). Jump-starting natural resilience reverses stress susceptibility. *Science* 346:555. doi: 10.1126/science.1260781

Friedman, A. K., Juarez, B., Ku, S. M., Zhang, H., Calizo, R. C., Walsh, J. J., et al. (2016). KCNQ channel openers reverse depressive symptoms via an active resilience mechanism. *Nat. Commun.* 7:11671. doi: 10.1038/ncomms11671

Friedman, A. K., Walsh, J. J., Juarez, B., Ku, S. M., Chaudhury, D., Wang, J., et al. (2014). Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. *Science* 344, 313–319. doi: 10.1126/science.1249240

Garmezy, N., Masten, A. S., and Tellegen, A. (1984). The study of stress and competence in children: a building block for developmental psychopathology. *Child Dev.* 55, 97–111. doi: 10.2307/1129837

Gilbert, L. K., Breiding, M. J., Merrick, M. T., Thompson, W. W., Ford, D. C., Dhingra, S. S., et al. (2015). Childhood adversity and adult chronic disease: an update from ten states and the District of Columbia, 2010. *Am. J. Prev. Med.* 48, 345–349. doi: 10.1016/j.amepre.2014.09.006

Golden, S. A., Covington, H. E. III., Berton, O., and Russo, S. J. (2011). A standardized protocol for repeated social defeat stress in mice. *Nat. Protoc.* 6, 1183–1191. doi: 10.1038/nprot.2011.361

Grace, A., West, A., Ash, B., Moore, H., and Floresco, S. (2003). Tonic versus phasic DA release in the nucleus accumbens is differentially regulated by pathways that selectively alter DA neuron spontaneous activity and burst firing. *Schizophr. Res.* 60, 106–107. doi: 10.1016/s0920-9964(03)80844-7

Guiard, B. P., El Mansari, M., and Blier, P. (2008). Cross-talk between dopaminergic and noradrenergic systems in the rat ventral tegmental area, locus ceruleus and dorsal hippocampus. *Mol. Pharmacol.* 74, 1463–1475. doi: 10.1124/mol.108.048033

Hamani, C., Mayberg, H., Stone, S., Laxton, A., Haber, S., and Lozano, A. M. (2011). The subcallosal cingulate gyrus in the context of major depression. *Biol. Psychiatry* 69, 301–308. doi: 10.1016/j.biopsych.2010.09.034

Han, M.-H., and Nestler, E. J. (2017). Neural substrates of depression and resilience. *Neurotherapeutics* 14, 677–686. doi: 10.1007/s13311-017-0527-x

Hanton, S., Neil, R., and Evans, L. (2013). Hardiness and anxiety interpretation: an investigation into coping usage and effectiveness. *Eur. J. Sport Sci.* 13, 96–104. doi: 10.1080/17461391.2011.635810

Hawes, J. J., and Picciotto, M. R. (2004). Characterization of GalR1, GalR2, and GalR3 immunoreactivity in catecholaminergic nuclei of the mouse brain. *J. Comp. Neurol.* 479, 410–423. doi: 10.1002/cne.20329

Heim, C., and Binder, E. B. (2012). Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions and epigenetics. *Exp. Neurol.* 233, 102–111. doi: 10.1016/j.expneurol.2011.10.032

Hemington, K. S., Cheng, J. C., Bosma, R. L., Rogachov, A., Kim, J. A., and Davis, K. D. (2017). Beyond negative pain-related psychological factors: resilience is related to lower pain affect in healthy adults. *J. Pain* 18, 1117–1128. doi: 10.1016/j.jpain.2017.04.009

Higuchi, F., Uchida, S., Yamagata, H., Abe-Higuchi, N., Hobara, T., Hara, K., et al. (2016). Hippocampal microRNA-124 enhances chronic stress resilience in mice. *J. Neurosci.* 36, 7253–7267. doi: 10.1523/JNEUROSCI.0319-16.2016

Horn, S. R., Charney, D. S., and Feder, A. (2016). Understanding resilience: new approaches for preventing and treating PTSD. *Exp. Neurol.* 284, 119–132. doi: 10.1016/j.expneurol.2016.07.002

Hu, T., Zhang, D., Wang, J., Mistry, R., Ran, G., and Wang, X. (2014). Relation between emotion regulation and mental health: a meta-analysis review. *Psychol. Rep.* 114, 341–362. doi: 10.2466/03.20.pr0.114k22w4

Hwang, W. J., Lee, T. Y., Lim, K.-O., Bae, D., Kwak, S., Park, H.-Y., et al. (2018). The effects of four days of intensive mindfulness meditation training (Templestay program) on resilience to stress: a randomized controlled trial. *Psychol. Health Med.* 23, 497–504. doi: 10.1080/13548506.2017.1363400

Isingrini, E., Perret, L., Rainer, Q., Amilhon, B., Guma, E., Tanti, A., et al. (2016). Resilience to chronic stress is mediated by noradrenergic regulation of dopamine neurons. *Nat. Neurosci.* 19, 560–563. doi: 10.1038/nn.4245

Janakiraman, U., Manivasagam, T., Thenmozhi, A., Essa, M. M., Barathidasan, R., SaravanaBabu, C., et al. (2016). Influences of chronic mild stress exposure on motor, non-motor impairments and neurochemical variables in specific brain areas of MPTP/probenecid induced neurotoxicity in mice. *PLoS One* 11:e0146671. doi: 10.1371/journal.pone.0146671

Jankord, R., and Herman, J. P. (2008). Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. *Ann. N Y Acad. Sci.* 1148, 64–73. doi: 10.1196/annals.1410.012

Johnson, D. R., Lubin, H., Rosenheck, R., Fontana, A., Southwick, S., and Charney, D. (1997). The impact of the homecoming reception on the development of posttraumatic stress disorder. The West Haven Homecoming Stress Scale (WHHSS). *J. Trauma. Stress* 10, 259–277. doi: 10.1002/jts.2490100207

Johnson, D. C., Thom, N. J., Stanley, E. A., Haase, L., Simmons, A. N., Shih, P. A., et al. (2014). Modifying resilience mechanisms in at-risk individuals: a controlled study of mindfulness training in Marines preparing for deployment. *Am. J. Psychiatry* 171, 844–853. doi: 10.1176/appi.ajp.2014.13040502

Juarez, B., Morel, C., Ku, S. M., Liu, Y., Zhang, H., Montgomery, S., et al. (2017). Midbrain circuit regulation of individual alcohol drinking behaviors in mice. *Nat. Commun.* 8:2220. doi: 10.1038/s41467-017-02365-8

Kim, J. W., Lee, H. K., and Lee, K. (2013). Influence of temperament and character on resilience. *Compr. Psychiatry* 54, 1105–1110. doi: 10.1016/j.comppsych.2013.05.005

Kinou, M., Takizawa, R., Marumo, K., Kawasaki, S., Kawakubo, Y., Fukuda, M., et al. (2013). Differential spatiotemporal characteristics of the prefrontal hemodynamic response and their association with functional impairment

in schizophrenia and major depression. *Schizophr. Res.* 150, 459–467. doi: 10.1016/j.schres.2013.08.026

Kivimäki, M., and Steptoe, A. (2018). Effects of stress on the development and progression of cardiovascular disease. *Nat. Rev. Cardiol.* 15, 215–229. doi: 10.1038/nrcardio.2017.189

Koek, R. J., Langevin, J. P., Krahl, S. E., Kosoyan, H. J., Schwartz, H. N., Chen, J. W., et al. (2014). Deep brain stimulation of the basolateral amygdala for treatment-refractory combat post-traumatic stress disorder (PTSD): study protocol for a pilot randomized controlled trial with blinded, staggered onset of stimulation. *Trials* 15:356. doi: 10.1186/1745-6215-15-356

Krishnan, V., Han, M. H., Graham, D. L., Berton, O., Renthal, W., Russo, S. J., et al. (2007). Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* 131, 391–404. doi: 10.1016/j.cell.2007.09.018

Kundakovic, M., Gudsnuk, K., Herbstman, J. B., Tang, D., Perera, F. P., and Champagne, F. A. (2015). DNA methylation of BDNF as a biomarker of early-life adversity. *Proc. Natl. Acad. Sci. U S A* 112, 6807–6813. doi: 10.1073/pnas.1408355111

Langley, A. K., Gonzalez, A., Sugar, C. A., Solis, D., and Jaycox, L. (2015). Bounce back: effectiveness of an elementary school-based intervention for multicultural children exposed to traumatic events. *J. Consult. Clin. Psychol.* 83, 853–865. doi: 10.1037/ccp0000051

Laukova, M., Alaluf, L. G., Serova, L. I., Arango, V., and Sabban, E. L. (2014). Early intervention with intranasal NPY prevents single prolonged stress-triggered impairments in hypothalamus and ventral hippocampus in male rats. *Endocrinology* 155, 3920–3933. doi: 10.1210/en.2014-1192

Levone, B. R., Cryan, J. F., and O'Leary, O. F. (2015). Role of adult hippocampal neurogenesis in stress resilience. *Neurobiol. Stress* 1, 147–155. doi: 10.1016/j.ynstr.2014.11.003

Li, B., Piriz, J., Mirrione, M., Chung, C., Proulx, C. D., Schulz, D., et al. (2011). Synaptic potentiation onto habenula neurons in the learned helplessness model of depression. *Nature* 470, 535–539. doi: 10.1038/nature09742

Li, X., Harrison, S. E., Fairchild, A. J., Chi, P., Zhao, J., and Zhao, G. (2017). A randomized controlled trial of a resilience-based intervention on psychosocial well-being of children affected by HIV/AIDS: effects at 6- and 12-month follow-up. *Soc. Sci. Med.* 190, 256–264. doi: 10.1016/j.socscimed.2017.02.007

Liu, D., Tang, Q. Q., Yin, C., Song, Y., Liu, Y., Yang, J. X., et al. (2018). Brain-derived neurotrophic factor mediated projection-specific regulation of depressive-like and nociceptive behaviors in the mesolimbic reward circuitry. *Pain* 159, 175–188. doi: 10.1097/j.pain.0000000000001083

Luthar, S. S., Cicchetti, D., and Becker, B. (2000). The construct of resilience: a critical evaluation and guidelines for future work. *Child Dev.* 71, 543–562. doi: 10.1111/1467-8624.00164

Marcovecchio, M. L., and Chiarelli, F. (2012). The effects of acute and chronic stress on diabetes control. *Sci. Signal.* 5:pt10. doi: 10.1126/scisignal.2003508

Maren, S. (2008). Pavlovian fear conditioning as a behavioral assay for hippocampus and amygdala function: cautions and caveats. *Eur. J. Neurosci.* 28, 1661–1666. doi: 10.1111/j.1460-9568.2008.06485.x

Martinez, R. C. R., Gupta, N., Lázaro-Muñoz, G., Sears, R. M., Kim, S., Moscarello, J. M., et al. (2013). Active vs. reactive threat responding is associated with differential c-Fos expression in specific regions of amygdala and prefrontal cortex. *Learn. Mem.* 20, 446–452. doi: 10.1101/lm.031047.113

Masten, A. S. (2001). Ordinary magic. Resilience processes in development. *Am. Psychol.* 56, 227–238. doi: 10.1037/0003-066x.56.3.227

McGowan, J. C., LaGamma, C. T., Lim, S. C., Tsitsiklis, M., Neria, Y., Brachman, R. A., et al. (2017). Prophylactic ketamine attenuates learned fear. *Neuropsychopharmacology* 42, 1577–1589. doi: 10.1038/npp.2017.19

Meichenbaum, D., and Cameron, R. (1989). "Stress inoculation training," in *Stress Reduction and Prevention*, eds D. Meichenbaum and M. E. Jaremko (Boston, MA: Springer), 115–154.

Miller, O. H., Yang, L., Wang, C. C., Hargroder, E. A., Zhang, Y., Delpire, E., et al. (2014). GluN2B-containing NMDA receptors regulate depression-like behavior and are critical for the rapid antidepressant actions of ketamine. *Elife* 3:e03581. doi: 10.7554/elife.03581

Mineur, Y. S., Einstein, E. B., Bentham, M. P., Wigestrand, M. B., Blakeman, S., Newbold, S. A., et al. (2015). Expression of the 5-HT_{1A} serotonin receptor in the hippocampus is required for social stress resilience and the antidepressant-like effects induced by the nicotinic partial agonist cytisine. *Neuropsychopharmacology* 40, 938–946. doi: 10.1038/npp.2014.269

Monyer, H., Sprengel, R., Schoepfer, R., Herb, A., Higuchi, M., Lomeli, H., et al. (1992). Heteromeric NMDA receptors: molecular and functional distinction of subtypes. *Science* 256, 1217–1221. doi: 10.1126/science.256.5060.1217

Moscarello, J. M., and LeDoux, J. E. (2013). Active avoidance learning requires prefrontal suppression of amygdala-mediated defensive reactions. *J. Neurosci.* 33, 3815–3823. doi: 10.1523/JNEUROSCI.2596-12.2013

Murrough, J. W., Losifescu, D. V., Chang, L. C., Al Jurdi, R. K., Green, C. E., Perez, A. M., et al. (2013). Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am. J. Psychiatry* 170, 1134–1142. doi: 10.1176/appi.ajp.2013.13030392

Nasca, C., Zelli, D., Bigio, B., Piccinin, S., Scaccianoce, S., Nistico, R., et al. (2015). Stress dynamically regulates behavior and glutamatergic gene expression in hippocampus by opening a window of epigenetic plasticity. *Proc. Natl. Acad. Sci. U S A* 112, 14960–14965. doi: 10.1073/pnas.1516016112

O'Leary, O. F., Felice, D., Galimberti, S., Savignac, H. M., Bravo, J. A., Crowley, T., et al. (2014). $GABA_{B(1)}$ receptor subunit isoforms differentially regulate stress resilience. *Proc. Natl. Acad. Sci. U S A* 111, 15232–15237. doi: 10.1016/s0924-977x(14)70197-x

Overstreet, D. H., Friedman, E., Mathé, A. A., and Yadid, G. (2005). The Flinders Sensitive Line rat: a selectively bred putative animal model of depression. *Neurosci. Biobehav. Rev.* 29, 739–759. doi: 10.1016/j.neubiorev.2005.03.015

Oxman, T. E., and Hull, J. G. (2001). Social support and treatment response in older depressed primary care patients. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 56, P35–P45. doi: 10.1093/geronb/56.1.p35

Ozbay, F., Fitterling, H., Charney, D., and Southwick, S. (2008). Social support and resilience to stress across the life span: a neurobiologic framework. *Curr. Psychiatry Rep.* 10, 304–310. doi: 10.1007/s11920-008-0049-7

Pellaprat, J., Ory-Magne, F., Canivet, C., Simonetta-Moreau, M., Lotterie, J.-A., Radji, F., et al. (2014). Deep brain stimulation of the subthalamic nucleus improves pain in Parkinson's disease. *Parkinsonism Relat. Disord.* 20, 662–664. doi: 10.1016/j.parkreldis.2014.03.011

Pena, C. J., Kronman, H. G., Walker, D. M., Cates, H. M., Bagot, R. C., Purushothaman, I., et al. (2017). Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2. *Science* 356, 1185–1188. doi: 10.1126/science.aan4491

Peterson, B. S., Wang, Z., Horga, G., Warner, V., Rutherford, B., Klahr, K. W., et al. (2014). Discriminating risk and resilience endophenotypes from lifetime illness effects in familial major depressive disorder. *JAMA Psychiatry* 71, 136–148. doi: 10.1001/jamapsychiatry.2013.4048

Price, R. B. (2016). From mice to men: can ketamine enhance resilience to stress? *Biol. Psychiatry* 79, E57–E59. doi: 10.1016/j.biopsych.2016.02.011

Razzoli, M., Andreoli, M., Michielin, F., Quarta, D., and Sokal, D. M. (2011). Increased phasic activity of VTA dopamine neurons in mice 3 weeks after repeated social defeat. *Behav. Brain Res.* 218, 253–257. doi: 10.1016/j.bbr.2010.11.050

Ressler, K. J., and Mayberg, H. S. (2007). Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. *Nat. Neurosci.* 10, 1116–1124. doi: 10.1038/nn1944

Richardson, G. E. (2002). The metatheory of resilience and resiliency. *J. Clin. Psychol.* 58, 307–321. doi: 10.1002/jclp.10020

Rive, M. M., van Rooijen, G., Veltman, D. J., Phillips, M. L., Schene, A. H., and Ruhé, H. G. (2013). Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. *Neurosci. Biobehav. Rev.* 37, 2529–2553. doi: 10.1016/j.neubiorev.2013.07.018

Robertson, I. T., Cooper, C. L., Sarkar, M., and Curran, T. (2015). Resilience training in the workplace from 2003 to 2014: a systematic review. *J. Occup. Organ. Psychol.* 88, 533–562. doi: 10.1111/joop.12120

Russo, S. J., Murrough, J. W., Han, M. H., Charney, D. S., and Nestler, E. J. (2012). Neurobiology of resilience. *Nat. Neurosci.* 15, 1475–1484. doi: 10.1038/nn.3234

Rutter, M. (1987). Psychosocial resilience and protective mechanisms. *Am. J. Orthopsychiatry* 57, 316–331. doi: 10.1111/j.1939-0025.1987.tb03541.x

Rutter, M. (2012). Resilience as a dynamic concept. *Dev. Psychopathol.* 24, 335–344. doi: 10.1017/S0954579412000028

Sachs, B. D., Ni, J. R., and Caron, M. G. (2015). Brain 5-HT deficiency increases stress vulnerability and impairs antidepressant responses

following psychosocial stress. *Proc. Natl. Acad. Sci. U S A* 112, 2557–2562. doi: 10.1073/pnas.1416866112

Santarelli, S., Zimmermann, C., Kalideris, G., Lesuis, S. L., Arloth, J., Uribe, A., et al. (2017). An adverse early life environment can enhance stress resilience in adulthood. *Psychoneuroendocrinology* 78, 213–221. doi: 10.1016/j.psyneuen.2017.01.021

Sarkar, K., Dasgupta, A., Sinha, M., and Shahbabu, B. (2017). Effects of health empowerment intervention on resilience of adolescents in a tribal area: a study using the Solomon four-groups design. *Soc. Sci. Med.* 190, 265–274. doi: 10.1016/j.socscimed.2017.05.044

Schlaepfer, T. E., Cohen, M. X., Frick, C., Kosel, M., Brodesser, D., Axmacher, N., et al. (2008). Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology* 33, 368–377. doi: 10.1038/sj.npp.1301408

Sciolino, N. R., Smith, J. M., Stranahan, A. M., Freeman, K. G., Edwards, G. L., Weinshenker, D., et al. (2015). Galanin mediates features of neural and behavioral stress resilience afforded by exercise. *Neuropharmacology* 89, 255–264. doi: 10.1016/j.neuropharm.2014.09.029

Serova, L. I., Laukova, M., Alaluf, L. G., Pucillo, L., and Sabban, E. L. (2014). Intranasal neuropeptide Y reverses anxiety and depressive-like behavior impaired by single prolonged stress PTSD model. *Eur. Neuropsychopharmacol.* 24, 142–147. doi: 10.1016/j.euroneuro.2013.11.007

Serova, L. I., Tillinger, A., Alaluf, L. G., Laukova, M., Keegan, K., and Sabban, E. L. (2013). Single intranasal neuropeptide Y infusion attenuates development of PTSD-like symptoms to traumatic stress in rats. *Neuroscience* 236, 298–312. doi: 10.1016/j.neuroscience.2013.01.040

Shin, S., Kwon, O., Kang, J. I., Kwon, S., Oh, S., Choi, J., et al. (2015). mGluR5 in the nucleus accumbens is critical for promoting resilience to chronic stress. *Nat. Neurosci.* 18, 1017–1024. doi: 10.1038/nn.4028

Skibicka, K. P., Shirazi, R. H., Rabasa-Papio, C., Alvarez-Crespo, M., Neuber, C., Vogel, H., et al. (2013). Divergent circuitry underlying food reward and intake effects of ghrelin: dopaminergic VTA-accumbens projection mediates ghrelin's effect on food reward but not food intake. *Neuropharmacology* 73, 274–283. doi: 10.1016/j.neuropharm.2013.06.004

Smith, P. A. (2015). The tantalizing links between gut microbes and the brain. *Nature* 526, 312–314. doi: 10.1038/526312a

Snow-Turek, A. L., Norris, M. P., and Tan, G. (1996). Active and passive coping strategies in chronic pain patients. *Pain* 64, 455–462. doi: 10.1016/0304-3959(95)00190-5

Stansfeld, S. A., Fuhrer, R., Head, J., Ferrie, J., and Shipley, M. (1997). Work and psychiatric disorder in the Whitehall II Study. *J. Psychosom. Res.* 43, 73–81. doi: 10.1016/s0022-3999(97)00001-9

Staub, E., and Vollhardt, J. (2008). Altruism born of suffering: the roots of caring and helping after victimization and other trauma. *Am. J. Orthopsychiatry* 78, 267–280. doi: 10.1037/a0014223

Steimer, T., and Driscoll, P. (2005). Inter-individual vs. line/strain differences in psychogenetically selected Roman High-(RHA) and Low-(RLA) avoidance rats: neuroendocrine and behavioural aspects. *Neurosci. Biobehav. Rev.* 29, 99–112. doi: 10.1016/j.neubiorev.2004.07.002

Suo, L., Zhao, L., Si, J., Liu, J., Zhu, W., Chai, B., et al. (2013). Predictable chronic mild stress in adolescence increases resilience in adulthood. *Neuropsychopharmacology* 38, 1387–1400. doi: 10.1038/npp.2013.67

Troy, A. S., Wilhelm, F. H., Shallcross, A. J., and Mauss, I. B. (2010). Seeing the silver lining: cognitive reappraisal ability moderates the relationship between stress and depressive symptoms. *Emotion* 10, 783–795. doi: 10.1037/a0020262

Tunariu, A. D., Tribe, R., Frings, D., and Albery, I. P. (2017). The iNEAR programme: an existential positive psychology intervention for resilience and emotional wellbeing. *Int. Rev. Psychiatry* 29, 362–372. doi: 10.1080/09540261.2017.1343531

Van Niel, C., Pachter, L. M., Wade, R. Jr., Felitti, V. J., and Stein, M. T. (2014). Adverse events in children: predictors of adult physical and mental conditions. *J. Dev. Behav. Pediatr.* 35, 549–551. doi: 10.1097/DBP.0000000000000102

Wang, M., Perova, Z., Arenkiel, B. R., and Li, B. (2014). Synaptic modifications in the medial prefrontal cortex in susceptibility and resilience to stress. *J. Neurosci.* 34, 7485–7492. doi: 10.1523/JNEUROSCI.5294-13.2014

Warden, M. R., Selimbeyoglu, A., Mirzabekov, J. J., Lo, M., Thompson, K. R., Kim, S. Y., et al. (2012). A prefrontal cortex-brainstem neuronal projection that controls response to behavioural challenge. *Nature* 492, 428–432. doi: 10.1038/nature11617

Warner, L. M., Schwarzer, R., Schüz, B., Wurm, S., and Tesch-Römer, C. (2012). Health-specific optimism mediates between objective and perceived physical functioning in older adults. *J. Behav. Med.* 35, 400–406. doi: 10.1007/s10865-011-9368-y

Weinshenker, D., and Holmes, P. V. (2016). Regulation of neurological and neuropsychiatric phenotypes by locus coeruleus-derived galanin. *Brain Res.* 1641, 320–337. doi: 10.1016/j.brainres.2015.11.025

Wilkinson, M. B., Xiao, G., Kumar, A., LaPlant, Q., Renthal, W., Sikder, D., et al. (2009). Imipramine treatment and resiliency exhibit similar chromatin regulation in the mouse nucleus accumbens in depression models. *J. Neurosci.* 29, 7820–7832. doi: 10.1523/JNEUROSCI.0932-09.2009

Wolmer, L., Hamiel, D., Barchas, J. D., Slone, M., and Laor, N. (2011). Teacher-delivered resilience-focused intervention in schools with traumatized children following the second Lebanon war. *J. Trauma. Stress* 24, 309–316. doi: 10.1002/jts.20638

Yang, Y., Cui, Y., Sang, K., Dong, Y., Ni, Z., Ma, S., et al. (2018). Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. *Nature* 554, 317–322. doi: 10.1038/nature25509

Yang, C., Shirayama, Y., Zhang, J. C., Ren, Q., Yao, W., Ma, M., et al. (2015). R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. *Transl. Psychiatry* 5:e632. doi: 10.1038/tp.2015.136

Yang, Y., Wang, Z. H., Jin, S., Gao, D., Liu, N., Chen, S. P., et al. (2016). Opposite monosynaptic scaling of BLP-vCA1 inputs governs hopefulness- and helplessness-modulated spatial learning and memory. *Nat. Commun.* 7:11935. doi: 10.1038/ncomms11935

Yano, J. M., Yu, K., Donaldson, G. P., Shastri, G. G., Ann, P., Ma, L., et al. (2015). Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* 161, 264–276. doi: 10.1016/j.cell.2015.02.047

Zanos, P., Moaddel, R., Morris, P. J., Georgiou, P., Fischell, J., Elmer, G. I., et al. (2016). NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature* 533, 481–486. doi: 10.1038/nature17998

Zarate, C. A. Jr., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., et al. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch. Gen. Psychiatry* 63, 856–864. doi: 10.1001/archpsyc.63.8.856

Zhu, Z., Wang, G., Ma, K., Cui, S., and Wang, J.-H. (2017). GABAergic neurons in nucleus accumbens are correlated to resilience and vulnerability to chronic stress for major depression. *Oncotarget* 8, 35933–35945. doi: 10.18632/oncotarget.16411

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Cognitive Flexibility Predicts PTSD Symptoms: Observational and Interventional Studies

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Introduction: Post-Traumatic Stress Disorder (PTSD) is a prevalent, severe and tenacious psychopathological consequence of traumatic events. Neurobehavioral mechanisms underlying PTSD pathogenesis have been identified, and may serve as risk-resilience factors during the early aftermath of trauma exposure. Longitudinally documenting the neurobehavioral dimensions of early responses to trauma may help characterize survivors at risk and inform mechanism-based interventions. We present two independent longitudinal studies that repeatedly probed clinical symptoms and neurocognitive domains in recent trauma survivors. We hypothesized that better neurocognitive functioning shortly after trauma will be associated with less severe PTSD symptoms a year later, and that an early neurocognitive intervention will improve cognitive functioning and reduce PTSD symptoms.

Methods: Participants in both studies were adult survivors of traumatic events admitted to two general hospitals' emergency departments (EDs) in Israel. The studies used identical clinical and neurocognitive tools, which included assessment of PTSD symptoms and diagnosis, and a battery of neurocognitive tests. The first study evaluated 181 trauma-exposed individuals one-, six-, and 14 months following trauma exposure. The second study evaluated 97 trauma survivors 1 month after trauma exposure, randomly allocated to 30 days of web-based neurocognitive intervention ($n = 50$) or control tasks ($n = 47$), and re-evaluated all subjects three- and 6 months after trauma exposure.

Results: In the first study, individuals with better cognitive flexibility at 1 month post-trauma showed significantly less severe PTSD symptoms after 13 months *($p = 0.002$).* In the second study, the neurocognitive training group showed more improvement in cognitive flexibility post-intervention *($p = 0.019$),* and lower PTSD symptoms 6 months post-trauma *($p = 0.017$)*, compared with controls. Intervention-induced improvement in cognitive flexibility positively correlated with clinical improvement *($p = 0.002$).*

Discussion: Cognitive flexibility, shortly after trauma exposure, emerged as a significant predictor of PTSD symptom severity. It was also ameliorated by a neurocognitive intervention and associated with a better treatment outcome. These findings support further research into the implementation of mechanism-driven neurocognitive preventive interventions for PTSD.

Keywords: Post-Traumatic Stress Disorder (PTSD), neurocognitive functioning, cognitive flexibility, resilience factors, risk factors, cognitive training intervention

INTRODUCTION

Post-Traumatic Stress Disorder (PTSD) is a severe mental disorder with profound public health impact due to its high prevalence, persistence, and associated functional impairment (1, 2). PTSD symptoms are commonly observed shortly after trauma exposure and their initial severity has been associated with a high risk of non-recovery (3–7). Longitudinal studies of stress exposure have documented significant heterogeneity in symptoms trajectories (i.e., PTSD symptoms in humans; freezing as avoidance in animals), suggesting a heterogeneity of underlying neurobiological mechanisms (3, 8–11).

Neurocognitive deficits linked with the emergence of PTSD (12, 13) concern working memory, information processing speed and verbal learning, and short-term and declarative memory (14, 15), attention, and executive functioning (16, 17). PTSD has been repeatedly associated with difficulties in response inhibition, attentional switching and flexibility (18–22), and these features were hypothetically linked with PTSD patients' difficulties to disengage attention from a salient stimuli (23). Neuroimaging studies of PTSD have, similarly, documented altered prefrontal network activity in tasks requiring inhibition and attentional switching [e.g., (24, 25)]. These neurocognitive targets may serve as risk-resilience factors for the development and/or maintenance of post traumatic symptoms. Evidence has also shown that better neurocognitive functions were associated with to lower rates of PTSD diagnosis (26).

Previous work suggests that the central nervous system's activity may be altered by experience at multiple levels of neural organization (27–29). These and other findings suggest that early aftermath of traumatic events might be a stage of increased brain plasticity and therefore a period of accelerated learning (30, 31). Furthermore, evidence suggests that targeted, intensive, repetitive and adaptive task engagement can powerfully shape neural organization and function (32), and as such it provides an exceptional opportunity to investigate neurobehavioral modifications and their implications.

To date, preventive interventions for PTSD have neither considered nor specifically targeted survivors' neurocognitive capabilities and did not evaluate PTSD clinical and neurocognitive dimensions over time. Longitudinally exploring the latter may enhance our understanding of disease progression and prevention, and provide important information on survivors' susceptibility to develop PTSD. Observing the temporal sequence of clinical and neurocognitive changes, shortly after trauma exposure, may, additionally lead to devising new and better-targeted preventive interventions.

This work longitudinally examines the association between clinical symptoms and neurocognitive functions in recent trauma survivors, and the contribution of specific neurocognitive functions to PTSD pathogenesis. In a first study we explored the relationship between neurocognitive functions recorded 1 month after trauma exposure and PTSD symptoms at different time intervals from trauma exposure ("Study 1"). In a second study, we evaluated the association between neurocognitive functions at 1 month and the effect of an early neurocognitive interventions ("Study 2"). Our main hypothesis was that better neurocognitive functioning shortly after trauma will be associated with less severe PTSD symptoms 13 months later ("Study 1"). Our auxiliary hypothesis was that an early neurocognitive intervention will improve cognitive functioning and reduce PTSD symptoms ("Study 2").

METHODS

Participants

Participants were adult survivors of traumatic events, admitted to two general hospital in Israel for treatment of traumatic injury. In both studies participants were considered for a telephone screening interview if they met the following inclusion criteria: (i) Age 18–65 years (ii) Able to read

and comprehend Hebrew or English (language used in neurocognitive tasks) (iii) Arrived in the ER because of one of the following: car accidents, terrorist attacks, work accidents, home accidents, burns, physical assault, large-scale disaster. To reduce confounds related to concurrent disorders, the studies' exclusion criteria included: (i) survivors with open head injury or in a coma upon ER arrival; (ii) survivors with known medical condition that interfere with their ability to give informed consent, cooperate with screening and/or treatment; (iii) survivors with chronic PTSD from previous events, and those with current or lifetime psychotic illness or current substance abuse, suicidal risk or mental disorders or conditions that constitute treatment priority; (iv) individuals using psychotropic medication or recreational drugs in the week that precedes the assessment. In addition, survivors currently treated with benzodiazepines or those receiving cognitive behavioral therapy for their posttraumatic symptoms were excluded.

Clinical Instruments

In both Study 1 & Study 2, we used the following measurements:

The Clinician-Administered PTSD Scale (CAPS)

Structured interview for assessing posttraumatic stress disorder (PTSD) diagnostic status and symptom severity. We used a version of the CAPS that combines DSM-IV and DSM-5 criteria in order to keep continuity. The CAPS contains explicit, behaviorally anchored probes for each PTSD symptom criteria. The CAPS symptom severity scores were obtained by summing all individual items. The Hebrew version used in this work was cross-translated and compared with the original English instruments. Internal consistency of CAPS-5 was 0.88 and test-retest reliability was 0.78 (33).

The Structured Clinical Interview for DSM-IV (SCID)

Structured clinical interview evaluating current and lifetime (pre-event) Axis I mental disorders (34).

Neurocognitive Functions Measurement

In both Study 1 & Study 2, we used the following measurements:

WebNeuro

An Internet-based, comprehensive battery of neurocognitive functioning, previously validated against traditional neurocognitive tests (35). To reduce the effect of learning between testing sessions, we used two WebNeuro versions that included the use of different stimuli and trial sequences. WebNeuro accommodates both Hebrew and English languages. To standardize testing conditions, all tests were taken in our laboratory in the receiving hospital rather than participants' homes. Performance in the different tasks were calculated using an automated software program, which derived standardized Z-scores for each participant at each of the following 11 neurocognitive composite domains: motor coordination, processing speed, sustained attention, controlled attention, cognitive flexibility, response inhibition, working memory, recall memory, executive function, emotion identification, and emotional bias.

The WebNeuro battery included the following main tasks:

(1) **Digit Span (working memory):** Participants indicated whether the current letter on the screen matches a letter presented N-steps back. Successful performance on this task required constant updating of memory storage and focus.

(2) **Memory Recognition Task (recall memory**): On each trial, a list of 20 words was presented. In part 1, participants were presented with 20 sets of three response words and were instructed to select the one word that was previously presented. In part 2, which was completed 10 min later, participants were again presented with 20 sets of three response words, from which they had to select one word from each set that they believed that was previously presented. Performance is measured on total immediate recall and delayed recall response.

(3) **Stroop Task (response inhibition)** (36): Participants were presented with color names printed in either matched or mismatched colors (e.g., the word RED printed red or in green ink). Their task was to indicate the ink color, while disregarding the meaning of the word. Successful performance on this task required participants to inhibit the reaction to the word and prioritize the reaction to the ink color.

(4) **Maze Task (executive function):** Participants were instructed to memorize a complicated sequence of flashing dots, and then to re-enact it three times in a row without errors. Successful performance on this task required storing information in working memory, resisting impulsive moves when re-enacting the sequence, and responding as fast as possible.

(5) **Emotional Identification Task:** In this task, a series of faces was presented on the screen, each displaying one of six emotional expressions (fear, anger, disgust, sadness, happiness, or neutral). On each trial, participants select as quickly as possible the emotion label that best matches each face from six response buttons displayed beneath the face ("fear," "anger," "disgust," "sad," "happy," "neutral"). Accuracy and RT for each emotion were measured.

(6) **Emotional Bias Task:** In this task, sets of two faces were presented. In each set, one face is repeated from the previous Emotion Identification task, and one face is new. Participants use the mouse to select which of the two faces they remember from the previous task. Response time for each emotion is measured.

(7) **Go/No-Go Task (response inhibition):** This classic task required maintaining balance between automatic responding (impulsivity) and response suppression (inhibition) to a stimulus presented.

(8) **Motor tapping Task (motor coordination):** Participants were required to tap a circle on the touch-screen with their index finger, as fast as possible for 60 s. The dependent variable was total number of taps with the dominant hand and pauses between taps.

(9) **Switching of Attention Task (cognitive flexibility):** This task is a computerized adaption of the manual Trail Making test (37). Each participant was presented with a mixture of

13 numbers and 12 letters, and was instructed to switch back and forth between numbers and letters in an ascending pattern (e.g., 1-A-2-B, etc.). Successful performance on this task required continuous shifting between task sets, while keeping in mind the previously connected items. Response accuracy, completion time and average connection time were measured.

Procedure

In both studies, a member of the research team identified potentially trauma-exposed patients using the ER medical records. Within 7–14 days after trauma exposure, and after being discharged from the hospital, the identified individuals were contacted by telephone for an initial screening. The telephone screening was conducted by MA level clinicians that were trained in the specific assessment tools [see (38) for detailed description]. After verbal consent, the PTSD Checklist (PCL) was administered to assess risk of PTSD development. Those who met PTSD symptom criteria (except the 1 month duration) and did not meet any of the exclusion criteria, received verbal information about the research and were invited to a clinical assessment session within 1 month post-trauma. The clinical assessment included 2-h structured clinical interviews (CAPS, SCID) and 1-h neurocognitive evaluation (WebNeuro). Participants received financial remuneration at the end of the assessment, according to the ethics committee regulations and approval. In both studies, two follow-up clinical and neurocognitive assessments were conducted; Study 1 assessments were conducted at 1, 6, and 14 months after trauma (TP1, TP2 and TP3 accordingly), whereas Study 2 assessments were conducted at 1, 3, and 6 months after trauma (T1, T2, and T3 accordingly).

Study 1 did not include any intervention or treatment, while Study 2 included a neurocognitive intervention of a daily 30 min sessions for 30 days. The intervention details in Study 2 are fully described in Fine et al. (38) and are only summarized here. Participants were blindly allocated to either a neurobehavioral training group or one of two control groups. The training group included classic paradigm tasks that specifically targeted executive function (e.g., working memory, task switching, resisting interference) and emotional reactivity and regulation. The first control group was engaged in web-based tasks with similar visual appeal that do not address specific neurobehavioral domains such as card games, Tetris, obstacle course, classic computer games (e.g., Pac-Man), visual search tasks, and different kinds of matching tasks. These tasks mainly train dexterity (such as clicking quickly with the computer mouse), however we can't fully ensure that they did not improve any neurocognitive domain (e.g., executive functions). The second control group consisted of visually appealing reading tasks whose contents were limited to emotionally neutral topics (e.g., nature, geography). Intervention included a combined regimen of "Lumosity" neurocognitive training games and "MyBrainSolutions" emotional bias training. On each training day, the active group were given eight tasks, chosen at a random sequence within each category (categories were: focus/inhibition, working memory, task shifting, emotion recognition/resisting distraction, positivity bias) and in the control groups they chose eight out of ten control tasks. All tasks were designed to be dynamic, adaptive, and continually engaging, such that they increase in difficulty level as performance improves

In Study 1, 2,944 trauma patients underwent a telephone screening interview. Of those, $n = 525$ (18%) had acute stress disorder (ASD) symptoms, and 350 (12%) were invited for clinical assessments. A total of 181 (6%) individuals were enrolled to the study. At the point of writing this work, 97 participants completed the second, 6 months' assessment (TP2), and 61 completed the third, 14 months' assessment (TP3).

In Study 2, 3,387 trauma patients underwent a telephone screening interview. Of those, $n = 643$ (19%) had ASD symptoms, and 347 (10%) were invited for clinical assessments. A total of 111 (3%) individuals were enrolled to the study, out of which $n = 14$ were assigned as a follow-up group without intervention, for technical reasons. The 97 remained participants were randomized into three groups: (1) Neurocognitive training ($n = 50$); (2) Game tasks ($n = 30$); (3) Reading tasks ($n = 17$). 86 participants completed the second, 3 months' assessment (T2), and 78 completed the third, 6 months' assessment (T3).

Data Analysis

IBM SPSS Statistics for windows, Version 23.0, was used for the statistical procedures. For each separate analysis, participants with extreme scores greater than 2.5 SD from the mean (in absolute values) in the relevant variables were defined as outliers, and hence were excluded from the analysis. Pearson correlations coefficients and their significance were computed between neurocognitive Z-scores (main predictors) and CAPS total scores (main outcome measure). Independent *t*-tests compared between-groups effects, for examining changes in both cognitive flexibility and PTSD symptom severity post-intervention. Effect sizes were reported using Cohen's *d* for the conducted *t*-tests. All statistical tests used α of 0.05 with one-sided a-priori hypothesis. Bonferroni correction was used when necessary to counteract the problem of multiple comparisons. For Study 2, in each group (treatment or control), we excluded participants which completed less than 60% of the practices (i.e., dropouts), under the assumption that neurocognitive modification requires repeated and extensive training "dose."

RESULTS

Demographic Characteristics

Study 1 included 181 participants at TP1 (Age = 34.59±11.80, 97 Females), 97 at TP2 (Age = 35.38 ± 12.20) and 61 at TP3 (Age = 35.46 ± 12.67, 31 Females). Study 2 included 97 participants at T1 (Age = 36.42±11.41, 53 Females), 86 at T2 (Age = 37.38 ± 12.49, 48 Females) and 78 at T3 (Age = 38.38±12.79, 44 Females). In each one of the studies, no significant differences in age or gender were found between the three time points ($p > 0.05$ for all).

In Study 2, the active group consisted of 50 participants (Age = 35.08 ± 10.13, 26 Females), and the control group (both games and reading) consisted of 47 participants (Age = 37.85 ± 12.58, 27 Females). No significant differences were found

between the two groups in age [$t_{(95)} = -1.198$, $p = 0.234$], gender [$\chi^2_{(1)} = 0.290$, $p = 0.590$], or initial symptom severity at T1 (CAPS-5: $p = 0.976$; CAPS-4: $p = 0.919$) and T2 (CAPS-5: $p = 0.545$; CAPS-4: $p = 0.868$). To combine the two control arms (reading vs. games) we tested that no differences were present between them in age ($p = 0.991$), gender ($p = 0.905$) and initial symptom severity (CAPS-5: $p = 0.374$; CAPS-4: $p = 0.826$), hence conjoined to one control arm. No significant differences were found between the 52 participants who completed at least 60% of the practices (i.e., completers) and the 45 participants who did not (i.e., dropouts), on age ($p = 0.818$), gender ($p = 0.142$) or initial symptom severity (CAPS-5: $p = 0.486$; CAPS-4: $p = 0.250$).

Early Cognitive Flexibility Predicts Subsequent PTSD Symptoms

To test our main hypothesis that better general neurocognitive functions at 1 month after trauma will predict less severe PTSD symptoms 14 months post trauma exposure (Study 1), Pearson correlations were calculated between all 11 neurocognitive domains Z-scores at TP1 and PTSD symptom severity (CAPS-4 and CAPS-5 total scores) at TP3 (see **Table 1**).

To test our main hypothesis that better general neurocognitive functions at 1 month after trauma will predict less severe PTSD symptoms 14 months post trauma exposure (Study 1), pearson correlations were calculated between all TP1 neurocognitive domains and TP3 PTSD symptom severity (CAPS-4/5 total scores). After bonferroni correction, results revealed a single significant correlation in cognitive flexibility domain (see **Table 1**), such that higher cognitive flexibility was associated with lower future symptoms (see **Figure 1**). Controlling for participants' age, gender, marital status, type of trauma and initial symptom severity, this correlation remained statistically significant (CAPS-5: $r = -0.292$, $p = 0.036$; CAPS-4: $r = -0.274$, $p = 0.046$). The association between flexibility and PTSD symptoms at earlier time-points was not significant among 126 TP1 participants (CAPS-5: $r = -0.061$, $p = 0.248$; CAPS-4: $r = -0.051$, $p = 0.284$), and marginally significant among 82 TP2 participants (CAPS-5: $r = -0.141$, $p = 0.098$; CAPS-4: $r = -0.177$, $p = 0.056$).

In study 2, among the follow-up group, pearson correlations were calculated between T1 cognitive flexibility and PTSD symptom severity (CAPS-5 total scores) at all time-points. Results revealed non-significant correlations at T1 ($n = 14$, $r = -0.013$, $p = 0.482$) and T2 ($n = 10$, $r = 0.049$, $p = 0.447$), but a significant negative correlation at T3 ($n = 10$, $r = -0.558$, $p = 0.047$).

TABLE 1 | Pearson correlations between Study 1 participants' neurocognitive domains Z-scores at 1 month after trauma (TP1) and PTSD symptom severity at 14 months after trauma (TP3).

TP1 Neurocognitive Domains Z-Scores	Number of Participants (*n*)	Correlation with CAPS-4 Total Scores (*r*)	Correlation with CAPS-5 Total Scores (*r*)
Motor Coordination	44	−0.196	−0.221
Controlled Attention	54	−0.067	−0.139
Sustained Attention	53	−0.217	−0.269*
Emotional Bias	54	−0.062	−0.136
Cognitive Flexibility	54	−0.389**	−0.394**
Response Inhibition	54	0.021	−0.027
Identifying Emotions	54	−0.085	−0.115
Processing Speed	52	−0.120	−0.215
Recall Memory	54	−0.175	−0.185
Working Memory	54	−0.210	−0.243*
Executive Function	54	−0.094	−0.079

*$p < 0.05$ one-sided; **$p < 0.004$ one-sided.

Early Treatment Improves Cognitive Flexibility and Subsequent PTSD Symptoms

To test the first part of our auxiliary hypothesis, that an early neurocognitive intervention will improve cognitive functioning and reduce PTSD symptoms (Study 2), the mean change in cognitive flexibility after treatment (T2-T1) was compared between the active ($n = 26$) and control group ($n = 27$). In line with our hypothesis, flexibility change was significantly different between groups [$t_{(51)} = 2.118$, $p = 0.0195$], indicating more improvement among the active (M = 0.4310, $SD = 0.5737$) compared to control group (M = 0.1028, $SD = 0.5546$) (see **Figure 2**). Cohen's effect size value (d = 0.58) represented a moderate to high practical significance.

To test the second part our auxiliary hypothesis, that an early neurocognitive intervention will reduce PTSD symptoms, the mean change in PTSD symptom severity (CAPS-5, T3-T2) was compared between the active ($n = 23$) and control group ($n = 26$). In line with our hypothesis, symptom change was significantly different between groups *($t(47) = -2.181$, $p = 0.0171$),* indicating more improvement among the active (M = −5.0435, $SD = 6.3923$) compared to control group (M = −0.2692, $SD = 8.600$) (see **Figure 3**). Cohen's effect size value (d = 0.63) represented a moderate to high practical significance.

Finally, the association between change in cognitive flexibility (T2-T1) and subsequent change in PTSD symptom severity (T3-T2) was tested among individuals in both active and control groups ($n = 49$). Results revealed a significant negative correlation ($r = -0.401$, $p = 0.002$), such that individuals who showed greater improvement in cognitive flexibility after treatment (T2-T1) also presented subsequent greater clinical improvement (T3-T2) (see **Figure 4**).

DISCUSSION

The current research established a link between cognitive flexibility and PTSD symptom severity among a population of recent trauma survivors, in two independent samples. Consistent with our main hypothesis, we demonstrated that better cognitive flexibility 1 month post-trauma predicted less severe PTSD symptoms at 6 and 14 months post-trauma. It appears that high

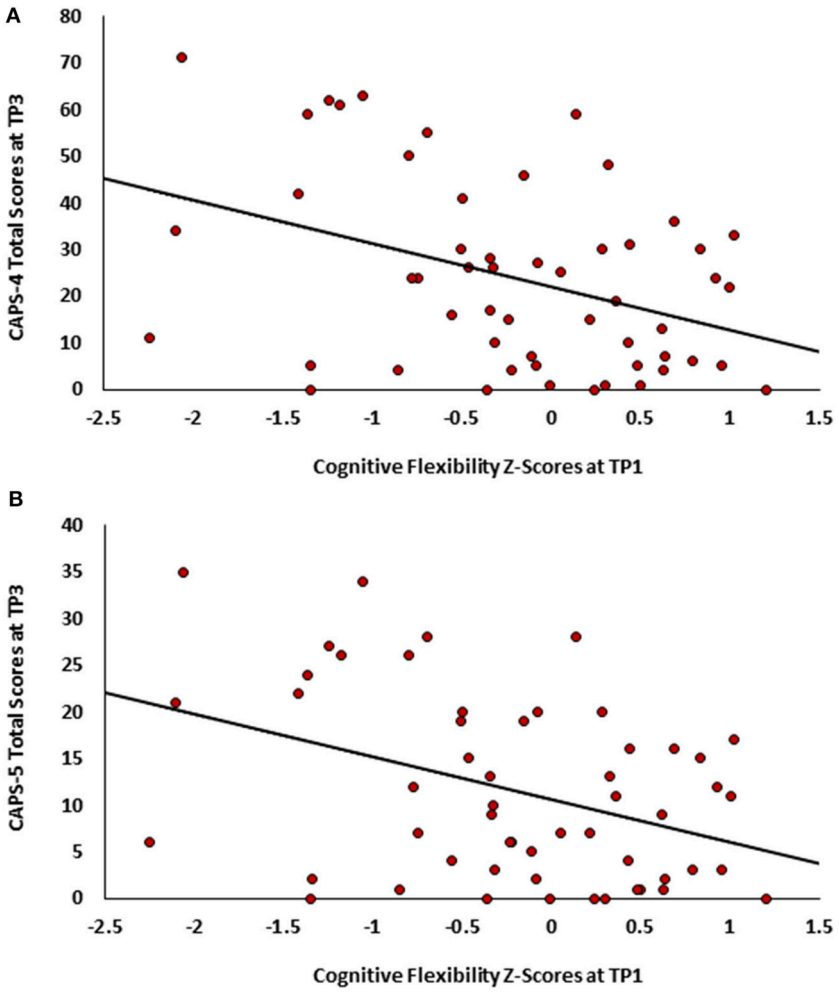

FIGURE 1 | Scatter plots depicting PTSD symptoms severity at TP3 as a function of cognitive flexibility at TPI. **(A)**- CAPS-4 total scores. **(B)** CAPS-5 total scores.

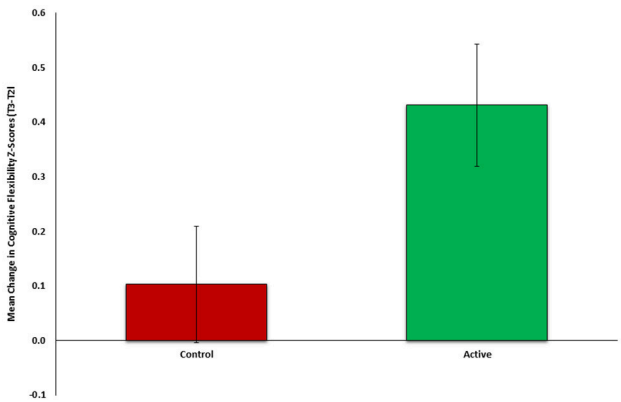

FIGURE 2 | Mean change in cognitive flexibility after intervention (T2-TI) between active ($n = 26$, green) and control ($n = 27$, red) groups of Study 2.

cognitive flexibility serves as an early resilience factor for PTSD symptom development, whereas low flexibility appears to be a risk factor. This linkage is in line with previous literature linking poor general neurocognitive functions, specifically cognitive flexibility, with increased PTSD symptoms (13, 19). Notably, prior research mostly used single samples and reported small effect sizes (39), whereas our two-independent samples design consisted of large populations of acute PTSD individuals and found medium to large effect sizes.

Consistent with our auxiliary hypothesis, early neurocognitive intervention both improved cognitive functioning and reduced PTSD symptoms. Furthermore, a significant relationship was found between change in early cognitive flexibility and change in subsequent PTSD symptom severity. That is, individuals who exhibit larger improvement in cognitive flexibility measured immediately after treatment, were more likely to show greater clinical improvement later on, and vice versa. These findings potentially suggest that cognitive flexibility serves as a modifiable target preceding and underlying PTSD symptom change. Uncovering such neurocognitive targets may lead to development of mechanism-based interventions specific for PTSD. Although there has been accumulated knowledge

regarding cognitive deficits in PTSD, few early neurocognitive based-intervention studies have been conducted (13, 38). However, neurocognitive remediation targeted specifically at aspects of prefrontal function have garnered increasing attention among other psychopathologies, such as depression (40) and schizophrenia (41), reinforcing the vast potential of such interventions. Taken together, our findings draw upon the potential of neuroplasticity-based early interventions which could promote recovery from post-traumatic stress symptoms.

Our findings highlight the significance of cognitive flexibility compared to other neurocognitive functions. The concept of cognitive flexibility is complex, involving several neurocognitive processes including attention, task switching, executive functions and inhibition. In general, it is defined as the readiness with which a person's concept system changes selectively in response to appropriate environmental stimuli. The greater an individual's flexibility, the greater is the likelihood that he will expand and change his categorization and tendency to gain information (19, 39). Furthermore, high cognitive flexibility enables the individual to better differentiate between threat-related and neutral situations, hence to be more flexible and adaptive to changes in the environment. Finally, flexibility assists in the extinction of fear-motivated learning, a core-element in PTSD recovery (39). In general, neuropsychological profiles remain inherently challenging due to the strong dependency between different neurocognitive functions (42). Thus, a deficit or improvement in one neurocognitive structure might be related to several other structures. Nonetheless, it is crucial to try and differentiate these inter-related constructs to target specific mechanisms of the disorder.

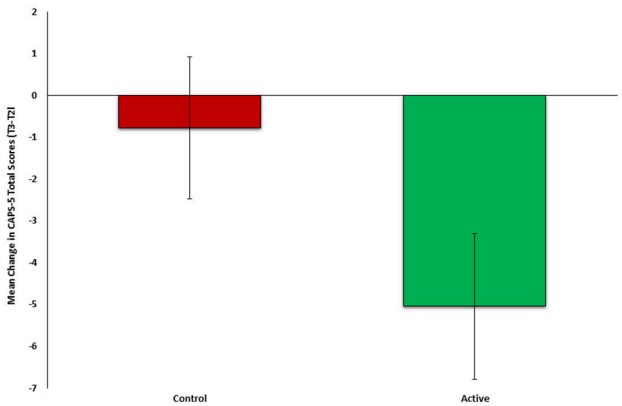

FIGURE 3 | Mean change in PTSD symptom severity (CAPS-5, T3-T2) between active ($n = 23$, green) and control ($n = 26$, red) groups of Study 2.

Our study implements an integrative and unique prospective approach to the relationship between acute PTSD symptoms and neuropsychological processes. This study was carried out in two large independent samples, at different recruitment sites, administered at different time periods, with different research teams. Nevertheless, we demonstrated similar results in both samples that did not receive treatment, increasing the validity, reliability and generalizability our findings. This study emphasizes the importance of cognitive flexibility both in spontaneous recovery and in targeted neurocognitive interventions. For PTSD.

Although our findings are promising, this work has several limitations. First, only one task with several subscales was used to assess cognitive flexibility. Additional measures and methods, as well as in-person and more thorough assessment, could provide additional insights into the complexity of cognitive flexibility, and neuropsychological functioning in general. Second, the majority of our participants suffered from a single trauma, mostly motor vehicle accidents (MVAs). Future work may explore the

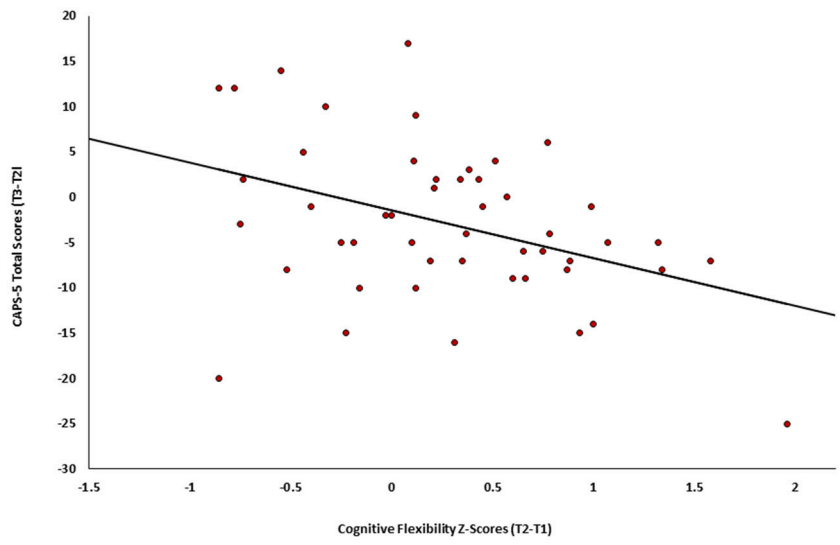

FIGURE 4 | Change in PTSD symptoms severity (CAPS-5, T3-T2) as a function of the change in cognitive flexibility (T2-TI) among individuals in both active and control groups of Study 2 ($n = 49$).

relationship between cognitive flexibility and PTSD symptom severity among varying traumatic events, such as terror attacks, interpersonal violence, and continuous traumatic experiences. Nevertheless, our results suggest that this intervention may be effective in treating MVA trauma survivors. Third, it is important to note that we cannot determine whether low cognitive flexibility serves as a pre-existing vulnerability factor, a result of the trauma, or an interaction between these two. Future research should add measurement of neurocognitive functions before trauma, in order to determine which option is the most plausible. Finally, this study did not assess early life trauma, thus limiting our ability to differentiate any earlier impact of trauma on neurocognitive impairment. However, the study excluded participants with chronic PTSD and other major affective disorders thus reducing effect of previous neurocognitive dysfunction due to psychopathology.

In summary, our findings shed light on the underlying neurocognitive mechanisms of PTSD symptoms, and demonstrate the effectiveness of an early neurocognitive intervention in relieving PTSD symptoms. Such findings may guide early mechanism-driven, stage-specific interventions for PTSD, thus improving life quality of trauma survivors and increasing cost-effectiveness of personalized interventions.

AVAILABILITY OF DATA AND MATERIALS

Data currently compiled and QA'd for analyses. Will be available upon demand once brought to maturity by contacting the study PI.

ETHICS STATEMENT

The research study meets all ethical regulations as required by ethics committee in Shaare-Zedek Medical Center (Reference number 0018/14) and in Tel-Aviv Sourasky Medical Center (Reference number 0207/14). All subjects gave written informed consent in accordance with the Declaration of Helsinki. Study 2 ClinicalTrials.gov registration number: NCT02085512.

AUTHOR CONTRIBUTIONS

NF, ZB, and NK carried out the procedural aspects of the study. NF, ZB and NK carried out the research assistants training, guidance and monitoring, management of participants and QA of data. NG, MH, and MA have conducted clinical and neurocognitive assessments. HS assisted in establishing and maintaining the connection with the ER at TLV site. OM and PH managed the hospital interfaces specifically with the ER of the medical centers. NF and ZB drafted the manuscript and finalized it. GF contributed to the study design and statistical analysis. RA, TH, AS, AE, and IL initiated and supervised all procedures at TLV site. AS designed, obtained funding and oversaw the implementation of study 2. AS TH and IL designed, obtained funding and oversaw the implementation of Study 1. AS and AE initiated and supervised all procedures at SZ site. All authors have read and approved the final manuscript.

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REFERENCES

1. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* (1995) 52:1048–60. doi: 10.1128/AAC.03728-14
2. Kessler RC. Posttraumatic stress disorder: the burden to the individual and to society. *J Clin Psychiatry* (2000) 61(Suppl. 5):4–12; discussion 13–4. doi: 10.1002/(ISSN)1097-4679
3. Galatzer-Levy IR, Ankri Y, Freedman S, Israeli-Shalev Y, Roitman P, Gilad M, et al. Early PTSD symptom trajectories: persistence, recovery, and response to treatment: results from the jerusalem trauma outreach and prevention study (J-TOPS). *PLoS ONE* (2013) 8:e70084. doi: 10.1371/journal.pone.0070084
4. Koren D, Arnon I, Klein E. Long term course of chronic posttraumatic stress disorder in traffic accident victims: a three-year prospective follow-up study. *Behav Res Ther.* (2001) 39:1449–58. doi: 10.1016/S0005-7967(01)00025-0
5. Perkonigg A, Pfister H, Stein MB, Höfler M, Lieb R, Maercker A, et al. longitudinal course of posttraumatic stress disorder and posttraumatic stress disorder symptoms in a community sample of adolescents and young adults. *Am J Psychiatry* (2005) 162:1320–7. doi: 10.1176/appi.ajp.162.7.1320
6. Galatzer-Levy IR, Karstoft KI, Statnikov A, Shalev AY. Quantitative forecasting of PTSD from early trauma responses: a machine learning application. *J Psychiatr Res.* (2014) 59:68–76. doi: 10.1016/j.jpsychires.2014.08.017
7. Stein DJ, Karam EG, Shahly V, Hill ED, King A, Petukhova M, et al. Post-traumatic stress disorder associated with life-threatening motor vehicle collisions in the WHO World Mental Health Surveys. *BMC Psychiatry* (2016) 16:257. doi: 10.1186/s12888-016-0957-8
8. Galatzer-Levy IR, Bonanno GA, Bush DEA, LeDoux JE. Heterogeneity in threat extinction learning: substantive and methodological considerations for identifying individual difference in response to stress. *Front Behav Neurosci.* (2013) 7:55. doi: 10.3389/fnbeh.2013.00055
9. Ursano RJ, Fullerton CS, Epstein RS, Crowley B, Kao TC, Vance K, et al. Acute and chronic posttraumatic stress disorder in motor vehicle accident victims. *Am J Psychiatry* (1999) 156:589–95. doi: 10.1176/ajp.156.4.589
10. Shalev AY, Ankri Y, Israeli-Shalev Y, Peleg T, Adessky R, Freedman S. Prevention of posttraumatic stress disorder by early treatment. *Arch Gen Psychiatry* (2012) 69:166–76. doi: 10.1001/archgenpsychiatry.2011.127
11. Shalev AY, Ankri YLE, Peleg T, Israeli-Shalev Y, Freedman S. Barriers to receiving early care for PTSD: results from the jerusalem trauma outreach and prevention study. *Psychiatric Serv.* (2011) 62:765–73. doi: 10.1176/ps.62.7.pss6207_0765
12. Shalev A, Liberzon I, Marmar C. Post-traumatic stress disorder. *New Engl J Med.* (2017) 376:2459–69. doi: 10.1056/NEJMra1612499

13. Scott JC, Matt GE, Wrocklage KM, Crnich C, Jordan J, Southwick SM, et al. A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychol Bull.* (2015) 141:105–40. doi: 10.1037/a0038039
14. Johnsen GE, Asbjørnsen AE. Consistent impaired verbal memory in PTSD: a meta-analysis. *J Affect Disord.* (2008) 111:74–82. doi: 10.1016/j.jad.2008.02.007
15. Samuelson KW. Post-traumatic stress disorder and declarative memory functioning: A review. *Dialog Clin Neurosci.* (2011) 13:346–51. doi: 10.1016/j.tics.2006.04.007
16. Aupperle RL, Melrose AJ, Paulus MP. Executive function and PTSD: disengaging from trauma. *Neuropharmacology* (2012) 62:686–94. doi: 10.1016/J.NEUROPHARM.2011.02.008
17. Polak AR, Witteveen AB, Reitsma JB, Olff M. The role of executive function in posttraumatic stress disorder: a systematic review. *J Affect Dis.* (2012) 141:11–21. doi: 10.1016/j.jad.2012.01.001
18. Casada JH, Roache JD. Behavioral inhibition and activation in posttraumatic stress disorder. *J Nerv Mental Dis.* (2005) 193:102–9. doi: 10.1097/01.nmd.0000152809.20938.37
19. Hart RP, Bagrodia R, Rahman N, Bryant RA, Titcombe-Parekh R, Marmar CR, et al. Neuropsychological Predictors of Trauma Centrality in OIF/OEF Veterans. *Front Psychol.* (2017) 8:1120. doi: 10.3389/fpsyg.2017.01120
20. Koenen KC, Driver KL, Oscar-Berman M, Wolfe J, Folsom S, Huang MT, et al. Measures of prefrontal system dysfunction in posttraumatic stress disorder. *Brain Cogn.* (2001) 45:64–78. doi: 10.1006/BRCG.2000.1256
21. Leskin LP, White PM. Attentional networks reveal executive function deficits in posttraumatic stress disorder. *Neuropsychology* (2007) 21:275–84. doi: 10.1037/0894-4105.21.3.275
22. Vasterling JJ, Constans JI, Brailey K, Sutker PB. Attention and memory dysfunction in posttraumatic stress disorder. *Neuropsychology* (1998) 12:125–33. doi: 10.1037/0894-4105.12.1.125
23. Pineles SL, Shipherd JC, Mostoufi SM, Abramovitz SM, Yovel I. Attentional biases in PTSD: More evidence for interference. *Behav Res Ther.* (2009) 47:1050–7. doi: 10.1016/J.BRAT.2009.08.001
24. Bryant RA, Felmingham KL, Kemp AH, Barton M, Peduto AS, Rennie C, et al. Neural networks of information processing in posttraumatic stress disorder: a functional magnetic resonance imaging study. *Biol Psychiatry* (2005) 58:111–8. doi: 10.1016/j.biopsych.2005.03.021
25. Falconer E, Bryant R, Felmingham KL, Kemp AH, Gordon E, Peduto A, et al. The neural networks of inhibitory control in posttraumatic stress disorder. *J Psychiatry* Neurosci. (2008) 33:413–22.
26. Kaplan Z, Weiser M, Reichenberg A, Rabinowitz J, Caspi A, Bodner E, et al. Motivation to serve in the military influences vulnerability to future posttraumatic stress disorder. *Psychiatry Res.* (2002) 109:45–9. doi: 10.1016/S0165-1781(01)00365-1
27. Scholz J, Klein MC, Behrens TEJ, Johansen-Berg H. Training induces changes in white-matter architecture. *Nat Neurosci.* (2009) 12:1370–1. doi: 10.1038/nn.2412
28. Takeuchi H, Sekiguchi A, Taki Y, Yokoyama S, Yomogida Y, Komuro N, et al. Training of working memory impacts structural connectivity. *J Neurosci.* (2010) 30:3297–303. doi: 10.1523/JNEUROSCI.4611-09.2010
29. Voss MW, Prakash RS, Erickson KI, Boot WR, Basak C, Neider MB, et al. Effects of training strategies implemented in a complex videogame on functional connectivity of attentional networks. *NeuroImage* (2012) 59:138–48. doi: 10.1016/j.neuroimage.2011.03.052
30. Bremner JD, Elzinga B, Schmahl C, Vermetten E. Structural and functional plasticity of the human brain in posttraumatic stress disorder. *Progress Brain Res.* (2008) 167:171–86. doi: 10.1016/S0079-6123(07)67012-5
31. Mahan AL, Ressler KJ. Fear conditioning, synaptic plasticity and the amygdala: Implications for posttraumatic stress disorder. *Trends Neurosci.* (2012) 35:24–35. doi: 10.1016/j.tins.2011.06.007
32. Olesen PJ, Westerberg H, Klingberg T. Increased prefrontal and parietal activity after training of working memory. *Nat Neurosci.* (2004) 7:75–9. doi: 10.1038/nn1165
33. Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, et al. Psychological assessment the clinician-administered PTSD scale for DSM−5 (CAPS- 5): development and initial psychometric evaluation in military veterans. *Psychol Assess.* (2017) 30:383–95. doi: 10.1037/pas0000486
34. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV) for DSMIV*. New York, NY: Columbia University Press (1997).
35. Silverstein SM, Berten S, Olson P, Paul R, Williams LM, Cooper N, et al. Development and validation of a World-Wide-Web-based neurocognitive assessment battery: WebNeuro. *Behav Res Methods* (2007) 39:940–9. doi: 10.3758/BF03192989
36. Stroop JR. Stroop color word test. *J Exp Physiol.* (1935) 643–62. doi: 10.1007/978-0-387-79948-3
37. Reitan R. Validity of the trail making test as an indicator of organic brain damage. *Percept Motor Skil.* (1958) 8:271–6. doi: 10.2466/PMS.8.7.271-276
38. Fine NB, Achituv M, Etkin A, Merin O, Shalev AY. Evaluating web-based cognitive-affective remediation in recent trauma survivors: study rationale and protocol. *Eur J Psychotraumatol.* (2018) 9:1442602. doi: 10.1080/20008198.2018.1442602
39. Scott WA. Cognitive complexity and cognitive flexibility. *Sociometry* (1962) 25:405. doi: 10.2307/2785779
40. Siegle GJ, Price RB, Jones NP, Ghinassi F, Painter T, Thase ME. You gotta work at it: Pupillary indices of task focus are prognostic for response to a neurocognitive intervention for rumination in depression. *Clin Psychol Sci.* (2014) 2:455–71. doi: 10.1177/2167702614536160
41. Medalia A, Saperstein AM. Does cognitive remediation for schizophrenia improve functional outcomes? *Curr Opin Psychiatry* (2013) 26:151–7. doi: 10.1097/YCO.0b013e32835dcbd4
42. Lezak MD, Howieson DB, Loring DW, Hannay HJ, Fischer JS. *Neuropsychological Assessment*. 4th ed. New York, NY: Oxford University Press (2004).

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REVIEW
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Brain Networks Reorganization During Maturation and Healthy Aging-Emphases for Resilience

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Maturation and aging are important life periods that are linked to drastic brain reorganization processes which are essential for mental health. However, the development of generalized theories for delimiting physiological and pathological brain remodeling through life periods linked to healthy states and resilience on one side or mental dysfunction on the other remains a challenge. Furthermore, important processes of preservation and compensation of brain function occur continuously in the cerebral brain networks and drive physiological responses to life events. Here, we review research on brain reorganization processes across the lifespan, demonstrating brain circuits remodeling at the structural and functional level that support mental health and are parallelized by physiological trajectories during maturation and healthy aging. We show evidence that aberrations leading to mental disorders result from the specific alterations of cerebral networks and their pathological dynamics leading to distinct excitability patterns. We discuss how these series of large-scale responses of brain circuits can be viewed as protective or malfunctioning mechanisms for the maintenance of mental health and resilience.

Keywords: resilience, lifespan, brain networks, brain reorganization, health maintenance

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INTRODUCTION

Aging is related to alterations of cognitive functioning accompanied by structural and functional brain reorganization (1, 2). Maintained cognitive function late in life is generally achieved by the integrated communication of specific brain regions (3, 4). The functional and structural reorganization of brain circuits occur continuously during the lifespan and play an essential role for preserving brain health (5–7). Hence, abnormal cognitive function may build upon specific alterations of brain networks and their dynamic responses to life events or physiological processes during maturation or aging (8–10). An exact understanding of structural and functional longitudinal properties and a precise characterization of the tissue properties are crucial for modeling the long-term processes and to distinguish between healthy and disease-specific alterations. Hence, modeling interregional connectivity and specific reorganization of cerebral networks topology is likely to promote our understanding of underlying mechanisms of mental health and resilience to life events (11).

Functional connectivity patterns can be obtained from the temporal correlations of spontaneous neurophysiological signal fluctuations between brain regions either by electroencephalography

(EEG) or functional magnetic resonance imaging (fMRI), and then analyzed within a graph-theoretical framework (7, 12, 13). On the other hand, the structural network connectivity can be accessed by pure structural MRI measures like cortical thickness and volume or by white matter fiber tracts obtained through tractography between predefined regions of interest (6, 14, 15) as shown in **Figure 1**. These network fingerprints are predictive measures of disease-related clinical symptoms (6, 7) or therapy outcomes (16).

In this review, we present existing evidence for a profound understanding of lifespan-related reorganization processes that can be related to protective mechanisms that help our brain to cope with age-related situations and reduce the burden for brain alterations linked to mental disorders. Unraveling complementary functional and structural fingerprints should give important insight on inter-individual courses. On the basis of our recent results on the importance of the cerebral networks in disease outcome (6, 13, 16–19), we discuss the impact of the structural gray matter tissue integrity and reorganization of normal appearing white matter and evolving functional adaptations for clinical phenotypes. Non-invasive structural and fMRI characterization of the neuronal circuits will be discussed from a longitudinal perspective.

We hypothesize that (i) cerebral networks in resilient subjects with preserved mental health despite traumatic events are characterized by a reorganization of the gray and white matter compartments with a strengthening of distinct regional connectivity patterns and preserved structural integrity in the key anatomical regions (prefrontal cortex, hippocampus and corpus callosum); (ii) these brain circuits remodeling processes are partially mirrored in age-related reorganization during maturation or healthy aging; (iii) neurocognitive and clinical impairment of mental health is associated with exhaustion of network compensation, which manifests in divergent lifespan patterns of network reorganization or a breakdown of functional responses; (iv) structural and functional lateralization patterns together with inter-hemispheric connections and the connectivity fingerprints in the above mentioned networks together with their functional interactions have a large impact on network compensation and thus inter-individual mental status. The overall aim of this work is to identify distinct network connectivity and integrity patterns reflecting compensation processes for global network functioning. We focus first on maturation processes and healthy aging and drive parallels to mechanisms of resilience behavior.

AGE-RELATED BRAIN REMODELING AND EXCITABILITY DYNAMICS DURING MATURATION

Accurate synaptic transmission is a fundamental requirement for normal brain function (20); signaling alterations at the excitatory synapse leading to cortical hyperexcitability have been related to psychiatric disorders such as schizophrenia (21–24). However, to what extent alterations in brain maturation leading to cortical miswiring and subsequent cortical hyperexcitability contribute to psychiatric disorders has not been fully elucidated. During brain development and maturation, neuronal activity is an important regulator of cortical connectivity. Experimental data suggests that disrupted neuronal activity during circuit maturation results in a failure of the refining of the circuit, inducing miswiring and increased network hyperexcitability due to alterations of the postsynaptic compartment (25, 26). In line with this, recent data shows that during juvenile brain development neuronal activity is needed for the proper formation of interhemispheric connections, while inhibition of neuronal activity resulted in decreased neuronal connectivity (27). In outgrowing axons, increased neuronal activity and proper connectivity was suggested to depend on axonal Ca^{2+}-signaling leading to activation of the CaMKK/CaMKI alpha cascade, thereby supporting axonal outgrowth (28). However, although neuronal activity was shown to be also important for subcortical-cortical projections, like the thalamo-cortical fibers (29), recent data suggests that pathological increased cortical excitability during juvenile brain development affects the formation of cortical connections leading to decreased cortical connectivity (30). Thus, neuronal activity during brain maturation has to be balanced: too low or too high neuronal activity levels are associated with cortical miswiring and cortical network hyperexcitability and may lead to psychiatric disorders at further adult ages. Indeed, alteration of cortical excitation/inhibition (E/I) balance and subsequent alteration of cortico-cortical modulation was shown to lead to increased cortical gamma oscillations (31, 32). Moreover, recent human data has shown that schizophrenia patients display increased spontaneous gamma activity during auditory steady-state stimulation reflecting a disrupted E/I balance (33).

A second critical period of cortical restructuring, which is present in distinct and interrelated connectivity development and cortical regions activity shaping, occurs during adolescence (34). Twin studies suggest that these cortical growth trajectories are determined by different sets of genes, which are active in interconnected brain subregions (35). Further studies revealed that regional alterations in the gray matter properties occurred in specific brain networks, which are relevant for the development of psychiatric disorders. Reorganization of these brain networks in adolescence is suggested to result in a particular vulnerability for psychiatric disorders (36, 37). Indeed, analyses in patients with childhood-onset schizophrenia have identified an abnormal pattern of cortical growth in the cingulo-fronto-temporal area of these patients, and suggest a specific impact of genetic systems in these neuroanatomical modules affecting their connectivity (38). Interestingly, network-specific alterations, which increase vulnerability to brain disorders, are not restricted to developmental periods, but have also been found to be present in different neurodegenerative disorders (39). These data suggest that developmental disturbances during adolescence, leading to increased vulnerability to psychiatric and neurodegenerative disorders rely on network-driven alterations of specific brain networks.

The idea that altered neuronal connectivity during brain maturation may lead to psychiatric disorders is supported by longitudinal studies focusing on delayed development

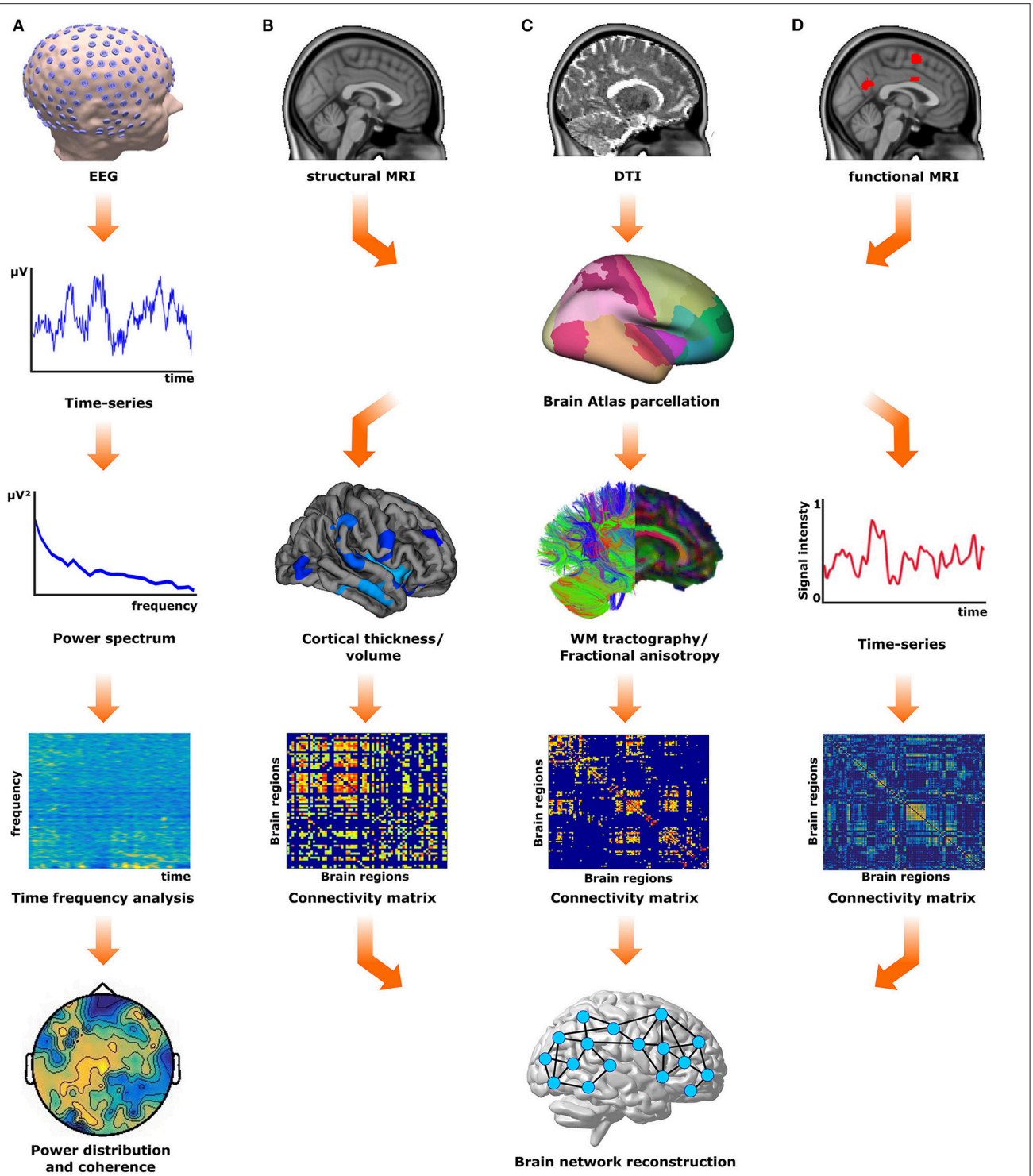

FIGURE 1 | Overview of network reconstruction methods. **(A)** The electrical activity of the brain is recorded using electroencephalography (EEG). These recordings (EEG time-series) are analyzed using time-frequency analysis approaches to investigate the spatiotemporal distribution of the frequency power. **(B)** From structural (T1) magnetic resonance images (MRI) morphological measures (cortical thickness/volume) for different brain regions can be extracted according to a predefined atlas. These measures are used to obtain a structural covariance matrix, from which the structural gray matter network is reconstructed. **(C)** The diffusion tensor images (DTI) are used to derive white matter tracts, from either probabilistic or deterministic tractography algorithms, or fractional anisotropy maps. These measures are used to obtain a connectivity matrix according to the brain atlas of choice, and subsequently, the structural white matter network is reconstructed. **(D)** The functional MRI (fMRI) time series from different brain regions obtained can also be used to generate the functional connectivity matrix and subsequently to reconstruct the functional brain network.

of brain connectivity. Adolescents with childhood-onset of schizophrenia, as well as their clinically unaffected siblings, showed reduced structural integrity and connectivity deficits in the left occipito-temporal areas (40). Although the maturation deficits of cortical connectivity have been shown to become normal with age in patients' siblings (41), this is not the case for the adolescents with childhood-onset schizophrenia (42). These findings support the hypothesis that maturation of cortical connectivity is an important factor for resilience to psychiatric disorders, in which alterations in cortical connectivity at certain life periods, as present in adolescents, may affect resilience toward psychiatric disorders. This is further supported by a recent study which correlated the microarchitecture of corpus callosum to the ability of individuals, who were exposed to high stress, to resist mental disorders (43). Here, young adolescents (mean age: 14.4 ± 1.31 years) with a high resilience to psychiatric disorders displayed higher fractional anisotropy (FA) values in the anterior corpus callosum when compared to adolescents at-risk for mental disorders or with controls (43).

In addition, findings showing altered morphological connectivity following abnormal adolescent brain maturation and associated with cortical hyperexcitability have taken a central role for the current view on the development of psychiatric disorders (24). This is in line with findings that early cortical hyperexcitability has a deleterious effect on brain development leading to sequelae later in life. For instance, Dube and co-workers (44) have shown that stress during sensitive early life periods led to cortical hyperexcitability at later life periods, where 57% of the individuals with early life stress developed epileptic seizures (44). However, and despite the immediate drastic effects like epileptiform discharges (5), continued and sustained cortical hyperexcitablility may lead to psychiatric disorders, as described in animal models for autism phenotypes (45), or may contribute to the pathological cascade of events that contribute to the development of Alzheimer's disease (46). Interestingly, not only generalized cortical excitability, but hyperexcitability of specific brain regions was shown be involved in fear reactions and reduced extinction suggesting an important link between neuronal excitability of specific brain regions like the dentate gyrus in the pathology of post-traumatic stress disorder. In sum, proper maturation from the synaptic level up to the cortical circuit level assuring correct neurotransmission and cortical connectivity is a prerequisite for proper resilient behavior at adult ages, while alterations in E/I balance and in cortico-cortical connectivity may lead to psychiatric disorders.

BRAIN REORGANIZATION AND NETWORK COMPENSATION DURING AGING

From early life through adulthood the brain is constantly changing; later in life the physiological aging process (i.e., free from neurodegeneration) is associated with modification of intrinsic neuronal excitability, together with functional and structural connectivity reorganization. These processes are typically associated with preservation or rather decline in performance across several cognitive domains. In elderly people, preserved function is thought to be underpinned by compensatory mechanisms (47), in which proximal or distal brain regions to those that decline over time because of natural aging, are recruited to maintain function (48).

From the functional perspective, age-associated adaptations of intrinsic neuronal excitability have been related with changes in cellular micro-architecture (i.e., membrane ion channels, receptors and vesicle fusion processes) and its molecular signaling (49, 50). Although the mechanisms of action are not yet fully understood, numerous evidence has shown involvement of ion-gated channels (e.g., voltage-gated Ca^{2+} channels and mechano-gated K^{+} channels) in mediating the loss of plasticity in neurons, making neurons more susceptible to deleterious processes such as oxidative stress (51). As an example, previous studies have shown increased loss of dopamine synthesis with healthy aging in the striatal system (52), which is particularly vulnerable to oxidative stress (53, 54). At this stage in life, the rate of dopamine loss is more prominent than the regional loss of gray matter tissue (52) and is related to cognitive performance (55), hence suggesting that this transition could be initiated by changes in the ion channels. However, further research is still needed in order to unveil the importance and to better characterize the impact of molecular changes related to the widespread functional and structural brain changes associated with healthy aging.

At the macro level, extra-cephalic electrophysiological recordings have repeatedly evidenced age-related alterations of oscillatory activity across distributed portions of the cortex. Since a loss of approximately 10% of all neocortical neurons over the lifespan occurs (56), alterations of local activity can be explained by an impaired synchronization of neuronal activity in specific frequency ranges. One possible cause of impaired synchronous firing activity can be an alteration of the cortico-cortical neuromodularity mechanisms or imbalances in the subcortico-cortical circuits, directly impacting spontaneous neuronal firing rates and changing the E/I balance. This appears to be the case for high frequency bands, for instance beta (13–30 Hz) and gamma (30–45 Hz) bands, in which increased power has been reported with increasing age (57), whereas decreases in lower alpha (8–10.5 Hz) and a slowing of peak alpha frequency appear with aging (58). Here, age-related interhemispheric asymmetry in power has been related to an increased excitability within the sucortico-cortical circuits (57), which is interpreted as a compensatory mechanism. However, a less consistent scenario emerges for frequencies in the slow wave range, delta (1–4 Hz) and theta (4–7.5 Hz) bands, in which both increases and decreases have been reported (59–62). Notably, apart from increased functional activity (47, 63), reduction of brain lateralization has been described as an important age-related mechanism for compensatory functions (64). However, this view considers only detrimental aspects of aging toward pathology and ignores a causal dynamical relationship with neural adaptation (i.e., plasticity) to life events (e.g., education, intellectual engagement and daily activities) during maturation.

On the structural part, although annual decreases on the order of 0.2–0.5% are well documented (65), MRI-derived morphometric measures (gray matter volume and thickness)

have demonstrated heterogeneous effects of aging, in which despite occurrence of disseminated atrophy across the whole brain, changes vary from region to region and tissue type, particularly over the cortical mantle (65, 66). Of all cortical regions, the frontal and parietal cortices appear the most susceptible to age-related changes (65, 67–70), with accumulating evidence showing increased involvement of the temporal regions (65). At the subcortical level, the hippocampus, caudate nucleus and cerebellum are the most age-susceptible regions (67), whereas involvement of regions belonging to the limbic system appear only limited (71–74). How these changes participate or guide aging processes is still unknown. For instance, reduction of the integrity in the prefrontal cortex is related with functional hyper-activation of the same region during task performance, suggesting the existence of compensatory mechanisms that support the maintenance of cognitive function (1, 75). Anatomical brain lateralization also seems to be nontrivial during aging, since for example, a trend for faster gray matter loss of the left prefrontal cortex relative to the right one has been described (76). Although this finding has not been consistently reported (77), individuals with smaller left than right hemispheric structural integrity are more likely to report cognitive deficits (78). Furthermore, converging evidence exists that an aging-related asymmetric loss of integrity in the parietal and temporal cortices is associated with cognitive functioning (79).

Examination of the white matter tissue has pointed to reduced microstructural integrity in the fiber tracts of the frontal and parietal lobes, as well as in the corpus callosum in elderly persons (80–82). White matter alterations are associated with decrements in cognitive performance, speed of processing, memory and executive functions (82). Moreover, age-related metabolic decreases in the middle and superior temporal cortex, albeit less pronounced than in frontal regions, have been related to white matter disturbances in the long fronto-temporo-occipital association pathways (83). Although these changes are likely to be explained by changes in myelin content (84), due to its influence on signal conduction (85), the effects of age on myelin are complex; even though some reduction in myelin sheaths is observed with age, the myelin is continuously produced throughout life, but perhaps in an uncontrolled or dysfunctional manner (86). Recent advances in MRI methods have successfully ascertained the *in-vivo* assessment of myelin content, showing a negative correlation with aging in the white matter (87, 88) and also to a lesser extent the gray matter (89). Notably, separation of myelin effects from cerebrovascular alterations is not easy using MRI approaches (90), because focal age-related anatomical changes in the white matter, e.g., white matter lesions, can also result from changes in blood pressure (91).

IMPACT OF DIVERGENT PATTERNS OF NETWORK REORGANIZATION FOR RESILIENCE AND SUSTAINED MENTAL HEALTH

Detection of altered brain circuits in the comparison between healthy subjects and patients only partially captures the neurobiological complexity of reorganization processes associated with maturation and aging and their influence on the development of pathological trajectories (92). The modern, network view of the human brain envisions circuits that are not only shaped by interactions (connections) between their constituent elements (brain regions), but also by their complex topological organization and temporal dynamics These factors mainly determine the differentiation between physiological vs. patholological processes and hold the key to describing reorganization associated with resilience and sustained mental health (11). Hence, the efficient organization of the brain networks results from delicate balancing of the opposing requirements for information integration and segregation, allowing effective complex cognitive and perceptual functions essential for mental health (93, 94).

Functional connectivity during resting state (i.e., individuals are relaxed and awake, but not engaged in task-directed cognition) has been increasingly applied to investigate the reorganization of the brain across the lifespan, showing that the network topology has a tendency to become randomly organized with increasing age, losing its efficient organization. Such dynamics seem to be good predictors of the individual transition from young to middle age (95), where the information flows from and to the frontal and parietal regions have a primordial role for physiological preservation of mental function.

Interestingly, despite the amount of research showing that chronic exposure to high levels of stress is associated with increased susceptibility to anxiety and other mental disorders (96–98), there is compelling evidence that more graded exposure to stress might reduce such vulnerabilities and promote resilience (99) or may even positively influence several cognitive domains such as memory functions influencing cerebral networks encompassing the hippocampus and amygdala (100). Of note, the stress responses mediated by the amygdala are regulated by the medial prefrontal cortex and their coupling (101–103); thus, stress exposure impairs prefrontal cortex-mediated cognitive functions and switches the control of stress behavior and emotion to interconnected brain circuits (104). These results support the hypothesis of compensation (105), establishing that the recruitment of secondary networks is a mediator of the relationship between structural brain damage and memory or targeted attacks (13). Hence, failure in the compensatory processes related to stress could reduce the ability of the brain circuits to compensate insults, increasing the rate at which functioning is impaired by new challenges (106). Indeed, sustained activation of the circuits involved in coping with stress situations could pass from being an adaptive or compensatory response, to lead to impairments in learning, memory, and the ability to regulate future stress responses (107, 108) and increase the vulnerability to a range of mental disorders over a lifetime (109). On the contrary, forms of early enrichment could induce an accurate heterotypic adjustment at molecular, synaptic and brain circuits levels that could strengthen resilience behavior (99, 110).

In some clinical conditions, such as depression or post-traumatic stress disorder (PTSD), an impaired structural network with abnormal hippocampal integrity and diminished function was described and considered as disease landmarks (111, 112). Smaller hippocampal volumes have been as well attested in

women with major depression and related to experiences of childhood trauma, while depressed individuals without similar trauma events had hippocampal volumes similar to healthy controls (113). Moreover, the unexposed twins of PTSD patients show a similar degree of hippocampal decrease, but without clinical implications (114). Hence, decreased hippocampal volume in these patients cannot be considered a mere disease outcome, but may be a pre-existing risk factor and could be related to early and continued exposure to aversive situations (115).

A further example largely associated with aging is that of Alzheimer's disease (AD), in which a continuum exists comprising a preclinical stage, a symptomatic predementia stage known as mild cognitive impairment (MCI), and the final stage of dementia (116). The molecular hallmarks of MCI subjects who progress to AD show positive biomarkers of amyloid-β (Aβ) and tau-related neural injury (117, 118). Periphery biomarkers, such as lower levels of cerebrospinal fluid (CSF) Aβ, indicate increased accumulation in the brain, whereas increased CSF tau levels indicate damaged neuronal microtubules, clearly evidencing synaptic dysfunction (i.e., desynchronization and hypersynchronization) due to AD (119) that negatively impacts synaptic plasticity and causes synaptic loss, which in turn leads to impairment of neural networks involved in memory and cognition.

Studying network organization patterns in such conditions offers the advantage of addressing developmental trajectories, with causal and longitudinal interpretation and offering the possibility to differentiate primary brain circuits alterations from secondary wide-spread function loss and to highlight

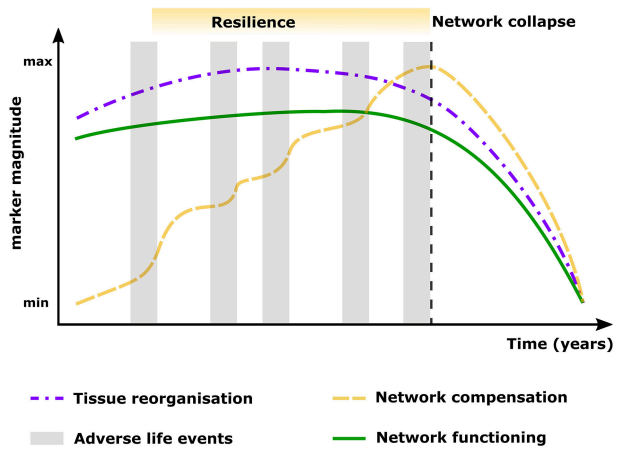

FIGURE 2 | Model showing the likely developmental trends of resilience, showing the maintenance or recovery of mental health during and after exposure to significant adverse event results from a dynamic process of adaptation to the given life circumstances (gray boxes), where global reorganization (purple line) and mechanisms of compensation (yellow line) across the whole brain network are in charge of maintaining optimal functioning and efficiency (green line) in relation to cognitive ability and mental health. However, increased or sustained exposure to adverse life events or inadequate network reorganization will lead to exhaustion or collapse of the network (black dashed line), which manifests as divergent lifespan patterns or breakdown of functional responses leading to loss of mental health.

the involvement of particular brain regions as network nodes or connectivity dynamics as active processes (120). In this sense, network compensation as an adaptive mechanism for resilience is not only of use to explain stress coping and to closely track and predict preserved mental health (7), but can be also illustratively studied to monitor adaptation and compensation that occur during the lifespan (69, 121). While age-related decreased connections from and to the frontal regions and increased connections to the posterior (parietal) modules have been described (122) these have been closely related with maintained cognitive function (123, 124). Moreover, variations in network efficiency predict memory function across different life periods and are suggested to reflect differences in information processing between association and sensorimotor systems (125). This all points to the fact that the adjustment of network organization is responsible for buffering alterations in cognitive ability (126, 127), and the loss of optimal topological organization is associated with disease development and impaired brain function (128, 129). Hence, the capacity to react to threats is built into specific brain circuits whose development is influenced by multiple experiences and present differential susceptibility during the lifespan.

BRAIN NETWORKS FINGERPRINTS OF REORGANIZATION DURING LIFESPAN AND RESILIENCE

The dynamics of brain reorganization during lifespan partly mirror structural (130) and functional networks behavior (131, 132), increasing efficiency during maturation through young adulthood until reaching a peak at about 30–40 years of age, that acts as an inflection point, after which the efficiency of brain circuits starts to decrease and physiological aging begins. More broadly, the structural integrity of the brain, as measured by the brain parenchymal fraction (BPF) presents a similar trend across the lifespan (133), whereas the cognitive ability increases throughout young adulthood and decreases in older adulthood (134). Variations in the trajectories are expected in relation to biological and environmental factors, such as genetics, lifestyle, education, socio-cultural background, exercise engagements and learning.

Despite the above mentioned age-related lifespan brain reorganization processes that explain links from structure to cognitive and mental function (1, 2), whether all these changes result from modifications in earlier or later life periods remains an open question. More importantly, which compensation patterns occur at different life points and how brain circuits can compensate for detrimental events is only partly understood (135–137). This is a central point of resilience research, which postulates that active processes of brain reorganization play an essential role for preserved mental function (11), where the connectivity patterns shaping excitability regulation mechanisms are principally involved in sustaining mental health and physiological trajectories of cognitive function (138). Accordingly, we propose an integrative model as shown in **Figure 2**.

To confront the increased endogenous challenges (i.e., changes to neural anatomy and physiology), as well as exogenous challenges (i.e., those brought about by traumatic events or by changes to the environment), brain circuits must present tremendous abilities to flexibly adapt. Maintained mental health can be generally achieved by the integrated communication between frontal and parietal brain regions (3, 4). Within this view, reorganization principles of the brain's topological architecture, beyond being mere compensatory mechanisms (47, 75), could be thought of as manifestations of neural plasticity, synaptic adaptation and reorganization of information flows (69, 139–142). This hypothesis is based on the fact that age-related functional and structural reorganization processes spatially correspond to evolving patterns of activation, and that these structure-function patterns are tightly associated with cognitive performance (1, 143). More supporting evidence shows that adults who do not show age-related adjustment in EEG theta-alpha power are more likely to exhibit cognitive deficits than those who adapt (62). Accordingly, the process of resilience cannot be restricted to early life but should operate throughout the entire lifespan.

Recent studies have emphasized that the integral topological architecture of the brain networks, i.e., modular organization, supports increased cognitive demands (144–146) and that the reorganization of its patterns are tightly related to aging (122, 125, 147). How this process of increased modularization of brain networks is related to mental health or resilience is not yet clear but should be a matter of future studies. Hence, adaptation of interregional connectivity and specific changes in network topology are likely to be contributing mechanisms to healthy aging (147, 148). This phenomenon is characterized by modification within different brain subsystems (122), which contain regions critical for several cognitive functions and/or are particularly sensitive to disease development. Specifically, the prefrontal, anterior and posterior cingulate cortices, as well as the precuneus and the inferior parietal lobe have been consistently shown to present age-related changes in connectivity relevant to preserved mental function and resilience (3, 4).

Common patterns of functional and structural network reorganization have been reported at different time scales (149), mainly involving reduced connectivity in the fronto-parietal or default mode networks which seem to be the normal adaptation to healthy aging. On the contrary, although the temporal cortex shows a similar trajectory with age as other regions (150, 151) the changes to this region show signs of neurodegeneration (152, 153). These findings pinpoint the possibility of specific regional contributions to differentiate healthy from abnormal aging trajectories, and opens the possibility that failures in age-related network reorganization predispose the brain to the development of the so-called disconnection syndromes.

In the same line, specific network topology patterns have already been related to the disease course and clinical progression in AD (154) and Parkinson's disease (16), multiple sclerosis (6, 15), schizophrenia (155, 156), depression (157) and PTSD (158, 159). These observations emphasize that the network adaptations are not merely a consequence of pathological alterations, but should be seen as integrative processes of functional and structural alterations and compensation for optimal network functioning (123), which act until the set-point at which the network performance cannot be maintained and compensation abates (7). Furthermore, patterns of network reorganization are linked to plasticity in the normal brain (160) and with maintenance of function despite continuous damage (161, 162). This suggests that the correct adaptation of distinct brain circuits may be the key mechanism underlying resilience (as in our proposed model shown in **Figure 2**), where parallel processes of lifespan-related reorganization in brain circuits can be drawn, and used to improve our understanding, under an holistic framework, of the interrelation between physiological and pathological developments and experienced life events (7).

CONCLUSION

Clearly, brain networks development and reorganization across the human lifespan are active and continuous processes, which allow the emergence of resilience mechanisms across the entire lifespan. Within these networks, the frontal and parietal regions are certainly modulators of maintained health, where the intrinsic dynamics and excitability patterns of these regions and their connections, for instance to the temporal lobe and hippocampus, are able to reduce vulnerability and risk for damage. Hence, correct adaptation of these connectivity patterns could be the key to healthy aging and diminish the risk for developing neurological and neuropsychiatric disease at different stages across the lifespan. Future research should aim for multivariate full-brain investigations using not only larger study populations, also with the help of combined biomarkers at the micro-level, such as blood markers or genetic profiling, and at macro-level, e.g., brain imaging and network analyses; all together with longitudinal designs in order to better capture the full dynamics of lifespan modifications.

AUTHOR CONTRIBUTIONS

GG-E, MM, JV, and SG made substantial contributions to the conception and design of the work; performed the literature search, drafted parts of the manuscript and revised it critically. GG-E, and MM prepared the first version and revised subsequent versions of the manuscript. JV and SG made substantial contributions to the interpretation of data. VC made substantial contributions to the interpretation of data; he made the figures and revised the manuscript critically. GG-E, MM, VC, JV, and SG give their final approval of the version to be published and agree to be responsible for all aspects of the work so that questions about the accuracy or integrity of any part of the work are adequately investigated and solved.

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REFERENCES

1. Grady C. The cognitive neuroscience of ageing. *Nat Rev Neurosci.* (2012) 13:491–505. doi: 10.1038/nrn3256
2. Song J, Birn RM, Boly M, Meier TB, Nair VA, Meyerand ME, et al. Age-related reorganizational changes in modularity and functional connectivity of human brain networks. *Brain Connect.* (2014) 4:662–76. doi: 10.1089/brain.2014.0286
3. Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, et al. Disruption of large-scale brain systems in advanced aging. *Neuron* (2007) 56:924–35. doi: 10.1016/j.neuron.2007.10.038
4. Sambataro F, Murty VP, Callicott JH, Tan HY, Das S, Weinberger DR, et al. Age-related alterations in default mode network: impact on working memory performance. *Neurobiol Aging* (2010) 31:839–52. doi: 10.1016/j.neurobiolaging.2008.05.022
5. Groppa S, Siebner HR, Kurth C, Stephani U, Siniatchkin M. Abnormal response of motor cortex to photic stimulation in idiopathic generalized epilepsy. *Epilepsia* (2008) 49:2022–9. doi: 10.1111/j.1528-1167.2008.01709.x
6. Fleischer V, Groger A, Koirala N, Droby A, Muthuraman M, Kolber P, et al. Increased structural white and grey matter network connectivity compensates for functional decline in early multiple sclerosis. *Mult Scler.* (2017) 23:432–41. doi: 10.1177/1352458516651503
7. Fleischer V, Radetz A, Ciolac D, Muthuraman M, Gonzalez-Escamilla G, Zipp F, et al. Graph theoretical framework of brain networks in multiple sclerosis: a review of concepts. *Neuroscience* (2017) S0306-4522(17)30761-3. doi: 10.1016/j.neuroscience.2017.10.033. [Epub ahead of print].
8. Van Den Heuvel MP, Sporns O. Network hubs in the human brain. *Trends Cogn Sci.* (2013) 17:683–96. doi: 10.1016/j.tics.2013.09.012
9. Stam CJ. Modern network science of neurological disorders. *Nat Rev Neurosci.* (2014) 15:683–95. doi: 10.1038/nrn3801
10. Medaglia JD, Pasqualetti F, Hamilton RH, Thompson-Schill SL, Bassett DS. Brain and cognitive reserve: translation via network control theory. *Neurosci Biobehav Rev.* (2017) 75:53–64. doi: 10.1016/j.neubiorev.2017.01.016
11. Kalisch R, Baker DG, Basten U, Boks MP, Bonanno GA, Brummelman E, et al. The resilience framework as a strategy to combat stress-related disorders. *Nat Hum Behav.* (2017) 1:784–90. doi: 10.1038/s41562-017-0200-8
12. Chirumamilla VC, Fleischer V, Droby A, Anjum T, Muthuraman M, Zipp F, et al. Functional connectivity analysis using whole brain and regional network metrics in MS patients. *Conf Proc IEEE Eng Med Biol Soc.* (2016) 2016:4039–42. doi: 10.1109/EMBC.2016.7591613
13. Droby A, Yuen KS, Muthuraman M, Reitz SC, Fleischer V, Klein J, et al. Changes in brain functional connectivity patterns are driven by an individual lesion in MS: a resting-state fMRI study. *Brain Imaging Behav.* (2016) 10:1117–26. doi: 10.1007/s11682-015-9476-3
14. He Y, Chen ZJ, Evans AC. Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cereb Cortex* (2007) 17:2407–19. doi: 10.1093/cercor/bhl149
15. Muthuraman M, Fleischer V, Kolber P, Luessi F, Zipp F, Groppa S. Structural Brain Network Characteristics Can Differentiate CIS from Early RRMS. *Front Neurosci.* (2016) 10:14. doi: 10.3389/fnins.2016.00014
16. Koirala N, Fleischer V, Glaser M, Zeuner KE, Deuschl G, Volkmann J, et al. frontal lobe connectivity and network community characteristics are associated with the outcome of subthalamic nucleus deep brain stimulation in patients with parkinson's disease. *Brain Topogr.* (2018) 31:311–21. doi: 10.1007/s10548-017-0597-4
17. Groppa S, Herzog J, Falk D, Riedel C, Deuschl G, Volkmann J. Physiological and anatomical decomposition of subthalamic neurostimulation effects in essential tremor. *Brain* (2014) 137:109–21. doi: 10.1093/brain/awt304
18. Deppe M, Tabelow K, Kramer J, Tenberge JG, Schiffler P, Bittner S, et al. Evidence for early, non-lesional cerebellar damage in patients with multiple sclerosis: DTI measures correlate with disability, atrophy, and disease duration. *Mult Scler.* (2016) 22:73–84. doi: 10.1177/1352458515579439
19. Muthuraman M, Raethjen J, Koirala N, Anwar A, Mideksa K, Elble R, et al. Cerebello-cortical network fingerprints differ among essential, Parkinson and mimicked tremors. *Brain* (2018) 141:1770–81. doi: 10.1093/brain/awy098
20. Turrigiano G. Too many cooks? Intrinsic and synaptic homeostatic mechanisms in cortical circuit refinement. *Annu Rev Neurosci* (2011) 34:89–103. doi: 10.1146/annurev-neuro-060909-153238
21. Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol psychiatry* (2005) 10:40. doi: 10.1038/sj.mp.4001630
22. Coyle JT. Glutamate and schizophrenia: beyond the dopamine hypothesis. *Cell Mol Neurobiol.* (2006) 26:365–84. doi: 10.1007/s10571-006-9062-8
23. Belforte JE, Zsiros V, Sklar ER, Jiang Z, Yu G, Li Y, et al. Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. *Nat Neurosci.* (2010) 13:76–83. doi: 10.1038/nn.2447
24. Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, O'shea DJ, et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature* (2011) 477:171–8. doi: 10.1038/nature10360
25. Galvan CD, Hrachovy RA, Smith KL, Swann JW. Blockade of neuronal activity during hippocampal development produces a chronic focal epilepsy in the rat. *J Neurosci.* (2000) 20:2904–16. doi: 10.1523/JNEUROSCI.20-08-02904.2000
26. Galvan CD, Wenzel JH, Dineley KT, Lam TT, Schwartzkroin PA, Sweatt JD, et al. Postsynaptic contributions to hippocampal network hyperexcitability induced by chronic activity blockade *in vivo*. *Eur J Neurosci.* (2003) 18:1861–72. doi: 10.1046/j.1460-9568.2003.02920.x
27. Mizuno H, Hirano T, Tagawa Y. Pre-synaptic and post-synaptic neuronal activity supports the axon development of callosal projection neurons during different post-natal periods in the mouse cerebral cortex. *Eur J Neurosci.* (2010) 31:410–24. doi: 10.1111/j.1460-9568.2009.07070.x
28. Ageta-Ishihara N, Takemoto-Kimura S, Nonaka M, Adachi-Morishima A, Suzuki K, Kamijo S, et al. Control of cortical axon elongation by a GABA-driven Ca2+/calmodulin-dependent protein kinase cascade. *J Neurosci.* (2009) 29:13720–9. doi: 10.1523/JNEUROSCI.3018-09.2009
29. Mire E, Mezzera C, Leyva-Diaz E, Paternain AV, Squarzoni P, Bluy L, et al. Spontaneous activity regulates Robo1 transcription to mediate a switch in thalamocortical axon growth. *Nat Neurosci.* (2012) 15:1134–43. doi: 10.1038/nn.3160
30. Vogt J, Kirischuk S, Unichenko P, Schluter L, Pelosi A, Endle H, et al. Synaptic phospholipid signaling modulates axon outgrowth via glutamate-dependent Ca2+-mediated molecular pathways. *Cereb Cortex* (2017) 27:131–45. doi: 10.1093/cercor/bhw370
31. Pinault D. N-methyl d-aspartate receptor antagonists ketamine and MK-801 induce wake-related aberrant gamma oscillations in the rat neocortex. *Biol Psychiatry* (2008) 63:730–5. doi: 10.1016/j.biopsych.2007.10.006
32. Thalman C, Horta G, Qiao L, Endle H, Tegeder I, Cheng H, et al. Synaptic Phosopholipids as a new target for cortical hyperexcitability and E/I-balance in psychiatric disorders. *Mol psychiatry* (In Press) 23:1699–710. doi: 10.1038/s41380-018-0053-1
33. Hirano Y, Oribe N, Kanba S, Onitsuka T, Nestor PG, Spencer KM. Spontaneous gamma activity in schizophrenia. *JAMA Psychiatry* (2015) 72:813–21. doi: 10.1001/jamapsychiatry.2014.2642
34. Brain Development Cooperative G. Total and regional brain volumes in a population-based normative sample from 4 to 18 years: the NIH MRI Study of Normal Brain Development. *Cereb Cortex* (2012) 22:1–12. doi: 10.1093/cercor/bhr018
35. Rimol LM, Panizzon MS, Fennema-Notestine C, Eyler LT, Fischl B, Franz CE, et al. Cortical thickness is influenced by regionally specific genetic factors. *Biol Psychiatry* (2010) 67:493–9. doi: 10.1016/j.biopsych.2009.09.032
36. Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? *Nat Rev Neurosci.* (2008) 9:947–57. doi: 10.1038/nrn2513
37. Paus T, Toro R, Leonard G, Lerner JV, Lerner RM, Perron M, et al. Morphological properties of the action-observation cortical network in adolescents with low and high resistance to peer influence. *Soc Neurosci.* (2008) 3:303–16. doi: 10.1080/17470910701563558
38. Alexander-Bloch AF, Reiss PT, Rapoport J, Mcadams H, Giedd JN, Bullmore ET, et al. Abnormal cortical growth in schizophrenia targets normative modules of synchronized development. *Biol Psychiatry* (2014) 76:438–46. doi: 10.1016/j.biopsych.2014.02.010

39. Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron* (2009) 62:42–52. doi: 10.1016/j.neuron.2009.03.024
40. Zalesky A, Pantelis C, Cropley V, Fornito A, Cocchi L, Mcadams H, et al. Delayed development of brain connectivity in adolescents with schizophrenia and their unaffected siblings. *JAMA psychiatry* (2015) 72:900–8. doi: 10.1001/jamapsychiatry.2015.0226
41. Gogtay N, Greenstein D, Lenane M, Clasen L, Sharp W, Gochman P, et al. Cortical brain development in nonpsychotic siblings of patients with childhood-onset schizophrenia. *Arch Gen Psychiatry* (2007) 64:772–80. doi: 10.1001/archpsyc.64.7.772
42. Greenstein D, Lerch J, Shaw P, Clasen L, Giedd J, Gochman P, et al. Childhood onset schizophrenia: cortical brain abnormalities as young adults. *J Child Psychol Psychiatry* (2006) 47:1003–12. doi: 10.1111/j.1469-7610.2006.01658.x
43. Galinowski A, Miranda R, Lemaitre H, Paillere Martinot ML, Artiges E, Vulser H, et al. Resilience and corpus callosum microstructure in adolescence. *Psychol Med.* (2015) 45:2285–94. doi: 10.1017/S0033291715000239
44. Dube CM, Molet J, Singh-Taylor A, Ivy A, Maras PM, Baram TZ. Hyper-excitability and epilepsy generated by chronic early-life stress. *Neurobiol Stress* (2015) 2:10–9. doi: 10.1016/j.ynstr.2015.03.001
45. Selimbeyoglu A, Kim CK, Inoue M, Lee SY, Hong ASO, Kauvar I, et al. Modulation of prefrontal cortex excitation/inhibition balance rescues social behavior in CNTNAP2-deficient mice. *Sci Transl Med.* (2017) 9:eaah6733. doi: 10.1126/scitranslmed.aah6733
46. Lam AD, Deck G, Goldman A, Eskandar EN, Noebels J, Cole AJ. Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease. *Nat Med.* (2017) 23:678–80. doi: 10.1038/nm.4330
47. Cabeza R, Anderson ND, Locantore JK, Mcintosh AR. Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage* (2002) 17:1394–402. doi: 10.1006/nimg.2002.1280
48. Meunier D, Stamatakis EA, Tyler LK. Age-related functional reorganization, structural changes, and preserved cognition. *Neurobiol Aging* (2014) 35:42–54. doi: 10.1016/j.neurobiolaging.2013.07.003
49. Oh MM, Oliveira FA, Disterhoft JF. Learning and aging related changes in intrinsic neuronal excitability. *Front Aging Neurosci.* (2010) 2:2. doi: 10.3389/neuro.24.002.2010
50. Yeoman M, Scutt G, Faragher R. Insights into CNS ageing from animal models of senescence. *Nat Rev Neurosci.* (2012) 13:435–45. doi: 10.1038/nrn3230
51. Annunziato L, Pannaccione A, Cataldi M, Secondo A, Castaldo P, Di Renzo G, et al. Modulation of ion channels by reactive oxygen and nitrogen species: a pathophysiological role in brain aging? *Neurobiol Aging* (2002) 23:819–34. doi: 10.1016/S0197-4580(02)00069-6
52. Ota M, Yasuno F, Ito H, Seki C, Nozaki S, Asada T, et al. Age-related decline of dopamine synthesis in the living human brain measured by positron emission tomography with L-[beta-11C]DOPA. *Life Sci.* (2006) 79:730–6. doi: 10.1016/j.lfs.2006.02.017
53. Cardoso HD, Passos PP, Lagranha CJ, Ferraz AC, Santos Junior EF, Oliveira RS, et al. Differential vulnerability of substantia nigra and corpus striatum to oxidative insult induced by reduced dietary levels of essential fatty acids. *Front Hum Neurosci.* (2012) 6:249. doi: 10.3389/fnhum.2012.00249
54. Jensen N, Oliveira JR. Basal ganglia vulnerability to oxidative stress. *Front Neurosci.* (2014) 8:80. doi: 10.3389/fnins.2014.00080
55. Backman L, Lindenberger U, Li SC, Nyberg L. Linking cognitive aging to alterations in dopamine neurotransmitter functioning: recent data and future avenues. *Neurosci Biobehav Rev.* (2010) 34:670–7. doi: 10.1016/j.neubiorev.2009.12.008
56. Pakkenberg B, Gundersen HJ. Neocortical neuron number in humans: effect of sex and age. *J Comp Neurol.* (1997) 384:312–20.
57. Zappasodi F, Marzetti L, Olejarczyk E, Tecchio F, Pizzella V. Age-related changes in electroencephalographic signal complexity. *PLoS ONE* (2015) 10:e0141995. doi: 10.1371/journal.pone.0141995
58. Chiang AK, Rennie CJ, Robinson PA, Van Albada SJ, Kerr CC. Age trends and sex differences of alpha rhythms including split alpha peaks. *Clin Neurophysiol.* (2011) 122:1505–17. doi: 10.1016/j.clinph.2011.01.040
59. Finnigan S, Robertson IH. Resting EEG theta power correlates with cognitive performance in healthy older adults. *Psychophysiology* (2011) 48:1083–7. doi: 10.1111/j.1469-8986.2010.01173.x
60. Michels L, Muthuraman M, Luchinger R, Martin E, Anwar AR, Raethjen J, et al. Developmental changes of functional and directed resting-state connectivities associated with neuronal oscillations in EEG. *Neuroimage* (2013) 81:231–42. doi: 10.1016/j.neuroimage.2013.04.030
61. Vlahou EL, Thurm F, Kolassa IT, Schlee W. Resting-state slow wave power, healthy aging and cognitive performance. *Sci Rep.* (2014) 4:5101. doi: 10.1038/srep05101
62. Trammell JP, Macrae PG, Davis G, Bergstedt D, Anderson AE. The relationship of cognitive performance and the theta-alpha power ratio is age-dependent: an EEG study of short term memory and reasoning during task and resting-state in healthy young and old adults. *Front aging Neurosci.* (2017) 9:364. doi: 10.3389/fnagi.2017.00364
63. Berlingeri M, Danelli L, Bottini G, Sberna M, Paulesu E. Reassessing the HAROLD model: is the hemispheric asymmetry reduction in older adults a special case of compensatory-related utilisation of neural circuits? *Exp Brain Res.* (2013) 224:393–410. doi: 10.1007/s00221-012-3319-x
64. Cabeza R. Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging* (2002) 17:85–100. doi: 10.1037/0882-7974.17.1.85
65. Fjell AM, Mcevoy L, Holland D, Dale AM, Walhovd KB, Initiative ASDN. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus *Prog Neurobiol.* (2014) 117:20–40. doi: 10.1016/j.pneurobio.2014.02.004
66. Tamnes CK, Walhovd KB, Dale AM, Ostby Y, Grydeland H, Richardson G, et al. Brain development and aging: overlapping and unique patterns of change. *Neuroimage* (2013) 68:63–74. doi: 10.1016/j.neuroimage.2012.11.039
67. Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, et al. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex* (2005) 15:1676–89. doi: 10.1093/cercor/bhi044
68. Dennis NA, Cabeza R. Neuroimaging of healthy cognitive aging. In: Craik FIM, Salthouse TA, editors. *The Handbook of Aging and Cognition*. 3rd ed. New York, NY: Psychology Press (2008). p. 1–54.
69. Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol.* (2009) 60:173–96. doi: 10.1146/annurev.psych.59.103006.093656
70. Lockhart SN, Decarli C. Structural imaging measures of brain aging. *Neuropsychol Rev.* (2014) 24:271–89. doi: 10.1007/s11065-014-9268-3
71. Good CD, Johnsrude I, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. *Neuroimage* (2001) 14:685–700. doi: 10.1006/nimg.2001.0857
72. Grieve SM, Clark CR, Williams LM, Peduto AJ, Gordon E. Preservation of limbic and paralimbic structures in aging. *Hum Brain Mapp.* (2005) 25:391–401. doi: 10.1002/hbm.20115
73. Long X, Zhang L, Liao W, Jiang C, Qiu B. Distinct laterality alterations distinguish mild cognitive impairment and Alzheimer's disease from healthy aging: statistical parametric mapping with high resolution MRI. *Human Brain Mapp.* (2013) 34:3400–10. doi: 10.1002/hbm.22157
74. Minkova L, Habich A, Peter J, Kaller CP, Eickhoff SB, Kloppel S. Gray matter asymmetries in aging and neurodegeneration: a review and meta-analysis. *Hum Brain Mapp.* (2017) 38:5890–904. doi: 10.1002/hbm.23772
75. Di X, Rypma B, Biswal BB. Correspondence of executive function related functional and anatomical alterations in aging brain. *Prog Neuropsychopharmacol Biol Psychiatry* (2014) 48:41–50. doi: 10.1016/j.pnpbp.2013.09.001
76. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. *Nat Neurosci.* (2003) 6:309–15. doi: 10.1038/nn1008
77. Raz N, Gunning FM, Head D, Dupuis JH, Mcquain J, Briggs SD, et al. Selective aging of the human cerebral cortex observed *in vivo*: differential vulnerability of the prefrontal gray matter. *Cereb Cortex* (1997) 7:268–82. doi: 10.1093/cercor/7.3.268

78. Cherbuin N, Réglade-Meslin C, Kumar R, Sachdev P, Anstey KJ. Mild cognitive disorders are associated with different patterns of brain asymmetry than normal aging: the PATH through Life Study. *Front psychiatry* (2010) 1:11. doi: 10.3389/fpsyt.2010.00011
79. Plessen KJ, Hugdahl K, Bansal R, Hao X, Peterson BS. Sex, age, and cognitive correlates of asymmetries in thickness of the cortical mantle across the life span. *J Neurosci* (2014) 34:6294–302. doi: 10.1523/JNEUROSCI.3692-13.2014
80. Nusbaum AO, Tang CY, Buchsbaum MS, Wei TC, Atlas SW. Regional and global changes in cerebral diffusion with normal aging. *AJNR Am J Neuroradiol.* (2001) 22:136–42. Available online at: http://www.ajnr.org/content/22/1/136/tab-article-info
81. O'sullivan M, Jones DK, Summers P, Morris R, Williams S, Markus H. Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology* (2001) 57:632–38. doi: 10.1212/WNL.57.4.632
82. Salthouse TA. Neuroanatomical substrates of age-related cognitive decline. *Psychol Bull.* (2011) 137:753–84. doi: 10.1037/a0023262
83. Chételat G, Landeau B, Salmon E, Yakushev I, Bahri MA, Mézenge F, et al. Relationships between brain metabolism decrease in normal aging and changes in structural and functional connectivity. *Neuroimage* (2013) 76:167–77. doi: 10.1016/j.neuroimage.2013.03.009
84. Steiger TK, Weiskopf N, Bunzeck N. Iron level and myelin content in the ventral striatum predict memory performance in the aging brain. *J Neurosci.* (2016) 36:3552–8. doi: 10.1523/JNEUROSCI.3617-15.2016
85. Pajevic S, Basser PJ, Fields RD. Role of myelin plasticity in oscillations and synchrony of neuronal activity. *Neuroscience* (2014) 276:135–47. doi: 10.1016/j.neuroscience.2013.11.007
86. Peters A. The effects of normal aging on myelin and nerve fibers: a review. *J Neurocytol.* (2002) 31:581–93. doi: 10.1023/A:1025731309829
87. Callaghan MF, Freund P, Draganski B, Anderson E, Cappelletti M, Chowdhury R, et al. Widespread age-related differences in the human brain microstructure revealed by quantitative magnetic resonance imaging. *Neurobiol Aging* (2014) 35:1862–72. doi: 10.1016/j.neurobiolaging.2014.02.008
88. Berman S, West KL, Does MD, Yeatman JD, Mezer AA. Evaluating g-ratio weighted changes in the corpus callosum as a function of age and sex *NeuroImage* (2017) 182:304–13. doi: 10.1016/j.neuroimage.2017.06.076
89. Keuken MC, Bazin PL, Backhouse K, Beekhuizen S, Himmer L, Kandola A, et al. Effects of aging on T(1), T(2)*, and QSM MRI values in the subcortex. *Brain Struct Funct.* (2017) 222:2487–505. doi: 10.1007/s00429-016-1352-4
90. Knight MJ, Mccann B, Tsivos D, Dillon S, Coulthard E, Kauppinen RA. Quantitative T2 mapping of white matter: applications for ageing and cognitive decline. *Phys Med Biol.* (2016) 61:5587–605. doi: 10.1088/0031-9155/61/15/5587
91. Longstreth WTJr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. *Stroke* (1996) 27:1274–82. doi: 10.1161/01.STR.27.8.1274
92. Rodrigue KM, Kennedy KM. The cognitive consequences of structural changes to the aging brain In: Schaie KW, Willis SL, editors. *Handbook of the Psychology of Aging*. 7th ed. New York, NY: Elsevier (2011). p. 73–91.
93. Sporns O, Tononi G, Edelman GM. Connectivity and complexity: the relationship between neuroanatomy and brain dynamics. *Neural Netw.* (2000) 13:909–22. doi: 10.1016/S0893-6080(00)00053-8
94. Friston KJ. Functional and effective connectivity: a review. *Brain Connect.* (2011) 1:13–36. doi: 10.1089/brain.2011.0008
95. Petti M, Toppi J, Babiloni F, Cincotti F, Mattia D, Astolfi L. EEG resting-state brain topological reorganization as a function of age. *Comput Intell Neurosci.* (2016) 2016:1–10. doi: 10.1155/2016/6243694
96. Krishnan V, Han MH, Graham DL, Berton O, Renthal W, Russo SJ, et al. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* (2007) 131:391–404. doi: 10.1016/j.cell.2007.09.018
97. Bradley RG, Binder EB, Epstein MP, Tang Y, Nair HP, Liu W, et al. Influence of child abuse on adult depression: moderation by the corticotropin-releasing hormone receptor gene. *Arch Gen Psychiatry* (2008) 65:190–200. doi: 10.1001/archgenpsychiatry.2007.26
98. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology* (2008) 33:693–710. doi: 10.1016/j.psyneuen.2008.03.008
99. Russo SJ, Murrough JW, Han MH, Charney DS, Nestler EJ. Neurobiology of resilience. *Nat Neurosci* (2012) 15:1475–84. doi: 10.1038/nn.3234
100. Mcewen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Ann N Y Acad Sci.* (2004) 1032:1–7. doi: 10.1196/annals.1314.001
101. Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. *Neuropsychopharmacology* (2008) 33:56–72. doi: 10.1038/sj.npp.1301555
102. Kim MJ, Whalen PJ. The structural integrity of an amygdala-prefrontal pathway predicts trait anxiety. *J Neurosci.* (2009) 29:11614–8. doi: 10.1523/JNEUROSCI.2335-09.2009
103. Vytal KE, Overstreet C, Charney DR, Robinson OJ, Grillon C. Sustained anxiety increases amygdala-dorsomedial prefrontal coupling: a mechanism for maintaining an anxious state in healthy adults. *J Psychiatry Neurosci.* (2014) 39:321–9. doi: 10.1503/jpn.130145
104. Arnsten AF. Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience* (2009) 10:410. doi: 10.1038/nrn2648
105. Cabeza R, Dennis NA. Frontal lobes and aging: Deterioration and Compensation In: *Principles of frontal lobe function,* In: Stuss DT, Knight RT editors. (New York, NY: Oxford University Press) (2013). p. 628–52.
106. Mcewen BS, Gianaros PJ. Stress- and allostasis-induced brain plasticity. *Annu Rev Med.* (2011) 62:431–45. doi: 10.1146/annurev-med-052209-100430
107. Lupien SJ, Mcewen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci.* (2009) 10:434–45. doi: 10.1038/nrn2639
108. Gotlib IH, Joormann J. Cognition and depression: current status and future directions. *Annu Rev Clin Psychol.* (2010) 6:285–312. doi: 10.1146/annurev.clinpsy.121208.131305
109. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev.* (2000) 21:55–89. doi: 10.1210/er.21.1.55
110. Mcewen BS. In pursuit of resilience: stress, epigenetics, and brain plasticity. *Ann N Y Acad Sci.* (2016) 1373:56–64. doi: 10.1111/nyas.13020
111. Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry* (2004) 161:1957–66. doi: 10.1176/appi.ajp.161.11.1957
112. Smith ME. Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: a meta-analysis of structural MRI studies. *Hippocampus* (2005) 15:798–807. doi: 10.1002/hipo.20102
113. Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, et al. Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry* (2002) 159:2072–80. doi: 10.1176/appi.ajp.159.12.2072
114. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci.* (2002) 5:1242–7. doi: 10.1038/nn958
115. Charney DS, Manji HK. Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention. *Sci STKE.* (2004) 2004:re5. doi: 10.1126/stke.2252004re5
116. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* (2011) 7:280–92. doi: 10.1016/j.jalz.2011.03.003
117. Braak H, Braak E. Evolution of the neuropathology of Alzheimer's disease. *Acta Neurol Scand Suppl.* (1996) 165:3–12. doi: 10.1111/j.1600-0404.1996.tb05866.x
118. Albert MS, Dekosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Focus* (2013) 11:96–106. doi: 10.1176/appi.focus.11.1.96

119. Vlassenko AG, Benzinger TL, Morris JC. PET amyloid-beta imaging in preclinical Alzheimer's disease. *Biochim Biophys Acta* (2012) 1822:370–9. doi: 10.1016/j.bbadis.2011.11.005
120. Kashtan N, Alon U. Spontaneous evolution of modularity and network motifs. *Proc Natl Acad Sci USA.* (2005) 102:13773–8. doi: 10.1073/pnas.0503610102
121. Gutchess AH, Welsh RC, Hedden T, Bangert A, Minear M, Liu LL, et al. Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. *J Cogn Neurosci.* (2005) 17:84–96. doi: 10.1162/0898929052880048
122. Meunier D, Achard S, Morcom A, Bullmore E. Age-related changes in modular organization of human brain functional networks. *Neuroimage* (2009) 44:715–23. doi: 10.1016/j.neuroimage.2008.09.062
123. Franzmeier N, Gottler J, Grimmer T, Drzezga A, Araque-Caballero MA, Simon-Vermot L, et al. Resting-state connectivity of the left frontal cortex to the default mode and dorsal attention network supports reserve in mild cognitive impairment. *Front Aging Neurosci.* (2017) 9:264. doi: 10.3389/fnagi.2017.00264
124. Franzmeier N, Hartmann JC, Taylor ANW, Araque Caballero MA, Simon-Vermot L, Buerger K, et al. Left frontal hub connectivity during memory performance supports reserve in aging and mild cognitive impairment. *J Alzheimers Dis.* (2017) 59:1381–92. doi: 10.3233/JAD-170360
125. Chan MY, Park DC, Savalia NK, Petersen SE, Wig GS. Decreased segregation of brain systems across the healthy adult lifespan. *Proc Natl Acad Sci USA.* (2014) 111:E4997–5006. doi: 10.1073/pnas.1415122111
126. Zhao T, Cao M, Niu H, Zuo XN, Evans A, He Y, et al. Age-related changes in the topological organization of the white matter structural connectome across the human lifespan. *Hum Brain Mapp.* (2015) 36:3777–92. doi: 10.1002/hbm.22877
127. Gallen CL, Turner GR, Adnan A, D'esposito M. Reconfiguration of brain network architecture to support executive control in aging. *Neurobiol Aging* (2016) 44:42–52. doi: 10.1016/j.neurobiolaging.2016.04.003
128. Pfefferbaum A, Adalsteinsson E, Sullivan EV. Frontal circuitry degradation marks healthy adult aging: evidence from diffusion tensor imaging. *Neuroimage* (2005) 26:891–9. doi: 10.1016/j.neuroimage.2005.02.034
129. Salat D, Tuch D, Greve D, Van Der Kouwe A, Hevelone N, Zaleta A, et al. Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiol Aging* (2005) 26:1215–27. doi: 10.1016/j.neurobiolaging.2004.09.017
130. Wu K, Taki Y, Sato K, Kinomura S, Goto R, Okada K, et al. Age-related changes in topological organization of structural brain networks in healthy individuals. *Hum Brain Mapp.* (2012) 33:552–68. doi: 10.1002/hbm.21232
131. Betzel RF, Byrge L, He Y, Goñi J, Zuo X-N, Sporns O. Changes in structural and functional connectivity among resting-state networks across the human lifespan. *Neuroimage* (2014) 102:345–57. doi: 10.1016/j.neuroimage.2014.07.067
132. Cao M, Huang H, Peng Y, Dong Q, He Y. Toward developmental connectomics of the human brain. *Front Neuroanat.* (2016) 10:25. doi: 10.3389/fnana.2016.00025
133. Vagberg M, Granasen G, Svenningsson A. Brain parenchymal fraction in healthy adults-a systematic review of the literature. *PLoS ONE* (2017) 12:e0170018. doi: 10.1371/journal.pone.0170018
134. Cai L, Chan JS, Yan JH, Peng K. Brain plasticity and motor practice in cognitive aging. *Front Aging Neurosci.* (2014) 6:31. doi: 10.3389/fnagi.2014.00031
135. Hamarat E, Thompson D, Steele D, Matheny K, Simons C. Age differences in coping resources and satisfaction with life among middle-aged, young-old, and oldest-old adults. *J Genet Psychol.* (2002) 163:360–7. doi: 10.1080/00221320209598689
136. Bowling A, Iliffe S. Psychological approach to successful ageing predicts future quality of life in older adults. *Health Qual Life Outcomes* (2011) 9:13. doi: 10.1186/1477-7525-9-13
137. Jeste DV, Savla GN, Thompson WK, Vahia IV, Glorioso DK, Martin AVS, et al. Association between older age and more successful aging: critical role of resilience and depression. *Am J Psychiatry* (2013) 170:188–96. doi: 10.1176/appi.ajp.2012.12030386
138. Buckner RL. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron* (2004) 44:195–208. doi: 10.1016/j.neuron.2004.09.006
139. Greenwood PM. Functional plasticity in cognitive aging: review and hypothesis. *Neuropsychology* (2007) 21:657–73. doi: 10.1037/0894-4105.21.6.657
140. Reuter-Lorenz PA, Park DC. Human neuroscience and the aging mind: a new look at old problems. *J Gerontol Series B* (2010) 65:405–15. doi: 10.1093/geronb/gbq035
141. Schneider-Garces NJ, Gordon BA, Brumback-Peltz CR, Shin E, Lee Y, Sutton BP, et al. Span, CRUNCH, and beyond: working memory capacity and the aging brain. *J Cogn Neurosci.* (2010) 22:655–69. doi: 10.1162/jocn.2009.21230
142. Park DC, Bischof, GN. Neuroplasticity, aging, and cognitive function, In: Schaie KW, Willis SL, editors. *Handbook of the Psychology of Aging*. San Diego, CA: Academic Press (2011). p. 109–117.
143. Rypma B, D'esposito M. Age-related changes in brain–behaviour relationships: Evidence from event-related functional MRI studies. *Eur J Cogn Psychol.* (2001) 13:235–56. doi: 10.1080/09541440042000296
144. Vatansever D, Menon DK, Manktelow AE, Sahakian BJ, Stamatakis EA. Default mode dynamics for global functional integration. *J Neurosci.* (2015) 35:15254–62. doi: 10.1523/JNEUROSCI.2135-15.2015
145. Wen X, Zhang D, Liang B, Zhang R, Wang Z, Wang J, et al. Reconfiguration of the brain functional network associated with visual task demands. *PLoS ONE* (2015) 10:e0132518. doi: 10.1371/journal.pone.0132518
146. Liang X, Zou Q, He Y, Yang Y. topologically reorganized connectivity architecture of default-mode, executive-control, and salience networks across working memory task loads. *Cereb Cortex* (2016) 26:1501–11. doi: 10.1093/cercor/bhu316
147. Geerligs L, Maurits NM, Renken RJ, Lorist MM. Reduced specificity of functional connectivity in the aging brain during task performance. *Hum Brain Mapp.* (2014) 35:319–30. doi: 10.1002/hbm.22175
148. Geerligs L, Renken RJ, Saliasi E, Maurits NM, Lorist MM. A brain-wide study of age-related changes in functional connectivity. *Cereb Cortex* (2015) 25:1987–99. doi: 10.1093/cercor/bhu012
149. Honey CJ, Kötter R, Breakspear M, Sporns O. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. *Proc Natl Acad Sci USA.* (2007) 104:10240–5. doi: 10.1073/pnas.0701519104
150. Hafkemeijer A, Altmann-Schneider I, Craen AJ, Slagboom PE, Grond J, Rombouts SA. Associations between age and gray matter volume in anatomical brain networks in middle-aged to older adults. *Aging Cell* (2014) 13:1068–74. doi: 10.1111/acel.12271
151. Liu K, Yao S, Chen K, Zhang J, Yao L, Li K, et al. Structural Brain Network Changes across the Adult Lifespan. *Front Aging Neurosci.* (2017) 9. doi: 10.3389/fnagi.2017.00275
152. Perry E, Blessed G, Tomlinson B, Perry R, Crow T, Cross A, et al. Neurochemical activities in human temporal lobe related to aging and Alzheimer-type changes. *Neurobiol Aging* (1981) 2:251–6. doi: 10.1016/0197-4580(81)90032-4
153. Salat DH, Kaye JA, Janowsky JS. Selective preservation and degeneration within the prefrontal cortex in aging and Alzheimer disease. *Arch Neurol.* (2001) 58:1403–8. doi: 10.1001/archneur.58.9.1403
154. De Haan W, Van Der Flier WM, Koene T, Smits LL, Scheltens P, Stam CJ. Disrupted modular brain dynamics reflect cognitive dysfunction in Alzheimer's disease. *Neuroimage* (2012) 59:3085–93. doi: 10.1016/j.neuroimage.2011.11.055
155. Van Den Heuvel MP, Fornito A. Brain networks in schizophrenia. *Neuropsychol Rev.* (2014) 24:32–48. doi: 10.1007/s11065-014-9248-7
156. Ganella EP, Seguin C, Bartholomeusz CF, Whittle S, Bousman C, Wannan CMJ, et al. Risk and resilience brain networks in treatment-resistant schizophrenia. *Schizophr Res* (2018) 193:284–92. doi: 10.1016/j.schres.2017.07.014
157. De Witte NAJ, Mueller SC. White matter integrity in brain networks relevant to anxiety and depression: evidence from the human

connectome project dataset. *Brain Imaging Behav.* (2017) 11:1604–15. doi: 10.1007/s11682-016-9642-2

158. Kennis M, Van Rooij SJ, Van Den Heuvel MP, Kahn RS, Geuze E. Functional network topology associated with posttraumatic stress disorder in veterans. *Neuroimage Clin.* (2016) 10:302–9. doi: 10.1016/j.nicl.2015.12.008
159. Shim M, Im CH, Lee SH. Disrupted cortical brain network in post-traumatic stress disorder patients: a resting-state electroencephalographic study. *Transl Psychiatry* (2017) 7:e1231. doi: 10.1038/tp.2017.200
160. Fan Y, Shi F, Smith JK, Lin W, Gilmore JH, Shen D. Brain anatomical networks in early human brain development. *Neuroimage* (2011) 54:1862–71. doi: 10.1016/j.neuroimage.2010.07.025
161. Meunier D, Lambiotte R, Bullmore ET. Modular and hierarchically modular organization of brain networks. *Front Neurosci.* (2010) 4:200. doi: 10.3389/fnins.2010.00200
162. Meunier D, Fonlupt P, Saive AL, Plailly J, Ravel N, Royet JP. Modular structure of functional networks in olfactory memory. *Neuroimage* (2014) 95:264–75. doi: 10.1016/j.neuroimage.2014.03.041

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Differences in Neural Recovery From Acute Stress Between Cortisol Responders and Non-responders

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Adaptive recovery from a stressor fosters resilience. So far, however, few studies have examined brain functional connectivity in the aftermath of stress, with inconsistent results reported. Focusing on the immediate recovery from psychosocial stress, the current study compared amygdala resting-state functional connectivity (RSFC) before and immediately after psychosocial stress between cortisol responders and non-responders. Differences between groups were expected for amygdala RSFC with regions involved in down-regulation of the physiological stress response, emotion regulation, and memory consolidation. Eighty-six healthy participants (36 males/50 females) underwent a social stress paradigm inside the MRI scanner. Before and immediately after stress, resting-state (RS) fMRI scans were acquired to determine amygdala RSFC. Next, changes in connectivity from pre- to post-stress were compared between cortisol responders and non-responders. Responders demonstrated a cortisol increase, higher negative affect, and decreased heart rate variability (HRV) in response to stress compared to non-responders. A significant Sex-by-Responder-by-Time interaction was found between the bilateral amygdala and posterior cingulate cortex (PCC) and precuneus ($p < 0.05$, corrected). As males were also more likely to show a cortisol increase to the stress task than females, follow-up analyses were conducted for both sexes separately. Whereas no difference was observed between female responders and non-responders, male non-responders showed an increase in FC after stress between the bilateral amygdala and the PCC and precuneus ($p < 0.05$, corrected). The increased coupling of the amygdala with the PCC/precuneus, a core component of the default mode network (DMN), might indicate an increased engagement of the amygdala within the DMN directly after stress in non-responders. Although this study was carried out in healthy participants, and the results likely reflect normal variations in the neural response to stress, understanding the mechanisms that underlie these variations could prove beneficial in revealing neural markers that promote resilience to stress-related disorders.

Keywords: stress recovery, fMRI, resting state, functional connectivity, amygdala, cortisol

INTRODUCTION

While we plan, set goals, and build expectations concerning our present and future, we are confronted with numerous situations that challenge our resources and our prospect of life. Both predictable and unpredictable events require a continuous adaptation to regain balance on a physiological and psychological level. McEwen and Wingfield (1) described this adaptive process as maintaining stability in life-essential systems ("homeostasis") through change ("allostasis"). The allostatic state is reflected by the adjustment or maintenance of physiological and behavioral systems in order to adapt to challenging or stressful situations. An imbalance in these physiological systems over a prolonged period of time may result in allostatic overload and in the long run in stress-related psychopathology, such as major depressive disorder or posttraumatic stress disorder (2), depending on individual experiences, genetic predispositions, and social factors. Studying the mechanisms supporting adaptive recovery from stress is thus of importance, as this may ultimately improve interventions aimed to maintain resilience after adversity.

Early work has mainly focused on the physiological stress response, which comprises an immediate and a delayed response. The immediate reaction is elicited by the activation of the sympatho-adrenomedullary pathway of the autonomic nervous system. It expresses itself in rapid physiological effects, caused by the release of epinephrine and norepinephrine from the adrenal medulla. The resulting autonomic alternations are typically known as the fight-or-flight response (3), and are directed toward preparing the organism to deal with a threatening or stressful situation. In general, the autonomic response is short-lived, as the parasympathetic nervous system—the antagonist of the sympathetic nervous system—exerts regulatory control after a short while (4). The neuroendocrine response entails a delayed secretion of glucocorticoids. Through the activation of the hypothalamus-pituitary-adrenal (HPA) axis, a sequence of different physiological processes leads to the release of glucocorticoids (GCs). The most important glucocorticoid in humans is the stress hormone cortisol (4). In general, GCs play a very heterogeneous role in stress, as they can serve permissive, stimulative, suppressive, and preparative functions (5). With respect to recovery from stress, two functions of GCs are especially of interest: First, GCs regulate their own secretion by acting back on the HPA axis in a negative feedback loop, thereby inhibiting further secretion of adrenocorticotropic hormone (ACTH) (6). Second, GCs are crucial in processes of memory consolidation, facilitating learning of emotional information (7).

An important function of the stress response is to prepare the organism for future stressful experiences by promoting the memory consolidation of current stressful events (7). Encountering a stressful situation in the future enables the organism for an adaptive stress response, as it can revert to stored contextual information from previous and similar stressful experiences. A well-known phenomenon that reflects this adaptive function of the stress response is that emotionally significant events are indeed more likely to be remembered (7–9). Stress agents, such as norepinephrine and cortisol, are involved in the enhanced memory consolidation of emotional information, as they directly influence the activation of brain structures supporting memory (7). Moreover, there is evidence that the amygdala interacts with the hippocampus in mediating the effects of stress on the consolidation of contextual information (7, 10). As a second function of the stress response, negative emotions, which often follow stressful experiences, need to be adjusted as part of emotion regulation. Therefore, emotion regulation initiates a more regulatory role in the stress response to allow the return to the initial state of homeostasis. Specifically, the interactions between the amygdala and medial PFC (mPFC) are deemed essential for successful emotion regulation and may be mediated by cortisol, as these interactions seem to strengthen after hydrocortisone administration (11), and were related to endogenous cortisol fluctuations as well (12).

Over the past decade, neuroimaging methods have given us more insight into the underlying neural mechanisms involved in the stress response (13, 14), primarily focusing on the activity of the amygdala during the stress experience or immediately thereafter. During stress, a decrease in the activity of limbic structures was found, including the amygdala, mPFC, and hippocampus (15, 16). In contrast, the amygdala showed increased reactivity to emotionally negative stimuli in the aftermath of psychological stress (17, 18). However, to understand how brain regions interact with each other in initiating and regulating stress responses, we need to resort to measures of connectivity between remote brain regions rather than assessing activation in single areas. Resting-state (RS) fMRI might be the most intuitive paradigm to study connectivity changes in the aftermath of stress, as it assumes diffuse mind states and allows a rather "naturalistic" and undirected assessment of neural recovery mechanisms. So far, only five studies have examined the effects of psychological stress on resting-state functional connectivity (RSFC) of the brain in healthy volunteers.

Van Marle et al. (19) studied amygdala RSFC following a stress induction paradigm, in which participants had to watch aversive film clips. The comparison between the stress and control group revealed increased RSFC of the amygdala with the dorsal anterior cingulate cortex (dACC), the anterior insula (AI), and a dorso-rostral pontine region after stress. As the dACC and AI are both involved in mediating autonomic responses, the connectivity pattern obtained was interpreted to represent a vigilant state following the stress induction.

In the second study, Vaisvaser et al. (20) studied a more fine-grained trajectory of the stress response in the brain, using a serial subtraction arithmetic task. They compared RSFC of two different seed regions, the PCC and hippocampus, between three different time-points: before stress, immediately after stress, and 2 h after stress. Immediately after stress, the PCC increased its functional connectivity with the following regions: mPFC, thalamus, caudate nucleus, and inferior parietal lobule. This RSFC pattern was reversed when measured 2 h after stress. In contrast, an increased RSFC between the hippocampus and amygdala following stress persisted up to 2 h, pointing to a prolonged effect of stress on RSFC of the brain.

Moreover, the authors found that non-responders specifically were characterized by a sustained increase in connectivity between these limbic regions.

Quaedflieg et al. (21) assessed RSFC before, immediately after, and 30 min after stress induction with the Maastricht Acute Stress Test, which includes both social and physical stress components. Choosing the amygdala as seed region, RSFC with the ventrolateral PFC, ventral PCC, cuneus, and culmen decreased after stress, whereas RSFC with the anterior hippocampal complex and the parahippocampal gyrus increased. Moreover, cortisol responders displayed stronger RSFC of the amygdala with the mPFC. During recovery, decreased RSFC was reported with the dorsolateral PFC (dlPFC), and ventral ACC, whereas an increase in RSFC was found for dACC and culmen. Again, differences between responders and non-responders were found: Responders were not only characterized by reduced connectivity with the left dlPFC, dACC, and culmen, but also by increased RSFC with the anterior hippocampal complex and the parahippocampal gyrus as compared with non-responders.

A more recent study applied the serial subtraction arithmetic task while comparing RSFC directly before and after stress induction (22). In contrast to the other studies, the authors refrained from a seed-based correlational analysis and instead, applied a data-driven approach. They reported strengthening of thalamo-cortical connectivity and weakening of cross-hemispheric parieto-temporal connectivity.

The last study focused on the late recovery phase from stress and studied amygdala RSFC 1 h after administration of the Trier Social Stress Task (23). Compared to a non-stressed control group, the stressed participants demonstrated increased amygdala RSFC with two cortical midline structures, the PCC/precuneus and mPFC. The authors concluded that the increased amygdala RSFC with the mPFC could represent top-down regulation of the amygdala by the mPFC, reflecting emotion regulation in the aftermath of stress. The increased amygdala RSFC with the PCC and precuneus was hypothesized to relate to memory consolidation of emotionally self-referential information, as those regions are involved in autobiographical memory processes (24, 25). An increase in RSFC between the amygdala and hippocampus was, contrary to the authors' expectations, not found in this study. In agreement with the study by Vaisvaser et al. (20), the amygdala RSFC pattern during late recovery from stress again points to effects of stress on the brain that stretch far beyond the immediate stress response.

In sum, previous research results showed divergent findings, which may be explained by differences in the type of stress induction, the experimental design, gender distribution of the study sample, and choice of seed regions. The focus of the current study was to examine the effects of psychosocial stress on amygdala RSFC in order to replicate and extend previous findings. For this purpose, moderate psychosocial stress was induced in healthy male and female volunteers inside the MRI scanner. To investigate the immediate recovery period from stress and its related functional connectivity patterns, RSFC of the amygdala was assessed during a resting-state fMRI scan acquired before and immediately after stress exposure. We expected that after stress the amygdala would demonstrate increased connectivity with regions involved in the down-regulation of the physiological stress response, in emotion regulation, and in memory consolidation. Moreover, as cortisol plays a key role in reaching homeostasis, we expected that these connections would be engaged differentially in people who demonstrate a cortisol increase in response to stress compared to those who do not.

MATERIALS AND METHODS

Participants

Hundred and four healthy volunteers were recruited through mailing lists of Berlin's universities, the experimental server platform PESA of the Humboldt-Universität zu Berlin, and through online advertorials. A compensation of 8 euro per hour was paid. An initial telephone-screening interview decided whether participants were eligible for inclusion or not. Exclusion criteria were: (history of) psychiatric diseases, as was checked by the screening questionnaire for Axis I disorders of the Structured Clinical Interview for DSM-IV (26), first-degree relatives with psychiatric diseases, contraindications for MRI scanning (e.g., metallic implants), acute or chronic neurological or physical diseases, history of alcoholism and/or drug abuse, current intake of prescription medication, color blindness, irregular sleep-wake rhythm, uncorrectable vision, and regular smoking (>5 cigarettes per day). Furthermore, students of psychology, medicine, or neuroscience were excluded because of potential previous knowledge about stress paradigms. Participants underwent a (neuro)psychological assessment containing the Edinburgh Handedness Inventory (27), Verbal Learning and Memory Test [VLMT; (28)], Multiple-Choice Vocabulary Intelligence Test [MWT-B; (29)], and German versions of the Beck Depression Inventory II [BDI-II; (30)], State-Trait Anxiety Inventory [STAI; (31)], Symptom Checklist-90 Revised [SCL-90-R; (32)], NEO-Five-Factor Inventory [NEO-FFI; (33)], Childhood-Trauma-Questionnaire [CTQ; (34)], as well as the English version of the Life-Events-Checklist [LEC; (35)]. The local ethics committee approved the study, and written informed consent was obtained from all participants.

Upon screening, a total of 104 participants were included in the study. Eighteen participants had to be excluded for the following reasons: Falling asleep during RS-fMRI ($n = 7$), severe image artifacts ($n = 1$), technical problems leading to delayed acquisition ($n = 6$), or early dropout from the study ($n = 4$). The final sample thus consisted of 86 participants (mean age 28.38 $\pm$ 7.25, range 20–58). Twenty-three females in our sample used contraceptives (19 oral contraceptive pill, 4 NuvaRing).

Stress Induction

To induce moderate psychosocial stress, a modified version of the Montreal Imaging Stress Task [MIST; (36)] was employed (ScanSTRESS) (37, 38). The stress paradigm is designed for use in a neuroimaging setting and combines social evaluative threat components (verbal and non-verbal feedback by the experimenters), as well as uncontrollable components (task difficulty, time constraints, and mock feedback of poor performance). Dickerson and Kemeny (39) demonstrated in a meta-analysis that stressors containing both these components

lead to the strongest neuroendocrine stress response. Specifically, participants performed challenging arithmetic and mental rotation tasks under time pressure during stress blocks. Time for processing a trial was adapted to individual performance, thereby ensuring a low success rate in all participants. In addition, participants were continuously shown a live video stream of the two experimenters, who put on a critical and disapproving look to convey negative non-verbal feedback. After slow or incorrect responses, a text field indicating "Work faster!" or "Error!" appeared on the screen. During control blocks participants solved simple figure and number matching tasks without any time pressure, and without any visual or non-verbal feedback. The live video stream was crossed out and the two stressors did not observe the participants. For further details on the stress task, please refer to Dahm et al. (40).

Physiological and Subjective Assessments of Stress

To assess cortisol levels, nine saliva samples were collected throughout the procedure, using the Salivette saliva collection device (Sarstedt, Germany). In stress research, salivary cortisol is a common biomarker of psychological stress (41). Three saliva samples were collected before, one sample during, and five further samples after the stress task (see **Figure 1** for an overview of the nine saliva sampling time-points). All samples were stored at −20°C until they were assayed at the Department of Biopsychology at the Technische Universität Dresden, Germany (https://tu-dresden.de/mn/psychologie/biopsychologie). To determine the cortisol concentrations in saliva (in nmol/l), the chemiluminescence-immuno-assay kit with high sensitivity (IBL, Hamburg, Germany) was employed. Inter- and intra-assay coefficients of variations were below 10%. For each participant, an aggregate measure of saliva cortisol secretion across all nine measurements was calculated: the area under the curve with respect to increase (in the following referred to as cortisol AUCi) (42). Positive values denote an increase in saliva cortisol over the course of the experiment, negative values a decrease.

Before the statistical analysis of amygdala RSFC, participants were categorized as cortisol responder or non-responder based on a baseline-to-peak cortisol increase >2.5 nmol/l in response to the stress task (43). As saliva cortisol levels reach their peak 10–30 min after the end of stress induction (44), the difference between the sixth (15 min after the end of the stress task) and third saliva sample (immediately before the onset of the stress task) was calculated to characterize the stress-induced increase in cortisol. Averaged across all participants, these two sample time points also reflected the minimum before and the maximum absolute cortisol concentration after stress induction (see **Figure 2**). To test for existing baseline-differences, the groups were compared on all baseline physiological and psychometric measures. Because the assumption of normality was violated, non-parametric Mann–Whitney *U*-tests were used instead of unpaired *t*-tests.

Furthermore, heart rate was continuously recorded using an infrared pulse oximeter placed on the left ring finger (sampling rate of 50 Hz). The heart rate data acquired during the RS scans were used to determine parameters of heart rate frequency (HRF) and heart rate variability (HRV). For each RS scan, peak-to-peak intervals between the heartbeats were extracted using MATLAB R2012a (The Mathworks Inc.). Next, heart rate data were manually checked and corrected for misdetection and ectopic beats using the tool Physiological Noise Modeling (45). Finally, text files containing the corrected interbeat intervals of each RS scan were imported into KUBIOS HRV, a common software suite for HRV analysis (46). Besides HRF, this software calculates several distinct HRV parameters. The spectral power in the high-frequency band (0.15–0.4 Hz) during rest (HF-HRV) was used as a measure of HRV in further analysis, as it is known to reflect the vagal influence on cardiac function (47). That is, higher values indicate stronger parasympathetic activity. To achieve a normal distribution, the HF-HRV values were log-transformed.

Subjective stress experience during the ScanSTRESS task was assessed after the last saliva sample was acquired. Six items asked about negative affect during the task. Items were rated on a four-point scale ranging from "fully agree" to "fully disagree."

HRF, HF-HRV, and cortisol were analyzed using three-way repeated measures ANCOVAs (mixed design) in SPSS Version 20 (IBM Corp.), with Group and Sex as between-subject factors, and Age as covariate, followed-up by relevant *Post hoc t*-tests. When the assumption of sphericity was violated, the degrees of freedom were corrected using the Greenhouse-Geisser adjustment. *Post-hoc t*-tests were conducted using Bonferroni adjusted alpha levels.

FMRI Data Acquisition

Imaging data were acquired on a Siemens MAGNETOM TIM Trio 3.0 Tesla MRI scanner equipped with a 12-channel head coil (Siemens, Erlangen, Germany). For each RS scan, a total of 154 images was acquired using T_2^* weighted gradient-echo echo-planar imaging with the following scan parameters: 37 slices using an interleaved slice-acquisition in a descending order; repetition time (TR) = 2,020 ms; echo time (TE) = 25 ms; flip angle = 80°; field of view (FOV) = 192 × 192 mm; 64 × 64 matrix; 3 mm isotropic voxels with a 0.6 mm slice gap. Participants were instructed to lie still with their eyes closed in the darkened scanner room, not to think of anything in particular, and to stay awake during the entire scan.

For registration to standard space, a high-resolution anatomical image of the whole brain (voxel size 1 mm^3) was obtained using a T_1 weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with the following scan parameters: 192 sagittal slices; TR = 1,900 ms; TE = 2.52 ms; flip angle = 9°; FOV = 256 × 256 mm; 256 × 256 matrix; slice gap = 0.5 mm; parallel imaging technique GRAPPA acceleration factor 2. The scan took 4 min and 26 s. Each subject's anatomical image was inspected for abnormalities by a neuroradiologist.

FMRI Data Preprocessing

The following preprocessing was carried out using FSL (48): motion correction, brain extraction, and spatial smoothing with a FWHM of 6 mm. Linear registration parameters were obtained for the functional-to-structural transformation, using FLIRT with the Boundary Based Registration (BBR) algorithm.

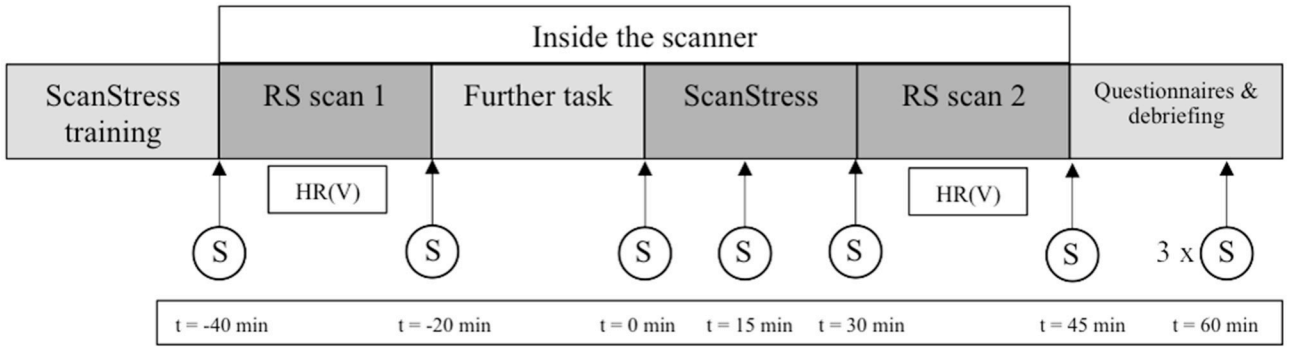

FIGURE 1 | Procedure on the second day of scanning including the time-points of the salivary cortisol samples. Time (t) of sampling is relative to the onset of the ScanSTRESS task. The three last saliva samples were acquired every 15min; S, saliva sample; HR (V), heart rate and heart rate variability, RS, resting state.

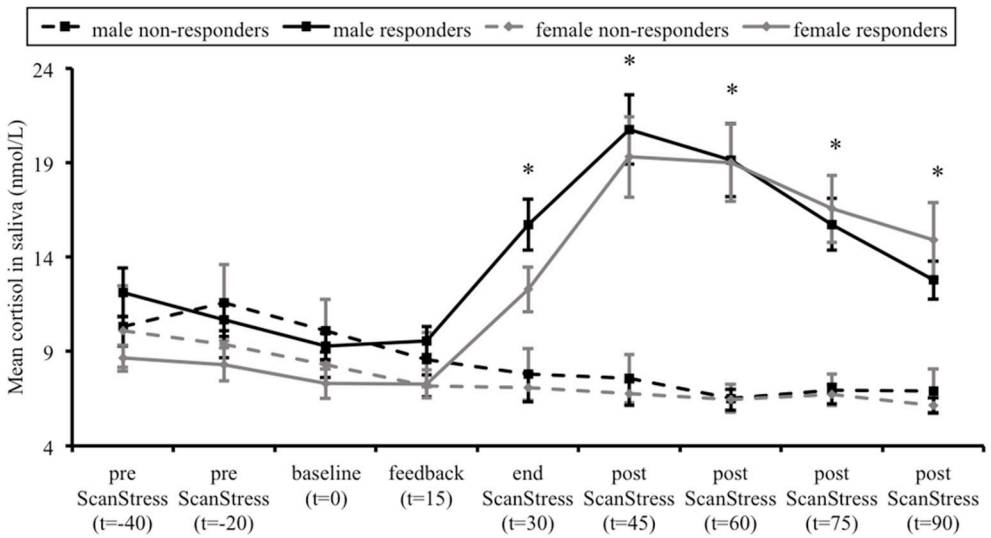

FIGURE 2 | Mean salivary cortisol levels in cortisol responders and non-responders, for males and females separately. Error bars represent standard errors of the mean. Time (t) is relative to the onset of the ScanSTRESS task. *$p <$ 0.001, indicating difference between responders and non-responders across both sexes.

Non-linear normalization parameters for the structural-to-standard-space (2 mm MNI) transformation were obtained with FNIRT, using the standard warp resolution setting of 10 mm. Next, functional data were further cleaned from artifacts using ICA-AROMA (49), which regresses out latent signal sources (independent components) that it classifies as noise. Lastly, a high-pass temporal filter of 125 s was applied to the cleaned 4D images, which were then normalized to standard space using the previously derived registration parameters.

FMRI Time-Course Extraction and Statistical Analysis

The goal of this study was to examine RSFC of the amygdala before and immediately after stress. For this purpose, a seed-based correlation analysis was employed. As a first step, binary masks of the left and right amygdala were anatomically defined by means of the Harvard Oxford Subcortical Probability Atlas, provided within FSL. Only voxels with ≥80% probability of belonging to the amygdala were used to create the seed masks. Next, these standard-space masks were registered to each participant's RS data set using the inverse of the MNI to native (fMRI) space transformation matrix. Afterwards, the first eigenvariate time series (i.e., most representative for all voxels within the mask) was extracted for each amygdala mask, for each participant, and for each RS scan separately. The same approach was applied to extract first eigenvariate time series of deep white matter (WM) and cerebrospinal fluid (CSF), to be used as covariates. Masks were created using FSL avg152 tissue priors (lower threshold value WM: 240, lower threshold value: CSF 160). For each seed and each RS scan, single subject general linear models (GLMs) were tested, including the seed's time-course as regressor of interest, together with the WM- and CSF-signal as covariate regressors. Four subject-level functional connectivity maps (left/right amygdala and pre/post stress) were thus obtained, representing voxels of which the time series were correlated

with the time series of the seed. The functional connectivity maps were then fed into a second-level fixed effects analysis to calculate a difference (z-statistic) map between pre- and post-stress amygdala connectivity.

The difference maps between pre- and post-stress were assessed for each amygdala in an ANCOVA, with Group (responder and non-responder), Sex (males and females), and the interaction between those factors as between-subject variables, adding Age as covariate. The resulting t-statistical maps then underwent Threshold-Free Cluster Enhancement [TFCE; (50)], using the default parameter settings ($H = 2$, $E = 0.5$, $C = 6$), and significance testing was carried out with permutation testing (4,000 iterations) using the in-house developed *TFCE_mediation* software (51). In the latter step, a null distribution of random results was generated against which the empirical findings were tested, which resulted in statistical images that are family-wise error corrected for multiple comparisons at $p < 0.05$. Follow-up test between responders and non-responders were conducted for males and females separately, using the same settings mentioned above.

The test was repeated using a small volume correction for regions that were expected to change their connectivity with the amygdala in response to stress a priori. For this purpose, a mask containing the mPFC, the hippocampus, as well as the PCC and precuneus was created using the Harvard Oxford (Sub)Cortical Probability Atlas. Here we applied no probability threshold, to be as unbiased as possible. The same multiple comparison correction as before was then applied, but this time only for voxels falling inside the mask.

The ROI mask and (un)corrected statistical images are available on Neurovault (52) via this link: http://neurovault.org/collections/3578.

General Procedure

After study inclusion, participants completed three sessions on three separate days. At the first appointment, the absence of exclusion criteria was confirmed. Furthermore, the session contained a neuropsychological assessment, including tests for verbal memory and intelligence.

The last two sessions were conducted around and inside the MRI scanner. On the days of scanning participants were required to be awake for at least 4 h upon arrival, to refrain from caffeine and nicotine, not to eat 2 h before arrival, and to abstain from physical exercise after 7 pm on the day before. The MRI sessions took place on two consecutive days at the same time of day. Participants either arrived at 11:30 a.m. or 2 p.m. During the MRI sessions, participants had to complete three different task scans, and several anatomical scans were acquired as well. All scans relevant for the current study were acquired on the second day of scanning. On this day, participants first completed the training session of the ScanSTRESS task. Next, participants were brought into the scanner room, where the two RS scans, one before and one immediately after the stress task, were acquired. Throughout the procedure, nine saliva samples were collected. After scanning, participants completed several psychological questionnaires outside the scanner. After completing all questionnaires, participants were debriefed, thanked, and paid. The experimental procedure of the second day of scanning is shown in the **Figure 1**.

RESULTS

Definition of Cortisol Responders and Non-responders

Due to missing saliva samples, one female participant could not be assigned to either one of the two groups, and therefore was excluded. The classification resulted in 47 cortisol responders and 38 cortisol non-responders. Importantly, males were more likely to show a cortisol increase to the stress task than females [χ^2 (1, $N = 85$) $= 7.24$, $p = 0.007$]. There was no significant difference between responders and non-responders for baseline cortisol concentrations, as well as for HRF and HRV before stress induction, independent of the factor Sex (all $p > 0.05$). Responders did show a higher mean score on the BDI-II, independent of the factor Sex. However, this difference between groups can be considered negligible, as the mean BDI scores of responders and non-responders were close to zero, far below the clinical cut-off (i.e., score > 13). Non-responders showed better performance during early recall on the VLMT than responders, though, on a descriptive level, between-group differences were small. Detailed between-group comparison results are reported in **Tables 1**, **2**.

Results for Physiological and Psychological Stress Measures

Figure 2 illustrates the average saliva cortisol levels for each group at each sampling time-point. Over the course of the experiment, responders showed a substantial increase in cortisol levels, while non-responders exhibited a gradual decline. This was confirmed by a significant interaction between Group and Time, $F_{(2.58,196.2)} = 42.23$, $p < 0.001$, $\eta^2_{partial} = 0.36$. Further *Post hoc* t-tests did not reveal any group differences at baseline cortisol levels. As expected, responders' cortisol levels were higher at all time-points after the stress induction compared to non-responders (all $p < 0.001$). Importantly, there was neither a main effect of Sex on the cortisol levels, $F_{(1,76)} = 1.8$, $p = 0.18$, $\eta^2_{partial} = 0.023$, nor a Time × Sex, $F_{(2.58,196.2)} = 2.2$, $p = 0.099$, $\eta^2_{partial} = 0.028$, Group × Sex, $F_{(1,76)} = 0.017$, $p = 0.897$, $\eta^2_{partial} < 0.001$, or Group × Time × Sex interaction, $F_{(2.58,196.2)} = 0.696$, $p = 0.535$, $\eta^2_{partial} = 0.009$.

Besides differences in cortisol levels, responders ($M = 11$, $SD = 4$) reported significantly more negative affect during the stress task than non-responders ($M = 8.57$, $SD = 4.01$), $t_{(82)} = -2.76$, $p = 0.007$, as did females ($M = 10.73$, $SD = 3.79$) compared to males ($M = 8.86$, $SD = 4.45$), $t_{(82)} = -2.08$, $p = 0.041$. Furthermore, higher subjective stress ratings were related to higher cortisol AUCi responses in responders irrespective of sex [$r_{(47)} = 0.325$, $p = 0.026$], and in females irrespective of being a responder or not [$r_{(48)} = 0.523$, $p < 0.001$].

Heart rate data were successfully acquired during 63 pre-stress and 67 post-stress RS scans. **Table 2** provides the mean

TABLE 1 | Demographic, psychometric, and baseline cortisol characteristics of responders and non-responders.

	Responders		Non-responders		*z*	*p*
	M	***SD***	***M***	***SD***		
Gender (male/female)	26/21		10/28			
Handedness (right/left/both)	43/2/2		36/1/1			
School education (10 yr/ ≥ 12 yr)	3/44		2/36			
Higher education (no/university/other)	2/38/7		2/34/2			
Age	28.66	7.15	28.24	7.46	0.75	0.45
BDI-II	4.63	4.15	3.13	4.86	2.23	0.026
STAI-T	33.85	7.49	30.82	5.75	1.89	0.059
SCL-90-R Depression	1.91	3.59	1.52	3.06	1.19	0.23
SCL-90-R Anxiety	0.85	2.03	0.37	0.68	1.23	0.22
SCL-90-R Global Severity Index	0.22	0.18	0.17	0.16	1.05	0.29
NEO-FFI Neuroticism	15.07	6.01	13.05	6.13	1.28	0.20
LEC	5.17	3.68	5.16	4.01	0.21	0.84
CTQ	30.91	4.52	30.27	4.83	1.00	0.32
VLMT (hits early recall)	64.04	5.93	68.13	4.82	−3.39	0.001
VLMT (hits delayed recall)	13.72	1.73	13.79	2.43	−0.89	0.37
VLMT (recognition)	14.68	0.70	14.79	0.53	−0.68	0.50
MWT-B	31.36	2.37	31.50	2.44	−0.07	0.95
Baseline cortisol (nmol/L)	8.38	3.66	8.77	4.09	−0.29	0.77

The Mann–Whitney U-Test was used for all group comparisons. BDI-II, Beck Depression Inventory II; STAI-T, State-Trait Anxiety Inventory-Trait; SCL-90-R, Symptom Checklist-90-Revised; NEO-FFI, NEO-Five-Factor Inventory; LEC, Life-Events-Checklist; CTQ, Childhood-Trauma-Questionnaire; VLMT, Verbal Learning and Memory Test; MWT-B, Multiple-Choice Vocabulary Intelligence Test.

TABLE 2 | Mean values and standard errors for HRF and HF-HRV before and after stress in responders and non-responders.

	Responders			Non-responders			*z*	*p*
	M	***SD***	***n***	***M***	***SD***	***n***		
BASELINE								
HRF	65.81	10.47	39	66.55	8.16	24	−0.28	0.777
HF-HRV[a]	6.83	1.04	39	6.78	0.97	24	0.28	0.777
AFTER STRESS								
HRF	70.37	12.58	41	68.13	9.72	26	0.55	0.58
HF-HRV[a]	6.44	1.12	41	6.57	1.26	26	−0.29	0.767

The Mann–Whitney U-Test was used for all group comparisons. HRF, heart rate frequency; HF-HRV, heart rate variability, measured as spectral power in the high-frequency band (0.15–0.4 Hz) during rest; [a]Values are log-transformed.

values of HRF and HRV before and after stress for responders and non-responders. Heart rate data for both RS scans were available for 57 participants (35 of them responders), which could thus be included in the further analysis of HRF and HRV. The repeated measures ANOVA for HRF showed a trend for the main effect of Time, $F_{(1,52)} = 3.91$, $p = 0.053$, $\eta^2_{partial} = 0.07$, indicating an increase in heart rate after stress in both groups. For the HF-HRV, a Group-by-Time interaction was revealed $F_{(1,52)} = 4.14$, $p = 0.047$, $\eta^2_{partial} = 0.074$. The group of responders drove this interaction, as they reacted with a decrease in HF-HRV in response to stress, $t_{(34)} = 3.50$, $p = 0.001$, while the HF-HRV of non-responders did not change. Furthermore, a main effect of Sex was found, $F_{(1,52)} = 8.95$, $p < 0.004$, $\eta^2_{partial} = 0.15$, indicating higher HF-HRV in women than in men. Lastly, stronger increases in HRF from pre- to post-stress were associated with higher cortisol in responders irrespective of sex [$r_{(35)} = 0.376$, $p = 0.026$], in females irrespective of being a responder or non-responder [$r_{(31)} = 0.37$, $p = 0.04$], and in male non-responders [$r_{(20)} = 0.46$, $p = 0.041$]. Stronger decreases in HF-HRV from pre- to post-stress were associated with higher cortisol in females irrespective of being a responder or non-responder [$r_{(31)} = -0.465$, $p = 0.008$].

Within females, there were not more non-responders taking contraceptives than responders, χ^2 (1, $N = 48$) = 1.443, $p < 0.23$ (note that information was missing from one female). No differences were found between females with or without contraceptive medication regarding psychometrics or physiology, except that females without contraception were older

($p = 0.008$), had higher CTQ ($p = 0.007$) and MWT-B ($p = 0.049$) scores, and demonstrated a trend for higher AUCi ($p = 0.067$).

In summary, these findings indicate an effective stress induction, mostly in the group of responders, which was characterized by an increase in salivary cortisol levels, higher stress ratings, as well as an increase in HRF and a decrease in the HF-HRV.

Resting-State Functional Connectivity Results

For both hemispheres, the seed-based correlation analysis across all participants and both RS scans revealed a pattern of amygdala functional connectivity that was highly comparable to patterns previously reported in literature by ourselves and others (23, 53), including the medial prefrontal cortex, lateral orbitofrontal cortex, temporal poles, hippocampus, and brainstem (see **Figure 3**).

We found a significant Responder-by-Sex-by-Time interaction for both the left and right amygdala (see **Figure 4A**). Given the significant interaction and the unequal distribution of cortisol responders and non-responders between males and females, follow-up group level comparisons between responders and non-responders were carried out in males and females separately.

In male participants, we found a significant Group-by-Time interaction between the left and right amygdala seed and the PCC and precuneus (left amygdala connectivity peak: $x = 10$, $y = -62$, $z = 20$, cluster size = 2,129 voxels; right amygdala connectivity peak: $x = 6$, $y = -62$, $z = 18$, cluster size = 821 voxels; see **Figure 4B**). Specifically, *post hoc* comparisons on the individual extracted connectivity scores (z-values) between the two time-points confirmed an increase for RSFC between amygdala and PCC/precuneus in non-responders from pre- to post-stress, $t_{(9)} = -6.95$, $p < 0.001$, and stronger RSFC in non-responders than responders post-stress, $t_{(34)} = 2.92$, $p = 0.006$. Considering Bonferroni correction for four *post-hoc* tests, a trend was found for stronger RSFC pre-stress in responders than non-responders, $t_{(34)} = -2.23$, $p = 0.033$ (see **Figure 4C**).

The between-group analysis in female participants did not reveal RSFC of the left or right amygdala with any other brain region. Importantly, the results did not change when use of contraceptive medication was included as confound regressor in the statistical model.

To test whether interindividual differences in baseline cortisol might have confounded our results, we ran a follow-up analysis that included baseline cortisol concentrations (i.e., the third saliva sample) as covariate. The Responder-by-Sex-by-Time interaction, as well as the effects in males only, remained significant, and were even slightly more pronounced.

DISCUSSION

Using a seed-based correlation approach, we examined the effects of psychosocial stress on amygdala RSFC in healthy volunteers, as a function of the acute cortisol response. To this end, RS-fMRI data were acquired before and immediately after stress induction inside the MRI scanner. Participants were classified as either cortisol responder or non-responder. At baseline, there was no difference between the groups in salivary cortisol concentrations. We found no differences between male and female participants in respect to cortisol levels. However, males were more likely to show a cortisol increase to the stress task than females. Furthermore, responders reported higher negative affect during the stress task than non-responders, while negative affect was associated with cortisol AUCi. Responders also demonstrated a decrease in HRV in the high-frequency range (HF-HRV) in response to stress, whereas non-responders showed no change. A decline of the HF-HRV points to a decline in vagal activity, and an increase in sympathetic influence (47). Thus, the decline of HF-HRV found in responders likely reflects a sustained autonomic arousal in the group of responders following the stress task. Taken together, the physiological and behavioral measures confirmed successful stress induction in the cortisol responders as compared to non-responders.

Based on the group differences in physiological stress reactivity, we expected amygdala RSFC to be differentially affected in responders and non-responders following stress as well. As responders and non-responders were distributed differently in males and females, with males being more likely to show a cortisol increase to the stress task than females, and the full factorial analysis demonstrated a significant Responder-by-Sex-by-Time interaction, group level comparisons between responders and non-responders were carried out in males and females separately. Whereas, we did not detect changes in amygdala RSFC between female responders and non-responders, the results showed a significant Group-by-Time interaction in males, demonstrating an increase in bilateral amygdala RSFC with the PCC and the adjacent precuneus from pre- to post-stress in non-responders, but not in responders. So far, previous studies that distinguished between responders and non-responders reported differential RSFC between other brain regions. Vaisvaser et al. (20), for example, found increased connectivity between the hippocampus and amygdala up to 2 h for non-responders. Quaedflieg et al. (21) reported increased FC between amygdala and dlPFC, dACC, and culmen, but decreased FC with the anterior hippocampal complex and the parahippocampal gyrus.

Considering that our connectivity analysis across participants and RS scans demonstrated strong RSFC between the amygdala and hippocampus, the RSFC between the amygdala and PCC/precuneus found here could in fact be driven or mediated by the hippocampus, a key region for storage and retrieval of episodic information (54). As the amygdala and hippocampus are bordering each other, and as the fMRI resolution is not high enough to completely disentangle signal from the amygdala and the anterior part of the hippocampus, the amygdala signal could be contaminated by signal from this area. Further, given that the hippocampus and the precuneus are directly connected through white matter pathways (55), amygdala RSFC with these regions may, in part, reflect connectivity of the hippocampus. This is, however, still in line with the assumption that increased RSFC with the PCC/precuneus after stress might be related to memory consolidation of emotionally salient information. The possibility that amygdala RSFC may have been mixed with

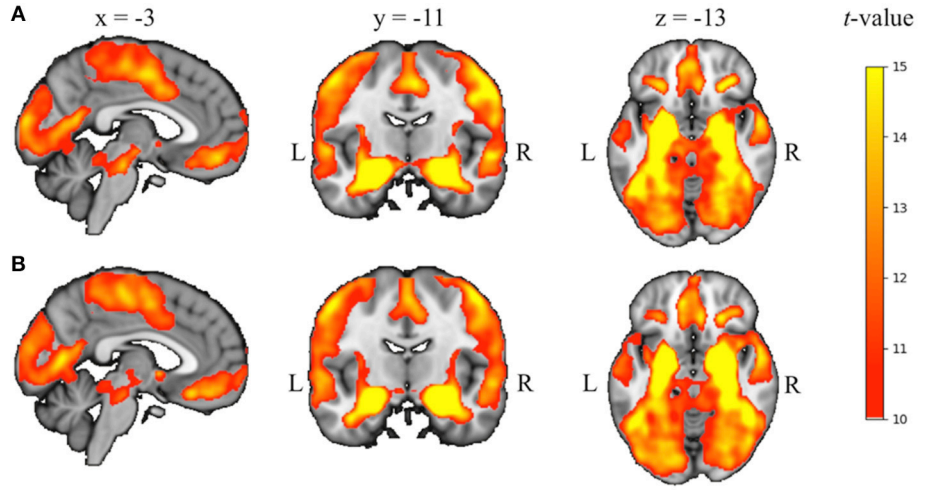

FIGURE 3 | Seed-based correlation results across all participants and both RS scans for left **(A)** and right **(B)** amygdala, overlaid on the 2 mm isotropic 152-MNI standard space brain ($p < 0.05$, TFCE and FWE-corrected for multiple corrections). R, right, L, left.

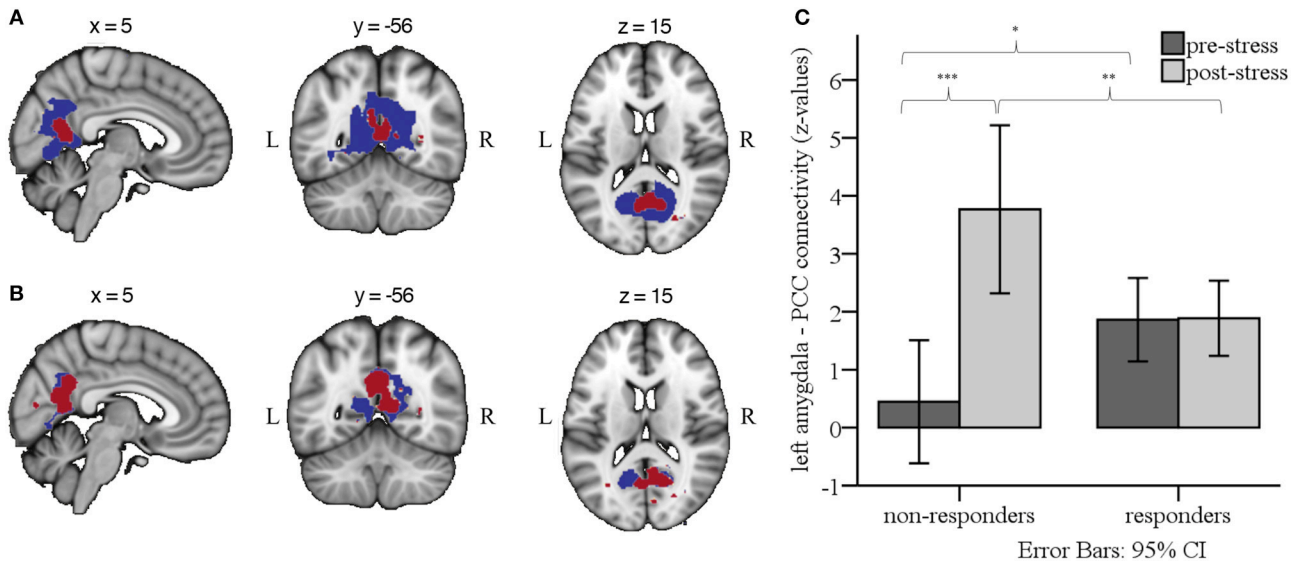

FIGURE 4 | (A) Group-by-Sex-by-Time interaction effects for left (blue) and right (red) amygdala RSFC ($p < 0.05$, whole brain TFCE and FWE-corrected for multiple corrections). **(B)** Group-by-Time interaction effects for left (blue) and right (red) amygdala RSFC in males only, indicating enhanced RSFC from pre- to post-stress for non-responders compared to responders ($p < 0.05$, whole brain TFCE and FWE-corrected for multiple corrections). Results are overlaid on the 2 mm isotropic 152-MNI standard space brain. R, right; L, left. **(C)** Bar graph illustrating the Group × Time interaction effect for left amygdala RSFC, depicting mean *z*-values from each of the RS scans in male responders and non-responders. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

hippocampal RSFC could also explain why we did not find any interaction effect for amygdala RSFC with the hippocampus. That is, artificially high functional connectivity may have been induced between the amygdala and hippocampus due to autocorrelation. This, in turn, could have obscured any underlying differences in connectivity between the two groups.

Consistent with the findings of the previous study of Veer et al. (23), the amygdala was coupled with the PCC/precuneus, a core component of the default mode network (DMN) (56). It should be noted, though, that the previous and current study diverge from each other not only in the time point of the assessment after stress, but also in the specific group that showed an effect. Whereas, the previous study assessed RSFC an hour after stress and reported increased FC in a stressed group compared to a non-stressed group, irrespective of being responder or non-responder, we assessed RSFC immediately after stress in the current study and found increased FC in non-responders compared to responders, as all participants were exposed to the stress task. The lack of a non-stressed control group and a second assessment at a later stage of recovery in

the current study hampers the comparison of results, though we could hypothesize that responders might have shown a similar increase of RSFC, but at a later time point. This would suggest that responders and non-responders might exhibit a different time line in terms of their neural response after psychosocial stress, which should be considered in future research.

The DMN is known to be implicated in several functions related to the self, including mind wandering (57), self-referential thought (58–60), autobiographical memory, as well as integrating past, present, and future experiences (61). Considering that DMN regions are functionally and structurally interconnected (55), the connectivity pattern between the amygdala and the PCC/precuneus could indicate an increased engagement of the amygdala within the DMN directly after stress in non-responders. Several explanations could underlie this finding: First, the stress paradigm we used may have been unable to induce stress in our non-responding participants. This could, for example, stem from earlier experiences with similar stressful situations, which then have led to a higher threshold of stress reactivity for this particular class of stressors (62). Accordingly, as Veer et al. (23) reported RSFC between amygdala and PCC/precuneus across all stressed participants an hour after stress, independent of cortisol responsivity, our results could mean that non-responders are able to activate this specific circuit more rapidly than responders, which could facilitate immediate updating of memory schemata by integrating recent experiences. Conversely, not responding to the stress task with an increase in cortisol might relate to maladaptive stress processing. For example, previous studies showed that a blunted cortisol response emerges in people who experienced adverse life-events (63) or, although preliminary, in schizophrenia patients (2). However, irrespective of whether a lack of a cortisol response should be considered maladaptive, reactions to stressful situations depend on many different factors, as Bonanno and Burton (64) discussed with their concept of "regulatory flexibility." Coping with stressors and regulating one's emotions properly is a dynamic process, which gives every individual a chance to adapt to adverse events in his or her own range of capabilities in the time they need.

It is important to note that the findings of the current study do not necessarily diverge with the results obtained in related studies in healthy volunteers that examined the effects of stress on brain functional connectivity. As van Marle et al. (19) used a different kind of stressor, containing neither social evaluative threat nor uncontrollable components, it is plausible that their stressor triggered a qualitatively different stress response, both physiologically and psychologically, and therefore different recovery processes compared to the stressor in our study. Although the study design of Vaisvaser et al. (20) was quite similar to the design of the current study, the selection of different seed regions makes it hard to compare our results to theirs. However, convergent with the current findings, Vaisvaser et al. did find sustained effects of stress on RSFC in non-responders. In contrast, Quaedflieg et al. (21) did use a similar design and the amygdala as seed region, yet conducted their analysis across female and male participants. They reported increased RSFC with dorsolateral PFC, dorsal ACC, and culmen in non-responders after stress. This illustrates that stress has prolonged effects on brain function, which might be related to adaptive recovery from a stressful situation.

Limitations and Future Directions

There are several limitations. First, data were acquired within a larger fMRI study, in which a fear extinction paradigm [adapted from Phelps and colleagues; (65)] was administered after the first resting-state scan, but prior to the ScanSTRESS task. We thus cannot rule out that the fear extinction paradigm had some effect on the stress reactivity of our participants. However, this task did not contain any aversive stimulation, as was used during fear acquisition on the day before. Further, all participants showed successful extinction learning, both directly after conditioning on day 1 of the study, as well as during late extinction prior to the stress task, as was confirmed by attenuation of the skin conductance response. Thus, it is quite likely that this task had rather negligible effects on stress reactivity.

Second, the study design did not include a non-stress control group. All participants underwent the stress task, and were classified *post hoc* as either cortisol responder or non-responder. This approach has the disadvantage that we could only reveal differences in amygdala RSFC related to cortisol differences between the groups, and not necessarily related to experiencing stress *per se*. In this context, it would be interesting to assess whether there are measurable differences in RSFC between cortisol non-responders and non-stressed controls that could account for non-hormonal effects of stress on amygdala RSFC.

Third, the difference in stress response between women and men found in the current study are in line with previous reports. In general, men tend to show larger salivary cortisol increases in response to a psychological stress task than women (66). Studies suggest that age (67), the use of contraceptives and phase of menstrual cycle (68–70), as well as sex hormones (71) contribute to differences in cortisol response. In our sample, 23 female participants took contraceptives. However, this could not account for the differences in any of our dependent variables. The number of days between the onset of the last menstrual cycle until the MRI assessment was enquired, but not individual cycle durations. As such, we could not estimate the exact menstrual phase of our female participants and test for its effects in our connectivity analyses. Furthermore, the ScanSTRESS task much relies on uncontrollable failure (i.e., achievement stress), which seems to affect men especially (72). This might thus have caused female participants to demonstrate a smaller stress response than males. Lastly, the composition of the stress panelists in terms of their sex was found to have an influence on the neuroendocrine stress response in both men and women (73). The authors reported cortisol increases only if the panel consisted of opposite sex members. Although we used male and female panelists, the panel in our study neither was composed of women and men in a consistent manner, nor was it composed depending on the subjects' sex. Additionally, we had more female than male panelists, which could explain the higher responder rate among the male subjects.

Fourth, it should be noted that our results are limited to amygdala-based circuits only, given the seed-based approach

used. Surely, stress affects many other brain regions, so there is a fair chance that we have missed changes in functional connectivity that emerged independent of the amygdala. Nonetheless, as the amygdala plays a pivotal role in most central stress-related processes, the selection of the amygdala as a seed is reasonable, and has provided a good insight in the role of stress-related brain circuits during recovery from stress.

Last, further studies are warranted to replicate the findings of the current study, and compare these to a control group. For this, one challenge would be to find an equivalent task for the control group, which does not induce any stress, but still is comparable to the stress task.

CONCLUSION

Taken together, the results of the current study add to the growing body of literature addressing the immediate recovery from stress. The neural circuits involved contain brain regions that are implicated in the regulation of the physiological stress response, in emotion regulation, and in memory consolidation, which underscores the necessity of these processes in recovering from stress. The current study extends findings from previous studies, which demonstrated differences in RSFC between cortisol responders and non-responders as well (20, 21). Together with studies that compared effects between a stressed and control group, these findings can provide a preliminary time line spanning both the immediate and long-term recovery from psychosocial stress. Interestingly, the results suggest a mediating role of cortisol on amygdala-posterior midline connectivity in the aftermath of stress. Although this study was carried out in healthy participants, and the results likely reflect normal variations in the neural response to stress, understanding the mechanisms that underlie these variations could prove beneficial in revealing neural markers that promote resilience to stress-related disorders.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of and after approval from the Medical Ethics Committee of Charité-Universitätsmedizin Berlin. All participants gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

SE, HW, PF, and IV were involved in the development of the study. PF, KD, and IV were involved in the data collection. AD, IV, KD, and SE were involved in the analysis and interpretation of data. All authors gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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REFERENCES

1. McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. *Horm Behav.* (2003) 43:2–15. doi: 10.1016/S0018-506X(02)00024-7
2. Zorn JV, Schür RR, Boks MP, Kahn RS, Joëls M, Vinkers CH. Cortisol stress reactivity across psychiatric disorders: a systematic review and meta-analysis. *Psychoneuroendocrinology* (2017) 77:25–36. doi: 10.1016/j.psyneuen.2016.11.036
3. Cannon WB. *Bodily Changes in Pain, Hunger, Fear and Rage: An Account of Recent Researches Into the Function of Emotional Excitement*. New York, NY: D. Appleton and Company (1922).
4. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci.* (2009) 10:397–409. doi: 10.1038/nrn2647
5. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev.* (2000) 21:55–89. doi: 10.1210/er.21.1.55
6. Herman JP, Ostrander MM, Mueller NK, Figueiredo H. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Prog Neuropsychopharmacol Biol Psychiatry* (2005) 29:1201–13. doi: 10.1016/j.pnpbp.2005.08.006
7. Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. *Nat Rev Neurosci.* (2009) 10:423–33. doi: 10.1038/nrn2651
8. Cahill L, Gorski L, Le K. Enhanced human memory consolidation with post-learning stress: interaction with the degree of arousal at encoding. *Learn Mem.* (2003) 10:270–4. doi: 10.1101/lm.62403
9. Buchanan TW, Lovallo WR. Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology* (2001) 26:307–17. doi: 10.1016/S0306-4530(00)00058-5
10. McGaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu Rev Neurosci.* (2004) 27:1–28. doi: 10.1146/annurev.neuro.27.070203.144157
11. Henckens MJAG, van Wingen GA, Joëls M, Fernández G. Time-dependent effects of corticosteroids on human amygdala processing. *J Neurosci.* (2010) 30:12725–32. doi: 10.1523/JNEUROSCI.3112-10.2010
12. Veer IM, Oei NYL, Spinhoven P, van Buchem MA, Elzinga BM, Rombouts SARB. Endogenous cortisol is associated with functional connectivity between the amygdala and medial prefrontal cortex. *Psychoneuroendocrinology* (2012) 37:1039–47. doi: 10.1016/j.psyneuen.2011.12.001
13. Dedovic K, D'Aguiar C, Pruessner JC. What stress does to your brain: a review of neuroimaging studies. *Can J Psychiatry* (2009) 54:6–15. doi: 10.1177/070674370905400104
14. Sapolsky RM. Stress and the brain: individual variability and the inverted-U. *Nat Neurosci.* (2015) 18:1344–6. doi: 10.1038/nn.4109
15. Pruessner JC, Dedovic K, Khalili-Mahani N, Engert V, Pruessner M, Buss C, et al. Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biol Psychiatry* (2008) 63:234–40. doi: 10.1016/j.biopsych.2007.04.041
16. Dedovic K, Duchesne A, Andrews J, Engert V, Pruessner JC. The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. *Neuroimage* (2009) 47:864–71. doi: 10.1016/j.neuroimage.2009.05.074
17. Oei NYL, Veer IM, Wolf OT, Spinhoven P, Rombouts SARB, Elzinga BM. Stress shifts brain activation towards ventral 'affective' areas during emotional distraction. *Soc Cogn Affect Neurosci.* (2012) 7:403–12. doi: 10.1093/scan/nsr024
18. van Marle HJF, Hermans EJ, Qin S, Fernández G. From specificity to sensitivity: how acute stress affects amygdala processing of biologically salient stimuli. *Biol Psychiatry* (2009) 66:649–55. doi: 10.1016/j.biopsych.2009.05.014

19. van Marle HJF, Hermans EJ, Qin S, Fernández G. Enhanced resting-state connectivity of amygdala in the immediate aftermath of acute psychological stress. *Neuroimage* (2010) 53:348–54. doi: 10.1016/j.neuroimage.2010.05.070
20. Vaisvaser S, Lin T, Admon R, Podlipsky I, Greenman Y, Stern N, et al. Neural traces of stress: cortisol related sustained enhancement of amygdala-hippocampal functional connectivity. *Front Hum Neurosci.* (2013) 7:313. doi: 10.3389/fnhum.2013.00313
21. Quaedflieg CWEM, van de Ven V, Meyer T, Siep N, Merckelbach H, Smeets T. Temporal dynamics of stress-induced alternations of intrinsic amygdala connectivity and neuroendocrine levels. *PLoS ONE* (2015) 10:e0124141. doi: 10.1371/journal.pone.0124141
22. Maron-Katz A, Vaisvaser S, Lin T, Hendler T, Shamir R. A large-scale perspective on stress-induced alterations in resting-state networks. *Sci Rep.* (2016) 6:21503. doi: 10.1038/srep21503
23. Veer IM, Oei NYL, Spinhoven P, van Buchem MA, Elzinga BM, Rombouts SARB. Beyond acute social stress: Increased functional connectivity between amygdala and cortical midline structures. *Neuroimage* (2011) 57:1534–41. doi: 10.1016/j.neuroimage.2011.05.074
24. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* (2006) 129:564–83. doi: 10.1093/brain/awl004
25. Summerfield JJ, Hassabis D, Maguire EA. Cortical midline involvement in autobiographical memory. *Neuroimage* (2009) 44:1188–200. doi: 10.1016/j.neuroimage.2008.09.033
26. Wittchen H-U, Zaudig M, Fydrich T. *SKID Strukturiertes Klinisches Interview für DSM-IV. Achse I und II*. Göttingen: Hogrefe (1997).
27. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* (1971) 9:97–113. doi: 10.1016/0028-3932(71)90067-4
28. Helmstaedter C, Lendt M, Lux S. *Verbaler Lern- und Merkfähigkeitstest (VLMT)*. Göttingen: Beltz (2001).
29. Lehrl S. *Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B)*. Göttingen: Hogrefe (2005).
30. Hautzinger H, Keller F, Kühner C. *BDI-II Beck Depressions-Inventar*. Frankfurt: Hartcourt Test Services (2006).
31. Laux L, Glanzmann P, Schaffner P, Spielberger CD. *STAI - Das State-Trait-Angstinventar*. Göttingen: Hogrefe (1981).
32. Franke GH. *SCL-90-R Symptom Checkliste von L. R. Derogatis (Deutsche Version)*. Göttingen: Beltz Test GmbH (2005).
33. Borkenau P, Ostendorf F. *NEO-FFI NEO-Fünf-Faktoren-Inventar nach Costa and McCrae*. Göttingen: Hogrefe (2008).
34. Wingenfeld K, Spitzer C, Mensebach C, Grabe HJ, Hill A, Gast U, et al. Die deutsche Version des Childhood Trauma Questionnaire (CTQ): Erste Befunde zu den psychometrischen Kennwerten. *Psychother Psychosom Med Psychol.* (2010) 60:442–50. doi: 10.1055/s-0030-1247564
35. Gray MJ, Litz BT, Hsu JL, Lombardo TW. Psychometric properties of the life events checklist. *Assessment* (2004) 11:330–41. doi: 10.1177/1073191104269954
36. Dedovic K, Renwick R, Mahani NK, Engert V, Lupien SJ, Pruessner JC. The Montreal imaging stress task: using functional imaging to investigate the effects of perceiving and processing psychosocial stress in the human brain. *J Psychiatry Neurosci.* (2005) 30:319–25.
37. Lederbogen F, Kirsch P, Haddad L, Streit F, Tost H, Schuch P, et al. City living and urban upbringing affect neural social stress processing in humans. *Nature* (2011) 474:498–501. doi: 10.1038/nature10190
38. Streit F, Haddad L, Paul T, Frank J, Schäfer A, Nikitopoulos J, et al. A functional variant in the neuropeptide S receptor 1 gene moderates the influence of urban upbringing on stress processing in the amygdala. *Stress* (2014) 17:352–61.doi: 10.3109/10253890.2014.921903
39. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull.* (2004) 130:355. doi: 10.1037/0033-2909.130.3.355
40. Dahm AS, Schmierer P, Veer IM, Streit F, Gorgen A, Kruschwitz J, et al. The burden of conscientiousness? Examining brain activation and cortisol response during social evaluative stress. *Psychoneuroendocrinology* (2017) 78:48–56. doi: 10.1016/j.psyneuen.2017.01.019
41. Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology* (2009) 34:163–71. doi: 10.1016/j.psyneuen.2008.10.026
42. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology* (2003) 28:916–31. doi: 10.1016/S0306-4530(02)00108-7
43. Miller R, Plessow F, Kirschbaum C, Stalder T. Classification criteria for distinguishing cortisol responders from nonresponders to psychosocial stress: evaluation of salivary cortisol pulse detection in panel designs. *Psychosom Med.* (2013) 75:832–40. doi: 10.1097/PSY.0000000000000002
44. Foley P, Kirschbaum C. Human hypothalamus–pituitary–adrenal axis responses to acute psychosocial stress in laboratory settings. *Neurosci Biobehav Rev.* (2010) 35:91–6. doi: 10.1016/j.neubiorev.2010.01.010
45. Brooks JCW, Beckmann CF, Miller KL, Wise RG, Porro CA, Tracey I, et al. Physiological noise modelling for spinal functional magnetic resonance imaging studies. *Neuroimage* (2008) 39:680–92. doi: 10.1016/j.neuroimage.2007.09.018
46. Tarvainen MP, Niskanen JP, Lipponen JA, Ranta-Aho PO, Karjalainen PA. Kubios HRV-heart rate variability analysis software. *Comput Methods Programs Biomed.* (2014) 113:210–20. doi: 10.1016/j.cmpb.2013.07.024
47. Thayer JF, Ahs F, Fredrikson M, Sollers JJ III, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neurosci Biobehav Rev.* (2012) 36:747–56. doi: 10.1016/j.neubiorev.2011.11.009
48. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* (2004) 23(Suppl. 1):S208–19. doi: 10.1016/j.neuroimage.2004.07.051
49. Pruim RHR, Mennes M, van Rooij D, Llera A, Buitelaar JK, Beckmann CF. ICA-AROMA: a robust ICA-based strategy for removing motion artifacts from fMRI data. *Neuroimage* (2015) 112(Suppl. C):267–77. doi: 10.1016/j.neuroimage.2015.02.064
50. Smith SM, Nichols TE. Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage* (2009) 44:83–98. doi: 10.1016/j.neuroimage.2008.03.061
51. Lett TA, Waller L, Tost H, Veer IM, Nazeri A, Erk S, et al. Cortical surface-based threshold-free cluster enhancement and cortexwise mediation. *Hum Brain Mapp.* 38:2795–807. doi: 10.1002/hbm.23563
52. Gorgolewski KJ, Varoquaux G, Rivera G, Schwarz Y, Ghosh SS, Maumet C, et al. NeuroVault.org: a web-based repository for collecting and sharing unthresholded statistical maps of the human brain. *Front Neuroinform.* (2015) 9:8. doi: 10.3389/fninf.2015.00008
53. Roy AK, Shehzad Z, Margulies DS, Kelly AMC, Uddin LQ, Gotimer K, et al. Functional connectivity of the human amygdala using resting state fMRI. *Neuroimage* (2009) 45:614–26. doi: 10.1016/j.neuroimage.2008.11.030
54. Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol Rev.* (1992) 99:195–231. doi: 10.1037/0033-295X.99.2.195
55. Greicius MD, Supekar K, Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cereb Cortex* (2009) 19:72–8. doi: 10.1093/cercor/bhn059
56. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network. *Ann N Y Acad Sci.* (2008) 1124:1–38. doi: 10.1196/annals.1440.011
57. Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN. Wandering minds: the default network and stimulus-independent thought. *Science* (2007) 315:393–5. doi: 10.1126/science.1131295
58. Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci USA.* (2001) 98:4259–64. doi: 10.1073/pnas.071043098
59. Northoff G, Bermpohl F. Cortical midline structures and the self. *Trends Cogn Sci.* (2004) 8:102–7. doi: 10.1016/j.tics.2004.01.004
60. Northoff G, Heinzel A, de Greck M, Bermpohl F, Dobrowolny H, Panksepp J. Self-referential processing in our brain—a meta-analysis of imaging studies on the self. *Neuroimage* (2006) 31:440–57. doi: 10.1016/j.neuroimage.2005.12.002

61. Buckner RL, Carroll DC. Self-projection and the brain. *Trends Cogn Sci.* (2007) 11:49–57. doi: 10.1016/j.tics.2006.11.004
62. Brosschot JF, Verkuil B, Thayer JF. The default response to uncertainty and the importance of perceived safety in anxiety and stress: an evolution-theoretical perspective. *J Anxiety Disord.* (2016) 41(Suppl. C):22–34. doi: 10.1016/j.janxdis.2016.04.012
63. Elzinga BM, Roelofs K, Tollenaar MS, Bakvis P, van Pelt J, Spinhoven P. Diminished cortisol responses to psychosocial stress associated with lifetime adverse events a study among healthy young subjects. *Psychoneuroendocrinology* (2008) 33:227–37. doi: 10.1016/j.psyneuen.2007.11.004
64. Bonanno GA, Burton CL. Regulatory flexibility: an individual differences perspective on coping and emotion regulation. *Perspect Psychol Sci.* (2013) 8:591–612. doi: 10.1177/1745691613504116
65. Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans: role of the amygdala and vmPFC. *Neuron* (2004) 43:897–905. doi: 10.1016/j.neuron.2004.08.042
66. Kudielka BM, Hellhammer DH, Wüst S. Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge. *Psychoneuroendocrinology* (2009) 34:2–18. doi: 10.1016/j.psyneuen.2008.10.004
67. Kudielka BM, Buske-Kirschbaum A, Hellhammer DH, Kirschbaum C. HPA axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: impact of age and gender. *Psychoneuroendocrinology* (2004) 29:83–98. doi: 10.1016/S0306-4530(02)00146-4
68. Stephens MAC, Mahon PB, McCaul ME, Wand GS. Hypothalamic–pituitary–adrenal axis response to acute psychosocial stress: effects of biological sex and circulating sex hormones. *Psychoneuroendocrinology* (2016) 66:47–55. doi: 10.1016/j.psyneuen.2015.12.021
69. Kudielka BM, Kirschbaum C. Sex differences in HPA axis responses to stress: a review. *Biol Psychol.* (2005) 69:113–32. doi: 10.1016/j.biopsycho.2004.11.009
70. Liu JJW, Ein N, Peck K, Huang V, Pruessner JC, Vickers K. Sex differences in salivary cortisol reactivity to the Trier Social Stress Test (TSST): a meta-analysis. *Psychoneuroendocrinology* (2017) 82:26–37. doi: 10.1016/j.psyneuen.2017.04.007
71. Juster R-P, Raymond C, Desrochers AB, Bourdon O, Durand N, Wan N, et al. Sex hormones adjust "sex-specific" reactive and diurnal cortisol profiles. *Psychoneuroendocrinology* (2016) 63:282–90. doi: 10.1016/j.psyneuen.2015.10.012
72. Dedovic K, Wadiwalla M, Engert V, Pruessner JC. The role of sex and gender socialization in stress reactivity. *Dev Psychol.* (2009) 45:45–55. doi: 10.1037/a0014433
73. Duchesne, A, Tessera, E, Dedovic, K, Engert, V, Pruessner, JC. Effects of panel sex composition on the physiological stress responses to psychosocial stress in healthy young men and women. *Biol Psychol.* (2012) 89:99–106. doi: 10.1016/j.biopsycho.2011.09.009

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REVIEW
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Neuroimaging Correlates of Resilience to Traumatic Events—A Comprehensive Review

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Improved understanding of the neurobiological correlates of resilience would be an important step toward recognizing individuals at risk of developing post-traumatic stress disorder (PTSD) or other trauma-related diseases, enabling both preventative measures and individually tailored therapeutic approaches. Studies on vulnerability factors allow drawing conclusions on resilience. Structural changes of cortical and subcortical structures, as well as alterations in functional connectivity and functional activity, have been demonstrated to occur in individuals with PTSD symptoms. Relevant areas of interest are hippocampus, amygdala, insula, anterior cingulate cortex, and prefrontal cortex, as well as related brain networks, such as the default-mode, salience, and central executive network. This review summarizes the existing literature and integrates findings from cross-sectional study designs with two-group designs (trauma exposed individuals with and without PTSD), three-group designs (with an additional group of unexposed, healthy controls), twin-studies and longitudinal studies. In terms of structural findings, decreased hippocampal volume in PTSD individuals might be either a vulnerability factor or a result of trauma exposure, or both. Reduced anterior cingulate cortex and prefrontal cortex volumes seem to be predisposing factors for increased vulnerability. Regarding functional connectivity, increased amygdala connectivity has been demonstrated selectively in PTSD individuals, as well as increased default-mode-network and salience network connectivity. In terms of functional activity, increased amygdala and anterior cingulate cortex activities, and decreased prefrontal cortex activity as a response to external stimuli have been associated with higher vulnerability. Increased prefrontal cortex activity seemed to be a protective factor. Selecting adequate study designs, optimizing the diagnostic criteria, as well as differentiating between types of trauma and accounting for other factors, such as gender-specific differences, would be well-served in future research. Conclusions on potential preventative measures, as well as clinical applications, can be drawn from the present literature, but more studies are needed.

Keywords: resilience, trauma, PTSD, magnetic resonance imaging, neuroimaging

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INTRODUCTION

Over the past decade, psychiatric, psychological and neurobiological research has increasingly focused on the phenomenon of resilience, which is conceptualized as the ability to maintain a normal, i.e., pre-trauma level of functioning and avoid deteriorating mental disorders, even after experiencing extreme stress or trauma (1). The term resilience does not describe a static component, but rather a dynamic adaptive process that involves cognition and/or emotion regulation, ultimately resulting in functional coping mechanisms (2). Consequently, a better understanding of the neurobiological underpinnings of involved dynamic neurocognitive processes might contribute to a better operationalization and understanding of the concept of resilience (3).

Traditionally, research on resilience focused on the identification of empirical behavioral parameters predictive of the outcome of coping strategies (4). To date, research has mainly focused on identification of neuronal mechanisms associated with greater vulnerability for the development of stress-associated psychiatric diseases, such as post-traumatic stress disorder (PTSD). Identification of such mechanisms are not just the flipside of resilience, but they may lead to a better understanding of the neurobiological correlates of resilience.

In general, specific cerebral structures have been demonstrated to play a crucial role in processing stimuli, as well as in generating reactions to stressors, both in healthy individuals and in patients with psychiatric disease following exposure to trauma. Structural changes of both cortical and subcortical areas have been described, with a particular relevance of hippocampus, amygdala, insular cortex, anterior cingulate cortex (ACC), and medial prefrontal cortex (PFC, see also **Figure 1** for a corresponding graphical presentation of relevant neuroanatomical structures) (5). Volume reduction of the hippocampus, a structure of core importance for declarative memory and for regulative processes via the hypothalamic-pituitary-adrenal axis (6), has been shown to be associated with increased emotional and hormonal reactions to stressors (7), as well as changes in conditioned fear reactions (8). Lesions of the amygdala, a structure capable of releasing stress-associated hormones via activation of the hypothalamic-pituitary-adrenal axis (8), have been shown to significantly affect reactions to negative stimuli (9). The insula plays an important role in the regulation of cognitive control and attention (10), as well as—along with the hippocampus—in processing potential threats (11). Changes in ACC activity have been shown to be associated with altered emotion regulation in affective and anxiety disorders (12). The conventional differentiation between ventral-rostral ACC as a modulator of emotional stimuli and dorsal-caudal ACC as a region associated with non-emotional cognitive processes seems to be mollified in more recent studies (12). The PFC plays a role in mediating higher cognitive functions and in regulating limbic structures, especially the amygdala (13, 14), which has been shown by numerous studies to actively be inhibited by the PFC (15).

Regarding the fact that resilience is regarded as a dynamic adaptation process, examining its functional neurobiological correlates besides analyzing structural findings is of core relevance. Functional magnetic resonance imaging (fMRI) is gold standard for such studies, allowing not only an analysis of neuronal activity patterns but also of network architecture in terms of interactions between spatially separate brain areas (16). The description of intrinsic brain networks and their reactions to intrinsic and extrinsic stimuli has contributed significantly to an improved understanding of the functional architecture of emotional and cognitive processes (17). Three main networks play a role in these processes: the default-mode-network (DMN), including hippocampus, PFC, precuneus and temporoparietal regions, mediates internally directed processes, such as self-referential cognitive tasks (18). The central executive network (CEN) includes lateralized fronto-parietal regions and mediates externally directed processes, such as the modulation of spatial attention (19). The salience network (SN) includes ACC, insula, and amygdala and mediates interaction between DMN and CEN regarding dynamic prioritizing of internal and external stimuli (20). Intrinsic functional connectivity, or the synchronous resting state activity fluctuation, is a surrogate of connectivity within the respective network and according to present knowledge has a high predictive value regarding emotional and cognitive processes in both healthy and mentally ill individuals. Its examination can thus provide a suitable approach to better describe functional correlates of resilience.

Studies involving specific tasks aimed at activating cognitive and/or emotional processes allow to determine the extent of activation for individual brain areas that are recruited during the respective tasks. Comparisons can thus be made between group-specific activity patterns as reactions to external stimuli (21).

The present state of trauma and vulnerability literature is critically reflected with regards to the above aspects, taking into consideration findings on structural changes, functional connectivity and functional activity. Traumatic events include war, natural catastrophes, physical/sexual abuse, or severe accidents. While a direct inverse relationship between resilience and vulnerability does not exist, drawing conclusions from vulnerability studies seems to present the best available approximation to the concept of resilience from a modern imaging point of view at present.

REVIEW OF THE CURRENT LITERATURE

Which types of fMRI studies are needed in order to draw meaningful conclusions about resilience in the context of trauma? Selecting a suitable study design is a great challenge of conducting scientific research into the concept of resilience. In order to determine structural and/or functional parameters predicting the development of PTSD following a traumatic event, recruiting study participants *before* their experiencing a trauma would be the desired approach. Comparing subjects developing clinically relevant PTSD symptoms to those proving resilient

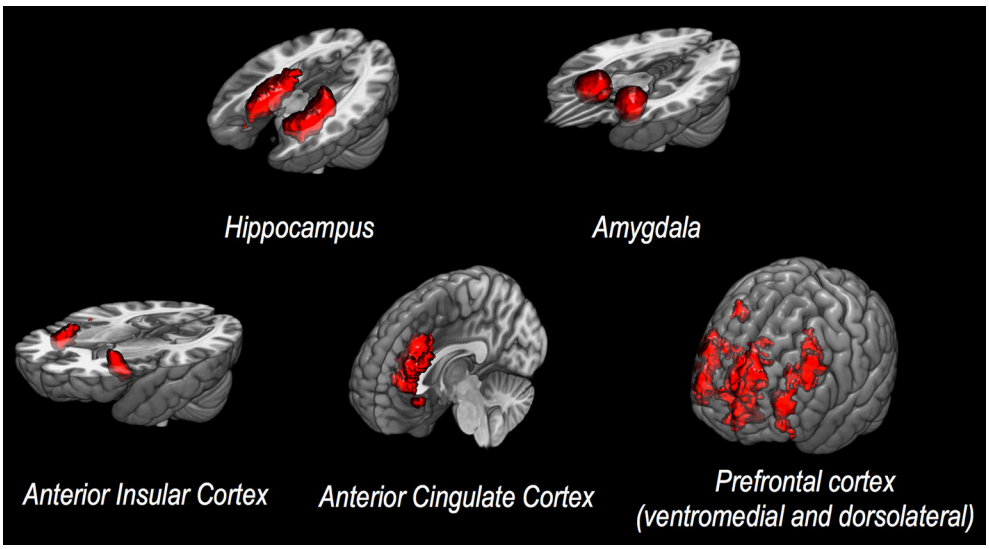

FIGURE 1 | Discussed neuroanatomical structures. This figure presents neuroanatomical target regions frequently investigated via structural or functional MRI in studies assessing potential neurobiological correlates of vulnerability to stress and/or resilience.

later, as well as taking into account the dynamic adaptation process inherent in the concept of resilience, would then enable the retrospective identification of such parameters (22). Since such a design is difficult to embrace for logistical reasons, present approaches include cross-sectional study designs with two-group designs (trauma exposed individuals with and without PTSD), three-group designs (with an additional group of unexposed, healthy controls), twin-studies and longitudinal studies.

Since the aim of the current review is to discuss potential structural or functional correlates of vulnerability/resilience to stress, literature research was conducted according to van der Werff and colleagues (22). Studies available by December 2017 were searched in the databases of PubMed at the National Library of Medicine, using the search terms proposed by van der Werff and colleagues, resulting in 45 studies explicitly investigating potential correlates of resilience as assessed via neuroimaging. In the following section, the identified studies are discussed with regards to structural changes, functional connectivity, and functional activity of relevant brain regions that distinguish resilient individuals from those who succumb to trauma and develop PTSD or other trauma-related disorders (see also **Tables 1**–**3** for detailed presentation of discussed studies).

Two-Group-Studies

The majority of studies compare in a cross-sectional design individuals who have developed PTSD symptoms after trauma exposure ("PTSD") to individuals who have not developed such symptoms post-trauma (trauma-exposed-non-PTSD, "TENP"). One major disadvantage of this design is the lack of a non-exposed control group. It can thus not be clearly identified whether findings are due to trauma exposure and the resulting stress, *per se*, or a result of other factors.

Structure

In one of the first studies to investigate a potential association between morphological properties of the hippocampus and clinical outcome of trauma, Bremner et al. found that hippocampal volume in veterans with PTSD was reduced compared to healthy, non-exposed controls (23). Lindauer et al. examined the hippocampal volume of 28 policemen following trauma exposure, of which 14 developed PTSD symptoms while 14 remained symptom-free. Bilaterally reduced hippocampal volume was shown in the PTSD group, and a correlation was shown between volume reduction and PTSD severity, especially flashbacks (24). A follow-up study of the same group demonstrated that successful psychotherapy did not influence hippocampal volume (25). Reduced hippocampal volume of PTSD groups compared to healthy controls were also shown in a cohort of 24 burn victims (26), a cohort of 200 war veterans (27), and a cohort of 20 victims in a coal mine flood (28). In addition, the latter study demonstrated a statistical correlation between hippocampal volume reduction and clinical symptom severity. Another study not only confirmed hippocampal volume reduction in PTSD individuals, but also demonstrated a correlation with PTSD symptom duration (29). Contrarily, a study on 25 victims of the Sarin terrorist attack in Tokyo failed to replicate these findings (30). Yehuda et al. found no differences in hippocampal volume between war veterans with or without PTSD symptoms, yet demonstrated a selective reduction of hippocampal volume in individuals developing PTSD symptoms immediately following trauma exposure (31). They also observed a correlation in the PTSD group of hippocampal volume and reduced memory capacity, as well as decreased urine cortisol, which might indicate permanently increased stress levels in affected individuals. Another study including 99 war veterans with or without PTSD symptoms also failed to demonstrate hippocampal volume differences

TABLE 1 | Summary of structural findings.

Authors	Study design	PTSD			TENP			HC			Results
		N	M/F	Age	*N*	M/F	Age	N	M/F	Age	
HIPPOCAMPUS											
Lindauer et al. (24)	2 groups	14	8/6	35.4 ± 11.2	14	8/6	36.9 ± 10.1	None			Decreased in PTSD
Lindauer et al. (25)	2 groups	18	8/10	39.6 ± 9.0	14	8/6	36.9 ± 10.1	None			No effect of psychotherapy
Chen et al. (26)	2 groups	12	8/4	34.56 ± 4.91	12	8/4	33.25 ± 5.27	None			Decreased in PTSD
Woodward et al. (32)	2 groups	51	38M	53.5 ± 2.6	48	25M	56.0 ± 3.5	None			Decreased in PTSD, but possibly associated with comorbid alcohol use disorder
Yehuda et al. (31)	2 groups	17	17M	60.6 ± 7.0	16	16M	65.1 ± 9.9	None			No effect, but selectively decreased in individuals with immediate onset PTSD
Felmingham et al. (29)	2 groups	21	NR	NR	17	NR	NR	None			Associated with duration of symptoms
Rogers et al. (30)	2 groups	9	5/4	44.56 ± 15.96	16	10/6	44.44 ± 1 3.60	None			No effect
Wang et al. (33)	2 groups	17	17M	41.0 ± 12.0	19	19M	38.0 ± 15.0	None			Only specific subregions decreased in PTSD
Zhang et al. (28)	2 groups	10	10	40.80 ± 6.83	10	10M	34.30 ± 5.37	None			Decreased in PTSD
Morey et al. (27)	2 groups	99	79/20	38.4 ± 9.9	102	86/16	37.5 ± 10.6	None			Decreased in PTSD
Gurvits et al. (46)	3 groups	7	7M	44.4 ± 1.7	7	7M	47.6 ± 2.9	8	8M	38.1 ± 10.0	Selectively decreased in PTSD, correlated with duration of trauma-exposure
Fennema-Notestine et al. (50)	3 groups	11	11F	33.5 ± 10.3	11	11F	35.4 ± 9.6	17	17F	35.3 ± 12.5	No effect
Bremner et al. (47)	3 groups	10	10F	35.0 ± 6.0	12	12F	32.0 ± 8.0	11	11F	38.0 ± 7.0	Strong decrease in PTSD, moderate decrease in TENP
Pederson et al. (51)	3 groups	17	17F	24.8 ± 5.2	17	17F	26.8 ± 6.6	17	17F	23.8 ± 5.6	No effect
Winter and Irle (49)	3 groups	15	15M	42.0 ± 10.0	15	15M	41.0 ± 11.0	15	15M	41.0 ± 17.0	Correlated with severity of trauma
Golier et al. (53)	3 groups	14	5/9	70.5 ± 5.6	13	6/7	68.5 ± 7.3	20	13/7	71.4 ± 6.4	No effect
Vythilingam et al. (54)	3 groups	14	8/6	35.0 ± 9.0	23	15/8	35.0 ± 7.0	23	9/20	34.0 ± 10.0	Decreased for distinct subregions in PTSD and TENP
Freeman et al. (52)	3 groups	10	10M	79.6 ± 3.2	10	10M	79.8 ± 2.8	6	6M	80.8 ± 3.5	No effect
Apfel et al. (48)	3 groups	41	32/9	42.1 ± 9.6	64	58/6	44.4 ± 9.6	95	81/14	46.4 ± 9.6	Correlated with current symptoms
Morey et al. (55)	3 groups	31	15/16	9.9 ± 2.5	32	15/17	10.0 ± 2.7	57	25/32	10.82 ± 2.5	Increased in TENP
Gilbertson et al. (11)	Twin study	12 (twin pairs)	12M	53.1 ± 3.3	23 (twin pairs)	23M	51.8 ± 2.3	None			Decreased in PTSD paires compared to TENP paires

(Continued)

TABLE 1 | Continued

Authors	Study design	PTSD			TENP			HC			Results
		N	M/F	Age	*N*	M/F	Age	N	M/F	Age	
Pitman et al. (64)	Twin study	25 (twin pairs)	25M	NR	24 (twin pairs)	24M	NR	None			Decreased in PTSD paires compared to TENP paires
Bonne et al. (67)	Longitudinal	10	3/7	33.7 ± 8.9	27	5/12	29.8 ± 10.1	None			No predictor for therapy outcome
Rubin et al. (68)	Longitudinal	Treatment responders/ nonresponders: *n* = 23/17	Responders: 5/18, non-responders: 7/10	Responders: 34.4 ± 8.5/ Non-responders: 37.5 ± 10.7	36	11/25	34.4 ± 10.8	None			Predictor for therapy outcome
AMYGDALA											
Lindauer et al. (24)	2 groups	14	8/6	35.4 ± 11.2	14	8/6	36.9 ± 10.1	None			No effect
Lindauer et al. (25)	2 groups	18	8/10	39.6 ± 9.0	14	8/6	36.9 ± 10.1	None			No effect
Rogers et al. (30)	2 groups	9	5/4	44.56 ± 15.96	16	10/6	44.44 ± 13.60	None			No correlation with symptom severity
Kuo et al. (35)	2 groups	42	42M	49.5 ± 8.6	45	45M	44.5 ± 7.3	None			Increased for TENP
Morey et al. (27)	2 groups	99	79/20	38.4 ± 9.9	102	86/16	37.5 ± 10.6	None			Decreased for PTSD
Gurvits et al. (46)	3 groups	7	7M	44.4 ± 1.7	7	7M	47.6 ± 2.9	8	8M	38.1 ± 10.0	No effect
Fennema-Notestine et al. (50)	3 groups	11	11F	33.5 ± 10.3	11	11F	35.4 ± 9.6	17	17F	35.3 ± 12.5	No effect
Morey et al. (55)	3 groups	31	15/16	9.9 ± 2.5	32	15/17	10.0 ± 2.7	57	25/32	10.82 ± 2.5	Selectively increased for TENP
Gilbertson et al. (11)	Twin study	12	12M	53.1 ± 3.3	23	23M	51.8 ± 2.3	None			No effect
Bonne et al. (67)	Longitudinal	10	3/7	33.7 ± 8.9	27	5/12	29.8 ± 10.1	None			No effect
INSULA											
Chen et al. (26)	2 groups	12	8/4	34.56 ± 4.91	12	8/4	33.25 ± 5.27	None			Decreased in PTSD
Kasai et al. (65)	Twin study	18 twin pairs	18M	52.8 ± 3.4	23 twin pairs	23M	51.8 ± 2.3	None			Decreased in combat-exposed individuals with PTSD
ACC											
Rauch et al. (37)	2 groups	9	9F	51.7 ± 1.9	9	9F	52.0 ± 1.9	None			Decreased (pgACC only) in PTSD
Woodward et al. (32)	2 groups	51	38M	53.5 ± 2.6	48	25M	56.0 ± 3.5	None			Decreased in PTSD
Chen et al. (26)	2 groups	12	8/4	34.56 ± 4.91	12	8/4	33.25 ± 5.27	None			Decreased in PTSD
Felmingham et al. (29)	2 groups	21	NR	NR	17	NR	NR	None			Decreased in PTSD
Rocha-Rego et al. (38)	2 groups	16	7/9	43.3 ± 5.78	16	7/9	44.9 ± 6.60	None			Decreased (pgACC only) in PTSD
Eckart et al. (56)	3 groups	20	20M	36.2 ± 7.7	19	19M	34.1 ± 9.9	13	13M	29.0 ± 7.2	Strong decrease in PTSD, moderate decrease in TENP

(Continued)

TABLE 1 | Continued

Authors	Study design	PTSD			TENP			HC			Results
		N	M/F	Age	*N*	M/F	Age	N	M/F	Age	
Kasai et al. (65)	Twin study	Kasai et al. (65)	18M	52.8 ± 3.4	23 twin pairs	23M	51.8 ± 2.3	None			PTSD diagnosis × combat exposure interaction in pgACC (in which combat-exposed PTSD twins had lower gray matter density than their own combat-unexposed cotwins and TENP-twins)
PFC											
Felmingham et al. (29)	2 groups	21	NR	NR	17	NR	NR	None			Decreased in PTSD and TENP
Fennema-Notestine et al. (50)	3 groups	11	11F	33.5 ± 10.3	11	11F	35.4 ± 9.6	17	17F	35.3 ± 12.5	Decreased in PTSD and TENP
Eckart et al. (56)	3 groups	20	20M	36.2 ± 7.7	19	19M	34.1 ± 9.9	13	13M	29.0 ± 7.2	Selectively decreased in PTSD
Morey et al. (55)	3 groups	31	15/16	9.9 ± 2.5	32	15/17	10.0 ± 2.7	57	25/32	10.82 ± 2.5	Selectively decreased in PTSD

Study design and study sample characteristics are presented for all discussed studies investigating potential correlates of vulnerability/resilience to stress as assessed via structural MRI. PTSD, post-traumatic stress disorder; TENP, trauma-exposed non-PTSD; HC, healthy controls; NR, not reported.

TABLE 2 | Summary of functional connectivity findings.

Authors	Study design	PTSD			TENP			HC			Results
		N	M/F	Age	*N*	M/F	Age	*N*	M/F	Age	
Rabinak et al. (39)	2 groups	17	17M	30.12 ± 7.70	17	17M	33.71 ± 9.12	None			PTSD: Increased connectivity between amygdala and insula
Sripada et al. (40)	2 groups	15	15M	27.3 ± 4.5	14	14M	26.6 ± 3.3	None			PTSD: Increased connectivity between amygdala and insula, decreased connectivity between amygdala and ACC
Brown et al. (41)	2 groups	20	16:4	44..1 ± 11.0	22	16:6	44.0 ± 8.9	None			Increased connectivity between amygdala (BLA) and ACC/PFC in PTSD
Zhang et al. (42)	2 groups	33	12:21	52.06 ± 6.77	33	16:17	48.85 ± 6.39	None			PTSD: Increased connectivity between amygdala and PFC/hippocampus and decreased connectivity between mPFC and insula.
Sripada et al. (40)	3 groups	15	15M	27.3 ± 4.5	15	15M	26.6 ± 3.3	15	15M	26 ± 5.9	PTSD: Increased connectivity between amygdala, insula and ACC (SN), decreased connectivity between vmPFC and hippocampus (DMN), increased overall connectivity between DMN and SN.
van der Werff et al. (60)	3 groups	11	8/3	39.73 ± 9.61	11	8/3	40.36 ± 10.94	11	8/3	40.45 ± 9.47	Increased connectivity between dACC and bilateral lingual gyrus/occipital fusiform gyrus in TENP
Kennis et al. (58)	3 groups	31	31M	35.58 ± 9.66	25	25M	36.04 ± 10.15	25	25M	34.16 ± 9.32	Reduced connectivity between PFC and pgACC for PTSD and TENP, increased connectivity between PFC and rACC for TENP
Zhou et al. (69)	Longitudinal	15	11/4	41.52 ± 12.56	None			None			Connectivity between posterior cingulate cortex and amygdala/hippocampus at baseline predicted symptom severity after 6 months.

Study design and study sample characteristics are presented for all studies assessing potential functional correlates of vulnerability/resilience to stress as assessed via resting-state fMRI. PTSD, post-traumatic stress disorder; TENP, trauma-exposed non-PTSD; HC, healthy controls; DMN, default-mode-network; SN, salience network.

TABLE 3 | Summary of functional activity findings.

Authors	Study design	PTSD			TENP			HC			Results
		N	M/F	Age	*N*	M/F	Age	*N*	M/F	Age	
Shin et al. (43)	2 groups	13	13M	52.8 ± 7.3	13	13M	49.7 ± 8.9	None			PTSD: Increased activity in amygdala, decreased activity in mPFC, mPFC activity correlated with symptom severity (passive viewing of faces)
Peres et al. (44)	2 groups	12 and 12	12M/12M	31.2 ± 5.8 (PT) and 27.6 ± 3.9 (WL)	12	12M	28.2 ± 7.8	None			PTSD: Increased activity in amygdala, decreased activity in mPFC (memory task)
Stevens et al. (45)	2 groups	37	37F	35.4 ± 12.5	53	53F	41.1 ± 12.2	None			Correlation between activity in ACC and trauma severity (inhibition task)
New et al. (63)	3 groups	14	14F	38.7 ± 11.2	14	14F	38.5 ± 10.8	14	14F	31.7 ± 10.3	Decreased activity in PFC in PTSD, increased activity in PFC in TENP (emotion regulation task)
Blair et al. (62)	3 groups	14	2/12	33.9 ± 9.98	15	4/11	31.4 ± 7.94	19	2/17	32.4 ± 8.79	Decreased activity in PFC in PTSD, increased activity in PC in TENP (executive task)
Falconer et al. (61)	3 groups	23	13F, 10M	38.3 ± 12.16	23	13F, 10M	32.40 ± 15.00	17	6F, 10M	39.3 ± 12.6	PTSD: decreased activity frontoparietal (executive task)
Shin et al. (66)	Twin study	12 (twin pairs, i.e., one exposed and one unexposed twin)	12M	55.0 ± 2.9	14 (twin pairs, i.e., one exposed and one unexposed twin)	14M	56.4 ± 2.2	None			Increased activity in ACC for PTSD and their twins

Study design, study sample characteristics and specific tasks are presented for all studies assessing potential functional correlates of vulnerability/resilience to stress as assessed via task-based fMRI. PTSD, post-traumatic stress disorder; TENP, trauma-exposed non-PTSD; HC, healthy controls; DMN, default-mode-network; SN, salience network.

initially, yet selectively observed such a reduction in PTSD patients also diagnosed with an alcohol dependence syndrome (32). Findings of a study in 36 war veterans implicate that volume reduction might be present only in certain hippocampal regions (cornu ammonis 3/dentate gyrus) (33), regions closely associated with neuroneogenesis (34). Regarding the amygdala, 2-group-studies on structural changes present heterogeneous findings. A study on policemen found no differences in amygdala volume between PTSD and TENP groups (24), and these findings were replicated by the same group later (25). A more recent study demonstrated reduced amygdala volume in PTSD individuals, yet did not find a correlation between volume reduction and symptom severity (27). A study on 25 terrorist victims observed both reduced amygdala volume and a correlation between reduction and symptom severity in PTSD individuals (30). Contrarily, yet another study found an increase in amygdala volume in PTSD individuals compared to TENP (35). With respect to the insular cortex, Chen et al. described bilaterally reduced insular volume in burn victims with PTSD compared to TENP (26). Across current literature, the volume of the ACC was consistently reduced in patients with PTSD symptoms compared to TENP individuals. In more detail, Gulf war veterans with PTSD symptoms had significantly reduced ACC volume compared to those without PTSD, even after controlling for other variables, such as alcohol dependence syndrome (36). Studies on 24 burn victims (26) and on 38 traffic accident or mugging victims without further comorbidities (29) confirmed these findings. Studies on Vietnam War nurses (37) and public violence victims (38) found selective volume reductions in pgACC of PTSD individuals compared to TENP, without changes in other ACC areas. Finally, PTSD individuals were found to have significantly reduced superior medial PFC and orbitofrontal gyrus volumes compared to TENP (29, 35).

Functional Connectivity

Connectivity between amygdala and insula has been shown to be increased in PTSD individuals (Iraq War veterans) compared to TENP individuals, while there were no between-group differences regarding amygdala-PFC connectivity (39). Increased amygdala-insula connectivity in the PTSD group was also observed in another study on war veterans (40), with the additional finding of decreased amygdala/hippocampus-ACC connectivity. Additionally, a more recent study on war veterans demonstrated increased amygdala-pgACC and amygdala-dorsomedial PFC connectivity in the PTSD group compared to the TENP group (41). Yet another study, using DSM-V diagnostic criteria (unlike the previously quoted studies), found increased connectivity between Amygdala and medial PCF, as well as hippocampus, in the PTSD group (42). Increased negative and reduced positive amygdala feedback on the insula was also observed in this study. A correlation between PTSD symptom severity and connectivity changes were shown when both PTSD and TENP group were included in a correlational analysis.

Functional Activity

Shin et al. presented stimuli (faces with different emotional expressions) to PTSD and TENP individuals (43). Significantly increased amygdala activity and decreased medial PFC activity were observed in the PTSD group when fearful facial expressions were presented. The degree of amygdala activity increase was correlated with the degree of medial PFC activity decrease, which was correlated with PTSD symptom severity. There was also a tendency for reduced habituation of amygdala activity in the PTSD group. An intervention study had policemen who had experienced trauma exposure undergo an fMRI scan while performing a memory task (44). Individuals with PTSD symptoms were subdivided into two groups, of which one received psychotherapy while the other was put on a waitlist for psychotherapy. Comparing scan results pre and post-psychotherapy revealed increased medial PFC activity and decreased amygdala activity in both the PTSD-psychotherapy group and the TENP group compared to the PTSD-waitlist group, where individuals still presented severe PTSD symptoms. A statistical connection was shown between imaging results and symptom severity. A more recent study included childhood abuse victims that were asked to perform a cognitive inhibition task while undergoing an fMRI scan (45). A statistical correlation was found between abuse severity and ACC activity in the PTSD group, suggesting that cognitive inhibition was significantly reduced in individuals with PTSD and severe abuse.

Three-Group-Studies

In order to more reliably distinguish between genuine vulnerability factors and findings that are the result of trauma *per se* or other factors, more recent studies often include a control group of non-trauma-exposed, healthy subjects. Between-group comparison allows for a relatively reliable identification of resilience factors not associated with trauma exposure-related stress.

Structure

The very first study conducted as early as 1996 found hippocampal volume to be reduced in the PTSD group compared to TENP and control groups (46). However, hippocampal volume in this study was also correlated with the duration of war exposure, suggesting that reduced hippocampal volume might be either a vulnerability factor or a result of stress, or both. A study on women with a childhood history of sexual abuse confirmed the finding of reduced hippocampal volume in PTSD compared to TENP and control groups, with the difference being more pronounced between PTSD and control group compared to PTSD and TENP (47). A Gulf War veteran study also discussing potential epiphenomena, such as alcohol dependency or depressive disorder found a correlation of hippocampal volume with current PTSD symptom severity, but not with formerly diagnosed PTSD or current depressive episodes (48). Neither did this study observe an effect of age, number of additional traumatic life events, alcohol or cannabis dependency, or antidepressant medication on hippocampal volume. A study on burn victims suggests a size-reducing effect of stress on the

hippocampus, finding smaller hippocampal volume in PTSD and TENP groups compared to controls but no differences between PTSD and TENP (49). Hippocampal volume was correlated negatively with burnt body surface, while it correlated positively with analgesic (and thus stress-reducing) medication with Ketamine. A number of additional studies were not able to replicate the above findings. No differences were found between hippocampal volumes of PTSD, TENP and control groups in populations of domestic violence victims (50), women with a history of childhood abuse (51), former prisoners of war (52), and holocaust survivors (53). As previously stated, certain epiphenomena need to be considered in the analysis of these results. One study on veterans demonstrated a selective volume reduction of the hippocampal head in the PTSD group but not a reduction of hippocampal volume, *per se* (54). A more recent study on adolescents with a history of abuse demonstrated increased hippocampal volume in the TENP group compared with both PTSD and control groups (55). Regarding the amygdala, studies investigating amygdala volume in populations of war veterans (46), domestic violence victims (50), and adolescents with a history of abuse (55) found no changes in amygdala volume for PTSD groups. However, the latter study reported a correlation of amygdala volume with PTSD symptom severity, as well as increased amygdala volume in the TENP group compared to PTSD and control groups (55). By contrast, one study demonstrated reduced ACC volume in the PTSD group of a study on refugees (56). ACC volume was also reduced in the TENP group compared to controls, yet to a much smaller degree. With respect to the PFC, one study on domestic violence victims found reduced PFC volume in both trauma-exposed groups compared to controls (50). More recent studies, contrarily, found a volume reduction of ventromedial PFC and orbitofrontal cortex in the PTSD groups of refugee (56) and childhood abuse victim populations (55) compared to TENP and control groups. In the refugee population, a slight reduction of ventromedial PFC volume was also observed in the TENP group.

Functional Connectivity

A study on war veterans found reduced default-mode network (DMN) connectivity, and increased salient network (SN) connectivity, especially with regards to increased amygdala-insula connectivity (57). There was also a significant increase in connectivity between DMN and SN networks. A study on war veterans demonstrated reduced connectivity between pgACC-PFC and pgACC-temporal lobe in both PTSD and TEMP groups compared to controls (58). Additionally, increased connectivity between rostral ACC and PFC was found in the TENP group. A follow-up study on the same population failed to demonstrate an effect of trauma-focused therapy on the above connectivity parameters, independently of therapeutic outcome (59). Contrarily, a study on adults with a history of childhood abuse did not replicate these results (60). An increase in ACC connectivity with occipital cortex regions was found, yet no changes in ACC connectivity with PFC, Amygdala, insula or core regions of other networks.

Functional Activity

One study found reduced neuronal activity, more specifically an increase in the number of inhibition-related mistakes during a task and a reduced recruitment of fronto-parietal brain areas (exclusive and reduced PFC activity), in the PTSD group compared to TENP and controls (61). These results were replicated in another study with participants undergoing an inhibition task while being MRI-scanned, with the task in the latter study, unlike the first, also including emotional components (62). The PTSD group again showed reduced PFC recruitment during the task, while an increased recruitment of fronto-temporal areas associated with conscious emotion regulation ("top-down control") was observed in the TENP group. Another study on female sexual abuse victims asked to down-regulate their emotional reaction to negative images during a scan found a generally reduced PFC activity in trauma-exposed women (PTSD and TENP group) compared to controls (63). Upon emotion regulation, increased PFC recruitment was found in the TENP group compared to both PTSD and control groups.

Twin Studies

This study design compares trauma-exposed individuals with PTSD symptoms and their non-exposed identical twin siblings to trauma-exposed individuals without PTSD symptoms and their non-exposed identical twin siblings. Using this study design, a number of factors can be reliably controlled for as genetic setup is identical between trauma-exposed and non-exposed groups. However, a number of lifestyle-related factors are nevertheless important contributors to potential differences found between twins, may interact with genetic factors and this needs to be accounted for in this design.

Structure

Analysis of hippocampal volumes of war veterans revealed a volume reduction in the PTSD group and their twins compared to TENP and their twins (11). The hippocampal volume of non-exposed twins of the PTSD group correlated with the PTSD symptom severity in the PTSD group, indicating strongly that reduced hippocampal volume is a vulnerability factor, rather than a result of exposure to stress. Other factors, such as alcohol dependency or major depressive disorder only had statistically significant effects on hippocampal volume in the PTSD group. The same research group later confirmed the above results and additionally found that specific characteristics of the PTSD group, such as increased vegetative reaction to trauma-associated stimuli, are not associated with the reduction in hippocampal volume (64). This is additionally confirmed by another study on war veterans finding reduced hippocampal volume in the PTSD group and their twins compared to TENP and their twins (65). Regarding other anatomical structures, a study on war veterans did not find any differences in amygdala volume between any of the groups, nor associations with psychopathological symptom severity (11). Reduced bilateral insular volume was found in the PTSD group and their twins compared to the TENP group and their twins (65). No differences in insular volumes were found between the respective twin groups. Finally, reduced pgACC

volume was observed in a PTSD group and their twins compared to TENP and their twins (65). Additionally, a reduction of pgACC volume was also found in the PTSD group compared to their non-exposed twins, suggesting reduced pgACC volume might be both a vulnerability factor and a consequence of exposure to stress.

Functional Connectivity and Activity

To the best of our knowledge, no study investigated so far functional connectivity according to a twin-study design. Regarding activity, one study used a task reliably causing ACC activation during an MRI scan in war veterans (66). Increased dACC activity and increased response latency were observed in the PTSD group and their twins, suggesting increased ACC activation to be a vulnerability factor rather than a result of stress exposure based on these findings. The extent of ACC activation increase was correlated with the severity of clinical symptoms, but not with other comorbidities, such as depressive episodes or alcohol dependency.

Longitudinal Studies

This study design examines trauma-exposed individuals immediately after the event and again at one or several follow-up time points. Parameters predicting the development of clinical symptoms are determined prospectively. Short-term effects of the traumatic event cannot be ultimately excluded in this design.

Structure

Hippocampus. Survivors of various catastrophic events were examined immediately after and again after a 6 months interval (67). Ten out of thirty-seven participants developed PTSD symptoms, but no difference was found between their hippocampal or amygdala volume and that of the TENP group for either time point. Contrarily, a more recent study involving 10 weeks of psychotherapy for trauma-exposed individuals suggests reduced hippocampal volume might be a vulnerability factor (68). Hippocampal volumes at the first measurement (i.e., before therapy started) were already significantly reduced in the group of individuals with persisting PTSD symptoms post-therapy compared to groups with TENP or PTSD with successful therapy. There were no differences in hippocampal volumes between the two latter groups.

Functional Connectivity and Activity

Presently, only one study has aimed at predicting clinical outcome immediately after trauma exposure based on connectivity patterns. In more detail, Zhou et al. examined 15 individuals 2 days after being exposed to a traumatic event and again 6 months later and found a negative correlation between amygdala-PCC connectivity and PTSD symptom severity after 6 months (69). To the extent of our knowledge, no study investigated so far potential associations between functional activity and resilience/vulnerability to stress in populations based on a longitudinal study design.

SUMMARY AND IMPLICATIONS ON THE NEUROBIOLOGY OF RESILIENCE

Structure

The present state of the literature is relatively heterogeneous, yet especially 3-group-studies and twin studies, as well as prospective longitudinal studies allow for first conclusions to be drawn. Reduced hippocampal volume, relatively consistently present in PTSD individuals compared to TENP or controls, might be either a vulnerability factor or a consequence of stress exposure or both. It seems reasonable to assume a multifactorial genesis. Amygdala volume does not seem to be a vulnerability factor, nor were any changes described consistently following stress exposure. Reduced ACC, especially pgACC, and PFC volumes seem to be predisposing factors for increased vulnerability, while they are only moderately influenced by stress exposure. In terms of the neurobiology of resilience, unchanged ACC and PFC volumes and potentially to some extent reduced hippocampal volume are likely to be morphological indicators of resilience (see **Table 1** for a detailed presentation of all discussed structural imaging studies).

Functional Connectivity

Amygdala connectivity seems to be increased selectively in PTSD, potentially also predicting clinical outcome and symptom severity. Neuroanatomically, these findings seem plausible since an association is thus established between increased interaction of danger-detecting and emotional/cognitive/physical homeostasis-regulating regions on the one hand and increased risk of developing PTSD symptoms on the other hand. Equally importantly, increased DMN and SN connectivity and thus increased interaction between one network associated with self-referential activities, such as memory and daydreams and another network evaluating the importance of internal vs. external stimuli seems to be characteristic for individuals more at risk of developing PTSD symptoms following trauma exposure. Inversely, weak connectivity between danger-sensitive and self-referential networks might thus be a neurofunctional indicator of increased resilience (see **Table 2** for a detailed presentation of all discussed functional connectivity imaging studies).

Functional Activity

Based on the present literature, increased amygdala and ACC activities as a response to external stimuli are consistently described as characteristic features of individuals with increased vulnerability. Therapeutic interventions, such as trauma-focused psychotherapy seem to enable return of amygdala activity to normal levels. PFC activity, both as a response to external stimuli or through conscious modulation, seems to be of core importance. While reduced PFC activity appears to be characteristic for vulnerable individuals, TENP groups were shown to have increased PFC activity even compared to control groups. Since strong inhibitory effects of PFC on brain areas associated with emotion regulation have been described, it seems reasonable to assume an increased ability to exert cognitive control over emotional processes in resilient individuals. A recent study confirms this assumption, finding

that PTSD individuals with increased dorsolateral PFC activity and decreased amygdala activity during an emotion regulation task prior to trauma-focused psychotherapy benefit significantly more from such therapy and achieve better symptom reduction (13). Additionally, the ability to consciously recruit brain areas associated with positive emotional experience during presentation of negative stimuli seems to have some importance for the neurobiology of resilience. Decreased activity in the amygdala/ACC and increased PFC activity during distinct tasks, particularly during neurocognitive processes associated with emotion-regulation in terms of top-down control mechanisms, may thus represent a neuro-functional correlate of increased resilience (see **Table 3** for a detailed presentation of all discussed functional connectivity imaging studies).

DISCUSSION

The present review aimed to investigate whether there are neurobiological correlates of resilience. Based on the data reviewed in this relatively recent area of research (1), a specific neurobiological correlate of resilience cannot be established, *per se*. A number of preliminary assumptions can be made on the basis of the reviewed above, however, which are discussed below.

First, there seems to be a spatial overlap between brain areas associated with increased resilience on the one hand and with emotion and stress regulation, on the other hand. Second, structural data suggest relatively consistently that increased gray matter volumes in ventromedial PFC, ACC (especially pgACC) and, to a lesser extent, hippocampus are associated with increased resilience, while amygdala morphology does not appear to play a vital role in this context. Third, decreased functional amygdala connectivity within the salience network, as well as decreased amygdala connectivity with default mode network structures seem to be associated with increased resilience. Fourth, more recent studies suggest an association of resilience with an increased ability to voluntarily recruit PFC and, to a lesser extent, ACC, suggesting a better "top-down" control due to the inhibitory effects of these brain areas on the amygdala. The latter findings provide options for future therapeutic interventions. One study demonstrated improved amygdala regulation through increased PFC influence in a neurofeedback-based MRI learning task in healthy individuals (15). Further research should explore whether such tasks can also prove beneficial in PTSD patients or as a preventive measure to improve resilience.

Resilience is a dynamic process of adapting to a significant and traumatic stressor that has to be investigated over time. Such a process of adaptation of a complex system will have neurobiological correlates itself. The study designs reviewed here, however, do not allow for a time-dependent description of neurobiological findings nor for the establishment of a causal relation between individual findings. The definition of inclusion and exclusion criteria is yet another challenge in the available literature. One issue is the definition of resilience as the absence of specific PTSD symptoms, with a large number of studies explicitly regarding individuals as resilient if they had other potentially trauma-related pathologies, such as depressive episodes or substance abuse disorders. Additionally, the number and types of traumatic experience vary greatly, as do other participant characteristics, such as age, gender, previous experience, etc., rendering between-study comparisons problematic. Yet another challenge is the diagnostic process, which itself is based on a categorical decision: if a certain number of PTSD symptoms is observed within a defined time period, a diagnosis is established. More recent approaches, such as the National Institute of Mental Health's concept of Research Domain Criteria, aim to develop trans-diagnostic systems to specifically match certain behavioral parameters and their neurobiological correlates at least for research purposes (70). This might lead to a shift from categorical systems toward trans-diagnostic, multidimensional inclusion criteria (71), which would potentially enable drawing conclusions between different study populations regarding findings on resilience.

Ideally, future studies would be based on longitudinal designs rather than cross-sectional ones. Participants should be recruited before (likely) traumatic exposure and should undergo multimodal examinations. Structural and functional neurobiological parameters should be determined in addition to detailed clinical assessment. Following traumatic exposure, during follow-ups and where applicable, following treatment, all physical and psychiatric comorbidities should be assessed along with the initially determined neurobiological parameters, allowing for the specific retrospective identification of clinical outcome predictors, as well as the demonstration of trauma- and therapy-associated changes.

Numerous other parameters can obviously influence the above observations. For example, genetic factors, such as a polymorphism of the gene encoding the catechol-O-methyl-transferase (COMT) can modulate the association between stress exposure and brain activity. One study demonstrates statistically significant associations between specific variations of this gene and increase or decrease in hippocampal activity, while associations between hippocampal activity and resilience are only shown in one group (72). Recent literature also increasingly demonstrates an increase in vulnerability when there is an attention shift toward negative stimuli, while a tendency toward prioritizing the processing of positive stimuli is associated with resilience (73). Additionally, there is increasing evidence for a gender-specific pattern of the described structural and functional changes: While male individuals largely present PFC, amygdala and hippocampus gray matter reductions following traumatic exposure, females often present with amygdala hyperactivity. This might not only explain the heterogeneity of study results, but also suggest far-reaching implications for the selection of adequate therapeutic measures (74).

CONCLUSION

Understanding and furthering resilience-increasing factors through better describing vulnerability, including neuroimaging findings from a structural, functional connectivity and functional activity point of view, would be well-served in terms of treating and preventing PTSD. The above findings suggest that reduced hippocampal, anterior cingulate and prefrontal cortex volumes were associated with higher vulnerability. Furthermore, increased amygdala, default-mode and salience network connectivities were associated with higher vulnerability.

Finally, increased amygdala and anterior cingulate cortex activities and decreased prefrontal cortex activity as a response to external stimuli were also associated with higher vulnerability, while increased prefrontal cortex activity was associated with lower vulnerability. Further research using suitable study designs is needed to better understand the underlying causalities and mechanisms.

AUTHOR CONTRIBUTIONS

ES, BK, and AM conceptualization of study concept/design; JB and AM literature screening; ES and BK quality control of data; JB, ES, BK, and AM data interpretation; JB manuscript preparation; ES, BK, and AM manuscript editing; JB, ES, BK, and AM manuscript review. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

1. Charney DS. Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am J Psychiatry* (2004) 161:195–216. doi: 10.1176/appi.ajp.161.2.195
2. Kleim B, Galatzer-Levy IR. Appreciating methodological complexity and integrating neurobiological perspectives to advance the science of resilience. *Behav Brain Sci.* (2015) 38:e108. doi: 10.1017/S0140525X14001587
3. Kalisch R, Müller MB, Tüscher O. A conceptual framework for the neurobiological study of resilience. *Behav Brain Sci*. (2015) 38:e92. doi: 10.1017/S0140525X1400082X
4. van der Werff SJ, Pannekoek JN, Stein DJ, van der Wee NJ. Neuroimaging of resilience to stress: current state of affairs. *Hum Psychopharmacol.* (2013) 28:529–32. doi: 10.1002/hup.2336
5. Dedovic K, D'Aguiar C, Pruessner JC. What stress does to your brain: a review of neuroimaging studies. *Can J Psychiatry* (2009) 54:6–15. doi: 10.1177/070674370905400104
6. Bremner JD. Neuroimaging in posttraumatic stress disorder and other stress-related disorders. *Neuroimaging Clin N Am*. (2007) 17:523–38, ix. doi: 10.1016/j.nic.2007.07.003
7. Lyons DM, Parker KJ, Zeitzer JM, Buckmaster CL, Schatzberg AF. Preliminary evidence that hippocampal volumes in monkeys predict stress levels of adrenocorticotropic hormone. *Biol Psychiatry* (2007) 62:1171–4. doi: 10.1016/j.biopsych.2007.03.012
8. Otto T, Poon P. Dorsal hippocampal contributions to unimodal contextual conditioning. *J Neurosci*. (2006) 26:6603–9. doi: 10.1523/JNEUROSCI.1056-06.2006
9. Funayama ES, Grillon C, Davis M, Phelps EA. A double dissociation in the affective modulation of startle in humans: effects of unilateral temporal lobectomy. *J Cogn Neurosci*. (2001) 13:721–9. doi: 10.1162/08989290152541395
10. Manoliu A, Meng C, Brandl F, Doll A, Tahmasian M, Scherr M, et al. Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. *Front Hum Neurosci*. (2013) 7:930. doi: 10.3389/fnhum.2013.00930
11. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci*. (2002) 5:1242–7. doi: 10.1038/nn958
12. Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn Sci*. (2011) 15:85–93. doi: 10.1016/j.tics.2010.11.004
13. Fonzo GA, Goodkind MS, Oathes DJ, Zaiko YV, Harvey M, Peng KK, et al. PTSD psychotherapy outcome predicted by brain activation during emotional reactivity and regulation. *Am J Psychiatry* (2017) 174:1163–74. doi: 10.1176/appi.ajp.2017.16091072
14. Phelps EA, Delgado MR, Nearing KI, LeDoux JE: Extinction learning in humans: role of the amygdala and vmPFC. *Neuron* (2004) 43:897–905. doi: 10.1016/j.neuron.2004.08.042
15. Koush Y, Meskaldji DE, Pichon S, Rey G, Rieger SW, Linden DE, et al. Learning control over emotion networks through connectivity-based neurofeedback. *Cereb Cortex* (2017) 27:1193–202. doi: 10.1093/cercor/bhv311
16. Brakowski J, Spinelli S, Dörig N, Bosch OG, Manoliu A, Holtforth MG, et al. Resting state brain network function in major depression–depression symptomatology, antidepressant treatment effects, future research. *J Psychiatr Res*. (2017) 92:147–59. doi: 10.1016/j.jpsychires.2017.04.007
17. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct*. (2010) 214:655–67. doi: 10.1007/s00429-010-0262-0
18. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci USA*. (2003) 100:253–8. doi: 10.1073/pnas.0135058100
19. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci USA*. (2009) 106:13040–5. doi: 10.1073/pnas.0905267106
20. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*. (2007) 27:2349–56. doi: 10.1523/JNEUROSCI.5587-06.2007
21. Rutledge RB, Moutoussis M, Smittenaar P, Zeidman P, Taylor T, Hrynkiewicz L, et al. Association of neural and emotional impacts of reward prediction errors with major depression. *JAMA Psychiatry* (2017) 74:790–7. doi: 10.1001/jamapsychiatry.2017.1713
22. van der Werff SJ, van den Berg SM, Pannekoek JN, Elzinga BM, van der Wee NJ. Neuroimaging resilience to stress: a review. *Front Behav Neurosci.* (2013) 7:39. doi: 10.3389/fnbeh.2013.00039
23. Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, et al. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry* (1995) 152:973–81. doi: 10.1176/ajp.152.7.973
24. Lindauer RJ, Vlieger EJ, Jalink M, Olff M, Carlier IV, Majoie CB, et al. Smaller hippocampal volume in Dutch police officers with posttraumatic stress disorder. *Biol Psychiatry* (2004) 56:356–63. doi: 10.1016/j.biopsych.2004.05.021
25. Lindauer RJ, Vlieger EJ, Jalink M, Olff M, Carlier IV, Majoie CB, et al. Effects of psychotherapy on hippocampal volume in out-patients with post-traumatic stress disorder: a MRI investigation. *Psychol Med.* (2005) 35:1421–31. doi: 10.1017/S0033291705005246
26. Chen S, Xia W, Li L, Liu J, He Z, Zhang Z, et al. Gray matter density reduction in the insula in fire survivors with posttraumatic stress disorder: a voxel-based morphometric study. *Psychiatry Res*. (2006) 146:65–72. doi: 10.1016/j.pscychresns.2005.09.006
27. Morey RA, Gold AL, LaBar KS, Beall SK, Brown VM, Haswell CC, et al. Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. *Arch Gen Psychiatry* (2012) 69:1169–78. doi: 10.1001/archgenpsychiatry.2012.50

28. Zhang J, Tan Q, Yin H, Zhang X, Huan Y, Tang L, et al. Decreased gray matter volume in the left hippocampus and bilateral calcarine cortex in coal mine flood disaster survivors with recent onset PTSD. *Psychiatry Res.* (2011) 192:84–90. doi: 10.1016/j.pscychresns.2010.09.001
29. Felmingham K, Williams LM, Whitford TJ, Falconer E, Kemp AH, Peduto A, et al. Duration of posttraumatic stress disorder predicts hippocampal grey matter loss. *Neuroreport* (2009) 20:1402–6. doi: 10.1097/WNR.0b013e3283300fbc
30. Rogers MA, Yamasue H, Abe O, Yamada H, Ohtani T, Iwanami A, et al. Smaller amygdala volume and reduced anterior cingulate gray matter density associated with history of post-traumatic stress disorder. *Psychiatry Res.* (2009) 174:210–6. doi: 10.1016/j.pscychresns.2009.06.001
31. Yehuda R, Golier JA, Tischler L, Harvey PD, Newmark R, Yang RK, et al. Hippocampal volume in aging combat veterans with and without post-traumatic stress disorder: relation to risk and resilience factors. *J Psychiatr Res.* (2007) 41:435–45. doi: 10.1016/j.jpsychires.2005.12.002
32. Woodward SH, Kaloupek DG, Streeter CC, Kimble MO, Reiss AL, Eliez S, et al. Hippocampal volume, PTSD, and alcoholism in combat veterans. *Am J Psychiatry* (2006) 163:674–81. doi: 10.1176/appi.ajp.163.4.674
33. Wang Z, Neylan TC, Mueller SG, Lenoci M, Truran D, Marmar CR, et al. Magnetic resonance imaging of hippocampal subfields in posttraumatic stress disorder. *Arch Gen Psychiatry* (2010) 67:296–303. doi: 10.1001/archgenpsychiatry.2009.205
34. Manoliu A, Bosch OG, Brakowski J, Brühl AB, Seifritz E. The potential impact of biochemical mediators on telomere attrition in major depressive disorder and implications for future study designs: a narrative review. *J Affect Disord.* (2018) 225:630–46. doi: 10.1016/j.jad.2017.08.022
35. Kuo JR, Kaloupek DG, Woodward SH. Amygdala volume in combat-exposed veterans with and without posttraumatic stress disorder: a cross-sectional study. *Arch Gen Psychiatry* (2012) 69:1080–6. doi: 10.1001/archgenpsychiatry.2012.73
36. Woodward SH, Kaloupek DG, Streeter CC, Martinez C, Schaer M, Eliez S. Decreased anterior cingulate volume in combat-related PTSD. *Biol Psychiatry* (2006) 59:582–7. doi: 10.1016/j.biopsych.2005.07.033
37. Rauch SL, Shin LM, Segal E, Pitman RK, Carson MA, McMullin K, et al. Selectively reduced regional cortical volumes in post-traumatic stress disorder. *Neuroreport* (2003) 14:913–6. doi: 10.1097/01.wnr.0000071767.24455.10
38. Rocha-Rego V, Pereira MG, Oliveira L, Mendlowicz MV, Fiszman A, Marques-Portella C, et al. Decreased premotor cortex volume in victims of urban violence with posttraumatic stress disorder. *PLoS ONE* (2012) 7:e42560. doi: 10.1371/journal.pone.0042560
39. Rabinak CA, Angstadt M, Welsh RC, Kenndy AE, Lyubkin M, Martis B, et al. Altered amygdala resting-state functional connectivity in post-traumatic stress disorder. *Front Psychiatry* (2011) 2:62. doi: 10.3389/fpsyt.2011.00062
40. Sripada RK, King AP, Garfinkel SN, Wang X, Sripada CS, Welsh RC, et al. Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. *J Psychiatry Neurosci.* (2012) 37:241–9. doi: 10.1503/jpn.110069
41. Brown VM, LaBar KS, Haswell CC, Gold AL, Mid-Atlantic MIRECCW, McCarthy G, et al. Altered resting-state functional connectivity of basolateral and centromedial amygdala complexes in posttraumatic stress disorder. *Neuropsychopharmacology* (2014) 39:351–9. doi: 10.1038/npp.2013.197
42. Zhang X, Zhang J, Wang L, Li R, Zhang W. Altered resting-state functional connectivity of the amygdala in Chinese earthquake survivors. *Prog Neuropsychopharmacol Biol Psychiatry* (2016) 65:208–14. doi: 10.1016/j.pnpbp.2015.10.003
43. Shin LM, Wright CI, Cannistraro PA, Wedig MM, McMullin K, Martis B, et al. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Arch Gen Psychiatry* (2005) 62:273–81. doi: 10.1001/archpsyc.62.3.273
44. Peres JF, Foerster B, Santana LG, Fereira MD, Nasello AG, Savoia M, et al. Police officers under attack: resilience implications of an fMRI study. *J Psychiatr Res.* (2011) 45:727–34. doi: 10.1016/j.jpsychires.2010.11.004
45. Stevens JS, Ely TD, Sawamura T, Guzman D, Bradley B, Ressler KJ, et al. Childhood maltreatment predicts reduced inhibition-related activity in the rostral anterior cingulate in PTSD, but not trauma-exposed controls. *Depress Anxiety* (2016) 33:614–22. doi: 10.1002/da.22506
46. Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, et al. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biol Psychiatry* (1996) 40:1091–9. doi: 10.1016/S0006-3223(96)00229-6
47. Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, et al. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *Am J Psychiatry* (2003) 160:924–32. doi: 10.1176/appi.ajp.160.5.924
48. Apfel BA, Ross J, Hlavin J, Meyerhoff DJ, Metzler TJ, Marmar CR, et al. Hippocampal volume differences in Gulf War veterans with current versus lifetime posttraumatic stress disorder symptoms. *Biol Psychiatry* (2011) 69:541–8. doi: 10.1016/j.biopsych.2010.09.044
49. Winter H, Irle E. Hippocampal volume in adult burn patients with and without posttraumatic stress disorder. *Am J Psychiatry* (2004) 161:2194–200. doi: 10.1176/appi.ajp.161.12.2194
50. Fennema-Notestine C, Stein MB, Kennedy CM, Archibald SL, Jernigan TL. Brain morphometry in female victims of intimate partner violence with and without posttraumatic stress disorder. *Biol Psychiatry* (2002) 52:1089–101.
51. Pederson CL, Maurer SH, Kaminski PL, Zander KA, Peters CM, Stokes-Crowe LA, et al. Hippocampal volume and memory performance in a community-based sample of women with posttraumatic stress disorder secondary to child abuse. *J Trauma Stress* (2004) 17:37–40. doi: 10.1023/B:JOTS.0000014674.84517.46
52. Freeman T, Kimbrell T, Booe L, Myers M, Cardwell D, Lindquist DM, et al. Evidence of resilience: neuroimaging in former prisoners of war. *Psychiatry Res.* (2006) 146:59–64. doi: 10.1016/j.pscychresns.2005.07.007
53. Golier JA, Yehuda R, De Santi S, Segal S, Dolan S, de Leon MJ. Absence of hippocampal volume differences in survivors of the Nazi Holocaust with and without posttraumatic stress disorder. *Psychiatry Res.* (2005) 139:53–64. doi: 10.1016/j.pscychresns.2005.02.007
54. Vythilingam M, Luckenbaugh DA, Lam T, Morgan CA, Lipschitz D, Charney DS, et al. Smaller head of the hippocampus in Gulf War-related posttraumatic stress disorder. *Psychiatry Res.* (2005) 139:89–99. doi: 10.1016/j.pscychresns.2005.04.003
55. Morey RA, Haswell CC, Hooper SR, De Bellis MD. Amygdala, hippocampus, and ventral medial prefrontal cortex volumes differ in maltreated youth with and without chronic posttraumatic stress disorder. *Neuropsychopharmacology* (2016) 41:791–801. doi: 10.1038/npp.2015.205
56. Eckart C, Stoppel C, Kaufmann J, Tempelmann C, Hinrichs H, Elbert T, et al. Structural alterations in lateral prefrontal, parietal and posterior midline regions of men with chronic posttraumatic stress disorder. *J Psychiatry Neurosci.* (2011) 36:176–86. doi: 10.1503/jpn.100010
57. Sripada RK, King AP, Welsh RC, Garfinkel SN, Wang X, Sripada CS, et al. Neural dysregulation in posttraumatic stress disorder: evidence for disrupted equilibrium between salience and default mode brain networks. *Psychosom Med.* (2012) 74:904–11. doi: 10.1097/PSY.0b013e318273bf33
58. Kennis M, Rademaker AR, van Rooij SJ, Kahn RS, Geuze E. Resting state functional connectivity of the anterior cingulate cortex in veterans with and without post-traumatic stress disorder. *Hum Brain Mapp.* (2015) 36:99–109. doi: 10.1002/hbm.22615
59. Kennis M, van Rooij SJ, van den Heuvel MP, Kahn RS, Geuze E. Functional network topology associated with posttraumatic stress disorder in veterans. *Neuroimage Clin.* (2016) 10:302–9. doi: 10.1016/j.nicl.2015.12.008
60. van der Werff SJ, Pannekoek JN, Veer IM, van Tol MJ, Aleman A, Veltman DJ, et al. Resilience to childhood maltreatment is associated with increased resting-state functional connectivity of the salience network with the lingual gyrus. *Child Abuse Negl.* (2013) 37:1021–9. doi: 10.1016/j.chiabu.2013.07.008
61. Falconer E, Bryant R, Felmingham KL, Kemp AH, Gordon E, Peduto A, et al. The neural networks of inhibitory control in posttraumatic stress disorder. *J Psychiatry Neurosci.* (2008) 33:413–22.
62. Blair KS, Vythilingam M, Crowe SL, McCaffrey DE, Ng P, Wu CC, et al. Cognitive control of attention is differentially affected in trauma-exposed individuals with and without post-traumatic stress disorder. *Psychol Med.* (2013) 43:85–95. doi: 10.1017/S0033291712000840
63. New AS, Fan J, Murrough JW, Liu X, Liebman RE, Guise KG, et al. A functional magnetic resonance imaging study of deliberate emotion regulation

in resilience and posttraumatic stress disorder. *Biol Psychiatry* (2009) 66:656–64. doi: 10.1016/j.biopsych.2009.05.020
64. Pitman RK, Gilbertson MW, Gurvits TV, May FS, Lasko NB, Metzger LJ, et al. Clarifying the origin of biological abnormalities in PTSD through the study of identical twins discordant for combat exposure. *Ann N Y Acad Sci.* (2006) 1071:242–54. doi: 10.1196/annals.1364.019
65. Kasai K, Yamasue H, Gilbertson MW, Shenton ME, Rauch SL, Pitman RK. Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. *Biol Psychiatry* (2008) 63:550–6. doi: 10.1016/j.biopsych.2007.06.022
66. Shin LM, Bush G, Milad MR, Lasko NB, Brohawn KH, Hughes KC, et al. Exaggerated activation of dorsal anterior cingulate cortex during cognitive interference: a monozygotic twin study of posttraumatic stress disorder. *Am J Psychiatry* (2011) 168:979–85. doi: 10.1176/appi.ajp.2011.09121812
67. Bonne O, Brandes D, Gilboa A, Gomori JM, Shenton ME, Pitman RK, et al. Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. *Am J Psychiatry* (2001) 158:1248–51. doi: 10.1176/appi.ajp.158.8.1248
68. Rubin M, Shvil E, Papini S, Chhetry BT, Helpman L, Markowitz JC, et al. Greater hippocampal volume is associated with PTSD treatment response. *Psychiatry Res.* (2016) 252:36–39. doi: 10.1016/j.pscychresns.2016.05.001
69. Zhou Y, Wang Z, Qin LD, Wan JQ, Sun YW, Su SS, et al. Early altered resting-state functional connectivity predicts the severity of post-traumatic stress disorder symptoms in acutely traumatized subjects. *PLoS ONE* (2012) 7:e46833. doi: 10.1371/journal.pone.0046833
70. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med.* (2013) 11:126. doi: 10.1186/1741-7015-11-126
71. Insel TR. The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry. *Am J Psychiatry* (2014) 171:395–7. doi: 10.1176/appi.ajp.2014.14020138
72. van Rooij SJ, Stevens JS, Ely TD, Fani N, Smith AK, Kerley KA, et al. Childhood trauma and COMT genotype interact to increase hippocampal activation in resilient individuals. *Front Psychiatry* (2016) 7:156. doi: 10.3389/fpsyt.2016.00156
73. Thoern HA, Grueschow M, Ehlert U, Ruff CC, Kleim B. Attentional bias towards positive emotion predicts stress resilience. *PLoS ONE* (2016) 11:e0148368. doi: 10.1371/journal.pone.0148368
74. Helpman L, Zhu X, Suarez-Jimenez B, Lazarov A, Monk C, Neria Y. Sex differences in trauma-related psychopathology: a critical review of neuroimaging literature (2014–2017). *Curr Psychiatry Rep.* (2017) 19:104. doi: 10.1007/s11920-017-0854-y

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REVIEW
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Resilience Against Traumatic Stress: Current Developments and Future Directions

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Given the high prevalence of stress-related mental disorders, their impact on person, family, and society and the paucity of treatment options for most of these disorders, there is currently a pressing need for innovative approaches to deal with these issues and enhance well-being. One approach which has received increasing attention over the last decade is to shift our scientific and clinical focus from risk factors for psychopathology to factors promoting resilience and mental well-being. In order to summarize and evaluate the current state of scientific affairs on the biological basis of resilience, we provide an overview of the literature on animal and human studies of resilience. Because resilience can only truly be operationalized through longitudinal data collection and analyses, we focus primarily on longitudinal studies. This review shows that the concept of resilience is currently being operationalized, measured and even defined in widely variable manners, both within animal and human studies. We further provide an overview of existing and new strategies that could help promote resilience and which are proposed to be implemented more often in clinical situations. Finally, we summarize the challenges the field is facing and provide recommendations for future research.

Keywords: resilience, stress, prospective longitudinal studies, resilience-promoting interventions, review

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INTRODUCTION

Over the past decade, research on resilience has received increasing attention. The heightened interest in understanding and promoting resilience is not surprising given that in Europe alone, anxiety disorders and major depressive disorder were among the most frequent mental disorders in 2011 with a 12-month prevalence of 14% (corresponding to 61.5 million individuals) and 6.9% (30.3 million), respectively (1). This is not much different than the prevalence of these disorders in North America and many other parts of the world. Moreover, a recent meta-analysis showed that relapse rates in patients suffering from depression remain high and that long-term effects of conventional treatment options are not always encouraging (2). These findings call for additional strategies and alternative interventions needed to prevent disease development and boost resilience.

Here, we conceptualize resilience as being an active and dynamic process through which a person adaptively overcomes a stressful or difficult situation or recovers swiftly from a period of ill-health (3). Thus, resilience is not a passive reaction to an adverse situation, nor is it merely the

reverse side of post-traumatic stress disorder (PTSD) or the absence of symptomatology (3, 4). Research on resilience is facing several challenges of which the most fundamental one consists of the enormous heterogeneity in defining and operationalizing resilience. Indeed, some researchers will conceptualize resilience as being a personality trait while others will use the terms outcome, coping strategy or dynamic process (see (5) for a critical overview of different theories on resilience). Such discrepancies impede its measurement and further hinder the comparison of obtained results across resilience studies. Therefore, the following proposals have recently been formulated to guide future resilience research; (i) the fast recovery of mental health following stress exposure reflects a dynamic adaptation process, (ii) resilience should not be understood as a personality trait, the result of a specific genotype or other hardwired characteristics, (iii) there is a strong need for prospective longitudinal studies, and (iv) resilience can only be operationalized following a stressful period or event (3). Such stressors can refer to various types of (potentially) traumatic or life-threatening events, injury, illness, or difficult life circumstances such as unemployment, grief or divorce. Although most individuals recover promptly following trauma exposure, gaining a deeper understanding of the mechanisms underlying resilience could be of use to those more at risk of developing a stress-related disorder.

Following the conceptualization of resilience as proposed by Kalisch et al. (3), the main aim of the present review is to summarize the findings from key longitudinal animal and human studies on resilience. Furthermore, we propose strategies aiming to promote resilience, discuss limitations and challenges of current resilience research, and suggest future directions to help this field evolve.

RESILIENCE STUDIES

Over the past years, most resilience studies used cross-sectional designs. However, susceptibility and resilience to past or ongoing stress are hard to capture when assessing mental health at one time point only. Moreover, these designs do not allow for the exclusion of baseline differences between subjects which further impairs obtaining a comprehensive interpretation of the obtained findings. Using a longitudinal design enables one to assess dynamic behavioral and biological fluctuations over time, enabling investigations of (baseline) predictors of differential susceptibility to future stress. This is highly relevant, especially in light of at-risk jobs where trauma exposure is more prevalent. In order to take this into account, the first part of this review only includes prospective longitudinal animal and human studies, i.e., studies in which the individuals' mental health or the animals' behavioral or physiological state were quantitatively assessed before the (natural or experimental) stress exposure and at least once after this period. Expanding on the review by Kalisch et al. (3), the literature was searched for studies published in 2017 which fulfilled several criteria. First, we only included studies in which the severity and duration of the stress exposure was precisely quantified. For the human studies specifically, we only included studies in which the baseline assessments of predictors of mental health were recorded. In addition, and as postulated by Kalisch et al. (3), in susceptible individuals, the severity of the stress exposure had to positively correlate with the development of mental health problems. Studies were also only considered when including adults and the study groups consisted of 30 subjects or more (3). Since stress responses in children vary depending on their developmental stage, discussing these findings would require a different focus which does not fit within the scope of the present review. Finally, it needs to be noted that no systematic search of the literature was performed given the wide variety of terms used by researchers to describe resilience.

ANIMAL STUDIES

In animal research, resilient phenotypes are often identified based on specific behavioral outcomes following a well-defined period of experimentally induced stress. Specifically, those animals showing a fast recovery from a stressful manipulation are said to be resilient. Although caution and critical evaluation of the observed phenotypes are needed when interpreting and translating the obtained findings, these models can provide us with some of the molecular underpinnings of differential susceptibility to stress. Using the above-mentioned eligibility criteria, we identified six studies which can be found in **Table 1**. Studies sharing similar features are discussed together in the next paragraphs.

Inflammatory Markers

One study examined acoustic startle responses (which has been related to PTSD) in rats before and after exposure to a single episode of inescapable footshocks and 1-min reminders for the next 6 weeks (10). Rats exhibiting a high baseline startle response showed a significantly higher startle response following the period of exposure. Interestingly, rats showing an increased startle response at baseline also exhibited elevated plasma corticosterone levels at follow-up as compared to the rats with low baseline startle responses (although it should be noted that corticosterone levels were not measured prior to the experimental manipulation). Links between increased corticosterone levels and stress-induced behavioral phenotypes have also been observed in other studies (8, 9). One of these studies investigated whether longitudinal changes in blood corticosterone levels were associated with measures of differential susceptibility to stress in mice (8). The authors found that mice with an increase in plasma corticosterone levels upon 2 weeks of repeated restraint stress exposure showed significant weight loss over the course of the experiment as well as anxiety-related behaviors at follow-up as measured through the Elevated Plus Maze (EPM) and Open Field Test (OFT). These mice were thus characterized as being susceptible while more resilient mice were identified when showing (i) a decrease in corticosterone levels from baseline to follow-up, (ii) a stable body weight, and (iii) no anxiety-related behavior. Furthermore, the authors found that corticosterone levels at baseline predicted the extent of change in corticosterone levels during stress exposure and correlated with behavioral measures at follow-up. Another study used a repeated social defeat stress paradigm of 10 days and showed that those mice that later became susceptible to stress exposure had higher baseline levels of leukocytes (7). Moreover, in response to acute stress and prior to the repeated stress exposure paradigm,

TABLE 1 | Longitudinal animal studies assessing biological outcomes associated with differential susceptibility to stress.

References	Species and sex	Stressor	Outcome of interest	Main finding
Chen et al. (6)	Male Sprague–Dawley rats	7 days of chronic social defeat stress	Circulating miRNAs (tail blood)	↓ Pre-stress miR-24-2-5p, miR-27a-3p, miR-30e-5p, miR-362-3p, associates with future vulnerability to chronic social stress. ↓ Post-stress miR-139-5p, miR-28-3p, miR-326-3p, miR-99b-5p associates with ongoing resilience.
Hodes et al. (7)	Male CD45.1+/CD 45.2+ C57BL/6 mice	10 days of repeated social defeat stress	Blood leukocytes and IL-6 levels	Higher pre-stress leukocyte levels in mice that later became stress vulnerable. Higher IL-6 levels following acute stress, only in those mice that later became stress vulnerable.
Kim et al. (8)	Male C57BL/6N mice	Chronic restraint stress	Plasma corticosterone	Longitudinal changes in corticosterone reflect differential stress susceptibility and pre-stress corticosterone predicts post-stress susceptibility or resilience.
Magalhaes et al. (9)	Male Wistar rats	3 weeks of chronic unpredictable stress	Neuroimaging—functional connectivity and structural changes	Pre-stress differences in functional connectivity in brainstem-limbic area between susceptible and resilient rats.
Rasmussen et al. (10)	Male Wistar rats	Inescapable footshock + weekly 1-min reminders for 6 weeks	Acoustic startle response	↑ Pre-stress acoustic startle response = ↑ post-stress plasma corticosterone levels and ↑ post-stress acoustic startle response.
Tse et al. (11)	Male C57BL/6 mice	10 days of chronic social defeat stress	Hippocampal volume	↑ Post-stress left hippocampal volume in resilient and control mice.

Studies were listed in alphabetical order based on the surname of the first author. miRNAs: microRNAs. IL-6: interleukin-6.

the same mice exhibited higher levels of the pro-inflammatory cytokine interleukin-6 (IL-6). Together, these results suggest that baseline levels of specific inflammatory markers might predict differential susceptibility to future stress exposure in mice.

MicroRNAs

Only one prospective study examined the potential of microRNAs (miRNAs) to distinguish resilient and vulnerable animals (6). miRNAs are small, non-coding RNAs which are involved in the post-transcriptional regulation of gene expression (12). miRNAs have been widely studied in cancer and cardiovascular disease as potential biomarkers, but less is known regarding their involvement in mental disorders. (6) examined whether miRNAs could serve as biomarkers of resilience or vulnerability to stress by using a chronic social defeat paradigm in rats that lasted for 7 days. Rats showing little or no avoidance behavior when encountering an unfamiliar rat in its own cage were identified as being resilient while susceptible rats spent less time interacting with the novel rat as compared to controls. The authors found that susceptible rats had lower baseline blood circulating levels of miR-24-2-5p, miR-27a-3p, miR-30e-5p, and miR-362-3p compared to unexposed controls. However, the more resilient rats had lower levels of blood circulating levels of miR-139-5p, miR-28-3p, miR-326-3p, miR-99b-5p at follow-up as compared to controls. At both time points, no differences in miRNA expression were found between resilient and susceptible animals. These results pinpoint a number of candidate microRNA species which could, at least in part, regulate vulnerability to future stress or reflect ongoing resilience to chronic social stress in rats.

Neuroimaging Data

Using magnetic resonance imaging (MRI) in mice, Tse et al. were the first to assess changes in hippocampal volume prior to and following stress exposure (11). The authors identified susceptible and resilient animals based on their behavioral profiles in the social defeat paradigm. Following stress exposure, approximately half of the mice were classified as susceptible to stress, while the other half was more resilient. In contrast to the susceptible mice which showed no hippocampal volume increase over time, resilient and non-stressed control mice showed an increase in the left hippocampal volume from baseline to post-stress exposure, suggesting that normal hippocampal growth was impaired in susceptible animals only. Intriguingly, a positive correlation was observed between hippocampal volume at baseline and social avoidance behavior at follow-up. These findings suggest that that differences in hippocampal volumes could be associated with vulnerability to future stress in mice, which is further supported by similar findings in humans (13).

More recently, another study assessed structural changes more broadly along with alterations in the brain's functional connectome upon stress exposure (9). In this study, rats underwent a chronic unpredictable stress protocol for 3 weeks. Blood corticosterone levels, MRI scans and anxiety-related behaviors (measured through the EPM) were measured before, 7 and 21 days after exposure to stress. The authors categorized the stress-exposed rats into susceptible and resilient groups based on aberrant behavior and plasma corticosterone levels. Those rats expressing lower levels of post-exposure corticosterone in combination with minimal anxiety-like behavior were categorized as being resilient. Among a broad variety of structural and functional alterations induced by stress, it was found that baseline differences in functional connectivity measures of a

specific brainstem-limbic network were able to distinguish the resilient and susceptible groups, with susceptible rats showing lower functional connectivity compared to the resilient ones. It is worth mentioning that in humans, distinct patterns of brain activity have also been linked to PTSD and treatment response (14–16). Together, these results suggest that imaging data can contribute to a better understanding of the psychopathology of PTSD and potentially serve as a predictive biomarker of future vulnerability to stress and/or treatment response.

HUMAN STUDIES

Various collaborative prospective approaches are currently being conducted and followed-up on, including longitudinal approaches such as PRISMO ("Stressgerelateerd Militia Onderzoek") (17–21), the Marine Resiliency Study (MRS) I and II (22–24), and the prospective-longitudinal component of the Prevalence, Incidence and Determinants of PTSD and Other Mental Disorders (PID-PTSD^{+3}) (25, 26). Following our eligibility criteria, 12 articles were identified. All dealt with deployment-related stress, i.e., long-lasting effects of events experienced during actual combat, assault or other living conditions experienced during deployment (3). Studies sharing similar features are discussed together in the following paragraphs and can be found in **Table 2**.

Genetics

Two studies examined the longitudinal effects of genetic variations on stress-related PTSD symptoms. Both studies focused on candidate genes, i.e., the serotonin transporter (*5-HTT*) gene and catechol-O-methyltransferase (*COMT*) gene, which are known to affect serotonergic and dopaminergic signaling, respectively.

In the first study, the effects of a serotonin transporter gene-linked polymorphic region [5-HTTLPR] and threat-related attention on post-deployment PTSD symptoms was evaluated in 1,085 male soldiers (28). PTSD symptoms and threat-related attention bias (measured with a computerized dot-probe task) were assessed three times with the last assessment taking place around 1 year after baseline. Combat exposure between the baseline and follow-up assessments was inferred by using geo-operational exposure data and self-report measures [i.e., the Combat Experiences Scale with two additional items (29)]. The authors observed that pre-deployment-threat bias interacted with combat exposure during deployment and 5-HTTLPR in predicting post-deployment PTSD symptoms. More specifically, fewer post-deployment PTSD symptoms after high combat exposure were found in those individuals who displayed pre-deployment threat vigilance and had the SS/SL-G alleles (i.e., reflecting low transcription 5-HTT) of the 5-HTTLPR genotypes. This study is particularly interesting in highlighting the complex interaction between context, stress-exposure, attention bias and genetics, suggesting that serotonergic transmission may be involved in the co-occurrence of avoidance and hypervigilance symptoms in PTSD (30).

In another study, 253 Iraq war veterans were assessed prior to and following a deployment period of 16 months (27). Deployment trauma was measured with the Post Deployment Stressors subscale of the Deployment Risk and Resilience Inventory (DRRI) (31) as well as by using one additional item on sexual assault experienced during deployment. DNA was extracted from blood or buccal swabs and was genotyped into COMT Met/Met ($n = 63$), Val/Met ($n = 131$), or Val/Val ($n = 42$). Regression analyses showed that the effect of deployment trauma on PTSD was dependent on COMT polymorphism with carriers of the homozygous genotypes (Met/Met and Val/Val) showing more PTSD symptoms than those carrying the heterozygous (Val/Met) genotype. This is in line with previous human and animal studies which highlight the role of the Met/Met genotype and show some preliminary support for the Val/Val genotype as a risk factor for the development of PTSD (32–34).

Epigenetics

Several cross-sectional studies support the putative role of epigenetic mechanisms, especially DNA methylation, in the impact of traumatic stress on mental health (35–38). Recently, prospective epigenetic studies have started to investigate the links between changes in PTSD symptom scores and changes in epigenetic profiles across the period of exposure to traumatic stress. These studies were conducted in subsamples of the PRISMO project and focus on the glucocorticoid receptor exon 1_F (GR-1_F) region and the predictive role of epigenetic markers in PTSD. In the first study, methylation signatures of the GR-1_F region (52 loci) were quantified in peripheral blood cells of 92 Dutch military personnel which were collected before and after a 4-month deployment period to Afghanistan. More specifically, the authors focused on mean methylation across all cytosine–phosphate–guanines (CpGs), the number of methylated loci and those CpGs of which methylation was known from previous publications to be associated with GR exon 1_F mRNA expression. The latter was termed "functional methylation". It was found that an increase in either of the methylation levels (i.e., mean, number, and functional) within this region was associated with increases in PTSD symptom scores in trauma-exposed subject. Increased functional methylation was associated with mental health. However, PTSD and mental health problems occurring 6 months post-deployment within individuals exposed to trauma were predicted by neither of the pre-deployment methylation levels (i.e., mean, number, or functional) (21).

In a recent prospective epigenetic study performed using two military cohorts (20), the impact of traumatic stress during combat on post-deployment PTSD symptoms and associated longitudinal epigenetic changes was investigated. In a discovery sample of 93 male Dutch servicemen [PRISMO cohort; same subjects as Schur et al. (21)], specific DNA methylation alterations were associated with the development of PTSD. This cohort displayed changes at 17 positions and 12 regions and subsequent bioinformatic analyses highlighted the role of different pathways linked to PTSD symptomatology. Interestingly, the associations between the development of PTSD symptoms and decreased DNA methylation at genomic regions in *ZFP57*, *RNF39,* and *HIST1H2APS2* were replicated in a male US marine cohort of MRS with a 7-month war-zone deployment to Iraq or Afghanistan ($n = 98$).

TABLE 2 | Longitudinal human studies assessing biological outcomes associated with differential susceptibility to stress.

References	Sample (N)	Main stressor	Outcome of interest	Main finding
GENETIC FACTORS				
Clark et al. (27)	RINGS; Male soldiers: $N = 253$	Deployment	PTSD	Met/Met and Val/Val genotypes had stronger trauma-responses than the Val/Met genotype.
Wald et al. (28)	Israeli Defense Force; Male soldiers: $N = 1,085$	Deployment	PTSD	Threat bias interacted with combat exposure and threat bias interacted with combat exposure and 5-HTTLPR.
EPIGENETIC FACTORS				
Rutten et al. (20)	PRISMO and MRS; Male soldiers/marines: $N = 93$, $N = 98$	Deployment	PTSD	Genome-wide changes at 17 positions and 12 regions were associated with PTSD status.
Schur et al. (21)	PRISMO, Male soldiers: $N = 92$	Deployment	Mental health and PTSD	Pre-deployment GR-1F region (52 loci) methylation did not predict mental health or PTSD status.
Van Zuiden et al. (17)	PRISMO Male soldiers: $N = 68$	Deployment	PTSD	mRNA expression of GR–α, GR-P, GR-β, glucocorticoid- induced leucine zipper (GILZ), serum and glucocorticoid-inducible kinase-1 (SGK-1), or FKBP5 does not predict PTSD status.
CIRCULATING MARKERS				
Inflammatory Markers				
Breen et al. (23)	MRS II and MRS; Male marines: $N = 124$, $N = 50$	Deployment	PTSD	PTSD status associated with gene co-expression networks related to innate immune responses.
Eraly et al. (22)	MRS, Male marines: $N = 1,719$	Deployment	PTSD	Baseline plasma levels of C-reactive protein (CRP) predicted PTSD symptoms.
Smid et al. (18)	PRISMO, $N = 693$	Deployment	PTSD	Interaction between cytokine production, stress exposure during combat and post-deployment stressful life events.
Torshizi et al. (24)	MRS II and MRS; Male marines: $N = 124$, $N = 50$	Deployment	PTSD	PTSD status associated with gene co-expression network master regulators: SOX3, TNFAIP3, TRAFD1, POU3F3, STAT2, and PML.
Hormonal Dysregulations				
Reijnen et al. (19)	PRISMO, Male soldiers: $N = 907$	Deployment	PTSD	No moderating effect of plasma oxytocin and arginine vasopressin on stress-related PTSD development.
Steudte-Schmiedgen et al. (25)	PID-PTSD+3, Male soldiers $N = 90$; $N = 80$	Deployment	PTSD	Decreased baseline hair cortisol and cortisol stress predict higher stress-related PTSD.
Trautmann et al. (26)	PID-PTSD+3, Male soldiers $N = 153$, $N = 145$	Deployment	Alcohol consumption	Decreased baseline hair cortisol stress predict higher stress-related alcohol use.
Van Zuiden et al. (17)	PRISMO, Male soldiers: $N = 68$	Deployment	PTSD	Plasma cortisol does not predict PTSD status.

MRS, MRS II, Marine Resiliency Study I, II; PID-PTSD^{+3}, Incidence and Determinants of PTSD and Other Mental Disorders; PRISMO, Stressgerelateerd Militia Onderzoek; RINGS, The Readiness and Resilience in National Guard Soldiers Study. Within each section, studies were listed in alphabetical order based on the surname of the first author.

It is worth mentioning that international efforts such as the Psychiatric Genomics Consortium (PGC) PTSD group, which includes data on a large combined sample of four military studies and three civilian cohorts ($N = 1,147$), might have increased statistical power to detect further relevant epigenetic variations and thereby provide deeper insights in the near future (39).

Blood Markers

Inflammatory Markers

Upon the observation that PTSD co-occurred with peripheral inflammation in cross-sectional studies, the question arose as to whether inflammatory markers are causally involved in the disorder or are one of its consequences (40). Since then, several prospective studies have attempted to evaluate the causal role of various inflammatory responses in the development of PTSD.

One study used a subset of the MRS dataset ($N = 1,719$) and found that in U.S. Marines, baseline plasma levels of C-reactive protein (CRP) was a strong predictor of post-deployment PTSD symptoms (22). Another study analyzed gene co-expression profiles obtained through RNA sequencing of peripheral blood leukocytes from Marines belonging to the MRS II ($N = 124$) and replicated the obtained findings in a separate subsample of the MRS ($N = 50$). It was found that both at pre- and post-deployment, co-expression gene networks linked to the innate immune responses, interferon signaling, and monocyte specificity were predictive of post-deployment PTSD (23). Following this and using the same

sample as Breen et al. (23), researchers (24) aimed to build upon these findings and ascertained several master regulators driving the previously identified networks. Using ARACNe (Algorithm for Reconstruction of Accurate Cellular Networks) and protein activity analysis they identified SOX3, TNFAIP3, TRAFD1, POU3F3, STAT2, and PML as important master regulators. Gene Ontology analyses enriched by TNFAIP3, TRAFD1, and PML again pointed toward the role of the innate immune responses in the development of PTSD.

In a subsample of the PRISMO dataset ($N = 693$), researchers addressed the immune activation by measuring *in vitro* cytokine production by leukocytes upon stimulation (18). Among other findings, the authors observed a three-way interaction between cytokine production at 1-month post-deployment, trauma exposure during combat (assessed 1-month post-deployment), and post-deployment stressful life events during 12 months post-deployment on the longitudinal changes in PTSD symptoms scores as measured between 1 month and 2 years post deployment. More specifically, increased mitogen-stimulated T-cell and innate cytokine production, greater exposure to stress during combat and during the 12-month post-deployment period were associated with increased PTSD symptoms between 1 month and 2 years post-deployment.

Hormonal Dysregulations

Another line of studies focused on the functioning of the hypothalamic–pituitary–adrenal (HPA) axis. In this regard, three studies investigated the links between cortisol levels and stress exposure on the development of PTSD. Two of these studies were part of the PID-PTSD^{+3} project and assessed hair cortisol concentration (HCC) and cortisol stress reactivity, measured through saliva cortisol levels before and after the Trier Social Stress Test (TSST), prior to and following a deployment period of ∼5 months (25, 26). Their main finding showed that when exposed to trauma, a lower baseline HCC and lower cortisol stress level were predictive of higher post-deployment PTSD symptomatology (25) while lower HCC predicted higher daily alcohol consumption (26). In another study done in the PRISMO cohort (N = 455), plasma cortisol levels at baseline did not predict PTSD status 6 months after a 4 months deployment period (17). Next to cortisol, these researchers further investigated other crucial molecules of the HPA axis. van Zuiden et al. evaluated the predictive role of mRNA expression of GR–α, GR-P, GR-β, glucocorticoid- induced leucine zipper (*GILZ*), glucocorticoid-inducible kinase-1 (*SGK-1*), or *FKBP5* in peripheral blood mononuclear cells (PBMCs) and the number of GRs in PBMCs on post-deployment PTSD status. Interestingly, only the number of GRs in PBMCs predicted post-deployment PTSD status (17).

Other researchers assessed whether plasma oxytocin (pOT) and arginine vasopressin (pAVP) levels could be used as biomarkers for stress-related development of PTSD (19) in PRISMO. By investigating a group of 907 military subjects, no effects of pOT and pAVP on post-deployment PTSD was observed (19).

Together, these studies highlight the value of prospective studies in linking circulating markers with the development of PTSD. While the first line of evidence suggests that elements of the immune system emerge as candidate biomarkers, there is apparent need for replications and larger longitudinal studies to confirm and extend these initial findings.

PROMOTING RESILIENCE

The previous sections provided an overview of prospective human and animal studies that aimed at gaining knowledge of the mechanisms underlying mental illness and resilience. Research in this field has also turned toward studying strategies which could potentially promote mental health and boost resilience. As postulated by McEwen et al., the notion that the brain holds the ability to successfully adapt to changing environments throughout the life course, encourages one to develop top-down interventions encompassing mind-body interactions in order to install fundamental changes in various aspects of one's sense of well-being (41). Given the previously mentioned need to expand alternative add-on strategies in order to promote resilience in today's society, this section will cover a range of psychological, behavioral and lifestyle interventions which aim to do so.

Mindfulness and Meditation

Over the last few decades, meditation techniques such as loving-kindness meditation and mindfulness meditation have been spreading in the western world. Today, mindfulness mainly owes its popularity to Professor Jon Kabat-Zinn who reintroduced it in his mindfulness-based stress reduction (MBSR) program. Described as the awareness that arises through paying purposeful and non-judgemental attention to the present moment (42), mindfulness is now employed as part of standardized programs aiming to promote general human well-being and install deeply rooted positive emotions.

Empirical evidences about the benefits of mindfulness-based programs are inciting a growing interest in the (neuro)biological underpinnings of mindfulness. Different mindfulness programs have shown to impact both gray and white matter density of several brain structures such as in the right basolateral amygdala (43) and bilateral clusters within the brainstem including the pontine tegmentum, locus coeruleus, nucleus raphe, and the sensory trigeminal nucleus (44). Moreover, findings show that other types of mind-body interventions also influence various parameters of the immune system. For example, one study showed that following a yogic meditation, the activity of the proinflammatory nuclear factor-kappa beta (NF-κB), known to have a prominent role in inflammation and stress, was reduced in peripheral blood leukocytes as compared to baseline measures (45). Another study found an increase in telomerase activity along with reduced levels of another inflammatory marker, CRP, in peripheral blood mononuclear cells (PBMCs) following the same type of meditation (46). Yet another study found that by measuring gene expression in peripheral blood prior to and following a deep relaxation session, the expression of genes associated with telomere maintenance were enhanced at follow-up while specific genes linked to stress-related pathways were reduced in expression (47). Although interesting, it is important to note that currently performed studies vary greatly in terms of

the type of (mindfulness) meditation used along with the research designs and (often small) sample sizes. Gaining knowledge in the mechanisms underlying the well-documented stress-reducing and mood-enhancing effects of meditation and mindfulness-based programs (48–51) holds the potential to further help the design of powerful strategies in healthcare settings to promote the cultivation of a healthy mind.

Cognitive Behavioral Therapy-Based Programs

Cognitive behavioral therapy (CBT) was originally developed by Aaron Beck to promote mental wellness and coping resources in patients suffering from mental distress such as depression, anxiety and chronic stress (52). The idea of CBT is to modify one's thinking and behavioral patterns which color the way life events are being experienced. Interestingly, combining CBT with pharmacological treatments such as cognitive enhancers (but not anxiolytics) has been shown to improve long-term treatment efficacy and fear extinction, potentially by enhancing memory consolidation [recently extensively reviewed in Singewald et al. (53)]. In addition, conducting CBT sessions such as exposure therapy before sleep has also been suggested to enhance treatment efficacy, raising the question whether pharmacological approaches can be implemented to enhance memory consolidations during sleep specifically (53, 54). Another intervention targeting memory consolidation involves playing a computer game with high visuospatial demands (e.g., Tetris) during the hours following a traumatic event. Interestingly, this approach has recently been suggested to disrupt the consolidation of trauma memories and lead to fewer intrusive visual memories of the traumatic event (55). In order to maximize treatment outcome, combinations of different behavioral approaches with or without various pharmacological options will need further testing.

Besides its well-documented therapeutic effect in treating mental distress and some other disorders, today's interest in CBT is also geared toward the construction of a personal model to boost resilience in the face of life's obstacles without necessarily targeting a particular mental disorder. Padesky and Mooney have proposed a CBT-based program entirely oriented toward "resiliency" research (56). Their so-called strengths-based CBT consists of four sessions in which the therapist and the client actively collaborate to explore and reinforce positive qualities such as interpersonal competences, self-efficacy or self-esteem. The therapist and client co-create a personal model of resiliency by turning the previously identified strengths into effective strategies that can be applied in everyday situations. Another CBT-based program is the Stress Inoculation Therapy (SIT) which was first introduced in 1985 (57). In social psychology, the concept of inoculation refers to the preventive effect of brief and moderately challenging stress exposures on one's reaction to subsequent, more intense stressors. More specifically, exposing animals or individuals to minor stressors has been shown to enhance one's resilience or "inoculate" them from later stressful situations (58–60). SIT incorporates this notion of inoculation in a psychotherapeutic intervention that combines cognitive and behavioral methods emphasizing coping skills learning. During a SIT session, an individual is exposed to and learns to cope with increasing amounts of stress through productive thoughts, mental images, self-statements, and relaxation training thereby enhancing his or her immunity to stress. Empirical evidence shows that SIT efficiently reduces stress, anxiety and depression in cancer patients (61) and effectively reduces psychological distress up to 3 months following the sessions when delivered through two half-day training sessions in the workplace (62).

Physical Activity

It is commonly known that practicing regular physical exercise leads to a plethora of positive health effects (63). These benefits not only include cardiovascular and metabolic effects, but also improvements in cognitive abilities. Previous studies on animals and humans have revealed increases in synaptic plasticity and neurogenesis (64), strengthened cortical activation when performing a cognitively challenging task (65) and improvements in learning, slowing the course of cognitive decline in aging (65, 66). Using a within-subject design and multiple momentary assessments collected through experience sampling method (ESM), a diary technique assessing daily moods and activities, one study provides support for a causal effect of physical activity on positive affect (67). Since the extent of positive affect levels varied between individuals based on their history of clinical depression, such findings call for individually tailored interventions in which clinicians could adapt the amount of physical exercise. Other studies showed that compared to training exercises with no cognitive component, specific exercises that promote mindfulness by means of calming techniques and cognitive strategies such as yoga or pilates were more effective in eliciting psychological benefits such as mood enhancements and improved executive functions over time (68–70). Mindful-based physical activities, thus, seem to help improve breathing rate and depth (71, 72) along with heart rate (72) while lowering arousal levels (73). Further comparative trials in populations at high risk of robust exposure to traumatic stress are needed in order to prospectively assess the putative protective properties of these interventions on trauma-related mental ill-health.

Social Support

Several lines of evidence confirm the importance of pursuing cognitive and social activities to maintain global mental and functional health (74–76). However, the exact biopsychological mechanisms underlying the positive impact of social support on mental well-being and resilience to stress still remain unclear (77). To enhance both cognitive and social aspects, programs such as the Experience Corps have been introduced. This intergenerational program was originally designed by Fried et al. in 1997 to promote health among the aging population. Specifically, this program encourages adults over the age of 50 to share their skills with children needing help at school. While students obtain greater academic outcomes, older adults get the opportunity to enrich their lives on a social and cognitive level (78). A recent study shows that this program further significantly slows the normal age-related decrease in cortical and hippocampal brain volumes (79).

Meaning and Purpose in Life

Programs such as the Experience Corps offer older adults a sense of meaning and purpose in life which is a crucial component of mental health. A meta-analysis found that purpose in life was strongly linked to social integration in a population of older individuals and was further related to factors such as quality of life, a better health, and socioeconomic status (80). Other studies have suggested that finding a sense of purpose in life is a partial mediator of the observed negative association between trait mindfulness and outcomes such as anxiety and depressive symptoms (81). Having meaning to life has further been negatively associated with suicidal ideation (82, 83) while being an important predictor of depressive symptoms (84). Taken together, these findings highlight the importance of establishing personal values and long-term goals in order to help one overcome or prevent psychological problems.

DISCUSSION

As reflected by the first part of this review, there is considerable variation in the way resilience is currently being understood, defined and measured both within animal and human studies.

In animals, the main challenge is to understand how one can identify a "resilient" animal and how this relates to resilience in humans. Most animal studies of resilience identify resilient animals based on the absence of stress-related behavioral features. However, when assessing an animal's behavior, one should evaluate both the absence of stress-related behavioral features or biological markers, and the presence of adaptive behaviors or markers. For an overview of studies that have started to identify such adaptive behavioral, neural and molecular mechanisms, the reader is referred to Pfau and Russo (85) and Russo et al. (86). Furthermore, only few animal studies have incorporated a baseline behavioral or physiological measure in order to assess dynamic changes over time. Using cross-sectional designs, recent studies identified distinct molecular signatures that were associated with adaptive or maladaptive behavioral responses to stress (87–89). Adding a baseline measurement to such approaches would be highly valuable in identifying baseline differences between animals along with the pattern of change from pre- to post-stressor within the same animal. Linking such markers with differential susceptibility to a stressor will further yield valuable insights into the molecular mechanisms of resilience which, in turn, will more efficiently lead to the identification of (a combination of) predictive biomarkers of resilience. Lastly, researchers need to carefully reflect upon their animal model (e.g., sex, strain, and age), phenotypes of interest and experimental designs (e.g., timing, duration, and type of stressor) (90) in order to fulfill different types of validities to make their tests and models translatable to the clinical situation (91, 92).

In humans, although conducting prospective studies has received increasing attention, most findings are still preliminary since replication is often lacking and most studies harbor low effect sizes and relatively small sample sizes. It is also important to note that (i) a wide variety of tools (which cannot be compared easily) are currently being used to measure "resilience" of which the validity needs critical examination, (ii) the majority of resilience studies focuses on PTSD-related outcomes instead of positive outcome measures, and (iii) most of the studies which fulfilled the rather strict inclusion and exclusion criteria were conducted in military cohorts. While such samples provide a unique opportunity to study the effects of trauma exposure, they are also subjected to a natural limitation since sampling bias cannot be excluded.

For future studies, researchers are encouraged to include a wider range of assessments when aiming to study and measure resilience in order to obtain a more reliable and objective operationalization of this concept. Using several techniques such as ESM (93), in-person interviews combined with self-evaluations or targeted questionnaires and physiological measures including heart rate and blood pressure will allow one to obtain a more global picture on general psychological and physiological health. Furthermore, ESM might help to better understand processes such as inoculation during which individuals may develop resilience through repeated stress exposure. When possible, this, again, should be embedded within large-scale longitudinal studies since these allow tracking the stability of one's mental health over a specific time period. Moreover, and in order to facilitate extrapolation to the general population, there is a strong need for the inclusion of women in these studies, which is currently underdone (94). This is crucial when knowing that women are more likely than men to develop stress-related mental disorders. Although this is a much broader phenomenon within science, both in animal and human research, women are even less likely to be included in studies using military cohorts in which they are underrepresented. An increase in the number of studies focusing on this population will undoubtedly enhance our current understanding of their stress responsiveness, health care and gender-specific needs. Lastly, in the context of searching for biological underpinnings or biomarkers that reliably predict differential susceptibility to future stress or psychological and biological resilience mechanisms, exploring the potential to combine several predictors, e.g., genetic, epigenetic, and/or imaging data on an individual basis is strongly encouraged. This further calls for more large-scale brain imaging studies in order to identify the brain regions involved in stress resilience.

Finally, establishing alternative strategies aiming to install positive emotions and improve cognitive abilities, social interactions, feelings of purpose and meaning of life along with physical health have obtained scientific evidence for their benefits in increasing one's global mental health, whilst the biological underpinning of these effects have remained understudied thus far. Gaining a deeper understanding of the underlying mechanisms of each of these strategies will undoubtedly aid in developing new treatment options for stress-related disorders such as PTSD.

AUTHOR CONTRIBUTIONS

CS and L-KP contributed equally to this manuscript. GAJ contributed to the interpretation of the obtained data.

NS, GAJ, NY, LdN, and SG reviewed the manuscript and provided comments/suggestions. BR reviewed the manuscript, provided comments/suggestions, and is the corresponding author.

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REFERENCES

1. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol.* (2011) 21:655–79. doi: 10.1016/j.euroneuro.2011.07.018
2. Steinert C, Hofmann M, Kruse J, Leichsenring F. Relapse rates after psychotherapy for depression - stable long-term effects? A meta-analysis. *J Affect Disord.* (2014) 168:107–18. doi: 10.1016/j.jad.2014.06.043
3. Kalisch R, Baker DG, Basten U, Boks MP, Bonanno GA, Brummelman E, et al. The resilience framework as a strategy to combat stress-related disorders. *Nat Hum Behav.* (2017) 1:784. doi: 10.1038/s41562-017-0200-8
4. Rutten BP, Hammels C, Geschwind N, Menne-Lothmann C, Pishva E, Schruers K, et al. Resilience in mental health: linking psychological and neurobiological perspectives. *Acta Psychiatr Scand.* (2013) 128:3–20. doi: 10.1111/acps.12095
5. Fletcher D, Sarkar M. Psychological resilience: a review and critique of definitions, concepts, and theory. *Eur Psychol.* (2013) 18:12–23. doi: 10.1027/1016-9040/a000124
6. Chen RJ, Kelly G, Sengupta A, Heydendael W, Nicholas B, Beltrami S, et al. MicroRNAs as biomarkers of resilience or vulnerability to stress. *Neuroscience* (2015) 305:36–48. doi: 10.1016/j.neuroscience.2015.07.045
7. Hodes GE, Pfau ML, Leboeuf M, Golden SA, Christoffel DJ, Bregman D, et al. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. *Proc Natl Acad Sci USA.* (2014) 111:16136–41. doi: 10.1073/pnas.1415191111
8. Kim JG, Jung HS, Kim KJ, Min SS, Yoon BJ. Basal blood corticosterone level is correlated with susceptibility to chronic restraint stress in mice. *Neurosci Lett.* (2013) 555:137–42. doi: 10.1016/j.neulet.2013.09.031
9. Magalhaes R, Barriere DA, Novais A, Marques F, Marques P, Cerqueira J, et al. The dynamics of stress: a longitudinal MRI study of rat brain structure and connectome. *Mol Psychiatry* (2017) 23:1998–2006. doi: 10.1038/mp.2017.244
10. Rasmussen DD, Crites NJ, Burke BL. Acoustic startle amplitude predicts vulnerability to develop post-traumatic stress hyper-responsivity and associated plasma corticosterone changes in rats. *Psychoneuroendocrinology* (2008) 33:282–91. doi: 10.1016/j.psyneuen.2007.11.010
11. Tse YC, Montoya I, Wong AS, Mathieu A, Lissemore J, Lagace DC, et al. A longitudinal study of stress-induced hippocampal volume changes in mice that are susceptible or resilient to chronic social defeat. *Hippocampus* (2014) 24:1120–8. doi: 10.1002/hipo.22296
12. Macfarlane LA, Mrphy PR. MicroRNA: biogenesis, function and role in cancer. *Curr Genomics* (2010) 11:537–61. doi: 10.2174/138920210793175895
13. Van Rooij S, Kennis M, Sjouwerman R, Van Den Heuvel M, Kahn R, Geuze E. Smaller hippocampal volume as a vulnerability factor for the persistence of post-traumatic stress disorder. *Psychol Med.* (2015) 45:2737–46. doi: 10.1017/S0033291715000707
14. van Wingen GA, Geuze E, Caan MW, Kozicz T, Olabarriaga SD, Denys D, et al. Persistent and reversible consequences of combat stress on the mesofrontal circuit and cognition. *Proc Natl Acad Sci USA.* (2012) 109:15508–13. doi: 10.1073/pnas.1206330109
15. Kennis M, Van Rooij S, Van Den Heuvel M, Kahn R, Geuze E. Functional network topology associated with posttraumatic stress disorder in veterans. *NeuroImage Clin.* (2016) 10:302–9. doi: 10.1016/j.nicl.2015.12.008
16. Van Rooij SJ, Kennis M, Vink M, Geuze E. Predicting treatment outcome in PTSD: a longitudinal functional MRI study on trauma-unrelated emotional processing. *Neuropsychopharmacology* (2016) 41:1156–65. doi: 10.1038/npp.2015.257
17. van Zuiden M, Geuze E, Willemen HL, Vermetten E, Maas M, Heijnen CJ, et al. Pre-existing high glucocorticoid receptor number predicting development of posttraumatic stress symptoms after military deployment. *Am J Psychiatry* (2011) 168:89–96. doi: 10.1176/appi.ajp.2010.10050706
18. Smid GE, van Zuiden M, Geuze E, Kavelaars A, Heijnen CJ, Vermetten E. Cytokine production as a putative biological mechanism underlying stress sensitization in high combat exposed soldiers. *Psychoneuroendocrinology* (2015) 51:534–46. doi: 10.1016/j.psyneuen.2014.07.010
19. Reijnen A, Geuze E, Vermetten E. Individual variation in plasma oxytocin and vasopressin levels in relation to the development of combat-related PTSD in a large military cohort. *J Psychiatr Res.* (2017) 94:88–95. doi: 10.1016/j.jpsychires.2017.06.010
20. Rutten BPF, Vermetten E, Vinkers CH, Ursini G, Daskalakis NP, Pishva E, et al. Longitudinal analyses of the DNA methylome in deployed military servicemen identify susceptibility loci for post-traumatic stress disorder. *Mol Psychiatry* (2017) 23:1145–56. doi: 10.1038/mp.2017.12
21. Schur RR, Boks MP, Rutten BPF, Daskalakis NP, de Nijs L, van Zuiden M, et al. Longitudinal changes in glucocorticoid receptor exon 1F methylation and psychopathology after military deployment. *Transl Psychiatry* (2017) 7:e1181. doi: 10.1038/tp.2017.150
22. Eraly SA, Nievergelt CM, Maihofer AX, Barkauskas DA, Biswas N, Agorastos A, et al. Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. *JAMA Psychiatry* (2014) 71:423–31. doi: 10.1001/jamapsychiatry.2013.4374
23. Breen MS, Maihofer AX, Glatt SJ, Tylee DS, Chandler SD, Tsuang MT, et al. Gene networks specific for innate immunity define post-traumatic stress disorder. *Mol Psychiatry* (2015) 20:1538–45. doi: 10.1038/mp.2015.9
24. Torshizi AD, Wang K. Deconvolution of transcriptional networks in post-traumatic stress disorder uncovers master regulators driving innate immune system function. *Sci Rep.* (2017) 7:14486. doi: 10.1038/s41598-017-15221-y
25. Steudte-Schmiedgen S, Stalder T, Schonfeld S, Wittchen HU, Trautmann S, Alexander N, et al. Hair cortisol concentrations and cortisol stress reactivity predict PTSD symptom increase after trauma exposure during military deployment. *Psychoneuroendocrinology* (2015) 59:123–33. doi: 10.1016/j.psyneuen.2015.05.007
26. Trautmann S, Muehlhan M, Kirschbaum C, Wittchen HU, Hofler M, Stalder T, et al. Biological stress indicators as risk markers for increased alcohol use following traumatic experiences. *Addict Biol.* (2018) 23:281–90. doi: 10.1111/adb.12487
27. Clark R, DeYoung CG, Sponheim SR, Bender TL, Polusny MA, Erbes CR, et al. Predicting post-traumatic stress disorder in veterans: interaction of traumatic load with COMT gene variation. *J Psychiatr Res.* (2013) 47:1849–56. doi: 10.1016/j.jpsychires.2013.08.013
28. Wald I, Degnan KA, Gorodetsky E, Charney DS, Fox NA, Fruchter E, et al. Attention to threats and combat-related posttraumatic stress symptoms: prospective associations and moderation by the serotonin transporter gene. *JAMA Psychiatry* (2013) 70:401–8. doi: 10.1001/2013.jamapsychiatry.188
29. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med.* (2004) 351:13–22. doi: 10.1056/NEJMoa040603
30. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®).* Washington, DC: American Psychiatric Pub (2013).
31. King LA, King DW, Vogt DS, Knight J, Samper RE. Deployment Risk and Resilience Inventory: a collection of measures for studying deployment-related experiences of military personnel and veterans. *Milit Psychol.* (2006) 18:89–120. doi: 10.1207/s15327876mp1802_1
32. Kolassa I-T, Kolassa S, Ertl V, Papassotiropoulos A, Dominique J-F. The risk of posttraumatic stress disorder after trauma depends on traumatic load and the catechol-O-methyltransferase Val158Met polymorphism. *Biol Psychiatry* (2010) 67:304–8. doi: 10.1016/j.biopsych.2009.10.009

33. Zuj DV, Palmer MA, Lommen MJ, Felmingham KL. The centrality of fear extinction in linking risk factors to PTSD: a narrative review. *Neurosci Biobehav Rev*. (2016) 69:15–35. doi: 10.1016/j.neubiorev.2016.07.014
34. Hayes JP, Logue MW, Reagan A, Salat D, Wolf EJ, Sadeh N, et al. COMT Val158Met polymorphism moderates the association between PTSD symptom severity and hippocampal volume. *J Psychiatry Neurosci.* (2017) 42:95–102. doi: 10.1503/jpn.150339
35. Uddin M, Galea S, Chang SC, Aiello AE, Wildman DE, de los Santos R, et al. Gene expression and methylation signatures of MAN2C1 are associated with PTSD. *Dis Markers* (2011) 30:111–21. doi: 10.1155/2011/513659
36. Mehta D, Klengel T, Conneely KN, Smith AK, Altmann A, Pace TW, et al. Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. *Proc Natl Acad Sci USA*. (2013) 110:8302–7. doi: 10.1073/pnas.1217750110
37. Vinkers CH, Kalafateli AL, Rutten BP, Kas MJ, Kaminsky Z, Turner JD, et al. Traumatic stress and human DNA methylation: a critical review. *Epigenomics* (2015) 7:593–608. doi: 10.2217/epi.15.11
38. Zannas AS, Provencal N, Binder EB. Epigenetics of posttraumatic stress disorder: current evidence, challenges, and future directions. *Biol Psychiatry* (2015) 78:327–35. doi: 10.1016/j.biopsych.2015.04.003
39. Ratanatharathorn A, Boks MP, Maihofer AX, Aiello AE, Amstadter AB, Ashley-Koch AE, et al. Epigenome-wide association of PTSD from heterogeneous cohorts with a common multi-site analysis pipeline. *Am J Med Genet B Neuropsychiatr Genet.* (2017) 174:619–30. doi: 10.1002/ajmg.b.32568
40. Baker DG, Nievergelt CM, O'Connor DT. Biomarkers of PTSD: neuropeptides and immune signaling. *Neuropharmacology* (2012) 62:663–73. doi: 10.1016/j.neuropharm.2011.02.027
41. McEwen BS, Gray JD, Nasca C. Redefining neuroendocrinology: stress, sex and cognitive and emotional regulation. *J Endocrinol.* (2015) 226:T67–T83. doi: 10.1530/JOE-15-0121
42. Kabat-Zinn J. Mindfulness-based interventions in context: past, present, and future. *Clin Psychol Sci Prac.* (2006) 10:144–56. doi: 10.1093/clipsy.bpg016
43. Hölzel BK, Carmody J, Evans KC, Hoge EA, Dusek JA, Morgan L, et al. Stress reduction correlates with structural changes in the amygdala. *Soc Cogn Affect Neurosci.* (2010) 5:11–7. doi: 10.1093/scan/nsp034
44. Singleton O, Holzel BK, Vangel M, Brach N, Carmody J, Lazar SW. Change in brainstem gray matter concentration following a mindfulness-based intervention is correlated with improvement in psychological well-being. *Front Hum Neurosci.* (2014) 8:33. doi: 10.3389/fnhum.2014.00033
45. Black DS, Cole SW, Irwin MR, Breen E, St Cyr NM, Nazarian N, et al. Yogic meditation reverses NF-kappaB and IRF-related transcriptome dynamics in leukocytes of family dementia caregivers in a randomized controlled trial. *Psychoneuroendocrinology* (2013) 38:348–55. doi: 10.1016/j.psyneuen.2012.06.011
46. Lavretsky H, Epel ES, Siddarth P, Nazarian N, Cyr NS, Khalsa DS, et al. A pilot study of yogic meditation for family dementia caregivers with depressive symptoms: effects on mental health, cognition, and telomerase activity. *Int J Geriatr Psychiatry* (2013) 28:57–65. doi: 10.1002/gps.3790
47. Bhasin MK, Dusek JA, Chang BH, Joseph MG, Denninger JW, Fricchione GL, et al. Relaxation response induces temporal transcriptome changes in energy metabolism, insulin secretion and inflammatory pathways. *PLoS ONE* (2013) 8:e62817. doi: 10.1371/journal.pone.0062817
48. Goleman DJ, Schwartz GE. Meditation as an intervention in stress reactivity. *J Consult Clin Psychol.* (1976) 44:456–66. doi: 10.1037/0022-006X.44.3.456
49. Jain S, Shapiro SL, Swanick S, Roesch SC, Mills PJ, Bell I, et al. A randomized controlled trial of mindfulness meditation versus relaxation training: effects on distress, positive states of mind, rumination, and distraction. *Ann Behav Med.* (2007) 33:11–21. doi: 10.1207/s15324796abm3301_2
50. Tang YY, Ma Y, Wang J, Fan Y, Feng S, Lu Q, et al. Short-term meditation training improves attention and self-regulation. *Proc Natl Acad Sci USA*. (2007) 104:17152–6. doi: 10.1073/pnas.0707678104
51. Ding X, Tang YY, Tang R, Posner MI. Improving creativity performance by short-term meditation. *Behav Brain Funct.* (2014) 10:9. doi: 10.1186/1744-9081-10-9
52. Beck AT. *Cognitive Therapy and the Emotional Disorders*. New York, NY: International Universities Press (1976).
53. Singewald N, Schmuckermair C, Whittle N, Holmes A, Ressler K. Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. *Pharmacol Ther.* (2015) 149:150–90. doi: 10.1016/j.pharmthera.2014.12.004
54. Pace-Schott EF, Verga PW, Bennett TS, Spencer RM. Sleep promotes consolidation and generalization of extinction learning in simulated exposure therapy for spider fear. *J Psychiatr Res.* (2012) 46:1036–44. doi: 10.1016/j.jpsychires.2012.04.015
55. Iyadurai L, Blackwell SE, Meiser-Stedman R, Watson PC, Bonsall MB, Geddes JR, et al. Preventing intrusive memories after trauma via a brief intervention involving Tetris computer game play in the emergency department: a proof-of-concept randomized controlled trial. *Mol Psychiatry* (2018) 23:674–682. doi: 10.1038/mp.2017.23
56. Padesky CA, Mooney KA. Strengths-based cognitive-behavioural therapy: a four-step model to build resilience. *Clin Psychol Psychother.* (2012) 19:283–90. doi: 10.1002/cpp.1795
57. Meichenbaum D. *Stress Inoculation Training*. Elmsford, NY: Pergamon Press (1985).
58. Gunnar MR, Frenn K, Wewerka SS, Van Ryzin MJ. Moderate versus severe early life stress: associations with stress reactivity and regulation in 10-12-year-old children. *Psychoneuroendocrinology* (2009) 34:62–75. doi: 10.1016/j.psyneuen.2008.08.013
59. Katz M, Liu C, Schaer M, Parker KJ, Ottet MC, Epps A, et al. Prefrontal plasticity and stress inoculation-induced resilience. *Dev Neurosci.* (2009) 31:293–9. doi: 10.1159/000216540
60. Parker KJ, Buckmaster CL, Schatzberg AF, Lyons DM. Prospective investigation of stress inoculation in young monkeys. *Arch Gen Psychiatry* (2004) 61:933–41. doi: 10.1001/archpsyc.61.9.933
61. Kashani F, Kashani P, Moghimian M, Shakour M. Effect of stress inoculation training on the levels of stress, anxiety, and depression in cancer patients. *Iran J Nurs Midwifery Res.* (2015) 20:359–64.
62. Flaxman PE, Bond FW. A randomised worksite comparison of acceptance and commitment therapy and stress inoculation training. *Behav Res Ther.* (2010) 48:816–20. doi: 10.1016/j.brat.2010.05.004
63. Penedo FJ, Dahn JR. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. *Curr Opin Psychiatry* (2005) 18:189–93. doi: 10.1097/00001504-200503000-00013
64. van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci USA*. (1999) 96:13427–31. doi: 10.1073/pnas.96.23.13427
65. Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, et al. Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci USA*. (2004) 101:3316–21. doi: 10.1073/pnas.0400266101
66. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci USA*. (2011) 108:3017–22. doi: 10.1073/pnas.1015950108
67. Wichers M, Peeters F, Rutten BP, Jacobs N, Derom C, Thiery E, et al. A time-lagged momentary assessment study on daily life physical activity and affect. *Health Psychol.* (2012) 31:135–44. doi: 10.1037/a0025688
68. Manjunath NK, Telles S. Improved performance in the Tower of London test following yoga. *Indian J Physiol Pharmacol.* (2001) 45:351–4.
69. Netz Y, Lidor R. Mood alterations in mindful versus aerobic exercise modes. *J Psychol.* (2003) 137:405–19. doi: 10.1080/00223980309600624
70. Dale LP, Mattison AM, Greening K, Galen G, Neace WP, Matacin ML. Yoga workshop impacts psychological functioning and mood of women with self-reported history of eating disorders. *Eat Dis.* (2009) 17:422–34. doi: 10.1080/10640260903210222
71. Robert McComb JJ, Tacon A, Randolph P, Caldera Y. A pilot study to examine the effects of a mindfulness-based stress-reduction and relaxation program on levels of stress hormones, physical functioning, and submaximal exercise responses. *J Altern Complement Med.* (2004) 10:819–27. doi: 10.1089/acm.2004.10.819
72. Danucalov MA, Simoes RS, Kozasa EH, Leite JR. Cardiorespiratory and metabolic changes during yoga sessions: the effects of respiratory exercises

and meditation practices. *Appl Psychophysiol Biofeedback* (2008) 33:77–81. doi: 10.1007/s10484-008-9053-2
73. Telles S, Reddy SK, Nagendra HR. Oxygen consumption and respiration following two yoga relaxation techniques. *Appl Psychophysiol Biofeedback* (2000) 25:221–7. doi: 10.1023/A:1026454804927
74. Cohen S. Social relationships and health. *Am Psychol.* (2004) 59:676–84. doi: 10.1037/0003-066X.59.8.676
75. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol.* (2004) 3:343–53. doi: 10.1016/S1474-4422(04)00767-7
76. Lorenz RA, Gooneratne N, Cole CS, Kleban MH, Kalra GK, Richards KC. Exercise and social activity improve everyday function in long-term care residents. *Am J Geriatr Psychiatry* (2012) 20:468–76. doi: 10.1097/JGP.0b013e318246b807
77. Ozbay F, Johnson DC, Dimoulas E, Morgan III C, Charney D, Southwick S. Social support and resilience to stress: from neurobiology to clinical practice. *Psychiatry* (2007) 4:35–40.
78. Fried LP, Carlson MC, Freedman M, Frick KD, Glass TA, Hill J, et al. A social model for health promotion for an aging population: initial evidence on the Experience Corps model. *J Urban Health* (2004) 81:64–78. doi: 10.1093/jurban/jth094
79. Carlson MC, Kuo JH, Chuang Y-F, Varma VR, Harris G, Albert MS, et al. Impact of the Baltimore Experience Corps Trial on cortical and hippocampal volumes. *Alzheimers Demen.* (2015) 11:1340–8. doi: 10.1016/j.jalz.2014.12.005
80. Pinquart M. Creating and maintaining purpose in life in old age: a meta-analysis. *Ageing Int.* (2002) 27:90–114. doi: 10.1007/s12126-002-1004-2
81. Pearson MR, Brown DB, Bravo AJ, Witkiewitz K. Staying in the moment and finding purpose: the associations of trait mindfulness decentering, and purpose in life with depressive symptoms, anxiety symptoms, and alcohol-related problems. *Mindfulness* (2014) 6:645–53. doi: 10.1007/s12671-014-0300-8
82. Orbach I, Mikulincer M, Gilboa-Schechtman E, Sirota P. Mental pain and its relationship to suicidality and life meaning. *Suicide Life Threat Behav.* (2003) 33:231–41. doi: 10.1521/suli.33.3.231.23213
83. Lee J, Cho D, Suh YJ. Purpose and meaning in life and job satisfaction among the aged. *Int J Aging Hum Dev.* (2017) 85:377–402. doi: 10.1177/0091415016688305
84. Lyon DE, Younger JB. Purpose in life and depressive symptoms in persons living with HIV disease. *J Nurs Scholarsh.* (2001). 33:129–33. doi: 10.1111/j.1547-5069.2001.00129.x
85. Pfau ML, Russo SJ. Peripheral and central mechanisms of stress resilience. *Neurobiol Stress* (2015) 1:66–79. doi: 10.1016/j.ynstr.2014.09.004
86. Russo SJ, Murrough JW, Han MH, Charney DS, Nestler EJ. Neurobiology of resilience. *Nat Neurosci.* (2012) 15:1475–84. doi: 10.1038/nn.3234
87. Krishnan V, Han M-H, Graham DL, Berton O, Renthal W, Russo SJ, et al. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* (2007) 131:391–404. doi: 10.1016/j.cell.2007.09.018
88. Friedman AK, Walsh JJ, Juarez B, Ku SM, Chaudhury D, Wang J, et al. Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. *Science* (2014) 344:313–9. doi: 10.1126/science.1249240
89. Wang M, Perova Z, Arenkiel BR, Li B. Synaptic modifications in the medial prefrontal cortex in susceptibility and resilience to stress. *J Neurosci.* (2014) 34:7485–92. doi: 10.1523/JNEUROSCI.5294-13.2014
90. Scharf SH, Schmidt MV. Animal models of stress vulnerability and resilience in translational research. *Curr Psychiatry Rep.* (2012) 14:159–65. doi: 10.1007/s11920-012-0256-0
91. Belzung C, Lemoine M. Criteria of validity for animal models of psychiatric disorders: focus on anxiety disorders and depression. *Biol Mood Anxiety Disord.* (2011) 1:9. doi: 10.1186/2045-5380-1-9
92. Stewart AM, Kalueff AV. Developing better and more valid animal models of brain disorders. *Behav Brain Res.* (2015) 276:28–31. doi: 10.1016/j.bbr.2013.12.024
93. Verhagen SJ, Hasmi L, Drukker M, van Os J, Delespaul PA. Use of the experience sampling method in the context of clinical trials. *Evid Based Mental Health* (2016) 19:86–9. doi: 10.1136/ebmental-2016-102418
94. Gururajan A, Kos A, Lopez JP. Preclinical stress research: where are we headed? An early career investigator's perspective. *Stress* (2018) 21:384–8. doi: 10.1080/10253890.2018.1446519

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REVIEW
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Developmental Trajectories of Early Life Stress and Trauma: A Narrative Review on Neurobiological Aspects Beyond Stress System Dysregulation

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Early life stressors display a high universal prevalence and constitute a major public health problem. Prolonged psychoneurobiological alterations as sequelae of early life stress (ELS) could represent a developmental risk factor and mediate risk for disease, leading to higher physical and mental morbidity rates in later life. ELS could exert a programming effect on sensitive neuronal brain networks related to the stress response during critical periods of development and thus lead to enduring hyper- or hypo-activation of the stress system and altered glucocorticoid signaling. In addition, alterations in emotional and autonomic reactivity, circadian rhythm disruption, functional and structural changes in the brain, as well as immune and metabolic dysregulation have been lately identified as important risk factors for a chronically impaired homeostatic balance after ELS. Furthermore, human genetic background and epigenetic modifications through stress-related gene expression could interact with these alterations and explain inter-individual variation in vulnerability or resilience to stress. This narrative review presents relevant evidence from mainly human research on the ten most acknowledged neurobiological allostatic pathways exerting enduring adverse effects of ELS even decades later (hypothalamic-pituitary-adrenal axis, autonomic nervous system, immune system and inflammation, oxidative stress, cardiovascular system, gut microbiome, sleep and circadian system, genetics, epigenetics, structural, and functional brain correlates). Although most findings back a causal relation between ELS and psychobiological maladjustment in later life, the precise developmental trajectories and their temporal coincidence has not been elucidated as yet. Future studies should prospectively investigate putative mediators and their temporal sequence, while considering the potentially delayed time-frame for their phenotypical expression. Better screening strategies for ELS are needed for a better individual prevention and treatment.

Keywords: early life stress, trauma, childhood adversity, stress, stress-related-disorders, neurobiology, gene × environment interaction, epigenetics

INTRODUCTION

Stress is defined as the state of threatened homeodynamic balance of the organism (1, 2). Inadequate, excessive or prolonged stress reactions may exceed the organism's natural adaptive capacity and permanently affect stress responses (2, 3). Excessive stress exposure, especially in stress-sensitive developmental stages of higher brain plasticity (e.g., early childhood), may over- or under-sensitize neuroendocrine responses to stress, leading to an altered homeodynamic state (i.e., allostasis/cacostasis) with profound and debilitating effects on physiological development and close association to chronic physical and mental morbidity (2, 4–10).

The term Early Life Stress (ELS) describes a broad spectrum of adverse and stressful experiences (e.g., maltreatment, neglect, separation, parental loss, extreme poverty, starvation, domestic/community/school violence) during the first months of life, early and late childhood and adolescence, while the term has been recently extended by some authors and includes also prenatal life events (11). Childhood Trauma (CT) represents a more specific form of ELS and is defined as "a traumatic event that threatens injury, death, or the physical integrity of self or others and also causes horror, terror, or helplessness at the time it occurs and overwhelms a person's ability to cope" (e.g., physical/sexual abuse, medical trauma, motor vehicle accident, acts of terrorism, war experiences, natural and human-made disasters, witnessed homicides/suicides) (12). ELS/CT constitute a major public health issue, as they occur at ominously high rates, with over 30–40% of the general adult population having experienced some form of disrupting early life adversities (13–16).

In addition, many studies report a negative association of ELS/CT with general adult mental and physical health-related quality of life (17–21). Especially an increased risk for mental disorders (e.g., depression, post-traumatic stress disorder, schizophrenia) and their unfavorable outcomes after ELS/CT experience has been repeatedly reported in several retrospective (5, 22–25) but also prospective studies (26–29). Similarly, history of ELS/CT has been associated with risk behavior patterns, such as substance abuse and suicide attempts in later life (30–35). Furthermore, several larger-scale studies and meta-analyses also suggest a close association of ELS/CT with adverse physical health and in particular with cardiovascular, gastrointestinal, neuromusculoskeletal, pulmonary, inflammatory, and metabolic diseases, chronic pain syndromes, frequency of medical consultations, as well as number of medical diagnoses (24, 36–42).

ELS/CT rarely occurs as a single event but frequently consists of continued maltreatment involving one or more malicious acts. In addition, in most cases, several negative risk factors may co-exist (e.g., poverty, parental absence and parental mental disease, drug addiction) leading to a multifaceted context of multiple chronic stressors. The severity of physical and psychological consequences may be also associated with the number of experienced ELS/CT events (13, 17, 43, 44). More recent studies confirmed that increasing number of ELS/CT may result in higher adult risk for psychopathological complexity and severity, mental comorbidities, prescribed psychotropic medication, poor mental and physical quality of life, as well as several physical conditions (e.g., chronic pain syndromes, cephalgias, heart disease, asthma, diabetes mellitus, and arthritis) (23, 24, 45–50). Apart from number of ELS/CT experiences, the specific nature of ELS/CT and particularly its exact timing could greatly influence downstream biological pathways. Furthermore, genetic factors, presence of caregivers and psychological support, family history of major psychiatric disorders, as well as additional traumatic stress experiences in adulthood may all further influence the individual vulnerability for later disease (51). The continuum of trauma-provoked aftermath reaches from healthy adaptation with high resilience, to severe maladjustment with co-occurring psychiatric and physical pathologies in children, adolescents, and adults. Despite the resilience of many abused individuals in their early years, ELS/CT significantly increases the risk for impaired physical and psychological well-being and adaptive functioning in adulthood.

All these findings suggest that ELS/CT may trigger a health-related risk cascade and be conceptualized as a common developmental risk factor and cumulative health risk mediator, associated with an increased physical and mental morbidity and all-cause mortality in later life (13, 15, 36, 52–59). Although prospective findings support the causal relation between ELS/CT and its long-term adverse health-related effects, so far, little is known about the exact pathways through which ELS/CT is translated into health risk. Observational human studies and experimental animal models suggest that ELS/CT is related to remarkable functional and structural changes even decades later in adulthood. The current hypothetical model suggests that ELS/CT may trigger enduring systemic alterations of fundamental, mainly brain-related plasticity mechanisms and so enhance the biological embedment of distinct "biological memories" of ELS/CT during the sensitive period of early organism development, thus enhancing disease vulnerability in later life (60). To date, most studies assessing the link between ELS/CT and adult disease risk suggest stress system related neuroendocrine alterations as the main pathway of disease development. However, many other related, but distinct biological systems may also play a role and have lately emerged as important pathophysiological pathways.

This current review discusses additionally further potential pathophysiological mechanisms exerting the enduring adverse effects of ELS/CT and mediating the cumulative long-term risk for disease vulnerability in later life, a topic that cannot yet be approached via systematic reviews. Therefore, the literature is presented as a narrative review, providing an overview on the most relevant and acknowledged neurobiological findings from mainly human research. Literature searches were undertaken using PubMed/Medline, PsychINFO, Scopus, and Google Scholar from inception to March 2018 to identify publications (reviews, discussion papers, clinical, observational, and preclinical studies, etc.) addressing neurobiological aspects of ELS/CT and relevant information was extracted. Additionally, the search was complemented through manual review of related terms and citations from article reference lists. The ten most important neurobiological concepts, as backed from current

evidence, were synthesized under the headings reported in this narrative review.

THE HUMAN STRESS SYSTEM

ELS/CT can irreversibly disrupt vital central neurobiological systems during vulnerable human development periods and lead to sustainable alterations in stress regulation and psychophysiological reactivity (13, 15, 36, 52–59, 61–63). Because of their pivotal role in the regulation of the dynamic stress response and perhaps also due to a historical focus on these two systems, the hypothalamic-pituitary-adrenal (HPA) axis and the locus ceruleus/autonomic nervous system (LC/ANS) have been more investigated and are considered more crucially affected by ELS/CT than other biological systems (64–66).

Hypothalamic-Pituitary-Adrenal (HPA) Axis

The chronic dysregulation of the HPA axis is of vital importance in the pathophysiology of stress-related disorders. However, our understanding is hampered by complex and often conflicting relations between HPA axis markers and history of ELS/CT (i.e., findings on both increased and decreased HPA axis activity) (2, 64), as well as the broad definition of ELS/CT (i.e., broad time window of 0–18 y.o.a.). For example, positive ELS/CT history has been repeatedly associated with HPA axis hyperactivity in adults patients with depression and anxiety, but also in healthy individuals [e.g., higher circulating cortisol levels, enhanced cortisol awakening response (CAR), increased adrenocorticotropic hormone (ACTH) and cortisol responses to psychosocial stress or endocrine challenges] (67–75). Chronic hyperactivation of the stress system is related to hypersecretion of corticotropin releasing hormone and arginine-vasopressin (CRH, AVP) by the hypothalamus and ACTH hypersecretion by the pituitary (76), resulting in higher circulating cortisol levels due also to an "insensitive" negative glucocorticoid (GC) feedback of the HPA axis loop (77). The typical example of chronic HPA axis hyperactivation is depression (2, 78), while other conditions such as anorexia nervosa, obsessive-compulsive disorder, panic disorder, alcohol withdrawal, excessive exercising, poorly controlled diabetes mellitus, and hyperthyroidism amongst others, are also associated with increased cortisol levels and HPA axis hyperactivation (79).

On the other hand, several ELS/CT studies have reported HPA axis hypo-activity (e.g., lower circulating cortisol levels, blunted cortisol stress responses) in similar populations and study designs (80–84). This diminished activity could represent a compensatory physiologic adaptation possibly related to a negative feedback hypersensitivity of GC by an up-regulated leukocyte GC-receptor (GR) number and sensitivity (5, 63, 85–87), downregulated secretion of CRH/AVP to the pituitary (76) or a long-lasting GC catabolism drop leading to higher active cortisol persistence in liver and kidney without elevation in the periphery (88). This seems to be the case for patients with post-traumatic stress disorder (PTSD), atypical depression, chronic fatigue syndrome, fibromyalgia, and hypothyroidism.

These results suggest a particularly vital role of GC-signaling in the pathophysiology of ELS/CT (89–91). Insufficient multilevel GC-signaling (resulting from either hyper- or hypo-activation of the HPA axis), may have comparable deleterious effects on the organisms' physiology, as for example seen in the development and long-term effects of both PTSD (i.e., HPA axis hypo-activation) and melancholic depression (i.e., HPA axis hyper-activation) (91–93). These effects appear even greater in individuals with ELS history, suggesting a developmental programming through GC signaling.

Thereby, several factors may have influenced study findings, such as the exact subtype and nature of trauma, sex, the timing and duration of exposure and the assessment of phasic (e.g., diurnal saliva cortisol, cortisol reactivity to challenge) vs. time-integrated cortisol values (e.g., hair cortisol) (94, 95). However, probably the most significant factor modulating the ELS/CT impact on future HPA axis activity may be its exact timing, suggesting a degree of developmental programming through GC signaling.

Timing of ELS/CT and Developmental Programming of HPA-Axis

The HPA axis activity trajectory develops from infancy to early adulthood and beyond. Together with the HPA axis, however, the amygdala and the hippocampus also develop during the same period following non-linear patterns until early adulthood (96–100). Thereby, periods of greater HPA axis plasticity may represent specific periods of greater vulnerability (96, 100, 101), while mounting evidence suggests a differential impact of ELS/CT on HPA axis activity according to the specific developmental age of exposure (102).

Infancy and early childhood (age 0–5 y.o.a.) represent one of the most vulnerable periods in brain development (6, 101, 103, 104). After an initial hyper-responsive period, the HPA axis may later transition into a stress hypo-responsive period (SHRP) with lower basal cortisol levels and blunted stress-induced cortisol reactivity (101, 104–106). Some longitudinal studies suggest that stress responsivity in early childhood decreases with age throughout the preschool period (101, 105–107), suggesting a potential social buffering of the HPA axis by a nurturing caregiver, who may operate as a safety signal (108–110). This could partly rely on important interactions of GC-signaling with oxytocin pathways, as recently reviewed by Struber et al. (111). Accordingly, this shift from a hyper- to a hypo-responsive stress axis in the first 5 years in life may be represent an particularly crucial stress-sensitive period, especially in the absence of a nurturing caregiver (104). ELS/CT together with higher cortisol during this SHRP could possibly lead to GR insensitivity through greater exposure to GC over time, thus altering the physiological of HPA axis development (101, 112). Studies from Kuhlman et al. (94, 113) confirmed that ELS/CT exposure in the first 2 years in life is associated with prolonged cortisol reactivity to acute social stressors among adolescents.

The later developmental stage of puberty/adolescence represents the second particularly sensitive and vulnerable

period with a new major change in HPA axis activity. In this phase, the HPA axis transitions from hypo-responsivity into a period of increased activity (101, 114–116) with progressive higher basal (106, 110, 117, 118) and reactive (106, 118–121) cortisol levels. Interestingly, parental support no longer buffers HPA axis reactivity during this developmental stage (110). On the other hand, it is rather sexual maturation, in interaction with sex and environmental cues, which represents a new major confounder of HPA axis reprogramming (113). The onset of gonadal hormone production plays a vital role in stress and HPA axis reactivity, since estrogen secretion influences GC hyperactivity (122). Some studies on ELS/CT during adolescence reported lower baseline cortisol (123) and blunted cortisol responses to psychosocial stress (124), accordingly suggesting an opposite effect of ELS/CT on HPA axis basal activity and reactivity than in infancy and early childhood.

Summarizing, ELS/CT during the first hypo-sensitive 2 years of life may lead to a hyper-activity and -responsiveness of HPA axis, while ELS/CT during the hyper-active phase of adolescence to a hypo-active and hypo-responsive HPA axis (101). Bosch et al. (125) confirmed this hypothesis showing a relation between ELS/CT in the first year of life, but not late childhood or adolescence, and higher cortisol reactivity in adult life. They could also show higher adult cortisol levels after ELS/CT experience during childhood, but lower cortisol output after experience of ELS/CT in adolescence. These age-dependent differences in HPA axis plasticity could be also reflected on the specific risk for a mental disorder in adulthood. Taken together, ELS/CT exposure in early childhood leads to a similarly higher risk for developing major depressive disorder or PTSD in adulthood, while after ELS/CT exposure in adolescence, the risk for PTSD is greater than for depression (22).

Locus Ceruleus/Autonomic Nervous System (LC/ANS)

The LC/ANS is also vitally implicated in the stress-related pathophysiological trajectories of trauma (126). LC/ANS and HPA axis are closely interconnected at several neuroendocrine levels throughout the brain and body and their activity normally shows a certain degree of analogy and complementarity. The appropriate regulation of the HPA axis depends at least in part on LC/ANS, especially on vagal influences (127). HPA axis and LC/ANS are both integrated components of an internal neural regulation system (central autonomic network, CAN) (128). Dysregulation of the CAN (129–131) may affect downstream autonomic core centers (i.e., PFC, amygdala, hypothalamus, brain stem nuclei), and alter peripheral ANS activity and overall stress responsivity (130, 132, 133). The significant overlap of the fear/arousal circuitry with the CAN (134) could be, at least partly, responsible for ELS/CT-related autonomic dysregulation. The very high comorbidity of stress- and trauma-related disorders and cardiovascular disease (135–140) confirms a central pathophysiological link between the stress axis and ANS (141–143).

With respect to ELS/CT in particular, a limited number of studies have reported altered autonomic activity in adults with ELS/CT exposure. For example, Otte et al. (144) reported higher catecholamine responses to psychological stress in police recruits, while O'Hare et al. (145) found higher rates of syncope frequency in adulthood in individuals with ELS/CT experience. Heleniak et al. (146) reported blunted cardiac output reactivity and increased vascular resistance associated during a social stress task in ELS/CT-exposed adolescents. However, most studies assessing ANS activity in adult population after trauma included PTSD patients with adult exposure to traumatic stress, repeatedly suggesting an increased sympathetic and/or decreased vagal activity in sequel of a trauma (147).

Some pediatric studies have also lately tried to better investigate the interplay of HPA axis and ANS after ELS/CT. For example, De Bellis et al. (148) reported significantly higher 24 h urinary concentrations of catecholamines in sexually abused girls in comparison to matched controls. Another pediatric study by Gordis et al. (149) reported an asymmetry between the HPA axis and ANS reactivity to a social stressor with absent associations between the peripheral biomarkers of HPA axis (cortisol) and sympathetic activity (salivary alpha-amylase, sAA) only in the maltreated group. In a study longitudinally assessing children after trauma exposure to a motor vehicle accident, Pervanidou et al. (150) could show a successive normalization of cortisol levels but continuously higher catecholamine levels 6 months after trauma exposure, suggesting a lifted cortisol-mediated restraint on catecholamine responses leading to a mid- and long-term enhanced ANS activity. Lower cortisol levels and higher ANS activity found in adult PTSD patients and after ELS/CT exposure may, thus, represent a resulting state of a progredient stress-axes divergence in trauma-related disorders (151). Accordingly, Pervanidou et al. (152) proposed that such a progredient divergence of the two limbs of the stress system following ELS/CT, may represent a vital pathophysiological pathway leading to the long-term impact of ELS/CT on health and the chronic preservation of related symptoms.

IMMUNE SYSTEM AND INFLAMMATION

Inflammation is a natural immune response to pathogens and injury, an integral part of the stress response and, thus, crucial to tissue healing, adaptation and survival (4, 153, 154). Acute stress activates the secretion of pro-inflammatory cytokines, presumably by adrenergic and CRH-peptidergic stimulation, which help orchestrate the further immune response (e.g., stimulation of systemic acute-phase proteins, such as C-reactive protein, CRP) (4, 155). Pro-inflammatory cytokines, however, unfold systemic effects far beyond the canonical immune response and also stimulate the secretion of CGs, while CGs, in turn, among their numerous pleiotropic effects, help terminate the inflammatory response (153, 154, 156, 157). This is part of a very complex, two-way neuroimmunoendocrine interaction between the central and peripheral limbs of the stress system and the immune axis (156, 158, 159). Growing evidence, accordingly, implicates the immune system in stress resilience and coping through peripheral and central immune mechanisms of action, affecting the brain and all stress-related

neurobiological and neuroendocrine responses (160). Vice versa, a dysregulated stress system could allow a disinhibition or excessive inhibition of inflammatory processes, promoting biological aging, inflammatory-related or immunosuppressed medical conditions and compromised overall health (63, 89, 161–163). There is growing evidence suggesting that positive ELS/CT history is an independent risk factor for peripheral immune dysregulation and long-term, low-grade inflammatory excess (i.e., a pro-inflammatory phenotype) in adulthood (101, 164–172).

Given this, the dysfunctional neuroendocrine interface following ELS/CT may be closely correlated to immunological alterations and related long-term health consequences (4, 36, 101, 153, 154, 172, 173), while adults with ELS/CT experience could be at increased risk of disease with potentially immune origin (36, 53). Most human research has been concentrating on pro-inflammatory cytokines and CRP for the immune status characterization. Among all cytokines assessed, interleukin-6 (IL-6) findings are the most robust.

Interleukin-6 and CRP

IL-6 is a pleiotropic cytokine and simultaneously one of the most suitable inflammatory markers for the characterization of inflammatory status in humans (174), but also an applicable stress biomarker (155), as IL-6 may have a reciprocal modulatory effect on the stress system (175). Indeed, animal and human research confirms that IL-6 stimulates the HPA axis at hypothalamic, pituitary and adrenal level (176–183). Basal IL-6, through activation of the JAK/STAT3 signaling cascade, is required for the sustained cortisol response to chronic stress and is therefore a possible mediator of HPA axis plasticity, in particular in chronic stress states (184). Conversely, cortisol exerts a mild inhibitory effect on the peripheral production of IL-6 (185) and is a major moderator of circadian IL-6 changes (186, 187), while prednisone administration flattens the diurnal rise of IL-6 in the early morning (188). Norepinephrine and epinephrine, on the other hand, lead to an increase of plasma IL-6 in both humans and rats (189–191), in part via beta-adrenergic receptor mechanisms regulating hepatic and splenic IL-6 production (192–194). A recent animal finding also suggested that basal IL-6 signaling in the hypothalamus is a potential determinant of plasticity in the HPA axis response, specifically during chronic stress exposure (184), suggesting that both central and peripheral IL-6 play crucials role on the development of stress susceptibility and related behaviors (175, 195). Several studies have reported dysregulated IL-6 levels in individuals with ELS/CT experience. Carpenter et al. (169) reported higher IL-6 baseline concentrations and a higher inflammatory IL-6 response to acute psychosocial stress challenge in healthy adults with a history of ELS/CT. Using the same paradigm (Trier Social Stress Test; TSST), Pace et al. (196) have shown the same exaggerated IL-6 response to an acute psychosocial stressor in depressed male patients with positive ELS/CT history, compared to depressed patients without ELS/CT history. Interestingly, Kunz-Ebrecht et al. (197) reported an inverse relation between IL-6 and cortisol release to mild mental stress challenges, while Pervanidou et al. (150) provided evidence that IL-6 was involved in the initial biological alterations in the aftermath of trauma, and predictive of PTSD development 6 months later in a longitudinal study design following motor vehicle accidents in children. Finally, in one of the few large (over 3,500 children) prospective studies, Slopen et al. (198) reported ELS/CT being associated with increased levels of IL-6 years later.

With respect to CRP, there are a large number of studies reporting on the association of ELS/CT with increased circulating CRP levels. Most findings, but not all, suggest a robust correlation between ELS/CT and adult CRP levels (165, 166, 170, 199–202). In their seminal study of a birth cohort followed to age 32 years, Danese et al. (165) reported an independent effect of ELS/CT on adult inflammation and suggested that more than 10% of the low-grade inflammation cases in the population may be attributable to ELS/CT. In their prospective study, Slopen et al. (198) found that ELS/CT is a significant independent predictor of persisting inflammation almost 10 years after ELS/CT exposure. Finally, a recent meta-analysis, including over 20,000 samples, confirmed that individuals exposed to ELS/CT show significantly elevated baseline peripheral levels of CRP, IL-6 and TNF-α (203). This study also suggested that specific types of ELS/CT may have differential impacts on single inflammatory markers.

Neuroimmune Pathways

Although numerous neurobiological links between ELS/CT and inflammation have been put forth, the underlying mechanisms are still not completely understood (159). On the one hand, ELS/CT-related autonomic imbalance with reduced vagal activity may further directly augment inflammation through a direct vagal efferent effect of autonomic brain regions (204–206). On the other hand, HPA axis dysregulation in ELS/CT affects GR-mediated transcriptional and post-transcriptional responses of immune-related genes with lower recovery ability (89, 207). Preclinical research has shown GC resistance in immune cells following repeated acute stress (208, 209), while in humans, prolonged or chronic stress leads also to GR insensitivity of immune cells and, respectively, altered GC inhibitory signal (112, 210). Respectively, several recent human gene expression studies show accumulating evidence for innate immune dysregulation after trauma and a particular and specific (i.e., comorbidity-independent) role of cytokines (211–215). Smid et al. (175) have recently reported both higher mitogen-stimulated T-cell cytokine and innate cytokine production with increasing PTSD symptoms, suggesting a direct effect of cytokine production in stress sensitization. Further human PTSD research suggested that elevated expression of pro-inflammatory cytokines after traumatic stress exposure is probably regulated by multiple epigenetic mechanisms, including dysregulation of microRNA expression (216–218). Interestingly, animal findings suggest that pro-inflammatory cytokines also mediate chronic, stress-induced impairments in hippocampal neurogenesis (167), suggesting that ELS/CT-related subsequent pro-inflammatory diathesis could impair neurogenesis in vital central nervous system (CNS) areas during critical developmental periods and result in a reduced hippocampal volume (see below) and a related malfunction of the fear response circuit in context-dependent situations in adulthood.

HUMAN MICROBIOME AND THE GUT-BRAIN-AXIS

During the last decade, the human microbiome and the microbiota-gut-brain (MGB)-axis have become a novel epicenter in mental health and specifically stress-related research and have been already acknowledged as a potentially vital new determinant in the field of neuroimmunoregulation, brain development and behavior (219–223). The MGB-axis represents a bidirectional, key communication pathway between the immune system and the CNS, thus partly mediating the regulation of stress response and early life programming of the neuroimmune system (221, 224). The gut microbiota is a complex ecosystem with a great organism variety and refined genomic structure that resides in the intestinal tract and has a central position in human health and disease (225).

The microbiome produces directly and indirectly significant amounts of antimicrobial peptides, hormones, short chain fatty acids, vitamins, and several neurotransmitters (e.g., 5-HT, catecholamines) and strongly influences our metabolic, endocrine, immune, and CNS (219). In addition, a special role of macrobiota wall constituents on CNS function and development has been suggested recently. For example, peptidoglycans and lipopolysaccharides have been shown to cross the intestinal epithelial barrier and to bind to specific pattern recognition receptors and lead to an activation of the central and peripheral immune system and HPA axis (226, 227). Furthermore, gut microbiota may modulate CNS microglia maturation and functioning and thus also affect neural circuitry of the developing brain (228, 229).

The other way around, the CNS can also modulate the composition and balance of the intestinal microbial community (and mostly Gram-negative bacteria) through the stress system (ANS, HPA axis), (230). For example, PTSD patients show differences in the total abundance of specific bacterial taxa in comparison to trauma-exposed controls (231), while chronic social defeat stress animals models have also lead to shifts in intestinal microbiota composition (232, 233). A chronic bacterial dysbiosis weakens the intestinal mucosal barrier and affects intestinal permeability ("leaky gut") (234), which possibly results in a microbiota-driven proinflammatory state (235). Thus, a major candidate source of systemic stress-related inflammation could be the disordered gut barrier function (236). A stress-driven microbiome imbalance could then feedback and affect brain functioning by reprogramming the HPA axis through cytokines-related CRH release in the hypothalamus and elsewhere (224, 237–240).

The human microbiome follows a dynamic trajectory development throughout the lifespan and establishes a symbiotic relationship with the organism early in life. Thereby, the development of the intestinal microbiota occurs in parallel with the CNS, having similar critical windows with rapid and profound developmental changes during infancy, childhood, and adolescence (241). Stress-related disruption of the dynamic host-microbe interaction at these critical periods can lead to alterations of the bacterial colonization of the gut in early life and *vice versa* (242, 243). As the microbiome plays an important role in the programming of the HPA axis and stress reactivity (244), ELS/CT may affect the signaling of the MGB axis in a major fashion and alter not only immune, but also CNS and stress system functioning with lifelong emotional and behavioral consequences (i.e., higher risk of neurodevelopmental disorders) (223, 239, 241, 245, 246).

Taken together, the imbalanced human microbiome might be another vital pathway linking ELS/CT with altered neuroimmune reactions and neurodevelopment, as well as long-lasting effects on general health, behavior, emotions, and cognition (247). Risk and resilience to stress- and immune-related disorders may, thus, depend on the diversity and complexity of gastrointestinal microbiota (229), which could play a pivotal role in the etiology of psychiatric illness and make individuals more susceptible to develop psychopathology after ELS/CT (241, 248, 249).

OXIDATIVE STRESS AND CARDIOVASCULAR SYSTEM

Redox State and Antioxidant Defenses

Oxidative stress (OXS), defined as a disequilibrium between oxidant generation and antioxidant defenses (i.e., an altered redox state), has been proposed recently to link ELS/CT to a higher risk of developing psychiatric but also physical morbidity in general (250). Animal findings confirmed that ELS (e.g., maternal separation) has a significant impact on parameters of OXS in mitochondrial function and has shown an association with reactive oxygen species, mitochondrial glutathione, ATP and cytochrome c release in cardiac tissue (251). Furthermore, decreased levels of superoxide dismutase and catalase activity, as well as higher levels of protein carbonylation have been reported in the brain of adult animals exposed to ELS (252). Human research been successfully replicated similar findings. For example, increased OXS markers (i.e., reduced glutathione peroxidase levels, increased protein carbonylation and total reactive antioxidant potential kinetics, etc.) have been reported recently in otherwise healthy ELS/CT-exposed adolescents (253). ELS/CT may so lead to long-term molecular consequences in the basal antioxidant defenses with elevated systemic levels of OXS, stimulating inflammation and driving oxidative damage and accelerated cellular aging in both the CNS and the periphery of the organism (254, 255).

Telomere Length

Telomeres are DNA-protein complexes located at the ends of linear chromosomes capping and protecting the genome from damage, while inflammation and OXS have been suggested to reduce telomere length. Telomere length is an emerging marker of biological age and OXS, with shorter length being associated with accelerated biological aging, premature cell death and increased morbidity and mortality from age-related diseases (256). Not only has PTSD been associated with shorter telomere length, but also the experience of ELS/CT (257–260). For example, Tyrka et al. (261) investigated healthy adults with absent Axis-I disorders and reported shorter whole-blood telomere length in association with ELS/CT. In a longitudinal study, Shalev et al. (262) showed higher telomere erosion in

children 5–10 years old exposed to more than 2 violent events. Chen et al. (263) reported that greater ELS/CT exposure was associated with reduced telomere length and normal telomerase activity in healthy volunteers. A recent study by Mitchell et al. (264) also found a significant association between father loss and children's telomere length, with the death of father showing the greatest effect, and a 90% greater effect in the children with the most reactive alleles of the 5-HTTLPR gene. Finally, two current meta-analytic studies, confirmed the significant association between ELS/CT and accelerated telomere erosion in adulthood (265, 266). ELS/CT could, thus, possibly partly mediate their long-term biological impact also through shorter telomere length, representing another biomarker of increased cacostatic load (51, 256).

OXIDATIVE STRESS AND ENDOTHELIAL DYSFUNCTION

Emerging epidemiologic evidence strongly supports that ELS/CT is an independent albeit silent risk factor of future chronic cardiovascular risk through various systemic and molecular mechanisms (267–272) and that its effect is particularly heightened among women (273). The recent American Heart Association scientific statement offers a comprehensive review of the literature on the influence of ELS/CT on cardiovascular outcomes (274). Besides genetic, metabolic, autonomic, circadian and inflammatory pathways reviewed elsewhere in this article, OXS-related endothelial dysfunction plays a similarly major role in total cardiovascular risk. Animal findings suggest that ELS/CT-related significant endothelial dysfunction is linked to increased superoxide production (275) and reduced endothelial nitrous oxide system buffering capacity with dysfunctional endothelial Angiotensin II-mediated signaling and sensitization to Angiotensin II-induced vasoconstriction (276).

METABOLISM

The stress system is closely interconnected with metabolism. GCs, as the end-effectors of the HPA axis, stimulate appetite (277), alter insulin and leptin secretion and target tissue effects by increasing body weight through the orexigenic and food reward effect of the hypothalamic feeding signal NPY (278, 279) [an effect inhibited by leptin and insulin (280)]. Consequently, in individuals with ELS/CT history, the disrupted biological background described above promotes a tendency toward a dysmetabolic syndrome (281, 282). Accordingly, in the obese population, rates of ELS/CT exposure are reported to be almost twice as high as in the non-obese population (69 vs. 39%) (283). Furthermore, ELS/CT has been repeatedly found to be independently associated with increased overall metabolic risk (284, 285), obesity and increased visceral fat deposition (286–288), decreased HDL, increased LDL levels and lower HDL/LDL ratio (289, 290), higher triglyceride levels (285), an overall prediabetic state (e.g., impaired insulin sensitivity) (291), reduced T3 levels and abnormal metabolism of thyroid hormones (292), enhanced risk for emotional eating as a self-regulatory coping strategy (293) and higher prevalence of metabolic syndrome (290, 294, 295) in later life, while some studies have suggested a dose-dependent relation in these associations (288, 296).

ELS/CT-induced metabolic derangements, such as hyperinsulinemia and altered insulin sensitivity on exposure to a high energy diet later in life, can be a result of altered peripheral gene expression. For example, the interaction between HPA axis activity and liver 11-beta hydroxysteroid dehydrogenase (11β-HSD1) could modulate both tissue and circulating GC availability, with adverse metabolic consequences (297). In addition, genetic interactions with ELS/CT could influence risk for dysmetabolic consequences. HPA axis related FKBP5 polymorphisms, in combination with ELS/CT exposure predict higher insulin and glucose values in midlife (298). Animal findings suggest that ELS/CT is associated with increased food intake, weight gain, increased deposition of abdominal fat, higher plasma triglycerides levels, n-3 PUFA deficiency, etc. (299).

On the other hand, there is also evidence that ELS/CT can exert a programming effect on the adipose tissue and alter the highly sensitive process of adipogenesis (282), leading for example to alterations in adipokine regulation and higher fat accumulations in mice (300). Leptin is an important, circadially secreted adipokine and a vital regulator of energy homeostasis and metabolism, reward processing, brain development and neuroendocrine and immune function (301). Leptin directly interacts with the HPA axis (302), showing an inverse relation to circulating corticotropin and cortisol in healthy men and exerts an anorexigenic effect in conjunction with inhibition of orexigenic pathways via leptin-responsive hypothalamic neurons (303). The adipose tissue–derived protein adiponectin, is another adipokine that may also play a central role in the metabolic dysregulation after ELS/CT. Adiponectin is decreased in obesity (304), whereas hypoadiponectinemia is related to adverse metabolic and cardiovascular outcomes in humans (305). Prospective pediatric studies of physical injury (i.e., burn, MVA) have shown a persistently elevated insulin resistance index up to 3 years (306) and decreased adiponectin levels up to 6 months after physical stress exposure (152).

Taken together, mounting evidence suggests that stress during critical periods of growth and development disrupts the interplay between the stress, circadian and metabolic system and has permanent adverse effects on body size and composition and is often accompanied by associated lifestyle and nutritional risk behaviors (i.e., physical inactivity, emotional eating, disrupted sleep) (282).

SLEEP AND CIRCADIAN SYSTEM

The human circadian system (CS) enables the nyctohemeral organization and coordination of many physiological processes and promotes homeostasis and environmental adaptation (307). The HPA axis activity is closely linked to the CS and displays circadian rhythmicity (308–311). Through various pathways, the central circadian system synchronizes hypothalamic

neuroendocrine neurons secreting CRH and AVP, modulates adrenal ACTH sensitivity, stimulates GC secretion and defines the peripheral circadian changes in target tissue GC sensitivity (308, 312–314). Circadian acetylation and deacetylation of the GR, modulated by melatonin, allows for these changes in tissue sensitivity (308, 312, 315, 316). In addition, animal studies demonstrated a circadian regulation of peripheral clock gene oscillation in the adrenal gland (317, 318) confirming a nyctohemeral change in its responsiveness to ACTH. Central and peripheral circadian rhythmicity also modulates ANS control through projections to pre-autonomic neurons of the hypothalamus and is essential for the physiologic diurnal fluctuations seen in humans (319–321). Finally, animal and human studies demonstrate responsiveness of cognitive performance to the CS (322, 323). Memory processing, formation and consolidation are directly influenced by the circadian clock and stress (322, 324, 325). Besides light, an important regulator of CS activity is sleep. Sleep acts synergistically and bidirectionally with the central CS, but also independently to reinstate the internal temporal synchrony (326). Specific sleep stages are associated with CLOCK gene expression in the suprachiasmatic nuclei and are tightly ruled by the CS (326–328).

A critical loss of this timed order across several organizational levels of the organism is defined as chronodisruption and promotes a dysharmony of internal biological systems and appropriate biobehavioral adaptations to external stimuli (329) with short- and long-term pathophysiologic and epigenetic impact (330, 331). Chronodisruption may progressively alter the fundamental properties of brain systems regulating neuroendocrine, immune and autonomic function, similar to ELS/CT-related stress axis dysregulation, and may play a central role in the development of stress-related disorders (328).

Direct and indirect human and animal stress research supports the important supraordinate role of CS on stress system and GCs, linking circadian misalignment in ELS/CT-related pathophysiology and potentially resulting in the extensive co-morbidities of ELS/CT through an impaired homeostatic balance. Some animal (332), but—most importantly—numerous human studies including large cohorts, have repeatedly confirmed that ELS/CT is independently associated with enduring adult sleep disruption including global sleep pathology (i.e., insomnia), as well as specific types of sleep problems, such as shortened total sleep time, prolonged sleep onset latency, decreased sleep efficiency, increased number of awakenings, nightmare related distress, sleep apnea and higher nocturnal activity in a probably dose-response manner (333–344).

Sleep deprivation, which is tightly associated with chronodisruption (326–328), has been recurrently related to HPA axis dysregulation findings, such as a flattened cortisol amplitude, decreased CAR and cortisol reactivity, increased but also decreased diurnal cortisol concentrations and increased CRH levels in humans (345–347). Both animal and human studies show that sleep deprivation is associated with increased sympathoadrenal activity and blunted cardiovascular autonomic rhythmicity and responsiveness, thus representing a key cardiovascular risk factor (347–349). Human and animal sleep deprivation studies have reported hypo-responsive medial-frontal cortical regions, hyper-responsive amygdala, and a smaller hippocampal volume (350–352), as shown in adults with ELS/CT history (see above). Sleep disturbances have been associated with altered CLOCK gene expression in humans, which vitally affects neurobiological response to stress (353, 354). Chronodisruption may, thus, sensitize individuals to stress and increase their vulnerability to stress-related disorders (347, 355).

Numerous human and animal studies suggest that acute and chronic physical and/or psychological stress affects the sleep centers of the brain (356–363). Stress, thus, influences sleep physiology and dream patterns and may cause both immediate and long-lasting sleep disruption (364–366), which may, in turn, enhance maladaptive stress regulation (367). For example, REM sleep disruption immediately after trauma exposure has been associated with higher REM-related sympathoadrenal activity, and represents an important predictive factor for the development of trauma-related disorders in humans (368–370). As sleep promotes memory consolidation, in particular for emotional content, sleep deprivation after stress exposure can affect amygdala-cortical connectivity and disrupt this process (371–373).

Such findings suggest that sleep disruption occurring after trauma exposure may represent a core, rather than a secondary pathway that mediates the enduring neurobiological correlates of ELS/CT (364, 368–370, 374, 375) and that chronodisruption may be the common underlying neurobiologic link (370, 374, 376).

GENETICS AND EPIGENETICS

Genome-wide association studies (GWAS) have identified several disease-associated candidate genes, which, however, explain only a minor part of heritability in such complex disorders. In recent few years, the interest has shifted to the central role of the interaction of specific candidate genes with environmental factors, as well as to gene programming through epigenetic regulation (e.g., DNA methylation, histone modification of chromatin, aberrant expression of miRNA) (377, 378). The combination of specific genetic polymorphism profiles and density or activity of functional sites controlling the human stress axis may increase or decrease the risk of psychobiological maladjustment after exposure to ELS/CT. A thorough understanding of the interaction between genes, environment, DNA methylation patterns (methylome) and subsequent gene expression profiles (transcriptome) is integral to our understanding and treatment of stress-related disorders (378).

GENE × ENVIRONMENT INTERACTIONS

Two of the first ground-breaking human studies investigating the interaction between ELS/CT and gene polymorphisms were conducted by Caspi and collaborators. In the first study, abused children with a monoamine oxidase A (*MAOA*) genotype associated with low levels of *MAOA* expression, were more likely to show antisocial-personality disorder and commit

violent crimes in adulthood (379). In the second prospective-longitudinal study of a representative birth cohort, functional polymorphisms in the promoter region of the serotonin transporter (5-HTT) gene (5-HTTLPR) was found to moderate the influence of ELS/CT on depression, with the presence of the short allele being associated with more depressive symptoms, diagnosable depression, and suicidality (380). These findings were later confirmed by Karg et al. (381) and are consistent with the assumption that 5-HTTLPR moderates emotional responsivity to stress in interaction with ELS/CT (382).

More recent findings suggest a vital role of genes involved with HPA axis function and GC sensitivity, in conjunction with exposure to child maltreatment or abuse (383). To date, findings mainly implicate two key genes: the GC response element (GRE) and the CRH-releasing hormone receptor 1 (CRHR1) of the FKBP5 gene (383, 384). The co-chaperone FKBP5 regulates steroid receptors such as the GR, resulting in a resistance (reduced sensitivity) against GCs. As first shown by Binder et al. (385), specific single-nucleotide poly-morphisms (SNPs) of the FKBP5 gene interacting with ELS/CT predict the level of adult PTSD symptoms. An allele-specific demethylation in the GREs of FKBP5 may result in a dysregulated expression of GRs (386). Further clinical studies confirm minor alleles of FKBP5 being particularly sensitive and interact with ELS/CT to increase aggressive behavior (387), suicide attempts (388), and depression (389). The CRHR1 acts as a mediator in initiating the stress response, possibly leading to a hypersensitive negative feedback loop of cortisol. Bradley et al. reported in two separate cohorts, independently, that specific CRHR1 polymorphisms interact with ELS/CT to increase the risk of adult depression (390), similar to Heim et al. (391), while Ben-Efraim et al. (392) reported comparable findings with respect to suicide attempts.

Taken together, *gene* × *environment* interactions of gene polymorphisms may affect the acute biological response to ELS/CT and mediate long-term risk of disease to some extent, most probably through their effects on stress responsiveness.

EPIGENETIC REGULATION

Epigenetic modifications are dynamic—and to some extend reversible—changes, that mediate the interaction between genetic predisposition and environmental factors through regulating functional expression of genes by decreasing, silencing or increasing gene expression (393, 394). The installment of such epigenetic marks by ELS/CT exposure and its genetic moderation by related factors represents a critical factor for vulnerability or resilience to stress-related disorders and may explain inter-individual variation. The interpretation of epigenetic findings is critical due to the complexity of the epigenetic mechanisms and the large number of involved genes.

ELS/CT exposure has been repeatedly related to epigenetic changes and altered gene expression profiles, particularly in the CNS (e.g., hippocampus, amygdala), thus affecting stress responses and memory consolidation (395–398). There is accumulating evidence for gene programming and epigenetic regulation of specific genes in the pathophysiology of PTSD in humans (399–402). Especially, several GC-signaling-related genes (e.g., GCR gene promoter 1F) are sensitive to traumatic-stress-related epigenetic regulation across the lifespan and may represent useful biomarkers related to the development, symptomology and prognosis of PTSD (403, 404). For example, in a recent human brain autopsy material study, history of childhood abuse was associated with changes in DNA methylation related to the neuron-specific GR (NR3C1) promoter in the hippocampus, suggesting distinct effects of ELS/CT on the epigenetic regulation of hippocampal GR expression (405). With respect to the promoter and exon 1F of the human GR gene Nr3c1, Oberlander et al. (406) showed specific epigenetic effects (gene hypermethylation) and elevated cortisol stress reactivity in the offspring due to maternal depression even during late pregnancy. Other animal findings also suggested ELS/CT-related epigenetic changes in the CNS growth and differentiation-related BDNF gene expression (407), while in a genome-wide blood DNA methylation analysis study by Houtepen et al. (408), a locus in the Kit ligand gene (KITLG; cg27512205) was shown to strongly modulate the relation between ELS/CT and cortisol stress reactivity.

Lately, various studies have investigated large-scale methylation patterns with respect to ELS/CT in cross-sectional settings. Bick et al. (409) reported significant differences in methylation in 72 of investigated 173 genes (responsible for HPA and immune system regulation) in children with and without foster care experience. Yang et al. (410) reported significant differences in methylation in 2,868 CpG sites on genes of all 23 chromosomes with respect to presence of ELS/CT, while Essex et al. (411) described similar transgenerational results in more than 150 of 28,000 CpG sites in a prospective study assessing parental stress and its consequences in their offspring. Interestingly, Mehta et al. (412) found that gene expression profiles of PTSD patients with and without ELS/CT are 98% non-overlapping. Moreover, these changes were mostly mediated by DNA methylation changes to a much larger proportion in the childhood abuse group, suggesting that changes in DNA methylation may exert a much greater impact during early life and possibly reflect differences in PTSD pathophysiology, depending on preceding exposure to ELS/CT.

Taken together, enduring changes in the transcriptome may facilitate the response to early developmental challenges and thus play a central role in the long-term (and sometimes transgenerational) biological trajectories of stress-related disease through programming effects for stress reactivity after ELS/CT exposure (104, 413, 414).

STRUCTURAL AND FUNCTIONAL IMAGING FINDINGS

ELS/CT during critical periods of brain development crucially affects the interaction between developing brain regions and neural circuits, exerts epigenetic influences and alters the functions of the HPA axis and GCs; indeed, it has been associated with remarkable structural and functional brain changes even decades later, in adulthood, defining both

vulnerability and resilience (383, 415, 416) [for an in-depth review see (417)]. Studies in animals have shown that elevated levels of GCs and catecholamines may lead to alterations in brain development through accelerated loss of neurons (418), delays in myelination (419), or abnormalities in developmentally appropriate synapse pruning (420). ELS/CT-related remodeling of structure, responsiveness and connectivity of specific brain areas and circuits can accordingly alter behavioral, cognitive, emotional, and physiologic responses (51, 421). For example, as cognitive function is heavily dependent on HPA axis and CG activity, childhood adversity associated with HPA axis dysfunction and GC excess or deficiency can result in diminished cognitive functioning and maladaptive emotional behavior (422). Accordingly, in a human resting activity neuroimaging PET study by Insana et al. (423), ELS/CT was associated with altered frontolimbic adult neural activity in the left orbital frontal cortex and left hippocampus, regions involved in executive functioning and emotional autoregulation, socioemotional processes, autonomic function, and sleep/wake regulation. ELS/CT has been also associated with several altered cognitive function findings, such as poor processing speed, defective executive functioning, and memory deficits (e.g., impaired spatial working memory performance, pattern recognition memory) in adulthood, which in turn might pose risks for the development of psychopathology (424–426).

There have been several additional studies assessing structural and functional brain correlates of ELS/CT, but the results have to be explored with caution, given the complexity of brain function, the simplicity of most study paradigms, the age of ELS/CT and assessment, the specific morbid population (i.e., type of psychopathology) and a number of other parameters not taken into account (427, 428). With respect to structural correlates, ELS/CT is associated with disruptive development and reduced volume of corpus callosum, insula, dorsolateral prefrontal cortex (PFC), orbitofrontal cortex (OFC), anterior cingulate gyrus, and caudate, as well as decreased cortical thickness of medial and lateral prefrontal and temporal lobe regions, and reduced overall brain volume in humans (416, 417, 425, 426, 428–434). A study of Teicher et al. (435), utilizing high-resolution T1-weighted MRI scans to assess network connectivity, also reported substantial changes in the cortical network architecture in these areas in young adults with ELS/CT history. Interestingly, the distinct neural plasticity during development can lead to cortical adaptation with very specific regionally altered cortical representation fields (436, 437) and be potentially protecting from the specific sensory processing of different ELS/CT (417). Thus, experience of sexual abuse has been associated with cortical thinning specifically in the genital representation field of the primary somatosensory cortex, while emotional abuse specifically in regions relevant to self-awareness and self-evaluation (438). Such plastic reorganization may be initially protective under abusive conditions, but may underlie later behavioral problems in the same areas (e.g., sexual dysfunction) and be selectively associated with increased vulnerability to internalizing and externalizing psychopathology (434).

The amygdala and the hippocampus are the two brain structures so far mostly reported to be impaired in adult victims of ELS/CT, suggesting most vital effects of ELS/CT on prefrontal-limbic gray matter. The hippocampus is of particular importance because of its role in cognition, but also its rich density of GR, while the amygdala because of its pivotal role in stress responsivity and the extensive related research in mood and anxiety disorders. There are numerous reports and meta-analytic studies confirming the association of ELS/CT with reduced hippocampal volume in adulthood (416, 417, 428, 430, 431, 433, 439). Interestingly, several studies assessing the effects of ELS/CT on hippocampal volume in patients with MDD, suggested that it is rather the history of ELS/CT than depression which is associated with hippocampal atrophy (440–442). However, hippocampal volume seems to be unaffected in children but not in adults with maltreatment-related PTSD, suggesting an initially volumetrically normal hippocampus with subsequent abnormal disrupted development (443). With respect to amygdala, the results from human studies regarding the volumetric effect of ELS/CT are inconclusive, with some studies reporting reduced volume (416, 428, 430, 444), some differential effects according to specific type of ELS/CT (432, 445), and some even greater amygdala volume (in non-human primates) (446). However, findings are conclusive concerning amygdala responsiveness, as ELS/CT has been repeatedly associated with facial threat- or negative-emotion-related amygdala hyper-responsiveness (416, 417, 447, 448). In addition, some studies even suggested that the relation between ELS/CT and risk for adult depression is actually mediated by this preceding amygdala hyperactivity (448, 449).

Finally, imaging studies have investigated the potential influence of genetics (i.e., specific polymorphisms in candidate genes) on the ELS/CT effects described above (417). For example, van Velzen et al. (444) showed that the magnitude of amygdala atrophy in maltreated individuals was significantly associated with the BDNF Val66Met genotype, while Booij et al. (450) demonstrated that greater peripheral serotonin transporter methylation in smaller hippocampal volume in adults with ELS/CT experience. More importantly, there have been a number of studies suggesting a moderating effect of FKBP5 (451–453) and mineralocorticoid receptor genotypes (454) on amygdala volume, reactivity and connectivity of ELS/CT exposed adults, thus implicating HPA axis-related genes in brain development. Genetic susceptibility may, thus, represent a crucial factor leading to related structural and functional trajectories of ELS/CT on brain development (455).

Taken together, altered amygdala-PFC connectivity with reduced top-down regulation of the amygdala by the PFC, reduced contextual input to the amygdala from the hippocampus, and increased connectivity of the amygdala with the LC (leading to increased limbic activity and PFC dysfunction), all suggest that ELS/CT plays a seminal role in functional and structural changes in the brain that may persist along the lifespan (51, 417, 430). Developmental differences in sensitivity to specific forms of childhood maltreatment may lead to different susceptibility of various brain regions and pathways to maltreatment at different ages (417). These results suggest that previously reported structural and functional findings in adolescent or adult

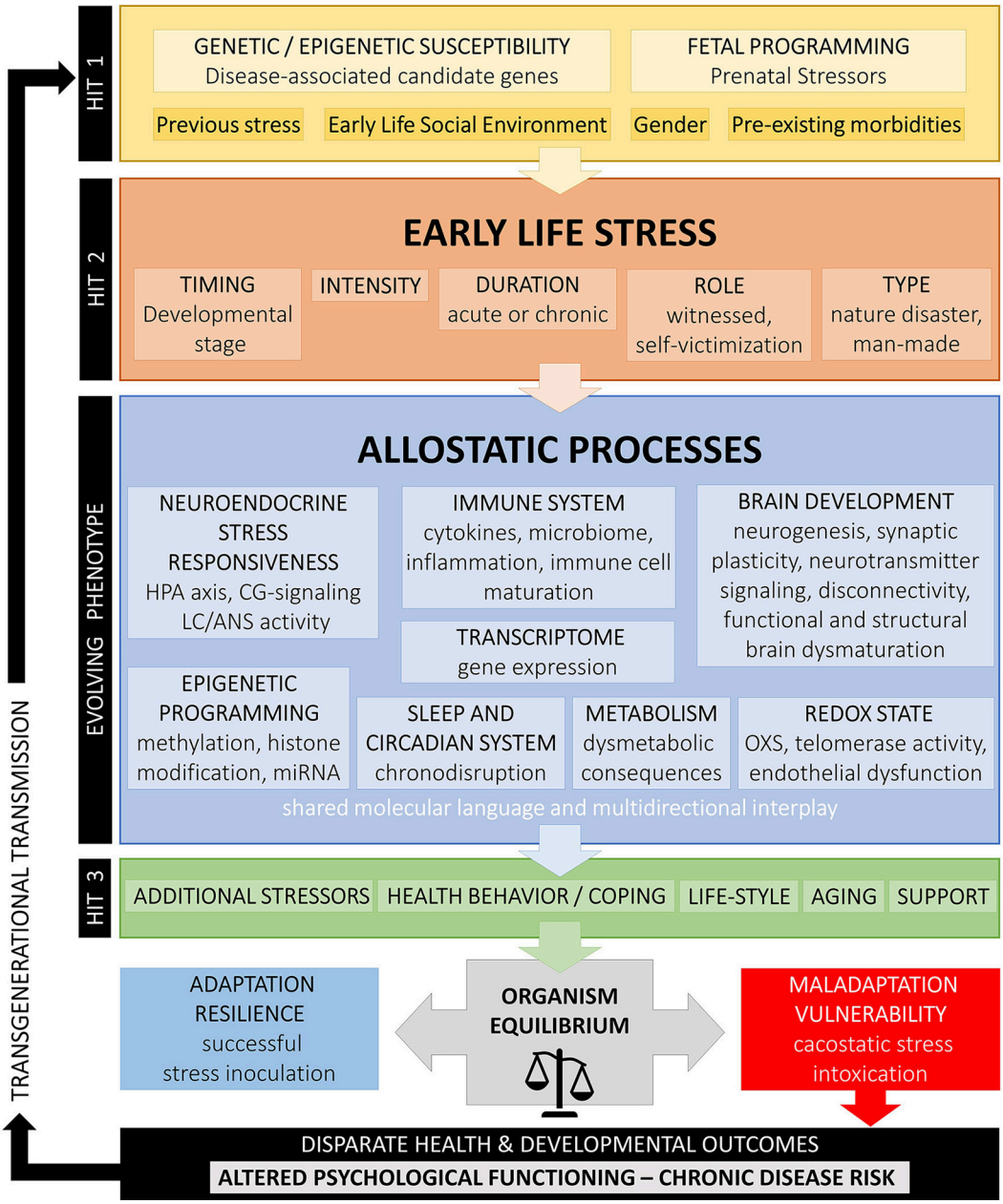

FIGURE 1 | Conceptual model on developmental trajectories of early life stress. Schematic model of moderating factors and allostatic neurobiological trajectory networks involved in the enduring biopsychological effects of ELS/CT. Exposure to ELS/CT can lead to disruption in critical phases of perinatal and juvenile brain development and an evolving programmed phenotype with altered allostatic processes and reduced adaptability to stress. The individual effects on ELS/CT on the organism depend on the specific genetic background and fetal programming (hit-1), the timing, duration, intensity and type of ELS/CT (hit-2) and other later-life challenges, such as additional stressors, coping strategies, support existence, life style, and aging (hit-3). Depending on their interaction, these factors explain inter-individual variation in resilience or vulnerability to altered biopsychological functioning and disparate health outcomes.

psychiatric disease should be re-evaluated addressing ELS/CT as a potential confounder (417).

EXPLANATORY MODELS

The developmental origin hypothesis of evolutionary biology suggests that the origins of adult disease are often found among early-life disruptions of physiological developmental processes, ranging from direct causal associations to complex, interacting environmental effects (58, 456–460). The previous sections confirm that ELS/CT during critical phases of perinatal and juvenile brain development is associated with increased cacostatic load and reduced stress adaptability in adulthood, leading to enhanced vulnerability to several chronic diseases.

Consequently, various explanatory models have been suggested during the past decades.

According to the cumulative stress model (diathesis-stress model) put forth by McEven et al. (4), when the accumulation of stressors along the life span exceeds a certain threshold, disease development is enhanced in individuals with higher stress exposure. Gluckman et al. (458, 459) suggested a pivotal role of ELS/CT that could prompt developmental (epigenetic) changes underlying predictive adaptive responses leading to a mismatch between the phenotypic outcome of adaptive plasticity and the ability to cope with current stressors increasing risk for disease (match/mismatch hypothesis). In contrast to the cumulative stress model, the mismatch hypothesis explicitly assumes that ELS/CT may also have advantageous effects by representing a possible source of adaptation, potentially even promoting active coping (stress inoculation) to moderate stressors and, thus, resilience. Similarly, the for-better-and-for-worse model suggested by Belsky and Beaver (461) assumes that genetic susceptibility should be contextually interpreted and, according to the specific environment, could be beneficial or not. Nederhof and colleagues have proposed an integrated model based on programming effects of ELS/CT interacting with individual genetic vulnerability (462, 463). Recently, Daskalakis et al. (104) have expanded this model suggesting a three-hit concept for vulnerability and resilience. Accordingly, vulnerability in a given context is enhanced when failure to cope with adversity accumulates. The interaction of the individual genetic background (hit-1) with ELS/CT exposure (hit-2) results in an evolving phenotype with altered stress axis regulation and sensitivity due to early developmental programming, which, in turn, interacts with later-life challenges (hit-3) to result in a higher or lower vulnerability risk according to the type of challenge experienced. This model underlines the extraordinary plasticity of the brain and suggests that "nothing is written in stone" (464).

DISCUSSION

Coordination of the stress, immune and circadian systems is essential to individual development, adaptation, survival, and well-being (1, 2, 153). ELS/CT, in interaction with genetic factors, disrupts developmental programming of the related neural circuitry and leads to alterations in neuroendocrine, immune, circadian, emotional, and autonomic (re-)activity, with related structural, functional, and epigenetic modifications both in the brain and peripheral tissues. These persistent structural and functional neuropsychobiological changes as sequelae of ELS/CT could mediate risk for chronic disease in adulthood, and lead to cumulative disadvantages and increased adult physical and mental health morbidity (15, 55, 58, 62). Nevertheless, although most studies support a causal relation between ELS/CT and psychobiological maladjustment in later life, the developmental course of such changes and its temporal coincidence has not been elucidated as yet. Thereby, non-linear patterns in neurodevelopment lead to specific periods of greater stress system plasticity, which represent important vulnerability periods (96, 100, 101). Thus, ELS/CT experience is probably associated with a differential impact on stress system activity according to the specific developmental period of exposure (102). ELS/CT exposure during the first hypo-sensitive 2 years of life may lead to a hyper-activity and -responsiveness of HPA axis and accordingly higher risk for developing depression than PTSD, while ELS/CT during the hyper-active phase of adolescence may lead to a hypo-active and hypo-responsive HPA axis and accordingly higher risk for developing PTSD than depression in adulthood (22, 101).

Figure 1 summarizes the above developmental approaches and provides an integrative schematic model of moderating factors and allostatic neurobiological trajectory networks involved in the enduring biopsychological effects of ELS. However, further biological pathways (i.e., gonadal steroids, amyloid beta, mitochondrial function, leptin/ghrelin system), psychiatric states (i.e., depression, PTSD), and behavioral patterns (i.e., substance abuse, physical exercise, nutrition) could also play an important role in the mediation of the overall biological risk after ELS/CT and should be better investigated.

CONCLUSIONS

The identification of factors related to risk and resilience in the wake of child abuse is a matter of central importance for public health interventions (465). Understanding the pathways susceptible to disruption following ELS/CT exposure and the effects of a dysregulated interconnection between all neural systems involved could provide new insights into the pathophysiologic trajectories that link toxic stress during developmental stages of childhood and adolescence to adult maladjustment and psychopathology. Future studies should prospectively investigate potential confounders, their temporal sequence and combined effects at the epidemiological, biological, and epigenetic level (466, 467), while considering the potentially delayed time-frame for the expression of their effects. Finally, screening strategies for ELS/CT and trauma need to be improved. Information about ELS/CT history and the number of adverse experiences could help to better identify the individual risk for disease development, predict individual treatment response and design prevention strategies to reduce the negative effects of ELS/CT (468). Detecting and healing of the "hidden wounds" left by ELS/CT should thus be a public health priority.

AUTHOR CONTRIBUTIONS

AA managed all literature searches. AA and PP and wrote the first draft of the paper. GC and DB contributed with significant text passages and revised the draft for important intellectual content. All authors have contributed to, read, and approved the final version of the manuscript.

REFERENCES

1. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. *Overview Phys Behav Homeost*. (1992) 267:1244–52. doi: 10.1001/jama.1992.03480090092034
2. Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinol.* (2009) 5:374–81. doi: 10.1038/nrendo.2009.106
3. Dhabhar FS, McEwen BS, Spencer RL. Adaptation to prolonged or repeated stress–comparison between rat strains showing intrinsic differences in reactivity to acute stress. *Neuroendocrinology*. (1997) 65:360–8. doi: 10.1159/000127196
4. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med.* (1998) 338:171–9. doi: 10.1056/NEJM199801153380307
5. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol Psychiatry*. (2001) 49:1023–39. doi: 10.1016/S0006-3223(01)01157-X
6. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci.* (2009) 10:434–45. doi: 10.1038/nrn2639
7. Koolhaas JM, Bartolomucci A, Buwalda B, de Boer SF, Flugge G, Korte SM, et al. Stress revisited: a critical evaluation of the stress concept. *Neurosci Biobehav Rev.* (2011) 35:1291–301. doi: 10.1016/j.neubiorev.2011.02.003
8. Frodl T, O'Keane V. How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. *Neurobiol Dis.* (2013) 52:24–37. doi: 10.1016/j.nbd.2012.03.012
9. Seo D, Tsou KA, Ansell EB, Potenza MN, Sinha R. Cumulative adversity sensitizes neural response to acute stress: association with health symptoms. *Neuropsychopharmacology*. (2014) 39:670–80. doi: 10.1038/npp.2013.250
10. Stults-Kolehmainen MA, Tuit K, Sinha R. Lower cumulative stress is associated with better health for physically active adults in the community. *Stress*. (2014) 17:157–68. doi: 10.3109/10253890.2013.878329
11. Reynolds RM, Labad J, Buss C, Ghaemmaghami P, Raikkonen K. Transmitting biological effects of stress *in utero*: implications for mother and offspring. *Psychoneuroendocrinology*. (2013) 38:1843–9. doi: 10.1016/j.psyneuen.2013.05.018
12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th Edition Washington, DC: American Psychiatric Association (2013).
13. Edwards VJ, Holden GW, Felitti VJ, Anda RF. Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: results from the adverse childhood experiences study. *Am J Psychiatry*. (2003) 160:1453–60. doi: 10.1176/appi.ajp.160.8.1453
14. Scher CD, Forde DR, McQuaid JR, Stein MB. Prevalence and demographic correlates of childhood maltreatment in an adult community sample. *Child Abuse Negl.* (2004) 28:167–80. doi: 10.1016/j.chiabu.2003.09.012
15. Gilbert R, Widom CS, Browne K, Fergusson D, Webb E, Janson S. Burden and consequences of child maltreatment in high-income countries. *Lancet*. (2009) 373:68–81. doi: 10.1016/S0140-6736(08)61706-7
16. Green JG, McLaughlin KA, Berglund PA, Gruber MJ, Sampson NA, Zaslavsky AM, et al. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. *Arch Gen Psychiatry*. (2010) 67:113–23. doi: 10.1001/archgenpsychiatry.2009.186
17. Walker EA, Gelfand A, Katon WJ, Koss MP, Von Korff M, Bernstein D, et al. Adult health status of women with histories of childhood abuse and neglect. *Am J Med.* (1999) 107:332–9. doi: 10.1016/S0002-9343(99)00235-1
18. Spertus IL, Yehuda R, Wong CM, Halligan S, Seremetis SV. Childhood emotional abuse and neglect as predictors of psychological and physical symptoms in women presenting to a primary care practice. *Child Abuse Negl.* (2003) 27:1247–58. doi: 10.1016/j.chiabu.2003.05.001
19. Elstad JI. Childhood adversities and health variations among middle-aged men: a retrospective lifecourse study. *Eur J Public Health*. (2005) 15:51–8. doi: 10.1093/eurpub/cki114
20. Draper B, Pfaff JJ, Pirkis J, Snowdon J, Lautenschlager NT, Wilson I, et al. Long-term effects of childhood abuse on the quality of life and health of older people: results from the depression and early prevention of suicide in general practice project. *J Am Geriatr Soc.* (2008) 56:262–71. doi: 10.1111/j.1532-5415.2007.01537.x
21. Dube SR, Cook ML, Edwards VJ. Health-related outcomes of adverse childhood experiences in Texas, 2002. *Prev Chronic Dis.* (2010) 7:A52.
22. Maercker A, Michael T, Fehm L, Becker ES, Margraf J. Age of traumatisation as a predictor of post-traumatic stress disorder or major depression in young women. *Br J Psychiatry*. (2004) 184:482–7. doi: 10.1192/bjp.184.6.482
23. Pirkola S, Isometsa E, Aro H, Kestila L, Hamalainen J, Veijola J, et al. Childhood adversities as risk factors for adult mental disorders: results from the Health 2000 study. *Soc Psychiatry Psychiatr Epidemiol.* (2005) 40:769–77. doi: 10.1007/s00127-005-0950-x
24. Scott KM, Von Korff M, Angermeyer MC, Benjet C, Bruffaerts R, de Girolamo G, et al. Association of childhood adversities and early-onset mental disorders with adult-onset chronic physical conditions. *Arch Gen Psychiatry*. (2011) 68:838–44. doi: 10.1001/archgenpsychiatry.2011.77
25. Nanni V, Uher R, Danese A. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. *Am J Psychiatry*. (2012) 169:141–51. doi: 10.1176/appi.ajp.2011.11020335
26. Koenen KC, Moffitt TE, Poulton R, Martin J, Caspi A. Early childhood factors associated with the development of post-traumatic stress disorder: results from a longitudinal birth cohort. *Psychol Med.* (2007) 37:181–92. doi: 10.1017/S0033291706009019
27. Wang Z, Inslicht SS, Metzler TJ, Henn-Haase C, McCaslin SE, Tong H, et al. A prospective study of predictors of depression symptoms in police. *Psychiatry Res.* (2010) 175:211–6. doi: 10.1016/j.psychres.2008.11.010
28. Berntsen D, Johannessen KB, Thomsen YD, Bertelsen M, Hoyle RH, Rubin DC. Peace and war: trajectories of posttraumatic stress disorder symptoms before, during, and after military deployment in afghanistan. *Psychol Sci.* (2012) 23:1557–65. doi: 10.1177/0956797612457389
29. Hovens JG, Giltay EJ, Wiersma JE, Spinhoven P, Penninx BW, Zitman FG. Impact of childhood life events and trauma on the course of depressive and anxiety disorders. *Acta Psychiatr Scand.* (2012) 126:198–207. doi: 10.1111/j.1600-0447.2011.01828.x
30. Spratt EG, Back SE, Yeatts SD, Simpson AN, McRae-Clark A, Moran-Santa Maria MM, et al. Relationship between child abuse and adult smoking. *Int J Psychiatry Med.* (2009) 39:417–26. doi: 10.2190/PM.39.4.f
31. Khoury L, Tang YL, Bradley B, Cubells JF, Ressler KJ. Substance use, childhood traumatic experience, and posttraumatic stress disorder in an urban civilian population. *Depress Anxiety*. (2010) 27:1077–86. doi: 10.1002/da.20751
32. Strine TW, Dube SR, Edwards VJ, Prehn AW, Rasmussen S, Wagenfeld M, et al. Associations between adverse childhood experiences, psychological distress, and adult alcohol problems. *Am J Health Behav.* (2012) 36:408–23. doi: 10.5993/AJHB.36.3.11
33. Fenton MC, Geier T, Keyes K, Skodol AE, Grant BF, Hasin DS. Combined role of childhood maltreatment, family history, and gender in the risk for alcohol dependence. *Psychol Med.* (2013) 43:1045–57. doi: 10.1017/S0033291712001729
34. Fuller-Thomson E, Filippelli J, Lue-Crisostomo CA. Gender-specific association between childhood adversities and smoking in adulthood: findings from a population-based study. *Public Health*. (2013) 127:449–60. doi: 10.1016/j.puhe.2013.01.006
35. Zatti C, Rosa V, Barros A, Valdivia L, Calegaro VC, Freitas LH, et al. Childhood trauma and suicide attempt: a meta-analysis of longitudinal studies from the last decade. *Psychiatry Res.* (2017) 256:353–8. doi: 10.1016/j.psychres.2017.06.082
36. Dong M, Giles WH, Felitti VJ, Dube SR, Williams JE, Chapman DP, et al. Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. *Circulation*. (2004) 110:1761–6. doi: 10.1161/01.CIR.0000143074.54995.7F
37. Springer KW, Sheridan J, Kuo D, Carnes M. Long-term physical and mental health consequences of childhood physical abuse: results from a large population-based sample of men and women. *Child Abuse Negl.* (2007) 31:517–30. doi: 10.1016/j.chiabu.2007.01.003
38. Paras ML, Murad MH, Chen LP, Goranson EN, Sattler AL, Colbenson KM, et al. Sexual abuse and lifetime diagnosis of somatic disorders: a systematic review and meta-analysis. *JAMA*. (2009) 302:550–61. doi: 10.1001/jama.2009.1091

39. Wegman HL, Stetler C. A meta-analytic review of the effects of childhood abuse on medical outcomes in adulthood. *Psychosom Med.* (2009) 71:805–12. doi: 10.1097/PSY.0b013e3181bb2b46
40. Korkeila J, Vahtera J, Korkeila K, Kivimaki M, Sumanen M, Koskenvuo K, et al. Childhood adversities as predictors of incident coronary heart disease and cerebrovascular disease. *Heart*. (2010) 96:298–303. doi: 10.1136/hrt.2009.188250
41. Stein DJ, Scott K, Haro Abad JM, Aguilar-Gaxiola S, Alonso J, Angermeyer M, et al. Early childhood adversity and later hypertension: data from the World Mental Health Survey. *Ann Clin Psychiatry*. (2010) 22:19–28.
42. Tamayo T, Christian H, Rathmann W. Impact of early psychosocial factors (childhood socioeconomic factors and adversities) on future risk of type 2 diabetes, metabolic disturbances and obesity: a systematic review. *BMC Public Health*. (2010) 10:525. doi: 10.1186/1471-2458-10-525
43. Huang MC, Schwandt ML, Ramchandani VA, George DT, Heilig M. Impact of multiple types of childhood trauma exposure on risk of psychiatric comorbidity among alcoholic inpatients. *Alcohol Clin Exp Res.* (2012) 36:1099–107. doi: 10.1111/j.1530-0277.2011.01695.x
44. Agorastos A, Pittman JO, Angkaw AC, Nievergelt CM, Hansen CJ, Aversa LH, et al. The cumulative effect of different childhood trauma types on self-reported symptoms of adult male depression and PTSD, substance abuse and health-related quality of life in a large active-duty military cohort. *J Psychiatr Res.* (2014) 58:46–54. doi: 10.1016/j.jpsychires.2014.07.014
45. Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield C, Perry BD, et al. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *Eur Arch Psychiatry Clin Neurosci.* (2006) 256:174–86. doi: 10.1007/s00406-005-0624-4
46. Afifi TO, Enns MW, Cox BJ, de Graaf R, ten Have M, Sareen J. Child abuse and health-related quality of life in adulthood. *J Nerv Ment Dis.* (2007) 195:797–804. doi: 10.1097/NMD.0b013e3181567fdd
47. Anda RF, Brown DW, Felitti VJ, Bremner JD, Dube SR, Giles WH. Adverse childhood experiences and prescribed psychotropic medications in adults. *Am J Prev Med.* (2007) 32:389–94. doi: 10.1016/j.amepre.2007.01.005
48. Briere J, Kaltman S, Green BL. Accumulated childhood trauma and symptom complexity. *J Trauma Stress*. (2008) 21:223–6. doi: 10.1002/jts.20317
49. Lang AJ, Aarons GA, Gearity J, Laffaye C, Satz L, Dresselhaus TR, et al. Direct and indirect links between childhood maltreatment, posttraumatic stress disorder, and women's health. *Behav Med.* (2008) 33:125–35. doi: 10.3200/BMED.33.4.125-136
50. Suliman S, Mkabile SG, Fincham DS, Ahmed R, Stein DJ, Seedat S. Cumulative effect of multiple trauma on symptoms of posttraumatic stress disorder, anxiety, and depression in adolescents. *Compr Psychiatry*. (2009) 50:121–7. doi: 10.1016/j.comppsych.2008.06.006
51. Nemeroff CB. Paradise lost: the neurobiological and clinical consequences of child abuse and neglect. *Neuron*. (2016) 89:892–909. doi: 10.1016/j.neuron.2016.01.019
52. Mullen PE, Martin JL, Anderson JC, Romans SE, Herbison GP. The long-term impact of the physical, emotional, and sexual abuse of children: a community study. *Child Abuse Negl.* (1996) 20:7–21. doi: 10.1016/0145-2134(95)00112-3
53. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) study. *Am J Prev Med.* (1998) 14:245–58. doi: 10.1016/S0749-3797(98)00017-8
54. Heim C, Nemeroff CB. The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biol Psychiatry*. (1999) 46:1509–22. doi: 10.1016/S0006-3223(99)00224-3
55. Kaufman J, Plotsky PM, Nemeroff CB, Charney DS. Effects of early adverse experiences on brain structure and function: clinical implications. *Biol Psychiatry*. (2000) 48:778–90. doi: 10.1016/S0006-3223(00)00998-7
56. Goodwin RD, Stein MB. Association between childhood trauma and physical disorders among adults in the United States. *Psychol Med.* (2004) 34:509–20. doi: 10.1017/S003329170300134X
57. Pole N, Neylan TC, Otte C, Metzler TJ, Best SR, Henn-Haase C, et al. Associations between childhood trauma and emotion-modulated psychophysiological responses to startling sounds: a study of police cadets. *J Abnorm Psychol.* (2007) 116:352–61. doi: 10.1037/0021-843X.116.2.352
58. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. *JAMA*. (2009) 301:2252–9. doi: 10.1001/jama.2009.754
59. Mock SE, Arai SM. Childhood trauma and chronic illness in adulthood: mental health and socioeconomic status as explanatory factors and buffers. *Front Psychol.* (2010) 1:246.
60. Glaser D. Child abuse and neglect and the brain–a review. *J Child Psychol Psychiatry*. (2000) 41:97–116. doi: 10.1017/S0021963099004990
61. Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP. Developmental neurobiology of childhood stress and trauma (2002). *Psychiatr Clin North Am.* 25:397–426. doi: 10.1016/S0193-953X(01)00003-X
62. Nemeroff CB. Neurobiological consequences of childhood trauma. *J Clin Psychiatry*. (2004) 65(Suppl 1.):18–28.
63. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology*. (2008) 33:693–710. doi: 10.1016/j.psyneuen.2008.03.008
64. Heim C, Newport DJ, Miller AH, Nemeroff CB. Long-term neuroendocrine effects of childhood maltreatment. *JAMA*. (2000) 284:2321. doi: 10.1001/jama.284.18.2317
65. Yehuda R. Biology of posttraumatic stress disorder. *J Clin Psychiatry*. (2000) 61 (Suppl. 7):14–21
66. Nemeroff CB, Bremner JD, Foa EB, Mayberg HS, North CS, Stein MB. Posttraumatic stress disorder: a state-of-the-science review. *J Psychiatr Res.* (2006) 40:1–21. doi: 10.1016/j.jpsychires.2005.07.005
67. Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA*. (2000) 284:592–7. doi: 10.1001/jama.284.5.592
68. Heim C, Newport DJ, Bonsall R, Miller AH, Nemeroff CB. Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. *Am J Psychiatry*. (2001) 158:575–81. doi: 10.1176/appi.ajp.158.4.575
69. Heim C, Mletzko T, Purselle D, Musselman DL, Nemeroff CB. The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. *Biol Psychiatry*. (2008) 63:398–405. doi: 10.1016/j.biopsych.2007.07.002
70. Muhtz C, Wester M, Yassouridis A, Wiedemann K, Kellner M. A combined dexamethasone/corticotropin-releasing hormone test in patients with chronic PTSD–first preliminary results. *J Psychiatr Res.* (2008) 42:689–93. doi: 10.1016/j.jpsychires.2007.08.006
71. Tyrka AR, Wier L, Price LH, Ross N, Anderson GM, Wilkinson CW, et al. Childhood parental loss and adult hypothalamic-pituitary-adrenal function. *Biol Psychiatry*. (2008) 63:1147–54. doi: 10.1016/j.biopsych.2008.01.011
72. Pesonen AK, Raikkonen K, Feldt K, Heinonen K, Osmond C, Phillips DI, et al. Childhood separation experience predicts HPA axis hormonal responses in late adulthood: a natural experiment of World War II. *Psychoneuroendocrinology*. (2010) 35:758–67. doi: 10.1016/j.psyneuen.2009.10.017
73. Kumari M, Head J, Bartley M, Stansfeld S, Kivimaki M. Maternal separation in childhood and diurnal cortisol patterns in mid-life: findings from the Whitehall II study. *Psychol Med.* (2013) 43:633–43. doi: 10.1017/S0033291712001353
74. Lu S, Gao W, Huang M, Li L, Xu Y. In search of the HPA axis activity in unipolar depression patients with childhood trauma: Combined cortisol awakening response and dexamethasone suppression test. *J Psychiatr Res.* (2016) 78:24–30. doi: 10.1016/j.jpsychires.2016.03.009
75. Butler K, Klaus K, Edwards L, Pennington K. Elevated cortisol awakening response associated with early life stress and impaired executive function in healthy adult males. *Horm Behav.* (2017) 95:13–21. doi: 10.1016/j.yhbeh.2017.07.013
76. Aguilera G, Liu Y. The molecular physiology of CRH neurons. *Front Neuroendocrinol.* (2012) 33:67–84. doi: 10.1016/j.yfrne.2011.08.002

77. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Psychosom Med.* (2011) 73:114–26. doi: 10.1097/PSY.0b013e31820ad12b
78. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. *Annu Rev Physiol.* (2005) 67:259–84. doi: 10.1146/annurev.physiol.67.040403.120816
79. Pervanidou P, Chrousos GP. Neuroendocrinology of post-traumatic stress disorder. *Prog Brain Res.* (2010) 182:149–60. doi: 10.1016/S0079-6123(10)82005-9
80. Carpenter LL, Tyrka AR, Ross NS, Khoury L, Anderson GM, Price LH. Effect of childhood emotional abuse and age on cortisol responsivity in adulthood. *Biol Psychiatry*. (2009) 66:69–75. doi: 10.1016/j.biopsych.2009.02.030
81. Carpenter LL, Shattuck TT, Tyrka AR, Geracioti TD, Price LH. Effect of childhood physical abuse on cortisol stress response. *Psychopharmacology*. (2011) 214:367–75. doi: 10.1007/s00213-010-2007-4
82. Hinkelmann K, Muhtz C, Dettenborn L, Agorastos A, Wingenfeld K, Spitzer C, et al. Association between childhood trauma and low hair cortisol in depressed patients and healthy control subjects. *Biol Psychiatry*. (2013) 74:e15–7. doi: 10.1016/j.biopsych.2013.04.021
83. Suzuki A, Poon L, Papadopoulos AS, Kumari V, Cleare AJ. Long term effects of childhood trauma on cortisol stress reactivity in adulthood and relationship to the occurrence of depression. *Psychoneuroendocrinology*. (2014) 50:289–99. doi: 10.1016/j.psyneuen.2014.09.007
84. Voellmin A, Winzeler K, Hug E, Wilhelm FH, Schaefer V, Gaab J, et al. Blunted endocrine and cardiovascular reactivity in young healthy women reporting a history of childhood adversity. *Psychoneuroendocrinology*. (2015) 51:58–67. doi: 10.1016/j.psyneuen.2014.09.008
85. Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology*. (2000) 25:1–35. doi: 10.1016/S0306-4530(99)00035-9
86. de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. *Nat Rev Neurosci.* (2005) 6:463–75. doi: 10.1038/nrn1683
87. de Kloet CS, Vermetten E, Bikker A, Meulman E, Geuze E, Kavelaars A, et al. Leukocyte glucocorticoid receptor expression and immunoregulation in veterans with and without post-traumatic stress disorder. *Mol Psychiatry*. (2007) 12:443–53. doi: 10.1038/sj.mp.4001934
88. Yehuda R, Seckl J. Minireview: Stress-related psychiatric disorders with low cortisol levels: a metabolic hypothesis. *Endocrinology*. (2011) 152:4496–503. doi: 10.1210/en.2011-1218
89. Raison CL, Miller AH. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am J Psychiatry*. (2003) 160:1554–65. doi: 10.1176/appi.ajp.160.9.1554
90. Pervanidou P. Biology of post-traumatic stress disorder in childhood and adolescence. *J Neuroendocrinol.* (2008) 20:632–8. doi: 10.1111/j.1365-2826.2008.01701.x
91. Rohleder N, Wolf JM, Wolf OT. Glucocorticoid sensitivity of cognitive and inflammatory processes in depression and posttraumatic stress disorder. *Neurosci Biobehav Rev*. (2010) 35:104–14. doi: 10.1016/j.neubiorev.2009.12.003
92. Sartor CE, Grant JD, Lynskey MT, McCutcheon VV, Waldron M, Statham DJ, et al. Common heritable contributions to low-risk trauma, high-risk trauma, posttraumatic stress disorder, and major depression. *Arch Gen Psychiatry*. (2012) 69:293–9. doi: 10.1001/archgenpsychiatry.2011.1385
93. Vaccarino V. *An inflammatory phenotype for posttraumatic stress disorder and depression? Brain Behav Immun.* (2018)
94. Kuhlman KR, Geiss EG, Vargas I, Lopez-Duran NL. Differential associations between childhood trauma subtypes and adolescent HPA-axis functioning. *Psychoneuroendocrinology*. (2015) 54:103–14. doi: 10.1016/j.psyneuen.2015.01.020
95. Schalinski I, Elbert T, Steudte-Schmiedgen S, Kirschbaum C. The cortisol paradox of trauma-related disorders: lower phasic responses but higher tonic levels of cortisol are associated with sexual abuse in childhood. *PLoS ONE*. (2015) 10:e0136921. doi: 10.1371/journal.pone.0136921
96. Thompson JV, Sullivan RM, Wilson DA. Developmental emergence of fear learning corresponds with changes in amygdala synaptic plasticity. *Brain Res.* (2008) 1200:58–65. doi: 10.1016/j.brainres.2008.01.057
97. Giedd JN. The digital revolution and adolescent brain evolution. *J Adolesc Health*. (2012) 51:101–5. doi: 10.1016/j.jadohealth.2012.06.002
98. Uematsu A, Matsui M, Tanaka C, Takahashi T, Noguchi K, Suzuki M, et al. Developmental trajectories of amygdala and hippocampus from infancy to early adulthood in healthy individuals. *PLoS ONE*. (2012) 7:e46970. doi: 10.1371/journal.pone.0046970
99. Qiu A, Mori S, Miller MI. Diffusion tensor imaging for understanding brain development in early life. *Annu Rev Psychol.* (2015) 66:853–76. doi: 10.1146/annurev-psych-010814-015340
100. Tallot L, Doyere V, Sullivan RM. Developmental emergence of fear/threat learning: neurobiology, associations and timing. *Genes Brain Behav.* (2016) 15:144–54. doi: 10.1111/gbb.12261
101. Kuhlman KR, Chiang JJ, Horn S, Bower JE. Developmental psychoneuroendocrine and psychoneuroimmune pathways from childhood adversity to disease. *Neurosci Biobehav Rev*. (2017) 80:166–84. doi: 10.1016/j.neubiorev.2017.05.020
102. Sullivan RM. The neurobiology of attachment to nurturing and abusive caregivers. *Hastings Law J.* (2012) 63:1553–70.
103. Gunnar MR. Quality of early care and buffering of neuroendocrine stress reactions: potential effects on the developing human brain. *Prev Med.* (1998) 27:208–11. doi: 10.1006/pmed.1998.0276
104. Daskalakis NP, Bagot RC, Parker KJ, Vinkers CH, de Kloet ER. The three-hit concept of vulnerability and resilience: toward understanding adaptation to early-life adversity outcome. *Psychoneuroendocrinology*. (2013) 38:1858–73. doi: 10.1016/j.psyneuen.2013.06.008
105. Gunnar M, Quevedo K. The neurobiology of stress and development. *Annu Rev Psychol.* (2007) 58:145–73. doi: 10.1146/annurev.psych.58.110405.085605
106. Gunnar MR, Wewerka S, Frenn K, Long JD, Griggs C. Developmental changes in hypothalamus-pituitary-adrenal activity over the transition to adolescence: normative changes and associations with puberty. *Dev Psychopathol.* (2009) 21:69–85. doi: 10.1017/S0954579409000054
107. Davis EP, Granger DA. Developmental differences in infant salivary alpha-amylase and cortisol responses to stress. *Psychoneuroendocrinology*. (2009) 34:795–804. doi: 10.1016/j.psyneuen.2009.02.001
108. Hostinar CE, Gunnar MR. Future directions in the study of social relationships as regulators of the HPA axis across development. *J Clin Child Adolesc Psychol.* (2013) 42:564–75. doi: 10.1080/15374416.2013.804387
109. Hostinar CE, Sullivan RM, Gunnar MR. Psychobiological mechanisms underlying the social buffering of the hypothalamic-pituitary-adrenocortical axis: a review of animal models and human studies across development. *Psychol Bull.* (2014) 140:256–82. doi: 10.1037/a0032671
110. Hostinar CE, Johnson AE, Gunnar MR. Early social deprivation and the social buffering of cortisol stress responses in late childhood: an experimental study. *Dev Psychol.* (2015) 51:1597–608. doi: 10.1037/dev0000029
111. Struber N, Struber D, Roth G. Impact of early adversity on glucocorticoid regulation and later mental disorders. *Neurosci Biobehav Rev.* (2014) 38:17–37. doi: 10.1016/j.neubiorev.2013.10.015
112. Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, et al. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proc Natl Acad Sci USA*. (2012) 109:5995–9. doi: 10.1073/pnas.1118355109
113. Kuhlman KR, Vargas I, Geiss EG, Lopez-Duran NL. Age of trauma onset and HPA axis dysregulation among trauma-exposed youth. *J Trauma Stress*. (2015) 28:572–9. doi: 10.1002/jts.22054
114. Somerville LH, Jones RM, Casey BJ. A time of change: behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. *Brain Cogn.* (2010) 72:124–33. doi: 10.1016/j.bandc.2009.07.003
115. Galvan A, McGlennen KM. Enhanced striatal sensitivity to aversive reinforcement in adolescents versus adults. *J Cogn Neurosci.* (2013) 25:284–96. doi: 10.1162/jocn_a_00326
116. Fuhrmann D, Knoll LJ, Blakemore SJ. Adolescence as a sensitive period of brain development. *Trends Cogn Sci.* (2015) 19:558–66. doi: 10.1016/j.tics.2015.07.008
117. Tornhage CJ. Reference values for morning salivary cortisol concentrations in healthy school-aged children. *J Pediatr Endocrinol Metab.* (2002) 15:197–204. doi: 10.1515/JPEM.2002.15.2.197

118. Stroud LR, Foster E, Papandonatos GD, Handwerger K, Granger DA, Kivlighan KT, et al. Stress response and the adolescent transition: performance versus peer rejection stressors. *Dev Psychopathol.* (2009) 21:47–68. doi: 10.1017/S0954579409000042
119. Sumter SR, Bokhorst CL, Miers AC, Van Pelt J, Westenberg PM. Age and puberty differences in stress responses during a public speaking task: do adolescents grow more sensitive to social evaluation? *Psychoneuroendocrinology*. (2010) 35:1510–6. doi: 10.1016/j.psyneuen.2010.05.004
120. Blumenthal H, Leen-Feldner EW, Badour CL, Trainor CD, Babson KA. Pubertal maturation and cortisol level in response to a novel social environment among female adolescents. *J Adolesc.* (2014) 37:893–900. doi: 10.1016/j.adolescence.2014.06.005
121. van den Bos E, de Rooij M, Miers AC, Bokhorst CL, Westenberg PM. Adolescents' increasing stress response to social evaluation: pubertal effects on cortisol and alpha-amylase during public speaking. *Child Dev.* (2014) 85:220–36. doi: 10.1111/cdev.12118
122. Solomon MB, Herman JP. Sex differences in psychopathology: of gonads, adrenals and mental illness. *Physiol Behav.* (2009) 97:250–8. doi: 10.1016/j.physbeh.2009.02.033
123. Vaillancourt T, Duku E, Decatanzaro D, Macmillan H, Muir C, Schmidt LA. Variation in hypothalamic-pituitary-adrenal axis activity among bullied and non-bullied children. *Aggress Behav.* (2008) 34:294–305. doi: 10.1002/ab.20240
124. Trickett PK, Gordis E, Peckins MK, Susman EJ. Stress reactivity in maltreated and comparison male and female young adolescents. *Child Maltreat.* (2014) 19:27–37. doi: 10.1177/1077559513520466
125. Bosch NM, Riese H, Reijneveld SA, Bakker MP, Verhulst FC, Ormel J, et al. Timing matters: long term effects of adversities from prenatal period up to adolescence on adolescents' cortisol stress response. The TRAILS study. *Psychoneuroendocrinology*. (2012) 37:1439–47. doi: 10.1016/j.psyneuen.2012.01.013
126. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord.* (2000) 61:201–16. doi: 10.1016/S0165-0327(00)00338-4
127. Thayer JF, Sternberg E. Beyond heart rate variability: vagal regulation of allostatic systems. *Ann NY Acad Sci.* (2006) 1088:361–72. doi: 10.1196/annals.1366.014
128. Licht CM, Vreeburg SA, van Reedt Dortland AK, Giltay EJ, Hoogendijk WJ, DeRijk RH, et al. Increased sympathetic and decreased parasympathetic activity rather than changes in hypothalamic-pituitary-adrenal axis activity is associated with metabolic abnormalities. *J Clin Endocrinol Metab.* (2010) 95:2458–66. doi: 10.1210/jc.2009-2801
129. Loewy AD, Spyer KM. *Central Regulation of Autonomic Functions*. Oxford: Oxford University Press (1990).
130. Davis AM, Natelson BH. Brain-heart interactions. The neurocardiology of arrhythmia and sudden cardiac death. *Tex Heart Inst J.* (1993) 20:158–69.
131. Saper CB. Central autonomic system. In: Paxinos G, editor. *The Rat Nervous System*. 3rd ed. Amsterdam: Elsevier (2004). p. 761–96. doi: 10.1016/B978-012547638-6/50025-0
132. Thayer JF, Lane RD. Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. *Neurosci Biobehav Rev.* (2009) 33:81–8. doi: 10.1016/j.neubiorev.2008.08.004
133. Stiedl O, Youn J, Jansen RF. Cardiovascular conditioning: neural substrates. In: Koob GF, LeMoal M, Thompson RF, editors. *Encyclopedia of Behavioral Neuroscience*. Amsterdam: Elsevier (2010). p. 226–35. doi: 10.1016/B978-0-08-045396-5.00130-5
134. Ter Horst GJ, Hautvast RW, De Jongste MJ, Korf J. Neuroanatomy of cardiac activity-regulating circuitry: a transneuronal retrograde viral labelling study in the rat. *Eur J Neurosci.* (1996) 8:2029–41. doi: 10.1111/j.1460-9568.1996.tb00723.x
135. Gorman JM, Sloan RP. Heart rate variability in depressive and anxiety disorders. *Am Heart J.* (2000) 140:77–83. doi: 10.1067/mhj.2000.109981
136. Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. *Ann NY Acad Sci.* (2004) 1032:141–53. doi: 10.1196/annals.1314.011
137. Bedi US, Arora R. Cardiovascular manifestations of posttraumatic stress disorder. *J Natl Med Assoc.* (2007) 99:642–9.
138. Boscarino JA. A prospective study of PTSD and early-age heart disease mortality among Vietnam veterans: implications for surveillance and prevention. *Psychosom Med.* (2008) 70:668–76. doi: 10.1097/PSY.0b013e31817bccaf
139. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biol Psychiatry*. (2010) 67:1067–74. doi: 10.1016/j.biopsych.2009.12.012
140. Kemp AH, Quintana DS. The relationship between mental and physical health: insights from the study of heart rate variability. *Int J Psychophysiol.* (2013) 89:288–96. doi: 10.1016/j.ijpsycho.2013.06.018
141. Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary heart disease. *Psychosom Med.* (2005) 67(Suppl 1.):S29–33. doi: 10.1097/01.psy.0000162254.61556.d5
142. Kamphuis MH, Geerlings MI, Dekker JM, Giampaoli S, Nissinen A, Grobbee DE, et al. Autonomic dysfunction: a link between depression and cardiovascular mortality? The FINE Study. *Eur J Cardiovasc Prev Rehabil.* (2007) 14:796–802. doi: 10.1097/HJR.0b013e32829c7d0c
143. Harrison NA, Cooper E, Voon V, Miles K, Critchley HD. Central autonomic network mediates cardiovascular responses to acute inflammation: relevance to increased cardiovascular risk in depression? *Brain Behav Immun.* (2013) 31:189–96. doi: 10.1016/j.bbi.2013.02.001
144. Otte C, Neylan TC, Pole N, Metzler T, Best S, Henn-Haase C, et al. Association between childhood trauma and catecholamine response to psychological stress in police academy recruits. *Biol Psychiatry*. (2005) 57:27–32. doi: 10.1016/j.biopsych.2004.10.009
145. O'Hare C, McCrory C, O'Leary N, O'Brien H, Kenny RA. Childhood trauma and lifetime syncope burden among older adults. *J Psychosom Res.* (2017) 97:63–9. doi: 10.1016/j.jpsychores.2017.03.019
146. Heleniak C, McLaughlin KA, Ormel J, Riese H. Cardiovascular reactivity as a mechanism linking child trauma to adolescent psychopathology. *Biol Psychol.* (2016) 120:108–19. doi: 10.1016/j.biopsycho.2016.08.007
147. Agorastos A, Kellner M, Baker DG, Stiedl O. Diminished vagal and/or increased sympathetic activity in post-traumatic stress disorder. In: Martin C, Preedy VR, Patel VB. *The Comprehensive Guide to Post-Traumatic Stress Disorders*. Berlin Springer. (2015). 1–15 doi: 10.1007/978-3-319-08613-2_30-1
148. De Bellis MD, Chrousos GP, Dorn LD, Burke L, Helmers K, Kling MA, et al. Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. *J Clin Endocrinol Metab.* (1994) 78:249–55.
149. Gordis EB, Granger DA, Susman EJ, Trickett PK. Salivary alpha amylase-cortisol asymmetry in maltreated youth. *Horm Behav.* (2008) 53:96–103. doi: 10.1016/j.yhbeh.2007.09.002
150. Pervanidou P, Kolaitis G, Charitaki S, Margeli A, Ferentinos S, Bakoula C, et al. Elevated morning serum interleukin (IL)-6 or evening salivary cortisol concentrations predict posttraumatic stress disorder in children and adolescents six months after a motor vehicle accident. *Psychoneuroendocrinology*. (2007) 32:991–9. doi: 10.1016/j.psyneuen.2007.07.001
151. Pervanidou P, Kolaitis G, Charitaki S, Lazaropoulou C, Papassotiriou I, Hindmarsh P, et al. The natural history of neuroendocrine changes in pediatric posttraumatic stress disorder (PTSD) after motor vehicle accidents: progressive divergence of noradrenaline and cortisol concentrations over time. *Biol Psychiatry*. (2007) 62:1095–102. doi: 10.1016/j.biopsych.2007.02.008
152. Pervanidou P, Margeli A, Lazaropoulou C, Papassotiriou I, Chrousos GP. The immediate and long-term impact of physical and/or emotional stress from motor vehicle accidents on circulating stress hormones and adipo-cytokines in children and adolescents. *Stress*. (2008) 11:438–47. doi: 10.1080/10253890801890622
153. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med.* (1995) 332:1351–62. doi: 10.1056/NEJM199505183322008
154. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. *Nat Rev Immunol.* (2005) 5:243–51. doi: 10.1038/nri1571

155. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain Behav Immun.* (2007) 21:901–12. doi: 10.1016/j.bbi.2007.03.011
156. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol.* (2017) 17:233–47. doi: 10.1038/nri.2017.1
157. Sternberg EM. Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. *Nat Rev Immunol.* (2006) 6:318–28. doi: 10.1038/nri1810
158. Pace TW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Brain Behav Immun.* (2007) 21:9–19. doi: 10.1016/j.bbi.2006.08.009
159. Pace TW, Heim CM. A short review on the psychoneuroimmunology of posttraumatic stress disorder: from risk factors to medical comorbidities. *Brain Behav Immun.* (2011) 25:6–13. doi: 10.1016/j.bbi.2010.10.003
160. Menard C, Pfau ML, Hodes GE, Russo SJ. Immune and neuroendocrine mechanisms of stress vulnerability and resilience. *Neuropsychopharmacology*. (2017) 42:62–80. doi: 10.1038/npp.2016.90
161. Rohleder N, Karl A. Role of endocrine and inflammatory alterations in comorbid somatic diseases of post-traumatic stress disorder. *Minerva Endocrinol.* (2006) 31:273–88.
162. Gill JM, Saligan L, Woods S, Page G. PTSD is associated with an excess of inflammatory immune activities. *Perspect Psychiatr Care.* (2009) 45:262–77. doi: 10.1111/j.1744-6163.2009.00229.x
163. Hoge EA, Brandstetter K, Moshier S, Pollack MH, Wong KK, Simon NM. Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. *Depress Anxiety*. (2009) 26:447–55. doi: 10.1002/da.20564
164. Chida Y, Sudo N, Sonoda J, Hiramoto T, Kubo C. Early-life psychological stress exacerbates adult mouse asthma via the hypothalamus-pituitary-adrenal axis. *Am J Respir Crit Care Med.* (2007) 175:316–22. doi: 10.1164/rccm.200607-898OC
165. Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. *Proc Natl Acad Sci USA.* (2007) 104:1319–24. doi: 10.1073/pnas.0610362104
166. Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Arch Gen Psychiatry*. (2008) 65:409–15. doi: 10.1001/archpsyc.65.4.409
167. Goshen I, Kreisel T, Ben-Menachem-Zidon O, Licht T, Weidenfeld J, Ben-Hur T, et al. Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. *Mol Psychiatry*. (2008) 13:717–28. doi: 10.1038/sj.mp.4002055
168. Powell ND, Bailey MT, Mays JW, Stiner-Jones LM, Hanke ML, Padgett DA, et al. Repeated social defeat activates dendritic cells and enhances Toll-like receptor dependent cytokine secretion. *Brain Behav Immun.* (2009) 23:225–31. doi: 10.1016/j.bbi.2008.09.010
169. Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. *Neuropsychopharmacology*. (2010) 35:2617–23. doi: 10.1038/npp.2010.159
170. Rooks C, Veledar E, Goldberg J, Bremner JD, Vaccarino V. Early trauma and inflammation: role of familial factors in a study of twins. *Psychosom Med.* (2012) 74:146–52. doi: 10.1097/PSY.0b013e318240a7d8
171. Wei L, Simen A, Mane S, Kaffman A. Early life stress inhibits expression of a novel innate immune pathway in the developing hippocampus. *Neuropsychopharmacology*. (2012) 37:567–80. doi: 10.1038/npp.2011.239
172. Danese A, J Lewis S. Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma? *Neuropsychopharmacology*. (2017) 42:99–114. doi: 10.1038/npp.2016.198
173. Elenkov IJ. Neurohormonal-cytokine interactions: implications for inflammation, common human diseases and well-being. *Neurochem Int.* (2008) 52:40–51. doi: 10.1016/j.neuint.2007.06.037
174. Browning LM, Krebs JD, Jebb SA. Discrimination ratio analysis of inflammatory markers: implications for the study of inflammation in chronic disease. *Metabolism*. (2004) 53:899–903. doi: 10.1016/j.metabol.2004.01.013
175. Smid GE, van Zuiden M, Geuze E, Kavelaars A, Heijnen CJ, Vermetten E. Cytokine production as a putative biological mechanism underlying stress sensitization in high combat exposed soldiers. *Psychoneuroendocrinology*. (2015) 51:534–46. doi: 10.1016/j.psyneuen.2014.07.010
176. Naitoh Y, Fukata J, Tominaga T, Nakai Y, Tamai S, Mori K, et al. Interleukin-6 stimulates the secretion of adrenocorticotropic hormone in conscious, freely-moving rats. *Biochem Biophys Res Commun.* (1988) 155:1459–63. doi: 10.1016/S0006-291X(88)81305-6
177. Vankelecom H, Carmeliet P, Van Damme J, Billiau A, Denef C. Production of interleukin-6 by folliculo-stellate cells of the anterior pituitary gland in a histiotypic cell aggregate culture system. *Neuroendocrinology*. (1989) 49:102–6. doi: 10.1159/000125097
178. Salas MA, Evans SW, Levell MJ, Whicher JT. Interleukin-6 and ACTH act synergistically to stimulate the release of corticosterone from adrenal gland cells. *Clin Exp Immunol.* (1990) 79:470–3. doi: 10.1111/j.1365-2249.1990.tb08114.x
179. Tominaga T, Fukata J, Naito Y, Usui T, Murakami N, Fukushima M, et al. Prostaglandin-dependent *in vitro* stimulation of adrenocortical steroidogenesis by interleukins. *Endocrinology*. (1991) 128:526–31. doi: 10.1210/endo-128-1-526
180. Mastorakos G, Chrousos GP, Weber JS. Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. *J Clin Endocrinol Metab.* (1993) 77:1690–4.
181. Stouthard JM, Romijn JA, Van der Poll T, Endert E, Klein S, Bakker PJ, et al. Endocrinologic and metabolic effects of interleukin-6 in humans. *Am J Physiol.* (1995) 268(5 Pt 1), E813–9. doi: 10.1152/ajpendo.1995.268.5.E813
182. Wilder RL. Neuroendocrine-immune system interactions and autoimmunity. *Annu Rev Immunol.* (1995) 13:307–38. doi: 10.1146/annurev.iy.13.040195.001515
183. Crofford LJ, Kalogeras KT, Mastorakos G, Magiakou MA, Wells J, Kanik KS, et al. Circadian relationships between interleukin (IL)-6 and hypothalamic-pituitary-adrenal axis hormones: failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. *J Clin Endocrinol Metab.* (1997) 82:1279–83. doi: 10.1210/jcem.82.4.3852
184. Girotti M, Donegan JJ, Morilak DA. Influence of hypothalamic IL-6/gp130 receptor signaling on the HPA axis response to chronic stress. *Psychoneuroendocrinology*. (2013) 38:1158–69. doi: 10.1016/j.psyneuen.2012.11.004
185. Papanicolaou DA, Tsigos C, Oldfield EH, Chrousos GP. Acute glucocorticoid deficiency is associated with plasma elevations of interleukin-6: does the latter participate in the symptomatology of the steroid withdrawal syndrome and adrenal insufficiency? *J Clin Endocrinol Metab.* (1996) 81:2303–6. doi: 10.1210/jcem.81.6.8964868
186. Fantidis P, Perez De Prada T, Fernandez-Ortiz A, Carcia-Touchard A, Alfonso F, Sabate M, et al. Morning cortisol production in coronary heart disease patients. *Eur J Clin Invest.* (2002) 32:304–8. doi: 10.1046/j.1365-2362.2002.00988.x
187. Alesci S, Martinez PE, Kelkar S, Ilias I, Ronsaville DS, Listwak SJ, et al. Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. *J Clin Endocrinol Metab.* (2005) 90:2522–30. doi: 10.1210/jc.2004-1667
188. Galbo H, Kall L. Circadian variations in clinical symptoms and concentrations of inflammatory cytokines, melatonin, and cortisol in polymyalgia rheumatica before and during prednisolone treatment: a controlled, observational, clinical experimental study. *Arthritis Res Ther.* (2016) 18:174. doi: 10.1186/s13075-016-1072-4
189. van Gool J, van Vugt H, Helle M, Aarden LA. The relation among stress, adrenalin, interleukin 6 and acute phase proteins in the rat. *Clin Immunol Immunopathol.* (1990) 57:200–10. doi: 10.1016/0090-1229(90)90034-N
190. DeRijk RH, Boelen A, Tilders FJ, Berkenbosch F. Induction of plasma interleukin-6 by circulating adrenaline in the rat. *Psychoneuroendocrinology*. (1994) 19:155–63. doi: 10.1016/0306-4530(94)90005-1
191. Sondergaard SR, Ostrowski K, Ullum H, Pedersen BK. Changes in plasma concentrations of interleukin-6 and interleukin-1 receptor antagonists in response to adrenaline infusion in humans. *Eur J Appl Physiol.* (2000) 83:95–8. doi: 10.1007/s004210000257

192. Judd AM. Cytokine expression in the rat adrenal cortex. *Horm Metab Res.* (1998) 30:404–10. doi: 10.1055/s-2007-978905
193. Engler H, Doenlen R, Riether C, Engler A, Besedovsky HO, Del Rey A, et al. Chemical destruction of brain noradrenergic neurons affects splenic cytokine production. *J Neuroimmunol.* (2010) 219:75–80. doi: 10.1016/j.jneuroim.2009.12.001
194. Hanke ML, Powell ND, Stiner LM, Bailey MT, Sheridan JF. Beta adrenergic blockade decreases the immunomodulatory effects of social disruption stress. *Brain Behav Immun.* (2012) 26:1150–9. doi: 10.1016/j.bbi.2012.07.011
195. Hodes GE, Menard C, Russo SJ. Integrating Interleukin-6 into depression diagnosis and treatment. *Neurobiol Stress.* (2016) 4:15–22. doi: 10.1016/j.ynstr.2016.03.003
196. Pace TW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, et al. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am J Psychiatry.* (2006) 163:1630–3. doi: 10.1176/ajp.2006.163.9.1630
197. Kunz-Ebrecht SR, Mohamed-Ali V, Feldman PJ, Kirschbaum C, Steptoe A. Cortisol responses to mild psychological stress are inversely associated with proinflammatory cytokines. *Brain Behav Immun.* (2003) 17:373–83. doi: 10.1016/S0889-1591(03)00029-1
198. Slopen N, Kubzansky LD, McLaughlin KA, Koenen KC. Childhood adversity and inflammatory processes in youth: a prospective study. *Psychoneuroendocrinology.* (2013) 38:188–200. doi: 10.1016/j.psyneuen.2012.05.013
199. Taylor SE, Lehman BJ, Kiefe CI, Seeman TE. Relationship of early life stress and psychological functioning to adult C-reactive protein in the coronary artery risk development in young adults study. *Biol Psychiatry.* (2006) 60:819–24. doi: 10.1016/j.biopsych.2006.03.016
200. Danese A, Caspi A, Williams B, Ambler A, Sugden K, Mika J, et al. Biological embedding of stress through inflammation processes in childhood. *Mol Psychiatry.* (2011) 16:244–6. doi: 10.1038/mp.2010.5
201. Hepgul N, Pariante CM, Dipasquale S, Diforti M, Taylor H, Marques TR, et al. Childhood maltreatment is associated with increased body mass index and increased C-reactive protein levels in first-episode psychosis patients. *Psychol Med.* (2012) 42:1893–901. doi: 10.1017/S0033291711002947
202. Miller GE, Cole SW. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. *Biol Psychiatry.* (2012) 72:34–40. doi: 10.1016/j.biopsych.2012.02.034
203. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. *Mol Psychiatry.* (2016) 21:642–9. doi: 10.1038/mp.2015.67
204. Matteoli G, Boeckxstaens GE. The vagal innervation of the gut and immune homeostasis. *Gut.* (2013) 62:1214–22. doi: 10.1136/gutjnl-2012-302550
205. Ohira H, Matsunaga M, Osumi T, Fukuyama S, Shinoda J, Yamada J, et al. Vagal nerve activity as a moderator of brain-immune relationships. *J Neuroimmunol.* (2013) 260:28–36. doi: 10.1016/j.jneuroim.2013.04.011
206. Michopoulos V, Powers A, Gillespie CF, Ressler KJ, Jovanovic T. Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. *Neuropsychopharmacology.* (2017) 42:254–70. doi: 10.1038/npp.2016.146
207. Daskalakis NP, Cohen H, Nievergelt CM, Baker DG, Buxbaum JD, Russo SJ, et al. New translational perspectives for blood-based biomarkers of PTSD: From glucocorticoid to immune mediators of stress susceptibility. *Exp Neurol.* (2016) 284(Pt B):133–40. doi: 10.1016/j.expneurol.2016.07.024
208. Engler H, Bailey MT, Engler A, Stiner-Jones LM, Quan N, Sheridan JF. Interleukin-1 receptor type 1-deficient mice fail to develop social stress-associated glucocorticoid resistance in the spleen. *Psychoneuroendocrinology.* (2008) 33:108–17. doi: 10.1016/j.psyneuen.2007.10.007
209. Avitsur R, Powell N, Padgett DA, Sheridan JF. Social interactions, stress, and immunity. *Immunol Allergy Clin North Am.* (2009) 29:285–93. doi: 10.1016/j.iac.2009.02.006
210. Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. *Health Psychol.* (2002) 21:531–41. doi: 10.1037/0278-6133.21.6.531
211. Lindqvist D, Janelidze S, Hagell P, Erhardt S, Samuelsson M, Minthon L, et al. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biol Psychiatry.* (2009) 66:287–92. doi: 10.1016/j.biopsych.2009.01.030
212. Glatt SJ, Tylee DS, Chandler SD, Pazol J, Nievergelt CM, Woelk CH, et al. Blood-based gene-expression predictors of PTSD risk and resilience among deployed marines: a pilot study. *Am J Med Genet B Neuropsychiatr Genet.* (2013) 162B:313–26. doi: 10.1002/ajmg.b.32167
213. Tursich M, Neufeld RW, Frewen PA, Harricharan S, Kibler JL, Rhind SG, et al. Association of trauma exposure with proinflammatory activity: a transdiagnostic meta-analysis. *Transl Psychiatry.* (2014) 4:e413. doi: 10.1038/tp.2014.56
214. Tylee DS, Chandler SD, Nievergelt CM, Liu X, Pazol J, Woelk CH, et al. Blood-based gene-expression biomarkers of post-traumatic stress disorder among deployed marines: a pilot study. *Psychoneuroendocrinology.* (2015) 51:472–94. doi: 10.1016/j.psyneuen.2014.09.024
215. Guardado P, Olivera A, Rusch HL, Roy M, Martin C, Lejbman N, et al. Altered gene expression of the innate immune, neuroendocrine, and nuclear factor-kappa B (NF-kappaB) systems is associated with posttraumatic stress disorder in military personnel. *J Anxiety Disord.* (2016) 38:9–20. doi: 10.1016/j.janxdis.2015.12.004
216. Smith AK, Conneely KN, Kilaru V, Mercer KB, Weiss TE, Bradley B, et al. Differential immune system DNA methylation and cytokine regulation in post-traumatic stress disorder. *Am J Med Genet B Neuropsychiatr Genet.* (2011) 156B:700–8. doi: 10.1002/ajmg.b.31212
217. Zhou J, Nagarkatti P, Zhong Y, Ginsberg JP, Singh NP, Zhang J, et al. Dysregulation in microRNA expression is associated with alterations in immune functions in combat veterans with post-traumatic stress disorder. *PLoS ONE.* (2014) 9:e94075. doi: 10.1371/journal.pone.0094075
218. Bam M, Yang X, Zhou J, Ginsberg JP, Leyden Q, Nagarkatti PS, et al. Evidence for epigenetic regulation of pro-inflammatory cytokines, interleukin-12 and interferon gamma, in peripheral blood mononuclear cells from PTSD patients. *J Neuroimmune Pharmacol.* (2016) 11:168–81. doi: 10.1007/s11481-015-9643-8
219. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci.* (2012) 13:701–12. doi: 10.1038/nrn3346
220. Rook GA, Raison CL, Lowry CA. Microbiota, immunoregulatory old friends and psychiatric disorders. *Adv Exp Med Biol.* (2014) 817:319–56. doi: 10.1007/978-1-4939-0897-4_15
221. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol.* (2015) 28:203–9.
222. Flowers SA, Ellingrod VL. The microbiome in mental health: potential contribution of gut microbiota in disease and pharmacotherapy management. *Pharmacotherapy.* (2015) 35:910–6. doi: 10.1002/phar.1640
223. Malan-Muller S, Valles-Colomer M, Raes J, Lowry CA, Seedat S, Hemmings SMJ. The gut microbiome and mental health: implications for anxiety- and trauma-related disorders. *OMICS.* (2018) 22:90–107. doi: 10.1089/omi.2017.0077
224. Dinan TG, Cryan JF. Regulation of the stress response by the gut microbiota: implications for psychoneuroendocrinology. *Psychoneuroendocrinology.* (2012) 37:1369–78. doi: 10.1016/j.psyneuen.2012.03.007
225. Sekirov I, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. *Physiol Rev.* (2010) 90:859–904. doi: 10.1152/physrev.00045.2009
226. Clarke TB, Davis KM, Lysenko ES, Zhou AY, Yu Y, Weiser JN. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. *Nat Med.* (2010) 16:228–31. doi: 10.1038/nm.2087
227. Arentsen T, Qian Y, Gkotzis S, Femenia T, Wang T, Udekwu K, et al. The bacterial peptidoglycan-sensing molecule Pglyrp2 modulates brain development and behavior. *Mol Psychiatry.* (2017) 22:257–66. doi: 10.1038/mp.2016.182
228. Schafer DP, Stevens B. Microglia function in central nervous system development and plasticity. *Cold Spring Harb Perspect Biol.* (2015) 7:a020545. doi: 10.1101/cshperspect.a020545
229. Rea K, Dinan TG, Cryan JF. The microbiome: a key regulator of stress and neuroinflammation. *Neurobiol Stress.* (2016) 4:23–33. doi: 10.1016/j.ynstr.2016.03.001

230. Galley JD, Bailey MT. Impact of stressor exposure on the interplay between commensal microbiota and host inflammation. *Gut Microbes*. (2014) 5:390–6. doi: 10.4161/gmic.28683
231. Hemmings SMJ, Malan-Muller S, van den Heuvel LL, Demmitt BA, Stanislawski MA, Smith DG, et al. The microbiome in posttraumatic stress disorder and trauma-exposed controls: an exploratory study. *Psychosom Med*. (2017) 79:936–46. doi: 10.1097/PSY.0000000000000512
232. Aoki-Yoshida A, Aoki R, Moriya N, Goto T, Kubota Y, Toyoda A, et al. Omics studies of the murine intestinal ecosystem exposed to subchronic and mild social defeat stress. *J Proteome Res*. (2016) 15:3126–38. doi: 10.1021/acs.jproteome.6b00262
233. Bharwani A, Mian MF, Foster JA, Surette MG, Bienenstock J, Forsythe P. Structural & functional consequences of chronic psychosocial stress on the microbiome & host. *Psychoneuroendocrinology*. (2016) 63:217–27. doi: 10.1016/j.psyneuen.2015.10.001
234. Soderholm JD, Perdue MH. Stress and gastrointestinal tract. II Stress and intestinal barrier function. *Am J Physiol Gastrointest Liver Physiol*. (2001) 280:G7–13. doi: 10.1152/ajpgi.2001.280.1.G7
235. Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Front Cell Neurosci*. (2015) 9:392. doi: 10.3389/fncel.2015.00392
236. Maes M, Kubera M, Leunis JC, Berk M. Increased IgA and IgM responses against gut commensals in chronic depression: further evidence for increased bacterial translocation or leaky gut. *J Affect Disord*. (2012) 141:55–62. doi: 10.1016/j.jad.2012.02.023
237. Carding S, Verbeke K, Vipond DT, Corfe BM, Owen LJ. Dysbiosis of the gut microbiota in disease. *Microb Ecol Health Dis*. (2015) 26:26191. doi: 10.3402/mehd.v26.26191
238. Dinan TG, Cryan JF. The impact of gut microbiota on brain and behaviour: implications for psychiatry. *Curr Opin Clin Nutr Metab Care*. (2015) 18:552–8. doi: 10.1097/MCO.0000000000000221
239. Dinan TG, Cryan JF. Microbes, immunity, and behavior: psychoneuroimmunology meets the microbiome. *Neuropsychopharmacology*. (2017) 42:178–92. doi: 10.1038/npp.2016.103
240. Moussaoui N, Jacobs JP, Larauche M, Biraud M, Million M, Mayer E, et al. Chronic early-life stress in rat pups alters basal corticosterone, intestinal permeability, and fecal microbiota at weaning: influence of sex. *J Neurogastroenterol Motil*. (2017) 23:135–43. doi: 10.5056/jnm16105
241. Borre YE, O'Keeffe GW, Clarke G, Stanton C, Dinan TG, Cryan JF. Microbiota and neurodevelopmental windows: implications for brain disorders. *Trends Mol Med*. (2014) 20:509–18. doi: 10.1016/j.molmed.2014.05.002
242. Bailey MT, Lubach GR, Coe CL. Prenatal stress alters bacterial colonization of the gut in infant monkeys. *J Pediatr Gastroenterol Nutr*. (2004) 38:414–21. doi: 10.1097/00005176-200404000-00009
243. O'Mahony SM, Marchesi JR, Scully P, Codling C, Ceolho AM, Quigley EM, et al. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. *Biol Psychiatry*. (2009) 65:263–7. doi: 10.1016/j.biopsych.2008.06.026
244. Farzi A, Frohlich EE, Holzer P. Gut microbiota and the neuroendocrine system. *Neurotherapeutics*. (2018) 15:5–22. doi: 10.1007/s13311-017-0600-5
245. Diaz Heijtz R, Wang S, Anuar F, Qian Y, Bjorkholm B, Samuelsson A, et al. Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci USA*. (2011) 108:3047–52. doi: 10.1073/pnas.1010529108
246. Doherty FD, O'Mahony SM, Peterson VL, O'Sullivan O, Crispie F, Cotter PD, et al. Post-weaning social isolation of rats leads to long-term disruption of the gut microbiota-immune-brain axis. *Brain Behav Immun*. (2018) 68:261–73. doi: 10.1016/j.bbi.2017.10.024
247. Foster JA, Rinaman L, Cryan JF. Stress & the gut-brain axis: regulation by the microbiome. *Neurobiol Stress*. (2017) 7:124–36. doi: 10.1016/j.ynstr.2017.03.001
248. Petra AI, Panagiotidou S, Hatziagelaki E, Stewart JM, Conti P, Theoharides TC. Gut-microbiota-brain axis and its effect on neuropsychiatric disorders with suspected immune dysregulation. *Clin Ther*. (2015) 37:984–95. doi: 10.1016/j.clinthera.2015.04.002
249. Leclercq S, Forsythe P, Bienenstock J. Posttraumatic stress disorder: does the gut microbiome hold the key? *Can J Psychiatry*. (2016) 61:204–13. doi: 10.1177/0706743716635535
250. Schiavone S, Colaianna M, Curtis L. Impact of early life stress on the pathogenesis of mental disorders: relation to brain oxidative stress. *Curr Pharm Des*. (2015) 21:1404–12. doi: 10.2174/1381612821666150105143358
251. Sahafi E, Peeri M, Hosseini MJ, Azarbyjani MA. Cardiac oxidative stress following maternal separation stress was mitigated following adolescent voluntary exercise in adult male rat. *Physiol Behav*. (2018) 183:39–45. doi: 10.1016/j.physbeh.2017.10.022
252. Reus GZ, Fernandes GC, de Moura AB, Silva RH, Darabas AC, de Souza TG, et al. Early life experience contributes to the developmental programming of depressive-like behaviour, neuroinflammation and oxidative stress. *J Psychiatr Res*. (2017) 95:196–207. doi: 10.1016/j.jpsychires.2017.08.020
253. do Prado CH, Grassi-Oliveira R, Wieck A, Zaparte A, Filho LD, da Silva Morrone, M., et al. The impact of childhood maltreatment on redox state: Relationship with oxidative damage and antioxidant defenses in adolescents with no psychiatric disorder. *Neurosci Lett*. (2016). 617:173–7. doi: 10.1016/j.neulet.2016.01.062
254. Marasco V, Spencer KA, Robinson J, Herzyk P, Costantini D. Developmental post-natal stress can alter the effects of pre-natal stress on the adult redox balance. *Gen Comp Endocrinol*. (2013) 191:239–46. doi: 10.1016/j.ygcen.2013.07.003
255. Miller MW, Lin AP, Wolf EJ, Miller DR. Oxidative Stress, Inflammation, and Neuroprogression in Chronic PTSD. *Harv Rev Psychiatry*. (2018) 26:57–69. doi: 10.1097/HRP.0000000000000167
256. Shalev I, Entringer S, Wadhwa PD, Wolkowitz OM, Puterman E, Lin J, et al. Stress and telomere biology: a lifespan perspective. *Psychoneuroendocrinology*. (2013) 38:1835–42. doi: 10.1016/j.psyneuen.2013.03.010
257. O'Donovan A, Epel E, Lin J, Wolkowitz O, Cohen B, Maguen S, et al. Childhood trauma associated with short leukocyte telomere length in posttraumatic stress disorder. *Biol Psychiatry*. (2011) 70:465–71. doi: 10.1016/j.biopsych.2011.01.035
258. Price LH, Kao HT, Burgers DE, Carpenter LL, Tyrka AR. Telomeres and early-life stress: an overview. *Biol Psychiatry*. (2013) 73:15–23. doi: 10.1016/j.biopsych.2012.06.025
259. Jergovic M, Tomicevic M, Vidovic A, Bendelja K, Savic A, Vojvoda V, et al. Telomere shortening and immune activity in war veterans with posttraumatic stress disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. (2014) 54:275–83. doi: 10.1016/j.pnpbp.2014.06.010
260. Zhang L, Hu XZ, Benedek DM, Fullerton CS, Forsten RD, Naifeh JA, et al. The interaction between stressful life events and leukocyte telomere length is associated with PTSD. *Mol Psychiatry*. (2014) 19:855–6. doi: 10.1038/mp.2013.141
261. Tyrka AR, Price LH, Kao HT, Porton B, Marsella SA, Carpenter LL. Childhood maltreatment and telomere shortening: preliminary support for an effect of early stress on cellular aging. *Biol Psychiatry*. (2010) 67:531–4. doi: 10.1016/j.biopsych.2009.08.014
262. Shalev I, Moffitt TE, Sugden K, Williams B, Houts RM, Danese A, et al. Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study. *Mol Psychiatry*. (2013) 18:576–81. doi: 10.1038/mp.2012.32
263. Chen SH, Epel ES, Mellon SH, Lin J, Reus VI, Rosser R, et al. Adverse childhood experiences and leukocyte telomere maintenance in depressed and healthy adults. *J Affect Disord*. (2014) 169:86–90. doi: 10.1016/j.jad.2014.07.035
264. Mitchell C, McLanahan S, Schneper L, Garfinkel I, Brooks-Gunn J, Notterman D. Father loss and child telomere length. *Pediatrics*. (2017) 140:e20163245. doi: 10.1542/peds.2016-3245
265. Hanssen LM, Schutte NS, Malouff JM, Epel ES. The relationship between childhood psychosocial stressor level and telomere length: a meta-analysis. *Health Psychol Res*. (2017) 5:6378. doi: 10.4081/hpr.2017.6378
266. Li Z, He Y, Wang D, Tang J, Chen X. Association between childhood trauma and accelerated telomere erosion in adulthood: a meta-analytic study. *J Psychiatr Res*. (2017) 93:64–71. doi: 10.1016/j.jpsychires.2017.06.002

267. Alastalo H, Raikkonen K, Pesonen AK, Osmond C, Barker DJ, Heinonen K, et al. Cardiovascular morbidity and mortality in Finnish men and women separated temporarily from their parents in childhood–a life course study. *Psychosom Med.* (2012) 74:583–7. doi: 10.1097/PSY.0b013e31825b3d76
268. Wilson RS, Boyle PA, Levine SR, Yu L, Anagnos SE, Buchman AS, et al. Emotional neglect in childhood and cerebral infarction in older age. *Neurology*. (2012) 79:1534–9. doi: 10.1212/WNL.0b013e31826e25bd
269. Loria AS, Ho DH, Pollock JS. A mechanistic look at the effects of adversity early in life on cardiovascular disease risk during adulthood. *Acta Physiol.* (2014) 210:277–87. doi: 10.1111/apha.12189
270. McCrory C, Dooley C, Layte R, Kenny RA. The lasting legacy of childhood adversity for disease risk in later life. *Health Psychol.* (2015) 34:687–96. doi: 10.1037/hea0000147
271. Su S, Jimenez MP, Roberts CT, Loucks EB. The role of adverse childhood experiences in cardiovascular disease risk: a review with emphasis on plausible mechanisms. *Curr Cardiol Rep.* (2015) 17:88. doi: 10.1007/s11886-015-0645-1
272. Murphy MO, Cohn DM, Loria AS. (2017). Developmental origins of cardiovascular disease: Impact of early life stress in humans and rodents. *Neurosci Biobehav Rev*. 74(Pt B):453–65. doi: 10.1016/j.neubiorev.2016.07.018
273. Garad Y, Maximova K, MacKinnon N, McGrath JJ, Kozyrskyj AL, Colman I. Sex-specific differences in the association between childhood adversity and cardiovascular disease in adulthood: evidence from a national cohort study. *Can J Cardiol.* (2017) 33:1013–9. doi: 10.1016/j.cjca.2017.05.008
274. Suglia SF, Koenen KC, Boynton-Jarrett R, Chan PS, Clark CJ, Danese A, et al. Childhood and adolescent adversity and cardiometabolic outcomes: a scientific statement from the American heart association. *Circulation*. (2018) 137:e15–28. doi: 10.1161/CIR.0000000000000536
275. Ho DH, Burch ML, Musall B, Musall JB, Hyndman KA, Pollock JS. Early life stress in male mice induces superoxide production and endothelial dysfunction in adulthood. *Am J Physiol Heart Circ Physiol.* (2016) 310:H1267–74. doi: 10.1152/ajpheart.00016.2016
276. Loria AS, Kang KT, Pollock DM, Pollock JS. Early life stress enhances angiotensin II-mediated vasoconstriction by reduced endothelial nitric oxide buffering capacity. *Hypertension*. (2011) 58:619–26. doi: 10.1161/HYPERTENSIONAHA.110.168674
277. Dallman MF, Strack AM, Akana SF, Bradbury MJ, Hanson ES, Scribner KA, et al. Feast and famine: critical role of glucocorticoids with insulin in daily energy flow. *Front Neuroendocrinol.* (1993) 14:303–47. doi: 10.1006/frne.1993.1010
278. Stephens TW, Basinski M, Bristow PK, Bue-Valleskey JM, Burgett SG, Craft L, et al. The role of neuropeptide Y in the antiobesity action of the obese gene product. *Nature*. (1995) 377:530–2. doi: 10.1038/377530a0
279. Figlewicz DP. Adiposity signals and food reward: expanding the CNS roles of insulin and leptin. *Am J Physiol Regul Integr Comp Physiol.* (2003) 284:R882–92. doi: 10.1152/ajpregu.00602.2002
280. Askari H, Liu J, Dagogo-Jack S. Energy adaptation to glucocorticoid-induced hyperleptinemia in human beings. *Metabolism*. (2005) 54:876–80. doi: 10.1016/j.metabol.2005.01.035
281. Pervanidou P, Chrousos GP. Post-traumatic stress disorder in children and adolescents: from Sigmund Freud's "trauma" to psychopathology and the (Dys)metabolic syndrome. *Horm Metab Res.* (2007) 39:413–9. doi: 10.1055/s-2007-981461
282. Pervanidou P, Chrousos GP. Metabolic consequences of stress during childhood and adolescence. *Metabolism*. (2012) 61:611–9. doi: 10.1016/j.metabol.2011.10.005
283. Mutlu H, Bilgic V, Erten S, Aras S, Tayfur M. Evaluation of the relationship between childhood traumas and adulthood obesity development. *Ecol Food Nutr.* (2016) 55:390–401. doi: 10.1080/03670244.2016.1198791
284. van Reedt Dortland AK, Giltay EJ, van Veen T, Zitman FG, Penninx BW. Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use. *Acta Psychiatr Scand.* (2010) 122:30–9. doi: 10.1111/j.1600-0447.2010.01565.x
285. van Reedt Dortland AK, Giltay EJ, van Veen T, Zitman FG, Penninx BW. Personality traits and childhood trauma as correlates of metabolic risk factors: the Netherlands Study of Depression and Anxiety (NESDA). *Prog Neuropsychopharmacol Biol Psychiatry*. (2012) 36:85–91. doi: 10.1016/j.pnpbp.2011.10.001
286. Hollingsworth K, Callaway L, Duhig M, Matheson S, Scott J. The association between maltreatment in childhood and pre-pregnancy obesity in women attending an antenatal clinic in Australia. *PLoS ONE*. (2012) 7:e51868. doi: 10.1371/journal.pone.0051868
287. Li L, Chassan RA, Bruer EH, Gower BA, Shelton RC. Childhood maltreatment increases the risk for visceral obesity. *Obesity*. (2015) 23:1625–32. doi: 10.1002/oby.21143
288. Wang Y, Wu B, Yang H, Song X. The effect of childhood abuse on the risk of adult obesity. *Ann Clin Psychiatry*. (2015) 27:175–84.
289. Spann SJ, Gillespie CF, Davis JS, Brown A, Schwartz A, Wingo A, et al. The association between childhood trauma and lipid levels in an adult low-income, minority population. *Gen Hosp Psychiatry*. (2014) 36:150–5. doi: 10.1016/j.genhosppsych.2013.10.004
290. Misiak B, Kiejna A, Frydecka D. The history of childhood trauma is associated with lipid disturbances and blood pressure in adult first-episode schizophrenia patients. *Gen Hosp Psychiatry*. (2015) 37:365–7. doi: 10.1016/j.genhosppsych.2015.03.017
291. Li L, Garvey WT, Gower BA. Childhood maltreatment is an independent risk factor for prediabetic disturbances in glucose regulation. *Front Endocrinol.* (2017) 8:151. doi: 10.3389/fendo.2017.00151
292. Machado TD, Salum GA, Bosa VL, Goldani MZ, Meaney MJ, Agranonik M, et al. Early life trauma is associated with decreased peripheral levels of thyroid-hormone T3 in adolescents. *Int J Dev Neurosci.* (2015) 47:304–8. doi: 10.1016/j.ijdevneu.2015.10.005
293. Michopoulos V, Powers A, Moore C, Villarreal S, Ressler KJ, Bradley B. The mediating role of emotion dysregulation and depression on the relationship between childhood trauma exposure and emotional eating. *Appetite*. (2015) 91:129–36. doi: 10.1016/j.appet.2015.03.036
294. Midei AJ, Matthews KA, Bromberger JT. Childhood abuse is associated with adiposity in midlife women: possible pathways through trait anger and reproductive hormones. *Psychosom Med.* (2010) 72:215–23. doi: 10.1097/PSY.0b013e3181cb5c24
295. Lee C, Tsenkova V, Carr D. Childhood trauma and metabolic syndrome in men and women. *Soc Sci Med*. (2014) 105:122–30. doi: 10.1016/j.socscimed.2014.01.017
296. Delpierre C, Fantin R, Barboza-Solis C, Lepage B, Darnaudery M, Kelly-Irving M. The early life nutritional environment and early life stress as potential pathways towards the metabolic syndrome in mid-life? A lifecourse analysis using the 1958 British birth cohort. *BMC Public Health*. (2016) 16:815. doi: 10.1186/s12889-016-3484-0
297. Maniam J, Antoniadis C, Morris MJ. Early-life stress, HPA axis adaptation, and mechanisms contributing to later health outcomes. *Front Endocrinol.* (2014) 5:73. doi: 10.3389/fendo.2014.00073
298. Suarez A, Lahti J, Kajantie E, Eriksson JG, Raikkonen K. Early life stress, FKBP5 polymorphisms, and quantitative glycemic traits. *Psychosom Med.* (2017) 79:524–32. doi: 10.1097/PSY.0000000000000439
299. Bernardi JR, Ferreira CF, Senter G, Krolow R, de Aguiar BW, Portella AK, et al. Early life stress interacts with the diet deficiency of omega-3 fatty acids during the life course increasing the metabolic vulnerability in adult rats. *PLoS ONE*. (2013) 8:e62031. doi: 10.1371/journal.pone.0062031
300. Yam KY, Naninck EFG, Abbink MR, la Fleur SE, Schipper L, van den Beukel JC, et al. Exposure to chronic early-life stress lastingly alters the adipose tissue, the leptin system and changes the vulnerability to western-style diet later in life in mice. *Psychoneuroendocrinology*. (2017) 77:186–95. doi: 10.1016/j.psyneuen.2016.12.012
301. Mantzoros CS, Magkos F, Brinkoetter M, Sienkiewicz E, Dardeno TA, Kim SY, et al. Leptin in human physiology and pathophysiology. *Am J Physiol Endocrinol Metab.* (2011) 301:E567–84. doi: 10.1152/ajpendo.00315.2011
302. Licinio J, Mantzoros C, Negrao AB, Cizza G, Wong ML, Bongiorno PB, et al. Human leptin levels are pulsatile and inversely related to pituitary-adrenal function. *Nat Med.* (1997) 3:575–9. doi: 10.1038/nm0597-575

303. Ahima RS, Qi Y, Singhal NS. Adipokines that link obesity and diabetes to the hypothalamus. *Prog Brain Res.* (2006) 153:155–74. doi: 10.1016/S0079-6123(06)53009-2
304. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun.* (1999) 257:79–83. doi: 10.1006/bbrc.1999.0255
305. Kynde I, Heitmann BL, Bygbjerg IC, Andersen LB, Helge JW. Hypoadiponectinemia in overweight children contributes to a negative metabolic risk profile 6 years later. *Metabolism*. (2009) 58:1817–24. doi: 10.1016/j.metabol.2009.06.014
306. Gauglitz GG, Herndon DN, Kulp GA, Meyer WJ 3rd, Jeschke MG. Abnormal insulin sensitivity persists up to three years in pediatric patients post-burn. *J Clin Endocrinol Metab.* (2009) 94:1656–64. doi: 10.1210/jc.2008-1947
307. Saper CB. The central circadian timing system. *Curr Opin Neurobiol.* (2013) 23:747–51. doi: 10.1016/j.conb.2013.04.004
308. Dickmeis T. Glucocorticoids and the circadian clock. *J Endocrinol.* (2009) 200:3–22. doi: 10.1677/JOE-08-0415
309. Gan EH, Quinton R. Physiological significance of the rhythmic secretion of hypothalamic and pituitary hormones. *Prog Brain Res.* (2010) 181:111–26. doi: 10.1016/S0079-6123(08)81007-2
310. Nader N, Chrousos GP, Kino T. Interactions of the circadian CLOCK system and the HPA axis. *Trends Endocrinol Metab.* (2010) 21:277–86. doi: 10.1016/j.tem.2009.12.011
311. Qian X, Droste SK, Lightman SL, Reul JMHM, Linthorst ACE. Circadian and ultradian rhythms of free glucocorticoid hormone are highly synchronized between the blood, the subcutaneous tissue, and the brain. *Endocrinology*. (2012) 153:4346–53. doi: 10.1210/en.2012-1484
312. Oster H, Damerow S, Kiessling S, Jakubcakova V, Abraham D, Tian J, et al. The circadian rhythm of glucocorticoids is regulated by a gating mechanism residing in the adrenal cortical clock. *Cell Metab.* (2006) 4:163–73. doi: 10.1016/j.cmet.2006.07.002
313. Wu YH, Zhou JN, Balesar R, Unmehopa U, Bao A, Jockers R, et al. Distribution of MT1 melatonin receptor immunoreactivity in the human hypothalamus and pituitary gland: colocalization of MT1 with vasopressin, oxytocin, and corticotropin-releasing hormone. *J Comp Neurol.* (2006) 499:897–910. doi: 10.1002/cne.21152
314. Clow A, Hucklebridge F, Stalder T, Evans P, Thorn L. The cortisol awakening response: more than a measure of HPA axis function. *Neurosci Biobehav Rev.* (2010) 35:97–103. doi: 10.1016/j.neubiorev.2009.12.011
315. Chrousos GP, Kino T. Glucocorticoid signaling in the cell. Expanding clinical implications to complex human behavioral and somatic disorders. *Ann NY Acad Sci.* (2009) 1179:153–66. doi: 10.1111/j.1749-6632.2009.04988.x
316. Charmandari E, Chrousos GP, Lambrou GI, Pavlaki A, Koide H, Ng SS, et al. Peripheral CLOCK regulates target-tissue glucocorticoid receptor transcriptional activity in a circadian fashion in man. *PLoS ONE*. (2011) 6:e25612. doi: 10.1371/journal.pone.0025612
317. Valenzuela FJ, Torres-Farfan C, Richter HG, Mendez N, Campino C, Torrealba F, et al. Clock gene expression in adult primate suprachiasmatic nuclei and adrenal: is the adrenal a peripheral clock responsive to melatonin? *Endocrinology*. (2008) 149:1454–61. doi: 10.1210/en.2007-1518
318. Torres-Farfan C, Mendez N, Abarzua-Catalan L, Vilches N, Valenzuela GJ, Seron-Ferre M. A circadian clock entrained by melatonin is ticking in the rat fetal adrenal. *Endocrinology*. (2011) 152:1891–900. doi: 10.1210/en.2010-1260
319. Vandewalle G, Middleton B, Rajaratnam SM, Stone BM, Thorleifsdottir B, Arendt J, et al. Robust circadian rhythm in heart rate and its variability: influence of exogenous melatonin and photoperiod. *J Sleep Res.* (2007) 16:148–55. doi: 10.1111/j.1365-2869.2007.00581.x
320. Kalsbeek A, Yi CX, la Fleur SE, Buijs RM, Fliers E. Suprachiasmatic nucleus and autonomic nervous system influences on awakening from sleep. *Int Rev Neurobiol.* (2010) 93:91–107. doi: 10.1016/S0074-7742(10)93004-3
321. Portaluppi F, Tiseo R, Smolensky MH, Hermida RC, Ayala DE, Fabbian F. Circadian rhythms and cardiovascular health. *Sleep Med Rev.* (2012) 16:151–66. doi: 10.1016/j.smrv.2011.04.003
322. Gerstner JR, Lyons LC, Wright KP Jr, Loh DH, Rawashdeh O, Eckel-Mahan KL, et al. Cycling behavior and memory formation. *J Neurosci.* (2009) 29:12824–30. doi: 10.1523/JNEUROSCI.3353-09.2009
323. Gerstner JR, Yin JC. Circadian rhythms and memory formation. *Nat Rev Neurosci.* (2010) 11:577–88. doi: 10.1038/nrn2881
324. Ruby NF, Hwang CE, Wessells C, Fernandez F, Zhang P, Sapolsky R, et al. Hippocampal-dependent learning requires a functional circadian system. *Proc Natl Acad Sci USA.* (2008) 105:15593–8. doi: 10.1073/pnas.0808259105
325. Albrecht U. The circadian clock, reward, and memory. *Front Mol Neurosci.* (2011) 4:41. doi: 10.3389/fnmol.2011.00041
326. Zisapel N. Sleep and sleep disturbances: biological basis and clinical implications. *Cell Mol Life Sci.* (2007) 64:1174–86. doi: 10.1007/s00018-007-6529-9
327. Richardson GS. The human circadian system in normal and disordered sleep. *J Clin Psychiatry*. (2005) 66(Suppl 9):3–9; quiz 42–43.
328. Morris CJ, Aeschbach D, Scheer FAJL. Circadian system, sleep and endocrinology. *Mol Cell Endocrinol.* (2012) 349:91–104. doi: 10.1016/j.mce.2011.09.003
329. Erren TC, Reiter RJ. Defining chronodisruption. *J Pineal Res.* (2009) 46:245–7. doi: 10.1111/j.1600-079X.2009.00665.x
330. Erren TC, Reiter RJ. Revisiting chronodisruption: when the physiological nexus between internal and external times splits in humans. *Naturwissenschaften*. (2013) 100:291–8. doi: 10.1007/s00114-013-1026-5
331. Zelinski EL, Deibel SH, McDonald RJ. The trouble with circadian clock dysfunction: Multiple deleterious effects on the brain and body. *Neurosci Biobehav Rev.* (2014) 24:80–101. doi: 10.1016/j.neubiorev.2014.01.007
332. Mrdalj J, Pallesen S, Milde AM, Jellestad FK, Murison R, Ursin R, et al. Early and later life stress alter brain activity and sleep in rats. *PLoS ONE.* (2013) 8:e69923. doi: 10.1371/journal.pone.0069923
333. Bader K, Schafer V, Schenkel M, Nissen L, Schwander J. Adverse childhood experiences associated with sleep in primary insomnia. *J Sleep Res.* (2007) 16:285–96. doi: 10.1111/j.1365-2869.2007.00608.x
334. Koskenvuo K, Hublin C, Partinen M, Paunio T, Koskenvuo M. Childhood adversities and quality of sleep in adulthood: a population-based study of 26,000 Finns. *Sleep Med.* (2010) 11:17–22. doi: 10.1016/j.sleep.2009.03.010
335. Greenfield EA, Lee C, Friedman EL, Springer KW. Childhood abuse as a risk factor for sleep problems in adulthood: evidence from a U.S. national study. *Ann Behav Med.* (2011) 42:245–56. doi: 10.1007/s12160-011-9285-x
336. Schafer V, Bader K. Relationship between early-life stress load and sleep in psychiatric outpatients: a sleep diary and actigraphy study. *Stress Health*. (2013) 29:177–89. doi: 10.1002/smi.2438
337. Baiden P, Fallon B, den Dunnen W, Boateng GO. The enduring effects of early-childhood adversities and troubled sleep among Canadian adults: a population-based study. *Sleep Med.* (2015) 16:760–7. doi: 10.1016/j.sleep.2015.02.527
338. Kajeepeta S, Gelaye B, Jackson CL, Williams MA. Adverse childhood experiences are associated with adult sleep disorders: a systematic review. *Sleep Med.* (2015) 16:320–30. doi: 10.1016/j.sleep.2014.12.013
339. Lind MJ, Aggen SH, Kendler KS, York TP, Amstadter AB. An epidemiologic study of childhood sexual abuse and adult sleep disturbances. *Psychol Trauma*. (2016) 8:198–205. doi: 10.1037/tra0000080
340. Petrov ME, Davis MC, Belyea MJ, Zautra AJ. Linking childhood abuse and hypertension: sleep disturbance and inflammation as mediators. *J Behav Med.* (2016) 39:716–26. doi: 10.1007/s10865-016-9742-x
341. Taylor DJ, Pruiksma KE, Hale WJ, Kelly K, Maurer D, Peterson AL, et al. Prevalence, correlates, and predictors of insomnia in the US army prior to deployment. *Sleep*. (2016) 39:1795–806. doi: 10.5665/sleep.6156
342. Thordardottir EB, Hansdottir I, Valdimarsdottir UA, Shipherd JC, Resnick H, Gudmundsdottir B. The manifestations of *sleep* disturbances 16 years post-trauma. *Sleep*. (2016) 39:1551–4. doi: 10.5665/sleep.6018
343. Wang Y, Raffeld MR, Slopen N, Hale L, Dunn EC. Childhood adversity and insomnia in adolescence. *Sleep Med.* (2016) 21:12–8. doi: 10.1016/j.sleep.2016.01.011
344. Steine IM, Winje D, Krystal JH, Bjorvatn B, Milde AM, Gronli J, et al. Cumulative childhood maltreatment and its dose-response relation with adult symptomatology: findings in a sample of adult survivors of sexual abuse. *Child Abuse Negl.* (2017) 65:99–111. doi: 10.1016/j.chiabu.2017.01.008
345. Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, et al. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J Clin Endocrinol Metab.* (2001) 86:3787–94. doi: 10.1210/jcem.86.8.7778

346. Backhaus J, Junghanns K, Hohagen F. Sleep disturbances are correlated with decreased morning awakening salivary cortisol. *Psychoneuroendocrinology*. (2004) 29:1184–91. doi: 10.1016/j.psyneuen.2004.01.010
347. Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Med Rev.* (2008) 12:197–210. doi: 10.1016/j.smrv.2007.07.007
348. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. *Prog Cardiovasc Dis.* (2009) 51:294–302. doi: 10.1016/j.pcad.2008.10.003
349. Ruger M, Scheer FA. Effects of circadian disruption on the cardiometabolic system. *Rev Endocr Metab Disord.* (2009) 10:245–60. doi: 10.1007/s11154-009-9122-8
350. Taki Y, Hashizume H, Thyreau B, Sassa Y, Takeuchi H, Wu K, et al. Sleep duration during weekdays affects hippocampal gray matter volume in healthy children. *Neuroimage*. (2012) 60:471–5. doi: 10.1016/j.neuroimage.2011.11.072
351. Killgore WD. Self-reported sleep correlates with prefrontal-amygdala functional connectivity and emotional functioning. *Sleep*. (2013) 36:1597–608. doi: 10.5665/sleep.3106
352. Motomura Y, Kitamura S, Oba K, Terasawa Y, Enomoto M, Katayose Y, et al. Sleep debt elicits negative emotional reaction through diminished amygdala-anterior cingulate functional connectivity. *PLoS ONE*. (2013) 8:e56578. doi: 10.1371/journal.pone.0056578
353. Ackermann K, Plomp R, Lao O, Middleton B, Revell VL, Skene DJ, et al. Effect of sleep deprivation on rhythms of clock gene expression and melatonin in humans. *Chronobiol Int.* (2013) 30:901–9. doi: 10.3109/07420528.2013.784773
354. Moller-Levet CS, Archer SN, Bucca G, Laing EE, Slak A, Kabiljo R, et al. Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome. *Proc Natl Acad Sci USA*. (2013) 110:E1132–41. doi: 10.1073/pnas.1217154110
355. Weibel L, Maccari S, Van Reeth O. Circadian clock functioning is linked to acute stress reactivity in rats. *J Biol Rhythms*. (2002) 17:438–46. doi: 10.1177/074873002237138
356. Gogenur I, Ocak U, Altunpinar O, Middleton B, Skene DJ, Rosenberg J. Disturbances in melatonin, cortisol and core body temperature rhythms after major surgery. *World J Surg.* (2007) 31:290–8. doi: 10.1007/s00268-006-0256-5
357. Paredes SD, Sanchez S, Parvez H, Rodriguez AB, Barriga C. Altered circadian rhythms of corticosterone, melatonin, and phagocytic activity in response to stress in rats. *Neuro Endocrinol Lett.* (2007) 28:489–95.
358. Couto-Moraes R, Palermo-Neto J, Markus RP. The immune-pineal axis: stress as a modulator of pineal gland function. *Ann NY Acad Sci.* (2009) 1153:193–202. doi: 10.1111/j.1749-6632.2008.03978.x
359. Pina G, Brun J, Tissot S, Claustrat B. Long-term alteration of daily melatonin, 6-sulfatoxymelatonin, cortisol, and temperature profiles in burn patients: a preliminary report. *Chronobiol Int.* (2010) 27:378–92. doi: 10.3109/07420520903502234
360. Christiansen S, Bouzinova EV, Palme R, Wiborg O. Circadian activity of the hypothalamic-pituitary-adrenal axis is differentially affected in the rat chronic mild stress model of depression *Stress*. (2012) 15:647–57. doi: 10.3109/10253890.2011.654370
361. Koresh O, Kozlovsky N, Kaplan Z, Zohar J, Matar MA, Cohen H. The long-term abnormalities in circadian expression of Period 1 and Period 2 genes in response to stress is normalized by agomelatine administered immediately after exposure. *Eur Neuropsychopharmacol.* (2012) 22:205–21. doi: 10.1016/j.euroneuro.2011.07.012
362. Takahashi K, Yamada T, Tsukita S, Kaneko K, Shirai Y, Munakata Y, et al. Chronic mild stress alters circadian expressions of molecular clock genes in the liver. *Am J Physiol Endocrinol Metab.* (2013) 304:E301–9. doi: 10.1152/ajpendo.00388.2012
363. Weber GF, Johnson BN, Yamamoto BK, Gudelsky GA. Effects of stress and MDMA on hippocampal gene expression. *Biomed Res Int.* (2014) 2014:141396. doi: 10.1155/2014/141396
364. Lavie P. Sleep disturbances in the wake of traumatic events. *N Engl J Med.* (2001) 345:1825–32. doi: 10.1056/NEJMra012893
365. Touma C, Fenzl T, Ruschel J, Palme R, Holsboer F, Kimura M, et al. Rhythmicity in mice selected for extremes in stress reactivity: behavioural, endocrine and sleep changes resembling endophenotypes of major depression. *PLoS ONE*. (2009) 4:e4325. doi: 10.1371/journal.pone.0004325
366. Philbert J, Pichat P, Beeske S, Decobert M, Belzung C, Griebel G. Acute inescapable stress exposure induces long-term sleep disturbances and avoidance behavior: a mouse model of post-traumatic stress disorder (PTSD). *Behav Brain Res.* (2011) 221:149–54. doi: 10.1016/j.bbr.2011.02.039
367. Germain A. Sleep disturbances as the hallmark of PTSD: where are we now? *Am J Psychiatry*. (2013) 170:372–82. doi: 10.1176/appi.ajp.2012.12040432
368. Mellman TA, Bustamante V, Fins AI, Pigeon WR, Nolan B. REM sleep and the early development of posttraumatic stress disorder. *Am J Psychiatry*. (2002) 159:1696–701. doi: 10.1176/appi.ajp.159.10.1696
369. Mellman TA, Knorr BR, Pigeon WR, Leiter JC, Akay M. Heart rate variability during sleep and the early development of posttraumatic stress disorder. *Biol Psychiatry*. (2004) 55:953–6. doi: 10.1016/j.biopsych.2003.12.018
370. Mellman TA, Hipolito MM. Sleep disturbances in the aftermath of trauma and posttraumatic stress disorder. *CNS Spectr.* (2006) 11:611–5. doi: 10.1017/S1092852900013663
371. Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep–a prefrontal amygdala disconnect. *Curr Biol.* (2007) 17:R877–8. doi: 10.1016/j.cub.2007.08.007
372. Hagewoud R, Whitcomb SN, Heeringa AN, Havekes R, Koolhaas JM, Meerlo P. A time for learning and a time for sleep: the effect of sleep deprivation on contextual fear conditioning at different times of the day. *Sleep*. (2010) 33:1315–22. doi: 10.1093/sleep/33.10.1315
373. Menz MM, Rihm JS, Salari N, Born J, Kalisch R, Pape HC, et al. The role of sleep and sleep deprivation in consolidating fear memories. *Neuroimage*. (2013) 75:87–96. doi: 10.1016/j.neuroimage.2013.03.001
374. Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. *Sleep Med Rev*. (2008) 12:185–95. doi: 10.1016/j.smrv.2007.09.003
375. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? *Sleep Med Rev.* (2008) 12:169–84. doi: 10.1016/j.smrv.2007.08.008
376. Agorastos A, Kellner M, Baker DG, Otte C. When time stands still. An integrative review on the role of chronodisruption in PTSD. *Curr Opin Psychiatry*. (2014) 27:385–92. doi: 10.1097/YCO.0000000000000079
377. Skelton K, Ressler KJ, Norrholm SD, Jovanovic T, Bradley-Davino B. PTSD and gene variants: new pathways and new thinking. *Neuropharmacology*. (2012) 62:628–37. doi: 10.1016/j.neuropharm.2011.02.013
378. Malan-Muller S, Seedat S, Hemmings SM. Understanding posttraumatic stress disorder: insights from the methylome. *Genes Brain Behav.* (2014) 13:52–68. doi: 10.1111/gbb.12102
379. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, et al. Role of genotype in the cycle of violence in maltreated children. *Science*. (2002) 297:851–4. doi: 10.1126/science.1072290
380. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. (2003) 301:386–9. doi: 10.1126/science.1083968
381. Karg K, Burmeister M, Shedden K, Sen S. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Arch Gen Psychiatry*. (2011) 68:444–54. doi: 10.1001/archgenpsychiatry.2010.189
382. Stein MB, Schork NJ, Gelernter J. Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders. *Neuropsychopharmacology*. (2008) 33:312–9. doi: 10.1038/sj.npp.1301422
383. Gillespie CF, Phifer J, Bradley B, Ressler KJ. Risk and resilience: genetic and environmental influences on development of the stress response. *Depress Anxiety*. (2009) 26:984–92. doi: 10.1002/da.20605
384. Hauger RL, Olivares-Reyes JA, Dautzenberg FM, Lohr JB, Braun S, Oakley RH. Molecular and cell signaling targets for PTSD pathophysiology

and pharmacotherapy. *Neuropharmacology*. (2012) 62:705–14. doi: 10.1016/j.neuropharm.2011.11.007
385. Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA*. (2008) 299:1291–305. doi: 10.1001/jama.299.11.1291
386. Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci*. (2013) 16:33–41. doi: 10.1038/nn.3275
387. Bevilacqua L, Carli V, Sarchiapone M, George DK, Goldman D, Roy A, et al. Interaction between FKBP5 and childhood trauma and risk of aggressive behavior. *Arch Gen Psychiatry*. (2012) 69:62–70. doi: 10.1001/archgenpsychiatry.2011.152
388. Roy A, Gorodetsky E, Yuan Q, Goldman D, Enoch MA. Interaction of FKBP5, a stress-related gene, with childhood trauma increases the risk for attempting suicide. *Neuropsychopharmacology*. (2010) 35:1674–83. doi: 10.1038/npp.2009.236
389. Zimmermann P, Bruckl T, Nocon A, Pfister H, Binder EB, Uhr M, et al. Interaction of FKBP5 gene variants and adverse life events in predicting depression onset: results from a 10-year prospective community study. *Am J Psychiatry*. (2011) 168:1107–16. doi: 10.1176/appi.ajp.2011.10111577
390. Bradley RG, Binder EB, Epstein MP, Tang Y, Nair HP, Liu W, et al. Influence of child abuse on adult depression: moderation by the corticotropin-releasing hormone receptor gene. *Arch Gen Psychiatry*. (2008) 65:190–200. doi: 10.1001/archgenpsychiatry.2007.26
391. Heim C, Bradley B, Mletzko TC, Deveau TC, Musselman DL, Nemeroff CB, et al. Effect of childhood trauma on adult depression and neuroendocrine function: sex-specific moderation by CRH receptor 1 gene. *Front Behav Neurosci*. (2009) 3:41. doi: 10.3389/neuro.08.041.2009
392. Ben-Efraim YJ, Wasserman D, Wasserman J, Sokolowski M. Gene-environment interactions between CRHR1 variants and physical assault in suicide attempts. *Genes Brain Behav*. (2011) 10:663–72. doi: 10.1111/j.1601-183X.2011.00703.x
393. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat Genet*. (2003) 33(Suppl):245–54. doi: 10.1038/ng1089
394. Bjornsson HT, Fallin MD, Feinberg AP. An integrated epigenetic and genetic approach to common human disease. *Trends Genet*. (2004) 20:350–8. doi: 10.1016/j.tig.2004.06.009
395. Trollope AF, Gutierrez-Mecinas M, Mifsud KR, Collins A, Saunderson EA, Reul JMHM. Stress, epigenetic control of gene expression and memory formation. *Exp Neurol*. (2012) 233:3–11. doi: 10.1016/j.expneurol.2011.03.022
396. McGowan PO. Epigenomic mechanisms of early adversity and HPA dysfunction: considerations for PTSD research. *Front Psychiatry*. (2013) 4:110. doi: 10.3389/fpsyt.2013.00110
397. Stankiewicz AM, Swiergiel AH, Lisowski P. Epigenetics of stress adaptations in the brain. *Brain Res Bull*. (2013) 98:76–92. doi: 10.1016/j.brainresbull.2013.07.003
398. Reul JMHM. Making memories of stressful events: a journey along epigenetic, gene transcription, and signaling pathways. *Front Psychiatry*. (2014) 5:5. doi: 10.3389/fpsyt.2014.00005
399. Schmidt U, Holsboer F, Rein T. Epigenetic aspects of posttraumatic stress disorder. *Dis Markers*. (2011) 30:77–87. doi: 10.1155/2011/343616
400. Wingo AP, Almli LM, Stevens JJ, Klengel T, Uddin M, Li Y, et al. DICER1 and microRNA regulation in post-traumatic stress disorder with comorbid depression. *Nat Commun*. (2015) 6:10106. doi: 10.1038/ncomms10106
401. Zannas AS, Provencal N, Binder EB. Epigenetics of posttraumatic stress disorder: current evidence, challenges, and future directions. *Biol Psychiatry*. (2015) 78:327–35. doi: 10.1016/j.biopsych.2015.04.003
402. Almli LM, Stevens JS, Smith AK, Kilaru V, Meng Q, Flory J, et al. A genome-wide identified risk variant for PTSD is a methylation quantitative trait locus and confers decreased cortical activation to fearful faces. *Am J Med Genet B Neuropsychiatr Genet*. (2015). 168B:327–36. doi: 10.1002/ajmg.b.32315
403. Yehuda R, Daskalakis NP, Desarnaud F, Makotkine I, Lehrner AL, Koch E, et al. Epigenetic biomarkers as predictors and correlates of symptom improvement following psychotherapy in combat veterans with PTSD. *Front Psychiatry*. (2013) 4:118. doi: 10.3389/fpsyt.2013.00118
404. Yehuda R, Flory JD, Bierer LM, Henn-Haase C, Lehrner A, Desarnaud F, et al. Lower methylation of glucocorticoid receptor gene promoter 1F in peripheral blood of veterans with posttraumatic stress disorder. *Biol Psychiatry*. (2015) 77:356–64. doi: 10.1016/j.biopsych.2014.02.006
405. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci*. (2009) 12:342–8. doi: 10.1038/nn.2270
406. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics*. (2008) 3:97–106. doi: 10.4161/epi.3.2.6034
407. Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biol Psychiatry*. (2009) 65:760–9. doi: 10.1016/j.biopsych.2008.11.028
408. Houtepen LC, Vinkers CH, Carrillo-Roa T, Hiemstra M, van Lier PA, Meeus W, et al. Genome-wide DNA methylation levels and altered cortisol stress reactivity following childhood trauma in humans. *Nat Commun*. (2016) 7:10967. doi: 10.1038/ncomms10967
409. Bick J, Naumova O, Hunter S, Barbot B, Lee M, Luthar SS, et al. Childhood adversity and DNA methylation of genes involved in the hypothalamus-pituitary-adrenal axis and immune system: whole-genome and candidate-gene associations. *Dev Psychopathol*. (2012) 24:1417–25. doi: 10.1017/S0954579412000806
410. Yang BZ, Zhang H, Ge W, Weder N, Douglas-Palumberi H, Perepletchikova F, et al. Child abuse and epigenetic mechanisms of disease risk. *Am J Prev Med*. (2013) 44:101–7. doi: 10.1016/j.amepre.2012.10.012
411. Essex MJ, Boyce WT, Hertzman C, Lam LL, Armstrong JM, Neumann SM, et al. Epigenetic vestiges of early developmental adversity: childhood stress exposure and DNA methylation in adolescence. *Child Dev*. (2013) 84:58–75. doi: 10.1111/j.1467-8624.2011.01641.x
412. Mehta D, Klengel T, Conneely KN, Smith AK, Altmann A, Pace TW, et al. Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. *Proc Natl Acad Sci USA*. (2013) 110:8302–7. doi: 10.1073/pnas.1217750110
413. Yehuda R, Bierer LM. The relevance of epigenetics to PTSD: implications for the DSM-V. *J Trauma Stress*. (2009) 22:427–34. doi: 10.1002/jts.20448
414. Klengel T, Pape J, Binder EB, Mehta D. The role of DNA methylation in stress-related psychiatric disorders. *Neuropharmacology*. (2014). 80:115–32. doi: 10.1016/j.neuropharm.2014.01.013
415. Taylor SE. Mechanisms linking early life stress to adult health outcomes. *Proc Natl Acad Sci USA*. (2010) 107:8507–12. doi: 10.1073/pnas.1003890107
416. Dannlowski U, Stuhrmann A, Beutelmann V, Zwanzger P, Lenzen T, Grotegerd D, et al. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biol Psychiatry*. (2012) 71:286–93. doi: 10.1016/j.biopsych.2011.10.021
417. Teicher MH, Samson JA, Anderson CM, Ohashi K. The effects of childhood maltreatment on brain structure, function and connectivity. *Nat Rev Neurosci*. (2016) 17:652–66. doi: 10.1038/nrn.2016.111
418. Sapolsky RM, Uno H, Rebert CS, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci*. (1990) 10:2897–902. doi: 10.1523/JNEUROSCI.10-09-02897.1990
419. Dunlop SA, Archer MA, Quinlivan JA, Beazley LD, Newnham JP. Repeated prenatal corticosteroids delay myelination in the ovine central nervous system. *J Matern Fetal Med*. (1997) 6:309–13. doi: 10.1002/(SICI)1520-6661(199711/12)6:6<309::AID-MFM1>3.0.CO;2-S
420. Lauder JM. Neurotransmitters as morphogens. *Prog Brain Res*. (1988) 73:365–87. doi: 10.1016/S0079-6123(08)60516-6
421. Chen Y, Baram TZ. Toward understanding how early-life stress reprograms cognitive and emotional brain networks. *Neuropsychopharmacology*. (2016) 41:197–206. doi: 10.1038/npp.2015.181
422. Ehlert U. Enduring psychobiological effects of childhood adversity. *Psychoneuroendocrinology*. (2013) 38:1850–7. doi: 10.1016/j.psyneuen.2013.06.007

423. Insana SP, Banihashemi L, Herringa RJ, Kolko DJ, Germain A. Childhood maltreatment is associated with altered frontolimbic neurobiological activity during wakefulness in adulthood. *Dev Psychopathol.* (2016) 28:551–64. doi: 10.1017/S0954579415000589
424. Majer M, Nater UM, Lin JM, Capuron L, Reeves WC. Association of childhood trauma with cognitive function in healthy adults: a pilot study. *BMC Neurol.* (2010) 10:61. doi: 10.1186/1471-2377-10-61
425. Hanson JL, Chung MK, Avants BB, Rudolph KD, Shirtcliff EA, Gee JC, et al. Structural variations in prefrontal cortex mediate the relationship between early childhood stress and spatial working memory. *J Neurosci.* (2012) 32:7917–25. doi: 10.1523/JNEUROSCI.0307-12.2012
426. Saleh A, Potter GG, McQuoid DR, Boyd B, Turner R, MacFall JR, et al. Effects of early life stress on depression, cognitive performance and brain morphology. *Psychol Med.* (2017) 47:171–81. doi: 10.1017/S0033291716002403
427. Daniels JK, Lamke JP, Gaebler M, Walter H, Scheel M. White matter integrity and its relationship to PTSD and childhood trauma–a systematic review and meta-analysis. *Depress Anxiety*. (2013) 30:207–16. doi: 10.1002/da.22044
428. Paquola C, Bennett MR, Lagopoulos J. Understanding heterogeneity in grey matter research of adults with childhood maltreatment-A meta-analysis and review. *Neurosci Biobehav Rev*. (2016) 69:299–312. doi: 10.1016/j.neubiorev.2016.08.011
429. De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, et al. A.E. Bennett Research Award. Developmental traumatology. Part II: Brain development. *Biol Psychiatry*. (1999) 45:1271–84. doi: 10.1016/S0006-3223(99)00045-1
430. Grassi-Oliveira R, Ashy M, Stein LM. Psychobiology of childhood maltreatment: effects of allostatic load? *Rev Bras Psiquiatr.* (2008) 30:60–8. doi: 10.1590/S1516-44462008000100012
431. Thomaes K, Dorrepaal E, Draijer N, de Ruiter MB, van Balkom AJ, Smit JH, et al. Reduced anterior cingulate and orbitofrontal volumes in child abuse-related complex PTSD. *J Clin Psychiatry*. (2010) 71:1636–44. doi: 10.4088/JCP.08m04754blu
432. Edmiston EE, Wang F, Mazure CM, Guiney J, Sinha R, Mayes LC, et al. Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. *Arch Pediatr Adolesc Med.* (2011) 165:1069–77. doi: 10.1001/archpediatrics.2011.565
433. Lim L, Radua J, Rubia K. Gray matter abnormalities in childhood maltreatment: a voxel-wise meta-analysis. *Am J Psychiatry*. (2014) 171:854–63. doi: 10.1176/appi.ajp.2014.13101427
434. Busso DS, McLaughlin KA, Brueck S, Peverill M, Gold AL, Sheridan MA. Child abuse, neural structure, and adolescent psychopathology: a longitudinal study. *J Am Acad Child Adolesc Psychiatry*. (2017) 56:321–328e321. doi: 10.1016/j.jaac.2017.01.013
435. Teicher MH, Anderson CM, Ohashi K, Polcari A. Childhood maltreatment: altered network centrality of cingulate, precuneus, temporal pole and insula. *Biol Psychiatry*. (2014) 76:297–305. doi: 10.1016/j.biopsych.2013.09.016
436. McEwen BS, Morrison JH. The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron*. (2013) 79:16–29. doi: 10.1016/j.neuron.2013.06.028
437. Semple BD, Blomgren K, Gimlin K, Ferriero DM, Noble-Haeusslein LJ. Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. *Prog Neurobiol.* (2013) 106–7:1–16. doi: 10.1016/j.pneurobio.2013.04.001
438. Heim CM, Mayberg HS, Mletzko T, Nemeroff CB, Pruessner JC. Decreased cortical representation of genital somatosensory field after childhood sexual abuse. *Am J Psychiatry*. (2013) 170:616–23. doi: 10.1176/appi.ajp.2013.12070950
439. Van Dam NT, Rando K, Potenza MN, Tuit K, Sinha R. Childhood maltreatment, altered limbic neurobiology, and substance use relapse severity via trauma-specific reductions in limbic gray matter volume. *JAMA Psychiatry*. (2014) 71:917–25. doi: 10.1001/jamapsychiatry.2014.680
440. Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, et al. Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry* .(2002) 159:2072–80. doi: 10.1176/appi.ajp.159.12.2072
441. Frodl T, Reinhold E, Koutsouleris N, Reiser M, Meisenzahl EM. Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. *J Psychiatr Res.* (2010) 44:799–807. doi: 10.1016/j.jpsychires.2010.01.006
442. Opel N, Redlich R, Zwanzger P, Grotegerd D, Arolt V, Heindel W, et al. Hippocampal atrophy in major depression: a function of childhood maltreatment rather than diagnosis? *Neuropsychopharmacology*. (2014) 39:2723–31. doi: 10.1038/npp.2014.145
443. Woon FL, Hedges DW. Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. *Hippocampus*. (2008) 18:729–36. doi: 10.1002/hipo.20437
444. van Velzen LS, Schmaal L, Jansen R, Milaneschi Y, Opmeer EM, Elzinga BM, et al. Effect of childhood maltreatment and brain-derived neurotrophic factor on brain morphology. *Soc Cogn Affect Neurosci.* (2016) 11:1841–52. doi: 10.1093/scan/nsw086
445. Aust S, Stasch J, Jentschke S, Alkan Hartwig E, Koelsch S, Heuser I, et al. Differential effects of early life stress on hippocampus and amygdala volume as a function of emotional abilities. *Hippocampus*. (2014) 24:1094–101. doi: 10.1002/hipo.22293
446. Coplan JD, Fathy HM, Jackowski AP, Tang CY, Perera TD, Mathew SJ, et al. Early life stress and macaque amygdala hypertrophy: preliminary evidence for a role for the serotonin transporter gene. *Front Behav Neurosci.* (2014) 8:342. doi: 10.3389/fnbeh.2014.00342
447. Dannlowski U, Kugel H, Huber F, Stuhrmann A, Redlich R, Grotegerd D, et al. Childhood maltreatment is associated with an automatic negative emotion processing bias in the amygdala. *Hum Brain Mapp.* (2013) 34:2899–909. doi: 10.1002/hbm.22112
448. Swartz JR, Williamson DE, Hariri AR. Developmental change in amygdala reactivity during adolescence: effects of family history of depression and stressful life events. *Am J Psychiatry*. (2015) 172:276–83. doi: 10.1176/appi.ajp.2014.14020195
449. Grant MM, Cannistraci C, Hollon SD, Gore J, Shelton R. Childhood trauma history differentiates amygdala response to sad faces within MDD. *J Psychiatr Res.* (2011) 45:886–95. doi: 10.1016/j.jpsychires.2010.12.004
450. Booij L, Szyf M, Carballedo A, Frey EM, Morris D, Dymov S, et al. DNA methylation of the serotonin transporter gene in peripheral cells and stress-related changes in hippocampal volume: a study in depressed patients and healthy controls. *PLoS ONE.* (2015) 10:e0119061. doi: 10.1371/journal.pone.0119061
451. White MG, Bogdan R, Fisher PM, Munoz KE, Williamson DE, Hariri AR. FKBP5 and emotional neglect interact to predict individual differences in amygdala reactivity. *Genes Brain Behav.* (2012) 11:869–78. doi: 10.1111/j.1601-183X.2012.00837.x
452. Holz NE, Buchmann AF, Boecker R, Blomeyer D, Baumeister S, Wolf I, et al. Role of FKBP5 in emotion processing: results on amygdala activity, connectivity and volume. *Brain Struct Funct.* (2015) 220:1355–68. doi: 10.1007/s00429-014-0729-5
453. Grabe HJ, Wittfeld K, Van der Auwera S, Janowitz D, Hegenscheid K, Habes M, et al. Effect of the interaction between childhood abuse and rs1360780 of the FKBP5 gene on gray matter volume in a general population sample. *Hum Brain Mapp.* (2016) 37:1602–13. doi: 10.1002/hbm.23123
454. Bogdan R, Williamson DE, Hariri AR. Mineralocorticoid receptor Iso/Val (rs5522) genotype moderates the association between previous childhood emotional neglect and amygdala reactivity. *Am J Psychiatry*. (2012) 169:515–22. doi: 10.1176/appi.ajp.2011.11060855
455. Hyman SE. How adversity gets under the skin. *Nat Neurosci.* (2009) 12:241–3. doi: 10.1038/nn0309-241
456. Gluckman PD, Cutfield W, Hofman P, Hanson MA. The fetal, neonatal, and infant environments-the long-term consequences for disease risk. *Early Hum Dev.* (2005) 81:51–9. doi: 10.1016/j.earlhumdev.2004.10.003
457. Gluckman PD, Hanson MA, Morton SM, Pinal CS. Life-long echoes–a critical analysis of the developmental origins of adult disease model. *Biol Neonate*. (2005) 87:127–39. doi: 10.1159/000082311
458. Gluckman PD, Hanson MA, Pinal C. The developmental origins of adult disease. *Matern Child Nutr.* (2005) 1:130–41. doi: 10.1111/j.1740-8709.2005.00020.x

459. Gluckman PD, Hanson MA, Spencer HG. Predictive adaptive responses and human evolution. *Trends Ecol Evol*. (2005) 20:527–33. doi: 10.1016/j.tree.2005.08.001
460. Gluckman PD, Hanson MA, Spencer HG, Bateson P. Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. *Proc Biol Sci*. (2005) 272:671–7. doi: 10.1098/rspb.2004.3001
461. Belsky J, Beaver KM. Cumulative-genetic plasticity, parenting and adolescent self-regulation. *J Child Psychol Psychiatry*. (2011) 52:619–26. doi: 10.1111/j.1469-7610.2010.02327.x
462. Nederhof E, Schmidt MV. Mismatch or cumulative stress: Toward an integrated hypothesis of programming effects. *Physiol Behav*. (2012) 106:691–700. doi: 10.1016/j.physbeh.2011.12.008
463. Nederhof E. The mismatch hypothesis of psychiatric disease. *Physiol Behav*. (2012) 106:689–90. doi: 10.1016/j.physbeh.2012.02.014
464. Levine S. Developmental determinants of sensitivity and resistance to stress. *Psychoneuroendocrinology*. (2005) 30:939–46. doi: 10.1016/j.psyneuen.2005.03.013
465. Cuijpers P, Smit F, Unger F, Stikkelbroek Y, Ten Have M, de Graaf R. The disease burden of childhood adversities in adults: a population-based study. *Child Abuse Negl*. (2011) 35:937–45. doi: 10.1016/j.chiabu.2011.06.005
466. Nelson EC, Agrawal A, Pergadia ML, Lynskey MT, Todorov AA, Wang JC, et al. Association of childhood trauma exposure and GABRA2 polymorphisms with risk of posttraumatic stress disorder in adults. *Mol Psychiatry*. (2009) 14:234–5. doi: 10.1038/mp.2008.81
467. Dinan TG, Cryan J, Shanahan F, Keeling PW, Quigley EM. IBS: An epigenetic perspective. *Nat Rev Gastroenterol Hepatol*. (2010) 7:465–71. doi: 10.1038/nrgastro.2010.99
468. Wiersma JE, Hovens JG, van Oppen P, Giltay EJ, van Schaik DJ, Beekman AT, et al. The importance of childhood trauma and childhood life events for chronicity of depression in adults. *J Clin Psychiatry*. (2009) 70:983–9. doi: 10.4088/JCP.08m04521

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Trauma, Resilience, and Mental Health in Migrant and Non-Migrant Youth: An International Cross-Sectional Study Across Six Countries

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Resilience is a dynamic process of positive adaptation to significant adversity. While there has been substantial focus on risks and negative outcomes associated with youth migrancy, there is limited evidence of the relationship between the adversity of migration, and resilience, wellbeing, and positive mental health in adolescents. This international study aimed to explore the differences in resilience, wellbeing, and mental health behaviors in migrant and non-migrant adolescents tested across six countries (Australia, New Zealand, UK, China, South Africa, and Canada) with varying levels of trauma exposure. The study was a cross-sectional survey design with a convenience sample of 194 10–17 year old migrants and non-migrants. The migrant sample included both "internal" migrants (change of residence within a country) and "external" migrants (change of residence across national borders) for comparison. Across the sites, migrants reported a higher mean number of traumatic events for the past year than non-migrants, with internal migrants reporting more events than external migrants overall. South African adolescents reported a higher mean number of traumatic events for the past year than all other sites. External migrants reported higher resilience scores yet reduced prosocial behaviors relative to internal migrants and non-migrants, whereas both internal and external migrants reported higher peer problems than non-migrants. When considering the interacting effects of trauma, the presence or absence of trauma did not appear to impact migrant scores in terms of resilience, wellbeing, or conduct problems. In comparison, trauma-exposed non-migrants showed detriments relative to trauma-exposed migrant peers for all of these measures. In conclusion, the survey tool was found to be reliable and acceptable for use in international studies of different samples of adolescent migrants. Overall, migrant adolescents showed greater resilience resources

than non-migrants and, although the migrants experienced more traumatic events, the impact of trauma on mental health outcomes was greater in the non-migrants. There is a need for further research with larger prospective sample sizes to investigate how levels of resilience and wellbeing vary over time and across countries, and the ways resilience can be promoted in adolescents exposed to trauma, regardless of migrancy status.

Keywords: trauma, resilience, mental health, migrant, youth, wellbeing, COMPAS-W, CYRM-28

INTRODUCTION

Understanding the mechanisms that underpin resilience to trauma is a surging field of enquiry in mental health research, particularly in adolescents. The impact of migration is another public health challenge and is sometimes precipitated by adversity experienced in the home country or region. Worldwide there are approximately 35 million migrants between the ages of 10 and 24, which represent 17% of the total migrant population. Of those, 9 million (25%) are in the 10–14 year age group and 11 million (32%) are in middle to late adolescence (15–19) (1). There are two basic types of migration; internal and external. Internal migration usually refers to a change of residence within a country such as movement from rural to urban settings or movement from state to state. External migration refers to a change of residence over national boundaries or moving to a different country. External migrants can be further classified into people who followed legal and illegal migrant routes, and refugees. The motivation for these different types of migration often differs, and which can provide diverse challenges to the migrant before and after their arrival in their new home (2, 3). However, current research is unclear as to whether there are common challenges for internal and external adolescent migrants and how these challenges may affect adolescence and the transition from childhood to adulthood during this crucial stage of development (4–6). This is unfortunate because adolescence is a key decade in the life-course where physical health, mental health, and behavioral problems can arise that will have an ongoing impact throughout adulthood.

Many of the risk factors for mental health and behavioral problems begin during adolescence and include tobacco use, harmful use of alcohol and cannabis, and unhealthy diets (7). The onset of mental disorders such as depression and anxiety disorders typically occur in childhood and adolescence, with 20% of the world's children and adolescents experiencing mental disorders, half of those beginning prior to age 14 (8). Left untreated, these conditions can severely impact development, educational attainment, and place young people at higher risk of suicide (9). Substance abuse, conduct problems, and mental disorders in adolescence are often triggered by psychological trauma, either by direct experience of a traumatic event such as interpersonal violence or through secondary traumatic stress that occurs when a close family member or friend has experienced a traumatic event (10, 11). The kind, number, and complexity of traumas experienced in early life have a differential impact on psychological and behavioral difficulties (12, 13). In addition, children exposed to trauma may continue to develop new symptoms over time as they encounter additional developmental or environmental challenges and stressors (14–16). Yet, it is still unclear as to why some children exposed to trauma develop emotional and behavioral problems while others do not (11).

Resilience as a construct is the process of positive adaptation and/or recovery from trauma or adversity (17). Multiple systems are understood to interact to provide the resources required for resilience (18, 19). Factors that have been associated with resilience in childhood and adolescence, include positive caregiver, family and peer relationships, religion, school environment, and personal characteristics such as self-regulation and coping skills (11, 20, 21). Low resilience to adversity puts individuals at higher risk of developing psychiatric problems with depression, anxiety, and conduct disorder being the most common (22, 23).

Research in adolescent migrants have identified protective factors for mental health, suggestive of resilience processes (2, 3, 24–26). In one study, pre-migration poverty combined with clandestine entry in the United States increased the risk for symptoms related to post-traumatic stress disorder (PTSD) (2). Post-migration discrimination and poor neighborhoods also increased the risk for PTSD whereas a positive family environment and social support mitigated risk (2). In a review of the mental health of refugee children resettled in high-income countries, risk of developing mental health problems was associated with trauma exposure, parental exposure to violence, loss of parent(s), limited family support, violence and discrimination in the host country, feeling disconnected to school, and neighborhood violence (25). Protective factors included stable settlement and social support in the host country, psychological wellbeing of the parents/guardians, and religious beliefs (25). Overall however, most studies have largely focused on vulnerability or risk in refugee populations relative to non-migrants with little focus on comparisons with immigrant youth, or within immigrant groups defined more broadly (e.g., immigrant youth who migrated at some undefined point in time, and/or second-generation immigrant youth with first-generation immigrant parents), with most, if not all, studies conducted within the one country, with no comparison across multiple country sites (27–30).

Recognizing the gaps in our understanding of mental health in adolescent migrants, an international collaboration was established through the Worldwide Universities Network to investigate resilience (31). The aim of this collaboration is to

establish a longitudinal study that would identify the mechanisms or processes that promote physical and mental wellbeing and prevent mental illness despite exposure to the adversity brought about by adapting to a new culture and the challenges of transitioning through adolescence. This collaboration includes a multidisciplinary group of researchers from Australia, Canada, China, New Zealand (NZ), South Africa, and the United Kingdom (UK). Through this collaboration a questionnaire battery was designed and piloted in these countries with the intention of comparing the resilience of adolescent migrants with non-migrants. The questionnaires were based on an in-house literature review of resilience in adolescent migrants, and qualitative data collected during focus groups in the NZ, South Africa, and the UK. The sites chosen for focus group discussions offered diverse contexts for the study, and were linked to the Worldwide Universities Network and had the resources and expertise to conduct qualitative interviews.

This aim of this report is to use our pilot data to explore the impact of country-specific factors, migrancy, and trauma exposure on resilience, wellbeing, and mental health among migrant and non-migrant adolescents aged 10–17 in countries where there are high rates of internal and external migration. The overall hypotheses are that migrants and non-migrants might vary in behavior and mental health outcomes by virtue of differences in exposure to trauma and adversity, and that higher resilience would be associated with better wellbeing, fewer symptoms of mental illness, and fewer behavioral problems. The specific questions addressed in this study are the following: (1) are the measures of resilience, wellbeing, mental health, and behavior reliable across country sites? (2) do differences exist between migrant and non-migrant adolescents (controlling for any site differences) in trauma exposure? (3) are there differences between migrants and non-migrants in behavioral and mental health outcomes? and (4) how is trauma and migration related to resilience, behavior, and wellbeing?

MATERIALS AND METHODS

This pilot study, conducted across six countries: Australia, Canada, China, NZ, South Africa, and the UK, used a cross-sectional survey design with a convenience sample of 194 10–17 year-old migrant and non-migrant youth. Migrants included internal migrants who had moved within a country, and external migrants who had moved across national borders.

Participants

The sample comprised 194 adolescents from: Australia (n = 25), Canada (n = 21), China (n = 77), NZ (n = 33), South Africa (n = 28), and the UK (n = 10). Participants ranged in age from 10 to 17 years (M = 13.9, SD = 1.36), with the sample made up of 52% males (n = 101), 46% females (n = 89), and 2% sex undisclosed (n = 4). Within the sample, 77% of participants were migrants and 23% were non-migrants. **Table 1** contains a breakdown of migrant status across research sites.

Youth were recruited from schools (Australia, UK, China), youth centers (South Africa), an after-school program for migrants (Canada), or community networks (New Zealand) (**Table 1**). Details regarding participant recruitment per site are as follows. In Australia, head teachers from several independent NSW schools were approached for study participation. For participating schools, the head teacher forwarded study information to students and their parents for written consent. Head teachers then organized testing days and times for students to complete the questionnaires during school hours with a research team member. In the UK, youth were recruited from two state secondary schools in Bristol: after written informed consent was obtained from a parent, the students completed the questionnaires during school hours with a research team member. In China, youth were recruited from one secondary school in the city of Guangzhou, Guangdong province, where many migrants concentrate. The school principal helped select one class randomly from each of the three grades (grade 7^{th}–9^{th}),

TABLE 1 | Age, sex, and migrant status by site.

Site	N	Age (mean ± SD)	Age range	Sex (N, %)	Migrant status	Country of birth (majority)
Australia	25	13.3 (0.61)	12–14 years	M: 17 (68%)	Migrant: 0	n = 0
				F: 8 (32%)	Non-migrant: 25	Australia (n = 24)*
Canada	21	14.1 (0.97)	13–15 years	M: 8 (38%)	Migrant^{E}: 21	Iraq (n = 9)**
				F: 13 (62%)	Non-migrant: 0	n = 0
China	77	13.2 (0.96)	12–17 years	M: 44 (57%)	Migrant^{I}: 77	Guangzhou, China (n = 25)***
				F: 29 (38%)	Non-migrant: 0	n = 0
New Zealand (NZ)	33	15.3 (1.11)	12–16 years	M: 9 (27%)	Migrant^{E}: 19	Philippines (n = 10)****
				F: 24 (73%)	Non-Migrant: 14	New Zealand (n = 19)
South Africa (SA)	28	13.8 (1.58)	10–16 years	M: 19 (68%)	Migrant^{I}: 28	South Africa (n = 20)*****
				F: 9 (32%)	Non-migrant: 0	n = 0
United Kingdom (UK)	10	15.7 (1.25)	13–17 years	M: 4 (40%)	Migrant^{E}: 4	Europe (n = 3)*****
				F: 6 (60%)	Non-migrant: 6	England (UK) (n = 6)
TOTAL	**194**	**13.9 (1.36)**	**10–17 years**	**M: 101 (52%)**	**Migrant: 105^{I}, 89^{E}**	**Guangzhou (n = 25), SA (n = 20)**
				F: 89 (46%)	**Non-migrant: 45**	**Australia (n = 24), NZ (n = 14)**

*M, male; F, female; migrant^{E}, external migrant (cross-country); migrant^{I}, internal migrant (within-country). Country of birth origin: *Australia non-migrants: 24 Australia, 1 USA; ** Canada external migrants: 9 Iraq, 2 Australia/China/Uganda, 1 Syria/Yeman/Nepal/Congo/Qatar/Pakistan; *** China internal migrants: 25 Guangzhou, China, 43 "other"; **** New Zealand external migrants: 10 Philippines, 4 England (UK), 2 China, 1 Oman/Malaysia/India; ***** South Africa internal migrants: 20 South Africa, 3 Congo, 2 Zimbabwe, 1 Burundi/Mozambique; ***** UK external migrants: 1 the Netherlands, 1 France, 1 Poland, 1 USA.*

collected informed consent from the students and their parents, and arranged the time for students to complete the survey in class, with the presence of a research team member. In South Africa, youth center staff acted as gatekeepers. They advertised the study and provided any interested youth with consent forms (which needed to be co-signed by a parent/caregiver). In Canada, participants were sampled through an after-school program run by the YMCA Centre for Immigrant Programs. An information sheet and consent form was sent to all parents of children in the program and then those children with a completed consent form were able to participate in the study. Students completed the questionnaire during the after-school program time. And in New Zealand, families with adolescents in the target age group were identified through advertisements posted in community centers and through Worldwide Universities Network (WUN) research staff and student networks.

Ethics approval was sought and gained from the respective sites according to the local Human Research Ethics Committee processes (Australia; University of New South Wales Human Research Ethics Committee: HC15672; Canada; Dalhousie University Social Sciences and Humanities Research Ethics Board: REB 2015-3666; China; Chinese University of Hong Kong; New Zealand; The University of Auckland Human Ethics Committee: 015968; South Africa: North-West University Humanities and Health Research Ethics Committee: NWU-HS-2015-0234; United Kingdom; University of Bristol Faculty of Medicine Research Ethics Committee: ref 2016/26061). Written and/or verbal information was provided to all participants. Informed verbal and/or written consent was obtained from parents and informed verbal or written assent was gained from youth.

Measures

A questionnaire battery was developed using established measures from the literature and information derived from qualitative focus groups with youth in three of the participating countries. The questionnaire commenced with a series of demographic questions (e.g., gender, country of birth, ethnicity), followed by questions about participants' family structure, schooling experiences, neighborhood, personal and familial health, as well as trauma exposure using items adapted from the Early Life Stress Questionnaire (32) (see **Figure 1** legend for a list of trauma exposure items). The battery also contained the following measures: 1) Child and Youth Resilience Measure (CYRM-28) (33); 2) Connor-Davidson Resilience Scale (CD-RISC) (34); 3) Warwick-Edinburgh Mental Well-being Scale (WEMWBS) (35); 4) COMPAS Wellbeing Scale (COMPAS-W) (36); 5) Depression, Anxiety, Stress Scale (DASS-21) (37); 6) Strengths and Difficulties Questionnaire (SDQ) (38); 7) CRAFFT Screening Tool for Adolescent Substance Abuse (39); and 8) Acculturation, Habits, and Interests Multicultural Scale for Adolescents (AHIMSA) (40).

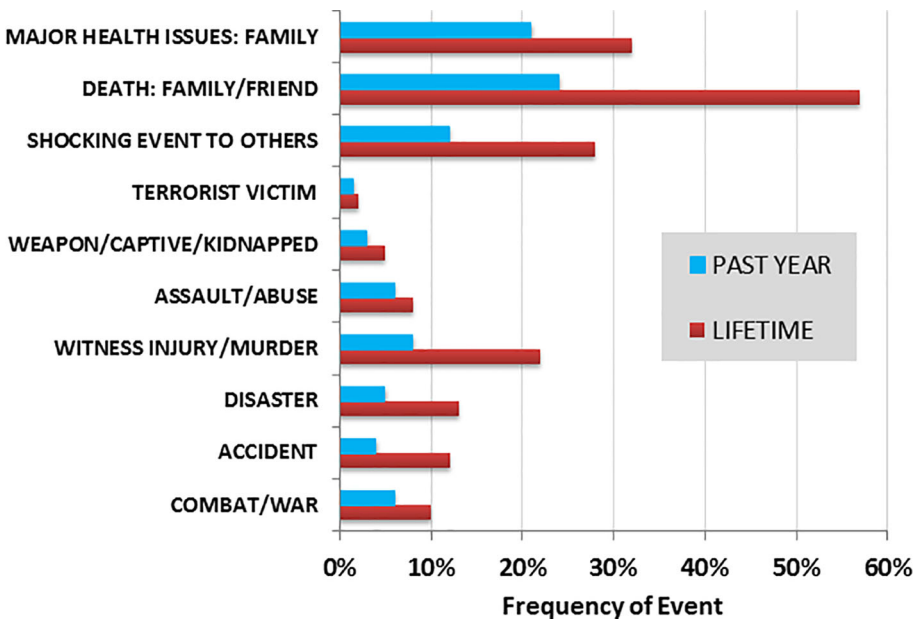

FIGURE 1 | Frequency (%) of childhood trauma exposure reported across the sample for the past year and lifetime (N = 194). The corresponding question items for each of the trauma categories are as follows: i) combat/war ("have you ever had direct combat experience in a war?"); ii) accident ("have you ever been involved in a life-threatening accident?"); iii) disaster ("have you ever been involved in a fire, flood, or other natural disaster?"); iv) witness injury/murder ("have you ever witnessed someone being badly injured or killed?"); v) assault/abuse ("have you ever been seriously attacked or assaulted?"); vi) weapon/captive/kidnapped ("have you ever been threatened with a weapon, held captive, or kidnapped?"); vii) terrorist victim ("have you ever been the victim of terrorists?"); viii) shocking event to others ("have you suffered a great shock because one of the events on the list happened to someone close to you?"); ix) death: family/friend ("have you experienced the death of a close family member or close friend?"); and x) major health issues: family ("have you experienced a major change in health or behavior of a family member?").

Here we report results for the first seven questionnaires, as the data for the AHIMSA questionnaire has been published separately (41).

Psychometric properties for the measures used are well-established. The Child and Youth Resilience Measure-28 (CYRM-28) is a 28-item measure of child and youth resilience that measures individual, peer, family, and community resources implicated in resilience processes (42). Responses are scored using a 5-point scale ranging from *1 = does not describe me at all* to *5 = describes me a lot*, where higher scores indicate greater resilience. Factor analyses confirmed three latent variables (i.e., individual characteristics; relationships with caregivers; and contextual elements contributing to a sense of belonging). These inter-related variables have been shown to load onto a single resilience factor (42, 43). Internal reliability for the CYRM-28 is good, with Cronbach's α reported as ranging between .65 and .91 for the three latent variables (42).

The Connor-Davidson Resilience Scale (CD-RISC) is a widely used measure of youth trait resilience comprising 25 items measured on a 5-point scale ranging from *0 = not at all* to *4 = true nearly all of the time* (34). Original factor analysis revealed a five factor model where factor one referred to personal competence, tenacity, and high standards, factor two related to trusting one's instincts, tolerance of negative affect, and a strengthening effect of stress, factor three corresponded to acceptance of change and positive relationships, factor four to personal control, and factor five to spiritual influences (34). Internal reliability tests reported Cronbach's α for the full scale at 0.89 and item-total correlations ranged between 0.30 and 0.70. Test-retest reliability was good with an intraclass correlation coefficient of 0.87. Convergent validity was established through positive correlations between the CD-RISC and Kobasa's measure of hardiness (44) (Pearson r = 0.83, $P < .0001$) and the Sheehan Social Support Scale (SSS) (45) (Spearman $r = 0.36$, $P < .0001$). Negative correlations have been established with the Perceived Stress Scale (PSS-10) (46) (Pearson $r = -0.76$, $P < .001$), the Sheehan Stress Vulnerability Scale (SVS) (45) (Spearman $r = -0.32$, $P < .0001$), the Sheehan Disability Scale (SDS) (47) (Pearson $r = -0.62$, $P < .0001$) (34).

The Warwick-Edinburgh Mental Well-being Scale (WEMWBS) is a measure of wellbeing containing 14 positively worded items relating to positive attributes of mental health (e.g., item 1: *I've been feeling optimistic about the future*; item 5: *I've had energy to spare*), and is measured on a 5-point scale ranging from *1 = none of the time to 5 = all of the time*. The WEMWBS has been quantitatively validated in a student and adult UK population, as well as with Chinese and Pakistani ethnic minority groups in the UK (35, 48, 49). Initial assessment showed content validity was good with confirmatory factor analysis revealing a single *wellbeing* factor (GFI = 0.93, AGFI = 0.8, RMSEA = 0.055). Internal reliability tests of the scale reported Cronbach's α at 0.89; suggesting some item redundancy, item total correlations ranged from 0.52 and 0.80. Test-retest reliability for the WEMWBS was high (0.83) at 1 week and was found to discriminate between youth and adult populations well (48). The WEMWBS was also robust in measuring wellbeing in different ethnic populations (49).

The COMPAS Wellbeing Scale (COMPAS-W) is a composite measure of wellbeing comprising six subcomponents: composure during stress, own-worth, mastery over the environment, positivity, achievement and satisfaction with physical, psychological health and social relationships (36). The 26-item scale accounts for both hedonic (i.e., subjective) and eudaimonic (i.e., psychological) wellbeing constructs, with individual subscales measured using a 5-point scale ranging from *1 = strongly disagree* to *5 = strongly agree*. A composite wellbeing score is produced from the sum of the subscale scores. Construct validity for the COMPAS-W had been established through strong correlations with other measures of physical and psychological health behaviors, such as the World Health Organization Quality of Life scale (WHOQOL-BREF) (50), the Satisfaction with Life Scale (SWLS) (51), the Internal Control Index (ICI) (52), and the Emotion Regulation Questionnaire (53). Internal consistency for the COMPAS-W is strong (average $r = 0.71$; wellbeing $r = 0.84$) and test-retest reliability was robust across a 12-month period (average $r = 0.62$; wellbeing $r = 0.82$) (36).

The Depression Anxiety Stress Scale (DASS-21) is 21-item measure of state depression, anxiety, and stress (37). The DASS-21 is made up of three subscales for depression, anxiety, and stress respectively, which are each measured on a 4-point scale ranging from *0 = never to 4 = almost always*. DASS subscales have been shown to correlate well with other measures of depression and anxiety, such as the Beck Depression Inventory (BDI) (54) and the Beck Anxiety Inventory (BAI) (37, 55). The DASS has been found to differentiate clinical and non-clinical populations, as well as to discriminate between different clinical diagnostic groups (37, 56). Internal consistency for each subscale of the DASS-21 was good in a recent non-clinical sample (Cronbach's α was reported at .91, .80, and .84 for depression, anxiety, and stress, respectively) (57).

The Strengths and Difficulties Questionnaire (SDQ) is a screening tool used to assess the psychological adjustment of children and youth (38). The 25-item scale is made up of positively and negatively worded statements (e.g., item 1: *I am considerate of other people's feelings;* item 2: *I am restless, overactive and cannot stay still for long*). Participants respond to statements using a 3-point scale from *0 = not true*; *1 = somewhat true*; and *2 = certainly true*. Factor analysis supported a five-factor model, which included 1) emotional symptoms, 2) conduct, 3) hyperactivity-inattention, 4) peer relationships, and 5) pro-social behavior (38). Internal consistency was sound with Cronbach's α reported at 0.73 for the scale (38). In a U.S. sample, Cronbach coefficients for subscale scores ranged from fair (α = 0.43) for peer problems to excellent for total difficulties (α = 0.83) and impairment scores (α = 0.80), and good to excellent for other subscales (α = 0.63–0.77) (58). Test-retest reliability was reasonable across a 4- to 6 month period (α = 0.62) (38).

The CRAFFT is a six-item screening test used to assess adolescents for substance use and abuse (39). Items ask directly about substance use (e.g., item 2: *do you ever use*

alcohol or drugs to relax, feel better about yourself or fit in?) and require a simple *yes/no* response, with items summed for a final score. CRAFFT scores have been shown to correlate strongly with substance use classifications: 1) *no use*, 2) *occasional use*, 3) *problem use*, 4) *abuse,* and 5) *dependence* (Spearman's r = 0.72, $p < .001$), and scores above 2 are indicative of *problem use*, *abuse,* and *dependence* categories (59).

The Acculturation, Habits, and Interests Multicultural Scale for Adolescents (AHIMSA) is a measure of cultural identification in adolescents (40). AHIMSA comprises seven items and generates scores for four sub-scales: 1) country of residence orientation (assimilation), 2) other country orientation (separation), 3) both countries orientation (integration), and 4) neither country orientation (marginalization) (40). Three of the sub-scales correlated with subscales of a modified Acculturation Rating Scale for Mexican-Americans-II, with English language usage, providing initial evidence of construct validity (60). Internal consistency of the sub-scales was acceptable, with Cronbach's α ranging from 0.50 (marginalization) to 0.79 (assimilation and integration) (40).

Procedure

The questionnaire was administered verbally (UK, New Zealand, South Africa) or completed by youth in hard copy (Canada, China) or *via* computer using Qualtrics survey software (Australia) (61); however, there were no differences in item content or ordering of items between the different administered versions. All research sites completed the full test battery, with the exception of the UK and South Africa for which participants did not complete the COMPAS-W Scale, and China for which participants did not complete the CRAFFT. In the UK, the WEMWBS wellbeing scale was preferred as a measure of wellbeing as this site had comparative data on this age group for another sample, and so the COMPAS-W was not administered to keep testing time minimal. Similarly in South Africa, the COMPAS-W was not administered due to ethical concerns that the administration of a second wellbeing questionnaire (in addition to the WEMWBS) would make the testing time too long. In China, the CRAFFT was not administered as it was not culturally acceptable to ask participants about the use of drugs and alcohol. Measures were translated and back-translated into Mandarin for the China cohort. All other country cohorts completed the questionnaire in English.

Statistical Analysis

Data were collected from each research site and compiled into a single data file using the SPSS Statistics 24 package. Internal reliability of each questionnaire was evaluated across the sample and per site using Cronbach alpha.

Mean differences in trauma exposure frequency was evaluated between migrants *versus* non-migrants (controlling for site), as well as non-migrants *versus* internal and external migrants using univariate ANOVA. Variation in the type of event per group was examined using crosstabs chi-square analysis. This analysis was repeated to also compare differences between sites.

To then consider whether trauma exposure in the past year moderated the impact of mental health in migrants *versus* non-migrants, we examined the interaction effects of trauma exposure x migrancy status on mental health and resilience outcomes using univariate ANOVA, covarying for age, sex, site differences, and whole life trauma exposure. This analysis included a comparison of external *vs.* internal migrants *vs.* non-migrants. A p value significance threshold of 0.05 was adopted in all analyses.

RESULTS

Internal Reliability

Internal reliability of each questionnaire across and within each site is shown in **Table 2**. Across the sample, all questionnaires showed high internal reliability. High internal reliability for most questionnaires was also evident within site, with some exceptions (e.g., lower estimates for the CYRM-28 and WEMWBS in the UK sample, likely due to its smaller sample size of 10; and lower estimates for the CRAFFT in the Australian, Canadian, and UK samples, likely due to increased variability in substance use/abuse within these sites).

Mean Differences in Trauma Exposure

Figure 1 presents the frequency (percentage) of types of childhood traumatic events reported across the sample, for both the past year and lifetime. Mean total events reported for the past year and lifetime were 1.26 (± 1.53) and 2.54 (± 1.85), respectively.

We next considered differences in traumatic events reported in migrant *versus* non-migrant groups, controlling for site

TABLE 2 | Internal reliability (Cronbach alpha) of each questionnaire by site.

Measure (no. of items)	Australia (*N* = 25)	Canada (*N* = 21)	China (*N* = 77)	New Zealand (*N* = 33)	South Africa (*N* = 28)	United Kingdom (*N* = 10)	Total (*N* = 194)
CYRM-28 (28)	0.831	0.869	0.926	0.929	0.874	0.333	**0.904**
CD-RISC (25)	0.811	0.896	0.932	0.925	0.916	0.792	**0.929**
WEMWBS (14)	0.829	0.877	0.922	0.896	0.840	0.537	**0.898**
COMPAS-W (26)	0.824	0.850	0.900	0.861	–	–	**0.883**
DASS-21 (21)	0.769	0.921	0.948	0.912	0.905	0.854	**0.931**
SDQ (20)	0.843	0.861	0.812	0.862	0.811	0.846	**0.823**
CRAFFT (6)	0.480	0.310	–	0.782	0.727	0.107	**0.721**

CYRM-28, Child and Youth Resilience Measure; CD-RISC, Connor-Davidson Resilience Scale; WEMWBS, Warwick-Edinburgh Mental Well-being Scale; COMPAS-W, COMPAS-W Wellbeing Scale; DASS-21, Depression, Anxiety, Stress Scale; SDQ, Strengths and Difficulties Questionnaire; and CRAFFT, CRAFFT Screening Tool for Adolescent Substance Abuse. "–" reflects missing data due to China not administering the CRAFFT, and South Africa/United Kingdom not administering the COMPAS-W.

differences. There were no significant differences between migrants and non-migrants in the total mean traumatic events reported over the *lifetime* (F = 3.70, p = .056). There was however a significant difference in the total mean traumatic events reported in the *past year* (F = 5.55, p = .019), with migrants reporting a higher mean number of events (M = 1.43, SD = 1.62) than non-migrants (M = 0.71, SD = 0.97). There were also differences between types of trauma reported by migrants and non-migrants. Relative to non-migrants, migrants reported more episodes of combat experience in war (NM: 0%, M: 13% exposure, p = .010) and death of a family member or close friend (NM: 44%, M: 62% exposure, p = .034) in their lifetime, plus more episodes of death of a family member or close friend than non-migrants in the past year (NM: 16%, M: 34%, p = .048).

We then considered whether the differences in traumatic events reported in migrants *versus* non-migrants varied when stratifying by internal *versus* external migrants. There were no significant differences between migrants (internal *vs*. external) and non-migrants in the total mean traumatic events reported over the *lifetime* (F = 2.24, p = .110). There was however a significant difference in the total mean traumatic events reported in the *past year* (F = 4.66, p = .011), with internal migrants reporting a higher mean number of events (M = 1.59, SD = 1.74) than external migrants (M = 1.05, SD = 1.26) and non-migrants (M = 0.71, SD = 0.97). There were also differences between exposure for certain types of events. For lifetime events (see **Figure 2A**), internal migrants reported a higher number of life threatening accidents (19%) relative to external migrants (7%) and non-migrants (4%, p = .009). For past year events (**Figure 2B**), internal migrants reported a higher number of combat/war experiences relative to external migrants and non-migrants (M^I: 14%, M^E: 3%, NM: 0%, p = .015), a higher number of life threatening accidents (M^I: 9%, M^E: 0%, NM: 0%, p = .030), and death of a close family member or friend (M^I: 36%, M^E: 29%, NM: 16%, p = .039).

We then examined reported traumatic event differences between the sites. There were no significant differences between sites in the total mean traumatic events reported over the *lifetime* (F = 1.95, p = .088). There was a significant difference in the total mean traumatic events reported in the *past year* (F = 5.25, p < .0001), with South African youth reporting a higher mean number of events (M = 2.43, SD = 2.13) relative to every other site: Australia (M = 0.80, SD = 1.08, p < .0001), Canada (M = 1.24, SD = 1.58, p = .005), China (M = 1.29, SD = 1.47, p < .0001), New Zealand (M = 0.73, SD = 0.84, p < .0001), and the UK (M = 0.80, SD = 0.92, p = .003). There were also differences between sites for exposure to specific types of traumatic events reported during the *lifetime* and *past year*. For lifetime events (see **Figure 3A**), significant differences between sites were evident for combat/war exposure (p = .0001), witnessing serious injury/murder (p = .001), attack/assault (p = .029), and death of family member/close friend (p = .023). There were also significant site differences for past year events (see **Figure 3B**) for combat/war exposure (p = .032), life threatening accident (p = .023), witnessing injury/murder (p = .001), attack/assault (p = .001), being threatened by a weapon, held captive or kidnapped (p = .0001), and death of family member or close friend (p = .005).

Main and Interacting Effects of Trauma and Migrancy on Wellbeing and Mental Health Outcomes

To then consider whether trauma exposure in the past year moderated the impact of mental health in migrants *versus* non-migrants, we examined the interaction effects of trauma exposure x migrancy status on mental health and resilience resources using univariate ANOVA, covarying for any age, sex, site differences, and whole life trauma exposure effects. We also considered the added comparison of external migrants *vs*. internal migrants *vs*. non-migrants to evaluate whether type of migrancy had a differential impact.

There was no significant difference between migrants and non-migrants in their resilience resources as measured by the CYRM-28. When considering types of migration, a main effect was found for migrancy (F = 3.37, df = 2, p = .037), whereby external migrants had a significantly higher CYRM-28 resilience score (M = 119.03, SE = 2.73) compared to internal migrants (M = 110.83, SE = 2.01; see **Figure 4A**). There was no main effect of trauma, or trauma by migrancy effects, on the CYRM-28.

For the CD-RISC resilience measure, there was a significant main effect for migrancy (F = 21.37, df = 1, p < .0001), whereby migrants demonstrated higher resilience (M = 69.92, SE = 1.52) than non-migrants (M = 56.33, SE = 2.44). When considering types of migration, a main effect was again found (F = 13.15, df = 2, p < .0001), whereby external migrants had a significantly higher resilience score (M = 74.64, SE = 2.68) compared to internal migrants (M = 66.86, SE = 1.99). There was no main effect of trauma on CD-RISC scores, yet there was a trauma by migrancy effect (F = 8.31, df = 1, p = .005). Higher resilience scores were evident in migrants exposed to trauma than non-trauma, whereas lower resilience scores were evident in non-migrants exposed to trauma *vs*. non-trauma. Moreover, trauma-exposed migrants showed higher resilience scores than trauma-exposed non-migrants. When considering types of migration, a trauma by migrancy effect was also evident (F = 5.61, df = 2, p = .005). External migrants showed higher resilience than internal migrants in the non-trauma group, but there were no differences between external and internal migrants in the trauma-exposed group (**Figure 5A**).

No significant main effects of migrancy or trauma were evident for wellbeing when measured using the WEMWBS. There were also no effects of migrancy when considering different types of migration. A significant interaction effect of trauma by migrancy was however evident (F = 6.43, df = 1, p = .012). Migrants and non-migrants showed similar wellbeing scores in the absence of trauma, yet in the trauma-exposed group, non-migrants (M = 48.93, SE = 2.16) showed significantly lower wellbeing than trauma-exposed migrants (M = 56.19, SE = 1.06). This interaction effect was also significant when considering types of migrants (F = 4.29, df = 2, p = .015). Again, no group differences were evident in wellbeing in the absence of trauma, yet in the trauma-exposed

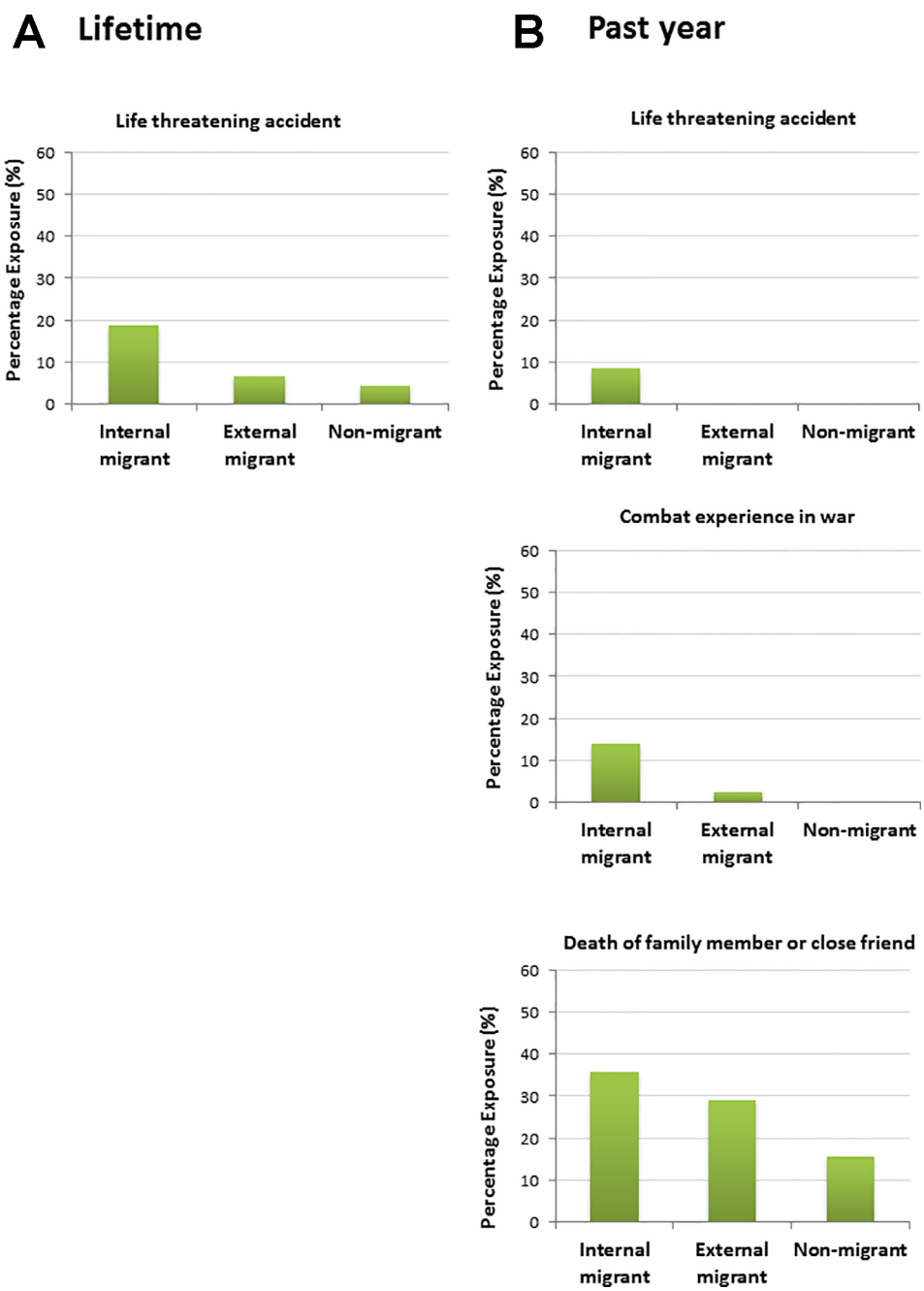

FIGURE 2 | Percentage exposure (% of "yes" responses) for significant differences by migrancy groups for total traumatic events reported during **(A)** the lifetime and **(B)** the past year.

group, it was the non-migrants (M = 49.23, SE = 2.17) which showed lower wellbeing than the internal migrants (M = 56.13, SE = 1.27) or external migrants (M = 55.92, SE = 1.97; **Figure 5B**).

Similar to the results above, no significant main effects of migrancy or trauma were evident for total wellbeing when measured using the COMPAS-W scale. A significant interaction effect of trauma by migrancy was however evident (F = 10.825, df = 1, p = .001). In the absence of trauma exposure, non-migrants (M = 106.98, SE = 3.29) showed higher levels of wellbeing than migrants (M = 97.41, SE = 2.45); yet in the trauma-exposed group, non-migrants (M = 94.10, SE = 3.52) showed reduced levels of wellbeing than trauma-exposed migrants (M = 102.08, SE = 1.98). This interaction effect was

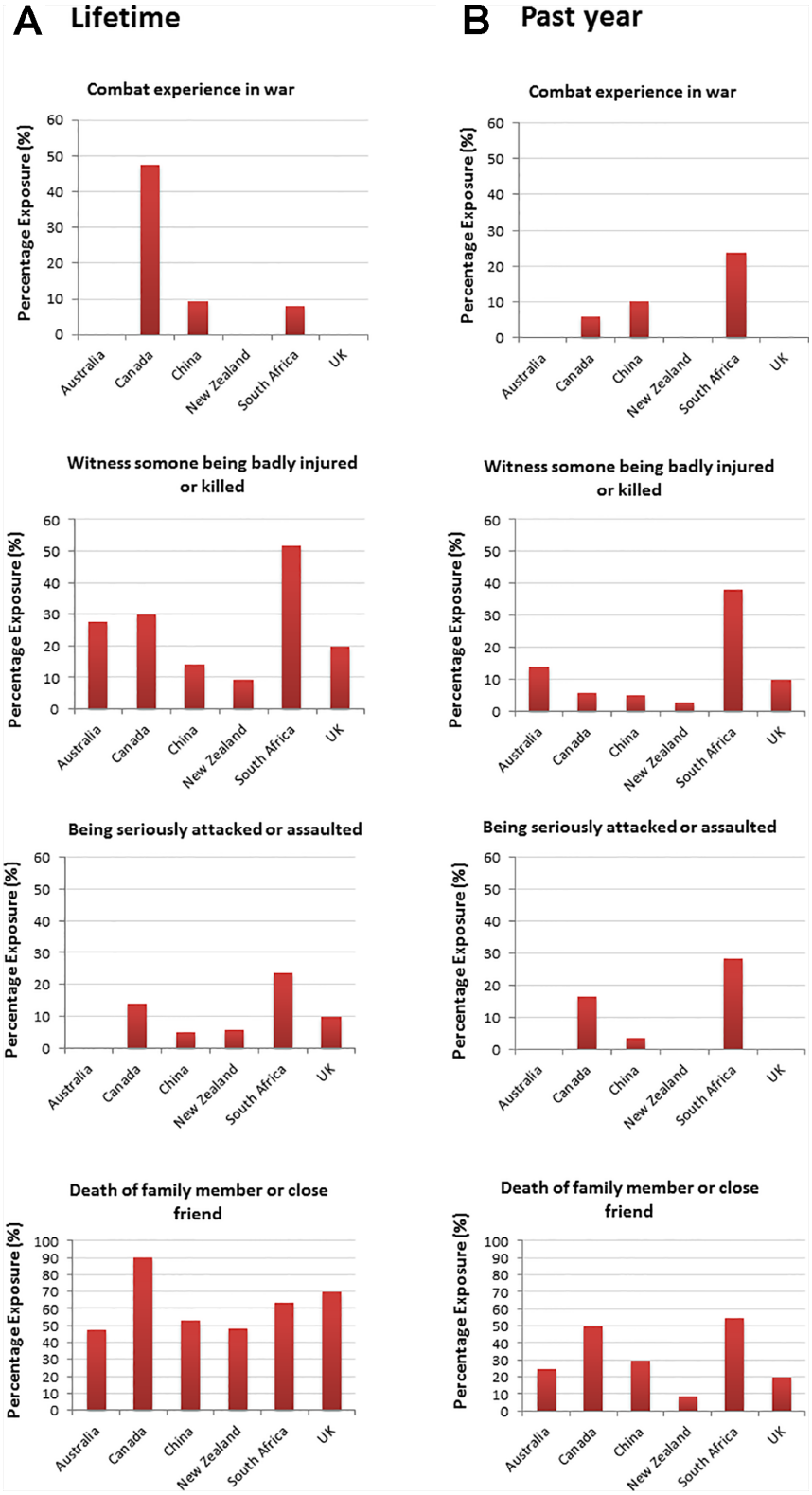

FIGURE 3 | Percentage exposure (% of "yes" responses) for significant site differences by total traumatic events reported during **(A)** the lifetime and **(B)** the past year. For **(B)**, site differences were also found for "life-threatening accidents" (China: 5%, South Africa: 20% percentage exposure), and "threatened by a weapon/held captive/kidnapped" (Australia: 100%, China: 3.4%, South Africa: 15% percentage exposure) (not presented here).

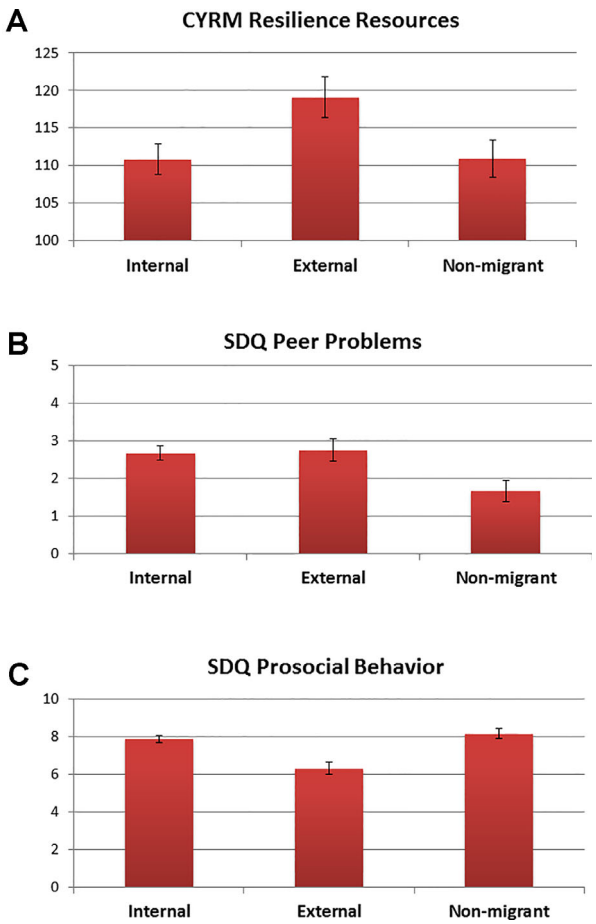

FIGURE 4 | Means and SE bars for significant main effects of migrancy for **(A)** Child and Youth Resilience Measure (CYRM) resilience resources, **(B)** Strengths and Difficulties Questionnaire (SDQ) peer problems, and **(C)** SDQ prosocial behavior.

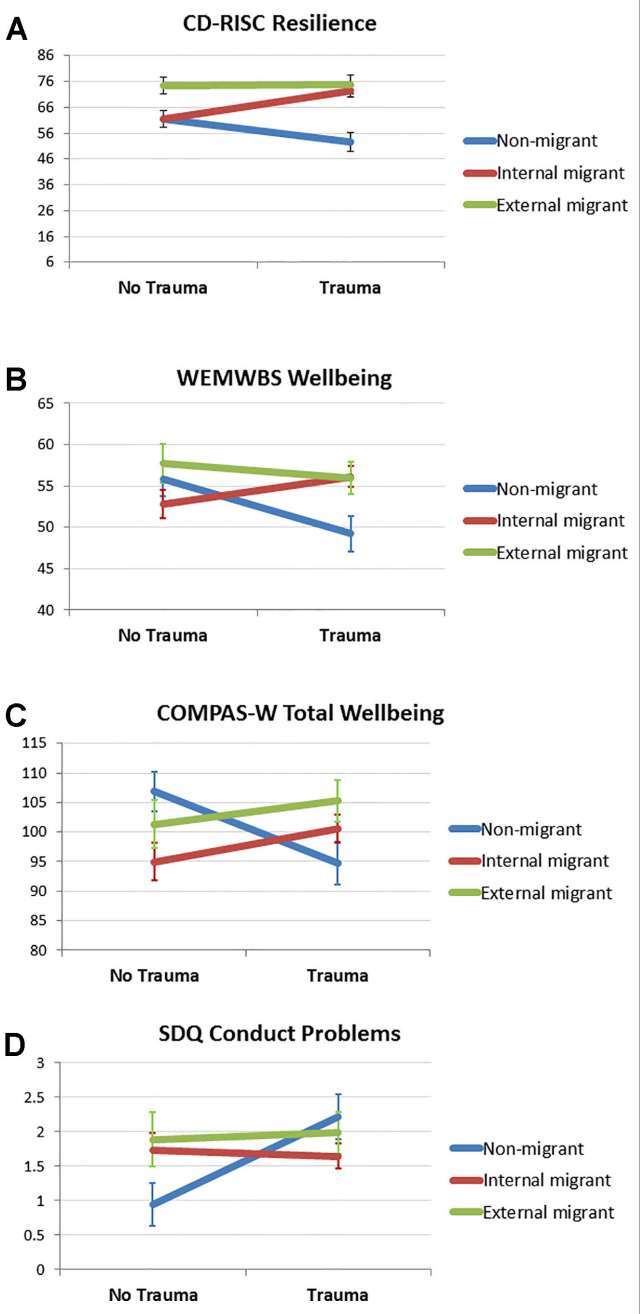

FIGURE 5 | Means and SE bars for significant interaction effects of trauma by migrancy for **(A)** Connor-Davidson Resilience Scale (CD-RISC) resilience scores, **(B)** Warwick-Edinburgh Mental Well-being Scale (WEMWBS) wellbeing scores, **(C)** COMPAS Wellbeing Scale (COMPAS-W) wellbeing scores, and **(D)** Strengths and Difficulties Questionnaire (SDQ) conduct problems.

also significant when considering types of migrants (F = 5.22, df = 2, p = .007). In the absence of trauma exposure, non-migrants (M = 106.83, SE = 3.28) showed higher levels of wellbeing than internal migrants in particular (M = 94.96, SE = 3.20) with external migrants showing no differences between the other two groups (M = 101.30, SE = 4.06). Yet, when trauma-exposed, the wellbeing scores of the two migrant groups appeared unaffected (IM: M = 100.55, SE = 2.37; EM: M = 105.26, SE = 3.52), whereas the non-migrants showed a reduction in wellbeing when trauma-exposed (M = 94.72, SE = 3.54; **Figure 5C**). A similar pattern of significant trauma x migrancy interaction effects were also found for the COMPAS-W subscales Composure, Mastery, Positivity, Achievement, and Satisfaction (see **Supplementary Materials**).

In respect to depression, anxiety, and stress as measured by the DASS-21, there were no significant main or interaction effects of trauma or migrancy in terms of total general distress or depression, anxiety, and stress subscores. There were also no significant main or interaction effects of trauma or migrancy for self-reported substance-related risks and problems as measured by CRAFFT.

When considering behavioral problems measured by the SDQ, several main and interaction effects were evident. First, we identified two main effects of migrancy for peer problems (F = 10.30, df = 1, p = .002) and prosocial behavior (F = 7.44, df = 1,

p = .007), for which migrants showed higher peer problems (M = 2.70, SE = 0.15) and lower prosocial behavior (M = 7.4, SE = 0.16) than non-migrants (peer problems: M = 1.66, SE = 0.28; prosocial: M = 8.34, SE = 0.29). When considering types of migrancy, these main effects were again significant for peer problems (F = 5.16, df = 2, p = .007) and prosocial behavior (F = 12.40, df = 2, p < .0001). In this case, both internal (M = 2.67, SE = 0.19) and external migrants (M = 2.76, SE = 0.31) showed higher peer problems than non-migrants (M = 1.67, SE = 0.28; **Figure 4B**). In addition, external migrants showed the lowest prosocial behavior (M = 6.33, SE = 0.30), followed by internal migrants (M = 7.89, SE = 0.20), with non-migrants showing the highest level of prosocial behavior (M = 8.16, SE = 0.28; **Figure 4C**). Second, we identified a main effect of trauma for conduct problems (F = 6.98, df = 1, p = .022), whereby trauma exposed participants showed higher conduct problems (M = 1.96, SE = 0.18) than non-trauma exposed participants (M = 1.35, SE = 0.19). There was also a trauma by migrancy effect for conduct problems (F = 6.98, df = 1, p = .009), whereby in the absence of trauma exposure, non-migrants showed fewer conduct problems (M = 0.92, SE = 0.30) than migrants (M = 1.78, SE = 0.20). Yet, in the presence of trauma exposure, migrants showed no difference in conduct problems (M = 1.74, SE = 0.16), whereas non-migrants showed an increase in conduct problems (M = 2.18, SE = 0.33). This interaction effect for conduct problems was also significant when considering types of migrancy (F = 3.59, df = 2, p = .030), whereby non-migrants showed fewer conduct problems in the absence of trauma exposure (M = 0.94, SE = 0.31) than both internal migrants (M = 1.73, SE = 0.24) and external migrants (M = 1.89, SE = 0.40), but in the presence of trauma exposure, non-migrants showed similar levels of conduct problems (M = 2.22, SE = 0.33) to internal migrants (M = 1.65, SE = 0.19) and external migrants (M = 1.99, SE = 0.31; **Figure 5D**).

DISCUSSION

This aim of this study was to use our pilot data to explore the impact of site, migrancy, and trauma exposure on resilience, wellbeing, and mental health among migrant and non-migrant adolescents aged 10–17 in multiple countries where there are high rates of internal and external migration. Our key research questions aimed to clarify 1) whether the measures of resilience, wellbeing, mental health, and behavior were reliable across country sites, 2) whether differences were apparent between migrant and non-migrant adolescents and between sites in trauma exposure, 3) whether there were differences between migrant and non-migrants in behavioral and mental health outcomes, and 4) how trauma and migration was related to resilience, behavior and wellbeing.

First, we have shown that the structured questionnaire administered in the current study was feasible and acceptable in this age group, and had good validity when used in different settings with youth of the same age. All questionnaires showed high internal reliability across the total sample, with some small variability in estimates for specific sites likely due to smaller sample sizes and variability in health behaviors for specific subsamples (particularly for the UK sample with N = 10).

With regard to the second question, a number of key differences in trauma exposure were found for migrants and non-migrants, and by site. Generally speaking, migrants reported a higher mean number of traumatic events in the past year than non-migrants, with internal migrants reporting the most events. The types of events that varied the most between migrant groups were exposure to life-threatening accidents, combat/war experience, and death of a family member or close friend. When we considered variation by site, South African youth reported a higher mean number of events relative to all other country sites. Importantly, the effects of migrancy were significant despite including site as a covariate, so the effects were not specific to any country of origin in particular but rather by virtue of migrancy status specifically.

Thirdly, we identified a number of differences between the migrant groups in terms of mental health and behavioral outcomes. Migrant youth reported higher CD-RISC resilience scores than non-migrants, yet they also reported more behavioral problems in terms of higher SDQ peer problems and lower prosocial behaviors. However, when we considered type of migrancy, the external migrants showed the higher resilience scores yet lower SDQ prosocial behavior scores than the internal migrants and non-migrants. External and internal migrant groups showed no difference in the SDQ peer problems (both higher than non-migrants). Together, this suggests that perhaps the external migrants showed higher resilience than internal migrants because they were able to move away from the trauma (by moving countries), whereas internal migrants may not have been able to move "away" from the adversity. This argument is strengthened by the fact that the internal migrants showed the highest percentage of past year traumatic events due to combat/war, life threatening accidents, and death of a family member/friend in particular, suggesting the adversity may still be present or having an impact. In contrast to these findings for resilience, migrants did however report more behavioral problems and less prosocial behaviors toward peers. This effect is likely a reflection of challenges that youth would experience when entering and assimilating into a new school system; in particular, the larger challenge of creating new peer networks within a new cultural environment, and often in another primary language for many external migrants.

Finally, we found that the presence of trauma modulated the mental health and behavioral outcomes of non-migrants in particular, rather than migrants who showed no differences in scores when comparing trauma and non-trauma exposed groups. For instance, in terms of CD-RISC resilience scores, migrants had higher resilience than non-migrants in the presence of trauma. This effect was apparent in both internal and external migrant groups, although in the absence of trauma, external migrants still showed higher resilience scores. Together, this suggests that migrant youth, particularly external migrants, show a resilient response to adversity, especially in the presence of trauma or hardship. As this is cross-sectional data, it is difficult to

delineate whether this effect is due to these migrant groups being able to move "away" from the trauma and hence they then feel they have more resilience resources, or because they had an inherent disposition of stronger adaptation or sense of agency which underscored the motivation for them (and their family) to change their living environment and move away. For wellbeing (measured using the WEMWBS and COMPAS-W scales), the migrant youth (both internal and external) showed higher levels of wellbeing than non-migrants in the presence of trauma. This effect may again reflect the increased positive mental health state of migrant youth compared to non-migrant youth given they were able to move away from the most recent trauma. Finally, in terms of SDQ conduct problems, the presence or absence of trauma did not appear to impact migrant conduct behavior for both internal and external migrants. Yet non-migrants showed lower conduct problems in the absence of trauma, but an increase in conduct problems in the presence of trauma. Overall, these effects suggest that the mental health behaviors of migrants appeared to be unaffected by the presence or absence of trauma, whereas non-migrants show significant detriments in resilience, wellbeing, and conduct problems in the presence of trauma. Migrant youth do however appear to demonstrate more peer problems than non-migrant youth and less prosocial behaviors for external migrants in particular.

Previous studies focusing on the mental health of migrant youth have either focused on refugee youth in particular, with limited direct comparisons of mental health outcomes to immigrant and non-migrant comparative groups, and/or broadly defined immigrant groups with limited consideration of time since migrancy, generational effects and/or cross-cultural differences (25, 27–30). Nonetheless, these studies have identified a number of protective factors for mental health including psychological wellbeing of the parents/guardians, peer and social support, religious beliefs, and integration into the host community, whereas risk factors of poorer mental health outcomes included trauma exposure, parental exposure to violence, loss of parent(s), limited family support, violence and discrimination in host country, and feeling disconnected to school and neighborhood (25, 27, 29). In contrast to some of these effects, our findings suggest that trauma-exposed migrant youth are more resilient and demonstrate higher levels of wellbeing in comparison to their non-migrant trauma-exposed peers. The presence of trauma had no impact on the conduct behaviors of migrant youth relative to non-migrants who *were* more significantly impacted by trauma exposure. Migrant youth did however demonstrate more peer problems and less prosocial behaviors than their non-migrant trauma-exposed peers, which is consistent with previous reports of increased behavioral problems in refugee youth (27). Given the current sample included both immigrants and refugee migrant youth, it is possible that the role of trauma in the current study showed a differential impact to previous studies focusing on refugee youth alone. Indeed, in the recent study comparing mental health outcomes of refugee *versus* immigrant youth aged 11–13 years in Canada, it was the refugee youth that demonstrated significantly higher emotional problems, aggressive behavior, and pre-post-migration trauma than immigrant youth (27). However, as participants needed to be living in Canada for 10 years or less, it is unclear whether any differences varied with the recency of migration. It is therefore worthwhile to compare these migrant subgroups over time. Examining these associations longitudinally will help determine whether these higher levels of resilience and wellbeing in migrant youth are sustained over time, or whether they are a short-term outcome from possibly moving away from the trauma. Recent studies in fact suggest that factors such as postarrival discrimination or acculturative stress can cause additional harm on mental health outcomes, whereas feeling welcomed at school can mitigate against mental and behavioral problems (27, 29). Thus, it would be important to confirm whether the behavioral problems linked to peers and prosocial behaviors is alleviated with time as the young people become more acquainted with their new school environment and peer networks, or whether this worsens and has a subsequent detrimental impact on their psychological and cognitive development.

The current study was an international pilot study conducted across a range of contexts in high and middle income countries, including both external and internal migrant adolescents and non-migrant adolescents. The migrants included refugees and economic migrants. To our knowledge this is the first reported study of its kind. The study also included wellbeing and resilience findings in addition to risk/vulnerability outcomes. As the study was cross-sectional and limited by sample size in each country, this restricted some statistical analyses and comparisons that could be made (e.g., refugee *vs*. economic migrant adolescents). The limited sample sizes of some specific sites may have also impacted the reliability of some measures, as reported earlier. Thus, it would be worthwhile to replicate these outcomes in a larger sample, controlling for multiple comparisons to minimize potential false positive reporting. Some questions were also not culturally acceptable in some sites, including for instance those asking about the use of drugs and alcohol in China, so had to be omitted. This limited the inclusion of some sites in the analyses, but is an issue that needs to be acknowledged in future international trials. Another limitation of this study is that recruitment was based on voluntary participation, so self-selecting participants (particularly some migrant adolescents) may have been more resilient to begin with. It would therefore be important to confirm the current findings in a larger and even more diverse sample of adolescents.

In conclusion, we found that, with some adjustment for cultural sensitivity, the current questionnaire included a reliable set of measures to use in an international study of migrant and non-migrant adolescent populations. Some interesting group differences in mental health outcomes were observed between migrants and non-migrants in the presence/absence of trauma exposure, which may open up avenues for future research. Our findings indicate that promoting mental health and wellbeing is an important strategy to implement for all young people, particularly those recovering from adversity, migrant or not. There is a need for further research with larger prospective sample sizes to investigate levels of resilience and mental health behaviors in migrant adolescents over time, and ways of promoting increased peer support networks in schools,

as well as resilience in trauma-exposed young people, regardless of migrancy status.

ETHICS STATEMENT

Ethics approval was sought and gained from the respective sites according to the local Human Research Ethics Committee processes (Australia; University of New South Wales Human Research Ethics Committee: HC15672; Canada; Dalhousie University Social Sciences and Humanities Research Ethics Board: REB 2015-3666; China; Chinese University of Hong Kong; New Zealand; The University of Auckland Human Ethics Committee: 015968; South Africa: North-West University Humanities and Health Research Ethics Committee: NWU-HS-2015-0234; United Kingdom; University of Bristol Faculty of Medicine Research Ethics Committee: ref 2016/26061). Written and/or verbal information was provided to all participants. Informed verbal and/or written consent was obtained from parents and informed verbal or written assent was gained from youth.

AUTHOR CONTRIBUTIONS

JG coordinated the study across the six country sites, including the Australian site, analyzed and interpreted the data, and wrote parts of the paper and revisions. RA collected data for the Australian site, completed data entry, and wrote parts of the paper. AE coordinated the data collection in the UK, and assisted with data interpretation and drafting of the paper. KF assisted with the coordination of the Australian study, data interpretation, and drafting of the paper. KH and MU coordinated the data collection in Canada, assisted with data interpretation and paper editing. AM-J assisted with data collection coordination in the UK, data interpretation, and paper editing. SR was the academic lead for the WUN group, and assisted with data interpretation and paper editing. LT coordinated the study in South Africa and assisted with data interpretation and paper editing. TW coordinated the study in New Zealand, wrote parts of the paper, and assisted with data interpretation and paper editing. QW coordinated the study in Hong Kong and assisted with data interpretation and editing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00997/full#supplementary-material

REFERENCES

1. WHO. (2014). *Health for the world's adolescents: a second chance in the second decade*. Retrieved from http://www.who.int/maternal_child_adolescent/documents/second-decade/en/.
2. Perreira KM, Ornelas I. Painful passages: traumatic experiences and post-traumatic stress among immigrant Latino adolescents and their primary caregivers. *Int Migration Rev* (2013) 47(4):1–25. doi: 10.1111/imre.12050
3. Wiese EB. Culture and migration: psychological trauma in children and adolescents. *Traumatology* (2010) 16(4):142–52. doi: 10.1177/1534765610388304
4. OECD. (2010). *Closing the gap for immigrant students: Policies, practice and performance*. Retrieved from https://www.oecd-ilibrary.org/education/closing-the-gap-for-immigrant-students_9789264075788-en.
5. UNICEF. (2010). *Children, Adolescents and Migration: Filling the Evidence Gap*. Retrieved from https://www.unicef.org.
6. UNICEF New Zealand. (2015). A Post 2015 world fit for children. Retrieved from https://www.unicef.org.nz.
7. Patton GC, Sawyer SM, Santelli JS, Ross DA, Afifi R, Allen NB, et al. Our future: a Lancet commission on adolescent health and wellbeing. *Lancet* (2016) 387(10036):2423–78. doi: 10.1016/S0140-6736(16)00579-1
8. Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Ustun TB. Age of onset of mental disorders: A review of recent literature. *Curr Opin Psychiatry* (2007) 20(4):359–64. doi: 10.1097/YCO.0b013e32816ebc8c
9. Viner RM, Coffey C, Mathers C, Bloem P, Costello A, Santelli J, et al. 50-year mortality trends in children and young people: a study of 50 low-income, middle-income and high income countries. *Lancet* (2011) 377(9772):1162–74. doi: 10.1016/S0140-6736(11)60106-2
10. Herzog J, Fleming T, Ferdik F, Durkin DW. The association between secondary trauma and mental health outcomes among adolescents: findings from a nationally representative cross-sectional survey. *Traumatology* (2016) 22(4):307–13. doi: 10.1037/trm0000099
11. Kisiel C, Summersett-Ringgold F, Weil LEG, McClelland. Understanding strengths in relation to complex trauma and mental health symptoms with child welfare. *J Child Family Studies* (2017) 26:437–51. doi: 10.1007/s10826-016-0569-4
12. Chu D, Williams LM, Harris AWF, Bryant RA. Early life trauma predicts self-reported levels of depressive and anxiety symptoms in nonclinical community adults: relative contributions of early life stressor types and adult trauma exposure. *J Psychiatric Res* (2013) 47(1):23–32. doi: 10.1016/j.jpsychires.2012.08.006

13. Flaherty EG, Thompson R, Dubowitz H, Harvey EM, English DJ, Proctor LJ, et al. Adverse childhood experiences and child health in early adolescence. *JAMA Pediatrics* (2013) 167(7):622–9. doi: 10.1001/jamapediatrics.2013.22
14. Bonanno GA, Mancini AD. Beyond resilience and PTSD: mapping the heterogeneity of responses to potential trauma. *Psychol Trauma* (2012) 4 (1):74–83. doi: 10.1037/a0017829
15. Hobfoll SE, de Jong TVM. Sociocultural and ecological views of trauma: Replacing cognitive-emotional models of trauma. In: Zoellner LA, Feeny NC, editors. *Facilitating resilience and recovery following trauma*. Guildford Press: New York (2014). p. 69–90.
16. Soleimanpour S, Geierstanger S, Brindis CD. Adverse childhood experiences and resilience: addressing the unique needs of adolescents. *Acad Pediatr* (2017) 17(7):S108–14. doi: 10.1016/j.acap.2017.01.008
17. Masten A. Resilience in children threatened by extreme adversity: frameworks for research, practice, and translational synergy. *Dev Psychopathol* (2011) 23:493–506. doi: 10.1017/S0954579411000198
18. Alexander R, Gatt JM. Resilience. In: Miu AC, Homberg JR, Lesch K-P, editors. *Genes, Brain and Emotions: Interdisciplinary and Translational Perspectives*. Oxford: Oxford University Press (2019). p. 286–303.
19. Ungar M. The social ecology of resilience: addressing contextual and cultural ambiguity of a nascent construct. *Am J Orthopsychiatry* (2011) 81(1):1–17. doi: 10.1111/j.1939-0025.2010.01067.x
20. Masten A, Osofsky J. Disasters and their impact on child development: introduction to the special section. *Child Dev* (2010) 81(4):1029–39. doi: 10.1111/j.1467-8624.2010.01452.x
21. Stratta P, Capanna C, Dell' Osso L, Carmassi C, Patriarca S, Di Emidio G, et al. Resiliience and coping in trauma spectrum symptoms prediction: a structural equation modeling approach. *Personality Individual Differences* (2015) 77:55–61. doi: 10.1016/j.paid.2014.12.035
22. Cicchetti D. Annual research review: resilient functioning in maltreated children–past, present, and future perspectives. *J Child Psychol Psychiaty* (2013) 54(4):402–22. doi: 10.1111/j.1469-7610.2012.02608.x
23. Hughes K, Bellis MA, Hardcastle KA, Sethi D, Butchart A, Mikton C, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health* (2017) 2(8):e356–66. doi: 10.1016/S2468-2667(17)30118-4
24. Betancourt TS, Abdi S, Ito B, Lilienthal M, Agalab N, Ellis H. We left one war and came to another: resource loss, acculturative stress, and caregiver-child relationships in Somali refugee families. *Cult Divers Ethnic Minority Psychol* (2014) 21(1):114–25. doi: 10.1037/a0037538
25. Fazel M, Reed RV, Panter-Brick C, Stein A. Mental health of displaced and refugee children resettled in high-income countries; risk and protective factors. *Lancet* (2012) 379:266–82. doi: 10.1016/S0140-6736(11)60051-2
26. Sotomayor-Peterson M, Montiel-Carbajal M. Psychological and family well-being of unaccompanied Mexican child migrants sent back from the U. S. border region of Sonora-Arizona. *Hispanic J Behav Sci* (2014) 36(2):111–23. doi: 10.1177/0739986314523560
27. Beiser M, Hou F. Mental health effects of premigration trauma and postmigration discrimination on refugee youth in canada. *J Nervous Mental Dis* (2016) 204(6):464–70. doi: 10.1097/NMD.0000000000000516
28. Chau K, Baumann M, Kabuth B, Chau N. School difficulties in immigrant adolescent students and roles of socioeconomic factors, unhealthy behaviours, and physical and mental health. *BMC Public Health* (2012) 12(1):453. doi: 10.1186/1471-2458-12-453
29. Sirin SR, Ryce P, Gupta T, Rogers-Sirin L. The role of acculturative stress on mental health symptoms for immigrant adolescents: a longitudinal investigation. *Dev Psychol* (2013) 49(4):736–48. doi: 10.1037/a0028398
30. Tummala-Narra P. Ethnic identity, perceived support, and depressive symptoms among racial minority immigrant-origin adolescents. *Am J Orthopsychiatry* (2015) 85(1):23–33. doi: 10.1037/ort0000022
31. WUN. (2017). Youth Resilience Network. Retrieved from https://wun.ac.uk/wun/research/view/resilience-in-youth-and-service-providers.
32. Sanders B, Becker-Lausen E. The measurement of psychological maltreatment: early data on the Child Abuse and Trauma Scale. *Child Abuse Negl* (1995) 19:315–23. doi: 10.1016/S0145-2134(94)00131-6
33. Ungar M, Liebenberg L. Assessing resilience across cultures using mixed methods: construction of the child and youth resilience measure. *J Mixed Methods Res* (2011) 5(2):126–49. doi: 10.1177/1558689811400607
34. Connor KM, Davidson JR. Development of a new resilience scale: The Connor-Davidson Resilience Scale (CD-RISC). *Depression Anxiety* (2003) 18(2):76–82. doi: 10.1002/da.10113
35. Tennant R, Hiller L, Fishwick R, Platt S, Joseph S, Weich S, et al. The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): development and UK validation. *Health Qual Life Outcomes* (2007) 5(1):63. doi: 10.1186/1477-7525-5-63
36. Gatt JM, Burton KL, Schofield PR, Bryant RA, Williams LM. The heritability of mental health and wellbeing defined using COMPAS-W, a new composite measure of wellbeing. *Psychiatry Res* (2014) 219(1):204–13. doi: 10.1016/j.psychres.2014.04.033
37. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the depression anxiety stress scales (DASS) with the beck depression and anxiety inventories. *Behav Res Ther* (1995) 33(3):335–43. doi: 10.1016/0005-7967(94)00075-U
38. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry* (2001) 40(11):1337–45. doi: 10.1097/00004583-200111000-00015
39. Knight JR, Shrier LA, Bravender TD, Farrell M, Vander Bilt J, Shaffer HJ. A new brief screen for adolescent substance abuse. *Arch Pediatr Adolesc Med* (1999) 153(6):591–6. doi: 10.1001/archpedi.153.6.591
40. Unger JB, Gallaher P, Shakib S, Ritt-Olson A, Palmer PH, Johnson CA. The AHIMSA acculturation scale: A new measure of acculturation for adolescents in a multicultural society. *J Early Adolesc* (2002) 22(3):225–51. doi: 10.1177/02731602022003001
41. Wu Q, Ge T, Emond A, Foster K, Gatt JM, Hadfield K, et al. Acculturation, resilience and the mental health of migrant youth: a cross-country comparative study. *Public Health* (2018) 162:63–70. doi: 10.1016/j.puhe.2018.05.006
42. Liebenberg L, Ungar M, Vijver FV. Validation of the Child and Youth Resilience Measure-28 (CYRM-28) among Canadian youth. *Res Soc Work Pract* (2012) 22(2):219–26. doi: 10.1177/1049731511428619
43. Daigneault I, Dion J, Hébert M, McDuff P, Collin-Vézina D. Psychometric properties of the Child and Youth Resilience Measure (CYRM-28) among samples of French Canadian youth. *Child Abuse Neglect* (2013) 37(2):160–71. doi: 10.1016/j.chiabu.2012.06.004
44. Kobasa SC. Stressful life events, personality, and health: an inquiry into hardiness. *J Personality Soc Psychol* (1979) 37(1):1. doi: 10.1037/0022-3514.37.1.1
45. Sheehan D. *The anxiety disease*. Charles Scribner and Sons: New York, NY (1983).
46. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* (1983) 24(4):385–96. doi: http://www.jstor.org/stable/2136404
47. Sheehan D. Sheehan disability scale. In: Rush AJ, First MB, Blacker D, editors. *Handbook of psychiatric measures*. American Psychiatric Pub.: Washington DC (2008).
48. Stewart-Brown SL, Platt S, Tennant A, Maheswaran H, Parkinson J, Weich S, et al. The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): a valid and reliable tool for measuring mental well-being in diverse populations and projects. *J Epidemiol Community Health* (2011) 65(Suppl 2):A38–9. doi: 10.1136/jech.2011.143586.86
49. Taggart F, Friede T, Weich S, Clarke A, Johnson M, Stewart-Brown S. Cross cultural evaluation of the Warwick-Edinburgh Mental Well-being Scale (WEMWBS): a mixed methods study. *Health Qual Life Outcomes* (2013) 11 (1):27. doi: 10.1186/1477-7525-11-27
50. WHO. Development of the World Health Organization WHOQOL-BREF quality of life assessment. *Psychol Med* (1998) 28(3):551–8. doi: 10.1017/s0033291798006667
51. Diener E, Emmons RA, Larsen RJ, Griffin S. The satisfaction with life scale. *J Personality Assess* (1985) 49(1):71–5. doi: 10.1207/s15327752jpa4901_13
52. Duttweiler PC. The internal control index: A newly developed measure of locus of control. *Educ Psychol Meas* (1984) 44(2):209–21. doi: 10.1177/0013164484442004
53. Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *J Soc Psychol* (2003) 85 (2):348. doi: 10.1037/0022-3514.85.2.348

54. Beck AT, Steer RA, Carbin MG. Psychometric properties of the beck depression inventory: twenty-five years of evaluation. *Clin Psychol Rev* (1988) 8(1):77–100. doi: 10.1016/0272-7358(88)90050-5
55. Steer RA, Beck AT. Beck anxiety inventory. In: Zalaquett CP, Wood RJ, editors. *Evaluating stress: A book of resources*. Scarecrow Education: Lanham, MD (1997). p. 23–40.
56. Brown TA, Chorpita BF, Korotitsch W, Barlow DH. Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. *Behav Res Ther* (1997) 35(1):79–89. doi: 10.1016/S0005-7967(96)00068-X
57. Sinclair SJ, Siefert CJ, Slavin-Mulford JM, Stein MB, Renna M, Blais MA. Psychometric evaluation and normative data for the depression, anxiety, and stress scales-21 (DASS-21) in a nonclinical sample of US adults. *Eval Health Professions* (2012) 35(3):259–79. doi: 10.1177/0163278711424282
58. Bourdon KH, Goodman R, Rae DS, Simpson G, Koretz DS. The strengths and difficulties questionnaire: us normative data and psychometric properties. *J Am Acad Child Adolesc Psychiatry* (2005) 44(6):557–64. doi: 10.1097/01.chi.0000159157.57075.c8
59. Knight JR, Sherritt L, Shrier LA, Harris SK, Chang G. Validity of the CRAFFT substance abuse screening test among adolescent clinic patients. *Arch Pediatr Adolesc Med* (2002) 156(6):607–14. doi: 10.1001/archpedi.156.6.607
60. Cuellar I, Arnold B, Maldonado R. Acculturation rating scale for mexican americans-ii: a revision of the original ARSMA scale. *Hispanic J Behav Sci* (1995) 17(3):275–304. doi: 10.1177/07399863950173001
61. Qualtrics. (2005). Qualtrics. Retrieved from http://www.qualtrics.com.

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