Aus der Klinik für Psychiatrie und Psychotherapie
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DISSERTATION

Neurobiological mechanisms of emotion inhibition under stress in severe early life trauma

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Abstract

Background: Early life trauma significantly increases the risk for most psychiatric disorders. Across disorders, a diminished capacity to regulate emotions and inhibit impulses has been observed in exposed individuals. While it is now becoming increasingly clear that early life trauma can have a lasting effect on the brain, direct comparisons between healthy individuals exposed to early trauma, but without a history of psychiatric disorder, to trauma-naive individuals are scarce. Moreover, it has remained challenging to understand pathways from early trauma to adulthood psychopathology. However, recent studies suggest that altered reactivity to stress during adulthood might play an important connective function.

Methods: We conducted an experiment to examine response inhibition towards emotional facial expressions under a condition of psychosocial (non-traumatic) stress compared to baseline. Twenty-five healthy women (mean age 31.5 ± 9.7 years) who were exposed to severe and multiple traumatic experiences before the age of 18 but never developed any psychiatric disorder and 25 age- and education-matched trauma-naïve women were included. In both groups, functional magnetic resonance imaging (fMRI) was used to assess brain activity, which was subsequently linked to behavioural performance and subsyndromal psychiatric symptoms. Endocrine (salivary cortisol and α-amylase), autonomic (heart rate) and self-report measurements were used to validate and compare acute stress responses.

Results: Stress reduced inhibition towards fearful, but not towards happy or neutral facial expressions in both groups. However, compared to trauma-naïve women, trauma-exposed women showed blunted activation of the left inferior frontal gyrus (IFG) and slightly increased activation of the right anterior insula (aIns) during response inhibition towards fearful facial expressions. Furthermore, divergent brain-behaviour correlations could be identified. In controls only, IFG activation was linked to better inhibitory performance related to fearful facial expressions. In turn, exclusively in trauma-exposed women, aIns activation was linked to decreased inhibitory performance related to fearful facial expressions. Across groups, lower IFG activation was negatively linked to more subsyndromal posttraumatic symptoms.

Discussion and Conclusion: These results suggest that early life trauma has a lasting effect on the brain, even in the absence of lifetime psychopathology. Dysregulation of IFG-initiated top-down control, in concert with heightened aIns-initiated salience detection may point to imbalances in neural resource allocation after acute stress in trauma-exposed individuals. This imbalance likely raises vulnerability to everyday stress and, in the long term to posttraumatic

psychopathology. Our results therefore have implications for approaches to early intervention and prevention.

Abstract (German)

Hintergrund: Lebensgeschichtlich frühe Traumata erhöhen das Risiko für die meisten psychiatrischen Erkrankungen. Bei Personen, die frühe Traumata erlitten haben, wird häufig über verschiedene Störungsbilder hinweg eine verminderte Fähigkeit beobachtet, Emotionen zu regulieren und Impulse zu inhibieren. Wenngleich erste Erkenntnisse der jüngeren Forschung nun nahelegen, dass sich frühe Traumatisierung dauerhaft auf das Gehirn auswirken kann, fehlt es an direkten Vergleichen zwischen gesunden Personen ohne und gesunden Personen mit früher Traumaerfahrung. Darüber hinaus bleiben die Mechanismen, die frühe Traumata mit der Entwicklung von Psychopathologie im Erwachsenenalter verbinden, weitgehend unklar. Aktuelle Studien lassen vermuten, dass eine veränderte Stressreaktivität im Erwachsenenalter hier eine wichtige verbindende Funktion darstellen könnte.

Methoden: Wir haben ein Experiment durchgeführt, um die Inhibition von Reaktionen *(response inhibition)* auf emotionale Gesichtsausdrücke sowohl unter Standardbedingungen als auch nach psychosozialem (nichttraumatischem) Stress, zu untersuchen. 25 gesunde Frauen (durchschnittliches Alter 31,5 ± 9,7 Jahre), die vor ihrem 18. Lebensjahr schweren und multiplen traumatischen Ereignissen ausgesetzt waren, aber nie eine psychiatrische Erkrankung entwickelt haben, wurden mit 25 im Hinblick auf Alter und Bildung parallelisierten, traumanaiven Kontrollprobandinnen verglichen. Mithilfe von funktioneller Magnetresonanztomografie (fMRT) wurde die Hirnaktivität in beiden Gruppen erfasst und diese daraufhin in Beziehung zur Inhibitionsleistung und zu subsyndromalen psychiatrischen Symptomen gesetzt. Um akute Stressreaktionen zu validieren und zu vergleichen, wurden endokrine (Cortisol- und α-Amylasekonzentrationen im Speichel) und autonome (Herzraten-) Werte gemessen sowie Selbstbeurteilungen erhoben.

Ergebnisse: In beiden Gruppen reduzierte Stress die Inhibitionsleistung bezogen auf ängstliche, jedoch nicht auf fröhliche oder neutrale Gesichtsausdrücke. Verglichen mit der Kontrollgruppe zeigte sich in der Traumagruppe eine verminderte Aktivierung des linken Gyrus Frontalis Inferior (IFG) zusammen mit einer leicht erhöhten Aktivierung des rechten anterioren Lobus Insularis (aIns) während der Response Inhibition auf ärgerliche Gesichtsausdrücke. Zudem konnten divergierende Hirn-Verhaltens-Korrelate identifiziert werden. Anders als bei traumaexponierten Probandinnen hing die IFG-Aktivierung bei den Kontrollprobandinnen mit verbesserter Inhibitionsleistung zusammen. Ausschließlich in der Traumagruppe korrelierte wiederum die aIns-Aktivierung mit reduzierter Inhibitionsleistung. In der Gesamtgruppe hing die IFG-Aktivierung negativ mit subklinischen posttraumatischen Symptomen zusammen.

Diskussion: Diese Ergebnisse weisen darauf hin, dass biografisch frühe Traumata selbst ohne psychiatrische Erkrankungen in der Lebensgeschichte einen dauerhaften Effekt auf das Gehirn haben. Dysregulation von IFG-initiierter top-down Kontrolle zusammen mit erhöhter aIns-initiierter Salienzerkennung könnte auf Ungleichgewichte in der neuronalen Ressourcenverteilung nach akutem Stress in traumaexponierten Personen deuten. Diese Ungleichverteilung erhöht mit großer Wahrscheinlichkeit die Stressvulnerabilität und damit auf lange Sicht die Anfälligkeit für posttraumatische Psychopathologie. Die vorliegenden Ergebnisse haben Implikationen für Frühinterventions- und Präventionsansätze.

1. Introduction and Background

Early life trauma is the most frequent preventable cause of psychopathology.[2] Green and colleagues estimated in a representative community survey of US households that it is responsible for approximately 32% of the population attributable risk for any mental disorder.[3] For adult-onset mental disorders alone, it raises the risk approximately tenfold.[4] A key breakthrough in recent years has been the discovery that early life trauma alters trajectories of brain development even before full-blown psychiatric disorder.[5] While the exact pathways between early life trauma and adult psychopathology remain unclear, daily, non-traumatic stress exposure during adulthood seems to play an important connective function.[6,7] Across different trauma-related disorders such as posttraumatic stress disorder (PTSD), depressive and anxiety disorders or Borderline Personality Disorder (BPD), difficulties inhibiting emotions and regulating attention represent common elements. These neuropsychological difficulties are believed to be stress-induced and key for the development of clinical symptoms.[8-11] It is for these reasons that the neurobiological mechanisms of emotion inhibition under stress in trauma-exposed individuals constitute the focus of the current thesis.

1.1. Assessment of inhibitory functioning related to emotional material

An established way to assess inhibitory functioning is by measuring response inhibition through 'go-nogo' tasks. Here, the ability to inhibit proponent motor responses to certain stimuli, which can be neutral or emotional, is tested. The general principle consists of participants responding to a majority of presented stimuli ('go') as fast as possible. On a fraction of trials, however, an infrequent ('no-go') stimulus is presented that requires the participant to withhold a response, thereby assessing inhibitory functioning. Response inhibition has been found to rely heavily on the neural executive network, in particular the inferior frontal gyrus (IFG), the ventromedial prefrontal cortex (PFC), as well as dorsolateral PFC.[12,13]

1.2. Neural aberrations in trauma-exposed psychiatric patients

Impaired response inhibition to emotional stimuli represents a core neuropsychological alteration that likely predates full-blown trauma-related psychopathology such as posttraumatic stress disorder (PTSD). PTSD patients often have difficulties inhibiting responses to stimuli, particularly emotional ones.[14] Neurally, these difficulties in emotion inhibition seem to be accompanied by impaired top-down inhibitory control by fronto-cortical brain areas in concert with overactivity of regions responsible for salience detection.[15,16] Furthermore, loss of top-down control and impaired inhibitory functioning contribute to impaired extinction of trauma-related stimuli in PTSD[17] and to problems with affect regulation.[18] Moreover, a hyperactive

salience network has been implicated in triggering hyperarousal and increased negative thoughts.[16] However, it has been largely unclear whether these neural alterations occur only in patients with full-blown psychopathology or whether they represent an effect of trauma itself – independent of psychopathology. To date only few studies, with mostly adult trauma focus and heterogenous methodologies, have directly compared neural processes between disorder-free trauma-exposed and healthy trauma-naïve participants.[5] With regards to inhibitory functioning, two EEG studies found alterations in frontal cognitive control systems signalling higher attention or arousal[19] and lower inhibitory control of distractors.[20] In contrast, an earlier fMRI-based study found no differences in neural inhibitory functioning.[21] With regards to emotion regulation, one fMRI study showed exploratory evidence for a diminished capacity to downregulate negative emotions, facilitated by prefrontal cortex regions,[22] and another study for altered resting-state prefrontal connectivity within emotion regulation networks.[23]

1.3. Brain activation following acute stress

The described neural alterations found in trauma-related psychopathology share similarities with transient effects of acute stress on healthy humans. Under acute stress, the salience and memory of emotional material is heightened,[24,25] threat detection, rapid reactions and habitual behaviour is strengthened. At the same time, interference control, controlled cognitive processes and performance in complex tasks are weakened.[26] Furthermore, recent neural network models describe an increased activity of areas serving neural salience detection in order to re-orient attention to potential threats and ensure immediate survival.[27,28] In addition, increased activation of the default-mode network has been reported under acute stress, although support for this effect has been less consistent.[29] At the same time, a temporary down-regulation of the neural cognitive control network occurs, which drives top-down inhibition. However, during recovery from acute stress, neural resources are re-balanced towards top-down control and away from salience detection.[28]

Taken together, altered neural responses to stress are likely relevant for the aetiology of many psychiatric disorders, in particular those related to early life trauma. While there is growing evidence for a persistent effect of early life trauma on the brain, direct investigations in trauma-exposed individuals without lifetime diagnosis of psychiatric disorder are scarce[5] and the neural effects of acute stress on these individuals largely unknown. This thesis therefore examines how acute, non-traumatic stress influences emotion inhibition in women who were exposed to severe forms of early life trauma but never developed any full-blown psychiatric disorder. While outlined in more detail in the accompanying publication (p. 45), the main hypothesis was

that trauma-exposed healthy women would show decreased activation of areas serving neural top-down control, and increased activation in areas serving emotion processing and salience detection under stress, compared to trauma-naïve healthy women.

2. Methods

2.1. Study design overview

The study consisted of three main procedural steps:

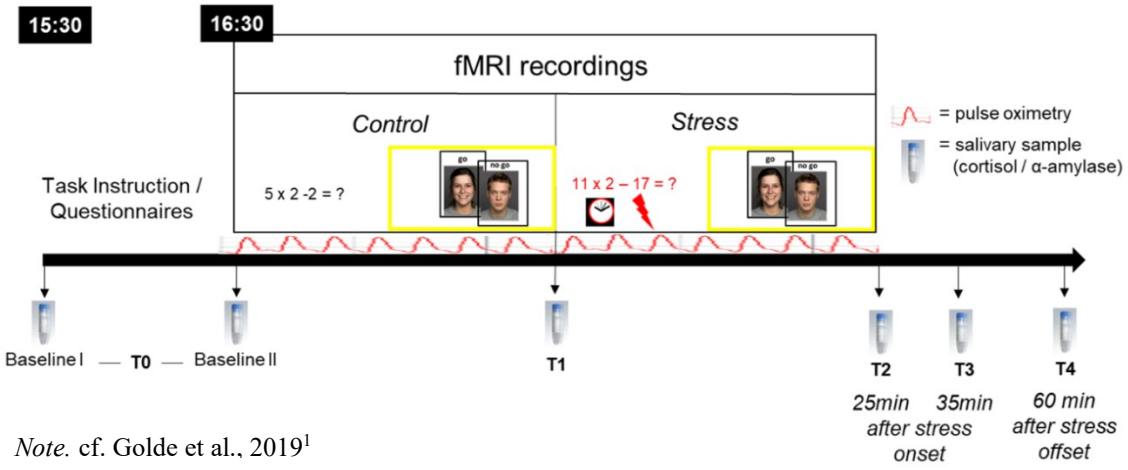
(1) recruitment and telephone interview,

(2) diagnostic session,

(3) experimental session (functional magnetic resonance imaging).

The telephone interview and diagnostic session are described in more detail below (2.2). During the experimental session, we administered two parallel versions of an emotional go-nogo (eGNG) paradigm during functional magnetic resonance imaging (fMRI). In between these two versions, we induced psychosocial stress by an adapted version of the Montreal Imaging Stress Task (MIST).[30,31] To measure stress, we took six saliva samples over the course of the experiment to determine cortisol and α-amylase concentrations, measured heart rate by pulse oximetry during fMRI and asked participants to rate their subjective stress experience (Figure 1). This session was scheduled on a different day than, and within a two-week period of the diagnostic session. Due to lower, more stable cortisol levels in the afternoon, and, an HPA axis that is more reactive to challenge at this time,[32] sessions started at 15:30 hours for all participants. The eGNG paradigm as well as the stress induction and measurement are described in more detail below.

Figure 1: Procedure of the experimental session



Note. cf. Golde et al., 2019[1]

2.2. Sample selection and diagnostic assessment

The sample consisted of 25 healthy women who experienced a minimum of three traumatic events (sexual or physical) before the age of 18 (T+) and 25 trauma-naïve healthy control women (T-). Traumatic events were defined based on Criterion A for PTSD in the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V), that is, exposure to "death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence."[33] Exclusion criteria for both experimental groups were a lifetime diagnosis of any psychiatric disorder as assessed by the Structured Clinical Interviews for DSM-IV (SCID) Axis I and II,[34] adverse health conditions affecting the central nervous or endocrine system function, non-removable ferromagnetic material, auto-immune and infectious diseases, hypertension, a transcontinental flight within the last four weeks, excessive physical exercise of more than 10 hours a week, left-handedness and pregnancy. We recruited all participants via public advertisements. The study was approved by the ethics committee of the Charité – Universitätsmedizin Berlin and conducted in accordance with the latest version of the Declaration of Helsinki. All participants provided written informed consent and were reimbursed with 100€ for participation.

We first conducted a thorough pre-screening via phone (duration approximately 45min) of all participants by a trained clinical psychologist. As a second step, we invited all individuals who were eligible for study participation for a diagnostic session. During this session, we conducted the SCID I and II[34] as well as the German version of the Early Trauma Inventory (ETI),[35,36] a 56-item semi-structured interview for the assessment of physical, emotional, and sexual abuse as well as general traumatic experience. The interview served to obtain in-depth information as well as specific information (e.g. onsets, offsets, perpetrators etc.) about the events and to assess authenticity of the report. In order to collect an interviewer-independent measure and to increase comparability with previous studies, participants additionally completed the Childhood Trauma Questionnaire (CTQ).[37] In addition, demographic and clinical variables as well as several self-report questionnaires were obtained (Table 1, p. 15).

2.3. fMRI experiment

2.3.1. (Functional) Magnetic Resonance Imaging

We used (f)MRI to investigate structural and functional properties of the brain non-invasively. MRI is based on the interaction of hydrogen nuclei present in water, and therefore in the whole body, with an external magnetic field. When an individual is positioned in the scanner the hydrogen nuclei change their spinning frequency to align with the magnetic field. Additional energy in form of radio waves in a specific frequency, which cause the hydrogen nuclei to

resonate, is then added to the magnetic field. These radiofrequency waves, which represent different charges of magnetic gradients and oscillating electromagnetic fields, are known as *pulse sequences*. When the radiofrequency source is turned off the nuclei fall back into their original equilibrium, and, at the same time emit another radio wave, which is recorded by receiver coils. The time taken for the nuclei to fully relax (*relaxation time*) is dependent on the tissue types and can thus be used to re-construct a three-dimensional volume of the brain.[38]
Functional MRI is based on a similar principle of physical properties of hydrogen nuclei, but additionally uses changes in oxygenation concentration in the brain (called *Blood Oxygen Level Dependent*, or *BOLD*). The BOLD contrast results from the change in the magnetic field surrounding red blood cells depending on the oxygen state of their haemoglobin. Oxygenated haemoglobin is diamagnetic (i.e. it exerts only a very weak effect on the regional magnetic field), while deoxygenated haemoglobin is paramagnetic (i.e. it more strongly disturbs the regional magnetic field). By identifying changes in blood oxygenation, this method thus allows us to measure neural activity indirectly through oxygen consumption of more active neurons. fMRI is generally accepted as a safe and non-harmful technique as long as magnetization related safety rules are strictly followed.[38]

Data was collected using a 3 Tesla Magnetom Trio fMRI scanner (Siemens Medical Systems, Erlangen, Germany), equipped with a 12-channel head coil. Functional imaging was conducted using axially aligned standard gradient echo planar imaging (EPI) and T1-weighted high-resolution magnetization prepared gradient-echo scan (MPRAGE) for anatomical reference. Details of data acquisition and pre-processing can be found on page 57.

2.3.2. Design of emotional go-nogo paradigm for fMRI

In order to be able to assess neural foundations of emotion inhibition under baseline and stress conditions, we designed two parallel versions of an emotional go-nogo paradigm to use during fMRI. We used a previously applied task by Hare, et al. [39] as a template and adapted, among other aspects, the included emotion conditions and the presented stimuli to best fit the purpose of this thesis.

Stimuli selection. We selected naturalistic face stimuli from the FACES database,[40] a database which comprises a set of two pictures per person and facial expression. In validation studies, these have been rated on mean accuracy (i.e. mean percentage of correct expression identification) and perceived age. We decided to use positive, negative and neutral facial expressions. Fearful faces were selected over angry faces as they have been shown to be more perceptually salient.[41] The following steps of stimuli selection were conducted: First, we pre-

selected faces of young and middle-aged actors with rated, as well as true age > 18. Second, we chose facial expressions of actors with the highest accuracy ratings to use as stimuli. We used the facial expressions of the same actor for all emotion conditions (i.e. neutral, happy, fearful) within one version and run, and then created a parallel set using pictures of a different actor, which best matched mean age of actors and mean accuracy.

Task procedure. Participants completed two runs (one in the control and one in the stress condition), each comprised of four blocks. Each block consisted of 30 go-trials and 10 nogo-trials. During go-trials, a target facial expression was presented, and subjects were asked to respond as fast as possible by pressing a button. During nogo-trials, non-target facial expressions were presented, and participants were asked to avoid any button press (inhibition trials). Two blocks used emotional target facial expressions (fearful or happy, respectively) in the presence of neutral non-targets, and two blocks employed neutral target faces in the presence of fearful or happy non-targets, respectively.

Randomisation and timing. The order of the blocks (i.e. the emotion condition) was counterbalanced for each participant but was kept constant within participants for both runs (i.e. control and stress). Stimuli were presented pseudo-randomly for 500 ms each and separated by a jittered inter-stimulus interval of 2,000-10,000 ms, during which participants viewed a blank screen. The jitter distribution was separated in steps of 250 ms and had an exponential slope with fewer long jitter times. The participants response was recorded until the stimulus disappeared after 500 ms. Presentation of the stimulus picture was taken as onset for fMRI trials. One whole block lasted at most 2:57 minutes (cf. Golde et al., 2019).[1]

2.3.3. Statistical analysis of emotional response inhibition performance

Together with the participants' response, the eGNG task design enables the analysis of four different trial types: correct go-trials (hits), correct nogo-trials (inhibition trials), incorrect nogo-trials (false alarms) and incorrect go-trials (misses). Based on Wager et al.,[42] we operationalized failures of response inhibition with the false alarm rate (FAR) on inhibition (nogo) trials, which represented our primary outcome measure. As the normality assumption was not met, we used non-parametric test procedures (see attached publication, p. 46).

2.3.4. Statistical fMRI analysis

For statistical analysis of the BOLD response, the general linear model approach was used as implemented in SPM12.[43] In an event-related design, onsets of stimuli presentations were convolved with the haemodynamic response function and a fixed-effect model was estimated.

The model contained regressors for the four blocks of trials, representing different emotion conditions, i.e. 1) fearful nogo faces – neutral go faces, 2) happy nogo faces – neutral go faces, 3) neutral nogo faces – fearful go faces, 4) neutral nogo faces – happy go faces. For each of these blocks, we modelled the control and stress condition separately. In addition, for each block (emotion condition) in each control / stress condition, we modelled four different trial types: correct go-trials, correct nogo-trials, false alarms (incorrect go), misses (incorrect nogo). Thus, there were 4 (emotion condition) × 2 (stress vs. control condition) × 4 (trial type) regressors. Only regressors with correct nogo-trials were the regressors of interest, which measured *successful inhibition*. To account for movement-associated variance, realignment parameters were additionally included as regressors of no interest. After parameter estimation, stress condition was contrasted to control condition [stress > control] for all correct inhibition (nogo) trials of all emotion conditions.

Data were taken to the second level and underwent a random effects analysis to allow for population inference. Group differences were interrogated with a mixed-effects ANOVA model created in a flexible factorial design. Individual *t*-maps of differences between stress and control condition [stress > control] were used. The model included a between-subject factor *group* (two levels: with trauma, T+ vs. without trauma, T-), a within-subject *emotion condition* factor (four levels: fearful nogo, happy nogo, neutral $nogo_{fear\text{-}go}$, neutral $nogo_{happy\text{-}go}$) and a *subject*s factor (number of levels equals the number of participants) that controlled for within-subject variability. Considering reported issues around thresholding,[44,45] we applied a recently developed probabilistic threshold-free cluster enhancement (pTFCE),[46] in addition to conservative whole brain peak-level (voxel-wise) FDR correction with $p < 0.05$ and a minimum cluster size threshold of $k > 30$ to correct for multiple comparisons.

2.4. Psychosocial stress induction

We used an adapted version of the MIST[30,31] to induce psychosocial stress. The MIST consists of mental arithmetic challenges that must be answered under time pressure and induces psychosocial stress using elements of uncontrollability and social evaluative threat. The task contained two stimulus conditions: easy arithmetic questions without feedback, progress bar or time constraint, and difficult arithmetic questions with a time limit, feedback and visible progress bar. In contrast to the original version, we did not present different stimulus conditions within one run but temporally separated them to avoid carry-over effects. During the control condition of the MIST (first run), only easy arithmetic questions with enough time allotted and no feedback were presented for seven minutes. For stress induction, two runs of eight-minute

duration containing difficult arithmetic questions and time pressure were administered. In between runs, a confederate who was introduced to the participant as head of the study delivered scripted negative feedback over the scanner's microphone emphasizing the need to subsequently improve performance for approximately one minute. The MIST algorithm continuously varied task difficulty based on user performance by adjusting the time constraints per question and the complexity of the arithmetic problems, to yield a 50-55% correct performance for all participants. A performance bar depicted the participants' cumulative performance progressively falling behind the performance of a fake comparison group regardless of actual performance.

2.5. Multi-level stress measurements

Participants were asked to rate their stress and strain level during the control and stress condition on a 10-point visual analogue scale. Physiological stress induction was quantified by heart rate as well as salivary cortisol and α-amylase measurements. For heart rate recordings, the integrated photoplethysmograph of the Siemens Physiological Monitoring Unit, placed under the left index finger, was used throughout the experiment. Pulse oximetry data was processed with TAPAS PhysIO toolbox, version r671, implemented in SPM12.[47] Automated peak detection was performed by the adaptive 'auto-matched' peak detection algorithm of the PhysIO toolbox. Afterwards, diagnostic plots of the toolbox were used to manually check each recording for outliers and wrongly detected heart beats due to movement and magnetic resonance signal related artefacts. All data sets with more than three wrongly detected heart beats (as indicated by the toolbox) were excluded from the analyses. Mean heart rate during all conditions of the stress task (MIST) and during all conditions of the emotional go-nogo paradigm eGNG were calculated. Six saliva samples were collected throughout the experiment using Salivette devices (Sarstedt, Rommelsdorf, Germany; Figure 1). Two baseline samples were collected. To collect T1, which was taken in-between control and stress condition, hence the participant was confined to the cylindrical tube of the scanner, the scanner bench was moved outside of the tube far enough to allow the participant's head to be reached, but not moved out completely. This way, the participant's position remained memorized by the scanner, and the participant could be returned to his/her original position for subsequent runs, without having to repeat localizer and structural scans. The Salivette was placed into the participant's left hand and the participant was instructed to put it into his/her mouth but refrain from chewing on it (to avoid head movement). After a period of two minutes, the participant was asked to expel the salivette using the tip of the tongue. The investigator removed the salivette, placed it into the

sterile plastic tube and left the scanner room for subsequent scanning. Collection took place at room temperature, after which samples were stored at -20°C until the end of the testing session and subsequently kept at -80°C until biochemical analysis. Salivary free cortisol concentration was used as a marker of hypothalamic-pituitary-adrenal (HPA) axis activity[48] and α-amylase as marker of sympathetic nervous system activity (see p. 55-56 for a description of biochemical analysis).[49] Cortisol and α-amylase data were winsorized (95th percentile) and log-transformed for statistical analysis. Mixed design analysis of variance (ANOVA) with Greenhouse-Geisser correction (when appropriate) was used for statistical analysis of subjective stress, mean heart rate, cortisol and α-amylase concentrations. Post-hoc *t*-tests were Bonferroni corrected.

3. Main Results

Groups significantly differed in depressive symptoms, trait anxiety, perceived stress, posttraumatic symptoms and early traumatic experiences (Table 1).

Table 1: Sample characteristics

	T+	T-	Statistics
Age in years (M ± SD)	31.52 ± 9.71	31.22 ± 10.42	$p = 0.919$*
Years of education (M ± SD)	11.57 ± 0.99	11.61 ± 0.89	$p = 0.876$*
Intake of OC (yes/no)	3/20	7/16	$p = 0.153^{+}$
Cycle phase if no intake of OC (follicular/luteal/postmeno)	5/12/2	3/11/2	$p = 0.543^{+}$
Smoker (yes/no)	6/17	5/18	$p = 0.730^{+}$
Cups of coffee per day (M ± SD)	1.32 ± 1.22	1.73 ± 1.74	$p = 0.370^{+}$
BDI II (M ± SD)	8.23 ± 6.19	2.91 ± 4.04	**$p = 0.001$***
STAI-T (M ± SD)	38.30 ± 9.83	33.26 ± 6.71	**$p = 0.048$***
PDS (M ± SD)	10.87 ± 10.68	0.96 ± 2.33	**$p < 0.001$***
PSS (M ± SD)	16.44 ± 6.25	14.35 ± 4.64	$p = 0.205$*
SRS (M ± SD)	56.64 ± 7.93	56.83 ± 6.57	$p = 0.201$*
CTQ sum score (M ± SD)	66.57 ± 16.43	28.82 ± 3.50	**$p < 0.001$***
− emotional abuse	16.96 ± 6.09	5.74 ± 1.18	**$p < 0.001$***
− physical abuse	11.78 ± 4.82	5.04 ± 0.21	**$p < 0.001$***
− sexual abuse	10.30 ± 6.07	5.00 ± 0.00	**$p < 0.001$***
− emotional neglect	17.00 ± 5.48	7.43 ± 2.45	**$p < 0.001$***
− sexual neglect	10.52 ± 4.76	5.57 ± 1.31	**$p < 0.001$***
ETI sum score (M ± SD)	490.87 ± 342.40	14.52 ± 13.25	**$p < 0.001$***
− general trauma	91.17 ± 73.45	8.78 ± 10.31	**$p < 0.001$***
− physical abuse	100.48 ± 75.20	2.70 ± 4.63	**$p < 0.001$***
− emotional abuse	271.61 ± 230.52	1.30 ± 4.07	**$p < 0.001$***
− sexual abuse	27.61 ± 48.97	1.74 ± 3.62	**$p = 0.019$***

Note: Information on cycle phase was unavailable for one T+ due to uterine agenesis. *calculated using two samples *t*-test, $^{+}$ calculated using Chi^2 test. T+ = trauma-exposed participants, T- = trauma-naïve control participants, OC = oral contraceptives, BDI II = Beck Depression Inventory II,[50] STAI-T = Spielberger Trait Anxiety Inventory,[51] PDS = Posttraumatic Stress Diagnostic Scale,[52] PSS = Perceived Stress Scale,[53] SRS = Stress Reactivity Scale,[54] CTQ = Child Trauma Questionnaire,[37] ETI = Early Trauma Inventory,[35,36] M = mean, SD = standard deviation; cf. Golde et al., 2019[1]

3.1. Subjectively experienced stress and strain

Two mixed ANOVAs were run, one for subjective stress and one for strain (group × condition). Results showed a main effect of stress or strain respectively across groups (stress: $F_{1,42} = 88.4$, $p < 0.001$; strain: N = 44, $F_{1,42} = 92.7$, $p < 0.001$). For strain, there was a significant interaction between subjective strain and group ($F_{1,42} = 7.1$, $p = 0.042$), which indicated that from control to stress condition the increase was larger in the T+ group (Table 2, see p. 67 for statistical details).

3.2. Physiological stress (pulse oximetry, cortisol, α-amylase)

Mean heart rate significantly increased from control to stress condition across groups (main effect condition) and was significantly higher during the MIST than during eGNG. Groups did not differ significantly in mean heart rate (no main effect group and no group × condition interaction; Table 2, see p. 49 for statistical details)

Table 2: Subjective stress, strain and pulse oximetry (heart rate) data

	Subjective Stress and Strain			
	Control Condition		**Stress Condition**	
	Reported Stress	Reported Strain	Reported Stress	Reported Strain
T- (M ± SD)	4.64 ± 2.13	5.36 ± 2.04	6.91 ± 2.18	7.41 ± 2.18
T+ (M ± SD)	3.59 ± 1.68	3.64 ± 2.06	6.86 ± 2.48	6.82 ± 2.34
	Heart Rate (bpm)			
	Control Condition		**Stress Condition**	
	MIST	eGNG	MIST	eGNG
T- (M ± SD)	74.02 ± 10.20	67.95 ± 9.19	76.86 ± 8.27	71.74 ± 11.29
T+ (M ± SD)	70.23 ± 9.34	66.45 ± 9.31	72.00 ± 9.69	68.64 ± 9.09

Note. T+ = trauma-exposed participants, T- = trauma-naïve control participants, bpm = beats per minute, MIST= Montreal Imaging Stress Task, eGNG = emotional go-nogo paradigm; cf. Golde et al., 2019[1]

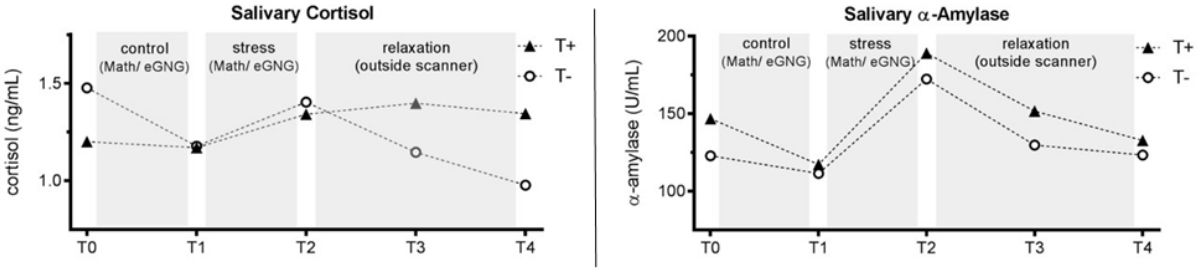
For cortisol, we found a main effect of time indicating significant increase from T1 to T2 and decrease from T2 to T3. Groups did not differ significantly (no main effect of group, or group × time interaction). For α-amylase, there was a main effect of time, no group effect and a time by group interaction. Bonferroni corrected paired-sample *t*-tests revealed a significant increase in both groups from T1 to T2 (i.e. during stress induction). They also revealed that the interaction was attributable to group differences in α-amylase changes from T0 to T1, resulting from higher α-amylase baseline levels (T0) in the T+ group (Table 3 and Figure 2; see p. 49 for statistical details).

Table 3: Salivary cortisol and *α*-amylase data

Cortisol				
Time Point	**Raw**		**LN**	
	T-	**T+**	**T-**	**T+**
T0	1.43 (0.13)	1.21 (0.22)	0.25 (0.11)	-0.08 (0.15)
T1	1.18 (0.17)	1.17 (0.37)	-0.07 (0.15)	-0.44 (0.19)
T2	1.40 (0.26)	1.34 (0.24)	0.06 (0.16)	-0.04 (0.19)
T3	1.14 (0.22)	1.40 (0.43)	-0.20 (0.18)	-0.29 (0.20)
T4	0.99 (0.19)	1.34 (0.36)	-0.30 (0.16)	-0.24 (0.19)
***α*-Amylase**				
Time Point	**Raw**		**LN**	
	T-	**T+**	**T-**	**T+**
T0	100.17 (13.57)	136.35 (14.00)	4.36 (0.18)	4.78 (0.12)
T1	114.13 (19.57)	117.24 (18.78)	4.41 (0.19)	4.51 (0.15)
T2	172.36 (25.13)	189.07 (24.77)	4.83 (0.20)	5.03 (0.15)
T3	130.86 (18.67)	151.67 (21.03)	4.60 (0.18)	4.79 (0.15)
T4	126.34 (19.17)	132.72 (19.36)	4.57 (0.18)	4.63 (0.16)

Note. Values represent mean and standard error. T- = trauma-naïve control participants, T+ = trauma-exposed participants, LN = natural logarithm. cf. Golde et al., 2019[1]

Figure 2: Depiction of salivary cortisol and *α*-Amylase levels over the course of the experiment.



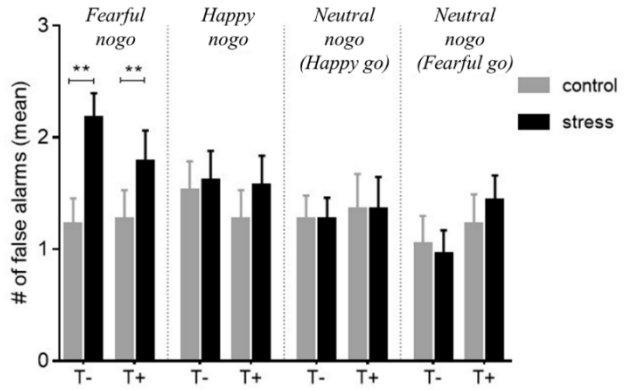
Note. See Table 3 for standard errors. Math = mental arithmetic of MIST paradigm; eGNG = emotional go-nogo paradigm, T+ = trauma-exposed participants, T- = trauma-naïve control participants. cf. Golde et al., 2019[1]

3.3. Emotional response inhibition (eGNG)

3.3.1. Performance

Across groups, false alarm rate (FAR) for fearful nogo stimuli significantly increased from control to stress condition, i.e. performance decreased (Wilcoxon Signed Rank Tests: N = 46, Z = -3.6, $p < 0.001$ adjusted, $r = 0.5$). There was no difference between control and stress condition for any other emotion condition (neutral, happy) and groups did not significantly differ in performance, neither for the effect of stress nor for any emotion condition (Figure 3). See p. 47 for further statistical details and p. 64 for analysis of hits.

Figure 3: False alarms for nogo trials of all emotion conditions

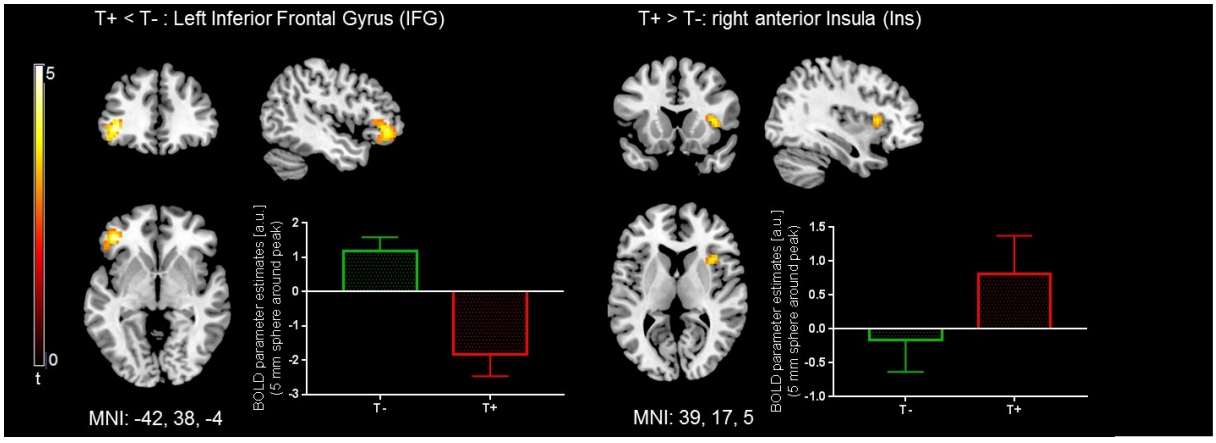


Note. Control = control condition, stress = stress condition, T- = trauma-naïve control participants T+ = trauma-exposed participants. cf. Golde et al. 2019[1]

3.3.2. Neural results

Stress only affected false alarms on fearful nogo stimuli. Adopting a stepwise procedure, we therefore focused on exploring the neural underpinnings of this condition. We compared fearful nogo to neutral nogo stimuli and tested for an interaction effect with the group factor i.e. [|fearful nogo – neutral nogo| × group]. We found a significant interaction in the left inferior frontal gyrus (left IFG), indicating that T+ individuals showed blunted left IFG activation under stress compared to T- (p = 0.010 pTFCE and peak-level FDR corrected, 355 voxels; Figure 4, left). The reverse interaction contrast testing for increased neural activation under stress in the T+ group compared to the T- group hinted at a higher stress-induced activation in the T+ group in the right anterior insula (aIns). This effect did, however, not survive whole brain pTFCE and FDR correction (t = 3.65, p = 0.5 pTFCE and peak-level FDR corrected, p < 0.001 *uncorrected,* 40 voxels; Figure 4 right). We additionally computed a second flexible factorial ANOVA in SPM, adding cortisol level as a covariate, which resulted in a similar pattern of results (p. 58).

Figure 4: fMRI results from flexible factorial ANOVA [|fearful nogo – neutral nogo| × group]

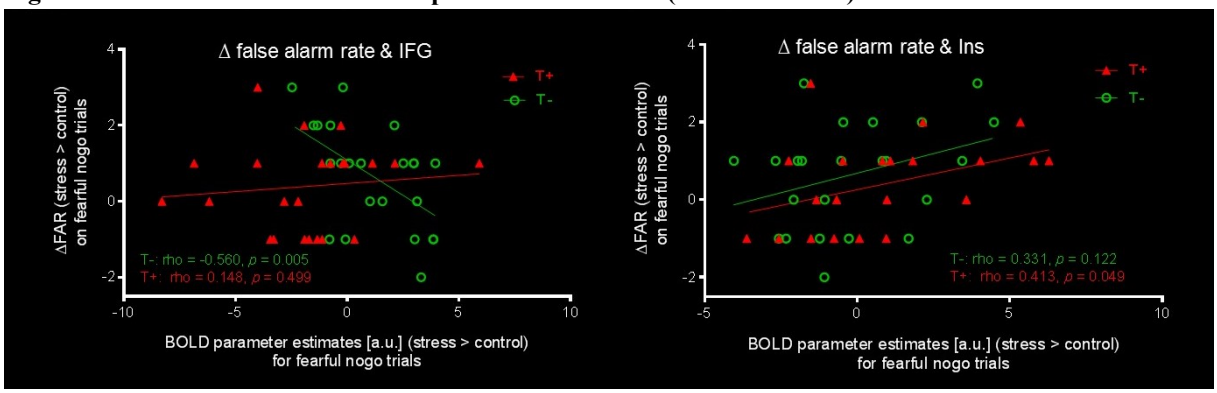


Note. Bar graphs depict mean BOLD parameter estimates from a 5 mm sphere around the clusters' peak voxel. MNI = Montreal Neurological Institute coordinates, T- = trauma-naïve control participants, T - = trauma-exposed participants; cf. Golde et al., 2019[1]

3.3.3. Association between neural measures and performance

Next, we extracted mean BOLD parameter estimates of the left IFG and right anterior insula (5 mm sphere around peak voxel) from individual contrast images (stress - control) during fearful nogo trials and correlated them with stress-induced increase in false alarms (ΔFAR = false alarms stress – false alarms control). The Spearman correlation coefficient was used to test for bivariate correlations as stress-induced increase in FAR values deviated significantly from a normal distribution. In T- participants, higher left IFG activation during stress correlated with better response inhibition of fearful faces under stress. This was not the case for the T+ group (Figure 5, left). For the right anterior insula, a higher activation was associated with higher increase in FAR on fearful nogo in T+ participants, but not in the T- group (Figure 5, right).

Figure 5: Correlation between BOLD parameter estimates (left IFG & aIns) and stress-induced false alarms

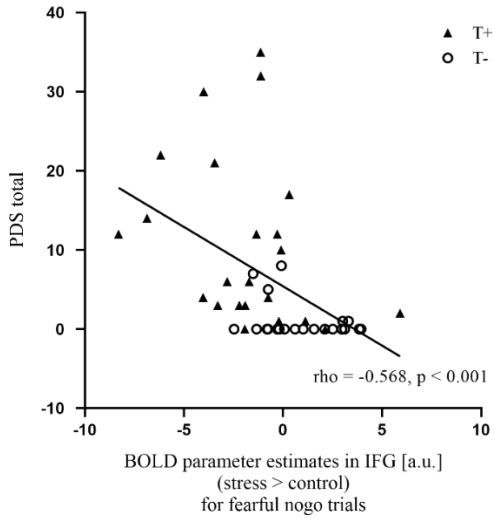


Note. T- = trauma-naïve control participants, T+ = trauma-exposed participants, IFG = left inferior frontal gyrus, Ins = right anterior insula, FAR = false alarm rate; cf. Golde et al., 2019[1]

3.3.4. Association between neural measures and psychiatric symptoms

In addition, we analysed associations between psychiatric scales for which we found significant group differences (i.e. posttraumatic symptom severity by PDS, trait anxiety by STAI-trait, depressive symptoms by BDI-II) and IFG and insula activation, for all participants. Left IFG activation correlated negatively with PDS (Spearman *rho* = -0.568, $p < 0.001$), and STAI-trait (Spearman *rho* = -0.370, $p = 0.011$), but not with BDI-II. Stress-induced insula activation was not significantly correlated with psychiatric symptoms. It is however also important to note that, as shown by results of an additional analysis of covariance, group differences remain significant when controlling for posttraumatic symptoms (see p. 60 for details).

Figure 5: Correlation between posttraumatic symptoms and stress-induced left IFG activation



Note. T- = trauma-naïve control participants, T+ = trauma-exposed participants, PDS = posttraumatic diagnostic scale, IFG = left inferior frontal gyrus, a.u. = arbitrary unit; cf. Golde et al., 2019[1]

4. Discussion

Altered response of the brain to psychosocial stress likely plays an important role in connecting early life trauma and adult psychopathology. It was therefore the main aim of the current thesis project to merge two central aspects in current trauma-related research: acute stress responses and emotional response inhibition. We found that under stress, women who have experienced severe early life trauma showed blunted activation of the left IFG and subtly increased right aIns activation during inhibition of fearful faces in comparison to controls with no trauma experience. Moreover, the study found a differential pattern of correlations between inhibitory performance, IFG and aIns in controls vs trauma-exposed participants. Finally, blunted IFG activation was linked to more posttraumatic symptoms, but was unrelated to depressive symptomatology. More detailed aspects of these results are discussed in the accompanying publication (p. 48-51). In this dissertation, the focus is placed on a more extensive consideration of these findings in light of recent theories on stress-associated neural resource shifts, their meaning with respect to psychopathology development in early life trauma-exposed individuals, and possible implications for future neuroscientific research and clinical practice.

4.1. Dynamic reallocation of neural resources, adaptive stress responses, and mental health

We found that, after stress induction, women who had experienced severe early life trauma, showed blunted activation of the left IFG and subtly increased right aIns activation during inhibition of fearful faces. The IFG is an important region of the central executive control and emotion regulation system,[55,56] supporting cognitive control and flexibility, goal-oriented

behaviour, and selective attention.[57,58] The anterior insula supports salience detection in addition to the coordination of brain networks.[59,60] Recent theories posit that during acute stress, vigilance and threat detection is heightened through allocation of neural resources to salience detection, likely taking away resources from executive cognitive control processes. In the aftermath of stress, these processes are reversed.[27] The findings in this thesis indicate, however, that trauma-exposed individuals show an aberration of salience-executive resource allocation after stress. In controls, neural resources appear to be adequately re-shifted toward cognitive control as indicated by IFG activation, supporting the inhibition of fearful stimuli. In trauma-participants, re-shifting, that is upregulation of neural cognitive control after stress seems to be hampered, possibly pointing to a prolongation of typical neural resource allocation patterns towards salience detection. Importantly, the timing and amplitude of these re-shifting processes after stress have been argued to be essential for adaptation to the environment.[61] Prolongation of neural resource shifts may drastically increase the allostatic load of environmental demands,[62] and therefore, raise susceptibility to stress-related disease in healthy, trauma-exposed individuals.

However, as this thesis is based on a cross-sectional study, it needs to be carefully considered whether the neural alterations found contribute to susceptibility or are in fact compensatory or resilience factors, thereby preventing the individual from developing a disorder. In case of the IFG, we showed that its activation after stress during inhibition of negative stimuli is (1) related to better inhibitory performance regarding fearful non-target stimuli in controls, and, (2) is negatively related to subsyndromal posttraumatic but not depressive symptoms. This adds evidence to the idea that the ability to re-activate the IFG after stress during fear inhibition is linked to the pathophysiology of PTSD, and therefore, likely influences the risk of developing this disorder. This is consistent with its sustained hypoactivation and altered connectivity underlying inhibition of impulses and emotion in full-blown PTSD even at baseline, that is, in the absence of any external stress challenge.[14,15] Further support for a role of IFG hypoactivation in the occurrence of posttraumatic symptoms comes from a treatment study conducted by MacNamara et al.[63] This study demonstrated that pre-treatment emotion regulation-related IFG activation predicted treatment gain from selective serotonin reuptake inhibitors (SSRIs) in PTSD patients. In addition, treatment gain from SSRIs was accompanied by normalization of neural activity in the IFG. The results of this thesis further suggest that IFG activation during inhibition after stress is linked to posttraumatic symptomatology, but not to trauma-related depressive symptoms. In trauma-related depression, aberrations in slightly

different frontal regions such as medial prefrontal and anterior cingulate cortices in addition to dorsolateral prefrontal cortices are underlying clinical symptoms[64-67] and relate to psychological processes such as self-referential processing and rumination (e.g. Cooney et al., 2010[68], Nejad et al., 2013[69]), rather than emotional response inhibition.

Interpretation of present insula-related effects and their relationship with mental health appears more complex, since this effect was weaker and activation was not correlated with subsyndromal psychiatric symptoms. Still, we found a correlation between this activation effect and performance during the task, supporting its validity. There is growing evidence that hyperactivity of the insula can be caused by early life trauma independent of clinical symptoms,[5] but that it also pre-disposes to psychiatric disorders (e.g. Downar et al., 2016, Namkung et al., 2017).[70,71] On a clinical level, sustained activation of right anterior insula after stress likely promotes a state of hypervigilance.[72,73] Hypervigilance is generally defined as responding to (potentially) threatening stimuli in a rapid but undifferentiated manner. We indeed found that in the trauma group, stress-associated insula activation was linked to less differentiated response behaviour. That is, insula activation was associated with worse discrimination between target and non-target fearful stimuli. This observation supports the assumed function of heightened insula activation in promoting hypervigilance in the trauma-exposed group.

It is important to note that groups did not differ significantly in their behavioural performance. Enhanced anterior insula activation might also be a neural alteration directly related to trauma-experience, but unrelated to mental or behavioural health outcome. This falls in line with studies generally supporting the existence of brain markers of early life trauma, irrespective of mental health outcome.[11,74] To the author's knowledge there has been no previous finding pointing to an increased activation of the anterior insula serving resilience, locally or within a network structure. However, a very recent study suggests that diminished structural connectivity between and within large-scale networks that also include the insula represents a key compensatory mechanism of resilience in psychological trauma.[75] Although seeming unlikely, given previous findings on insula hyperactivity, it cannot be excluded that increased functional activation of the insula results from these changed network interactions, and thus, serves resilience. Future studies should use functional connectivity measures, which are an especially powerful method to study subtle, large-scale neural networks,[76] to gain further insight into the role of anterior insula in resilience-associated functional network changes. Task-based designs rather than resting-state measurements would allow incorporation of a stress-exposure that

mimics everyday challenges perturbating the system, as was applied in the current study. This could help amplify highly subtle changes in network communication and highlight those abnormalities that indeed bear relevance of the individual's ability to manage everyday life demands.

4.2. Endocrine, autonomic and subjective stress anticipation and response

Concerning subjective, endocrine and autonomic measurements, we found that reaction to stress was mostly comparable in both groups. This is in contrast to previous studies suggesting that early life trauma is associated with altered HPA, SNS and autonomic function.[77-79] However, it falls in line with a previous study from our lab group where we also did not find any changes in cortisol response in healthy trauma participants.[80] The extensive clinical interviewing and resultant strict exclusion of many potential participants who might have fulfilled criteria for a psychiatric disorder in the past, might explain the lack of deviations in these other stress dimensions. Moreover, a relevant meta-analysis of neuroendocrine investigations suggests that differences in stress-reactions between trauma-exposed and trauma-naïve healthy participants are highly subtle. They report only specific differences in HPA-axis feedback response, that were not detectable in salivary cortisol concentrations.[81] This highlights the importance of multimodal research, as conducted by the present project, when investigating stress responses in order to understand complex susceptibility to stress-related psychopathology.

Notably, however, we did observe significantly increased α-amylase concentrations at baseline in T+ pointing to heightened anticipatory stress in this group. This did not constitute an a priori focus of the thesis project and needs replication by future studies. However, it appears to be a relevant observation adding evidence to previous investigations of raised anticipatory stress in trauma-exposed individuals. The notion of anticipation is an important aspect regarding the adjustment of biological systems to external challenges. Heightened anticipatory stress may raise the wear and tear that these challenges are associated with for the individual, that is, their allostatic load.[62,82] Anticipatory stress refers to psychological states, such as apprehension, worry, and anxiety, as well as cognitive preparation for a forthcoming, potentially threatening event. Aberrant and excessive anticipatory response to conditions of threat uncertainty has been found to be a common feature across anxiety disorders[83] and may thus, play an important role in the aetiology of these disorders. However, investigations into factors causing elevated anticipatory stress to ordinary challenges in disorder-free trauma-exposed individuals, including its potentially negative health effects, are currently lacking. Future studies should,

thus, investigate endocrine and neural responses to *anticipated* challenges or uncertainty more systematically.

4.3. Limitations

Important limitations that need to be considered are discussed in the accompanying publication (see p. 51). However, as the topic of susceptibility and compensation factors has been discussed here, it is important to note that our results leave open the question of pre-existing neurobiological factors. It is possible that healthy trauma-exposed individuals were a small subgroup endowed with the optimal neurobiology to tackle their severe trauma-exposure, e.g. through genetic factors. If the trauma happened during childhood, it is of course difficult to conduct prospective (i.e. pre- and post-trauma) studies in humans. Such studies would, however, be required to determine the role of pre-existing factors that might protect or predispose to a disorder after early life trauma. Only animal studies in rodents or non-human primates can establish direct causality and disentangle pre-childhood trauma and trauma-induced changes (e.g. Anderson et al., 2004, Bock et al., 2004, Meaney et al., 2002).[84-86] However, large longitudinal studies in exposed humans, which capture more fully neural population variability may explore causal relationships between (1) neural abnormalities post early life trauma, (2) neural reactivity to stress in the aftermath and, (3) later development of a disorder. To the author's knowledge only one larger neurostructural study with two MRI time-points currently exists.[87] It would, therefore, be exciting to follow-up on the current sample, which would likely bring us closer to predicting psychopathology during life course based on interactions between daily stress and brain function. In general, longitudinal neuro-imaging studies in early life trauma research, ideally with stress challenges, are highly needed.

4.4. Possible implications and future directions

Taken together, results from the current thesis suggest that disorder-free individuals exposed to severe early life trauma exhibit durable brain abnormalities that become manifest under acute stress. We only included participants that reported multiple highly severe traumatic events throughout their childhood and adolescence. Previous studies related to the topic, in contrast, vary broadly in the severity and chronicity of the events experienced by their participants, both within a study and between studies. Additionally, their terminology also varies broadly, using terms such as 'childhood trauma', 'early life stress', 'childhood maltreatment', 'childhood abuse', or 'childhood adversity' interchangeably. Whether these traumatic events indeed have a durable effect on the brain and exactly how they affect it, has been shown to be dependent on these very variables (e.g. De Bellis et al., 1999, 2002, Cicchetti et al., 2001, Putnam et al.,

2013.)[88-91] As with other kinds of stress, early adversities can be labelled as 'tolerable', 'toxic' or even 'traumatic', depending on the quality of the events and their duration, and on the extent to which an individual has perceived control, the support systems and the resources (inside or outside the parental home) for coping with these early stressors.[92] Demands imposed by less severe early stressful experiences or adversities can even lead to growth and positive adaption,[93-95] but severe and chronic stress may lead to disturbances within the developing brain due to the traumatic qualities of the events. It thus appears that standardizing or at least more clearly defining the terminology will be important. Likewise, better controlling of chronicity and severity might serve well as a pre-requisite for consistent scientific advancement in this field and for comparability between studies.

Furthermore, stress increases the risk for almost all psychiatric disorders[96] and stress responses seem to be altered in many at-risk groups. For example, a previous study on emotion processing after acute stress reported neural activation imbalances in healthy siblings of schizophrenic patients that shared some important similarities with present results.[97] In general, however, little is known about the neural recovery process in the aftermath of stress, even in healthy non-vulnerable humans.[29] When conceptualizing mental health on a dimensional scope, neural and psychological functioning after stress may indeed qualify as a transdiagnostic mechanism across risk-groups. Future research should probe whether similar neural patterns are found in other at-risk groups, such as first-degree relatives of patients with affective or anxiety disorder. This research would help advance our understanding of whether changes in neural and psychological functioning under stress qualifies as a fundamental underlying mechanism that precipitates the development of psychopathology. Linking these neural pattern to Research Domain Criteria (Rdoc) dimensions might additionally help in this endeavour.[98]

The results presented here have implications for clinical practice and prevention. Together with previous evidence, they indicate that the differential brain activity of trauma-exposed individuals may result in a diminished capacity to regulate emotional impulses and a heightened experience of internal emotions and vigilance under stress. This fits with psychotherapeutic approaches that have been designed over the years to enhance emotion regulation, to diminish focus on internal feelings, and to learn skills that help reduce arousal states.[18,99,100] However, psychiatric and psychotherapeutic treatment is often focused on disorder diagnosis, while stress-related symptoms might originate from early trauma itself, as indicated by current results. As previously discussed elsewhere, trauma exposure has been a frequently unrecognized confound in neurobiologically-based clinical research,[2,101] and by extension, therapeutic

practice. We found further support for this important point in another recent fMRI study, in which we used 10 mg of hydrocortisone to mimic physiological stress during an autobiographical memory test in patients with PTSD, BPD, and healthy controls. No neural differences between psychiatric disorders were seen, but a link between hydrocortisone-induced neural activation and early life trauma was observed across groups.[102] However, traditionally, psychiatric practice has been driven by diagnostic categories and asking about traumatic childhood experiences is still not standard practice in many health care settings.[103-105] In addition, while there currently are a variety of specialized assessment instruments, the majority of these assess standard PTSD. They, however, may not capture the subtle but important abnormalities associated with complex early life trauma.[106] Routinely implementing differentiated and specialized diagnostic instruments might therefore help to develop and implement trauma-informed treatments across disorders.

Lastly, neural vulnerability to everyday life stress in disorder-free early life trauma exposed women emphasizes the potential value of secondary prevention programs (i.e. those aimed at preventing psychiatric disorder after trauma), particularly those that reduce adverse effects of daily challenges. Unfortunately, however, research on prevention lags far behind that of therapeutic intervention. Programs fostering everyday psychosocial stress management and regulation should be scientifically evaluated with respect to their ability to prevent development of adult psychopathology, that is, to reduce the number of adults that develop full-blown psychiatric disorder after early life trauma. Promising candidates for secondary prevention programs aimed at stress management include Mindfulness-Based Stress Reduction (MBSR),[107,108] stress inoculation against daily stressful experiences[109-111] as well as elements from Dialectical Behaviour Therapy (DBT) that aim to enhance distress tolerance and emotion regulation.[112,113] From a neuroscientific perspective, it would be intriguing to understand whether effective secondary prevention programs normalize stress-related neural risk markers associated with trauma exposure, or whether they foster the development or maintenance of compensatory brain changes. As such, as a next sensible step, neuroimaging-supported prevention studies could inform about the neural systems' ability to ensure healthy functioning despite disadvantageous neural changes. These studies would hold potential for establishing new brain-informed interventions to maintain long-term mental health, which are not limited to merely reversing trauma-induced neural changes.

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I. Eidesstattliche Versicherung

„Ich, Sabrina Helena Golde, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Neurobiological mechanisms of emotion inhibition under stress in severe early life trauma“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Berlin, 05.11.2019

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Datum, Unterschrift

II. Detailed declaration of contribution (Detaillierte Anteilserklärung)

Publication: Golde, S., Wingenfeld, K., Riepenhausen, A., Schröter, N., Fleischer, J., Prüssner, J., Grimm, S., Fan, Y., Hellmann-Regen, J., Beck, A., Gold, S. M. & Otte, C. Healthy women with severe early life trauma show altered neural facilitation of emotion inhibition under acute stress. *Psychol Med*, e-pub ahead of print 29 August 2019, doi:10.1017/S0033291719002198 (2019).

Ms. Golde's contribution to this scientific publication is tantamount to 85%. The tasks she completed were conducted with the utmost care, independence and scientific integrity. In co-operation with her supervisors, Ms. Golde developed the research question underlying the study and its publication, developed and established the experimental design and implemented all necessary administrative and technical requirement to conduct the fMRI-study that underlies this publication. In the following, the components are outlined in more detail.

Study preparation

During the preparation of the study, Ms. Golde independently contributed the following parts, supervised by her PhD supervisors:

- Preparation of study flyer and online study advertisements
- Composition of standardised telephone interview to evaluate all potential study participants and assess their suitability for the study (trauma and control group)
- Selection and adaptation of all study materials for the diagnostic session based on thorough examination of preceding studies. More specifically, she selected questionnaires and materials that were best suitable for her research question, compiled the case report form including clinical interviews, patient-reported measures, clinical documentation forms and set-up all required study logistics.
- Ms. Golde developed and established the complex experimental procedure that the publication is based on, including:
    - > selection of potential fMRI paradigms based on preceding studies
    - > adaptation of stress-task design (Montreal Imaging Stress Task) to fit the current study (timing, during, order of runs, difficulty of conditions, etc.)
    - > conceptualizing and designing the emotional go-nogo paradigm; programming this fMRI paradigm together with colleagues

- planning experimental procedure and timing, setting up all study logistics necessary including salivary and heart rate measurements during the fMRI measurements, establishing standardized processes for management and storage of imaging data
- implementing experiment at the laboratory of the Magnetic Resonance Imaging Laboratory at the Center for Cognitive Neuroscience Berlin (CCNB), conduction of thorough and extensive piloting to ensure successful measurement of imaging and autonomic data and to guarantee high quality of physiological data as well as technical stability of the measurement processes

Recruitment of participants and study conduction

Ms. Golde recruited all healthy trauma participants and about 1/3 of the control participants. Due to strict inclusion and exclusion criteria for the trauma group (especially the exclusion of any lifetime psychiatric disorder in addition to all fMRI-relevant exclusion criteria) in addition to the particular sensitivity of these participants, this process was by nature highly intricate and complex, but handled with utmost diligence and success by Ms. Golde. More specifically, Ms. Golde completed the following steps:

- Contribution to the public advertisement of the study via regular online postings and flyer distribution
- Conduction of telephone interviews with all potential healthy trauma participants (duration approx. 40mins each; 410 in total) and with approximately 1/3 of the (potential) control participants
- Scheduling and conduction of all diagnostic sessions including all structured psychiatric and trauma interviews (duration approx. three hours per trauma and two hours per control group participant).
- Scheduling and leading all fMRI-based experimental sessions. This included taking all salivary samples, handing out self-report scales and explaining the experimental tasks, operating the MRI scanner, ensuring that all data is appropriately saved afterwards, transporting salivary samples to the neurobiological laboratory after each session.

Data Processing and Analysis

Ms. Golde processed and analysed all behavioural, physiological and fMRI data presented in this publication, except for the biochemical analysis of salivary samples.

Manuscript composition and publication process

Ms. Golde completed the following steps under supervision of her PhD supervisors:

- Writing of the first draft of the manuscript, including abstract, introduction, methods, results, discussion, figures and tables, supplementary information and materials.
- Incorporating co-author feedback into the manuscript
- Writing the cover letter to the editor of the journal, submission of manuscript, handling of all correspondence with the journal and co-authors.
- Composing the manuscript revision including all required additional analyses, additions and changes to manuscript, writing point-by-point responses to reviewer comments.

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Unterschrift der Doktorandin

III. Journal Summary List (ISI Web of Knowledge)

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI Selected Categories: **"PSYCHOLOGY, CLINICAL"** Selected Category Scheme: WoS

Gesamtanzahl: 129 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	Annual Review of Clinical Psychology	5,555	14.098	0.011120
2	CLINICAL PSYCHOLOGY REVIEW	16,566	9.904	0.021110
3	Health Psychology Review	1,748	9.070	0.005540
4	CLINICAL PSYCHOLOGY-SCIENCE AND PRACTICE	3,382	6.028	0.002690
5	NEUROPSYCHOLOGY REVIEW	2,971	5.739	0.003940
6	PSYCHOLOGICAL MEDICINE	25,176	5.641	0.038080
7	JOURNAL OF ABNORMAL PSYCHOLOGY	15,807	5.519	0.014930
8	DEPRESSION AND ANXIETY	8,537	4.935	0.014490
9	Personality Disorders-Theory Research and Treatment	1,608	4.687	0.004930
10	JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY	23,559	4.358	0.014920
11	JOURNAL OF CLINICAL CHILD AND ADOLESCENT PSYCHOLOGY	5,622	4.356	0.008140
12	BEHAVIOUR RESEARCH AND THERAPY	17,427	4.309	0.013920
13	JOURNAL OF CLINICAL PSYCHIATRY	19,074	4.023	0.019900
14	ASSESSMENT	4,413	3.804	0.007380
15	CLINICAL CHILD AND FAMILY PSYCHOLOGY REVIEW	2,667	3.558	0.002540
16	HEALTH PSYCHOLOGY	11,641	3.530	0.016210
17	INTERNATIONAL JOURNAL OF EATING DISORDERS	8,728	3.523	0.008910
18	JOURNAL OF ANXIETY DISORDERS	6,639	3.472	0.009030
19	PSYCHOLOGICAL ASSESSMENT	11,711	3.469	0.013760
20	SEXUAL ABUSE-A JOURNAL OF RESEARCH AND TREATMENT	1,743	3.433	0.001740

Psychological Medicine

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Healthy women with severe early life trauma show altered neural facilitation of emotion inhibition under acute stress

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Original Article

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Key words:
Acute psychosocial stress; anterior insula; early life trauma; emotion inhibition; fMRI; inferior frontal gyrus

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Abstract

Background. Across psychopathologies, trauma-exposed individuals suffer from difficulties in inhibiting emotions and regulating attention. In trauma-exposed individuals without psychopathology, only subtle alterations of neural activity involved in regulating emotions have been reported. It remains unclear how these neural systems react to demanding environments, when acute (non-traumatic but ordinary) stress serves to perturbate the system. Moreover, associations with subthreshold clinical symptoms are poorly understood.

Methods. The present fMRI study investigated response inhibition of emotional faces before and after psychosocial stress situations. Specifically, it compared 25 women (mean age 31.5 ± 9.7 years) who had suffered severe early life trauma but who did not have a history of or current psychiatric disorder, with 25 age- and education-matched trauma-naïve women.

Results. Under stress, response inhibition related to fearful faces was reduced in both groups. Compared to controls, trauma-exposed women showed decreased left inferior frontal gyrus (IFG) activation under stress when inhibiting responses to fearful faces, while activation of the right anterior insula was slightly increased. Also, groups differed in brain–behaviour correlations. Whereas stress-induced false alarm rates on fearful stimuli negatively correlated with stress-induced IFG signal in controls, in trauma-exposed participants, they positively correlated with stress-induced insula activation.

Conclusion. Neural facilitation of emotion inhibition during stress appears to be altered in trauma-exposed women, even without a history of or current psychopathology. Decreased activation of the IFG in concert with heightened bottom-up salience of fear related cues may increase vulnerability to stress-related diseases.

Introduction

Exposure to trauma is a significant risk factor for psychopathology (Nemeroff, 2004). However, some individuals exposed to severe traumatic events do not develop full-blown psychiatric disorders. There are growing indications that these trauma-exposed individuals show neural alterations, even in the absence of clinical symptoms (Stark *et al.*, 2015; Teicher and Samson, 2016). Tasks requiring the regulation of emotions and impulses seem to be particularly affected. Concurrently, in trauma-exposed psychiatric patients, significant impairments in these domains are observed, across psychopathologies. These deficiencies are believed to be responsible for hallmark trauma-associated psychiatric symptoms such as hyperarousal in post-traumatic stress disorder (PTSD) (Shalev *et al.*, 2017) and depression (Goldsmith *et al.*, 2013) or impulsivity in borderline personality disorder (van Zutphen *et al.*, 2015).

Previously, studies have extracted distinct neural dysregulations associated with PTSD by comparing PTSD patients to trauma-exposed controls (Fani *et al.*, 2012*a*, 2012*b*). More recently, there has been an increasing focus on trauma-exposed participants without clinical symptoms. Despite some earlier reports of decreased inhibitory performance associated with trauma (Aupperle *et al.*, 2012), trauma-exposed participants without current psychopathology frequently do not suffer from significant behavioural impairments (Falconer *et al.*, 2008; Covey *et al.*, 2013; Quidé *et al.*, 2017; Melara *et al.*, 2018). However, studies of neural underpinnings paint a complex picture. For example, a recent fMRI-based study by Quidé *et al.* (2017) examined

non-affective response inhibition in patients with psychotic disorders and healthy controls. While not finding any effects of psychosis, the authors found altered left inferior frontal gyrus (IFG) functioning in a subgroup of participants that was exposed to childhood trauma. Furthermore, Melara *et al.* (2018) compared neural correlates of distractor inhibition between PTSD patients, trauma-exposed participants without PTSD and trauma-naïve healthy controls by means of EEG. Results were generally highly similar for both non-PTSD groups. However, in trauma-exposed without PTSD only, the ventromedial prefrontal cortex was associated with inhibitory control. Thus, these participants may require more active inhibition when processing emotional stimuli than trauma-naïve participants. An EEG-based study conducted by Covey *et al.* (2013) compared response inhibition of trauma-exposed policemen without the current psychiatric disorder to trauma-naïve civilian controls. Here, greater P3 amplitude, suggesting greater arousal, was found in police men compared to controls. An earlier fMRI study by Falconer *et al.* (2008), however, examining response inhibition did not find any neural differences between healthy trauma-exposed and trauma-naïve controls.

Overall, previous results are highly heterogeneous. They may point to subtle alterations that remain difficult to detect but can figure prominently. In fact, it has been suggested that differences in inhibitory functioning increase vulnerability to subsequent psychopathology (Teicher and Samson, 2016). Alternatively, they may mark psychiatric resilience, either as a pre-existing factor or as a product of early stress experiences. Notably, previous studies have not controlled for a lifetime diagnosis of any psychiatric disorder. Also, associations with clinical symptomatology in these trauma groups are poorly understood.

Importantly, differences may amplify in more demanding environments that induce everyday life stress. Subtle deficits in emotion regulation and inhibition may not significantly influence daily functioning until acute, ordinary and non-traumatic stress perturbates the system. Stress strengthens threat detection and rapid reactions but at the same time, it decreases the ability to inhibit automatic reactions (Starcke and Brand, 2012; Shields *et al.*, 2016). Furthermore, the sensitivity of neural emotion regulation processes to psychological everyday stress might be particularly relevant for the aetiology of trauma-related disorders (Nemeroff, 2004).

Several candidate brain areas are known to play an important role in top-down inhibition of emotions. The ventrolateral prefrontal cortex including the IFG represent the core areas facilitating response inhibition and top-down control of emotion (Kohn *et al.*, 2014). Also, the bilateral middle frontal gyrus, as well as the anterior cingulate and medial prefrontal cortex, have consistently been associated with emotion inhibition (Cromheeke and Mueller, 2014; Kohn *et al.*, 2014). Moreover, the anterior insula fulfils a central role in emotion regulation processes by marking events as salient and coordinating the involvement of different, large-scale neural networks (Menon and Uddin, 2010; Menon, 2011). Previous studies have further suggested that trauma-related psychopathology is associated with altered neural responses during emotion processing and inhibition in the lateral and medial prefrontal cortex as well as anterior insula (van Zutphen *et al.*, 2015; Aupperle *et al.*, 2016). Some studies in trauma-exposed participants without current clinical symptoms have pointed to only slight anomalies in overlapping areas (Stark *et al.*, 2015).

However, it is unknown how these neural systems in trauma-exposed individuals react to demanding environments and challenging circumstances. In this study, we therefore examined the effect of acute ordinary, non-traumatic stress on subsequent emotion inhibition in healthy women who had experienced multiple severe sexual or physical traumatic events before the age of 18, but never developed any psychiatric disorder (neither on DSM Axis I nor II; T+) and matched trauma-naïve healthy controls (T−).

We expected no significant differences in behavioural performance between trauma-exposed and trauma-naïve individuals, and neural differences to be subtle under baseline conditions. However, under stress, we hypothesized that trauma-exposed participants would, compared to trauma-naïve participants, show decreased top-down control, particularly in the IFG, and increased activation in areas of emotion and salience processing (Stark *et al.*, 2015; Homberg *et al.*, 2017). In addition, we assessed the exploratory hypothesis that healthy trauma-exposed participants might show different (compensatory) mechanisms to facilitate emotion inhibition.

Methods

Participants

Twenty-five healthy women who experienced multiple severe sexual or physical traumatic events (T+) were recruited. The inclusion criterion for this group was a minimum of three traumatic events (sexual or physical) before the age of 18 with neither a history of nor current psychiatric disorders. We conducted a thorough pre-screening via phone (duration approximately 40 min) to pre-assess the authenticity of the trauma criterion. In addition, 25 matched healthy control participants without a history of trauma (T−) participated. All were recruited via public advertisements. Participants underwent a detailed diagnostic interview by a trained clinical psychologist to assess inclusion and exclusion criteria. For both groups, psychiatric disorders (lifetime and current) were assessed by the Structured Clinical Interviews for DSM-IV Axis I and II (SCID I and II; Wittchen *et al.*, 1997). The inclusion criterion of severe early life trauma (sexual or physical) was further assessed using the German version of the Early Trauma Inventory (ETI; Bremner *et al.*, 2000; Wingenfeld *et al.*, 2011), a 56-item semi-structured interview for the assessment of physical, emotional and sexual abuse as well as general traumatic experience. The interview served to obtain in-depth information as well as specific (e.g. onsets, offsets, perpetrators, etc.) information about the events and to assess authenticity of the report. In order to collect an interviewer-independent measure and to increase comparability with previous studies, participants additionally completed the Childhood Trauma Questionnaire (CTQ; Bernstein *et al.*, 2003). All participants of the trauma group also fulfilled Criterion A for PTSD of the DSM-V. This criterion requires the person having been exposed to 'death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence' (American Psychiatric Association, 2013).

Criteria for exclusion were (1) lifetime diagnosis of a psychiatric disorder as assessed by the Structured Clinical Interviews for DSM-IV Axis I and II (SCID I and II; Wittchen *et al.*, 1997), (2) adverse health conditions affecting the central nervous or endocrine system function, (3) non-removable ferromagnetic material, (4) auto-immune and infectious diseases, (5) hypertension, (6) a transcontinental flight within the last 4 weeks, (7) excessive physical exercise of more than 10 h a week and (8) left-handedness. The study was conducted in accordance with the latest version of the Declaration of Helsinki and received approval by the local ethics committee (protocol number EA4/104/13). All participants provided written informed consent and were financially reimbursed.

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Two T+ and two T− participants had to be excluded due to excessive head movement (more than 3 mm translation or 3° rotation). These participants were hence excluded from all analyses.

Study design and procedure

The study consisted of a diagnostic and an experimental session that took place on different days within a 2-week period. During the diagnostic session, inclusion and exclusion criteria were assessed and the following self-report questionnaires were obtained: Beck Depression Inventory II (BDI II; Beck *et al.*, 1996), the Spielberger State-Trait Anxiety Inventory (STAI-T; Spielberger *et al.*, 1983), the Posttraumatic Diagnostic Scale (PDS; Foa *et al.*, 1997), the Perceived Stress Scale (PSS; Cohen *et al.*, 1983) as well as the Stress Reactivity Scale (SRS; Schulz *et al.*, 2005).

During the experimental session, participants completed two runs of an emotional go-nogo (eGNG) paradigm during fMRI, one before and one after psychosocial stress induction by an adapted version of the Montreal Imaging Stress Task (MIST; Dedovic *et al.*, 2005; Pruessner *et al.*, 2008). The experimental procedure is depicted in Fig. 1, and the fMRI paradigm is described in more detail below.

eGNG paradigm

We used a modified version of an eGNG paradigm previously employed by Hare *et al.* (2008). Subjects completed two runs (one in the control and one in the stress condition), comprised of four blocks each. Each block consisted of 30 go-trials and 10 nogo-trials. During go-trials, a target facial expression was presented, and subjects were asked to respond as fast as possible by pressing a button. During nogo-trials, non-target facial expressions were presented and subjects were asked to avoid any button press (inhibition trials). Two blocks used emotional target facial expressions (fearful or happy, respectively) in the presence of neutral non-targets, and two blocks employed neutral target faces, one in the presence of fearful non-targets and one in the presence of happy ones. Together with the participants' response, this task design provides for the analysis of four different trial types: correct go-trials (hits), correct nogo-trials (inhibition trials), incorrect nogo-trials (false alarms) and incorrect go-trials (misses).

At the beginning of each block, written instructions were displayed telling the subject to respond to the target facial expression as fast as possible by pressing with the right thumb and not to press any button for non-target facial expressions. In addition, the current task was verbally explained to the participants by the experimenter over the microphone. See Supplementary materials M1 and methods for details on stimuli selection, presentation and timing.

Stress induction and response measures

For psychosocial stress induction, we employed an adapted version of the MIST (Dedovic *et al.*, 2005; Pruessner *et al.*, 2008). See Supplementary materials and methods M2 for details. In short, during the control condition, easy arithmetic questions were presented. Stress induction then consisted of difficult arithmetic questions under time pressure in addition to negative social feedback.

To evaluate subjectively experienced stress, we asked participants to rate their stress and strain level on a 10-point scale during the control and stress condition after the experiment. Heart rate was recorded using the integrated photoplethysmograph of the Siemens Physiological Monitoring Unit under the left index finger. As a manipulation check of physiological stress induction, six saliva samples were collected, the first two were averaged as a single baseline value (T0) to reduce situational influences on baseline measures (see Fig. 1). Details on peak detection and biochemical analysis of saliva samples are provided in the Supplementary materials and methods M3 and M4.

fMRI first-level model

Please refer to Supplementary materials and methods M5 for details on acquisition parameters and pre-processing. Effects were estimated using an event-related general linear model convolving each trial with a haemodynamic response function. A fixed-effect model was performed to create images of parameter estimates. We modelled four different emotion conditions, corresponding to four blocks of trials. These were blocks with (1) fearful nogo faces–neutral go faces, (2) happy nogo faces–neutral go faces, (3) neutral nogo faces–fearful go faces, (4) neutral nogo faces–happy go faces. For each emotion condition, we also modelled the control and stress condition separately. Within each control/stress condition and each emotion condition in turn, we modelled four different trial types: correct go trials, correct nogo trials, false alarms (incorrect go), misses (incorrect nogo). Thus there were 4 (emotion condition) × 4 (trial type) × 2 (stress *v.* control condition) regressors. Regressors containing correct nogo trials were the regressors of interest. Please refer to online Supplementary Table S1 for a complete list of regressors and belonging trials. Additionally, realignment parameters were included as additional regressors in the model. Individual *t*-contrast maps of (stress>control) for all correct inhibition (nogo) trials of all emotion conditions were computed.

Statistical group analysis

Sample characteristics and stress induction measure

All non-imaging data related analyses were carried out using IBM SPSS Statistics 22 for Windows (SPSS Inc., Chicago, IL, USA). Demographic and clinical data were analysed with two sample *t* tests or χ^2 tests. Salivary data was winsorized (95^{th} percentile) and log-transformed. Subjective stress, mean heart rate, cortisol and α-amylase values were analysed with a mixed design analysis of variance (ANOVA), Greenhouse-Geisser correction was used when appropriate. Post-hoc *t* tests were Bonferroni corrected.

eGNG paradigm

Behavioural. We explored stress-induced failures of response inhibition as indexed by false alarm rate (FAR) on inhibition (nogo) trials in the stress *v.* control condition (cf. Wager *et al.*, 2005). First, the effect of stress on FAR in all four nogo emotion conditions: fearful, happy, neutral (fearful go), neutral (happy go) was assessed by Wilcoxon signed-rank testing. Second, the stress-induced increase ΔFAR was calculated by subtracting the control from the stress runs and Mann–Whitney *U* testing was employed to test group differences in ΔFAR. The Bonferroni method was used to correct for multiple testing.

Imaging (*group level*). On the group level, individual *t*-contrast images (stress>control) from first level were entered into a flexible factorial ANOVA with group (T+ *v.* T−), emotion condition (fearful nogo, happy nogo, neutral $\text{nogo}_{\text{fear–go}}$, neutral $\text{nogo}_{\text{happy–go}}$) and subject as factors. We used probabilistic threshold-free cluster enhancement (pTFCE) (Spisák *et al.*, 2019) in addition to whole brain peak-level (voxel-wise) FDR

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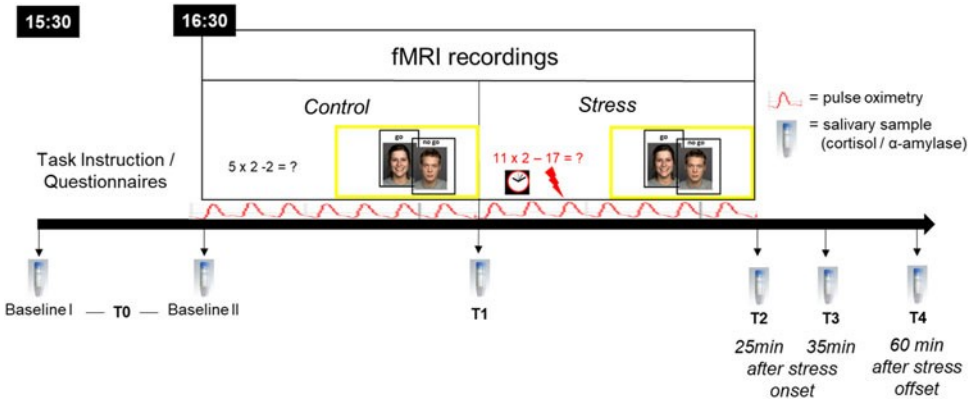

Fig. 1. Experimental procedure. All participants arrived at 15:30 h at the laboratory to control for circadian rhythmicity of cortisol release, fMRI testing began at 16:30 h. During fMRI, participants completed two runs of an emotional go-nogo (eGNG) paradigm (yellow boxes), one in the control condition and one after psychosocial stress induction. Six salivary samples were taken over the course of the experimental session. Baseline I (upon arrival) and II (before scanning, 45 min later) were averaged to a single baseline value (T0) to reduce situational influences on baseline measures. The T1 sample was taken inside the scanner, in-between control and stress condition, approximately 20–25 min after Baseline II. T2 = 25 min after stress onset, T3 = 35 min after stress onset, T4 = 60 min after stress offset. Pulse oximetry was used to measure heart rate over the course of the fMRI session.

correction with $p < 0.05$ and a minimum cluster size threshold of $k > 30$.

Results

Stress induction

Demographic and clinical data are shown in Table 1.

Subjective stress and heart rate increases

An ANOVA for subjective stress showed a main effect of stress indicating higher values in the stress compared to the control condition ($F_{1,42} = 88.4$, $p < 0.001$), but no main effect of group or group by stress interaction. For subjective strain, we also saw a significant main effect of strain ($N = 44$, $F_{1,42} = 92.7$, $p < 0.001$) and a significant condition by group interaction, indicating higher strain increase in T+ ($F_{1,42} = 7.1$, $p = 0.042$, see online Supplementary Fig. S1).

Heart rate was significantly higher during the stress compared to the control condition as well as during the MIST compared to eGNG in both groups (see Fig. 2*a* and online Supplementary Table S2).

Salivary cortisol and α-amylase

Cortisol levels significantly increased during stress induction (T2 to T3) and significantly decreased afterwards (T3 to T4), there were no group differences or time by group interactions. The α-amylase levels also significantly increased during stress induction (T2 to T3) in both groups; in addition, the T+ group had significantly higher baseline values (T1; see Fig. 2*b–c*).

Emotional response inhibition

Behavioural

The effect of stress on FARs on nogo stimuli in the four emotion conditions was examined across all participants. Stress significantly increased FAR on fearful faces (Wilcoxon: $N = 46$, $Z = -3.6$, $p < 0.001$ adjusted, $r = 0.5$), but had neither an effect on happy ones ($N = 46$, $Z = -1.1$, $p = 0.29$ unadjusted) nor on one of the neutral stimuli conditions (*fearful go*: $N = 46$, $Z = -0.3$, $p = 0.76$ unadjusted; *happy go*: $N = 46$, $Z = -0.04$, $p = 0.98$ unadjusted) (Fig. 3). The stress-associated increase in false alarms ΔFAR did not significantly differ between the groups for any emotion condition [Mann–Whitney U tests: $N = 46$ for all, $Z_{happy} = -0.9$, $p = 0.39$, $Z_{fear} = -0.8$, $p = 0.46$, $Z_{neut(happy-go)} = -0.2$, $p = 0.84$, $Z_{neut(fear-go)} = -0.8$, $p = 0.46$]. Thus, stress decreased inhibition of fearful nogo stimuli to a similar degree in both groups but had no effect on happy or neutral ones. Statistics on go stimuli are provided in online Supplementary Table S4.

Imaging

Results for neural correlates during stress induction (MIST) can be found in online Supplementary Tables S5 and S6. As stress only affected response inhibition of fearful nogo stimuli, we focused on exploring neural foundations of this stress effect on fearful stimuli in both groups. The analysis was hence on average based on 26.3 correct nogo trials for baseline and another 25.5 correct nogo trials for the stress condition. The principal contrast compared fearful nogo to neutral nogo faces and tested for an interaction effect with the group factor, i.e. [|fearful nogo–neutral nogo| × group]. This analysis revealed a significant interaction in the left IFG, indicating that T+ individuals showed blunted left IFG activation under stress compared to T− participants (MNI: −42, 38, −4, $t = 5.33$, $p = 0.010$ pTFCE and peak-level FDR corrected, 355 voxels). The reverse interaction contrast testing for increased neural activation under stress in the T+ group compared to the T− group hinted at a higher stress-induced activation in the T+ group in the right anterior insula (aIns) compared to the T− group, which however did not survive whole brain pTFCE and FDR correction (MNI: 39, 17, 5, $t = 3.65$, $p = 0.5$ pTFCE and peak-level FDR corrected, $p < 0.001$ *uncorrected*, 40 voxels) (Fig. 4*a*). Additionally, an analysis was run comparing the subgroup of neutral nogo trials that were part of fearful go-blocks with fearful nogo trials [|fearful nogo–neutral $nogo_{fearful-go}$| × group]. Here, we found that the anterior insula cluster was slightly larger (IFG: cluster: MNI: −39, 38, −1, $t = 5.51$ $p = 0.037$ TFCE and peak-level FDR corrected, 305 voxels; insula: MNI: 33, 14, 8, $t = 4.8$, $p = 0.1$ TFCE and peak-level FDR corrected, $p < 0.001$ uncorrected, 57 voxels). To assess whether our findings were lateralized, we lowered the threshold to $p < 0.001$ uncorrected, $k > 5$ voxels, but did not see the respective

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Table 1. Sample characteristics

	T+ (M ± SD)	T− (M ± SD)	Statistics
Age (years)	31.52 ± 9.71	31.22 ± 10.42	$p = 0.919$
Education (years)	11.57 ± 0.99	11.61 ± 0.89	$p = 0.876$
Intake of OC (no/yes)	20/3	16/7	$p = 0.153$
Cycle phase if no intake of OC (follicular/luteal/postmeno)	5/12/2	3/11/2	$p = 0.543$
Smoker (yes/no)	6/17	5/18	$p = 0.730$
Coffee per day (cups)	1.32 ± 1.22	1.73 ± 1.74	$p = 0.370$
BDI II	8.23 ± 6.19	2.91 ± 4.04	**$p = 0.001$**
STAI-T	38.30 ± 9.83	33.26 ± 6.71	**$p = 0.048$**
PDS	10,87 ± 10.68	0.96 ± 2.33	**$p < 0.001$**
PSS	16.44 ± 6.25	14.35 ± 4.64	$p = 0.205$
SRS	56.64 ± 7.93	56.83 ± 6.57	$p = 0.201$
CTQ sum score	66.57 ± 16.43	28.82 ± 3.50	**$p < 0.001$**
Emotional abuse	16.96 ± 6.09	5.74 ± 1.18	**$p < 0.001$**
Physical abuse	11.78 ± 4.82	5.04 ± 0.21	**$p < 0.001$**
Sexual abuse	10.30 ± 6.07	5.00 ± 0.00	**$p < 0.001$**
Emotional neglect	17.00 ± 5.48	7.43 ± 2.45	**$p < 0.001$**
Sexual neglect	10.52 ± 4.76	5.57 ± 1.31	**$p < 0.001$**
ETI sum score	490.87 ± 342.40	14.52 ± 13.25	**$p < 0.001$**
General trauma	91.17 ± 73.45	8.78 ± 10.31	**$p < 0.001$**
Physical abuse	100.48 ± 75.20	2.70 ± 4.63	**$p < 0.001$**
Emotional abuse	271.61 ± 230.52	1.30 ± ± 4.07	**$p < 0.001$**
Sexual abuse	27.61 ± 48.97	1.74 ± 3.62	**$p = 0.019$**

T+, trauma-exposed participants; T−, trauma-naïve control participants; OC, oral contraceptives; BDI II, Beck Depression Inventory II; STAI-T, Spielberger Trait Anxiety Inventory; PDS, Posttraumatic Stress Diagnostic Scale; PSS, Perceives Stress Scale; SRS, Stress Reactivity Scale; CTQ, Child Trauma Questionnaire; ETI, Early Trauma Inventory.
Information on cycle phase was unavailable for one T+ due to uterine agenesis.

bilateral activation difference (i.e. in the right IFG or left anterior insula). Next, we extracted mean BOLD parameter estimates of the left IFG and right anterior insula (5 mm sphere around peak voxel) from individual contrast images showing stress *v.* control during fearful nogo trials and analysed associations with a stress-induced increase in FAR. A sphere around the peak has been shown to be a reliable and sensible single-value ROI and was therefore chosen instead of the whole cluster (Tong *et al.*, 2016). The Spearman correlation coefficient was used to test for bivariate correlations as a stress-induced increase in FAR values deviated significantly from a normal distribution.

For the left IFG, activation increase under stress in the T− group correlated negatively with a stress-induced increase in FAR ($N = 23$, Spearman $\rho = -0.6$, $p < 0.01$), which was not observed in the T+ group ($N = 23$, Spearman $\rho = 0.1$, $p = 0.50$). This indicates that in T− participants, higher left IFG activation during stress tends to amount to better response inhibition of fearful faces under stress (Fig. 4*b*, left).

For the right anterior insula, we observed that stress-induced activation in the T+ group was positively related to a stress-induced increase in FAR ($N = 23$, Spearman $\rho = 0.4$, $p = 0.049$), but not in the T− group ($N = 23$, Spearman $\rho = 0.3$, $p = 0.12$). Thus, a higher activation of the right anterior insula in T+ participants is associated with a higher increase in FAR on fearful nogo faces (Fig. 4*b*, right).

Furthermore, we analysed associations of stress-induced neural activation with psychiatric anomalies (posttraumatic symptom severity by PDS, trait anxiety by STAI-trait, depressive symptoms by BDI-II). Left IFG activation for the whole sample correlated negatively with PDS total score ($N = 46$, Spearman $\rho = -0.568$, $p < 0.001$), as well as with all PDS subscales, see online Supplementary Fig. S2. There was also a significant negative correlation of left IFG activation with STAI-trait ($N = 46$, Spearman $\rho = -0.370$, $p = 0.011$), but none with BDI-II. There was no significant correlation between stress-induced insula activation and psychiatric symptoms.

Discussion

We investigated response inhibition in an eGNG paradigm using emotional face stimuli. We compared women who had experienced severe and multiple traumatic events before the age of 18 (T+) but have not (yet) developed any psychiatric disorder, with trauma-naïve control subjects (T−). In both groups, non-traumatic stress significantly impaired response inhibition of fearful facial expressions but did not affect inhibition of happy or neutral stimuli. When inhibiting responses to fearful faces under stress, T+ participants demonstrated a decreased brain signal in the left IFG but a marginally increased signal in the right anterior insula compared to T− controls. In T− only, IFG

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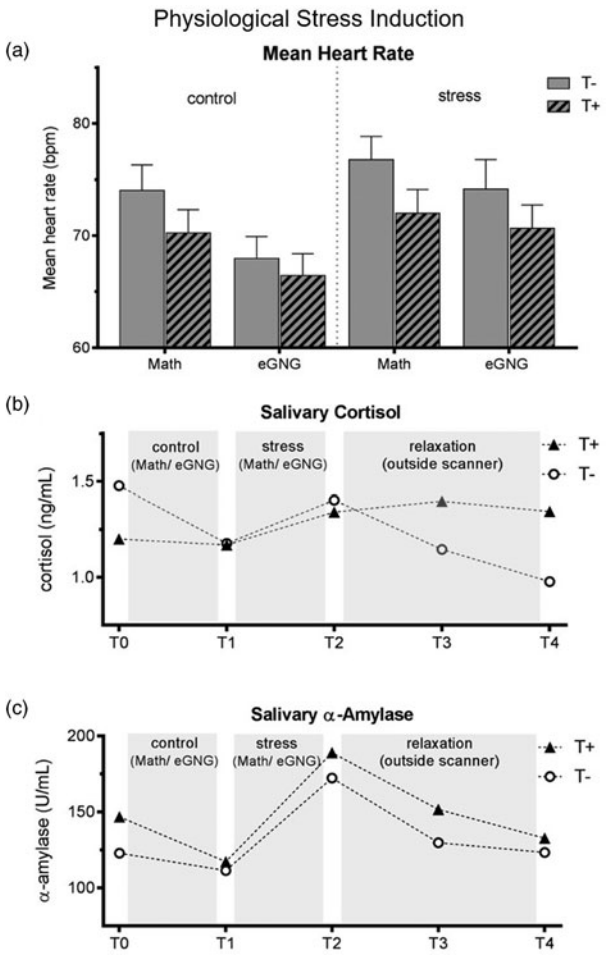

Fig. 2. (*a*) Mean heart rate over the experiment. Heart rate data of eight participants (3 T+ and 5 T−) had to be excluded due to scanner and movement related artefacts. We computed a mixed ANOVA including condition (control *v.* stress) and task (MIST *v.* eGNG) as within-subject factors and group as a between-subject factor. A significant main effect of condition ($N = 38$, $F_{1,37} = 13.8$, $p = 0.001$) demonstrated elevated heart rate in the stress condition compared to control, while a main effect of task ($N = 38$, $F_{1,37} = 61.8$, $p < 0.001$) indicated higher mean heart rate during presentation of math questions than during the eGNG paradigm. There was no main effect of group and no significant interactions. (*b*) Raw salivary cortisol data. Before the analysis of salivary cortisol and salivary α-amylase levels, one participant (T−) had to be discarded due to food consumption at sampling time. For statistical analysis, data were winsorized and log-transformed. Two mixed ANOVAs including a within-subject factor time (5 measurement points) and a between-subject factor group were conducted. For cortisol, we found a main effect of time ($N = 45$, $F_{4,43} = 4.8$, $p = 0.009$), but no main effect of group or interaction effect. Post-hoc Bonferroni corrected paired samples *t* tests examining the increase during stress condition (T1 *v.* T2) and subsequent recovery (T2 *v.* T3) across all participants showed a significant cortisol increase during stress (T1 *v.* T2: $N = 45$, $t_{44} = 2.4$, $p = 0.044$ adjusted) and recovery afterwards (T2 *v.* T3: $N = 45$, $t_{44} = 5.2$, $p = < 0.001$ adjusted). (*c*) For α-amylase, there was a main effect of time ($N = 45$, $F = _{4172} = 17.3$, $p < 0.001$), no main effect of group, but a time by group interaction ($N = 45$, $F_{4172} = 2.6$, $p = 0.037$). To decode the interaction, we conducted Bonferroni corrected paired sample *t* tests between all consecutive time points (T1 *v.* T2, T2 *v.* T3, etc.) for both groups separately (four tests per group). This analysis revealed a marginally significant salivary α-amylase decrease from T0 to T1 in T+ participants ($N = 23$, $t_{22} = 2.7$, $p = 0.056$ adjusted) but not in T− participants ($p > 0.999$ adjusted), as well as large increases from T1 to T2 in both groups (T+ group: $N = 23$, $t_{22} = 7.4$, $p < 0.001$ adjusted, $d = 1.6$; T− group: $N = 22$, $t_{21} = 3.8$, $p = 0.004$ adjusted, $d = 0.9$). There were no significant differences in any other paired tests. Thus, the interaction was attributable to group differences in α-amylase changes from T0 to T1, resulting from higher α-amylase baseline levels (T0) in the T+ group (two-sample *t* test of T0 values: $N = 45$, $t_{44} = 2.$ 2, $p = 0.030$). See online Supplementary Table S3 for all means and standard errors. T−, trauma-naïve control participants; T+, trauma-exposed participants; control, control condition; stress, stress condition; eGNG, emotional go-nogo paradigm; bpm, beats per minute.

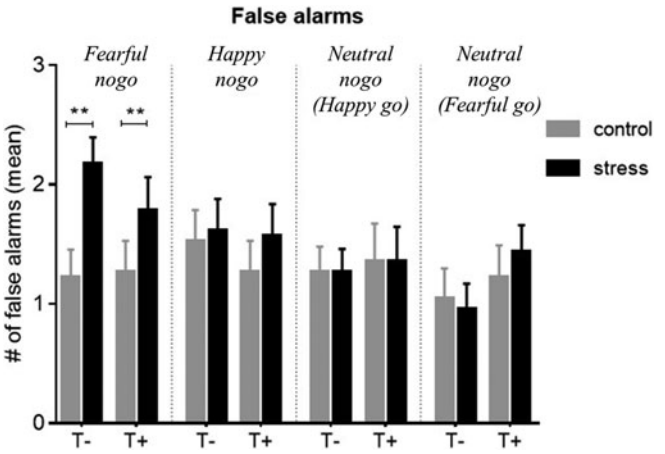

Fig. 3. Mean false alarm rate (FAR) for non-target (nogo) trials of all emotional conditions, compared between control and stress conditions. There was a significant stress-induced increase in FAR on fearful non-targets in both groups ($p < 0.001$), but no group differences. Stress had no significant effect on FAR in any other emotion condition. Control, control condition; stress, stress condition; T+, trauma-exposed participants; T−, trauma-naïve control participants.

activation was linked to a lower rate of stress-induced false alarms, whereas in T+, insula activation was linked to a higher number of false alarms. To our knowledge, this is the first study demonstrating that trauma, in the absence of lifetime psychiatric disorder, affects neural emotion inhibition under acute stress.

While the IFG represents a central area for the top-down cognitive control of emotions (Cromheeke and Mueller, 2014), the insula is seen as the neural locus for bottom-up salience detection and interoception (Menon and Uddin, 2010). It has been suggested that stress temporarily lowers top-down control in exchange for a reallocation of resources to salience detection (Homberg *et al.*, 2017). Our results show blunted IFG activation under stress when inhibiting responses to fearful faces in T+ participants compared to T− controls. Additionally, we found a trend towards increased response from the anterior insula in T+ participants under stress. Taken together, this pattern points to more pronounced stress-induced neural resource allocations in T+ individuals, shifting neural resources away from top-down control to salience detection, thereby likely rendering them more vulnerable to detrimental stress effects.

Alternatively, it is possible that these group differences represent markers of resilience in T+ individuals. We thoroughly excluded participants with a prior or current psychiatric disorder and did not find behavioural impairments, which indicates a relatively high level of resilience in this group. However, the current T + group showed subtle psychiatric alterations on the behavioural level (i.e. higher depressive symptoms, higher trait anxiety, more posttraumatic stress symptoms). Importantly, a blunted IFG signal under stress was related to more posttraumatic symptom severity as well as higher anxiety values. This association further suggests that the observed alteration in the IFG signal in T+ participants is indicative of increased vulnerability rather than resilience. In line with this, both, hypoactivity of the IFG as well as hyperactivity of the right anterior insula has been implicated in the development of trauma-associated psychiatric diseases (e.g. Rauch *et al.*, 1996; Stein *et al.*, 2007; Hayes *et al.*, 2012). In contrast, studies on neural markers of resilience point to increased PFC activation during top-down control (New *et al.*, 2009; Blair *et al.*, 2013), lower limbic activation during emotionally evocative

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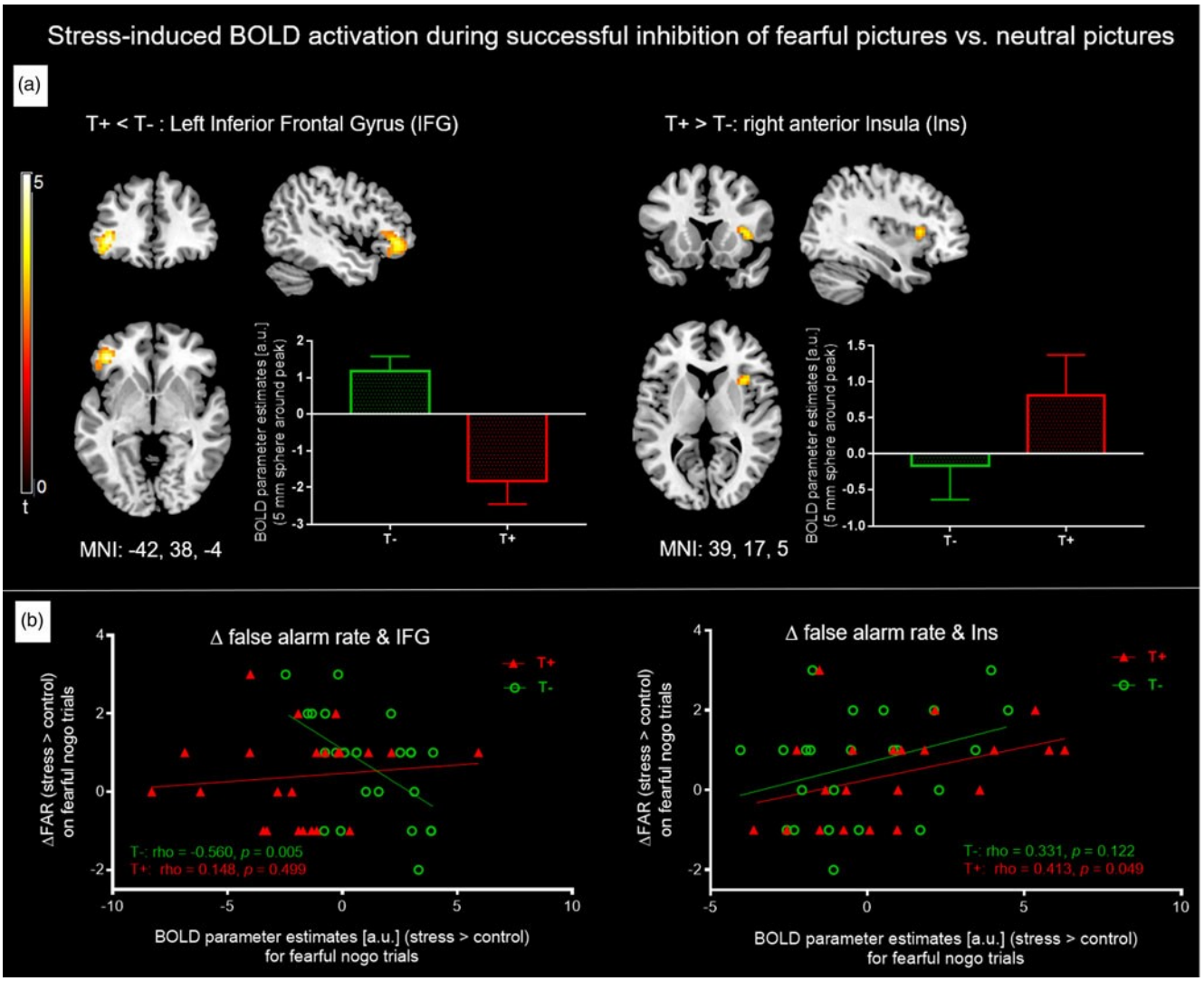

Fig. 4. (*a*) Individual *t*-maps of stress-induced BOLD increases (stress > control) for non-target (i.e. nogo) trials of all four emotion conditions were entered into a flexible factorial ANOVA and for both groups, fearful nogo-pictures were compared to neutral nogo ones [|fearful-nogo – neutral-nogo| × group]. The T– group showed higher stress-associated left IFG activation (left), whereas T+ participants showed marginally higher stress-associated right anterior insula activation. Bar graphs depict mean BOLD parameter estimates from a 5 mm sphere around the clusters' peak voxel. For IFG, results are pTFCE and FDR peak-corrected ($p < 0.05$) for the whole brain, minimum cluster size $k > 30$ voxels. For anterior insula, results are uncorrected, $p < 0.001$, $k > 30$. (*b*) Left: Significant negative Spearman correlation between ΔFAR (increase in FAR on fearful nogo trials from control to stress condition) and stress induced left IFG activation during fearful nogo-trials (i.e. stress > control) in T– controls but not T+ participants. Right: Significant positive Spearman correlation between ΔFAR and stress-induced right insula activation during fearful nogo-trials in the T+ but not the T– group. IFG, inferior frontal gyrus; FAR, false alarm rate; T–, trauma-naïve control participants; T+, trauma-exposed participants; control, control condition; stress, stress condition; a.u., arbitrary unit.

events (Britton *et al.*, 2005) and higher reactivity of the reward system (Vythilingam *et al.*, 2009). Although the period of greatest risk of developing a psychiatric disorder has passed considering the mean age of T+ participants, a subgroup may still develop a mental disorder over time, depending on the magnitude of environmental stressors. Future studies should employ a longitudinal approach to consider neural differences between those that do and those that do not.

Functional differences of the IFG only arose under stress but did not appear at baseline. In contrast, previous studies in PTSD and other trauma-related disorders have consistently found decreased IFG activity at baseline across tasks. In their meta-analysis, Hayes *et al.* (2012) highlighted the IFG as a promising target for evaluating therapeutic success in PTSD. The lack of baseline differences in our study indicates that trauma *per se* might not be associated with baseline IFG reactivity, but that baseline IFG activity changes only occur after the development of PTSD. Our findings therefore support the idea of a gradient in terms of durable effects of trauma upon exposed individuals.

We found an increased anterior insula response to stress in T+ participants. This finding needs to be interpreted with caution because neural activation differences did not survive our very conservative *a-priori* threshold ($p < 0.05$ whole brain pTFCE and peak-level FDR correction). However, using a more liberal threshold, we found a large cluster of activation ($p < 0.001$ uncorrected, $k = 40$ voxels). Underlining the relevance of the observed neural activation for the behavioural process in T+ individuals, anterior insula activation was related to FARs on fearful faces. Moreover, heightened insula activation is in accordance with numerous reports of trauma-induced insula sensitization and an overactive

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salience network in trauma-related disorders (Patel *et al.*, 2012; Ruocco *et al.*, 2013; Stark *et al.*, 2015). Furthermore, our finding is plausible from a computational network perspective. This perspective suggests that the insula has three central characteristics: it represents the focal point of the salience network, it coordinates the interplay of different large-scale neural networks and it provides access to the motor system via strong coupling with the anterior cingulate cortex (Menon and Uddin, 2010). As executive and salience networks are believed to be competing for resources (Fox *et al.*, 2009; Hermans *et al.*, 2014; Homberg *et al.*, 2017), heightened responsivity of the anterior insula might thus prevent adequate IFG-initiated regulation. Moreover, aberrant coordination by the anterior insula may cause impaired prefrontal network activation (Patel *et al.*, 2012), potentially paving the way to typical trauma-related symptoms. Lastly, the positive correlation between stress-induced insula activation and false alarms on fearful faces in T+ participants may be due to increased coupling with the motor system.

In line with our hypothesis, we moreover observed group differences in brain–behaviour correlations. In the T− group, IFG activation under stress was related to better inhibition of fearful faces under stress, which seems to be disrupted in T+ individuals. Moreover, in T+ only, stress-associated anterior insula activation positively correlated with stress-associated false alarms on fearful stimuli. Contrary to our expectation, we did not find a compensatory mechanism that preserves neural facilitation of emotion inhibition under stress in trauma-exposed individuals. As previous studies have demonstrated alterations in neural connectivity in trauma-exposed individuals (Brown *et al.*, 2013; Cisler *et al.*, 2013), future studies may examine potential compensatory mechanisms at the brain network level.

Furthermore, stress effects on emotion inhibition were limited to fearful stimuli. Previous investigations have been inconsistent with respect to the valence specificity of stress effects (e.g. Li *et al.*, 2014; van Leeuwen *et al.*, 2018). Here, relative levels of activation of sympathetic nervous system stimulation and the hypothalamic–pituitary–adrenal (HPA) axis might play a role. While exogenous cortisol (the end product of HPA axis activity) administration has mostly been found to lead to valence nonspecific effects, elevated noradrenergic signalling from the sympathetic nervous system may modulate stress-induced bias to negative cues, particularly in the presence of elevated cortisol levels (Kukolja *et al.*, 2008). As stress induction in the present study activated noradrenergic signal increase as marked by α-amylase levels, combined with moderate HPA axis activation marked by cortisol levels, this could explain the observed specificity of stress effects on fearful stimuli inhibition. Fearful stimuli might be particularly difficult to regulate for T+ individuals under stress.

Finally, we would like to offer some additional considerations regarding our study. It is noteworthy that we carefully selected our experimental group of individuals exposed to severe and repeated early life trauma. Lifetime psychopathology and psychotropic medication were excluded by extensive diagnostic measures including structural clinical interviewing by a trained psychologist for every participant. While trauma exposure was assessed retrospectively, and thus susceptible to recall bias, unlike most related studies, we used the ETI (Bremner *et al.*, 2000; Wingenfeld *et al.*, 2011), a semi-structured interview to assess traumatic events in addition to questionnaires. Furthermore, we only recruited women to ensure homogeneity, but due to sex differences in acute HPA and autonomic reactivity (Kudielka and Kirschbaum, 2005), it is unclear whether results can be extrapolated to males. Due to a technical problem at the scanner during psychosocial stress induction, we were unable to record BOLD activation during the MIST in nine trauma participants and four controls. We therefore cannot draw reliable conclusions from this neural data during the MIST. Nonetheless, subjective stress ratings, the increase in heart rate and the endocrine data clearly show a pronounced stress response to the MIST. We provide details on MIST acquisition in the Supplementary materials and methods M7 and results in online Supplementary Tables S5 and S6.

It is important to note that we did not investigate acute trauma-exposure or exposure to trauma-trigger. The present study examined emotional response inhibition after an everyday life stressor, which is distinct from stress resulting from trauma or associated triggers. Moreover, early-life trauma-exposure was not associated with differences in ordinary stress-response when considering cortisol or α-amylase levels or reported stress.

Further, for power reasons, correct inhibition trials were used for the analysis of the BOLD signal underlying emotion inhibition. While the observed brain–behaviour correlations support the link between our chosen behavioural and neural substrates, the analysis of neural correlates of erroneous trials (misses as well as false alarms) would be of significant interest. Future studies might exclusively focus on fearful/neutral pictures to provide a sufficient number of erroneous trials. Moreover, replication in a larger sample is advisable in order to confirm results and potentially give insight into subtler (potentially compensatory) mechanisms at the brain network level. Lastly, participants were subjected to the eGNG task twice. Although we used parallel versions to minimize learning effects, we cannot exclude that learning effects might have influenced the results.

In summary, our data suggest that early life trauma has a durable effect on the brain, even in the absence of lifetime full-blown psychopathology. Dysregulation of top-down control by the IFG together with heightened bottom-up salience of fear related cues may alter neural stress processing and potentially increase vulnerability to adverse effects of everyday life stress.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291719002198.

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Supplementary Information

"Healthy women with severe early life trauma show altered neural facilitation of emotion inhibition under acute stress"

SUPPLEMENTARY MATERIALS AND METHODS

M1) Order and timing of emotional go-nogo paradigm (eGNG)

The naturalistic face stimuli used were drawn from the FACES database (Ebner et al., 2010), which are rated on mean accuracy (i.e. mean percentage of correct expression identification) and perceived age. Only faces of young and middle-aged actors with true as well as perceived (i.e. rated) ages of at least 18 and with highest possible accuracy ratings were selected. We chose to use fearful faces over angry faces as they have been found to be more perceptually salient and capable of holding attention (Engen et al., 2017). Pictures of the same actors, displaying the respective emotions, were used for all emotion conditions of one run. However, different sets of stimuli were used for each run (control vs. stress) to minimize learning effects. These sets were matched on mean age of actors and mean accuracy of facial expressions. The order of the blocks (i.e. the emotion condition) was counterbalanced for each participant but kept the same within participants for both runs. Stimuli were presented pseudo-randomly for 500 ms each and separated by a jittered inter-stimulus interval of 2000-10000 ms, during which participants viewed a blank screen. The jitter distribution was separated in steps of 250 ms and had an exponential slope with fewer long jitter times. The participants response was recorded until the stimulus disappeared after 500 ms. Presentation of the stimulus picture was taken as onset for fMRI trials, the duration of trials was 500 ms. One whole block lasted at most 2:57 minutes.

M2) Psychosocial stress induction by an adapted version of the Montreal Imaging Stress Task (Dedovic *et al.*, 2005)

The control condition consisted of easy arithmetic questions for which sufficient time was allotted (7 min). The stress condition included two runs (8 min each) with difficult arithmetic questions under time pressure. Here, time constraints and difficulty were automatically adapted to the subjects' performance to result in failure rates of 50-55%, and a performance bar depicted the participants' cumulative performance progressively falling behind the performance of a fake comparison group regardless of actual performance. After the first and

before the second stress run, a confederate, introduced to the participant as the head of the study, delivered scripted negative feedback over the microphone emphasizing the need to subsequently improve performance for ~1min.

M3) Peak detection of pulse oximetry data (heart rate)

TAPAS PhysIO toolbox, version r671, implemented in SPM12 (Kasper *et al.*, 2017) was used for processing of pulse oximetry data. Automated peak detection was performed by the adaptive 'auto-matched' peak detection algorithm of the PhysIO toolbox. Afterwards, diagnostic plots of the toolbox were used to manually check for outliers and wrongly detected heart beats due to movement and MR-signal related artefacts. All data sets with more than three wrongly detected heart beats (as indicated by the toolbox) were excluded from the analyses. Mean heart rate for presentation of arithmetic questions (Montreal Imaging Stress Task) and eGNG under control and stress condition was calculated.

M4) Storage and biochemical analysis of salivary cortisol and alpha-amylase

Salivette sampling device (Salivettes®, blue cap; Sarstedt Inc.) was used to collect samples. Collection took place at room temperature, after which samples were stored at -20°C until the end of the testing session and subsequently kept at -80°C until biochemical analysis. Salivary free cortisol and α-amylase levels were determined by the Neurobiology Laboratory of the Department of Psychiatry, Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin. After thawing, Salivettes® were centrifuged for 2 minutes at 1000 x g.

Free cortisol was analysed using an adapted homogenous time-resolved fluorescence resonance energy transfer (HTR-FRET)-based competitive immunoassay, which is based on an anti-cortisol antibody labelled with Europium 3+-cryptate as the donor dye, and authentic cortisol conjugated with a second generation acceptor dye (D2) (Cisbio International, Codolet, France). In brief, 2 parts of the sample were subjected to a fluorescence microtiter plate and 1 part of D2-conjugated cortisol was added immediately thereafter. Both components (saliva and D2-conjugate) were thoroughly mixed using a multi-channel pipette and centrifuged for 2 minutes at 1000 x g using a microtiter plate centrifuge (Heraeus Biofuge, Thermo Fisher Scientific, Braunschweig, Germany). After centrifugation, 1 part of Eu3+-cryptate-labelled anti-cortisol antibody was added, again thoroughly mixed, centrifuged (2 minutes at 1000 x g) and allowed to incubate for at least 2h. Appropriate authentic standards, negative, positive and blank controls were included according to the manufacturer's instructions. After incubation, time-resolved fluorescence was measured at 620 nm and 665 nm using a Clariostar multimode plate reader (BMG Labtech, Ortenberg,

Germany). Increase in fluorescence at 665 nm (acceptor fluorescence of D2) was normalized to fluorescence at 620 nm (donor fluorescence of Eu3+-cryptate) to account for differences in plating volumes or micro bubbles, and calculated as relative increase in fluorescence over Eu3+-cryptate-only containing blanks. Intraassay coefficients of variation were below 8%, interassay coefficients of variation were below 10 %. All samples and standards were measured in duplicates. The limit of detection of free cortisol was 0.2 nM. Intra-assay coefficients of variation were below 8%, inter-assay coefficients of variation were below 10% for both cortisol and α-amylase. All samples and standards were measured in duplicates (also see Duesenberg *et al.*, 2016).

Alpha-amylase activity was determined using a modified protocol of a previously published direct alpha-amylase assay (Rombold *et al.*, 2016). In brief, saliva samples were assessed in triplicates using 2-chloro-4-nitro-phenyl-a-D-maltotrioside (CNPG) as a chromogenic substrate, kinetic measurements were performed by measuring changes in optical density at 405 nm after 2, 4, 6 and 8 minutes.

In detail, alpha-amylase activity was determined using a modified protocol of a previously published direct alpha-amylase assay (Lorentz et al., Clin Chem Lab Med 1999; 37(11/12):1053–1062). The assay principle follows an IFCC method using 2-chloro-4-nitro-phenyl-a-D-maltotrioside (CNPG) as the chromogenic substrate and was adapted to be run at room temperature using six authentic alpha-amylase standards (Sigma-Aldrich, Taufkirchen, Germany) for absolute quantification. In brief, samples and standards were diluted 1:200 and 1 part of sample/standard was subjected to a clear microtiter plate. Plates were subsequently allowed to equilibrate to 20 °C inside the temperature-controlled multimode plate-reader and 20 parts of CNPG-containing chromogenic substrate (substrate start procedure) were injected in a time-controlled manner. Following each automated injection, the plate was shaken and an increase in absorbance was read at 405 nm periodically after exactly 2, 4, 6 and 8 minutes in each well. A linear increase in absorbance was assured for all samples and average increase in absorbance per minute (delta OD405 / min) was calculated for all samples and standards. Absolute quantification of alpha-amylase activity in samples was realized by 4-parameter nonlinear regression analysis of the calibration standards (r2 > 0,998). Inter- and intraassay coefficients of variation were both lower than 10 % for alpha-amylase activity. All samples and standards were measured in triplicates.

M5) fMRI acquisition parameters and pre-processing of the emotional go-nogo paradigm

FMRI data were collected with a 3 Tesla Magnetom Trio scanner system (Siemens Medical Systems, Erlangen, Germany) using a 12-channel radiofrequency head coil. Stimuli were projected onto a screen at the end of the magnet bore by a video projector (NEC GT950 NEC Corporation, Itasca, IL, USA, resolution 1024×768 pixels), which participants viewed via a mirror on the head coil. Participants responded by pushing a fiber-optic light sensitive key press. Functional images were collected using a standard echo planar imaging (EPI) sequence with 37 axial slices of 3 x 3 mm (interleaved ascending order, field of view (FoV) 192 mm, repetition time (TR) 2 s, echo time (TE) 30 ms, flip angle 70°, matrix size = 64 x 64). Two sessions, each with 4 runs of 94 volumes were acquired. For anatomical reference, a T1-weighted high-resolution magnetization prepared gradient-echo scan (MPRAGE) was obtained (176 slices, TR = 1900, flip angle 9°, TE = 2.52 ms, FoV = 256 mm, matrix size = 256 x 256, voxel size = 1 x 1 x 1 mm^3).

FMRI data were analysed using MATLAB R2014a (The Mathworks Inc., Natick, MA, USA) and SPM12 (Statistical parametric mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK). First, EPI-images were slice-timing corrected and realigned to the first volume, thereby correcting for head movement (six-parameter rigid body transformation). The anatomical MPRAGE was co-registered to the mean EPI and segmented. The acquired segmentation matrix was further used for the normalization of functional (voxel size = 3 x 3 x 3 mm^3) and structural images (voxel size = 1 x 1 x 1 mm^3) to the stereotactic normalized standard space of the Montreal Imaging Institute. In a last step, data were spatially smoothed utilizing an 8 mm (full width at half maximum) Gaussian kernel. The time series was high-pass filtered to eliminate low-frequency components (filter width 128 s).

M6) Supplementary analysis assessing neural response during the emotional go-nogo paradigm when controlling for cortisol levels

As a supplementary analysis, we added cortisol level increases during stress induction (ΔT2 to T3) as a covariate into the flexible factorial ANOVA. The model thus contained the main factors group, emotion condition, subject as well as an interaction term cortisol x group. The same thresholding approach as in the main analysis was used (probabilistic threshold-free cluster enhancement and whole brain peak level FDR-correction with $p < 0.05$ and a minimum cluster size of $k > 30$).

Results for the principal controls comparing fearful faces (fearful nogo) to neutral nogo ones and testing for group differences were similar. The difference in left IFG activation between the groups became slightly more pronounced (MNI: -42, 38, -4, $t = 5.77$, $p = 0.003$ pTFCE and peak-level FDR-corrected, 941 voxels) whereas the group difference in right anterior insula activation was slightly smaller (MNI: 33, 14, 11, $t = 3.51$, $p < 0.001$ uncorrected, 24 voxels).

M7) Analysis of neural correlates during stress induction (Montreal Imaging Stress Task)

Due to a technical problem at the scanner in 13 cases during the Montreal Imaging Stress Task, the final sample for the analysis of neural correlates during this paradigm was restricted to 14 trauma participants and 19 trauma-naïve control participants for control and stress run 2, and 18 control participants (14 trauma) for stress run 1. Therefore, these data are not reported or discussed in the main text, but for completeness, results are reported in Table S6.

Acquisition parameters

Three EPI sequences were acquired, the first (control) consisting of 220 volumes and the other two (stress) sessions of 250 volumes.

Acquisition parameters for the EPIs were identical with those reported for the EPI sequences of the eGNG. Also, the same T1-weighted MPRAGE (176 slices) was used for anatomical reference.

Imaging analysis of stress induction

Effects were estimated with a general linear model (GLM) convolving each block with a hemodynamic response function. The time-series was high-pass filtered with a cut-off frequency of 300 s. A fixed-effect model was performed to create images of parameter estimates. The model contained three regressors (control, stress 1, stress 2) as well as six motion regressors of no interest. Individual *t*-maps of contrasts [stress 2 > control] as well as [stress 2 vs. stress 1] were computed and taken to group level.

At the group level, these individual *t*-maps were entered into two one-sample *t*-tests across all participants to examine neural correlates of stress. Subsequently, two two-sample *t*-test were computed (using the same *t*-maps) to evaluate group differences (T+ vs. T-).

M8) one-way ANCOVA to analyse group differences in stress-associated left IFG activation when controlling for posttraumatic symptoms and trait anxiety

With this one-way analysis of covariance (run in SPSS) we followed up on observed significant negative correlations between left stress-induced IFG activation and both PDS total score and STAI-trait. Group was entered as a between subject factor, PDS total score and STAI-trait scores as covariates, and extracted parameter estimates for stress-associated left IFG activation as a dependent variable. The assumptions for an ANCOVA were met. Results showed a significant effect of group even when controlling for posttraumatic symptoms and trait anxiety ($F_{1,42} = 6.278$, $p = 0.016$).

SUPPLEMENTARY TABLES

Table S1: Regressors for emotion condition fearful nogo – neutral go (for illustrative purposes) in first level model

Regressors	Trials
Regressor 1	All trials presented in control condition where participant correctly pressed a button when a neutral face was displayed (correct go).
Regressor 2	All trials presented in control condition where participant correctly refrained from pressing a button when a fearful face was displayed (correct nogo).
Regressor 3	All trials presented in control condition where participant failed to press to press a button when a neutral face was displayed (misses).
Regressor 4	All trials presented in control condition where participant incorrectly pressed a button when a fearful face was displayed (false alarms).
Regressor 5	All trials presented in stress condition where participant correctly pressed a button when a neutral face was displayed (correct go).
Regressor 6	All trials presented in stress condition where participant correctly refrained from pressing a button when a fearful face was displayed (correct nogo).
Regressor 7	All trials presented in stress condition where participant failed to press to press a button when a neutral face was displayed (misses).
Regressor 8	All trials presented in stress condition where participant incorrectly pressed a button when a fearful face was displayed (false alarms).

Note: Regressors were equivalent for the other three emotion conditions.

Table S2: Means and standard deviation for heart rate measurement during control and stress condition for both groups

Heart Rate

		T- (N=18) Mean (SD)	**T+** (N=20) Mean (SD)
Control	Math	74.02 (10.20)	70.23 (9.34)
	eGNG	67.95 (9.19)	66.45 (9.31)
Stress	Math	76.86 (8.27)	72.00 (9.69)
	eGNG	71.74 (11.29)	68.64 (9.09)

Note: 3 T+ data sets and 5 T- had to be excluded due to movement and scanner related artefacts (N_{T-} = 18, N_{T+} = 20); *Abbreviations:* eGNG = emotional go-nogo task, T+ = trauma-exposed participants, T- = trauma-naïve participants, SD = standard deviation

Table S3: Means and standard error for cortisol and α-amylase for all time points

Cortisol

Time Point	Raw Mean (SEM)		LN Mean (SEM)	
	T-	**T+**	**T-**	**T+**
T1	1.43 (0.13)	1.20 (0.22)	0.25 (0.11)	-0.08 (0.15)
T2	1.18 (0.17)	1.17 (0.37)	-0.07 (0.15)	-0.44 (0.19)
T3	1.40 (0.26)	1.34 (0.24)	0.06 (0.16)	-0.04 (0.19)
T4	1.14 (0.22)	1.40 (0.43)	-0.20 (0.18)	-0.29 (0.20)
T5	0.99 (0.19)	1.34 (0.36)	-0.30 (0.16)	-0.24 (0.19)

α-Amylase

Time Point	Raw Mean (SEM)		LN Mean (SEM)	
	T-	**T+**	**T-**	**T+**
T1	100.17 (13.57)	136.35 (14.00)	4.36 (0.18)	4.78 (0.12)
T2	114.13 (19.57)	117.24 (18.78)	4.41 (0.19)	4.51 (0.15)
T3	172.36 (25.13)	189.07 (24.77)	4.83 (0.20)	5.03 (0.15)
T4	130.86 (18.67)	151.67 (21.03)	4.60 (0.18)	4.79 (0.15)
T5	126.34 (19.17)	132.72 (19.36)	4.57 (0.18)	4.63 (0.16)

Note: One T- participant had to be excluded (N_{T-}= 22, N_{T+} = 23); *Abbreviations:* LN = natural logarithm, T+ = trauma-exposed participants, T- = trauma-naïve participants, SEM = standard error of the mean

Table S4: Statistics of stress effects on emotional response inhibition (eGNG)

Hits

Stimulus	**Control** Mean (SEM)	**Stress** Mean (SEM)	**WSR**	**Effect Size** (Pearson)
Fearful go	27.76 (.538)	29.54 (.155)	Z=-4.08, $p < 0.001$	$r = 0.60$
Happy go	29.67 (.094)	29.98 (.022)	Z=-3.13, $p < 0.001$	$r = 0.46$
Neutral go (Fearful nogo)	28.76 (.214)	29.65 (.104)	Z=-3.96, $p < 0.001$	$r = 0.58$
Neutral go (Happy nogo)	28.43 (.433)	29.63 (.133)	Z=-3.46, $p < 0.001$	$r = 0.51$

Reaction Time on Hits

Stimulus	**Control** Mean (SEM)	**Stress** Mean (SEM)	**WSR**	**Effect Size** (Pearson)
Fearful go	0.50 (.012)	0.47 (.019)	Z=-3.49, $p < 0.001$	$r = 0.51$
Happy go	0.46 (.010)	0.45 (.010)	Z= 1.34, $p = 0.183$	$r = 0.20$
Neutral go (Fearful nogo)	0.50 (.011)	0.49 (.018)	Z=-3.91, $p < 0.001$	$r = 0.58$
Neutral go (Happy nogo)	0.51 (.012)	0.49 (.015)	Z=-3.55, $p < 0.001$	$r = 0.52$

Note. SEM = standard error; WSR = Wilcoxon signed-rank test

Table S5: Comparison between control and high stress run with one-sample *t*-test (N=33)

Region	H	Cluster size (voxels)	T (peak)	p (FDR cluster level)	MNI coordinates (peak)		
					x	y	z
T-contrast: Stress 2 > control							
Middle Temporal	R	247	7.15	0.001	42	-64	5
Superior Occipital	R	257	5.87	0.001	24	-88	26
Middle Occipital	L	192	5.08	0.002	-36	-70	11
Precuneus	R	99	4.71	0.029	12	-43	56
Occipital Pole	L	82	5.40	0.042	-18	-100	14
T-contrast: control > Stress 2							
Posterior-Medial Frontal	L	864	6.52	<0.001	-9	23	65
Middle Temporal	L	223	6.19	0.002	-48	-34	-4
Angular	L	119	5.75	0.025	-45	-67	47
Inferior Temporal	R	102	5.45	0.033	48	2	-34

Note. Abbreviations: H = hemisphere, R = right, L = left

Table S6: Comparison between high stress (stress 2) and moderate stress (stress 1) run with one-sample *t*-test (N=32)

REGION	H	CLUSTER SIZE (VOXELS)	T (PEAK)	P (FDR CLUSTER LEVEL)	MNI COORDINATES (PEAK)		
					x	y	z
T-CONTRAST: STRESS 2 > STRESS 1							
Calcarine / Precuneus / Lateral Occipital	L	64	6.00	0.044	-30	-55	14
T-CONTRAST: STRESS 1 > STRESS 2							
Middle Temporal / Angular	R	706	6.09	<0.001	51	-4	-25
Middle/ Superior Temporal	L	423	6.39	<0.001	-60	-43	11
Calcarine / fusiform	bil	350	5.52	<0.001	0	-97	-1
Precuneus / Posterior Cingulate	R	289	4.75	<0.001	3	-55	26
Superior Frontal	R	282	6.05	<0.001	15	65	23
Posterior-Medial Frontal	R	170	7.34	<0.001	9	23	68
Superior Occipital	R	142	5.19	0.003	21	-91	32
Hippocampus / Parahippocampal	L	82	6.60	0.026	-24	-25	-22
Middle Frontal	R	81	4.47	0.026	45	14	53
Superior Frontal	L	80	6.15	0.026	-24	59	26
Cerebellum	L	66	5.02	0.045	-27	-85	-25

Note. Group comparisons (T+ vs. T-) by means of two-sample t-tests did not yield any suprathreshold clusters. Abbreviations: H = hemisphere, R = right, L = left, bil = bilateral

SUPPLEMENTARY FIGURES

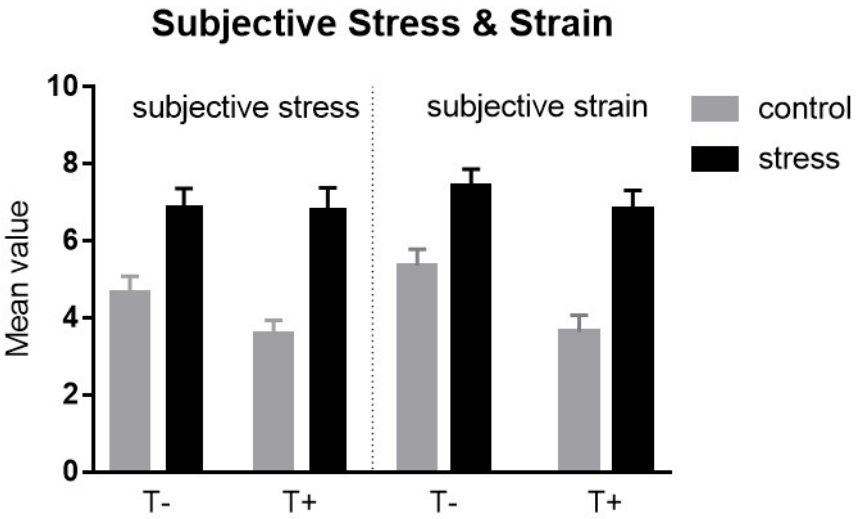

Figure S1. Subjective stress and strain during control versus stress condition in both groups. A mixed ANOVA with within-subject factor subjective stress (control vs. stress condition) and between subject factor group showed a significant main effect of subjective stress (N = 44, $F_{1,42}$ = 88.4, p < 0.001) with higher subjective stress in the stress compared to the control condition across groups ($M_{control}$ = 4.1 ± 2.0, M_{stress} = 6.9 ± 2.3), no main effect of group (p = 0.346) and a trend for a group by stress interaction (p = 0.097). In an equivalent mixed ANOVA of subjective strain, there was a main effect of strain (N = 44, $F_{1,42}$ = 92.7, p < 0.001), a marginally significant group effect ($F_{1,42}$ = 3.9, p = 0.056) and a significant group by strain interaction ($F_{1,42}$ = 7.1, p = 0.042). Thus, subjective strain increased in both groups. Since in the control condition, subjective strain was slightly lower for the T+ group compared to the T- group, the increase from control to stress condition was slightly larger in the T+ group. Error bars represent standard errors.

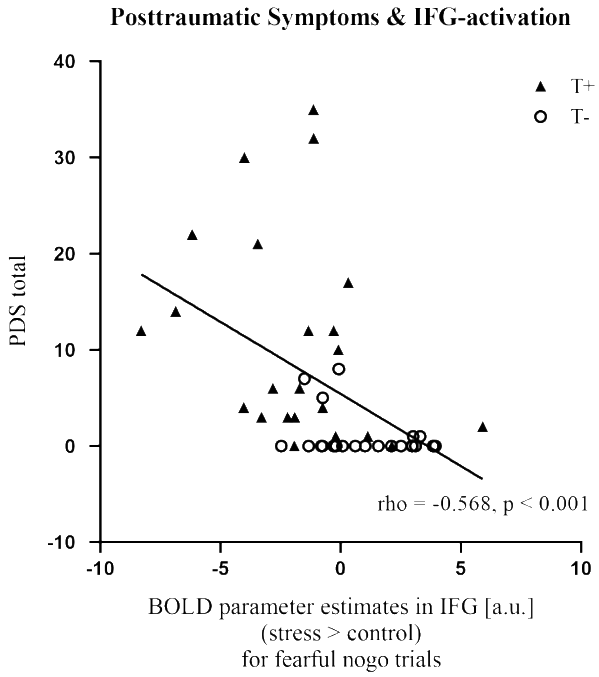

Figure S2. Significant negative Spearman correlation between posttraumatic symptoms during the last month (PDS total) and stress induced left IFG activation during fearful nogo-trials [i.e. stress > control]. *Abbreviations:* T- = trauma-naïve control participants, T+ = trauma-exposed participants, PDS = posttraumatic diagnostic scale, IFG = inferior frontal gyrus

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VI. Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

VII. Publications and scientific contributions

Journal articles

Golde, S.*, Heine, J*., Pöttgen, J., Mantwill, M., Lau, S., Engel, A. K, Otte, C., Heesen, C., Stellmann, J.-P., Dziobek, I., Finke, C.*, Gold, S.M*. Distinct functional connectivity signatures of impaired social cognition in MS. *Under review*

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*equal contribution

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