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Blocking under stress: Sustained attention to stimuli without predictive value?

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ABSTRACT

Learning is blocked when a stimulus is followed by an outcome that is identical to what was expected and thus contains no new information. This classic 'blocking' effect exemplifies that learning is driven by the predictive value of stimuli, which in turn should guide the allocation of attentional resources. Stress is known to be a powerful modulator of learning and memory. However, whether stress may affect attentional processing during predictive learning is largely unknown. Here, we combined electroencephalography and eye-tracking with an experimental stress manipulation and a fear conditioning paradigm designed to probe the blocking effect, to determine if and how stress impacts efficient attentional processing during predictive learning. Participants' explicit ratings indicated, irrespective of stress, a blocking effect. The control group further showed preferential attentional processing of predictive vs. unpredictive stimuli, reflected in differential fixation durations and a differential N2pc. Stress abolished this differentiation and led even to sustained attention, indicated by higher late positive potentials, to stimuli with low predictive value. Moreover, stress resulted in an overall increase in the P3b during the blocking phase, suggesting increased attentional processing, presumably due to impaired access to previously learned associations. Together, our results suggest that while control participants paid particular attention to predictive stimuli and reduced attention to unpredictive stimuli, in line with the classic blocking effect, stress before learning reduced this preferential processing. Thus, the present findings highlight the role of attention allocation for predictive fear learning and suggest that stress may impair efficient information processing against the background of prior experiences.

1. Introduction

Learning to predict significant events in the environment is crucial for survival. Associative learning theory suggests that such learning is driven by the predictive relationship between two stimuli and that learning should only occur if a discrepancy between an expected and actual outcome, i.e. a prediction error, is encountered (Mackintosh, 1975; Pearce & Hall, 1980; Rescorla & Wagner, 1972). The critical relevance of the predictive relationship between stimuli for learning is demonstrated by the classic blocking phenomenon (Kamin, 1968): when a neutral stimulus A is repeatedly followed by an unconditioned stimulus (US), the fully predictive stimulus A becomes a conditioned stimulus (CSA). If a new stimulus X (CSX) is added to the CSA and the compound CSAX is also repeatedly followed by the US, conditioning to the CSX is strongly reduced (or blocked). The CSX has no predictive value as the US can be fully predicted based on the CSA alone, thus there will be no new learning to the CSX. In contrast, if another stimulus B is never followed by the US, stimulus B is a non-predictive stimulus (CSB) for this outcome. If another stimulus Y is added to the CSB and the compound stimulus CSBY is followed repeatedly by the US, learning to the CSY should occur because it is predictive of the US, i.e. it contains new information. Here, we aimed to investigate attentional processes that are critical for the blocking effect and whether the blocking phenomenon may be affected by acute stress.

The blocking effect has been repeatedly demonstrated in humans (Balaz, Gutsin, Cacheiro, & Miller, 1982; Beesley & Le Pelley, 2011; Eippert, Gamer, & Buchel, 2012; Luque, Vadillo, Gutierrez-Cobo, & Le Pelley, 2018; Tobler, O'Doherty, Dolan, & Schultz, 2006; Wills, Lavric, Croft, & Hodgson, 2007; but see Maes et al., 2016) and several studies aimed at investigating its cognitive and neural basis. Based on the existing literature, we assume that attentional processes may be involved in the blocking effect. In particular, previous eye-tracking studies suggested less allocation of attentional resources to the redundant stimulus compared to a predictive one, when presented together (Beesley & Le Pelley, 2011; Eippert et al., 2012; Kruschke, Kappenman, & Hetrick, 2005; Le Pelley, Beesley, & Griffiths, 2014; Wills et al., 2007). Further

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evidence for altered attentional processing depending on the informational value associated with a stimulus comes from two studies using electroencephalography (EEG; Sanchez-Nacher, Campos-Bueno, Sitges, & Montoya, 2011; Wills et al., 2007). For instance, stimuli that contained no predictive value and to which learning was therefore blocked were shown to be associated with reduced early event-related potentials (ERPs), suggesting reduced attentional processing (Wills et al., 2007). Moreover, a functional magnetic resonance imaging (fMRI) study revealed decreased amygdala activity to a blocked versus non-blocked CS in fear conditioning, suggesting less fear learning to the blocked stimulus. Additionally, different parts of the prefrontal cortex, i.e. dorsolateral prefrontal cortex (dlPFC) and ventromedial prefrontal cortex (vmPFC), appear to be differently involved in the acquisition of the blocking effect. Specifically, whereas the vmPFC was specifically active when conditioned stimuli were established as predictive for an outcome, the dlPFC was active when conditioned stimuli had to be established as both predictive or non-predictive (Eippert et al., 2012). Together, these studies provide first evidence that the allocation of attentional resources plays an important role in the development of the blocking effect and that the blocked stimulus may attract less attention. However, the few studies that used EEG to study the blocking effect so far used reward learning paradigms and the only study assessing the neural basis of the blocking effect in fear learning used fMRI, which is less well suited to assess fast attentional processes (Woodman, 2010). Thus, in aversive learning the attentional processing of stimuli depending on their predictive value remains not well understood.

Moreover, to date it remains unclear which factors determine the extent to which we efficiently process stimuli based on their informational value and, more specifically, to which extent learning to stimuli with low predictive value is blocked. Research over the past decades has demonstrated that acute stress is a major modulator of cognitive processing in general and learning and memory in particular (Diamond, Campbell, Park, Halonen, & Zoladz, 2007; Joels, Fernandez, & Roozendaal, 2011; Lupien, McEwen, Gunnar, & Heim, 2009; Roozendaal, 2002; Schwabe, Joels, Roozendaal, Wolf, & Oitzl, 2012; Vogel, Fernandez, Joels, & Schwabe, 2016). Furthermore, stress and stress hormones are known to affect the activity of the amygdala and prefrontal areas (de Voogd, Klumpers, Fernandez, & Hermans, 2017; Lovallo, Robinson, Glahn, & Fox, 2010; Pruessner et al., 2008; Schwabe, Tegenthoff, Hoffken, & Wolf, 2012; Wirz, Reuter, Felten, & Schwabe, 2018; for a review see Arnsten, 2009), which are critically involved in the blocking effect (Eippert et al., 2012; LeDoux, Cicchetti, Xagoraris, & Romanski, 1990), and to modulate attentional processing (Hermans, Henckens, Joels, & Fernandez, 2014; Schwabe & Wolf, 2010). However, so far, the effect of stress on aversive predictive learning and the blocking effect, in particular has not been investigated yet. Based on findings showing that acute stress interferes with prefrontal cortex functioning (Arnsten, 2009; Bogdanov & Schwabe, 2016; Qin, Hermans, van Marle, Luo, & Fernandez, 2009) and the efficient use of prior knowledge (Buchanan, Tranel, & Adolphs, 2006; de Quervain, Roozendaal, & McGaugh, 1998; Kluen, Nixon, Agorastos, Wiedemann, & Schwabe, 2017; Vogel, Kluen, Fernandez, & Schwabe, 2018a, 2018b), we hypothesized that stress would impair the efficient allocation of attention based on the predictive value of a stimulus and hence reduce the blocking effect. In particular, we expected that the eye-tracking data would reveal differential effects during the acquisition of blocking, when two stimuli were presented at the same time. Specifically, we expected reduced attention to the CSX in controls relative to stressed participants, reflecting the successful blocking effect for this stimulus. Regarding the EEG data, we expected in anticipation of a shock an increased SPN in the initial conditioning phase for the CSA, for which participants learned that this stimulus will be followed by a shock, relative to the CSB. For the blocking phase, we did not have specific hypotheses for the newly introduced compound stimuli. For the final test phase, we expected reduced early attentional processing towards the blocked stimulus CSX, mirrored by the N2pc and heightened late attentional processing, mirrored by the P3b and LPP for the control group. Furthermore, we expected that for the stress group these effects would be diminished.

Thus, the present experiment aimed to examine (i) how attentional resources are allocated during aversive predictive learning and which neural mechanisms are involved in this process and (ii) whether acute stress modulates the blocking effect. Therefore, participants completed first a classical fear acquisition phase in which one stimulus (CSA) was paired with an unpleasant shock (i.e. US), whereas another stimulus was never paired with a shock (CSB). Afterwards, participants underwent either a stress or control manipulation, followed by a blocking phase in which CSA and CSB were presented together with a new stimulus (CSAX and CSBY, respectively) and both compounds were paired with the US. Thus, a blocking effect should develop for the CSX, paired with the fully predictive CSA, but not for the CSY. Whether the CSX and CSY acquired the potency to elicit a fear response was tested in a final phase, in which CSX and CSY were presented individually. In order to track the development of a blocking effect and related attentional processing, we measured EEG and eye-tracking. We focused on several ERPs that are associated with attentional and anticipatory mechanisms and may therefore be relevant in the context of the blocking effect. Specifically, we focused on the N2pc, reflecting fast attentional reallocation towards relevant information (Eimer, 1996), the P3b and the late positive potential (LPP) that are associated with sustained emotional processing of task-relevant stimuli (Mangun & Hillyard, 1990; Polich, 2007; Schupp, Flaisch, Stockburger, & Junghöfer, 2006) and the stimulus-preceding negativity (SPN), that is considered to be an indicator of anticipatory attention (Böcker, Baas, Kenemans, & Verbaten, 2001; van Boxtel & Böcker, 2004). Because electrodermal activity (EDA) is a widely used indicator of fear learning (Lonsdorf et al., 2017), we measured EDA throughout the learning task. In particular, we expected an increased EDA to the CSA compared to the CSB, as an indicator for successful fear learning and a reduced EDA to the CSX compared to the CSY, as an indicator for successful blocking. Additionally, we expected the stress group to show a higher EDA towards the CSX compared to the control group, representing a failure in successful blocking.

2. Methods and materials

2.1. Participants and experimental design

Eighty-eight healthy men and women between 18 and 35 years of age participated in this experiment. Four participants had to be excluded due to technical failure (n = 2) or because they did not complete the learning task (n = 2), thus leaving a final sample of 84 participants (44 women; mean age = 25.79 years; SD = 4.34 years). Participants were screened for the following eligibility criteria before testing: right-handedness, Body Mass Index between 19 and 26 kg/m^2, no intake of medication, no current or lifetime mental disorders, no current or history of drug abuse. In addition, we excluded smokers and women taking hormonal contraceptives as both factors may affect the endocrine stress response (Kudielka, Hellhammer, & Wust, 2009; Rohleder & Kirschbaum, 2006). Menstrual cycle phase in women did not differ between stress and control group (stress: 10 in follicular phase, 9 in luteal phase; control: 14 in follicular phase, 6 in luteal phase; $\chi 2(1) = 2.077$; $p = .150$). The study protocol was approved by the Ethics Committee of the Faculty of Psychology and Human Movement at the University of Hamburg. All participants provided written informed consent and received a monetary compensation (35 €) for participation.

In a between-subjects design, participants were pseudo-randomly assigned to a stress or control condition, ensuring an equal number of men and women in both groups (22 women, 20 men in each group).

2.2. Stress induction and control manipulation

Participants in the stress condition were exposed to the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993). The TSST is a standardized stress-induction protocol for humans that reliably increases subjective stress levels and activates both the autonomic nervous system and the hypothalamus-pituitary-adrenal axis (Kirschbaum et al., 1993). Briefly, the TSST mimics a job interview, consisting of a 5-minute public speech in which participants have to indicate why they are the ideal candidate for a job tailored to their interests as well as a 5-minute mental-arithmetic task (counting backwards from 2043 in steps of 17). Throughout the TSST, participants were standing in front of a panel of two experimenters, introduced as experts in behavioral analysis, who were dressed in white lab coats, acted in a rather reserved and non-reinforcing manner, and evaluated participants' performance continuously. In addition, participants were videotaped and saw themselves on a screen, placed behind the panel, while performing the two tasks.

In the control condition, participants gave a 5-minute talk about a topic of their choice and performed a simple arithmetic task (counting forward from zero in steps of 15), without being evaluated by a committee or videotaped.

To validate the successful stress induction by the TSST, subjective stress ratings, measurements of blood pressure and heart rate as well as saliva samples for subsequent cortisol analysis were taken at several time points before, during and after the experimental manipulation. Subjective ratings were assessed with three visual analogue scales (VAS; anchors: 0 = "not at all"; 100 = "extremely") on which participants rated the difficulty, unpleasantness and stressfulness of the task. Measurements of blood pressure and heart rate were taken using a Critikon Dinamap system (Tampa, FL, USA), with a cuff placed on the right upper arm. Saliva samples were obtained with Salivette® collection devices (Sarstedt, Germany) and stored immediately after testing at −18 °C (−0.4°F). At the end of data collection, free cortisol concentrations were analyzed from saliva samples with a luminescence immunoassay (IBL-International, Hamburg, Germany).

2.3. Associative learning task

In order to test the impact of stress on the blocking effect, we employed a paradigm that had been used before to study blocking effects in appetitive (Tobler et al., 2006; Waelti, Dickinson, & Schultz, 2001) as well as aversive conditioning (Eippert et al., 2012). In this paradigm, eight colored, abstract visual stimuli displayed on white background served as CSs and an unpleasant electrical shock as US. For each participant, one of the stimuli was randomly assigned to one out of four possible CS types (CSA, CSB, CSX and CSY; see below). The intensity of the US was individually set to a level that was experienced as unpleasant but not painful (see below).

On each trial, participants saw either a single CS, presented in one of the four corners of the screen (randomized), or a CS compound, consisting of two stimuli that appeared both either on the left or right of a fixation cross, for 5 s. For those CSs that were paired with the US, a train of three 2 ms electrical pulses (separated by 50 ms) was presented 4.7 s after CS onset. Between trials there was an interval (ITI) of 3–7 s, during which the black fixation cross stayed on the screen and participants were instructed to fixate on the cross. In order to keep participants attentive, we further implemented a simple attentional control task, requiring participants to indicate via a button press on ten percent of the trials whether the CS appeared on the left or right side of the fixation cross. Due to technical failure, responses in this attentional control task were not recorded for nine participants. The basic trial procedure was practiced in 12 trials before the start of the actual learning task. In this training phase, four stimuli not used in the main task were presented and no US was applied.

The actual learning task consisted of three phases (Fig. 1). Throughout all phases, CS presentation order was pseudorandomized with the constraint that no CS could occur more than twice in a row. The first phase was the fear acquisition phase in which participants were presented the CSA, which was always paired with the US (100 percent reinforcement), and the CSB, which was never paired with the US. During the acquisition phase, which lasted about 15 min, the CSA and CSB were presented 30 times each.

In the second phase, which took about 20 min, the blocking effect should develop. Therefore, the CSA that previously always co-terminated with the US was now additionally presented together with a new stimulus X to form the compound stimulus CSAX. The CSB, which was never paired with the US during the initial fear acquisition phase, was now additionally presented together with the new stimulus Y, thus forming the compound stimulus CSBY. Each compound was presented 30 times, with pseudorandomized position of the individual stimuli in the compound (top or down; see Fig. 1). Both compounds were always paired with the US (100 percent reinforcement). Since the CSA reliably predicted the US during conditioning, the CSX had no predictive value, consequently learning to the new stimulus CSX should be blocked. In contrast, learning to the CSY should occur because the CSB was never paired with the US before. To maintain the CS-US association acquired during initial conditioning, CSA and CSB were presented also 15 times each alone, with the same contingency as during conditioning (i.e. CSA always and CSB never paired with the US). To induce a rather elemental mode of processing (instead of a configural mode), the spatial distance of the CSs in a compound was maximized (Eippert et al., 2012; Glautier, 2002; Livesey & Boakes, 2004).

The blocking effect was tested in a final phase, which took about 30 min and in which the CSX and CSY were presented individually, i.e. without the CSA and CSB, respectively, 60 times each and without the US. The presentation of CSX and CSY was pseudo-randomly intermixed with the presentation of the CSA and CSB (each presented 15 times, with the same contingency as during conditioning) and the compound stimuli CSAX and CSBY (each presented 30 times, both always paired with the US). Thus, each single CS and CS compound was presented 60 times in total. In line with previous conditioning studies, a new phase always started with the presentation of a known CS-type to facilitate the transition between the different phases (Eippert et al., 2012; Hinchy, Lovibond, & Ter-Horst, 1995).

At the end of the task, participants' contingency awareness was assessed by presenting each stimulus again individually. Participants were instructed to indicate on a VAS (anchors: 0 = "Certain, no shock", 100 = "Certain, shock") whether the respective CS was paired with the US in the experiment.

2.4. Study procedure

In order to control for the diurnal rhythm of cortisol, all testing took place in the afternoon between 1 and 8 pm. Upon their arrival in the lab, participants provided written informed consent and completed questionnaires assessing depressive mood, subjective chronic stress, and anxiety (Beck Depression Inventory (BDI-II); Beck, Steer, & Brown, 1996; Trier Inventory for the Assessment of Chronic Stress (TICS); Schulz & Schlotz, 1999; State-Trait Anxiety Inventory (STAI); Spielberger & Syndeman, 1994, respectively). Afterwards, participants were prepared for the EEG, eye-tracking and SCR measurements. In addition, the electrode for shock administration was attached to the right lower leg. Next, participants provided a first saliva sample for subsequent cortisol analysis, their vital signs (blood pressure, heart rate) were measured, and they completed a German questionnaire assessing subjective mood (Mehrdimensionaler Befindlichkeitsfragebogen (MDBF); Steyer, Schwenkmezger, Notz, & Eid, 1994). After these baseline measurements, the individual pain threshold was determined. We aimed at reaching a moderate level of pain (unpleasant but not painful). Participants received an electric shock and should rate its painfulness on a numerical rating scale (anchors: 0 = "no pain",

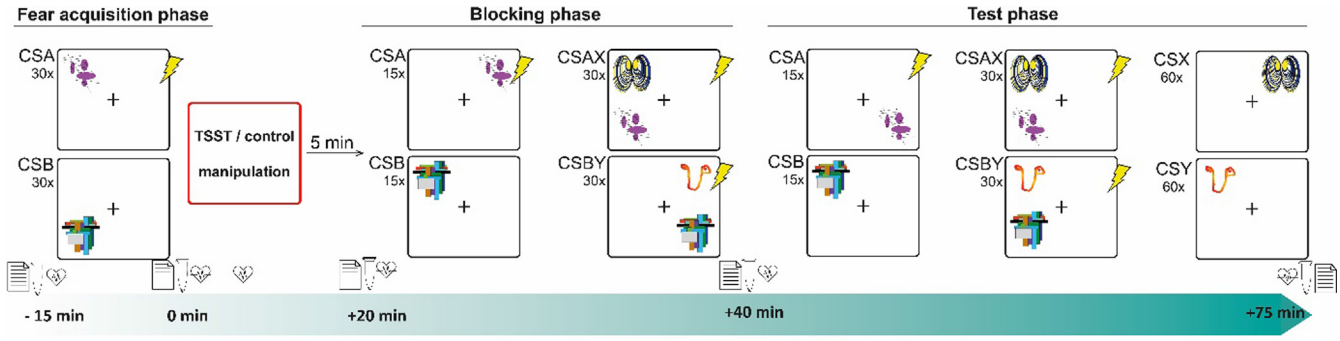

Fig. 1. Blocking paradigm and stress measurements over time. In the initial fear acquisition phase, two stimuli were presented at an equal rate. A CSA was always followed by the US, whereas a CSB was never paired with the US. During the second phase, the blocking phase, in addition to CSA and CSB, two compound stimuli CSAX and CSBY were introduced, comprised of the old stimuli and two new stimuli. Compound stimuli were continuously followed by the US. Contingencies for the CSA and CSB stayed the same as in the fear acquisition phase. In the final test phase, the CSX and CSY were presented individually, never followed by the US. In addition, CSA, CSB and the compound stimuli CSAX and CSBY were presented, with the same contingency as introduced. In addition, the time points are depicted when cortisol, ANS and subjective measures were taken.

10 = "worst pain imaginable"). After having rated a shock twice with a rating of 5, the mean of the two measures was taken as individual pain threshold. To further promote the development of a blocking effect, an additivity and submaximality manipulation followed (Beckers, De Houwer, Pineno, & Miller, 2005; Eippert et al., 2012; Mitchell & Lovibond, 2002). This was done by presenting two stimuli separately (different from those used in the associative learning task) for 5 s, both co-terminated with a shock (intensity equals the individual pain threshold). Afterwards, the two stimuli were presented as a compound for 5 s and co-terminated with a shock of an intensity that was previously determined as being twice as painful as the individual pain threshold. This procedure should inform participants that the outcome of conditioned stimuli may be additive and that receiving a shock stronger than the individual pain threshold is possible (although in the actual experiment the shock intensity always stayed the same). Next, the eye-tracker was calibrated applying a 12-point calibration and validation procedure before the acquisition phase of the associative learning task started (the calibration procedure was repeated before each phase of the task). After the acquisition phase, participants provided another saliva sample and their vital signs and mood were assessed. This was followed by either the TSST or control manipulation in a different room. Back in the testing room, participants completed the VAS-based subjective stress ratings and a MDBF, provided a third saliva sample and their vital signs were measured. About five minutes after the stress/control manipulation, the second phase (blocking phase) of the learning task started. Afterwards, another saliva sample was collected, and vital signs and mood were assessed. This was followed by the final phase of the learning task, the test phase. At the end of the learning task, a final saliva sample was taken as was a last measurement of vital signs and mood. Finally, all the electrodes were removed, participants were debriefed, compensated and thanked for their participation.

2.5. Manipulation check and behavioral data analysis

Analyses of behavioral performance, physiological and subjective stress responses were performed with SPSS 25.0 (IBM), using a α-error threshold of $p = 0.05$. Significant main or interaction effects were pursued using *post-hoc* planned comparisons, with Sidak correction if indicated. If the sphericity assumption was violated, Greenhouse-Geisser correction was applied. Physiological stress responses (i.e. cortisol response, blood pressure and heart rate) were subjected to a repeated measures analysis of variance (ANOVA), with the between-subjects factor group (control and stress) and within-subjects factor time (time points of measurement). To further test whether the observed stress effects were mainly driven by stress-induced cortisol, we subdivided our stress group into cortisol responders (baseline to peak increase > 1.5 nmol/l) and cortisol non-responders (baseline to peak increase < 1.5 nmol/l; Schwabe, Bohringer, Chatterjee, & Schachinger, 2008). Subjective stress ratings were assessed with a univariate ANOVA and mood assessments were subjected to a repeated measure ANOVA as was the US-contingency rating. For four participants (two of each experimental group), subjective stress ratings were missing, so were the measurements of mood for three participants (one of the stress group, two of the control group). To assess task compliance, we calculated the number of missed responses to the attentional control task. For nine participants, no responses were recorded due to technical failure.

2.6. Shock administration and SCR analysis

Shock administration was performed using a constant voltage stimulator (STM200, BIOPAC Systems, Goleta USA) and consisted of a train of three 2 ms pulses (separated by 50 ms) which were delivered to the participant's right lower leg via a surface bar electrode.

EDA was recorded from the distal phalanx of the index and middle fingers of the left hand, using two 8 mm Ag/AgCl electrodes, connected to the MP-160 BIOPAC System (BIOPAC Systems, Goleta USA). The EDA can be divided into the slowly varying tonic activity which is represented by the skin conductance level (SCL) and a rather rapidly varying phasic activity, mirrored by the SCRs, which we were interested in. From the raw skin conductance recordings, the SCRs were computed using a continuous decomposition analysis as implemented in Ledalab version 3.4.9 (Benedek & Kaernbach, 2010). Specifically, we were interested in the anticipatory SCR within a response window from 0.5 s to 4 s after stimulus onset. Anticipatory SCR refers to the SCR that is expected to evolve in anticipation of a consequence to a certain stimulus, independent of any other influence but the immediately preceding stimulus. Importantly, the US always occurred exactly 5 s after stimulus onset, thus leaving the anticipatory SCR unaffected by the shock itself. The minimum amplitude threshold was set to 0.01 μS. Because of a too low SCR, two participants were lost for the SCR analysis. From the other participants 64.11% of all trials over all three phases entered the analyses. Due to group differences in the baseline phase (see below), we computed ΔSCR, by subtracting the SCR to CSB from the SCR to CSA, thus mirroring the response difference to CSA vs. CSB and included this difference score as a covariate in all further analyses.

2.7. Eye-tracking recordings and analysis

Eye-tracking data were acquired with an EyeLink 1000 Plus (SR Research) device using the desktop mount installation and recorded from the right eye. We predefined four regions of interest by a rectangle

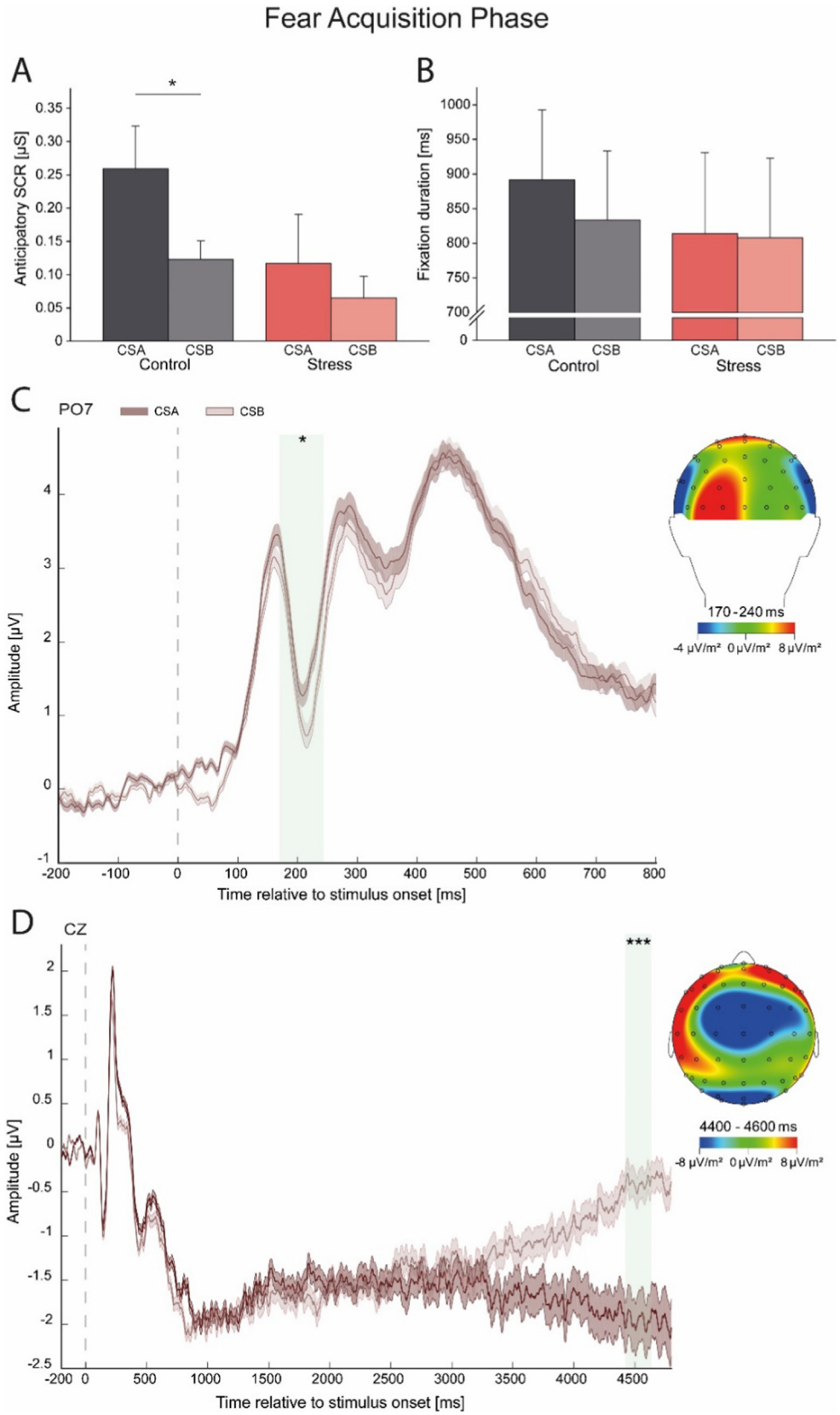

Fig. 2. Fear acquisition phase. (A) Participants' mean anticipatory SCRs were higher for the shocked CSA vs. the non-shocked CSB, in particular in the control group. (B) Participants' spend more time fixating the CSA compared to the CSB, in particular in the control group. (C) Participants' N2pc and (D) SPN was in both groups higher for the CSA compared to the CSB. Error bars and shaded error bars represent standard error. Asterisks denote difference between CSA and CSB: *$p < .05$, **$p < .01$, ***$p < .001$.

of 530 × 532 pixels in the four corners of the screen. The Data Viewer software (SR Research) was used to extract the total fixation duration participants spend on each CS, either presented individually or in a compound, in each trial and the sum of first saccades made to the different CS types when presented in a compound. To ensure the same starting point for each first saccade in every trial, the subsequent trial started only when participants had fixated on the fixation cross for at least the last second of the ITI. In addition, we excluded saccades from the analysis that occurred earlier than 150 ms or later than 1000 ms after CS onset. For the analysis of the fixation duration, we calculated a cumulative fixation duration on every CS (presented alone and presented in a compound) within a time window from 150 to 5000 ms after stimulus onset. For the analysis of first saccades to one of the compound stimuli, we computed a mean sum score for each CS type. Due to group differences in the fixation duration to CSA and CSB in the baseline phase (see below), we computed a ΔFixDur variable, subtracting the fixation duration to CSB from the fixation duration to CSA, thus mirroring the difference in fixation duration to CSA vs. CSB and included this difference score as a covariate in all further analyses. For statistical analysis, we used either paired *t* tests or repeated measures ANCOVAs. For one participant of the stress group eye-tracking data were missing, leaving eighty-three participants for eye-tracking analyses.

2.8. EEG recordings and analysis

EEG data were acquired with a BioSemi Active Two electrode system at 2048 Hz (BioSemi, Amsterdam, the Netherlands). Brain electrical activity was recorded from 64 Ag/AgCl electrodes including two mastoids according to the 10–20 electrode reference system. All sites were referenced to Cz. A bipolar horizontal and vertical electrooculography (EOG) was recorded from the epicanthus of each eye and the supra- and infraorbital positions of the right eye, respectively. Raw data was processed offline with BrainVision Analyzer 2.1 (Brain Products, Gilching, Germany). After down sampling the data to 512 Hz, a band-pass filter was applied with high and low cutoffs of 0.1 Hz and 30 Hz, respectively. Because data of the electrode sites Iz, P9 and P10 was too noisy and the electrode at O2 was damaged for the last ten participants, we excluded those electrodes from further pre-processing. Then, an ocular intercomponent analysis (ICA) was conducted and data was re-referenced to the average activity of all electrodes. Continuous EEG data were segmented into epochs with a length of 5000 ms (−200–4800 ms with respect to stimulus onset) and baseline-corrected with respect to the 200 ms pre-stimulus interval. Epochs were excluded if at any EEG electrode the following criteria were exceeded: a maximal voltage step of ± 75 μV, a maximal allowed absolute difference of 200 μV and lowest allowed activity of 0.1 μV within 1000 ms intervals. For each participant, separate ERP averages were computed for each stimulus for each phase. Based on previous stress, blocking and conditioning studies (Bublatzky & Schupp, 2012; Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Nelson, Weinberg, Pawluk, Gawlowska, & Proudfit, 2015; Sanchez-Nacher et al., 2011; Sanger, Bechtold, Schoofs, Blaszkewicz, & Wascher, 2014; Weymar, Schwabe, Löw, & Hamm, 2012) and corroborated by visual inspection of the grand-averaged ERPs and topographical maps of the different waveforms, the chosen electrode sites and the time windows for component analyses were set as follows: 170–240 ms (N2pc at P5, P6, PO3, PO4, PO7, PO8, POz, Oz), 300–450 ms (P3b at P7, P8, PO7 and PO8), 400–1000 ms (LPP at C1, C2, Cz, CP1, CP2, CPz) and 4400–4600 ms (SPN at C1, C2, Cz). Mean amplitude measures were separately submitted to repeated measures ANOVA including the factors electrode site and group. Separate ANOVAs were performed for each component (N2pc, P3b, LPP and SPN). One participant from the stress group had to be excluded from EEG data analysis because of missing data. In addition, only participants who contributed at least 80% of trials after artifact rejection were included in the EEG analyses. This resulted in an exclusion of 19 participants for phase one (stress: $n = 9$, control: $n = 10$), 6 participants for phase two (stress: $n = 2$, control: $n = 4$) and 8 participants for phase three (stress: $n = 4$, control: $n = 4$).

3. Results

3.1. Fear acquisition phase

3.1.1. SCR data

Successful fear acquisition should be reflected in stronger responding to the CSA, which was paired with the US, than to the CSB, which was never paired with the US. We assessed fear acquisition at three levels: SCR, eye-tracking and ERPs. Furthermore, we obtained explicit shock expectancy ratings at the end of the task (see below).

SCR analysis revealed a significant stimulus main effect ($F(1,80) = 4.03$, $p = .048$, $\eta^2 = 0.048$), indicating that the CSA elicited a significantly higher SCR than the CSB, representing successful fear acquisition (Fig. 2, A). However, there was also a significant stimulus × group interaction ($F(1,80) = 4.54$, $p = .036$, $\eta^2 = 0.054$), suggesting that whereas the control group showed stronger SCR responding to the CSA than to the CSB ($t(39) = 2.14$, $p = .038$, $d = 1.202$), the stress group did not ($t(41) = -0.186$, $p = .853$, $d = 0.309$). In order to check for possible habituation effects which might have been stronger for the stress group and therefore resulted in a non-successful discrimination, we divided the acquisition phase into two halves. However, the pattern of results stayed the same. We found a significant stimulus main effect ($F(1,80) = 4.36$, $p = .040$, $\eta^2 = 0.052$) and a significant stimulus × group interaction ($F(1,80) = 4.51$, $p = .037$, $\eta^2 = 0.053$) replicating the results of the overall analysis.

3.1.2. Eye-tracking data

In order to make sure that participants paid a comparable amount of attention to the CSA and CSB, which is an important requirement for the development of a reliable blocking effect, we analyzed the fixation duration participants spend on each of the two stimuli. As expected, we did not find a significant stimulus main effect ($F(1,81) = 0.08$, $p = .773$, $\eta^2 = 0.001$), indicating that both stimuli got the same amount of attention. However, there was a significant stimulus × group interaction effect ($F(1,81) = 3.98$, $p = .049$, $\eta^2 = 0.047$), showing that participants in the control group spend more time fixating the CSA than fixating the CSB ($t(41) = 2.44$, $p = .019$, $d = 0.374$), whereas participants in the stress group did not ($t(40) = -0.96$, $p = .344$, $d = 0.149$; see Fig. 2B).

3.1.3. ERP results

At brain level, we found a significant main effect of stimulus type for the N2pc ($F(1,61) = 4.23$, $p = .044$, $\eta^2 = 0.065$), showing that the N2pc was more negative for the CSA compared to the CSB, which might reflect a higher degree of early attention to the threat stimulus CSA compared to the safe stimulus CSB (Bublatzky & Schupp, 2012; see Fig. 2 C). Interestingly, there was also a significant stimulus main effect for the SPN ($F(1,62) = 14.99$, $p < .001$, $\eta^2 = 0.195$), showing that the SPN was more negative for CSA compared to CSB, which might point to an anticipatory preparation for the CSA co-terminating with the US (Bocker, Baas, Kenemans, & Verbaten, 2004; see Fig. 2D). For the LPP, we did not find any significant difference between stimuli (all $p > .417$). There were no group differences for any of the ERPs (all $p > .275$), indicating that the CSA vs. CSB differentiation that was observed in the N2pc and SPN was equally strong in the stress and control groups.

Together, these data show (i) successful fear acquisition in the control group, both at the SCR, eye-tracking and brain level and (ii) successful fear acquisition in the stress group shown in differential brain responses to CSA and CSB, despite no differentiation in the SCR and eye-tracking data.

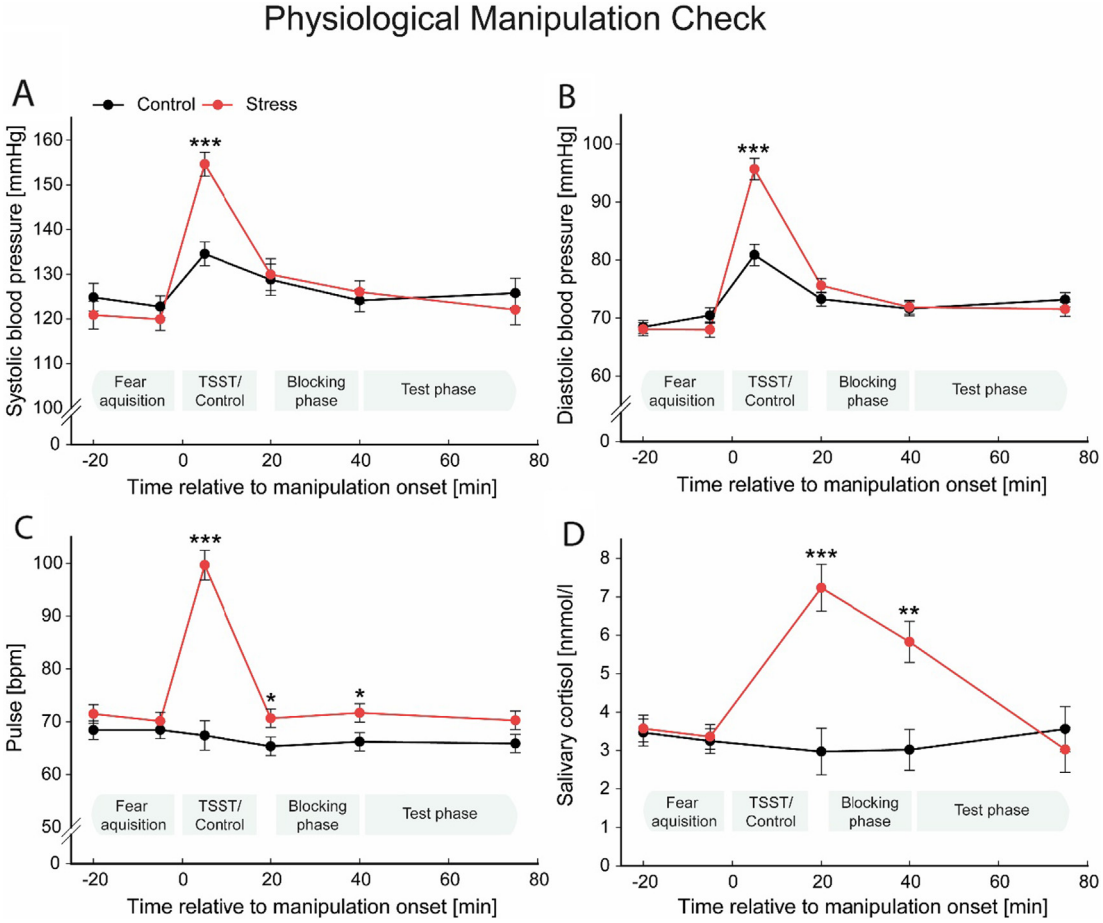

Fig 3. Autonomic and endocrine response to the psychosocial stressor. Successful stress manipulation as indicated by higher (A) mean systolic blood pressure, (B) mean diastolic blood pressure and (C) mean pulse during the TSST for participants of the stress compared to the control group. (D) In addition successful stress induction was shown by participants' mean salivary cortisol response, that was higher 20 and 40 min post TSST for the stress compared to the control group. Error bars represent mean standard error. Asterisks denote difference between control and stress group: *$p < .05$, **$p < .01$, ***$p < .001$.

3.2. Successful stress induction

Subjective, autonomic and endocrine changes confirmed the successful stress induction by the TSST (Fig. 3). Compared to the control group, participants in the stress group experienced the experimental manipulation as significantly more difficult ($t(78) = -3.753$, $p < .001$, $d = 0.839$), unpleasant ($t(78) = -3.398$, $p = .001$, $d = 0.760$) and stressful ($t(78) = -3.538$, $p = .001$, $d = 0.791$; see Table 1). At the autonomic level, there was a significant time × group interaction for systolic blood pressure ($F(3.92,321.22) = 13.539$, $p < .001$, $\eta^2 = 0.142$), diastolic blood pressure ($F(2.57,210.38) = 25.743$, $p < .001$, $\eta^2 = 0.239$) and pulse ($F(1.73,142.11) = 65.33$, $p < .001$, $\eta^2 = 0.44$). As shown in Fig. 3, systolic and diastolic blood pressure as well as pulse were significantly higher in the stress group than in the control group during the experimental manipulation (all $p < .001$), whereas groups did not differ in these measures at baseline (all $p > .219$). The pulse remained even significantly higher for the stress compared to the control group until 40 min after the treatment (20 min post stress: $t(82) = -2.14$, $p = .035$, $d = 0.467$; 40 min post stress: $t(82) = -2.25$, $p = .027$, $d = 0.490$). Finally, there was also a significant increase in salivary cortisol in response to the TSST (group × time interaction: $F(2.52,206.82) = 15.842$, $p < .001$, $\eta^2 = 0.162$). Although groups had comparable cortisol concentrations before the experimental manipulation ($t(82) = -0.210$, $p = .834$, $d = 0.046$), cortisol concentrations were significantly elevated in the stress relative to the control group 20 min after treatment onset, when the associative learning task started, as well 40 min after treatment onset (both $p < .001$, $d = 1.085$ and $d = 0.812$, respectively). By applying the predefined criterion for cortisol responders and cortisol non-responders (Schwabe et al., 2008), we obtained n = 25 cortisol responders and n = 17 cortisol non-responders. Since analyses of the two stress groups did not yield any significant difference in any of the baseline measures (all $p \geq 0.227$), we decided to conduct all further analyses with our two groups, i.e. control and stress.

Table 1
Subjective stress ratings and assessments of depressive mood, chronic stress and state anxiety.

	Control	Stress
Subjective stress assessments		
Difficulty	5.30 (1.26) ***	22.35 (4.36)
Unpleasantness	6.08 (1.49) **	22.15 (4.48)
Stressfulness	5.78 (1.32) **	22.50 (4.53)
Control variables		
Depressive score (BDI-II)	5.11 (0.91)	4.83 (0.833)
Subjective chronic stress (TICS)	13.98 (1.50)	12.45 (1.31)
State anxiety (STAI-S)	37.19 (1.09)	35.52 (0.88)

Data represent mean (standard error). Asterisks denote difference between Control and Stress group.
** $p < .01$.
*** $p < .001$.

3.3. Acquisition of the blocking effect

3.3.1. SCR data

Directly after the stress or control manipulation, participants underwent the blocking phase of the associative learning task. Because of group differences during the acquisition phase, we included the difference variable ΔSCR as a covariate. In terms of SCR, participants did not differentiate between the CSAX and the CSBY ($F(1,79) = 0.94$, $p = .335$, $\eta^2 = 0.012$), without any differences between groups (stimulus × group interaction: $F(1,79) = 0.15$, $p = .704$, $\eta^2 = 0.002$, main effect group: $F(1,79) = 0.116$, $p = .735$, $\eta^2 = 0.001$). This was expected because both compounds were paired continuously with the US.

3.3.2. Eye-tracking data

During the blocking phase, it is more informative to investigate the extent of attention participants paid to the individual parts of the compounds (e.g., CSA and CSX in compound CSAX). Therefore, we analyzed the fixation duration and the number of first saccades to the different parts. For the CSAX compound, we observed that participants fixated the previously shocked CSA and the new stimulus CSX for a comparable time ($F(1,80) = 0.49$, $p = .488$, $\eta^2 = 0.006$), without differences between groups (no interaction effect or main effect of group; both $p > .273$). For the CSBY compound, however, the new stimulus CSY attracted significantly longer fixation durations than the old stimulus CSB ($F(1,80) = 8.65$, $p = .004$, $\eta^2 = 0.098$), again without differences between groups (stimulus × group interaction: $F(1,80) = 1.95$, $p = .167$, $\eta^2 = 0.024$, main effect group: $F(1,80) = 0.18$, $p = .669$, $\eta^2 = 0.002$). When formally testing for interaction effects, we found a main effect for old (CSA, CSB) vs. new (CSX, CSY) stimuli ($F(1,80) = 7.94$, $p = .006$, $\eta^2 = 0.090$), indicating that participants were spending significant more time on the new stimuli in the compounds (i.e. CSX and CSY). Furthermore, we observed a non-significant trend for a compound × old/new × group interaction ($F(1,80) = 2.84$, $p = .096$, $\eta^2 = 0.034$). Post-hoc tests revealed that the control group fixated the CSY part significantly longer than the CSB part of the compound ($t(41) = -3.02$, $p = .004$, $d = 0.467$) but showed no difference in fixation duration to the individual parts of the CSAX compound ($t(41) = 0.21$, $p = .834$, $d = 0.032$, respectively), in line with the blocking effect. In contrast, participants of the stress group did not show such a differentiation (both $p > .151$; Fig. 4A).

When analyzing the number of first saccades, indicating fast attentional processes, we observed, for both compounds, that the new stimulus (i.e. CSX in CSAX and CSY in CSBY) attracted more first saccades than the old one ($F(1,74) = 10.90$, $p = .001$, $\eta^2 = 0.128$ and $F(1,77) = 10.31$, $p = .002$, $\eta^2 = 0.118$, respectively), irrespective of the experimental group (all $p > .401$; Fig. 4B).

3.3.3. ERP results

For the N2pc component, there was no main effect of stimulus but a strong trend towards a stimulus × group interaction ($F(1,73) = 3.54$, $p = .064$, $\eta^2 = 0.046$). A post-hoc t test revealed that the control group showed a more negative N2pc to CSAX than to CSBY ($t(37) = -2.64$, $p = .012$, $d = 0.429$). The stress group, in contrast, did not show such a differentiation ($t(38) = 0.80$, $p = .428$, $d = 0.128$; Fig. 4C). In addition, we obtained a similar pattern of results for the individual presentation of the CSA and CSB. Specifically, this analysis revealed a trend towards a stimulus × group interaction ($F(1,73) = 3.16$, $p = .080$, $\eta^2 = 0.042$) and post-hoc t test revealed that the control group showed a more negative N2pc to CSA than to CSB ($t(37) = -2.50$, $p = .017$, $d = 0.406$), thus replicating the results of the acquisition phase. The stress group in contrast, did not show such a differentiation ($t(38) = 0.63$, $p = .535$, $d = 0.100$). For the compound stimuli CSAX and CSBY, the later components, LPP and SPN, remained unaffected by stimulus type and group (all $p > .203$). We further replicated to some extent the findings of the acquisition phase as there was no difference in the LPP but a trend for a main effect of stimulus type for the SPN, indicating a more negative SPN for the CSA compared to the CSB ($F(1,75) = 3.05$, $p = .085$, $\eta^2 = 0.039$).

As displayed in Fig. 4C, groups differed also in the P3b, which evolved between 250 and 500 ms, with its maximum at parietal electrodes. A stimulus × electrode × group repeated measures ANOVA yielded a group main effect, indicating that the stress group showed, irrespective of the stimulus type, a significantly larger P3b compared to the control group ($F(1,73) = 5.73$, $p = .019$, $\eta^2 = 0.073$).

3.4. Test of blocking effect

3.4.1. SCR data

To test for a possible blocking effect, we compared the responses to CSX and CSY in the test phase, in which these stimuli were presented individually and never co-terminated with the US. Our results showed no differential SCRs to the CSX and CSY, in none of the groups (all $p > .219$). Because of possible habituation and/or extinction effects of the SCR, as already seen in previous fear conditioning studies (Bach, Flandin, Friston, & Dolan, 2009; Eippert et al., 2012), we further analyzed the initial response (defined as the response to the first presentation) to the CSX and CSY, i.e. before any extinction could have occurred. Again, we did not obtain a different response to CSX vs. CSY in none of the groups (all $p > .290$), in line with the habituation account (Fig. 5A).

3.4.2. Eye-tracking data

Next, we investigated the eye-tracking data. Although we were primarily interested in the responses to CSX and CSY not presented in a compound, we also analyzed the fixation duration and number of first saccades using the compound stimuli. Because participants were explicitly instructed to fixate the stimuli, for single stimulus presentations they had no choice which stimulus to fixate, why we did not expect to find any differences between CSX and CSY presented individually. Results indicated no different responses to the stimuli of the CSBY compound. Neither regarding the number of first saccades (all $p > .180$) nor regarding the fixation duration (all $p > .378$). Interestingly, the analysis for the CSAX compound revealed a significant stimulus × group interaction for the number of first saccades ($F(1,80) = 5.58$, $p = .021$, $\eta^2 = 0.068$) and a trending stimulus × group interaction for the fixation duration ($F(1,80) = 3.30$, $p = .073$, $\eta^2 = 0.040$). Control participants showed more first saccades and longer fixation duration to the informative stimulus CSA compared to the non-informative stimulus CSX whereas stressed participants showed the opposite pattern, suggesting successful blocking for the control group but not for the stress group (see Fig. 5C & D).

3.4.3. ERP results

Thus, most informative in terms of the actual blocking effect in the test phase were the ERP data. We were particularly interested in whether CSX and CSY attract a different amount of early or late attention. The N2pc analysis revealed a main effect of stimulus type ($F(1,74) = 4.74$, $p = .033$, $\eta^2 = 0.060$), indicating a more negative N2pc for CSX than CSY (Fig. 5C). Moreover, for the LPP we obtained a significant stimulus main effect ($F(1,74) = 4.41$, $p = .039$, $\eta^2 = 0.056$) as well as a significant stimulus × group interaction ($F(1,74) = 6.90$, $p = .010$, $\eta^2 = 0.085$). Post-hoc t tests revealed that the control group did not show a different LPP to CSX than to CSY ($t(37) = -0.39$, $p = .699$, $d = 0.063$), whereas the stress group showed a significant higher LPP to CSX than to CSY ($t(37) = 3.21$, $p = .003$, $d = 0.520$), indicating a sustained attention to the blocked stimulus CSX in contrast to the non-blocked stimulus CSY (Fig. 5D). The SPN analysis revealed no main or interaction effect (all $p > .262$).

3.4.4. Explicit fear learning and blocking

At the end of the test phase, we showed each of the four stimuli

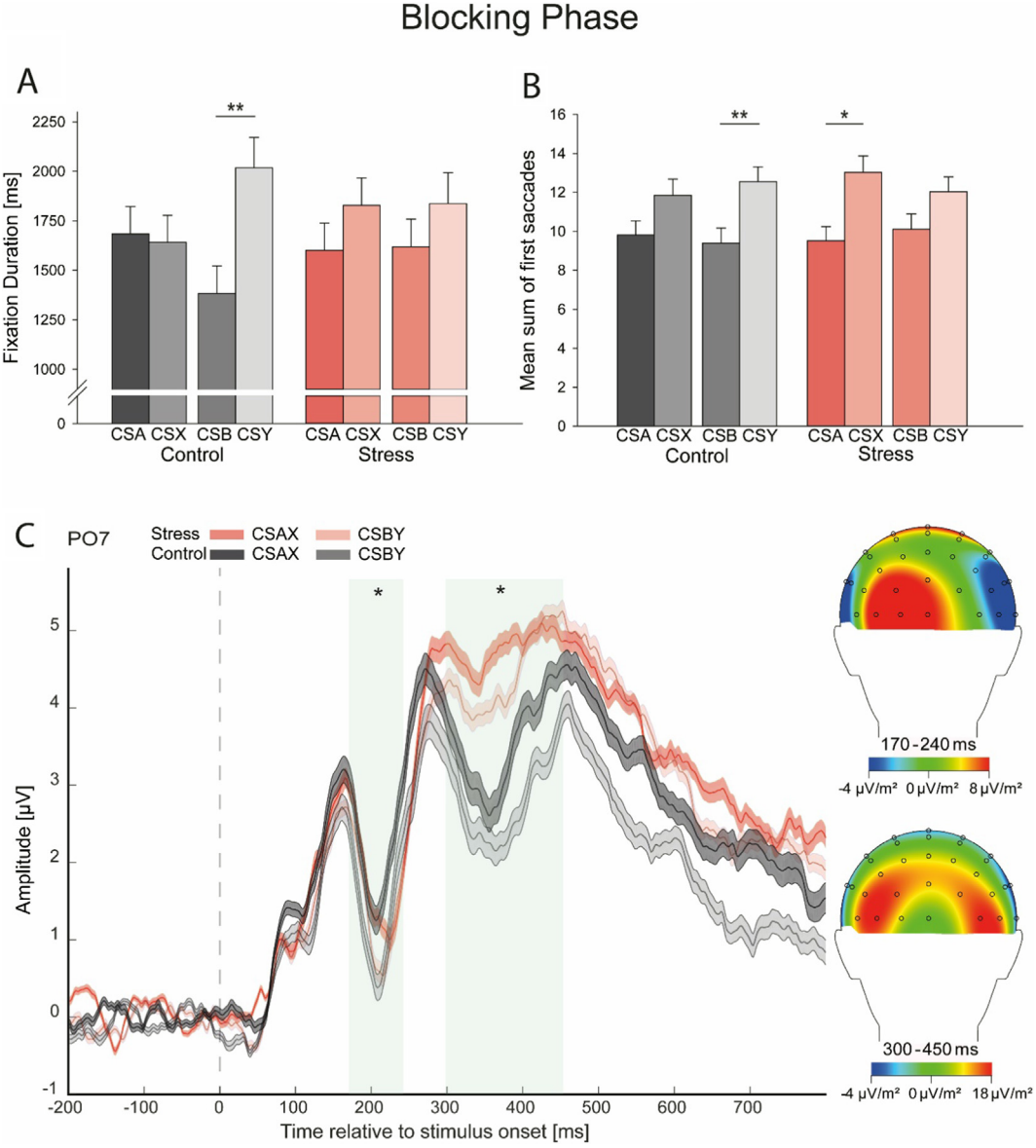

Fig. 4. Blocking phase. (A) Participants' mean fixation duration was higher for the new CSY compared to the old CSB in the CSBY compound, especially in the control group. No differentiation was found for the individual parts of the CSAX compound. (B) Participants' made more first saccades to the new stimuli (i.e. CSX and CSY) compared to the old stimuli (i.e. CSA and CSB) when presented in a compound, in particular participants of the control group regarding the CSBY compound and participants of the stress group regarding the CSAX compound. (C) Participants of the control group showed a more negative N2pc for the CSAX compared to the CSBY; participants of the stress group showed a higher P3b for the compound stimuli in general. Error bars and shaded error bars represent standard error. Asterisks in behavioral measurements denote difference between stimuli for each group; for N2pc the asterisk reflects the difference between stimuli for the control group only: for P3b, the asterisk shows the main group effect: $*p < .05$, $**p < .01$.

again individually and asked participants about their CS-US contingency awareness. When comparing CSA and CSB, there was a main effect of stimulus type ($F(1,82) = 77.66$, $p < .001$, $\eta^2 = 0.486$) and no interaction effect or main effect of group, indicating that participants were aware of the CS-US contingency, without differences between groups. Moreover, we compared the rating for CSX vs. CSY and obtained a trend towards a main effect of stimulus type ($F(1,82) = 3.72$, $p = .057$, $\eta^2 = 0.043$): Participants associated the CSY more strongly with the US then with the CSX (mean rating: 30.27, $SE = 3.11$ vs. 37.56, $SE = 3.49$, respectively), in line with a blocking effect. In addition, we found a trend towards a main effect of group ($F(1,82) = 2.80$, $p = .098$, $\eta^2 = 0.033$): The stress group tended to show a stronger US-CS association in general for CSX and CSY compared to the control group ($F(1,82) = 2.80$, $p = .098$, $\eta^2 = 0.033$; Fig. 6).

3.4.5. Analysis of a subsample showing robust fear acquisition in the SCR

Although the neural signature of fear acquisition was comparable in the two groups and the explicit ratings indicated successful fear learning in both groups, the SCR and eye-tracking data reported above suggested that the stress and control groups might have differed already in initial fear acquisition, i.e. before the actual stress manipulation took place. To control for these differences, we included the respective baseline differences as a covariate in all further analyses. Furthermore, we analyzed in an additional analysis only participants of the stress and control groups that showed a robust fear acquisition effect, i.e. stronger SCRs to CSA vs. CSB across the acquisition phase. We ran all our analyses again in this reduced sample (stress: n = 17, control: n = 20). In short, in this reduced sample both groups showed a higher SCR and more attention, expressed as longer fixation durations, to the CSA than to the CSB, indicative of successful fear acquisition, without any

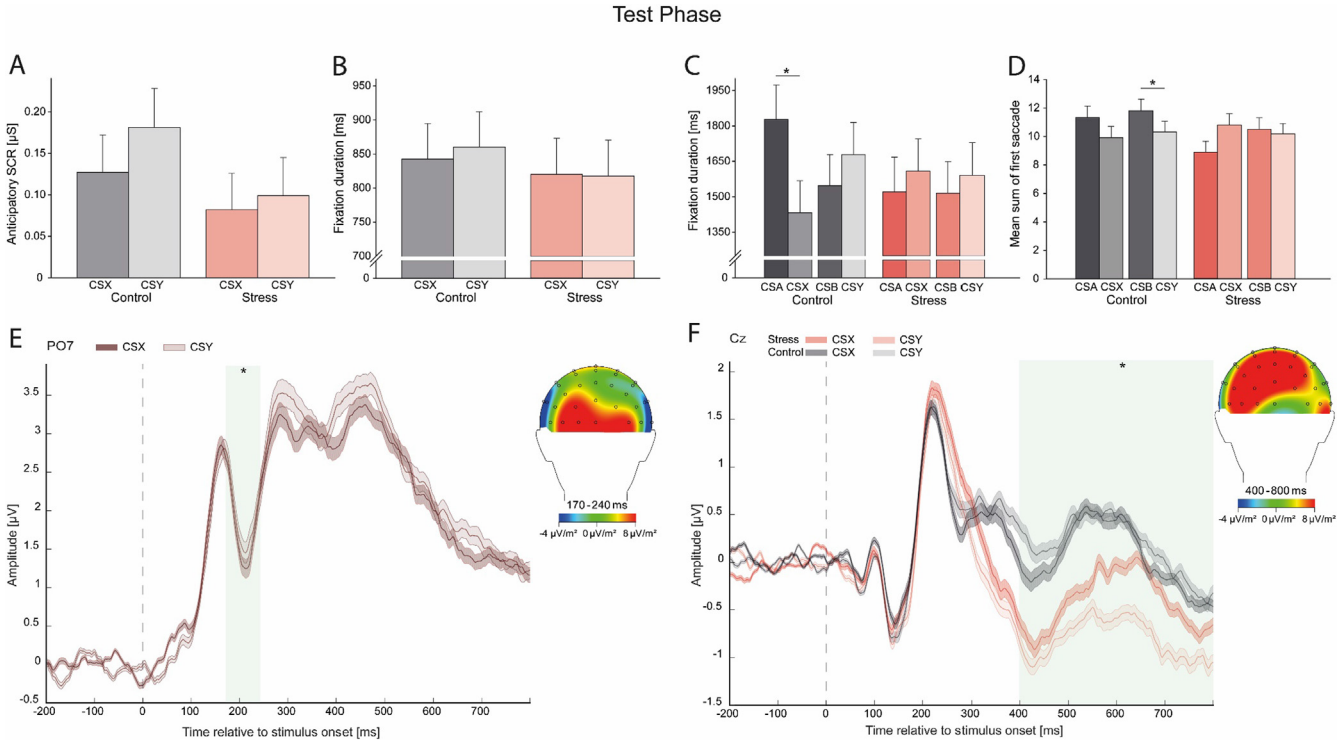

Fig. 5. Test phase. (A) Participants of both groups showed a higher mean anticipatory SCR to the initial presentation of CSX vs. CSY but did not differ significantly. (B) Participants of both groups did not show a different mean fixation duration to CSX vs. CSY. Participants of the control group fixated the predictive CSA longer (C) and showed less first saccades towards the blocked CSX of the CSAX compound compared to the stress group (D). (E) Both groups showed no significant difference regarding in their N2pc in regard to CSX vs. CSY. However, (F) the control group showed a higher LPP to the CSX and CSY compared to the stress group. Error bars and shaded error bars represent standard error. Asterisks denote difference between CSX and CSY: *$p < .05$.

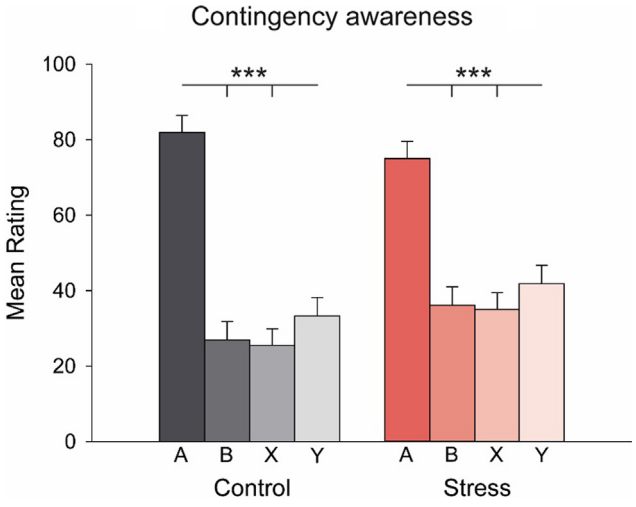

Fig. 6. Explicit rating after test phase. (A) Participants' mean US-association for each stimulus type. Asterisks and dagger denote difference between stimuli: ***$p < .001$.

differences between groups. Notably, however, in this reduced sample the N2pc response to the CSA was stronger in control than in stressed participants. During the blocking phase, the SCR, eye-tracking and ERP data for the reduced sample were largely comparable to the data obtained in the whole sample. In general, participants allocated a higher degree of attention to the newly introduced stimuli when being presented in compounds. Moreover, stressed participants tended to show more first saccades to the uninformative CSX than to the CSA, whereas control participants did not. The ERP results were identical to those found in the whole sample, i.e. a more negative N2pc to the CSAX vs. CSBY and CSA vs. CSB in the control group compared to the stress group and no effects on the later components LPP and SPN. In the test phase, we now obtained a trending difference between control and stress group, that is control participants tended to show stronger SCRs to the CSY than to the CSX, whereas the stress group did not. For the eye-tracking data, we obtained also a differentiation for the CSBY compound, i.e. that participants of both groups spend more time fixating the new stimulus CSY compared to the old CSB. In contrast, participants show longer fixation durations to the old, informative CSA compared to the CSX, independent of experimental manipulation. ERP results for the test phase were completely identical to those of the whole sample. The CSX attracted more early attention compared to the CSY in both groups as indicated by a more negative N2pc. In addition, the LPP result suggests sustained attention to the previously blocked stimulus only for the control group. In sum, this additional analysis indicates that the pattern of results observed for the whole sample remains largely unchanged when analyzing only participants showing a differential SCR to CSA and CSB. For details of these additional analyses and the referring statistics, please see the supplemental material.

3.4.6. Control variables

Depressive mood, subjective chronic stress, and anxiety levels of our sample were all rather low. Groups did not differ in these variables (all $p > .145$; see Table 1). Furthermore, we assessed general attention to the task and found that attention was overall very high (92.4% correct answers), without differences between groups ($t(73) = 0.13$, $p = .540$, $d = 0.125$).

4. Discussion

Contemporary learning theory assumes that learning depends on the predictive relationship between stimuli, rather than on the mere temporal contiguity (Mackintosh, 1975; Pearce & Hall, 1980; Rescorla &

Wagner, 1972). Although this assumption is supported by a plethora of studies (for a review see Le Pelley, Mitchell, Beesley, George, & Wills, 2016), the neural and attentional mechanisms involved in predictive learning are not fully understood, in particular in aversive learning. Moreover, while it is by now well-established that acute stress can modulate learning and memory (Diamond et al., 2007; Schwabe, Joels, et al., 2012), it remains unclear whether acute stress may modulate predictive processes in the context of aversive learning. Thus, we studied here the impact of stress on the blocking phenomenon, a classic effect demonstrating the predictive nature of learning. In order to elucidate the neural and attentional mechanisms involved in blocking and its potential modulation by stress, we combined a fear learning paradigm with EEG measurements, SCR recordings and eye-tracking. Our results showed a blocking effect at the behavioral level, reflected in lower US expectancy ratings for the blocked compared to the non-blocked stimulus. In line with our hypothesis of differential attentional allocation depending on the predictive value of stimuli, our eye-tracking data revealed higher sustained attention to the predictive compared to the blocked stimulus. Both, our eye-tracking and EEG data indicated that stress led to sustained attention to stimuli with low predictive value, suggesting that stress may impair the ability to efficiently use prior knowledge to guide learning.

Our behavioral and eye-tracking data corroborate previous findings showing (i) that (explicit) aversive learning depends on the predictive relationship between events (Eippert et al., 2012; Sanchez-Nacher et al., 2011) and (ii) that the amount of attention allocated to a stimulus depends on its predictive value (Eippert et al., 2012; Luque, López, Marco-Pallares, Càmara, & Rodríguez-Fornells, 2012; Wills et al., 2007). Previous fMRI evidence further showed stronger amygdala responses to predictive compared to non-predictive stimuli (Eippert et al., 2012). The rather sluggish fMRI signal, however, is not well suited for the investigation of fast attentional processing in predictive learning. Equipped with a significantly higher temporal resolution, our EEG data showed differential processing of predictive vs. non-predictive stimuli in the N2pc and LPP. During the blocking phase, when learning to the new (but uninformative) stimulus CSX should be blocked and learning to CSY should evolve, non-stressed controls showed a heightened N2pc to the CSAX compound compared to the CSBY compound. This is in the line with the assumption that the N2pc is thought to reflect covert attention (Eimer, 1996; Luck & Hillyard, 1994), which might be primarily guided by the previously acquired relevance of a stimulus. Moreover, it is in line with the filtering hypothesis (Luck & Hillyard, 1994) assuming that the N2pc is more negative for task relevant items when suppression of distractor items is necessary. In this case, it can be assumed that successful filtering of the CSX of the CSAX was implemented by the control group to guide attention towards the relevant CSA whereas such filtering for the CSBY would not have been advantageous. This idea is further supported by the fact that participants from the control group still showed a significant differentiation between the previously learned threatening CSA and the safety signaling stimulus CSB, i.e. the N2pc was more negative for the CSA than for the CSB, whereas the stress group did not show this differentiation. In further support of our idea, when testing for the blocking effect in a third phase, participants from the control group showed longer fixation durations and more first saccades to the predictive stimulus compared to the non-predictive stimulus when presented in a compound, suggesting successful blocking to the non-predictive stimulus. In contrast, participants from the stress group did not show this differentiation.

Somewhat surprisingly, we did not find evidence for increased attentional processing of the non-blocked stimulus in our data in the test phase of the learning task, as an earlier study did (Wills et al., 2007). This discrepancy may be partly explained by methodological differences between this earlier and the present study. In particular, we used a pavlovian fear conditioning protocol, whereas this previous study used an instrumental learning protocol, which may have required participants to be generally more attentive than it was the case in our experiment, thus increasing its sensitivity to detect neural attentional differences. Moreover, in contrast to the present study, this previous study investigated the N1, a component thought to reflect perceptual discrimination processing (Vogel & Luck, 2000). We did not focus on this early component because it is highly refractory and its reliable measurement would require significantly more trials than feasible in a fear learning task (Woodman, 2010). In addition, we were more interested in attention related components that are sensitive for top-down modulated processes, due to our aim to investigate the influence of stress.

Predictive learning requires that prior experiences are retrieved and translated to the ongoing learning situation. There is an extensive literature showing that stress can impair the retrieval of previously acquired information (de Quervain et al., 1998; Roozendaal, 2002; Schwabe, Joels, et al., 2012). Moreover, stress appears to hinder the integration of new information and stored knowledge (Kluen et al., 2017; Sanger et al., 2014; Vogel et al., 2018a, 2018b). The present data show – to the best of our knowledge – for the first time that stress may modulate aversive predictive learning, in general, and the blocking effect in particular. More specifically, our eye-tracking data showed that stress abolished the attentional discrimination between predictive and unpredictive stimuli in a compound, which was observed in non-stressed controls. Furthermore, stress led, during the blocking phase, to a higher P3b compared to the control group. This component is thought to be related to attention-driven comparisons between task-relevant stimuli and assumed to reflect the evaluation of the current stimulus with the representation of previous stored information (for a review see Polich, 2007). Additionally, the P3b is thought to be mediated by the release of noradrenaline from the locus coeruleus (Nieuwenhuis, Aston-Jones, & Cohen, 2005), which is also part of the stress mediated influence on memory processes (McGaugh, 2000). An increased P3b for the stress group may be indicative of an increased overall attention to and evaluation of the compound stimuli. This increase in overall attentional processing may be interpreted as an indication of impaired recall of previously made experiences (i.e. learning to CSA and CSB), thus requiring stressed participants to spend more resources evaluating the new compound stimuli. Our data further showed a heightened LPP for the blocked stimulus compared to the non-blocked stimulus in the stress group relative to the control group, which may further point to sustained attention to irrelevant stimuli after stress (Cuthbert et al., 2000; Hajcak & Olvet, 2008; Schupp et al., 2006). This latter finding is also in line with the idea that stress disrupts later stages of attentional processing associated with the evaluation of task-relevant information (Shackman, Maxwell, McMenamin, Greischar, & Davidson, 2011). Based on previous research on the LPP and its relevance in emotional processing, we would have expected an increased LPP towards the CSA compared to the CSB also in the fear acquisition phase. There was however no increased LPP in the acquisition phase but only later in the test phase. One potential explanation for this finding is that most of the previous LPP research compared attention towards affective and neutral pictures, whereas we used here an aversive conditioning paradigm with shock administration (Cuthbert et al., 2000; Schupp et al., 2000; Weinberg & Hajcak, 2010). Furthermore, some authors suggest that earlier components mirror fast attentional capture while later components more elaborative processes must take place (Dieterich, Endrass, & Kathmann, 2016; Lin et al., 2015). The fully deterministic reinforcement rate that we used here may have reduced the need for such elaborative processes because there was no uncertainty.

In contrast to other fear learning studies, we did not record explicit fear learning ratings on a trial-by-trial basis during the task but at the end of the experiment to avoid a possible influence on implicit measures such as SCR (Kroes et al., 2016; Phelps et al., 2001; Raio, Carmel, Carrasco, & Phelps, 2012). This, however, reduces the sensibility of the explicit rating data to some extent. Although we obtained a blocking effect in the explicit ratings measured at the end of the task, the absence of a blocking effect in SCR measurement was somewhat unexpected and

is in contrast to previous studies investigating the blocking effect (Hinchy et al., 1995; Lovibond, Siddle, & Bond, 1988). However, the study that introduced the blocking paradigm we used here, obtained also no blocking effect in the SCR (Eippert et al., 2012). The absence of a blocking effect in the SCR in this paradigm may be due to its long duration and the continuous reinforcement for the CSA and both compounds (i.e., CSAX and CSBY), both of which may have led to a strong habituation effect making a differentiation between the stimuli more difficult (Bach et al., 2009; Eippert et al., 2012). In addition, the SCR results are of limited information because only the control group showed a significant differentiation between CSA and CSB, indicating successful discrimination learning, whereas the stress group only showed a non-significant descriptive discrimination. To control for this baseline difference in further analyses, we included ΔSCR as covariate in all of the following analyses. Without changing the pattern of result, the ANCOVAs for the SCR did not reveal any significant results in the blocking or test phase. However, when analyzing only those participants who showed a robust fear acquisition effect in the SCR in the first place (see supplementary results), we did obtain evidence for a blocking effect in the SCR when comparing the initial presentation of CSX vs. CSY, suggesting that the blocking effect in the SCR may indeed depend on the overall SCR level, although such single trial comparisons can only be interpreted with caution.

Finally, it should be noted that the stress system was still activated during the test phase, as reflected in elevated cortisol concentrations, and that one might thus argue that stress affected primarily retrieval processes during the test phase. We chose this study design, in which one stage followed immediately after another, to be as close as possible to the study in which this specific blocking paradigm was introduced (Eippert et al. (2012)). Extending the interval between the blocking stage and stress/control manipulation on the one hand and the test phase on the other hand might have diluted potential blocking effects or resulted in stress effects on blocking consolidation. Moreover, the test phase included stimuli from the previous stage, and we found no effect on, for example, the CSA or CSB. These findings speak against a general retrieval deficit after stress and we consider a retrieval deficit specifically for blocking-related stimuli rather unlikely.

To conclude, we examined here the neural and attentional processes involved in predictive fear learning and tested whether acute stress may modulate the efficient processing of information against the background of prior knowledge. Our results show that attentional resources were allocated depending on the predictive value of a stimulus and, most importantly, that stress interferes with predictive learning, most likely through interfering with the efficient use of prior knowledge during learning. This stress-induced deficit was reflected in the absence of a differential N2pc for compound stimuli during the blocking phase. In addition, the stress group showed a heightened P3b for both compound stimuli, which may suggest that the impaired access to previously learned associations requires participants to spend more resources on the evaluation of stimuli, irrespective of its actual predictive value. This idea is further supported by the stress-induced increase in the LPP for the CSX compared to the CSY, which may point to sustained attention to non-predictive stimuli. The reduced processing efficiency of stimuli that were not directly relevant to the stressor may be due to a prioritized processing and consolidation of the stressful encounter itself, thus leaving less resources for processing competing events (Joels, Pu, Wiegert, Oitzl, & Krugers, 2006; Schwabe, Joels, et al., 2012). This prioritization, however, may amplify biases in predictive processing that are thought to contribute to stress-related mental disorders, such as posttraumatic stress disorder (Homan et al., 2019).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nlm.2020.107158.

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