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Stress-induced modulation of multiple memory systems during retrieval requires noradrenergic arousal

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ABSTRACT

Stress has been shown to favor dorsal striatum-dependent 'habit' memory over hippocampus-dependent 'cognitive' memory during learning. Here, we investigated whether stress may modulate the engagement of these 'cognitive' and 'habit' systems also during memory retrieval and if so, whether such a stress-induced shift in the control of memory retrieval depends on noradrenergic activation. To this end, participants acquired a probabilistic classification learning (PCL) task that can be solved by both the 'cognitive' and the 'habit' system, reflected in the distinct behavioral strategies. Twenty-four hours later, participants received either the beta-adrenergic receptor antagonist propranolol or a placebo before they underwent a psychosocial stressor or a non-stressful control manipulation, followed by a retrieval version of the PCL task. Overall, participants showed a practice-dependent shift from 'cognitive' to 'habit' memory. Stressed participants that had received a placebo fell back to a 'cognitive' strategy during retrieval, which was linked to an impairment in retrieval performance. Propranolol blocked this stress-induced shift towards the less efficient strategy. Moreover, our results showed that salivary cortisol was related to the retrieval strategy only when paralleled by increased autonomic arousal. Together, these results indicate that stress effects on the modulation of multiple memory system during retrieval necessitate noradrenergic arousal, with relevant implications for retrieval performance under stress.

1. Introduction

Memory is supported by multiple systems that differ in the mode of operation, the information processed, and the underlying neural circuit (Packard and McGaugh, 1996; Myers et al., 2003; White et al., 2013). A prominent distinction is made between a flexible, but resource intensive, 'cognitive' memory system based on the hippocampus or prefrontal cortex and an efficient, but rather rigid 'habit' memory system mainly based on the dorsal striatum (White and McDonald, 2002; Eichenbaum and Cohen, 2004; Squire, 2004). These memory systems can acquire information independently and in parallel (McDonald and White, 1994; Packard, 1999), but may also interact in a cooperative or competitive manner (Kim and Baxter, 2001; Poldrack et al., 2001; Poldrack and Packard, 2003; Voermans et al., 2004). Over the past two decades, it has been repeatedly demonstrated that acute stress biases the balance between memory systems during learning in favor of the 'habit' memory system (Kim et al., 2001; Schwabe et al., 2007; Schwabe and Wolf, 2009; Vanelzakker et al., 2011; Packard and Goodman, 2012; Schwabe and Wolf, 2012; Wirz et al., 2018; Simon-Kutscher et al., 2019). This stress-induced shift from 'cognitive' to 'habit' memory during learning is critically mediated by glucocorticoids, presumably acting through the mineralocorticoid receptor (Schwabe et al., 2010a, 2013; Vogel et al., 2016; Siller-Pérez et al., 2017), and noradrenaline (Packard and Wingard, 2004; Wirz et al., 2017). Moreover, studies on the modulation of multiple memory systems in instrumental learning suggested that glucocorticoid and noradrenergic activity interact to induce habitual responding (Schwabe et al., 2010b, 2012).

During learning, parallel 'cognitive' and 'habit' memory traces are formed (Chang and Gold, 2003), thus raising the question which memory system guides later retrieval. May stress – in addition to modulating the balance of memory systems during learning – also bias the control of retrieval? It is well established that stress may affect quantitative memory retrieval (de Quervain et al., 1998; Roozendaal, 2002; Diamond et al., 2006) and that these stress effects depend on

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concurrent glucocorticoid and noradrenergic activity (Roozendaal et al., 2004, 2006; de Quervain et al., 2007), in line with the idea that the interaction of these major stress mediators underlies stress effects on memory. Beyond stress effects on retrieval performance, there is also initial evidence in rodents showing that pre-retrieval injection of an anxiogenic drug that increases noradrenergic activity can bias retrieval in favor of 'habit' memory (Elliott and Packard, 2008), suggesting that key stress mediators may play an important role in the control of memory retrieval as well. Moreover, we provided recently initial evidence in humans that the pharmacological elevation of glucocorticoid or noradrenergic activity before retrieval can modulate which memory system guides retrieval (Zerbes et al., 2019). In addition, we showed that stress-induced cortisol increases dorsal striatal activation as well as the engagement of 'habitual' strategies during retrieval (Zerbes et al., 2020). While these data suggest that stress may alter the balance of 'habitual' over 'cognitive' memory systems during retrieval and that glucocorticoids or noradrenergic activity are sufficient to produce this effect, it remains completely unclear whether noradrenergic activity is necessary for the stress-induced bias of memory retrieval. If so, a blockade of noradrenergic activity would be an effective way to prevent the stress-induced bias in the recruitment of multiple memory systems during retrieval.

The present study therefore aimed to determine whether the impact of stress on the control of memory retrieval is dependent on noradrenergic activation. To this end, participants first performed a probabilistic classification learning (PCL) task that can be solved by both the 'cognitive' and the 'habit' memory system (Knowlton et al., 1996; Poldrack et al., 2001; Shohamy et al., 2004b). The relative contribution of 'cognitive' and 'habit' systems to task performance can be inferred from the use of different behavioral strategies (Gluck et al., 2002; Shohamy et al., 2004a; Schwabe and Wolf, 2012). Twenty-four hours after learning, participants were first administered either a placebo or the β-adrenoceptor antagonist propranolol. Next, they underwent a standardized psychosocial stressor or a non-stressful control procedure before completing a retrieval test for the PCL task. Based on results showing that noradrenergic arousal is critical for the stress (hormone)-induced modulation of quantitative memory retrieval (Roozendaal et al., 2004; de Quervain et al., 2007), we hypothesized that the stress effect on the control of memory retrieval depends on noradrenergic arousal and should thus be abolished by the administration of propranolol.

2. Materials and methods

2.1. Participants and experimental design

One hundred and twenty healthy volunteers without lifetime history of any mental or neurological disease, drug or tobacco use or current medication intake participated in this study (61 women; age (mean ± SD): 25.20 ± 3.80). In addition, women did not use hormonal contraceptives and were not tested during their menses. The sample size was based on an a-priori power analysis using G*Power (Faul et al., 2007), showing that a sample of 120 participants was sufficient to detect a medium-sized effect of $f = 0.25$ with a power of 0.95 given an α of .05. All participants provided informed consent before taking part in the study. The study protocol was approved by the medical ethics committee Hamburg and in accordance with the declaration of Helsinki.

In a placebo-controlled, double-blind, between-subjects design with the factors drug (placebo vs. 40 mg propranolol) and treatment (control vs. stress), participants were randomly assigned to one of four experimental groups: placebo/control (PLAC/CON), placebo/stress (PLAC/STRESS), propranolol/control (PROP/CON) and propranolol/stress (PROP/STRESS). Seventeen participants had to be excluded from the analysis because they did not acquire the learning task (criterion for successful learning: ≥ 60 % correct trials in the second half of learning, see Zerbes et al., 2019), which is required in order to test stress and propranolol effects on the control of memory retrieval. Thus, the final sample consisted of 103 participants (54 women; age (mean ± SD): 25.34 ± 3.78; PLAC/CON: $n = 29$; PLAC/STRESS: $n = 29$; PROP/CON: $n = 24$; PROP/STRESS: $n = 21$).

2.2. Pharmacological manipulation

On the second experimental day, participants received orally either a placebo or 40 mg propranolol, a β-adrenergic antagonist inhibiting noradrenergic activity, according to their experimental group. After pill intake, participants waited 50 min, until the drug was expected to be fully active. Timing and dosage of the pharmacological manipulation were based on previous studies examining the effects of propranolol on stress-induced changes in learning and memory (de Quervain et al., 2007; Schwabe et al., 2009, 2011). The effectiveness of the manipulation was assessed via blood pressure and pulse measurements before the manipulation as well as 50 min, 60 min, 70 min and 85 min after pill intake using a Critikon Dinamap system (Tampa, FL) with the cuff placed around the right upper arm.

2.3. Stress manipulation

After the 50-minute break following pill intake, psychosocial stress was induced with the Trier Social Stress Test (TSST, Kirschbaum et al., 1993), a standardized protocol which reliably activates the autonomic nervous system and the hypothalamic-pituitary-adrenal axis (Kudielka et al., 2007). In the TSST, participants were asked to give a 5-minute free speech and perform a difficult mental arithmetic task (counting backwards in steps of 17 from 2043). Throughout both tasks, participants were video-recorded and evaluated by a cold, non-responsive interview panel consisting of a man and a woman, both dressed in white lab coats. In the control condition, participants gave a 5-minute speech on a topic of their choice and performed an easy arithmetic task (counting upwards from 0 in steps of 15) while being alone in a room. Participants in the control condition were not videotaped.

After the TSST/control manipulation, participants rated how stressful, challenging and unpleasant they had experienced the task on a scale ranging from 0 (not at all) to 100 (very much). In addition, the effectiveness of the stress manipulation was assessed using subjective and physiological measures at several time points throughout the experiment. Subjective mood was assessed using the German version of the Positive and Negative Affect Schedule (PANAS, Krohne et al., 1996) before the pharmacological manipulation as well as 50 min, 70 min and 85 min after pill intake. The blood pressure and pulse measurements acquired to assess the effectiveness of the pharmacological manipulation (see section 2.2) served also as indicators for the effectiveness of the stress manipulation. Further, saliva samples were collected before the pharmacological manipulation as well as 50 min, 70 min and 85 min after pill intake, using Salivette (Sarstedt, Nümbrecht, Germany) devices and were stored at −18 °C until analysis. After data collection was completed, free cortisol concentrations were analyzed using a chemoluminescence immunoassay (IBL International, Hamburg, Germany). All inter- and intra-assay coefficients of variance were < 8%.

2.4. Experimental task

In order to assess the engagement of multiple memory systems, participants completed a Probabilistic Classification Learning (PCL) task that is referred to as the 'Weather Prediction Task' (Fig. 1, Knowlton et al., 1994, 1996). This task can be solved by both a 'cognitive', hippocampus-based memory system and a 'habitual' dorsal striatum-based memory system (Knowlton et al., 1996; Poldrack et al., 2001; Shohamy et al., 2004a). On each trial, a pattern of one to three (out of four possible) cards was presented and participants were asked to predict the weather (rain vs. sun) based on these cards. After participants made their response, feedback about the correct weather outcome

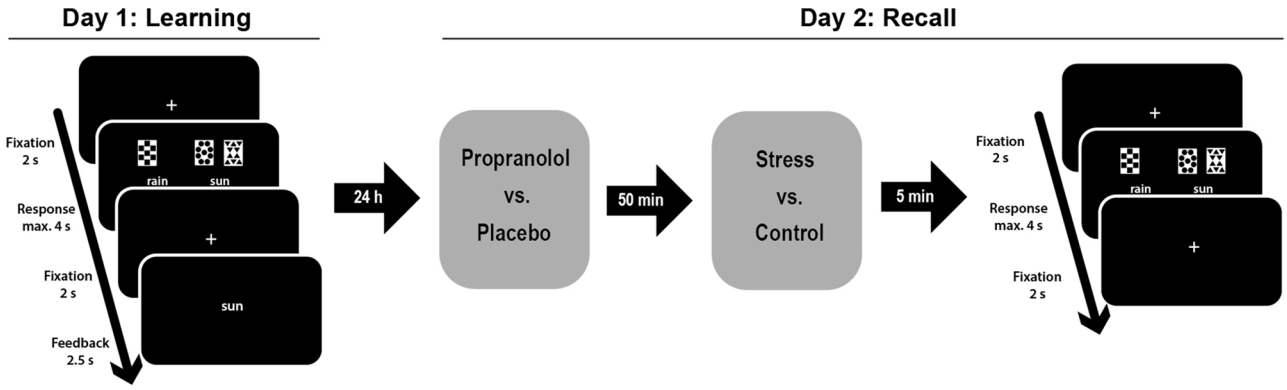

Fig. 1. Experimental procedure. On the first experimental day, participants completed 200 trials of the PCL task including trial-by-trial feedback. Twenty-four hours later, participants were administered either a placebo or the β-adrenergic antagonist propranolol. Subsequently, they underwent a stress-induction procedure or a non-stressful control procedure before completing a retrieval version of the PCL task. In the retrieval task, no feedback was provided to prevent further learning.

was presented, enabling the participant to learn the correct associations. There were 14 possible card patterns, each probabilistically linked to the weather outcomes. These probabilities were determined in a way that each of the four possible cards was independently linked to the outcome "sun" with a probability of 75.6, 57.5, 42.5 or 24.4 percent across the task, in line with previous studies (Knowlton et al., 1994, 1996; Gluck et al., 2002; Schwabe and Wolf, 2012; Schwabe et al., 2013; Wirz et al., 2017). A response was counted as correct when it corresponded to the most likely weather outcome indicated by the specific pattern.

During the learning phase on experimental day one, participants performed 200 trials of the PCL task. On each trial, one of the 14 possible card patterns was presented and participants were asked to give the response within 4 s. Once the response was made, the cards disappeared and a fixation cross was presented for 2 s. Next, feedback was presented for 2.5 s in form of the word "rain" or "sun" in the middle of the screen. Between trials there was an interval of 2 s, during which a fixation cross was presented.

On experimental day two, after the pill intake and the stress/control manipulation, participants completed a retrieval version of the PCL task, which was identical to the learning version completed on day 1, except that no feedback was presented. Hence, further learning was prevented during the test session, allowing us to specifically investigate retrieval processes. Participants completed 100 trials of the retrieval task.

2.5. Strategy analysis

The PCL task can be solved using different strategies (Gluck et al., 2002) which provide insight into the engagement of different memory systems. More specifically, the use of 'single-cue' strategies has been associated with the engagement of the 'cognitive', hippocampal memory system, while the use of 'multi-cue' strategies has been linked to the 'habitual', dorsal striatal memory system (Knowlton et al., 1996; Shohamy et al., 2004b; Schwabe and Wolf, 2012). The used strategy was assessed by comparing participants' actual responses with the ideal responses for each strategy. Using least mean squares estimates, a fit score was derived ranging from 0 to 1 (0 indicating a perfect fit). The strategy with the lowest fit score was determined as the 'best-fitting strategy', categorizing participants as single- or multi-cue strategy users. If none of the fit scores was < 0.15, the strategy was considered unidentifiable (Wirz et al., 2017; Zerbes et al., 2019). In retrospect, the proportion of unidentifiable strategies was 11.65 % for the first half of the learning session, 2.91 % for the second half of the learning session and 6.80 % in the retrieval phase. Using Fisher's exact test (Fisher, 1934) to control for low expected values, we compared the proportions of unidentifiable strategies between the four experimental groups. There was a significant difference between groups during the first half of the learning session ($p = .017$) but not during the second half of the learning session ($p = .621$), nor during the retrieval session ($p = .338$).

The categorization of participants on the basis of their fit scores has been validated in several studies (Gluck et al., 2002; Schwabe and Wolf, 2012; Wirz et al., 2017). However, the engagement of multiple memory systems may vary in a more subtle way that is difficult to be captured by this categorical measure. Hence, we applied an additional approach by computing the difference between the fit scores ($Fit_{single\text{-}cue} - Fit_{multi\text{-}cue}$, 'strategy dominance score'; Zerbes et al., 2020). This score reflects the relative dominance of one strategy over the other, with negative scores reflecting the dominance of the single-cue strategy and positive scores indicating the dominance of the multi-cue strategy.

2.6. Control variables

In order to control for potential group differences in chronic stress, depressive mood, sleep quality over the previous four weeks as well as state and trait anxiety, participants completed the Trier Inventory for the Assessment of Chronic Stress (TICS, Schulz and Schlotz, 1999), the Beck Depression Inventory (BDI_II, Beck et al., 1961), the Pittsburgh Sleep Quality Index (PSQI, Buysse et al., 1989) and the State-Trait Anxiety Inventory (Spielberger and Sydeman, 1994). In addition, since sleep between day 1 (learning) and day 2 (retrieval) might play a role in memory consolidation, participants were asked to indicate their sleep duration between experimental days and to rate their sleep quality on a scale from 0 (very bad) to 100 (very good). All questionnaires were completed on the second experimental day.

2.7. Procedure

The study was conducted on two consecutive days and all testing took place between 13:00 and 20:00. On the first experimental day, after a baseline measurement of blood pressure, pulse, salivary cortisol and subjective mood, participants completed the learning phase of the PCL task. Twenty-four hours later, participants were administered the drug/placebo according to the experimental group and completed the questionnaires for the control variables. Next, participants completed the TSST or control procedure. Afterwards (20 min after stressor onset), the retrieval phase of the PCL task was completed.

2.8. Data analysis

Subjective and physiological data were analyzed by means of mixed-design ANOVAs with the between-subjects factors treatment (stress vs. control) and drug (propranolol vs. placebo) as well as the within-subject factor time point of measurement. Classification performance on day 1 (learning) was analyzed with a mixed-design ANOVA with blocks of 10 trials as within-subject factor. The between-subject factors treatment

and drug were treated as one four-level factor in the ANOVA, because the manipulations only occurred after learning and this factor served only the purpose of identifying potential group differences at baseline. For the classification performance on day 2 (retrieval), the factor block was disregarded, because no further learning was to be expected. The performance was thus analyzed with a two-way ANOVA with the between-subjects factors treatment (stress vs. control) and drug (propranolol vs. placebo).

The strategy dominance score was analyzed by means of mixed-design ANOVAs with the between-subject factor treatment (stress vs. control) and drug (propranolol vs. placebo) as well as the within-subject factor phase (learning vs. retrieval). We used the strategy during the second half of the learning session as a measure for learning strategy in this analysis, as the most rapid strategy changes are expected during early stages of learning and the strategy was assumed to stabilize during the second half of the learning session. The best-fitting strategy was either analyzed with χ^2-tests (for analyzing between-subject effects) or McNemar tests (for analyzing within-subject effects).

In addition to the effects of the experimental manipulation, we also assessed the effect of the physiological stress response on classification accuracy, the strategy dominance score as well as the best-fitting strategy during retrieval. To this end, we conducted a linear regression model (or a logistic regression model for the best-fitting strategy) with the predictors cortisol peak (measurement after the stress/ control manipulation) and systolic blood pressure peak (measurement during the manipulation) as well as their interaction. In order to control for possible baseline differences, we also included learning strategy as a regressor of no interest. All predictors were mean-centered. All variables included in the regression models were examined for potential outliers within the experimental groups using the criterion mean ± 3 standard deviations (Tabachnick et al., 2007). All reported p-values are two-tailed. In case of violations of the sphericity assumption, Greenhouse-Geisser corrections were applied. All statistical analyses were carried out using R (version 3.5.2, Team, 2018).

3. Results

3.1. Day 1: Successful learning of the PCL task

Over the course of the learning task, classification performance increased significantly from 46 percent correct classifications in the first block to 82 percent in the last block (Fig. 2A, $F(11.98, 1173.62) = 31.02$, $p < .001$, $\eta^2_G = .185$), indicating that participants learned the task successfully. There were no effects of experimental group (main effect and interaction with block: both $F < 1.11$, both $p > .265$, both $\eta^2_G < .024$), suggesting that the groups did not differ in their learning performance.

The engagement of multiple memory systems in this task can be inferred from the use of single-cue or multi-cue strategies (Knowlton et al., 1996; Poldrack et al., 2001; Shohamy et al., 2004a). Across the entire learning phase, approximately 60 percent of the participants used the single-cue strategy, indicative of 'cognitive' system engagement. However, strategy use changed dynamically over the course of the learning phase: The multi-cue strategy, indicative of 'habit' system engagement, was increasingly utilized over the course of learning. This practice-dependent, relative shift from single-cue to multi-cue learning was reflected both in the best-fitting strategy ($\chi^2(1, N = 88) = 6.76$, $p = .009$, *Odd's Ratio* = 3.167, Fig. 2B) and the strategy dominance score ($F(2.24, 222.16) = 29.32$, $p < .001$, $\eta^2_G = .113$, Fig. 2C). There was no difference between experimental groups in the best-fitting strategy (neither for the first nor the second half of the learning phase: both $\chi^2 < 3.93$, both $p > .269$, *Cramer's V* < .208) or the strategy dominance score (no main effect or interaction with block: both $F < 0.64$, both $p > .760$, both $\eta^2_G < .008$), indicating that the four experimental groups did not differ in the used learning strategy during acquisition.

3.2. Day 2: Successful stress induction and effective pharmacological manipulation

The effectiveness of both the stress manipulation and the pharmacological manipulation was verified by changes in physiological as well as subjective measures.

3.2.1. Blood pressure and pulse

The stress manipulation led to marked changes in systolic and diastolic blood pressure as well as pulse (treatment × time interaction: all $F > 48.58$, all $p < .001$, all $\eta^2_G > .065$, Fig. 3). In particular, the measurements before the TSST/control manipulation did not differ between the stress and control groups for systolic and diastolic blood pressure (all $t < 1.18$, all $p > .241$) and were even lower in the stress group than in the control group for pulse (both $t < -2.09$, both $p < .040$). During the TSST, systolic and diastolic blood pressure as well as pulse were significantly increased compared to the control manipulation (all $t > 5.01$, all $p < .001$). This difference between stress and control group rapidly subsided for both time points of measurement after the TSST/control manipulation, completely disappearing for pulse (both $t < 0.22$, both $p > .824$) and partially remaining on trend-level for systolic (after manipulation: $t(99.78) = 1.76$, $p = .081$; after retrieval task: $t(97.93) = 1.65$, $p = .101$) and diastolic (after manipulation: $t(79.57) = 1.07$, $p = .289$; after retrieval task: $t(98.71) = 1.77$, $p = .078$) blood pressure.

Moreover, the effect of the pharmacological manipulation was reflected in changes of systolic blood pressure and pulse as well (drug × time interaction: both $F > 7.78$, both $p < .001$; both $\eta^2_G > .012$). While there was no significant difference between the propranolol and the placebo groups for systolic blood pressure or pulse before drug intake

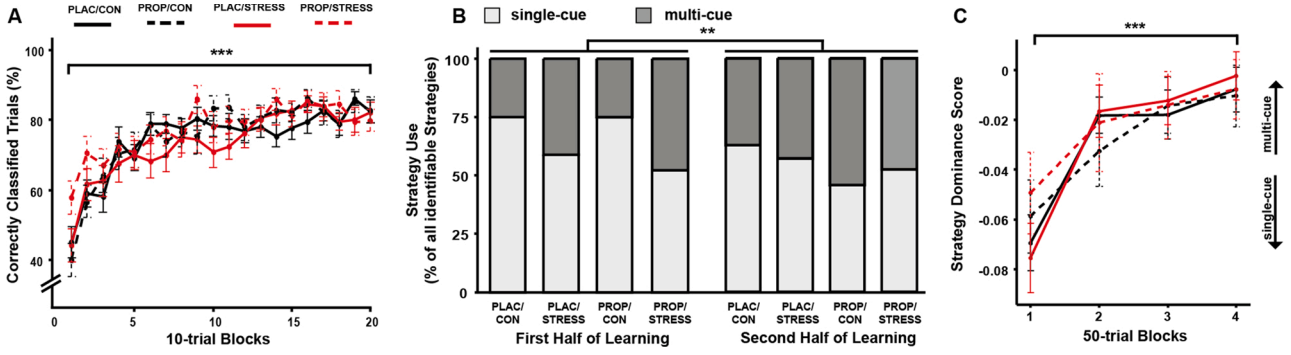

Fig. 2. Learning performance and strategy (day 1). (A) Classification performance improved over the course of learning, independent of experimental group, suggesting successful task acquisition. Both for the best-fitting strategy (B) and the strategy dominance score (C) there was an overall dominance of single-cue strategy use. However, this dominance shifted over the course of the learning task in favor of multi-cue strategies, independent of experimental group. Error bars represent standard errors of the mean. ** $p < .01$, *** $p < .001$.

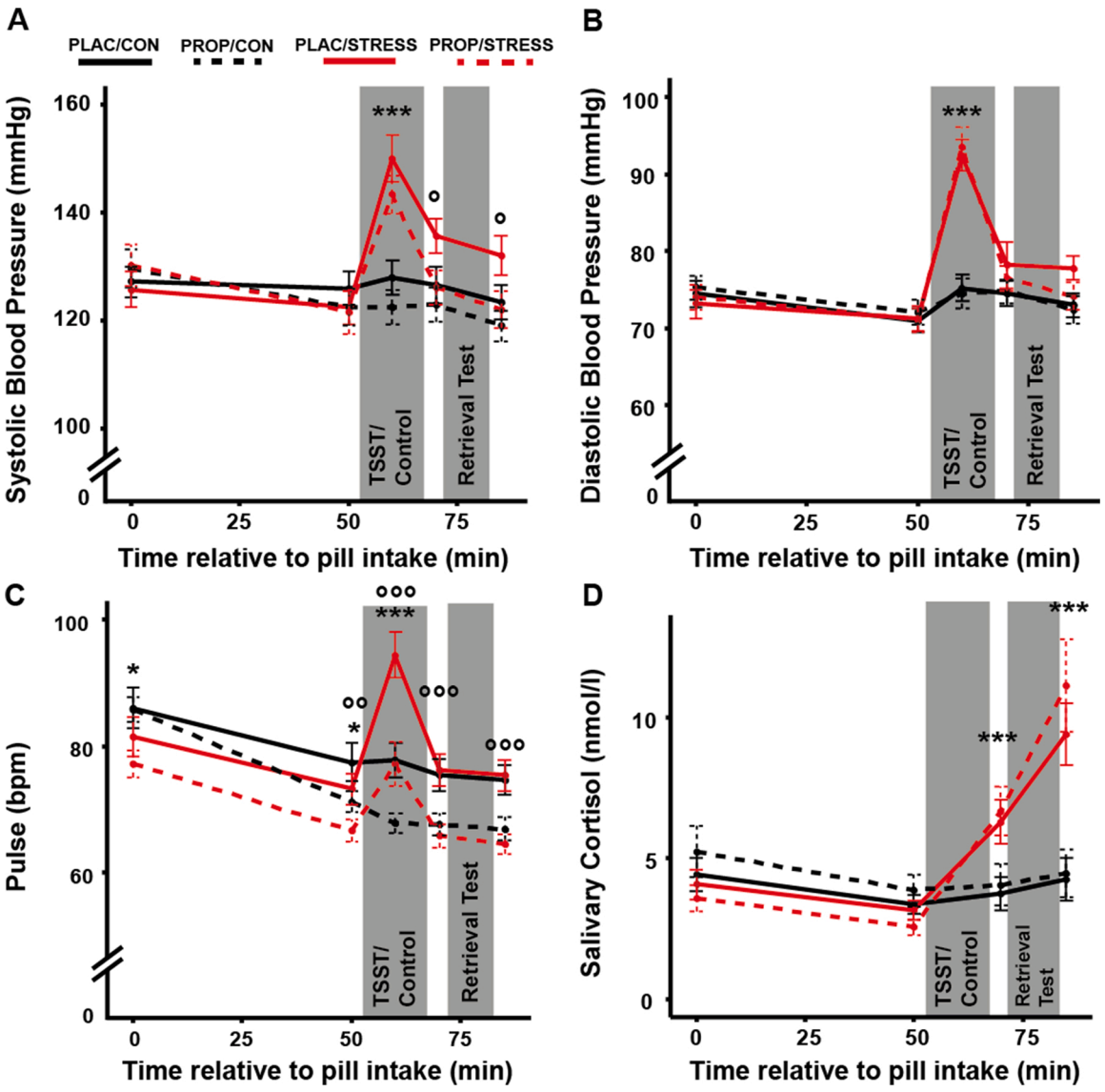

Fig. 3. Successful stress induction and pharmacological manipulation. Stress led to significant increases in (A) systolic blood pressure, (B) diastolic blood pressure, (C) pulse and (D) salivary cortisol. Propranolol administration led to decreases in systolic blood pressure and pulse, but did not affect stress-induced changes in salivary cortisol. Error bars represent standard errors of the mean. Stress vs. control: * $p < .05$, *** $p < .001$; propranolol vs. placebo: ° $p < .05$, °° $p < .01$, °°° $p < .001$.

(both $|t| < 0.62$, both $p > .341$), systolic blood pressure was decreased for the propranolol group compared to the placebo group both after the TSST/control manipulation (+70 min relative to pill intake: $t(99.80) = 2.45$, $p = .016$) and after the retrieval task (+85 min relative to pill intake: $t(99.96) = 2.45$, $p = .016$). For pulse, the decrease for the propranolol group compared to the placebo group occurred even earlier, before the TSST/control manipulation (+50 min relative to pill intake: $t(92.95) = 2.92$, $p = .004$) and remained significant for all subsequent time points of measurement (all $t > 4.21$, all $p < .001$). For diastolic blood pressure, there was no propranolol-induced change (drug × time interaction: $F(2.92, 286.16) = 1.72$, $p = .165$, $\eta^2_G = .004$). Moreover, the stress-induced changes in systolic and diastolic blood pressure were not modulated by propranolol (treatment × drug × time interaction: both $F < 1.58$, both $p > .190$, both $\eta^2_G < .002$), suggesting that stress also affected blood pressure after propranolol administration. For pulse, however, there was a non-significant trend for a treatment × drug × time interaction ($F(2.24, 219.79) = 2.63$, $p = .068$, $\eta^2_G = .006$), but none of the post-hoc tests reached statistical significance (treatment × drug interaction for the separate time points: all $F < 3.07$, all $p > .083$, all $\eta^2_G <$ .030).

3.2.2. Salivary cortisol

The stress manipulation led further to marked changes in salivary cortisol concentrations (treatment × time interaction: $F(1.49,143.16) = 29.38$, $p < .001$, $\eta^2_G = .124$, Fig. 3D). While the stress and control groups did not differ during the measurements before the TSST/control manipulation (both $t < 1.12$, both $p > .267$), the stress group showed significantly increased cortisol concentrations compared to the control group immediately after the TSST/control manipulation ($t(90.39) = 4.11$, $p < .001$) as well as after the retrieval of the PCL task ($t(76.88) = 5.88$, $p < .001$), implicating that cortisol levels were elevated throughout the retrieval task. Salivary cortisol levels were not affected by propranolol administration (no significant main effect or interactions: all $F < 1.30$, all $p > .276$, all $\eta^2_G < .006$).

3.2.3. Subjective ratings

Participants in the stress group experienced the experimental manipulation as significantly more challenging, unpleasant and stressful

than participants in the control group (all $F > 94.74$, all $p < .001$, all $\eta^2_G > .489$, Table 1). Except for a trend for reduced unpleasantness in the propranolol group compared to the placebo group ($F(1,99) = 3.47$, $p = .065$, $\eta^2_G = .034$), subjective ratings were not affected by the drug administration (all main effects or drug × treatment interactions: all $F < 1.25$, all $p > .266$, all $\eta^2_G < .012$).

Positive mood decreased over time on experimental day 2 ($F(2.62,258.90) = 25.80$, $p < .001$, $\eta^2_G = .040$, Table 1) and tended to be decreased in the stress group compared to the control group ($F(1,99) = 3.31$, $p = .072$, $\eta^2_G = .027$; no other significant main or interaction effects: all $F < 1.22$, all $p > .272$, all $\eta^2_G < .010$). Conversely, the change in negative mood over the course of experimental day 2 was modulated by both stress (treatment × time interaction: $F(1.76,174.67) = 28.10$, $p < .001$, $\eta^2_G = .089$) and propranolol (drug × time interaction: $F(1.76,174.67) = 6.35$, $p < .003$, $\eta^2_G = .022$). Specifically, neither stress nor propranolol influenced negative mood for the measurement time points before the TSST/ control manipulation (all $|t| < 0.94$, all $p > .350$), but for all time points after the TSST/ control manipulation, negative mood was increased in the stress group compared to the control group (both $t > 2.64$, both $p < .010$) and tended to be decreased in the propranolol group compared to the placebo group (both $t > 1.95$, both $p < .054$).

3.3. Strategy use during retrieval is modulated by an interaction of cortisol and autonomic arousal

During the retrieval phase, 24 h after learning, participants showed an overall classification performance of 82 percent, even though no feedback was provided, thus demonstrating successful retrieval of the PCL task (Fig. 4A). The classification performance during retrieval was not affected by stress or propranolol (all main effects or interaction: all $F < 0.95$, all $p > .332$, all $\eta^2_G < .001$).

The relative dominance of single-cue strategy utilization increased from learning to retrieval ($F(1,99) = 5.94$, $p = .017$, $\eta^2_G = .012$, Fig. 4B), suggesting an overall shift back to the 'cognitive' strategy from learning to retrieval, as observed before (Zerbes et al., 2020). However, this change in strategy use tended to be modulated by stress and propranolol (treatment × drug × phase interaction: $F(1,99) = 3.00$, $p = .086$, $\eta^2_G = .012$). This interaction was mainly driven by an increase in single-cue strategy dominance from learning to retrieval in the PLAC/STRESS group ($t(28) = 2.08$, $p = .047$), which was completely blocked in the PROP/STRESS group ($t(20) = -0.03$, $p = .976$; PLAC/CON: $t(28) = 0.65$, $p = .523$; PROP/CON: $t(23) = 1.84$, $p = .079$), suggesting that the shift to 'cognitive' memory system engagement from learning to retrieval occurred primarily in stressed participants that had not received propranolol.

In order to further elucidate the effects of major stress mediators on the control of memory retrieval, we performed regression analyses including the predictors cortisol as well as systolic blood pressure (as indicator of sympathetic activity), with learning strategy as predictor of no interest, thereby controlling for potential individual differences in strategy use during task acquisition. Overall, the model fit the data well ($F(4,97) = 12.68$, $p < .001$, $R^2_{Adj} = .316$). In particular, cortisol levels or systolic blood pressure alone did not influence strategy use (both $|\beta| < .04$, both $|t|(97) < 0.47$, both $p > .628$). Most interestingly, however, there was a significant cortisol × systolic blood pressure interaction ($\beta = -.22$, $t(97) = -2.51$, $p = .014$). In order to further examine this interaction, we performed a median split for systolic blood pressure (median = 134 mmHg), indicating that cortisol was negatively associated with the strategy dominance score for high levels of systolic blood pressure ($r = -.28$, $p = .043$), but not for low levels of systolic blood pressure ($r = .18$, $p = .191$). In other words, the combination of high salivary cortisol concentrations and high systolic blood pressure was associated with single-cue strategy use (Fig. 4C). This effect remained significant when excluding two outliers for salivary cortisol ($\beta = -.21$, $t(95) = -2.16$, $p = .034$).

The best-fitting strategy did not change from learning to retrieval ($\chi^2(1,N = 93) = 0.53$, $p = .465$, *Odd's Ratio* = 1.308) and was not affected by stress or propranolol (all $\chi^2 < 0.163$, all $p > .686$, all *Cramer's* $V < .048$). In addition, we examined the effects of the physiological stress response on the best-fitting strategy by conducting a logistic regression model including the predictors cortisol, systolic blood pressure and learning strategy (in analogy to the model conducted for the strategy dominance score). The model provided a good fit to the data (compared to a null model: $\chi^2(4) = 21.54$, $p = .006$), revealing that high levels of systolic blood pressure tended to be associated with an increase in multi-cue strategy use, indicative of 'habit' memory engagement ($\beta = .47$, $z = 1.82$, $p = .069$). This effect reached significance when two outliers for cortisol were excluded ($\beta = .56$, $z = 2.041$, $p = .041$). There were no effects of cortisol on the best-fitting strategy (main effect or interaction with systolic blood pressure: both $\beta < .11$, both $z < 0.46$, both $p > .648$).

Table 1
Subjective stress responses.

	PLAC/ CON	PLAC/ STRESS	PROP/ CON	PROP/ STRESS
Subjective rating				
challenging	3.72 (0.40)	7.97 (0.38)	3.17 (0.38)	7.57 (0.57)
unpleasant	3.59 (0.37)	7.62 (0.45)	2.54 (0.34)	7.05 (0.59)
stressful	3.14 (0.28)	7.52 (0.44)	2.79 (0.37)	7.00 (0.60)
Positive subjective mood				
baseline	31.76 (1.29)	28.21 (1.32)	29.46 (1.09)	28.95 (1.52)
+50 min	28.72 (1.53)	24.66 (1.36)	26.83 (1.31)	26.95 (1.54)
+70 min	29.52 (1.39)	25.59 (1.48)	29.04 (1.29)	26.48 (1.42)
+85 min	27.38 (1.45)	24.24 (1.58)	25.58 (1.55)	25.57 (1.59)
Negative subjective mood				
baseline	11.97 (0.39)	12.21 (0.55)	13.00 (0.67)	12.33 (0.90)
+50 min	11.48 (0.30)	11.41 (0.41)	11.46 (0.43)	12.10 (0.83)
+70 min	11.69 (0.33)	19.03 (1.58)	11.13 (0.28)	15.52 (1.08)
+85 min	11.69 (0.50)	15.34 (1.44)	11.17 (0.30)	12.14 (0.76)

Data represent mean (standard error of the mean). Timings are relative to pill intake.

3.4. Simultaneous autonomic and glucocorticoid activity impairs retrieval performance

In order to investigate whether the observed effects of cortisol and autonomic arousal on memory system engagement are also reflected in the quantitative classification performance during retrieval, we conducted an additional regression model including classification performance as outcome variable and salivary cortisol as well as systolic blood pressure as predictors. The predictors significantly explained variance in the criterion ($F(3,98) = 2.87$, $p = .040$, $R^2_{Adj} = .053$). In line with the results observed for the retrieval strategy, cortisol or systolic blood pressure alone did not affect the retrieval performance (both $|\beta| < .11$, both $|t|(98) < 1.09$, both $p > .280$), but high levels of both cortisol and systolic blood pressure combined were associated with impaired retrieval performance (cortisol × systolic blood pressure interaction: $\beta = -.30$, $t(98) = -2.88$, $p = .005$, Fig. 4D). This effect remained significant when excluding outliers (two outliers for the variable cortisol: $\beta = -.31$, t

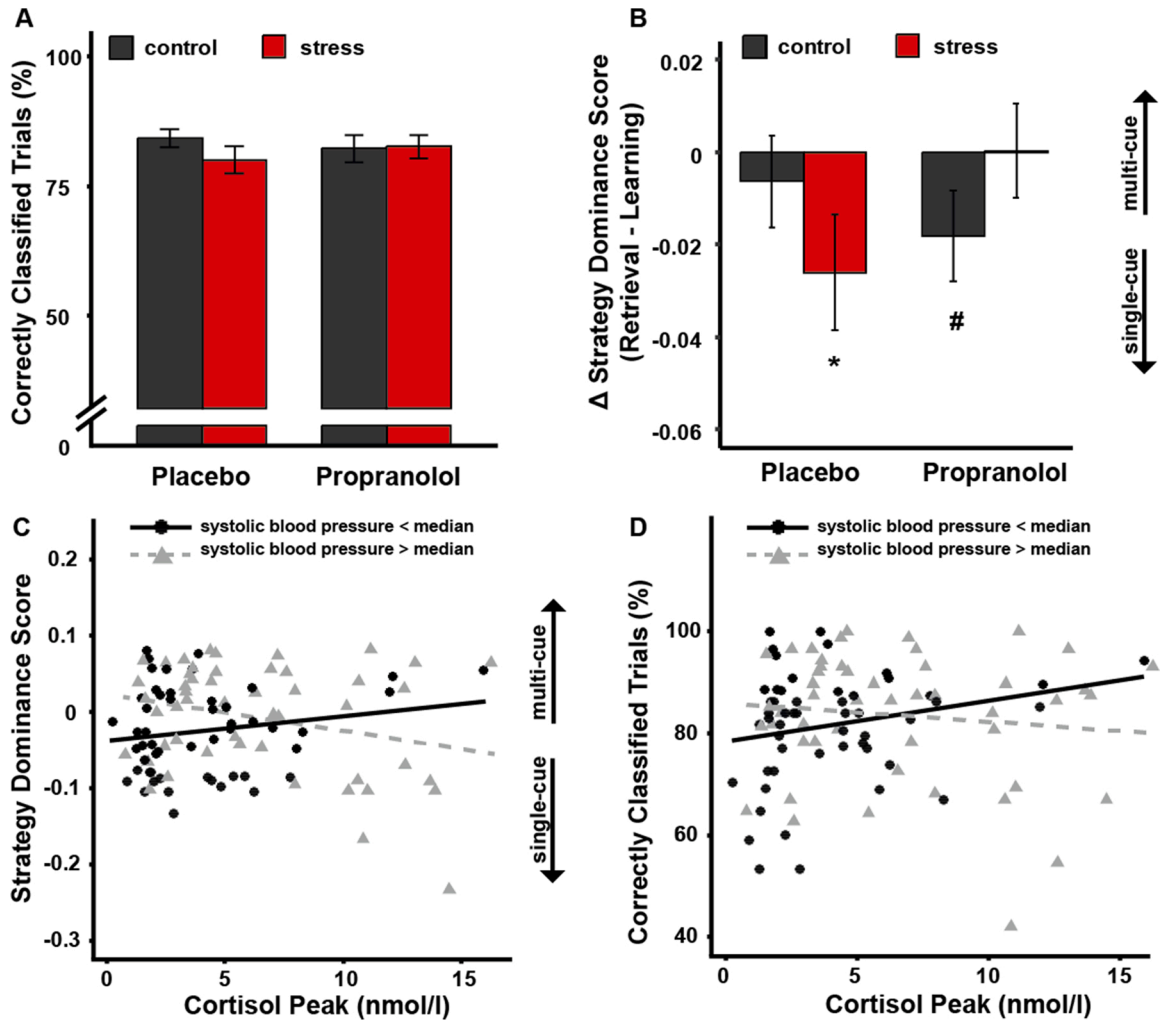

Fig. 4. Retrieval performance and strategy (day 2). (A) The proportion of correctly classified trials in the PCL task did not differ between experimental groups. (B) The strategy dominance score revealed a general shift to single-cue strategies from learning to retrieval, which was most pronounced for the PLAC/STRESS group. (C) There was an interactive association of systolic blood pressure and salivary cortisol with the strategy dominance score, showing that only for high levels of systolic blood pressure, salivary cortisol was associated with a relative preference for using the single-cue strategy. (D) Classification Performance was impaired for high levels salivary cortisol combined with high systolic blood pressure, mirroring the shift in retrieval strategy. Error bars represent standard errors of the mean. * $p < .05$, # $p < .10$.

(96) = -2.74, $p = .007$). Importantly however, when also including the retrieval strategy as predictor in the regression model, this interaction effect disappeared (β = -.09, $t(97)$ = -1.19, $p = .238$), suggesting that the stress-induced impairment in classification performance was driven by the cortisol- and blood pressure-related changes in the strategy employed during retrieval.

3.5. Control variables

There were no significant group differences in blood pressure, pulse, salivary cortisol or subjective mood before task acquisition on Day 1 (Table 2, all $F < 1.45$, all $p > .234$, all $\eta^2_G < .043$). Moreover, the groups did not differ with respect to state and trait anxiety, sleep quality in the last four weeks or chronic stress levels (all $F < 1.42$, all $p > .243$, all $\eta^2_G < .041$). There were group differences on trend-level for depressive mood ($F(3,99) = 2.36$, $p = .076$, $\eta^2_G = .067$) as well as for sleep quality in the night between experimental days ($F(3,99) = 2.33$, $p = .079$, $\eta^2_G = .066$). We included these variables as predictors in our main analyses of retrieval performance and strategy and found that depressive mood was negatively associated with retrieval performance (β = -.29, $t(96)$ = -3.01, $p = .003$). Importantly however, including these variables let our effects largely unchanged (supplementary Tables S1 and S2). Finally, most participants (77 %) guessed that they had received a placebo and the treatment guess did not differ between groups ($F(3,98) = 1.40$, $p = .248$, $\eta^2_G = .041$).

4. Discussion

It is well established that stress – most likely through the action of glucocorticoids and noradrenaline – can affect the balance of flexible, 'cognitive' and more rigid, 'habit' memory systems during learning (Packard and Goodman, 2012; Wirz et al., 2018). Here, we aimed to elucidate whether stress may also bias which memory system guides memory retrieval and if so, whether such an effect is critically dependent on noradrenergic activity. Our results showed a general shift in favor of less efficient single-cue strategies from learning to retrieval, which was most pronounced in stressed participants that had received a placebo but completely abolished in participants that had received the beta blocker propranolol before they underwent the stressor. We further showed that combined increases in salivary cortisol and systolic blood pressure were associated with the use of the single-cue strategy and linked to a marked impairment in retrieval performance.

Over the course of the learning task, participants increasingly utilized the multi-cue strategy, consistent with a practice-induced shift in

Table 2
Control variables.

	PLAC/ CON	PLAC/ STRESS	PROP/ CON	PROP/ STRESS
Positive subjective mood				
Day 1 baseline	30.76	29.38	30.79	28.71
	(1.10)	(1.01)	(1.12)	(1.42)
Day 2 baseline	31.76	28.27	29.46	28.95
	(1.29)	(1.32)	(1.09)	(1.52)
Negative subjective mood				
Day 1 baseline	12.72	13.48	13.13	13.14
	(0.42)	(1.13)	(0.78)	(0.77)
Day 2 baseline	11.97	12.21	13.00	12.33
	(0.39)	(0.55)	(0.67)	(1.88)
State anxiety (STAI-S)	34.97	37.48	37.33	36.81
	(1.05)	(1.07)	(1.45)	(1.27)
Trait anxiety (STAI-T)	35.34	36.86	35.67	37.62
	(1.52)	(1.51)	(1.59)	(1.53)
Subjective chronic stress (TICS)	11.21	14.34	12.13	14.86
	(1.40)	(1.99)	(1.99)	(1.83)
Depressive mood (BDI)	5.31	7.89	4.50	7.48
	(0.95)	(1.28)	(0.96)	(0.93)
Sleep quality over the last four weeks (PSQI)	6.72	8.59	8.25	9.24
	(0.84)	(0.85)	(1.02)	(0.90)
Sleep quality rating (last night)	76.48	67.03	70.71	63.29
	(3.08)	(3.85)	(3.21)	(4.63)

Data represent mean (standard error of the mean).

favor of the 'habit' memory system (Poldrack et al., 2001; Chang and Gold, 2003; Iaria et al., 2003). Interestingly, this shift was reversed in stressed participants who had received a placebo during retrieval. These participants showed a relative dominance of the less effective single-cue strategies indicative of 'cognitive' memory system engagement, indicating that stressed participants were less well able to use the routine established the day before and fell back to a more explicit strategy. This finding is in line with studies suggesting that also 'habitual', striatum-based retrieval processes are sensitive to stress and stress hormones (Guenzel et al., 2013; Atsak et al., 2016). This result further corroborates a previous study from our lab demonstrating that the pharmacological elevation of major stress response systems abolished a shift towards the 'habit' system from learning to retrieval (Zerbes et al., 2019). Together, these findings suggest that stress and stress hormones may shift the control of memory retrieval back to a system that is usually recruited at the beginning of a task, during initial acquisition. However, it is important to point out that the interaction effect of stress and propranolol on the strategy shift was only a non-significant trend and future studies are required to replicate this effect. It is to be noted, however, that the idea of an interaction of glucocorticoids and noradrenaline is further supported by the significant interaction between salivary cortisol and autonomic arousal.

Importantly, both the finding that the β-adrenoceptor antagonist propranolol tended to block the stress-induced shift in the control of memory retrieval and the observed interaction between salivary cortisol levels and autonomic arousal indicate a critical role of noradrenaline in the stress-induced modulation of multiple memory systems during retrieval. These findings are well in line with previous reports suggesting an interaction of glucocorticoid and noradrenergic activation in the stress-induced modulation of multiple memory systems during learning (Schwabe et al., 2010b, 2011; Schwabe et al., 2012). Furthermore, the present findings dovetail with earlier findings in rodents showing that the injection of yohimbine, leading to increased noradrenergic stimulation, biases the recruitment of memory systems during retrieval (Elliott and Packard, 2008) and our previous pharmacological study demonstrating a similar effect of yohimbine in humans (Zerbes et al., 2019). However, while these previous studies suggest that noradrenergic arousal may be sufficient to alter the contribution of multiple memory systems to retrieval, the present findings suggest that noradrenergic arousal is necessary for stress to bias the control of memory retrieval.

Interestingly, there was no direct effect of stress or propranolol on classification performance, which is in line with previous studies on stress and multiple memory system use during learning (Schwabe and Wolf, 2012; Schwabe et al., 2013; Wirz et al., 2017). Importantly, however, even if there are no direct changes in memory performance, the stress-related changes in the engagement of multiple memory system may translate into performance changes when the flexibility of memory is probed (Schwabe and Wolf, 2013; Quaedflieg and Schwabe, 2018; Wirz et al., 2018). Moreover, our findings did show that the parallel increase of (salivary) cortisol and autonomic arousal was linked to impaired memory retrieval performance. This finding is in line with the common view that stress disrupts memory retrieval performance (de Quervain et al., 1998; Diamond et al., 2006) and studies showing that this retrieval impairment is due to the interaction of glucocorticoids and noradrenergic arousal (Roozendaal et al., 2004, 2006; de Quervain et al., 2007). The present findings, however, extend these previous reports in several important ways. First, we used a task that can be solved by (at least) two distinct memory systems and focused in our analyses specifically on behavioral strategies that are indicative for these different memory systems. Our findings do not only show an impairment in memory performance but also suggest a stress (hormone)-induced change in the system that guides memory retrieval, thereby changing the nature of remembering. Moreover, we show that the impairment of memory retrieval performance that was observed if both autonomic arousal and cortisol levels were increased was closely linked to the change in the engaged behavioral strategy. Controlling for the change in behavioral strategy and, by implication, the engaged memory system during retrieval abolished the retrieval performance deficit. This result might be explained as impaired retrieval performance resulting from the stress (hormone)-induced shift to a disadvantageous strategy. Alternatively, the strategy shift could be driven by an impairment of a specific memory system and thus be an adaptive mechanism to rescue performance under stress (Schwabe et al., 2010a, 2013).

In our previous study, we found that the pharmacological elevation of either glucocorticoid or noradrenergic activity alone was sufficient to produce a shift towards the 'cognitive' memory system during retrieval (Zerbes et al., 2019). At first glance, this finding might seem to contradict the interactive influence of these major stress mediators suggested in the present study. However, it is important to note that the pharmacological elevation of glucocorticoid and noradrenergic activity in our previous study was considerably stronger than the increase in these systems after a psychosocial stress exposure, suggesting that supraphysiological levels of these stress mediators may be able to induce a change in the control of memory retrieval and, at the same time, result in a 'ceiling effects' that prevents a further interactive effect. Alternatively, the pill intake may have been accompanied by a moderate increase in stress systems activity, which was sufficient to interact with the parallel pharmacological increase in glucocorticoid and noradrenergic activity, respectively.

Notably, the observed shift in the engaged behavioral strategy after stress was a relative shift in the contribution of 'cognitive' and 'habitual' memory processes. 'Cognitive' and 'habitual' memory systems are assumed to be active in parallel (McDonald and White, 1994; Chang and Gold, 2003) and while one system may dominate, the dominance of one system does not necessarily imply the inactivity of the other. The relative contributions of multiple memory systems at the same time are explicitly reflected in the strategy dominance score that we introduced recently (Zerbes et al., 2020). The present findings showing stress and stress hormone effects in this dominance score but not in the categorical strategy analysis suggest that this score is more sensitive to potential modulations in the engagement of multiple memory systems than the previous categorical analysis.

Finally, it is important to note that the direction of the stress (hormone)-induced modulation of multiple memory systems during retrieval appears to be more variable than during learning. Whereas stress induces a shift towards 'habitual' systems during learning, the present

study as well as a previous study (Zerbes et al., 2019) suggested a stress (hormone)-induced shift back to 'cognitive' memory during retrieval while another study and findings in rodents suggest a stress- or arousal-related shift towards 'habitual' memory retrieval (Elliott and Packard, 2008). A critical factor that may explain these heterogeneities appears to be the extent of initial training. Pre-retrieval stress or arousal before retrieval led to a shift towards habitual performance when initial training was limited and therefore memory traces were weak (Elliott and Packard, 2008, Zerbes et al., 2020). However, after intense training, stress or stress hormones induced an opposite shift towards a more explicit, but less efficient 'cognitive' strategy both in the present and a previous study (Zerbes et al., 2019).

To conclude, our results suggest that stress effects on the relative engagement of multiple memory systems during memory retrieval require noradrenergic activation. More specifically, stress favored the use of a less efficient 'cognitive' strategy, which was most likely driven by parallel increases in cortisol and autonomic arousal but absent in participants who had received the beta-adrenergic receptor antagonist propranolol. The present results further linked a change in the recruited memory system to stress-induced impairments in retrieval performance. Our finding that stress effects on the nature of remembering in general and on the use of efficient behavioral routines in particular can be prevented by blocking noradrenergic arousal may have relevant implications for stress-related mental disorders in which retrieval deficits are prominent.

Contributors

L. S. conceived and designed the study. Testing and data acquisition was performed by G.Z. and F.M.K.. G.Z. analyzed the data and G.Z., F.M. K., J.C.M., K.W. and L.S. interpreted the data. G.Z. and L.S. drafted the manuscript. All authors contributed to and have approved the final manuscript.

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Declaration of Competing Interest

The authors reported no declarations of interest.

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Appendix A. Supplementary data

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