Glucocorticoids, Noradrenergic Arousal, and the Control of Memory Retrieval

Gundula Zerbes[1], Franziska Magdalena Kausche[1], Jana Christina Müller[2], Klaus Wiedemann[2], and Lars Schwabe[1]

Abstract

■ Glucocorticoids and noradrenaline can enhance memory consolidation but impair memory retrieval. Beyond their effects on quantitative memory performance, these major stress mediators bias the engagement of multiple memory systems toward "habitual" control during learning. However, if and how glucocorticoids and noradrenaline may also affect which memory system is recruited during recall, thereby affecting the control of retrieval, remain largely unknown. To address these questions, we trained healthy participants in a probabilistic classification learning task, which can be supported both by cognitive and habitual strategies. Approximately 24 hr later, participants received a placebo, hydrocortisone, yohimbine (an α2-adrenoceptor antagonist increasing noradrenergic stimulation), or both drugs before they completed a recall test for the probabilistic classification learning task. During training, all groups showed a practice-dependent shift toward more habitual strategies, reflecting an "automatization" of behavior. In the recall test, after a night of sleep, this automatization was even more pronounced in the placebo group, most likely due to offline consolidation processes and with beneficial effects on recall performance. Hydrocortisone or yohimbine intake abolished this further automatization, preventing the shift to a more efficient memory system and leading, in particular in the hydrocortisone group, to impaired recall performance. Our results suggest that glucocorticoids and noradrenergic stimulation may modulate the engagement of different strategies at recall and link the well-known stress hormone-induced retrieval deficit to a change in the system controlling memory retrieval. ■

INTRODUCTION

Memory can be supported by multiple, anatomically, and functionally distinct systems. A prominent dichotomy distinguishes between "cognitive" systems, including the hippocampus and PFC, and "habitual" systems, such as the dorsal striatum (Eichenbaum & Cohen, 2004; Squire, 2004; White & McDonald, 2002). These systems operate in parallel and process information simultaneously (Packard, 1999; McDonald & White, 1994) but differ in the mode of operation, the type of information processed, and the degree of behavioral flexibility (Myers et al., 2003; Packard & McGaugh, 1996). Over the past decade, it has been demonstrated across tasks and species that stress as well as major stress mediators, in particular glucocorticoids and noradrenaline, modulate the engagement of cognitive and habit systems during learning (Schwabe, Tegenthoff, Höffken, & Wolf, 2012; Schwabe & Wolf, 2012; Bohbot, Gupta, Banner, & Dahmani, 2011; VanElzakker et al., 2011; Schwabe, Schächinger, de Kloet, & Oitzl, 2010; Schwabe et al., 2007; Packard & Wingard, 2004; Kim, Lee, Han, & Packard, 2001). Specifically, stress or elevated glucocorticoid or noradrenaline levels before acquisition were shown to induce a shift from cognitive toward habitual control of learning (Wirz, Bogdanov, & Schwabe, 2018; Vogel, Fernández, Joëls, & Schwabe, 2016; Goodman, Leong, & Packard, 2012).

Although there is by now strong evidence that stress or stress hormones may impact the nature of learning, it remains largely unclear whether stress, through the action of glucocorticoids and noradrenaline, may also affect the control of memory retrieval. If both cognitive and habitual systems were involved in learning and different forms of memory were established (Chang & Gold, 2003), may glucocorticoids and noradrenaline affect whether cognitive or habit memory guides retrieval? It is well known that stress or glucocorticoids, in interaction with noradrenaline, may disrupt the retrieval of hippocampus-dependent memories (de Quervain, Aerni, & Roozendaal, 2007; Diamond et al., 2006; de Quervain, Roozendaal, & McGaugh, 1998), and recent evidence points to similar effects on the retrieval of nonhippocampal memories (Atsak et al., 2016; Guenzel, Wolf, & Schwabe, 2013). Furthermore, there is first evidence in rats suggesting that the pharmacological elevation of noradrenergic activity may affect the engagement of multiple memory systems during retrieval (Elliott & Packard, 2008). However, whether major stress mediators, in particular glucocorticoids and noradrenaline,

[1]University of Hamburg, [2]University Clinic Hamburg-Eppendorf

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may bias the systems controlling memory retrieval in humans is completely unknown.

In the present experiment, we examined if and how glucocorticoids and noradrenergic stimulation modulate the recruitment of cognitive and habitual memory systems during retrieval. Therefore, healthy participants completed first a probabilistic classification learning (PCL) task that can be acquired by both the hippocampal, cognitive system and the dorsal striatal, habitual system (Wirz, Wacker, Felten, Reuter, & Schwabe, 2017; Schwabe & Wolf, 2012; Foerde, Knowlton, & Poldrack, 2006; Poldrack et al., 2001; Knowlton, Mangels, & Squire, 1996). The engagement of these systems can be inferred at the behavioral level from the analysis of different learning strategies, as demonstrated in studies in patients with medial-temporal lobe or basal ganglia damage as well as neuroimaging studies (Schwabe & Wolf, 2012; Shohamy, Myers, Onlaor, & Gluck, 2004). Because the contribution of the cognitive system develops more rapidly during learning than the contribution of the habit system (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Gluck, Shohamy, & Myers, 2002; Poldrack et al., 2001), we trained participants extensively to ensure that both systems have developed during learning. Twenty-four hours after learning, participants received a placebo (PLAC), hydrocortisone (CORT), the α2-adrenoceptor antagonist yohimbine (YOH), which leads to increased noradrenergic stimulation, or both drugs before they completed a retention test for the PCL task. In this test, we provided no feedback to prevent new learning, enabling us to probe the impact of glucocorticoids and noradrenergic stimulation on the systems controlling memory retrieval.

METHODS

Participants and Experimental Design

One hundred thirty-six healthy volunteers (68 women, age: M = 25.41 years, SEM = 0.36 years) without a lifetime history of any mental or neurological disease, current medication, drug or tobacco use, or intake of hormonal contraceptives in women participated in this experiment. Women were not tested during their menses. The sample size was based on an a priori sample size calculation using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007), showing that a sample of 136 participants is required to detect a medium-sized effect of f = 0.25 with a power of .95, given an α of .05. All participants provided informed consent before taking part in the experiment and received a compensation of €60. The study protocol was approved by the medical ethics committee Hamburg and in accordance with the Declaration of Helsinki.

In a double-blind, placebo-controlled, fully crossed, between-subject design with the factors noradrenergic arousal (yohimbine vs. placebo) and cortisol (hydrocortisone vs. placebo), participants were randomly assigned to one of four experimental groups: PLAC, CORT, YOH, and CORT + YOH. Two participants had to be excluded because of data loss during acquisition on experimental Day 1. In addition, 22 participants had to be excluded from the analyses because they did not acquire the task on experimental Day 1 (performance below 60% in the second half of the learning task), which precluded an assessment of the control of memory retrieval. For about 77% of these participants, no strategy was identifiable (fit score > .15); the other participants were classified as single-cue users. Thus, the final sample included 112 participants (56 women; age: M = 25.39 years, SEM = 0.39 years; PLAC: n = 28, CORT: n = 26, YOH: n = 32, CORT + YOH: n = 26).

PCL Task

To examine the control of memory retrieval, participants were tested on two consecutive days (Figure 1). All testing took place between 13:00 and 19:00.

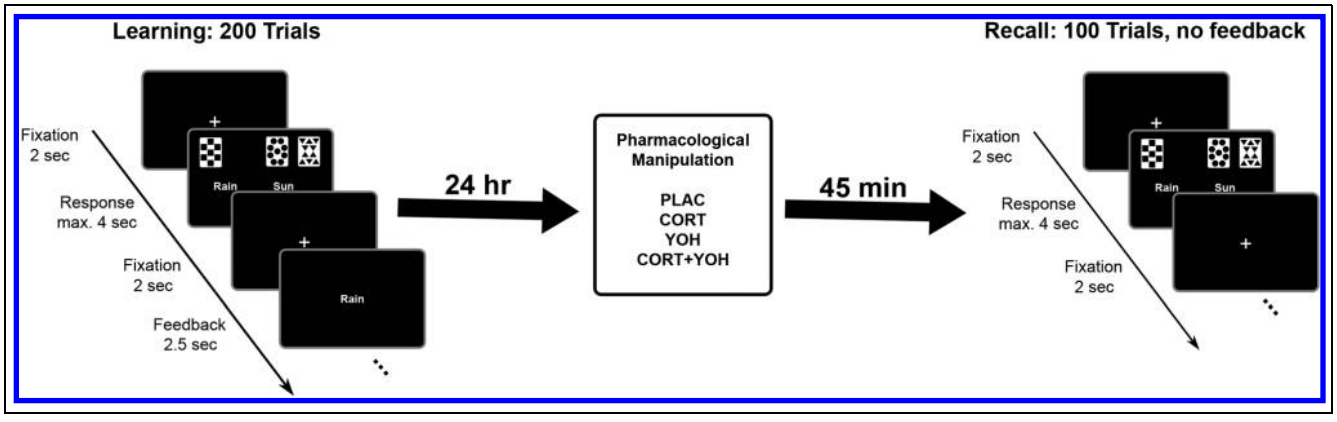

Figure 1. Procedure. On Day 1, participants learned the probabilistic classification learning task using trial-by-trial feedback. Overall, they completed 200 trials. Twenty-four hours after learning, they received the pharmacological manipulation (hydrocortisone, yohimbine, both drugs, or a placebo). After a break of 45 min to allow the drugs to be absorbed, participants completed the recall phase of the probabilistic classification learning task, consisting of 100 trials without feedback to prevent further learning.

Day 1 (Learning)

On the first experimental day, participants completed a PCL task, known as the Weather Prediction Task (Knowlton et al., 1996), which can be supported both by a hippocampal and by a dorsal striatal system (Shohamy, Myers, Grossman, et al., 2004; Poldrack et al., 2001; Knowlton et al., 1996). Participants were instructed that they would see cards and that they should learn to predict "the weather" (rain vs. sunshine) based on the presented cards (Figure 1). One to three (out of four) cards were present on each trial, yielding 14 possible card patterns. These patterns were probabilistically associated with one of two weather outcomes (sun vs. rain). In line with previous studies (Wirz, Wacker, et al., 2017; Schwabe, Tegenthoff, Höffken, & Wolf, 2013; Schwabe & Wolf, 2012; Gluck et al., 2002), outcome probabilities for the different card patterns were determined in a way that a particular cue was associated with the outcome "sun" with a probability of 75.6%, 57.5%, 42.5%, or 24.4% across the task. A response was counted as correct if the predicted outcome corresponded to the outcome with the highest probability for that card pattern.

Participants completed 200 trials of the PCL task. On each of these trials, participants saw 1 of the 14 card patterns and were requested to respond "rain" or "sun" within 4 sec via button press. After a short fixation period of 2 sec, participants received feedback about the actual weather outcome by presenting the word "rain" or "sun" on the screen (2.5 sec). Between trials, there was an interval of 2 sec.

Day 2 (Recall)

About 24 hr after learning and 45 min after the pharmacological manipulation (see below), participants performed the PCL task again as described above, with two differences. First and foremost, participants did not receive feedback to prevent further learning, allowing us to investigate specifically retrieval processes. Furthermore, participants completed only 100 trials of the task in the recall phase.

Strategy Analysis

The PCL task can be solved using different strategies (Shohamy, Myers, Grossman, et al., 2004; Gluck et al., 2002), which provide insight into the engagement of hippocampal and dorsal striatal memory systems (Schwabe & Wolf, 2012; Shohamy, Myers, Grossman, et al., 2004; Knowlton et al., 1996). To assess the used strategy, participants' actual responses were compared with the ideal responses for each strategy. Least mean squares estimates (ranging between 0 and 1) indicated the fit of the behavior to each strategy, with 0 indicating a perfect fit. The strategy with the lowest score was chosen as the best fit for each participant. If none of the fit scores was $<.15$, the strategy was considered unidentifiable (Wirz, Reuter, Wacker, Felten, & Schwabe, 2017; Wirz, Wacker, et al., 2017; Gluck et al., 2002). Retrospectively, the proportions of unidentifiable strategies were 6.3–19.2% for the first half of learning, 0–3.8% for the second half, and 3.6–15.4% for the recall phase. The experimental groups did not differ in the number of participants with unidentifiable strategies (all $\chi^2(3) < 3.337$, all $p > .342$, all Cramer's $V < .173$). In the learning phase, strategies were computed based on the first and the second 100 trials to investigate changes in strategy use across the task. Because we did not provide feedback in the recall phase and hence no changes in strategy use were expected in this phase, the strategy analysis for the recall phase focused on the task as a whole. For the sake of simplicity and in line with previous studies (Wirz, Wacker, et al., 2017; Schwabe et al., 2013; Schwabe & Wolf, 2012), strategies were divided into "single-cue," hippocampus-dependent strategies (referring to one-cue or singleton strategies) and "multicue," dorsal striatum-dependent strategies.

Pharmacological Manipulation

Depending on the experimental condition, participants received orally a placebo, 20 mg hydrocortisone, 20 mg yohimbine (a α2-adrenoceptor antagonist increasing noradrenergic activation), or both drugs. Timing and dosage of the drugs were chosen in accordance with previous studies (Kluen, Nixon, Agorastos, Wiedemann, & Schwabe, 2017; Schwabe et al., 2012). On the first experimental day, baseline measurements of blood pressure and salivary cortisol were taken before the start of the task. To verify the action of the drugs on the second experimental day, blood pressure and salivary cortisol were measured before drug intake, 45 min after drug intake, after the PCL task (~60 min after drug intake), 90 min after drug intake, and 120 min after drug intake. Blood pressure was measured using a Critikon Dinamap system (Tampa, FL) with the cuff placed around the nondominant arm. Saliva samples were collected using Salivette (Sarstedt, Nümbrecht, Germany) devices and stored at -20°C until analysis. Free cortisol and alpha-amylase concentrations were measured using an immunoassay or enzyme assay, respectively (IBL International, Hamburg, Germany). In addition, we tracked potential changes in subjective mood with a German version of the Positive and Negative Affect Schedule (Krohne, Egloff, Kohlmann, & Tausch, 1996), assessed also at baseline as well as 45, 60, 90, and 120 min after pill intake.

Control Variables

To control for differences in subjective chronic stress, depressive mood, and anxiety, participants completed the Trier Inventory for the Assessment of Chronic Stress (TICS; Schulz & Schlotz, 1999), the Beck Depression

Inventory (BDI-II; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and the State–Trait Anxiety Inventory (STAI, Spielberger & Sydeman, 1994). All of these control measurements were completed on the second day. Moreover, we asked participants at the end of the second experimental day what they thought which treatment they had received (treatment guess).

Statistical Analysis

Subjective and physiological data were analyzed with mixed-design ANOVAs with Time as a within-subject factor and Cortisol (placebo vs. hydrocortisone) and Noradrenergic arousal (placebo vs. yohimbine) administration as between-subject factors. Classification performance was analyzed with a mixed-design ANOVA with blocks of 10 trials as within-subject factor. For learning performance, the pharmacological manipulation was treated as a single factor with four levels, because there was no experimental treatment before learning, and this analysis served solely to identify potential baseline differences in strategy use. For recall performance, the pharmacological manipulation was split into the two factors Cortisol (placebo vs. hydrocortisone) and Noradrenergic stimulation (placebo vs. yohimbine) to test also for potential interactions between cortisol and noradrenergic stimulation.

Group differences in PCL strategies during learning were analyzed by means of χ^2 tests. Similar to the analysis of the classification performance, the groups were treated as one factor for the learning phase, and the two factors Cortisol and Noradrenergic stimulation were separated for the recall phase. Changes in strategy use over time were analyzed using McNemar tests. Recall strategies were analyzed using logistic regression enabling us to examine interactions between the factors cortisol and noradrenergic stimulation against the background of the strategy used during learning. All reported p values are two-tailed. In case of violation of the sphericity assumption, Greenhouse–Geisser corrections were applied.

RESULTS

Experimental Day 1: Successful Classification Learning

Before the beginning of the learning phase on experimental Day 1, the four groups did not differ in subjective mood, salivary cortisol, and systolic or diastolic blood pressure (all $F \leq 0.712$, all $p \geq .547$; see Table 1). Across the learning phase, participants improved in classification performance, $F(11.12, 1200.45) = 24.771$, $p < .001$, $\eta^2 = .187$, and reached a performance of more than 80% correctly classified trials at the end of the learning session, thus demonstrating successful classification learning. The four groups differed neither in performance nor in the learning rate (main effect of Group and Group × Block interaction: both $F \leq 1.633$, both $p \geq .186$, both $\eta^2 \leq .043$; Figure 2A).

To assess the engagement of multiple memory systems, we examined learning strategies that are known to be based on the hippocampus and dorsal striatum, respectively (Shohamy, Myers, Grossman, et al., 2004; Poldrack et al., 2001; Knowlton et al., 1996). In line with earlier findings reporting a shift from "cognitive" hippocampal to more "habitual" dorsal striatal learning with increased practice (Iaria et al., 2003; Gluck et al., 2002; Poldrack et al., 2001), we obtained overall significant changes in the engaged learning strategy across the task, $\chi^2(1) = 15.559$, $p < .001$, $OR = 5.800$: Whereas the vast majority of participants used a single-cue strategy in the first half of the learning task, about 50% used a multicue strategy in the second half (Figure 2B). Notably, when testing for potential group differences in strategy use during learning, before any treatment, we obtained a trend for group differences in the used learning strategy across the task, $\chi^2(3) = 6.421$, $p = .093$, Cramer's $V = .239$, and a significant difference in the strategy used in the second half of the task, $\chi^2(3) = 9.467$, $p = .024$, Cramer's $V = .292$, indicating that the strategy use during learning needs to be taken into account when testing the influence of cortisol and noradrenergic stimulation on the control of memory retrieval.

Experimental Day 2: Manipulation Check

Changes in blood pressure, alpha-amylase, and salivary cortisol concentrations verified the action of the drugs. Both systolic and diastolic blood pressure increased over time in the YOH and YOH + CORT groups (all $F \geq 3.011$, all $p \leq .022$, all $\eta^2 \geq .107$; Table 1), whereas there was no such increase in the CORT group (all $F \leq 2.354$, all $p \geq .060$, all $\eta^2 \leq .093$) and even a slight decrease in the PLAC group (all $F \geq 3.030$, all $p \leq .043$, all $\eta^2 \geq .101$; time point of Measurement × Noradrenergic stimulation: both $F \geq 5.323$, both $p \leq .001$, both $\eta^2 \geq .047$). The increase in blood pressure was apparent after the task (see Table 1), indicating that the effect of yohimbine developed during the task. Furthermore, changes in alpha-amylase levels over time were modulated by yohimbine intake, $F(3.08, 326.48) = 4.097$, $p = .007$, $\eta^2 = .037$. Conversely, administration of hydrocortisone led to an increase in salivary cortisol in the CORT and CORT + YOH groups (both $F \geq 12.045$, both $p \leq .001$, both $\eta^2 \geq .334$), whereas there was even a trend for a decrease, most likely due to the diurnal rhythm of cortisol, in the PLAC and YOH groups (both $F \geq 2.801$, both $p \leq .083$, both $\eta^2 \geq .083$; time point of Measurement × Cortisol interaction: $F(1.51, 161.49) = 34.644$, $p < .001$, $\eta^2 = .245$; Table 1). There were no interactive effects of Cortisol and Yohimbine, neither for blood pressure nor for salivary cortisol or alpha-amylase (all interaction effects including the factor Noradrenergic stimulation and Cortisol on blood pressure or salivary

Table 1. Physiological, Endocrine, and Subjective Response to the Pharmacological Manipulation

Variable	*PLAC*	*CORT*	*YOH*	*CORT + YOH*
Systolic blood pressure (mmHg)				
Day 1	123.93 (2.67)	123.92 (2.89)	125.95 (2.50)	123.71 (2.77)
Day 2 baseline	120.79 (3.11)	117.77 (3.36)	122.55 (2.91)	121.69 (3.22)
Day 2 45 min post drug	118.16 (2.88)	113.60 (3.12)	119.81 (2.70)	118.87 (2.99)
Day 2 60 min post drug	115.14 (2.88)***	113.35 (3.11)	122.73 (2.69)	119.00 (2.99)
Day 2 85 min post drug	117.27 (2.85)*	114.08 (3.08)	**127.72** (2.67)**	123.94 (2.96)
Day 2 115 min post drug	116.68 (3.00)*	113.63 (3.24)	**132.30** (2.80)***	124.37 (3.11)
Diastolic blood pressure (mmHg)				
Day 1	70.38 (1.98)	70.70 (2.10)	70.39 (1.85)	73.73 (2.06)
Day 2 baseline	64.64 (1.44)	65.62 (1.52)	64.80 (1.35)	67.19 (1.49)
Day 2 45 min post drug	66.50 (1.71)	64.84 (1.81)	65.13 (1.60)	67.73 (1.77)
Day 2 60 min post drug	62.82 (1.52)	64.86 (1.61)	66.17 (1.43)	66.77 (1.58)
Day 2 85 min post drug	65.05 (1.65)	64.06 (1.75)	**69.45** (1.54)***	**70.65** (1.71)*
Day 2 115 min post drug	67.50 (1.82)	64.94 (1.93)	69.20 (1.71)***	68.37 (1.89)
Salivary cortisol (nmol/L)				
Day 1	3.86 (0.82)	4.87 (0.87)	4.37 (0.77)	4.86 (0.86)
Day 2 baseline	3.69 (0.61)	3.61 (0.65)	4.82 (0.57)	3.81 (0.64)
Day 2 45 min post drug	2.32 (6.78)***	**38.78** (7.17)**	2.89 (6.34)	**62.96** (7.03)***
Day 2 60 min post drug	2.64 (4.90)**	**43.91** (5.19)***	2.95 (4.59)	**61.80** (5.09)***
Day 2 85 min post drug	2.03 (3.40)**	**45.92** (3.60)***	3.94 (3.17)**	**47.28** (3.53)***
Day 2 115 min post drug	1.83 (2.88)**	**40.02** (3.05)***	3.38 (2.69)**	**39.61** (2.99)***
Alpha-amylase (U/ml)				
Day 1	105.81 (17.51)	115.77 (20.49)	134.69 (19.02)	107.87 (18.61)
Day 2 baseline	100.36 (17.09)	118.49 (20.76)	119.04 (17.16)	98.51 (19.45)
Day 2 45 min post drug	95.79 (18.79)	84.76 (19.69)**	134.37 (15.54)	113.25 (24.01)
Day 2 60 min post drug	88.83 (16.78)	80.45 (17.63)***	124.09 (17.80)	107.50 (20.52)
Day 2 85 min post drug	89.22 (17.02)	99.05 (21.43)	**157.60** (18.71)*	114.51 (21.63)
Day 2 115 min post drug	95.15 (17.99)	83.35 (15.62)*	**167.67** (20.48)**	118.58 (20.94)
Positive subjective mood				
Day 1	26.74 (1.01)	27.41 (1.12)	28.55 (0.94)	28.42 (1.07)
Day 2 baseline	26.78 (1.21)	27.82 (1.34)	29.39 (1.13)	27.63 (1.28)
Day 2 45 min post drug	23.56 (1.23)***	24.91 (1.36)**	**27.10** (1.15)**	24.17 (1.30)***
Day 2 60 min post drug	23.26 (1.30)***	24.55 (1.45)***	26.90 (1.22)**	23.42 (1.38)***
Day 2 85 min post drug	19.82 (1.24)***	21.68 (1.37)***	**24.77** (1.51)***	**23.00** (1.31)***
Day 2 115 min post drug	21.70 (1.22)***	22.50 (1.35)***	23.77 (1.13)***	23.04 (1.29)***
Negative subjective mood				
Day 1	12.26 (0.56)	12.33 (0.63)	12.65 (0.52)	12.13 (0.60)
Day 2 baseline	12.44 (0.60)	11.52 (0.68)	12.10 (0.56)	11.83 (0.65)

Table 1. (*continued*)

Variable	*PLAC*	*CORT*	*YOH*	*CORT + YOH*
Day 2 45 min post drug	11.56 (0.47)*	11.24 (0.53)	11.58 (0.44)	11.22 (0.51)
Day 2 60 min post drug	11.70 (0.49)	11.10 (0.55)	11.42 (0.45)*	11.44 (0.53)
Day 2 85 min post drug	11.89 (0.73)	12.57 (0.83)	12.29 (0.67)	12.48 (0.80)
Day 2 115 min post drug	10.63 (0.44)**	11.24 (0.50)	11.55 (0.41)	10.83 (0.48)*

Data represent mean (standard error). Asterisks denote difference to Day 2 baseline: *$p < .05$, **$p < .01$, ***$p < .001$. **Bold** values denote difference to placebo group at $p < .05$.

cortisol: all $F \leq 2.913$, all $p \geq .072$, all $\eta^2 \leq .027$). Positive mood decreased across the experiment, independent of the experimental treatment (main effect Time: $F(3.117, 311.683) = 54.454$, $p < .001$, $\eta^2 = .353$; all main or interaction effects containing treatment: all $F \leq 2.178$, all $p \geq .143$, all $\eta^2 \leq .021$; Table 1).

Experimental Day 2: Cortisol and Noradrenergic Stimulation Alter the Control of Memory Retrieval

The analysis of the engaged strategies during retrieval, 24 hr, including one night of sleep, after learning, revealed a striking pattern in the PLAC group: Participants who received a placebo showed a strong preference for the multicue strategy; more than 80 percent of the PLAC group used this strategy during recall (Figure 3A). Compared with the PLAC group, the CORT, $\chi^2(1, N = 51) = 16.371$, $p < .001$, Cramer's $V = .567$, and YOH, $\chi^2(1, N = 57) = 7.402$, $p = .007$, Cramer's $V = .360$, groups used single-cue strategies significantly more often (YOH + CORT vs. PLAC: $\chi^2(1, N = 49) = .534$, $p < .51$, Cramer's $V = .104$). These group differences at recall, however, are difficult to interpret given the reported group differences during learning. To take these differences in learning strategies into account, we ran a logistic regression predicting recall strategies using the factors cortisol, yohimbine, and the Cortisol × Yohimbine interaction as well as the learning strategy used on Day 1. Thus, in this analysis, learning strategy is treated as a covariate, taking baseline differences in strategy use before drug administration into account. The model was well able to predict the retrieval strategy, $\chi^2(4, N = 102) = 51.499$, $p < .001$, Nagelkerke's $R^2 = .531$, with a significant impact for all predictors (cortisol: $b = -2.686$, $p = .001$, $OR = 0.068$; yohimbine: $b = -2.026$, $p = .007$, $OR = 0.132$; Cortisol × Yohimbine: $b = 3.269$, $p = .003$, $OR = 26.284$; learning strategy: $b = 2.810$, $p < .001$, $OR = 16.608$). To pursue the significant main and interaction effects of cortisol and yohimbine, we implemented goodness-of-fit chi-square tests using the learning strategies as expected values, thus examining differences between learning and recall strategies. This analysis confirmed that the PLAC group showed relative to the learning phase a striking shift toward more multicue strategies, $\chi^2(1, N = 27) = 6.531$, $p = .011$, Cramer's $V = .492$ (Figure 3B). Critically, after the administration of hydrocortisone, $\chi^2(1, N = 24) = 0.045$, $p = .832$, Cramer's $V = .043$; yohimbine, $\chi^2(1, N = 30) = 0.001$, $p = .975$, Cramer's $V = .004$; or both drugs in combination, $\chi^2(1, N = 22) = 0.226$, $p = .635$, Cramer's $V = .101$, no such shift was observed. Thus, the Cortisol × Yohimbine interaction in the logistic regression was driven by the effect observed when none of the drugs was administered (i.e., in the

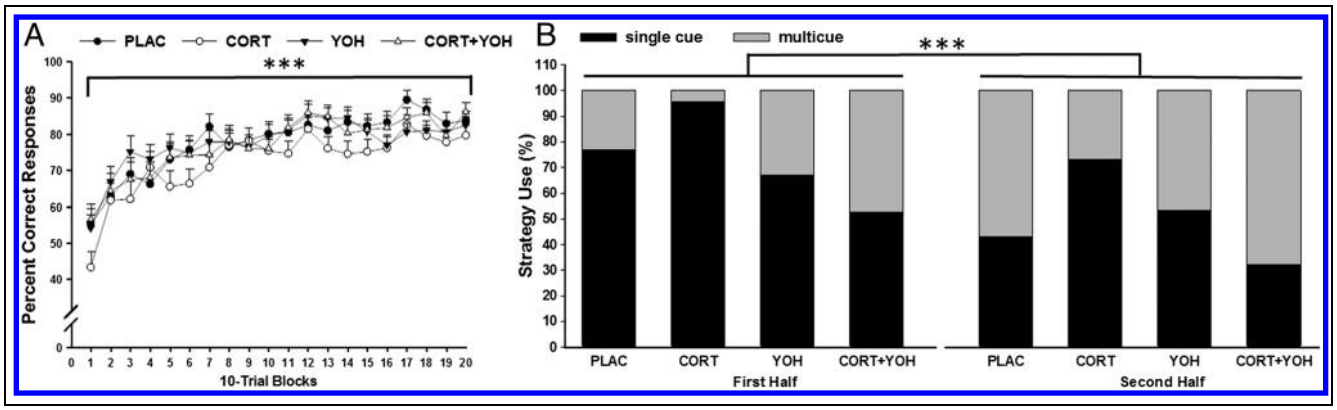

Figure 2. Performance and strategy use during learning (Day 1). (A) The proportion of correctly classified trials increased over the learning task, indicating successful learning. (B) Strategy use shifted, across groups, from the predominant use of single-cue strategies in the first half of the task to more multicue strategies in the second half. ***$p < .001$.

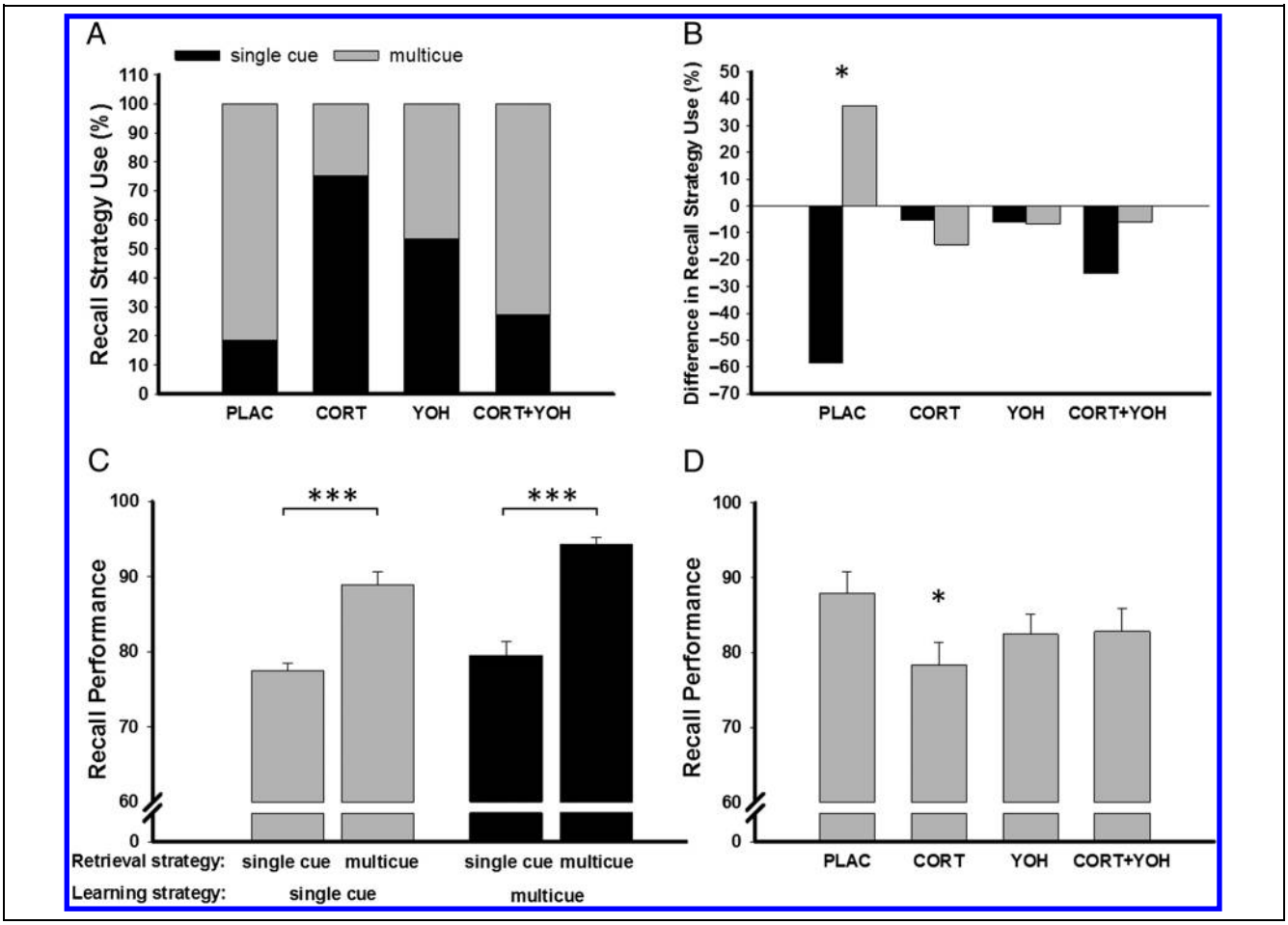

Figure 3. Strategy use and performance during recall (Day 2). (A) Group differences in strategy use during recall. (B) Although there was, relative to Day 1, a further shift toward more multicue and less single-cue strategies during 24-hr recall in the placebo (PLAC) group, this shift was absent in participants that had received hydrocortisone (CORT) or yohimbine (YOH). (C) Participants who shifted toward a multicue strategy from Day 1 to Day 2 (or who kept using this strategy from Day 1) performed significantly better than those who kept using a single-cue strategy (or shifted back to a single-cue strategy). (D) In particular CORT led to impaired recall performance. *$p < .05$, ***$p < .001$.

PLAC group), which was then abolished by either of the drugs. In order to test whether the influence of the pharmacological manipulation differed depending on the initial learning strategy, we also included interactions between the pharmacological manipulation and learning strategy in the regression model. None of these interactions were significant (Learning Strategy × CORT: $b = 1.540$, $p = .391$, $OR = 4.667$; Learning Strategy × YOH: $b = 1.110$, $p = .479$, $OR = 3.033$; Learning Strategy × CORT × YOH: $b = 1.540$, $p = .391$, $OR = 4.667$), suggesting that the effects of hydrocortisone and yohimbine did not depend on the learning strategy.

The strategy employed during retrieval had a significant impact on recall performance. Overall, recall performance was better for participants who used multicue than for those that used single-cue strategies, $F(1, 95) = 114.855$, $p < .001$, $\eta^2 = .547$. Accordingly, participants who switched to multicue strategies during recall performed significantly better than participants who continued to use single-cue strategies, $t(46) = 5.110$, $p < .001$ (Figure 3C). Thus, the altered strategy use during retrieval in the CORT, YOH, and CORT + YOH was also, at least partly, reflected in retrieval performance. Participants in the CORT group were significantly impaired relative to the PLAC group ($p = .022$). The YOH and CORT + YOH group showed a descriptive trend in the same direction, which, however, did not reach statistical significance (both $p > .166$; Figure 3D). There were no effects of Task block on recall performance, nor any interactions of Block with Recall strategy or the pharmacological manipulation (all $F \leq 1.717$, all $p \geq .093$, all $\eta^2 \leq .018$).

Control Variables

Participants in the four experimental groups were not aware of the respective pharmacological manipulation. Most participants (about 65%) guessed that they had received a placebo, irrespective of the experimental group, $\chi^2(3, N = 65) = 4.529$, $p = .210$, Cramer's $V = .264$. Moreover, there were neither group differences in state

Table 2. Control Variables

Variable	*PLAC*	*CORT*	*YOH*	*CORT + YOH*
Depression score (BDI-II)	5.43 (0.86)	5.73 (0.92)	6.75 (1.12)	5.42 (1.01)
Subjective chronic stress (TICS)	67.29 (5.77)	73.31 (6.33)	71.94 (5.86)	67.54 (5.81)
State anxiety (STAI-S)	38.27 (1.36)	37.50 (1.55)	37.69 (1.60)	37.28 (1.26)
Trait anxiety (STAI-T)	36.65 (1.32)	38.39 (1.74)	38.84 (1.86)	36.35 (1.72)

Data represent mean (standard error).

or trait anxiety, depressive mood, or perceived chronic stress (all $F \leq 0.547$, all $p \geq .651$, all $\eta^2 \leq .016$; see Table 2). Because previous evidence indicated that, in addition to acute stress, chronic stress may bias learning strategies during acquisition (Dias-Ferreira et al., 2009; Schwabe, Dalm, Schächinger, & Oitzl, 2008), we correlated the chronic stress score with participants' strategy during the learning phase (i.e., before the pharmacological manipulation). Interestingly, this analysis showed indeed a significant correlation between chronic stress and the engaged learning strategy ($r = .196$, $p = .039$): Participants with high levels of chronic stress used more often a multicue strategy during learning (Figure 4). This finding corroborates previous results showing that chronic stress (Dias-Ferreira et al., 2009; Schwabe et al., 2008) may, similar to acute stress (Schwabe & Wolf, 2012; Schwabe et al., 2007), bias learning toward habitual control. To test whether chronic stress affected also the strategy at recall, we also exploratively included chronic stress and its interactions with the pharmacological manipulation in the regression model for the strategy during recall. Neither the main effect nor the interactions were significant (Chronic Stress: $b = -0.003$, $p = .850$, $OR = 0.997$; Chronic Stress × CORT: $b = 0.001$, $p = .970$, $OR = 1.001$; Chronic Stress × YOH: $b = -0.003$, $p = .901$, $OR = 0.997$; Chronic Stress × CORT × YOH: $b = 0.045$, $p = .308$, $OR = 1.046$), suggesting that the recall strategy remained largely unaffected by the subjectively reported chronic stress. In addition, we exploratively included sex as a predictor in the regression analysis, and this analysis yielded a marginally significant main effect of sex ($b = -2.577$, $p = .062$, $OR = 0.076$), indicating that men tended to use more multicue strategies. None of the interaction effects with the factor sex were significant (Sex × CORT: $b = 1.744$, $p = .352$, $OR = 5.720$; Sex × YOH: $b = 2.070$, $p = .226$, $OR = 7.925$; Sex × CORT × YOH: $b = -3.807$, $p = .116$, $OR = 0.022$).

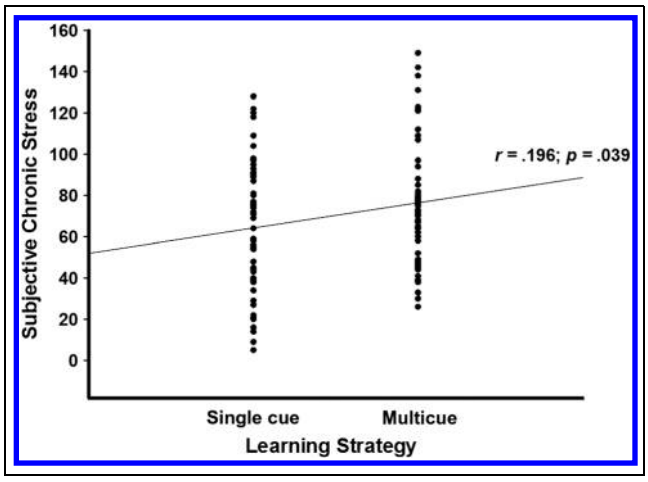

Figure 4. Correlation between chronic stress level and learning strategy. Higher levels of chronic stress, assessed by the TICS, were associated with the engagement of multicue strategies during learning.

DISCUSSION

Acute stress has been shown to promote, through the action of glucocorticoids and noradrenaline, a shift from cognitive, hippocampus-dependent to habitual, dorsal striatum-dependent control of learning (Schwabe, 2013; Packard & Goodman, 2012; Schwabe & Wolf, 2012; Schwabe et al., 2007; Kim et al., 2001). Here, we asked whether glucocorticoids and noradrenergic stimulation may also affect the memory system that controls memory retrieval, thereby changing the nature of remembering. Based on previous evidence, the engaged memory system was inferred from the strategies used to solve the task (Schwabe & Wolf, 2012; Shohamy, Myers, Onlaor, et al., 2004). Our results showed across all groups a shift from hippocampal to more dorsal striatal strategies during learning. This shift was even more pronounced during the recall session, after a night of sleep, in the PLAC group, with beneficial effects for task performance. After CORT or YOH intake, however, this shift did largely disappear, and participants kept using the strategy of the previous day, with an at least partly detrimental impact on performance.

The overall shift from hippocampal, single-cue strategies toward more dorsal striatal, multicue strategies corroborates previous reports, which showed a training-induced shift from cognitive to habit memory (Chang & Gold, 2003; Iaria et al., 2003; Poldrack et al., 2001; Packard & McGaugh, 1996). This shift is further in line with a practice-dependent proceduralization or automatization

of well-trained behaviors, during which cognitive resources are set free for other tasks (Logan, 1988). In the retention test, after a full night of sleep, there was even a further increase of multicue learning in the PLAC group, which was associated with better recall performance. This "offline" enhancement is most likely owing to the well-known effects of sleep on consolidation processes (Diekelmann & Born, 2010). Cortisol and noradrenergic stimulation interfered with the increased engagement of dorsal striatal multicue strategies at recall, disrupting the further automatization of behavior. Thus, the present findings may be taken as further evidence that glucocorticoids and noradrenaline affect not only hippocampal but also dorsal striatal memory processes (Atsak et al., 2016; Guenzel et al., 2013; Vanelzakker et al., 2011). More specifically, we assume that both hippocampal and dorsal striatal memory had developed during learning (Chang & Gold, 2003; Poldrack et al., 2001). Overnight sleep may have changed in particular the hippocampal memory, for instance, through early systems consolidation processes (Diekelmann & Born, 2010). The elevated stress hormone levels at retrieval may have interfered with both hippocampal and dorsal striatal memory, thus preventing a shift toward the latter.

As a consequence of the disrupted automatization of behavior reflected in a reduced shift toward more multicue strategies, participants in the CORT and YOH groups relied more often on single-cue strategies. The continued reliance on these strategies was detrimental to recall performance, and indeed, participants of the CORT group were significantly impaired in performance compared with the placebo controls (with similar, nonsignificant trends in the YOH and CORT + YOH groups). This impairment in recall performance is well in line with previous studies reporting a stress-induced deficit in quantitative memory retrieval (de Quervain et al., 1998, 2007; Diamond et al., 2006; Roozendaal, Hahn, Nathan, de Quervain, & McGaugh, 2004), although it should be noted that these studies used memory tasks in which a possible contribution of habit learning is less clear. The present findings link this retrieval deficit for the first time to a change in the strategies that are engaged during retrieval (and by inference to the recruitment of different memory systems).

Although earlier studies provided compelling evidence for an interactive influence of cortisol and noradrenergic stimulation on memory retrieval (de Quervain et al., 2007; Roozendaal et al., 2004), there was no such interaction in the present experiment. CORT and YOH alone were sufficient to prevent the increased use of multicue strategies, with no additional effect of the combined administration of both drugs. However, as CORT and YOH blocked the shift seen in the PLAC already almost completely, there was no room for an additional influence of the concurrent glucocorticoid and noradrenergic stimulation. Thus, there may have been a kind of "ceiling effect" in our test, and it cannot be ruled out that more sensitive behavioral tests or other measures, such as fMRI, would reveal an interactive influence of glucocorticoids and noradrenergic stimulation.

At first glance, our findings might seem to be in conflict with an earlier study in rodents, suggesting that YOH administration before retrieval promotes a shift toward more habit memory (Elliott & Packard, 2008). These findings, however, may be reconciled with our present results, when taking, in addition to species differences, important methodological differences between these studies into account. First, the previous study applied a plus maze, in which habit memory consisted of a simple left or right turn. This form of habit memory is by far simpler than the rather abstract multicue strategies indicative of habit memory engagement in the present experiment, and it may well be that this simpler form of habit memory was less vulnerable to the effects of stress mediators. One could argue that this complex nature of our task might hinder habit learning, yet previous studies demonstrated that the single-cue and multicue strategies in the PCL task map onto the hippocampal "cognitive" system and the dorsal striatal "habit" system, respectively (Schwabe & Wolf, 2012; Shohamy, Myers, Grossman, et al., 2004; Knowlton et al., 1996). Second, the plus maze was presented in a water tank; thus, rats had to swim to avoid drowning. This rendered learning in rats significantly more stressful, compared with the rather nonarousing PCL task we used here, which may well have strengthened habit memory during training (Schwabe et al., 2007; Packard & Wingard, 2004). Third and perhaps most importantly, there were striking differences in the extent of training between this study and the previous rodent study. Whereas rats were trained in 12 trials distributed over 2 days, our participants completed a massed training session of 200 trials. We decided for such an extensive learning session because habit learning requires repetition, and for the purpose of this study, it was important that both cognitive and habit learning have developed. Extensive training has been shown to induce a shift from cognitive to habit memory (Iaria et al., 2003; Gluck et al., 2002; Poldrack et al., 2001), and our data confirm this shift. Furthermore, there is very recent evidence indicating that glucocorticoids have a different impact on the engagement of multiple memory systems, depending on the extent of training (Siller-Pérez, Serafín, Prado-Alcalá, Roozendaal, & Quirarte, 2017). Glucocorticoids induced a shift from cognitive toward habit memory after moderate training, in line with evidence from human studies (Schwabe et al., 2007). After extensive training, however, there was no effect of glucocorticoids because there was also a training-related shift toward more habit memory in controls (Siller-Pérez et al., 2017). Thus, stress hormones appear to accelerate the shift toward habit memory ("automatization") during learning. Our findings extend these data by showing that, after a night of sleep, there is a further "offline" automatization, resulting in the predominance of multicue strategies during recall in

controls. Because stress hormones do not affect selectively hippocampal but also dorsal striatal retrieval processes (Atsak et al., 2016; Guenzel et al., 2013), CORT and YOH interfered with further automatization, leading participants to rely more often on the same strategy that was used at the end of learning, which tended to impair recall performance (Siller-Pérez et al., 2017). It should be noted, however, that groups differed in the predominant strategy already during learning, that is, before the pharmacological manipulation. Although we controlled for these baseline differences in our statistical analysis, it might be possible that the initial learning strategy modulates the effect of a subsequent rise in stress hormones. Thus, we tested explicitly whether hydrocortisone and yohimbine had differential effects depending on the strategy used during learning but found no evidence for such a modulatory effect.

To conclude, we tested here whether major stress mediators, glucocorticoids and noradrenaline, may affect the control of memory retrieval. Our results show that both glucocorticoids and noradrenergic stimulation may indeed alter the strategy and, by inference, the memory system, which is engaged during recall. More precisely, these stress mediators appeared to abolish the effects of an offline consolidation period, resulting in the engagement of a less effective memory system during retrieval. Thus, although the stress-induced modulation of multiple memory systems during learning is thought to facilitate performance (Vogel et al., 2016; Schwabe et al., 2010), the stress-induced modulation of memory control during recall appears to be rather detrimental, mirroring the known opposite effects of stress and glucocorticoids on quantitative memory formation and retrieval (Roozendaal, Okuda, de Quervain, & McGaugh, 2006).

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Reprint requests should be sent to Lars Schwabe, Department of Cognitive Psychology, University of Hamburg, Von-Melle-Park 5, 20146 Hamburg, Germany, or via e-mail: lars.schwabe@uni-hamburg.de.

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