Psychopharmacology (2007) 194:261–269
DOI 10.1007/s00213-007-0836-6

ORIGINAL INVESTIGATION

Emotion-induced retrograde amnesia varies as a function of noradrenergic-glucocorticoid activity

René Hurlemann · Andreas Matusch · Barbara Hawellek · Dietrich Klingmuller · Heike Kolsch · Wolfgang Maier · Raymond J. Dolan

Received: 25 March 2007 / Accepted: 21 May 2007 / Published online: 24 June 2007

Abstract
Rationale Privileged episodic encoding of an aversive event often comes at a cost of neutral events flanking the aversive event, resulting in decreased episodic memory for these neutral events. This peri-emotional amnesia is amygdala-dependent and varies as a function of norepinephrine activity. However, less is known about the amnesiogenic potential of cortisol.
Objective We used a strategy of pharmacologically potentiating cortisol and norepinephrine activity to probe the putative neurochemical substrates of peri-emotional amnesia.
Materials and methods Fifty-four healthy individuals participated in a randomized double-blind placebo-controlled study. Within the experimental context of an established peri-emotional amnesia paradigm, we tested the amnesiogenic potential of hydrocortisone (30 mg p.o.) in the presence or absence of the norepinephrine-reuptake inhibitor reboxetine (4 mg p.o.).
Results Under dual challenge conditions, we observed a linear dose–response relationship in the magnitude and duration of emotion-induced retrograde amnesia.
Conclusions Our results are consistent with a phenotypic expression of retrograde amnesia varying as a function of norepinephrine and cortisol coactivation during episodic encoding of aversive events. Our study demonstrates that the adverse cognitive and behavioral sequelae of aversive emotion can be experimentally modeled by a pharmacological manipulation of its putative neurochemical substrates.

Keywords Emotion · Amnesia · Memory · Stress · Cortisol · Norepinephrine · Reboxetine

Electronic Supplementary Material The online version of this article (doi:10.1007/s00213-007-0836-6) contains supplementary material, which is available to authorized users.

R. Hurlemann (✉) · B. Hawellek · H. Kolsch · W. Maier
Department of Psychiatry, University of Bonn,
Sigmund-Freud-Str. 25,
53105 Bonn, Germany
e-mail: renehurlemann@gmx.de

D. Klingmuller
Department of Clinical Biochemistry, Division of Endocrinology,
University of Bonn,
53105 Bonn, Germany

R. Hurlemann · A. Matusch
Brain Imaging Center West, Research Center Juelich,
52425 Juelich, Germany

R. J. Dolan
Wellcome Trust Centre for Neuroimaging,
University College London,
London WC1N 3BG, UK

Introduction

Although abundant scientific evidence confirms anecdotal observations that emotion enhances episodic memory formation (Dolan 2002), it is also evident that emotion impairs episodic memory formation and can even induce amnesia (Loftus and Burns 1982; Christianson 1984). Thus, to advance our understanding of the interaction of emotion and episodic memory formation, it is important to address how emotion corrupts episodic memory formation.

Experimentally, emotion-induced amnesia can be modeled by oddball paradigms where privileged encoding of an emotional oddball into episodic memory (the emotional *von Restorff* effect; von Restorff 1933; Wallace 1965) disrupts encoding of preceding and following neutral stimuli (Tulving 1969; Detterman 1975; Angelini et al. 1994), particularly if the oddball is aversive (Strange et al. 2003; Hurlemann et al. 2005). One hypothesis is that aversive

emotion interferes with episodic encoding by activating an ensemble of neurochemical responses related to acute stress (de Kloet et al. 2005). Support for this hypothesis comes from pharmacological and lesion evidence that the emotional *von Restorff* effect—and the peri-emotional amnesia driven by this effect—both depend on locus coeruleus (LC)-norepinephrine (NE) input to the basolateral amygdala (BLA; Strange et al. 2003; Hurlemann et al. 2006), which modulates hippocampal function during encoding (Strange and Dolan 2004; van Stegeren et al. 2005) and consolidation (Cahill et al. 1994, 1995) of emotional episodic memories. Peri-emotional amnesia is amplified by the NE reuptake inhibitor reboxetine and suppressed by the nonselective β-adrenergic antagonist propranolol, underscoring its susceptibility to experimental changes in central NE tone (Hurlemann et al. 2005).

In addition, acute stress activates the hypothalamic-pituitary-adrenal (HPA) axis. Central concentrations of adrenal cortisol (CORT) rise to peak stress levels within 15–30 min and normalize to prestress levels 60–90 min later (de Kloet et al. 2005). Stress levels of CORT appear to impair hippocampal function during retrieval (de Quervain et al. 1998, 2000; Roozendaal et al. 2004; Kuhlmann et al. 2005; Cai et al. 2006; Soravia et al. 2006) but to enhance amygdala function during encoding (Cahill et al. 2003) and consolidation (Buchanan and Lovallo 2001; Roozendaal 2002; Abercrombie et al. 2003; Okuda et al. 2004) of emotional episodic memories. This profile suggests a synergistic effect of CORT and NE coactivation in stimulating amygdala–hippocampal interactions expressed during emotional episodic memory formation (Nathan et al. 2004; van Stegeren et al. 2007). Moreover, pharmacological manipulations in rodents indicate that emotional arousal-evoked NE input to the BLA is essential for enabling CORT enhancement of memory formation (Quirarte et al. 1997; Roozendaal et al. 2006).

Given this empirical background, we hypothesized that amnesia in response to aversive emotion would exacerbate under conditions of elevated CORT and NE availability. To prove this hypothesis, we devised a randomized double-blind placebo-controlled trial where healthy volunteers were administered a single oral dose of synthetic CORT (hydrocortisone) on top of either placebo or reboxetine pretreatment and tested on the established behavioral indices of peri-emotional amnesia (Hurlemann et al. 2005). The rationale of these pharmacological manipulations was to induce stress levels of CORT and determine its amnesiogenic potential in the presence or absence of elevated NE availability.

Materials and methods

Volunteers Fifty-seven right-handed subjects (28 men and 29 women; age range, 20.6–29.3 years; mean age 25.3±1.8 years) provided written informed consent to this study, which was approved by the local ethics committee and the German Federal Institute for Drugs and Medical Devices. Individuals who met any one of the following exclusion criteria were not enrolled in the study: previous exposure to the oddball memory test used in this study, current or past Diagnostic and Statistical Manual of Mental Disorders IV axis I or axis II disorder, physical illness, and night shift work, as assessed by an experienced clinician. All subjects were nonsmokers and free of any medication apart from contraceptive pills (23 women). Psychological screening before study enrollment included the Verbaler Lern- und Merkfähigkeitstest (Helmstaedter et al. 2001), a German version of the Rey Auditory Verbal Learning Test, to assess immediate verbal learning span, new learning, susceptibility to interference, and recognition memory. The Rey-Osterrieth Complex Figure Test (Rey 1941; Osterrieth 1944) was used to test incidental visual memory and the visuospatial constructional ability. Motor speed and visual attention were examined with the Trail Making Test (Raitan 1958). All volunteers performed within the normal to above-normal range of the psychological screening instruments (data not shown). Mean verbal IQ was 106.88±9.70 (90–122) as determined with the Hamburg-Wechsler Intelligenztest für Erwachsene, a German Version of the Wechsler Adult Intelligence Scale-Revised (Tewes 1991).

Oddball memory test Stimulus setup and experimental task have been detailed elsewhere (Hurlemann et al. 2005). As illustrated in Fig. 1a, the paradigm was restricted to the presentation of emotionally neutral (*P*) and negative (*E*) oddballs. In total, subjects were exposed to 24 study–distraction–test sequences over 45 min. Episodic memory was tested by free recall. Recall profiles were pooled according to the two oddball categories, thus yielding a neutral and a negative condition. As outcome parameter, memory performance was determined condition-wise by calculating the percentage of correct recall (i.e., the output/input ratio) for the following five list positions: oddball, oddball±1, and oddball±2. Additionally, a standard item score (SI) based on the seven non-oddball list positions was calculated for each condition (e.g., SI_p). Contrasting the negative condition with the neutral condition yielded relative recall changes for each list position and thus allowed us to isolate retrograde and anterograde effects of negative emotion on two adjacent standard items (*E*±1 and *E*±2) corresponding to a maximum time window of ±10 sec. To assess potential pharmacological effects on the cognitive appraisal of emotion, all volunteers performed valence and arousal ratings to P and E oddballs on a 9-point scale after the oddball memory test.

Whereas our previous paradigm was designed to demonstrate a causal link between the emotional *von*

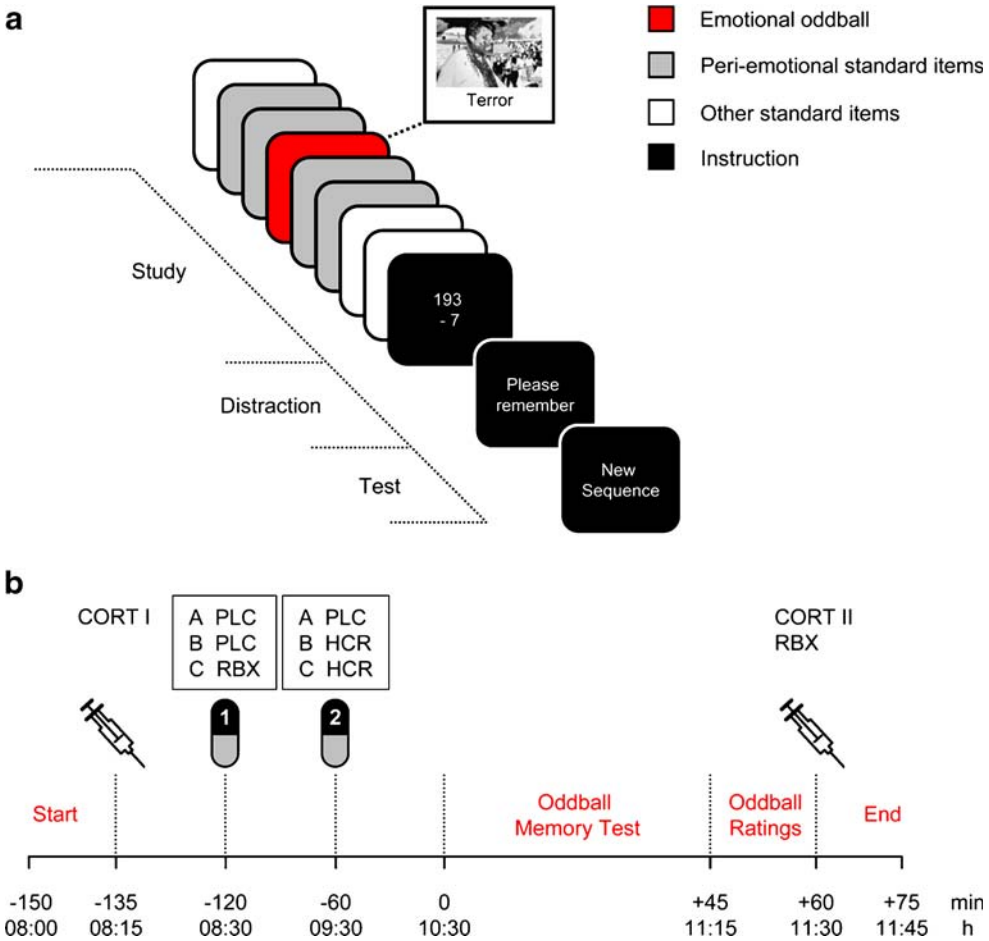

Fig. 1 Experimental design. **a** Oddball memory test. Subjects were exposed to 24 study–distraction–test sequences. During each 40-s study phase, they were presented with a list of eight items, including seven standard items and one oddball inserted on list position 3, 4, 5, or 6. After a 30-s arithmetic distraction task (e.g., count back in sevens), encoding strength for the eight list items was tested by free recall. In each list, the oddball, either emotionally negative or neutral, was temporally flanked by ≥2 surrounding standard items. Results from list recall were pooled according to the two oddball types, yielding a negative and neutral condition. Contrasting the negative condition with the neutral condition allowed to quantify retrograde and anterograde amnesic responses to negative emotion within a time window of ±2 standard items or ±10 s. **b** Experimental timeline. Subjects (n=54) were administered two capsules, the first at 08:30 h (t=−120 min) and the second at 09:30 h (t=−60 min), in a double-blind randomized parallel-group design. Control group A received lactose placebo (*PLC*) twice (capsule 1 and 2), whereas group B received PLC (capsule 1) followed by 30 mg of hydrocortisone (*HCR*; capsule 2). Group C received 4 mg of reboxetine mesilate (*RBX*; capsule 1) followed by 30 mg of HCR (capsule 2). Drug allocation was balanced for age, IQ, and gender, i.e., nine men and nine women were assigned to each treatment group (n=18). The oddball memory test started at t=0 min and finished at t=+45 min. Thereafter, subjects performed paper–pencil emotion ratings. At t=−135 min and t=+60 min, venous blood samples were drawn for prechallenge (baseline) and postchallenge plasma level analyses

Restorff effect and the $E-1$ retrograde amnesic response (Strange et al. 2003), the present paradigm was optimized to measure pharmacologically induced variation in $E-1$ retrograde and $E+1$ anterograde amnesic responses by using a subtractive design (Hurlemann et al. 2005)

Pharmacological dosing Experiments in rodents demonstrate that an inverted U-shaped function characterizes the relation between memory and arousal (Yerkes and Dodson 1908). However, dose–response studies in humans have yet to replicate these effects. In the present study, a 30-mg single oral dose of hydrocortisone (HCR) was administered to elevate CORT activity to levels ranging between moderate (20 mg) and extreme (40 mg) acute stress (Abercrombie et al. 2003). A 4-mg single oral dose of reboxetine mesilate (RBX) was administered, as it has previously been shown effective in amplifying peri-emotional amnesia (Hurlemann et al. 2005).

Experimental procedure Subjects were requested to refrain from alcohol, caffeine, and food intake for 12 h before the experiment. The experiment started at 08:00 h (t=−150 min) and finished at 11:45 h (t=+75 min). Subjects were administered two capsules, the first at 08:30 h (t=−120 min) and the second at 09:30 h (t=−60 min), in a double-blind randomized parallel-group design. Control group A received

lactose placebo (PLC; capsule 1 and 2), whereas group B received PLC (capsule 1) followed by 30 mg of HCR (capsule 2). Group C received 4 mg of RBX (capsule 1) followed by 30 mg of HCR (capsule 2). Three subjects dropped out of the study due to acute RBX-related side effects in the form of dizziness and tachycardia. Drug allocation was balanced for age, IQ, and gender, i.e., nine men and nine women were assigned to each treatment group (n=18).

To ensure that the start of the oddball memory test coincided with peak plasma concentrations of HCR and RBX, we scheduled the intake of capsule 1 and 2 according to the plasma kinetics of both agents (HCR, time to peak plasma concentration, 1 h, elimination half-life, 1.5 h; RBX, 2 h and 13 h, respectively). Blood pressure and pulse frequency were monitored throughout the experiment. The oddball memory test started at t=0 min and finished at t=+45 min. Within the following 15 min, subjects performed a paper–pencil emotion rating. At t=−135 min and t=+60 min, venous blood samples were drawn for analyses of prechallenge (baseline; CORT I) and postchallenge (CORT II, RBX) plasma levels. Figure 1b illustrates the experimental timeline.

Plasma assays The CORT plasma level analyses were performed by an extramural biomedical laboratory (Gaal, 53115 Bonn, Germany) using a fluorescence polarization immunoassay technique. The RBX plasma level analyses were performed in-house by high-performance liquid chromatography (HPLC) and UV detection as previously described (Hurlemann et al. 2005). As expected, RBX plasma levels (133±38 μg/l, 94–231 μg/l) exceeded those reported in our previous study (75±16 μg/l, 44–104 μg/l; Hurlemann et al. 2005). This discrepancy is explained largely by the fact that subjects had fasted for the 12 h before RBX intake in the present study, resulting in increased resorption. Moreover, 2 of 18 subjects assigned to the RBX/HCR group were phenotyped as poor metabolizers (209 and 231 μg/l, respectively).

Pharmacokinetic interactions between coadministered RBX and HCR also contributed to elevated measures of RBX plasma levels in the present study. CYP3A4 is the predominant cytochrome P450 expressed in human liver (Shimada et al. 1994) and responsible for the catabolism of both RBX and CORT. In view of the plasma kinetics of RBX, competitive inhibition of CYP3A4 by CORT could account for 5–10% higher RBX plasma levels in the present study. In addition, as demonstrated by a series of in vitro assays, displacement of RBX from plasma protein binding by CORT dose-dependently increased the recovery of the analyte RBX. Based on the resulting calibration curve (supplementary Fig. 5), we propose the following correction term for RBX plasma levels: $RBX_{corrected}=RBX_{measured}-0.025\ l/\mu g\times CORT$. Application of this correction term yielded RBX plasma levels of 121±37 μg/l (84–216 μg/l), which is consistent with peak plasma levels of 130 μg/l after ingestion of a single 4-mg RBX tablet as reported by the manufacturer (Merz Pharmaceuticals).

As illustrated in Fig. 3a, CORT I plasma levels did not differ between groups (two-sample t tests: p values>0.05). CORT II plasma levels were increased in the PLC/HCR and RBX/HCR groups as a result of HCR treatment but decreased in the PLC/PLC group (one-sample t tests: p values<0.0001), which reflects the physiological circadian flux in endogenous CORT levels (de Kloet et al. 2005). Moreover, CORT II plasma level elevations were greater in the RBX/HCR group than in the PLC/HCR group (two-sample t test: $t_{(34)}=3.902$; $p<0.0001$). This finding is consistent with a stimulation of HPA axis activity and elevated CORT plasma/saliva levels after intake of a single 4-mg oral dose of RBX (Hill et al. 2003).

Statistics Recall parameters (E, $E\pm1$, $E\pm2$, SI_E) of the negative condition were analyzed in relation to the corresponding recall parameters (P, $P\pm1$, $P\pm2$, SI_P) of the neutral condition. Two-factor within-subjects and three-factor mixed analysis of variance (ANOVAs) were followed by two-tailed one-sample and two-sample t tests to determine the source of significance. Greenhouse–Geisser correction for inhomogeneity of variance was applied whenever the sphericity assumption was violated. To account for an inflation of the type I error rate due to multiple post hoc testing, the threshold for significance was Bonferroni-adjusted. Effect sizes were quantified by calculating the values of partial Eta squared $\left(\eta_p^2\right)$ and Cohen's d. Pearson correlation coefficients were computed to investigate a potential relationship between the individual plasma levels of CORT and RBX and the magnitude of emotion-induced amnesia.

Results

In a first analysis, we showed that neither oddball recall nor standard item recall in the neutral condition differed between groups as a function of treatment. The percentages (%) of mean recall (±SD) for oddballs (P) and standard items (SI_P) in the neutral (control) condition were as follows: PLC/PLC group, 95.37 (5.87) and 55.62 (6.03); PLC/HCR group, 96.30 (6.53) and 53.57 (4.64); RBX/HCR group, 95.37 (5.13) and 52.84 (6.93). A series of one-way ANOVAs with group as between-subjects factor confirmed no changes in $P-1$, P, $P+1$, and SI_P recall as a function of treatment (p values>0.05). This result is consistent with reports that immediate retrieval of nonemotional items is not compromised by either HCR (Elzinga et al. 2005) or RBX (Harmer et al. 2003) administration.

In a second analysis, we demonstrated the presence of $E-1$ retrograde and $E+1$ anterograde amnesic effects in the PLC/PLC group. These effects served as baseline for subsequent comparisons with the PLC/HCR group and the RBX/HCR group. A condition (negative, neutral) × position (oddball, oddball ± 1) 2×3 ANOVA restricted to the PLC/PLC group yielded effects of condition ($F_{(1,17)}$=21.640; p<0.0001; $\eta_p^2 = 0.560$), position ($F_{(2,34)}$=832.467; p <0.0001; $\eta_p^2 = 0.980$), and condition × position interaction ($F_{(2,34)}$=17.116; p< 0.0001; $\eta_p^2 = 0.502$) effects. Post hoc one-sample t tests confirmed the presence of $E-1$ retrograde (−14.35%; $t_{(17)}$= −6.200; p<0.0001) and $E+1$ anterograde (−11.57%; $t_{(17)}$= −3.828; p=0.001) amnesic effects engendered by the negative items, replicating our previous findings [Hurlemann et al. 2005; Fig. 2a(i) and b(i)].

Analyzing the influence of PLC/HCR treatment, a group (PLC/PLC, PLC/HCR) × condition × position 2×2×3 ANOVA yielded group ($F_{(1,34)}$=7.076; p=0.012; $\eta_p^2 =$ 0.172), condition ($F_{(1,34)}$=69.627; p<0.0001; $\eta_p^2 = 0.672$), position ($F_{(2,68)}$=1323.883; p<0.0001; $\eta_p^2 = 0.975$), two-way group × position ($F_{(2,68)}$=4.586; p=0.014; $\eta_p^2 = 0.119$), and condition × position ($F_{(2,68)}$=39.710; p<0.0001; $\eta_p^2 = 0.539$) interaction effects. Post hoc two-sample t tests demonstrated a subtle, but significant, enhancement of the $E-1$ retrograde amnesic effect in the PLC/HCR group relative to the PLC/PLC group. The percent (%) recall change relative to the $E-1$ ($P-1$) scores measured in the PLC/PLC group was −9.72 [−24.07; $t_{(34)}$=−3.378; p= 0.002; d=1.16; Fig. 2a(ii) and b(ii)].

Analyzing the influence of additional RBX pretreatment, a group (PLC/HCR, RBX/HCR) × condition × position 2×2×3 ANOVA yielded group ($F_{(1,34)}$=20.336; p<0.0001; $\eta_p^2 =$ 0.375), condition ($F_{(1,34)}$=234.936; p<0.0001; $\eta_p^2 = 0.878$), position ($F_{(2,68)}$=856.855; p<0.0001; $\eta_p^2 = 0.962$), two-way group × condition ($F_{(1,34)}$=22.664; p<0.0001; $\eta_p^2 = 0.400$), group × position ($F_{(2,68)}$=7.656; p=0.001; $\eta_p^2 = 0.184$), condition × position ($F_{(2,68)}$=130.681; p<0.0001; $\eta_p^2 = 0.794$), and three-way group × condition × position ($F_{(2,68)}$=12.997; p<0.0001; $\eta_p^2 = 0.277$) interaction effects. Post hoc two-sample t tests demonstrated robust enhancements of both the $E-1$ retrograde and $E+1$ anterograde amnesic effect in the RHBX/HCR group relative to the PLC/HCR group. An additional 2×2×5 ANOVA followed by post hoc two-sample t tests revealed that the retrograde amnesia now extended to span $E-2$ recall.The percent (%) recall changes relative to the $E-2$ and $E\pm1$ scores of the PLC/HCR group ($P-2$ and $P\pm1$ scores measured in the PLC/PLC group) were as follows: $E-2$, −16.67 (−22.22; $t_{(34)}$=−7.109; p<0.0001; d=2.44); $E-1$, −18.98 (−43.06; $t_{(34)}$=−7.241; p<0.0001; d=2.48); $E+1$, −9.72 (−24.07; $t_{(34)}$=−4.220; p<0.0001; d=1.66). The constraints of our paradigm precluded examination of more enduring retrograde amnesic effects. [Fig. 2a(iii) and b(iii)].

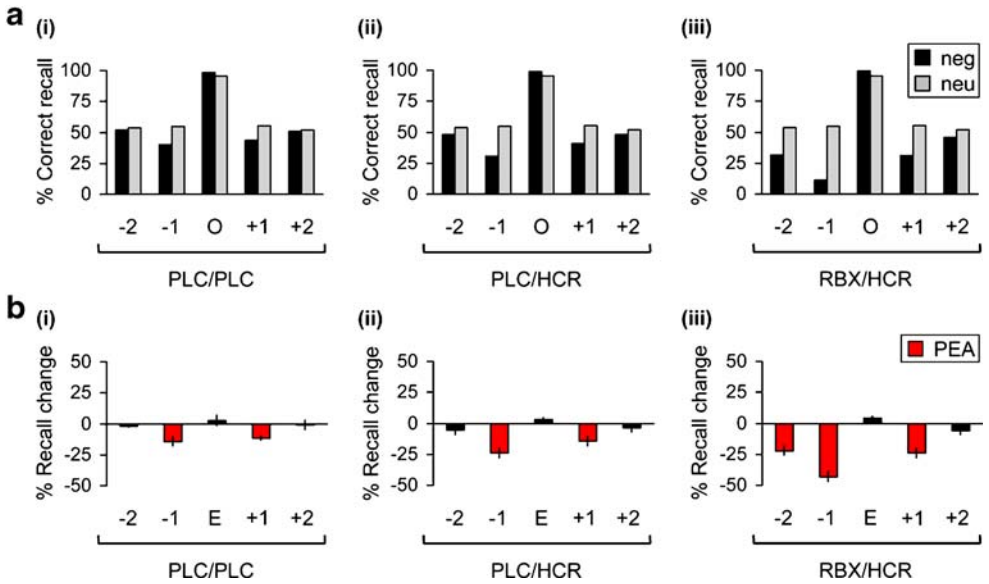

Fig. 2 Results of the oddball memory test. **a** Percentage (%) correct recall as determined in the PLC/PLC *(i)*, PLC/HCR *(ii)*, and RBX/HCR *(iii)* groups (n_{group}=18). Independent of the type of pharmacological treatment, equal (near-ceiling) *von Restorff* effects were present for aversive and neutral oddballs. None of the applied treatments altered task performance in the neutral condition, i.e., treatment effects were restricted to the emotional condition. **b** Percentage (%) of recall change in the emotional condition contrasted with the neutral condition. *(i)* The PLC/PLC group displayed a characteristic pattern of $E-1$ retrograde (−14.35%) and $E+1$ anterograde amnesic responses (−11.57%). *(ii)* PLC/HCR treatment selectively enlarged the $E-1$ retrograde (−24.07%) amnesic effect. *(iii)* Under RBX/HCR dual challenge conditions, increases of both $E-1$ retrograde (−43.06%) and $E+1$ anterograde (−24.07%) amnesic effects were measured. The retrograde amnesic effect extended to $E-2$ items (−22.22%) and thus spanned a period of 10 s. *Error bars* indicate SE. *E* Emotion contact, *HCR* hydrocortisone, *neg* negative condition, *neu* neutral condition, *O* oddball, *PEA* peri-emotional amnesia, *PLC* placebo, *RBX* reboxetine

In a third analysis, we examined a potential variation of $E-1$ retrograde and $E+1$ anterograde amnesic effects as a function of gender or treatment. A series of three-factor mixed ANOVAs with gender as between-subjects factor revealed no influence of gender (p values>0.05). However, individual drug plasma levels were significantly correlated to task performance in the RBX/HCR group but not in the PLC/HCR group. Specifically, the magnitude of $E-1$ retrograde amnesic effects correlated with RBX (r=0.670; p=0.002) and CORT II (r=0.626; p=0.005) plasma levels, whereas the magnitude of $E+1$ anterograde amnesic effects correlated with the RBX (r=0.731; p=0.001) plasma level only [Fig. 3b(i) and b(ii)]. These findings are compatible with a linear dose–response relationship under RBX/HCR dual treatment conditions.

We performed a fourth analysis to assess whether treatment affected the cognitive appraisal of emotion. The oddball arousal and valence judgments (mean±SD) obtained after the oddball memory test were as follows: PLC/PLC group, E oddballs (5.28±0.46, 2.56±0.51), P oddballs (2.39±0.50, 5.11±0.58); PLC/HCR group, E oddballs (5.44±0.51, 2.61±0.48), P oddballs (2.67±0.49, 5.22±0.43); RBX/HCR group, E oddballs (7.06±0.54, 2.33±0.49), P oddballs (2.56±0.51, 5.06±0.54). A series of group × condition ANOVAs followed by post hoc two-sample t tests demonstrated that treatment with PLC/HCR had no influence on either valence or arousal ratings, whereas pretreatment with RBX increased subjects' emotional arousability ($t_{(34)}$=−9.198; p<0.0001; d=3.15), which replicates our previous results (Hurlemann et al. 2005). However, this finding is not compatible with a cognitive bias towards negative emotion, as valence ratings were not affected by RBX/HCR treatment. Additional analyses demonstrated no correlations between the subjective arousal scores and the individual drug plasma levels or the individual E±1 amnesic responses (p values>0.05).

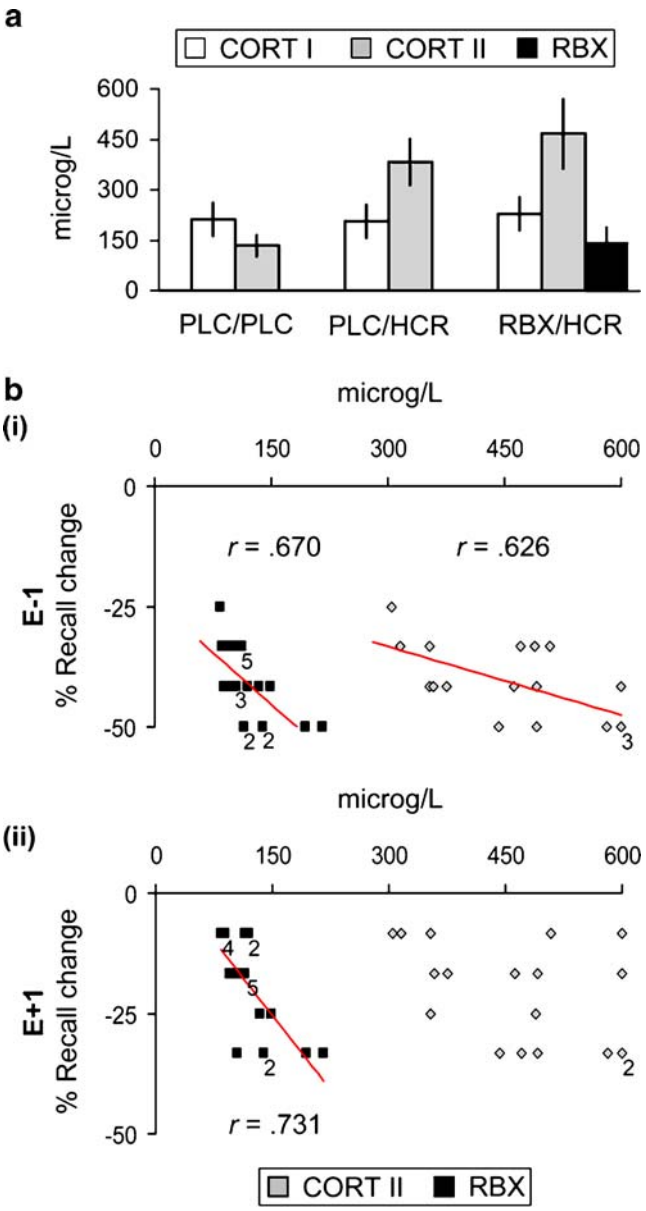

Fig. 3 Dose-dependent variation of peri-emotional amnesia. **a** Results of the plasma level analyses. Prechallenge (baseline) cortisol (CORT I) plasma levels did not differ between groups. Postchallenge cortisol (CORT II) plasma levels were increased in the PLC/HCR and RBX/HCR groups as a result of HCR treatment but decreased in the PLC/PLC group, which reflects the physiological diurnal variation in HPA axis activity. CORT II plasma level elevations were greater in the RBX/HCR group than in the PLC/HCR group, consistent with reports of a stimulation of HPA axis activity and elevated CORT plasma/saliva levels after intake of a single 4-mg oral dose of RBX. *Error bars* indicate SE. **b** Dose–response correlations as detected under RBX/HCR dual treatment conditions. *(i)* The magnitude of emotion-induced $E-1$ retrograde amnesic responses varied as a function of CORT II and RBX plasma levels. *(ii)* In contrast, $E+1$ anterograde amnesic responses correlated with the RBX plasma level only. *CORT I* Prechallenge (baseline) cortisol plasma level, *CORT II* postchallenge cortisol plasma level, *E* emotion contact, *HCR* hydrocortisone, *NE* norepinephrine, *PLC* placebo, *RBX* reboxetine

Discussion

Within the experimental context of peri-emotional amnesia, we determined the E±1 amnesiogenic potential of HCR (30 mg p.o.) in the presence or absence of RBX (4 mg p.o.). As neither pharmacological manipulation affected P±1 recall performance in the neutral (control) condition, RBX and/or HCR treatment do not mimic or replace emotional arousal but interact with it. These interactions likely involve neural circuits engaged in the encoding and/or retrieval of emotional episodic memories. However, evidence from electrophysiological and functional imaging studies points to emotional episodic encoding as the core neural process underlying the emotional *von Restorff* effect (Fabiani and Donchin 1995; Strange and Dolan 2001; Wiswede et al.

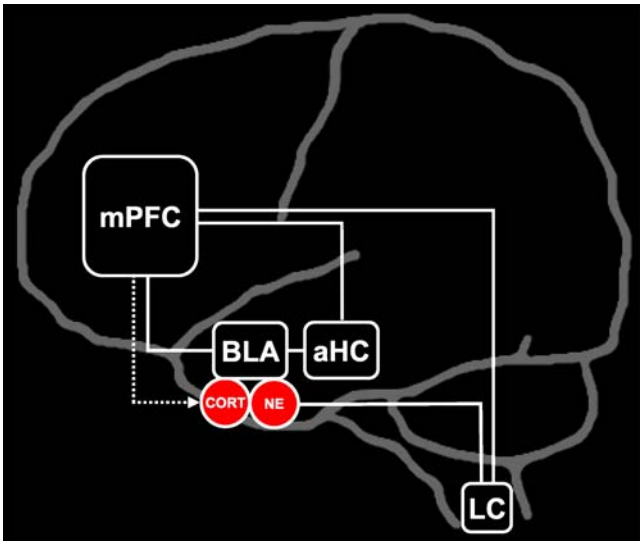

Fig. 4 Neurocircuitry model of peri-emotional amnesia. Whereas anterograde amnesic responses most likely result from a transient failure of attentional reorienting after emotion contact, retrograde amnesic responses appear to reflect a filter mechanism that controls episodic memory access based upon criteria of behavioral significance indexed by emotion. According to this model, basolateral amygdala (*BLA*)—when activated by ascending locus coeruleus (*LC*)-noradrenergic (*NE*) signaling—communicates emotional arousal to anterior hippocampus (*aHC*), thus rendering it susceptible to descending emotional valence input from medial prefrontal cortex (*mPFC*). Circulating cortisol (*CORT*) interacts with LC-NE in amplifying BLA activation. Both CORT and LC-NE signaling are under mPFC top-down inhibitory control. Prioritized encoding of emotional episodic memories in aHC is realized at the cost of ongoing encoding of nonemotional episodic memories, as indicated by robust retrograde amnesic responses. During uncontrollable acute stress, mPFC top-down control is insufficient to inhibit CORT and LC-NE signaling, resulting in exaggerated BLA responses to aHC. As a consequence, there is hyper-encoding of the stressor event coupled with exacerbated peri-emotional amnesia

2006) and the peri-emotional amnesia driven by this effect (Hurlemann 2006).

Our results indicate that the HCR single challenge selectively augmented the $E-1$ retrograde amnesic response. RBX pretreatment further amplified this $E-1$ retrograde amnesic response in both magnitude and temporal extent, such that it impaired $E-2$ recall and spanned a period of 10 sec. Given our previous results (Hurlemann et al. 2005), it seems that CORT and NE both act as agonists on the neurochemical pathways underpinning emotion-induced retrograde amnesia. Under RBX/HCR dual challenge conditions, we observed a linear dose–response relationship, i.e., the higher the individual plasma levels of both drugs, the greater the magnitude and duration of $E-1$ retrograde amnesic responses. These results implicate peripheral HCR and RBX plasma levels as a proxy of central CORT and NE activity. While we cannot rule out that the observed correlations are primarily driven by RBX effects alone, the absence of any dose–response relationship under RBX (Hurlemann et al. 2005) and HCR monotreatment suggests a pharmacodynamic interaction of CORT and NE in enhancing E-1 retrograde amnesic responses under RBX/HCR dual challenge conditions. However, the limited dynamic range of amnesic responses obtained with the present oddball paradigm precludes accurate distinction between additive and over-additive (synergistic) effects of CORT and NE.

The finding that HCR monotreatment did not modulate either the magnitude of $E+1$ anterograde amnesic responses or the subjective report of emotional arousal contrasts sharply with the previously observed effects of RBX monotreatment (Hurlemann et al. 2005). $E+1$ anterograde amnesic responses have been interpreted as resulting from a BLA-dependent capture of attention to enable preferential encoding of emotionally arousing stimuli. In principle, such allocation of attentional resources as a function of emotional arousal might be regarded as adaptive and can provoke a transient refractory period, of at least 5-s duration. This process disrupts attentional reorienting and is supposed to be a prerequisite for encoding a following $E+1$ nonemotional stimulus in anterior hippocampus (Hurlemann et al. 2006).

While $E+1$ anterograde amnesia appears to reflect the cost of a BLA-dependent bias of attention to emotionally arousing stimuli, $E-1$ retrograde amnesia most likely results from an interference of privileged encoding of aversive episodic memories with ongoing (premature) encoding of nonemotional episodic memories in anterior hippocampus (Hurlemann et al. 2005). This view is in line with the prevailing concept that BLA-dependent arousal signals transmitted to anterior hippocampus render it susceptible to valence input from specific prefrontal cortex (PFC) subregions (Dolcos et al. 2004; Kensinger 2004; Kensinger and Corkin 2004). According to this model, negative vs positive valence assessment in medial PFC (mPFC) is critical for a differential expression of $E-1$ retrograde amnesic vs hypermnesic effects, with the magnitude of these effects varying as a function of BLA activation. Specifically, we suggest that positive valence input triggers associative encoding of a rewarding stimulus and nonpredictive stimuli preceding this rewarding stimulus, whereas negative valence input eliminates encoding of preceding stimuli to prioritize encoding of an aversive stimulus (Hurlemann 2006).

At the timing and dosing regimen applied in the present study, $E-1$ retrograde, but not $E+1$ anterograde, amnesic responses were amenable to experimental changes in central CORT tone. This discrepancy suggests that stress levels of CORT enhance emotional episodic encoding by amplifying amygdala–hippocampal interactions rather than increasing attentional bias to emotional stimuli. Substantial evidence in support of this view comes from in vitro studies in rodents that document enhanced excitability of BLA neurons treated with stress doses of CORT (Duvarci and Paré 2007). By

increasing the susceptibility of BLA neurons to LC-NE input, stress levels of CORT could enhance amygdalar input to anterior hippocampus during emotional episodic memory formation. This interpretation would be in keeping with reports of synergistic CORT and NE effects in the BLA of behaving rodents (Quirarte et al. 1997; Roozendaal et al. 2006). Extending this rodent model to the human, interactions of endogenous CORT plasma levels with increasing amygdala activation under placebo, but not under propranolol administration, have been demonstrated (van Stegeren et al. 2007). This finding is consistent with the results of another human study that revealed a positive correlation of endogenous CORT plasma levels with enhanced memory formation only in those individuals who were emotionally aroused (Abercrombie et al. 2003).

The enhancement of $E-1$ retrograde amnesic responses by CORT in our study could be caused by early genomic effects of CORT (e.g., through enhancement of BLA neuronal activity; Duvarci and Paré 2007) and/or instantaneous nongenomic CORT action. The latter has been investigated in rodent experiments that provide evidence of a direct inhibition of the extra-neuronal monoamine transporter (EMT) on glia cells with CORT (Grundemann et al. 1998). The close proximity between synaptic and glia cell processes implicates EMT in rapid inactivation of presynaptically released NE. While this rodent model has not been replicated in humans explicitly, CORT-induced blockade of EMT-mediated NE reuptake would be compatible with an immediate increase in NE synaptic levels in the BLA, thereby enhancing $E-1$ retrograde amnesic responses under RBX/HCR dual challenge conditions. A potentiation of NE neurotransmission by CORT could thus allow rapid allocation of limited episodic encoding resources in anterior hippocampus based upon criteria of emotional significance (Hurlemann 2006). Such filtering would be rendered ineffective if only the slower genomic responses to CORT occurred.

Our finding of exacerbated retrograde amnesic responses under RBX/HCR dual challenge conditions is consistent with a phenotypic expression of retrograde amnesia varying as a function of CORT and NE coactivation during acute stress. A model of the underlying neurocircuitry is suggested in Fig. 4. Extrapolating this model to conditions of uncontrollable acute stress (e.g., during emotional trauma) allows to predict the maladaptive effects that an emotional regulation of episodic encoding can have. Under normal circumstances, both HPA axis (Radley et al. 2006) and LC function (Aston-Jones and Cohen 2005) are under top-down inhibitory control by mPFC (Maier et al. 2006). However, when it comes to uncontrollable acute stress, disinhibited CORT and LC-NE signaling due to insufficient mPFC top-down control may result in exaggerated amygdalar input to anterior hippocampus. As a consequence, hyper-encoding of the aversive episodic memory paralleled by peri-emotional amnesia might occur, further augmenting decontextualization of the aversive episodic memory. Thus, what may clinically manifest as a dissociative (or peri-traumatic) amnesia due to a deficit in episodic retrieval may eventually prove to be a true amnesia driven by a neurobiological mechanism fundamental to privileged encoding of aversive episodic memories.

In conclusion, our results implicate CORT and NE coactivation during acute stress in mediating clinically relevant forms of emotion-induced retrograde amnesia. In addition, our study demonstrates that the adverse cognitive and behavioral sequelae of aversive emotion can be experimentally modeled by pharmacologically interacting with its putative neurochemical substrates.

Acknowledgments The authors wish to thank R.-E. Berg and C. Santoro for excellent assistance and T. Schlaepfer for his valuable comments on a previous version of the manuscript. R. Hurlemann was supported by a German Federal Ministry of Education and Research (BMBF) grant (01GW0671) and a BONFOR fellowship.

Disclosure/Conflict of interest statement The authors have no conflicts of interest to report, nor any involvement to disclose, financial or otherwise, that may bias the conduct, interpretation, or presentation of this work.

References

Abercrombie HC, Kalin NH, Thurow ME, Rosenkranz MA, Davidson RJ (2003) Cortisol variation in humans affects memory for emotionally laden and neutral information. Behav Neurosci 117:505–516

Angelini R, Capozzoli F, Lepore P, Grossi D, Orsini A (1994) "Experimental amnesia" induced by emotional items. Percept Mot Skills 78:19–28

Aston-Jones G, Cohen JD (2005) An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annual Rev Neurosci 28:403–450

Buchanan TW, Lovallo WR (2001) Enhanced memory for emotional material following stress-level cortisol treatment in humans. Psychoneuroendocrinology 26:307–317

Cahill L, Prins B, Weber M, McGaugh JL (1994) Beta-adrenergic activation and memory for emotional events. Nature 371:702–704

Cahill L, Babinsky R, Markowitsch HJ, McGaugh JL (1995) The amygdala and emotional memory. Nature 377:295–296

Cahill L, Gorski L, Le K (2003) Enhanced human memory consolidation with post-learning stress: interaction with the degree of arousal at encoding. Learn Mem 10:270–274

Cai WH, Blundell J, Han J, Greene RW, Powell CM (2006) Postreactivation glucocorticoids impair recall of established fear memory. J Neurosci 26:9560–9566

Christianson SA (1984) The relationship between induced emotional arousal and amnesia. Scand J Psychol 25:147–160

de Kloet ER, Joels M, Holsboer F (2005) Stress and the brain: from adaptation to disease. Nat Rev Neurosci 6:463–475

de Quervain DJ, Roozendaal B, McGaugh JL (1998) Stress and glucocorticoids impair retrieval of long-term spatial memory. Nature 394:787–790

de Quervain DJ, Roozendaal B, Nitsch RM, McGaugh JL, Hock C (2000) Acute cortisone administration impairs retrieval of long-term declarative memory in humans. Nat Neurosci 3:313–314

Detterman DK (1975) The von Restorff effect and induced amnesia: production by manipulation of sound intensity. J Exp Psychol Hum Learn Mem 1:614–628

Dolan RJ (2002) Emotion, cognition, and behavior. Science 298:1191–1194

Dolcos F, LaBar KS, Cabeza R (2004) Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: an event-related fMRI study. Neuroimage 23:64–74

Duvarci S, Paré D (2007) Glucocorticoids enhance the excitability of principal basolateral amygdala neurons. J Neurosci 27:4482–4491

Elzinga BM, Bakker A, Bremner JD (2005) Stress-induced cortisol elevations are associated with impaired delayed, but not immediate recall. Psychiatry Res 134:211–223

Fabiani M, Donchin E (1995) Encoding processes and memory organization: a model of the von Restorff effect. J Exper Psychol Learn Mem Cogn 21:224–240

Grundemann D, Schechinger B, Rappold GA, Schomig E (1998) Molecular identification of the corticosterone-sensitive extra-neuronal catecholamine transporter. Nat Neurosci 1:349–351

Harmer CJ, Hill SA, Taylor MJ, Cowen PJ, Goodwin GM (2003) Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. Am J Psychiatr 160:990–992

Helmstaedter C, Lendt M, Lux S (2001) Verbaler Lern- und Merkfähigkeitstest (VLMT). Hogrefe, Göttingen

Hill SA, Taylor MJ, Harmer CJ, Cowen PJ (2003) Acute reboxetine administration increases plasma and salivary cortisol. J Psychopharmacol 17:273–275

Hurlemann R (2006) Noradrenergic control of emotion-induced amnesia and hypermnesia. Rev Neurosci 17:525–532

Hurlemann R, Hawellek B, Matusch A, Kolsch H, Wollersen H, Madea B, Vogeley K, Maier W, Dolan RJ (2005) Noradrenergic modulation of emotion-induced forgetting and remembering. J Neurosci 25:6343–6349

Hurlemann R, Wagner M, Hawellek B, Reich H, Pieperhoff P, Amunts K, Oros-Peusquens AM, Shah NJ, Maier W, Dolan RJ (2006) Amygdala control of emotion-induced forgetting and remembering: evidence from Urbach-Wiethe disease. Neuropsychologia 45:877–884

Kensinger EA (2004) Remembering emotional experiences: the contribution of valence and arousal. Rev Neurosci 15:241–251

Kensinger EA, Corkin S (2004) Two routes to emotional memory: distinct neural processes for valence and arousal. Proc Natl Acad Sci USA 101:3310–3315

Kuhlmann S, Piel M, Wolf OT (2005) Impaired memory retrieval after psychosocial stress in healthy young men. J Neurosci 25:2977–2982

Loftus EF, Burns TE (1982) Mental shock can produce retrograde amnesia. Mem Cogn 10:318–323

Maier SF, Amat J, Baratta MV, Paul E, Watkins LR (2006) Behavioral control, the medial prefrontal cortex, and resilience. Dialogues Clin Neurosci 8:397–406

Nathan SV, Griffith QK, McReynolds JR, Hahn EL, Roozendaal B (2004) Basolateral amygdala interacts with other brain regions in regulating glucocorticoid effects on different memory functions. Ann N Y Acad Sci 1032:179–182

Okuda S, Roozendaal B, McGaugh JL (2004) Glucocorticoid effects on object recognition memory require training-associated emotional arousal. Proc Natl Acad Sci USA 101:853–858

Osterrieth PA (1944) Le test de copie d'une figure complexe. Arch Psychol 30:206–356

Quirarte GL, Roozendaal B, McGaugh JL (1997) Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala. Proc Natl Acad Sci USA 94:14048–14053

Radley JJ, Arias CM, Sawchenko PE (2006) Regional differentiation of the medial prefrontal cortex in regulating adaptive responses to acute emotional stress. J Neurosci 26:12967–12976

Raitan RM (1958) Validity of the trail making test as an indication of organic brain damage. Percept Mot Skills 8:271–276

Rey A (1941) L'examen psychologique dans les cas d'encéphalopathie traumatique. Arch Psychol 30:286–340

Roozendaal B (2002) Stress and memory: opposing effects of glucocorticoids on memory consolidation and memory retrieval. Neurobiol Learn Mem 78:578–595

Roozendaal B, Hahn EL, Nathan SV, de Quervain DJ, McGaugh JL (2004) Glucocorticoid effects on memory retrieval require concurrent noradrenergic activity in the hippocampus and basolateral amygdala. J Neurosci 24:8161–8169

Roozendaal B, Okuda S, Van der Zee EA, McGaugh JL (2006) Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. Proc Natl Acad Sci USA 103:6741–6746

Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP (1994) Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharmacol Exp Ther 270:414–423

Soravia LM, Heinrichs M, Aerni A, Maroni C, Schelling G, Ehlert U, Roozendaal B, de Quervain DJ (2006) Glucocorticoids reduce phobic fear in humans. Proc Natl Acad Sci USA 103:5585–5590

Strange BA, Dolan RJ (2001) Adaptive anterior hippocampal responses to oddball stimuli. Hippocampus 11:690–698

Strange BA, Dolan RJ (2004) Beta-adrenergic modulation of emotional memory-evoked human amygdala and hippocampal responses. Proc Natl Acad Sci USA 101:11454–11458

Strange BA, Hurlemann R, Dolan RJ (2003) An emotion-induced retrograde amnesia in humans is amygdala- and beta-adrenergic-dependent. Proc Natl Acad Sci USA 100:13626–13631

Tewes U (1991) Hamburg-Wechsler-Intelligenztest für Erwachsene-Revision 1991. Hogrefe, Göttingen

Tulving E (1969) Retrograde amnesia in free recall. Science 164: 88–90

van Stegeren AH, Goekoop R, Everaerd W, Scheltens P, Barkhof F, Kuijer JP, Rombouts SA (2005) Noradrenaline mediates amygdala activation in men and women during encoding of emotional material. Neuroimage 24:898–909

van Stegeren AH, Wolf OT, Everaerd W, Scheltens P, Barkhof F, Rombouts SA (2007) Endogenous cortisol level interacts with noradrenergic activation in the human amygdala. Neurobiol Learn Mem 87:57–66

von Restorff H (1933) Ueber die Wirkungen von Bereichsbildung im Spurenfeld. Psychol Forsch 18:299-342

Wallace WP (1965) Review of the historical empirical and theoretical status of the von Restorff phenomenon. Psychol Bull 63:410–424

Wiswede D, Russeler J, Hasselbach S, Munte TF (2006) Memory recall in arousing situations—an emotional von Restorff effect? BMC Neuroscience 24:7:57

Yerkes RM, Dodson JD (1908) The relation of strength of stimulus to rapidity of habit-formation. J Comp Neurol Psychol 18:459–482