Psychopharmacology (2008) 197:13–23
DOI 10.1007/s00213-007-1002-x

REVIEW

Noradrenergic–glucocorticoid mechanisms in emotion-induced amnesia: from adaptation to disease

René Hurlemann

Received: 14 September 2007 / Accepted: 22 October 2007 / Published online: 23 November 2007

Abstract
Discussions The interaction of emotion and episodic encoding has costs and benefits. These costs and benefits have been characterized in oddball experiments, where a violation of prevailing neutral context through aversive oddballs is associated with subsequent hypermnesia for the aversive oddball and peri-emotional amnesia for the neutral context. Both hypermnesia and peri-emotional amnesia are amygdala-dependent and vary as a function of noradrenergic–glucocorticoid input to the amygdala during emotional episodic encoding. Pharmacological enhancement of this input allows to model the maladaptive effects of emotion on episodic encoding. Extrapolation of these findings to conditions of emotional trauma suggests that disinhibited noradrenergic–glucocorticoid signaling could serve as a crucial etiological contributor to the pathogenesis of peri-traumatic amnesia (PTA) and post-traumatic stress disorder (PTSD).
Conclusions Immediate pharmacological blockade of noradrenergic–glucocorticoid signaling might prove effective in the secondary prevention of PTA and PTSD.

Keywords Emotion · Memory · Encoding · Amnesia · Noradrenaline · Cortisol · Stress · Trauma · PTSD

R. Hurlemann (✉)
Department of Psychiatry, University of Bonn,
Sigmund-Freud-Str. 25,
53105 Bonn, Germany
e-mail: renehurlemann@gmx.de

R. Hurlemann
Brain Imaging Center West, Institute of Medicine,
Research Center Juelich,
52425 Juelich, Germany

Introduction

From an evolutionary perspective, emotion, whether of an appetitive or aversive nature, signals an event that is likely to have immediate and future relevance to survival and reproductive success. Thus, enhanced episodic (autobiographical) memory for emotional events is of adaptive importance (Hamann 2001). However, the interaction of emotion and episodic memory is associated with two contradictory effects in the form of emotion-induced increments and decrements in memory (Christianson 1992). The underlying neurochemical mechanisms and their potential contribution to maladaptive influences of emotion on episodic memory provide the focus of this article. Four topics are explored: (1) emotion–consolidation interactions, (2) emotion-encoding interactions, (3) peri-emotional amnesia, (4) peri-traumatic amnesia and post-traumatic stress disorder.

Emotion–consolidation interactions

Emotional episodic memories constitute the core of human personal history. This has been well documented in naturalistic observations and laboratory studies of flashbulb memories (Brown and Kulik 1977), particularly for shocking events such as the assassination of US President *Lincoln* (Colegrove 1899), the *Loma Prieta* earthquake in 1989 (Neisser et al. 1996), or the terrorist attacks on 9/11 (Talarico and Rubin 2003; Sharot et al. 2007). A striking feature of the neurobiology of emotional episodic memory is a dependence on the amygdala (Dolan 2002). Patients with selective bilateral amygdala calcification lesion caused by congenital lipoid proteinosis of *Urbach* and *Wiethe* (OMIM 247100) typically lack an advantage in recall of emotional items (Adolphs et al. 1997). The crucial role of

the amygdala is also evidenced by elegant studies using positron emission tomography (PET; Cahill et al. 1996) and functional magnetic resonance imaging (fMRI; Canli et al. 2000; Dolcos et al. 2004), where amygdala responses during encoding of emotional items predict later memory for these items (the so-called *difference-due-to-subsequent-memory* or *Dm* effect; Paller and Wagner 2002). Importantly, amygdala responses to both appetitive and aversive items are predictive of later memory (Hamann et al. 1999). The emotional *Dm* effect has been interpreted in support of the *memory modulation hypothesis* (Dolcos et al. 2004; LaBar and Cabeza 2006), which posits a malleability of episodic consolidation in the service of emotion (McGaugh 2000, 2002, 2004). Episodic consolidation refers to a time-dependent stabilization process, whereby fresh memories become increasingly resistant to interference from competing or disrupting amnesiogenic agents, including the encoding of new lists of items (the so-called *retroactive inhibition*; Müller and Pilzecker 1900; see also Lechner et al. 1999), cerebral trauma (McDougall 1901; Burnham 1903), electroconvulsion (Duncan 1949; Gerard 1949), or the administration of protein synthesis inhibitors (Davis and Squire 1984). Human lesion studies have shown that episodic consolidation is hippocampus-dependent (Scoville and Milner 1957; Zola-Morgan et al. 1986; Rempel-Clower et al. 1996; Stefanacci et al. 2000), although, with time, stored memories may become reorganized in a way that makes their retrieval gradually less dependent on the hippocampus (the so-called *system-level consolidation*; Teng and Squire 1999; Eichenbaum 2000; Squire et al. 2004).

Since the seminal findings of Kleinsmith and Kaplan (1963), behavioral studies in humans have accumulated evidence that retention advantages for emotional items relative to neutral items are greater when episodic memory is tested after long (e.g., 1 h to 1 day), relative to short (immediate) delays (LaBar and Cabeza 2006). Findings that *Urbach–Wiethe* patients are impaired in delayed recall and recognition tests of emotional words, pictures, and narratives (Markowitsch et al. 1994; Cahill et al. 1995; Adolphs et al. 1997) support the *memory modulation hypothesis* and suggest that emotion interacts with episodic memory by engaging the amygdala to modulate hippocampal plasticity during episodic consolidation. The involved anatomical and neurochemical substrates have been extensively studied in lesion and pharmacological experiments in rodents that provide evidence for an endogenous modulation of amygdala function by activation of adrenal stress hormones (McGaugh 2000, 2002, 2004): Adrenaline (epinephrine) does not freely pass the blood–brain barrier and is thought to modulate memory consolidation via activation of β-adrenergic receptors located peripherally on vagal afferents projecting to the nucleus of the solitary tract in the brainstem; noradrenergic (norepinephrine, NE) projections from this region influence neuronal activity in other brain regions, including the basolateral amygdala (BLA; McGaugh 2000, 2002, 2004). In contrast, adrenal glucocorticoids such as cortisol (CORT) readily enter the brain and promote gene expression by interacting with glucocorticoid receptors (McGaugh and Roozendaal 2002; de Kloet et al. 2005). In addition, there is increasing evidence for instantaneous nongenomic CORT action (Losel and Wehling 2003; Tasker et al. 2006; see also Grundemann et al. 1998). BLA activation is critical for mediating the memory-enhancing effects of adrenaline and CORT because pharmacological manipulations and lesions of the BLA eliminate these effects (McGaugh 2000, 2002, 2004). In humans, an emotion-induced enhancement of episodic consolidation can be blocked by administration of *propranolol* (40 mg p.o.; Cahill et al. 1994), a nonselective β-adrenoreceptor antagonist used for hypertension and social anxiety disorder. This blockade is centrally mediated (van Stegeren et al. 1998) and equivalent to that observed in *Urbach–Wiethe* patients (Cahill et al. 1995), thus, providing indirect evidence that the amygdala is a critical locus for *propranolol*'s effects.

The neural circuitry underlying the modulatory impact of emotion on episodic consolidation in humans has been characterized in PET (Kilpatrick and Cahill 2003) and fMRI studies (Kensinger and Corkin 2004; Dolcos et al. 2004) that provide evidence of amygdala–hippocampal interactions. Specifically, the evidence suggests a functional coupling of amygdala and hippocampus during emotional episodic encoding (Richardson et al. 2004). However, these demonstrations of amygdala–hippocampal connectivity per se do not confirm that the amygdala's role in emotion–memory interactions stems from its exclusive influence on consolidation rather than encoding of episodic memories. Moreover, no consensus has evolved on the time course of emotional episodic consolidation. Even if the shorter estimates (several hours of slow-wave sleep) are correct (Holland and Lewis 2006; Hu et al. 2006; Wagner et al. 2006), it is evident from numerous observations that episodic memories can be enhanced by emotion even at immediate delays (Hamann 2001). Thus, there must be relevant interactions of emotion and episodic memory that take place during encoding, i.e., before the onset of consolidation.

Emotion-encoding interactions

The observation that humans note and remember the exceptional over the mundane has been the subject of extensive electrophysiological research using oddball paradigms, where a deviant or novel stimulus, i.e., the oddball, violates the prevailing context and elicits a P3 event-related potential (ERP; Goldstein et al. 2002; Ranganath and Rainer 2003). Multiple lines of evidence suggest similari-

ties between conditions evoking the P3 ERP and those evoking phasic responses in the locus coeruleus (LC; Nieuwenhuis et al. 2005)—a collection of neurons (~16,000 per hemisphere) that resides in the dorso-rostral pons and provides the principle source of ascending NE projections in the brain (Berridge and Waterhouse 2003; Aston-Jones and Cohen 2005a, b). Findings of diminished neural responses to oddballs after administration of *propranolol* (40 mg p.o.) confirm that oddball detection critically involves phasic LC–NE signaling (Strange and Dolan 2007). Isolating an oddball against a homogeneous background of standard stimuli facilitates episodic encoding of the oddball (Fabiani and Donchin 1995), particularly if the oddball is emotional (the so-called *von Restorff* or *VR* effect; von Restorff 1933; see also Wallace 1965; Wiswede et al. 2006).

However, psychological evidence indicates that the influence of oddballs on episodic encoding is associated with two phenomenologically contradictory effects in the form of enhanced (the VR effect) and impaired memory. In a pioneering study, Tulving (1969) described a behavioral effect of retrograde amnesia in a single-trial immediate free-recall task of word lists including 15 items, produced by inserting semantic oddballs (names of famous people such as *Columbus*, *Freud*, *Aristotle*). This novelty-induced retrograde amnesia was interpreted as a premature termination of episodic encoding and stimulated a burst of studies of experimental amnesia, which revealed that amnesic responses are largest to emotional oddballs and affect standard items that precede (retrograde amnesia) and/or follow (anterograde amnesia) emotional oddballs (Detterman and Ellis 1972; Loftus and Burns 1982; Christianson 1984; Angelini et al. 1994). The experimental strategy typically used in these studies was to expose subjects to a series of neutral slides (e.g., pittoresc landscapes), in which were randomly inserted slides of aversive content (e.g., mutilated bodies).

The question raises about the neurobiological substrates of the emotional *VR* effect and the peri-emotional memory changes that occur in response to this effect. Because abundant evidence implicates both amygdala- and β-adrenergic-dependent mechanisms in an emotional modulation of episodic memory at long retention intervals (Cahill et al. 1994, 1995; McGaugh 2000, 2002, 2004), similar modulatory mechanisms could hold for emotion-induced memory increments and decrements at short retention intervals. This prediction was tested in a landmark series of behavioral experiments involving an oddball paradigm that allowed to demonstrate a phenotypic variation in retrograde amnesia as a function of the underlying emotional *VR* effect (Strange et al. 2003). It turned out that both phenomena are coupled and depend on a common neurobiological mechanism, in that memory increments and decrements are abolished by *propranolol* (40 mg p.o.), as well as by bilateral amygdala damage in a patient (A.M.) with *Urbach–Wiethe* disease (Strange et al. 2003).

Follow-up experiments showed that—consistent with a widely accepted psychological taxonomy of emotion along the orthogonal dimensions of valence and arousal (Russell 1980; Lang 1995; Lang et al. 1997)—there is a dimensional organization of emotional-cognitive interference underlying peri-emotional memory changes (Hurlemann et al. 2005): Retrograde interference is primarily determined by valence, with negative emotion evoking amnesic responses and positive emotion evoking hypermnesic responses, whereas anterograde interference is primarily determined by arousal, with both negative and positive emotion eliciting amnesic responses. Both retrograde and anterograde interference are absent in two monozygotic female twins (A.M. and B.G.) with *Urbach–Wiethe* disease and a focal disease emphasis on the BLA (Fig. 1; Hurlemann et al. 2007a). Moreover, both retrograde and anterograde interference are eliminated by *propranolol* (40 mg p.o.) and enhanced by *reboxetine* (4 mg p.o.), a NE reuptake inhibitor (NARI) with antidepressant activity (Hurlemann et al. 2005). Together, these findings point to NE as a control neurochemical substrate of emotion-induced amnesia and hypermnesia.

Peri-emotional memory changes induced by emotional oddballs have been interpreted as resulting from dissociable forms of emotional–cognitive interference: Anterograde amnesic responses might be caused by an emotional arousal-evoked fixation of attention, whereas retrograde amnesic vs hypermnesic responses might reflect a valence-dependent filter mechanism that operates during emotional episodic encoding and controls access to consolidation upon criteria of behavioral significance indexed by emotion (Hurlemann 2006). Such filter mechanism may originate in amygdala–hippocampal interactions that are modulated by ascending LC–NE input and descending inputs from prefrontal cortex (PFC; Hurlemann 2006). This hypothesis is in line with the prevailing concept that BLA-dependent arousal signals transmitted to anterior hippocampus render it susceptible to valence input from 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 retrograde amnesic vs hypermnesic effects, with the magnitude of these effects varying as a function of BLA activation. Specifically, it has been suggested that positive valence input triggers associative encoding of an appetitive item and nonpredictive items preceding this appetitive item, whereas negative valence input eliminates encoding of preceding items to prioritize encoding of an aversive item (Hurlemann 2006).

This circuitry might be dysfunctional in pathological conditions such as borderline personality disorder (BPD), which has been conceptualized as a hyperarousal–dyscontrol

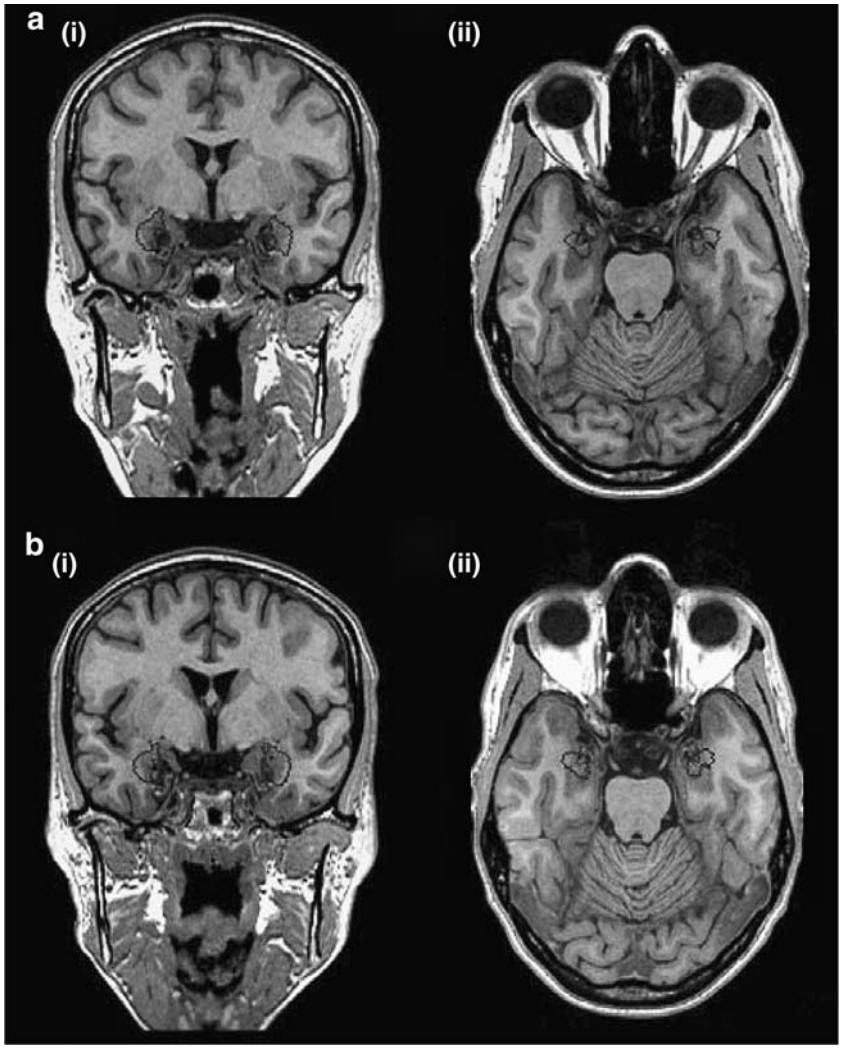

Fig. 1 Superposition of BLA stereotaxic cytoarchitectonic probabilistic maps on the calcified amygdalae of two female patients A.M. and B.G. with congenital lipoid proteinosis of Urbach and Wiethe (OMIM 247100). Equiprobability contures in *black* indicate a 50% likelihood of a given voxel to be localized within the BLA. **a** Medial temporal lobe of patient A.M. in coronal (*i*) and horizontal view (*ii*). **b** Medial temporal lobe of patient B.G. in coronal (*i*) and horizontal view (*ii*). *BLA* Basolateral amygdala constituted by the lateral, basolateral, and basomedial nuclei (reproduced with permission from Hurlemann et al. 2007a)

syndrome (Lieb et al. 2004). Indeed, current theories emphasize the disruptive effects of dysregulated negative emotion on cognition in patients with BPD (Fertuck et al. 2005). To examine emotional–cognitive interference in BPD, Hurlemann et al. (2007b) tested a homogeneous sample of 16 unmedicated female patients with *Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)*-confirmed diagnosis of BPD and florid self-harm on the behavioral indices of emotion-induced amnesia and hypermnesia established in a comparison sample. BPD patients displayed enhanced peri-emotional amnesia in response to aversive oddballs, whereas appetitive oddballs elicited no peri-emotional memory changes. This profile implicates amygdala hyperresponsiveness to negative emotion, perhaps driven by a hypersensitive LC–NE system, as a crucial etiological contributor to cognitive dysfunction in BPD. The aforementioned findings suggest that an antidepressant therapy with *reboxetine* should be carefully considered in BPD patients, as further potentiation of NE neurotransmission might initially worsen cognitive dysfunction in these patients (Hurlemann et al. 2007b; see also Anghelescu et al. 2005).

Peri-emotional amnesia

Oddball experiments demonstrate that the influence of emotion on episodic encoding is associated with subsequent hypermnesia for aversive information and peri-emotional amnesia for the surrounding neutral context (Strange et al. 2003; Hurlemann et al. 2005, 2007a). Whereas retrograde amnesia can be interpreted as reflecting competition of emotional and neutral information for consolidation resources, anterograde amnesia may result from an emotional capture of attentional resources. The latter has been confirmed in fMRI experiments, where emotional distracters interfere with attentional reorienting and compromise task performance (Mitchell et al. 2007; see also Yamasaki et al. 2002; Dolcos and McCarthy 2006). Perhaps related to this phenomenon is the allocation of attention to central gist information at the expense of peripheral details

of complex emotional stimuli that require serial information processing (e.g., social encounters), as exemplified by 'weapon focus' in eyewitness testimony research (Loftus et al. 1987).

Easterbrook (1959) originally described this type of emotional–cognitive interference in his cue-utilization theory by proposing that emotion would narrow the focus of attention, such that information central to the source of emotion would be encoded, whereas peripheral details would not. Consistent with this theory, *Urbach–Wiethe* patients do not focus on central gist information when memory is tested for emotional narratives (Adolphs et al. 2005). This becomes obvious when these patients generate intact skin conductance responses and normal arousal/valence ratings, implying specific deficits in emotional episodic memory rather than global impairments in the cognitive assessment of emotion. However, critical characteristics of emotional episodic memory are preserved after bilateral amygdala damage. Amygdalectomized patients preferentially remember information that is emotionally valent but low in arousal, as well as neutral information encoded in emotional contexts (Phelps 2006). These patients appear to access other cognitive resources that enhance emotional episodic memory, most likely by recruiting mPFC–hippocampal routes that code emotional valence (Kensinger 2004; Kensinger and Corkin 2004). Together, these findings suggest a critical role of mPFC in emotional episodic encoding and extend current rodent-based models, which emphasize the role of the amygdala.

Pharmacological manipulations in humans have implicated both β-adrenergic- and CORT-dependent mechanisms in emotion–memory interactions, although with less anatomical specificity than in rodents. The memory advantage of emotional information relative to neutral information is abolished by drugs acting as functional NE antagonists (e.g., *propranolol*; Cahill et al. 1994; van Stegeren et al. 1998) and amplified by drugs acting as functional NE agonists (e.g., the α_2-adrenoreceptor antagonist *yohimbine*; O'Carroll et al. 1999). Although these results have been interpreted in support of the *memory modulation hypothesis*, it should be noted that in the majority of these experiments, drug manipulations were performed before encoding; when β-adrenergic blockade was established after encoding, no effect of *propranolol* on emotional episodic memory was observed (van Stegeren et al. 2002). These findings suggest that β-adrenergic-dependent interactions of emotion and episodic memory emerge during encoding, i.e., before the onset of consolidation. Observations that the emotional *VR* effect—and the peri-emotional amnesia induced by this effect—are absent in two *Urbach–Wiethe* patients with a focal disease emphasis on the BLA (Fig. 1), as well as in controls administered with *propranolol* (40 mg p.o.; Strange et al. 2003; Hurlemann et al. 2005), confirm pharmacological fMRI findings that converge on the BLA as a likely mediator of β-adrenergic influences on emotional episodic encoding (van Stegeren et al. 2005, 2007).

A crucial question is the contribution of CORT to the phenotypic expression of peri-emotional amnesia. Central concentrations of CORT rise to peak stress levels within 15–30 min and normalize to pre-stress levels 60–90 min later (de Kloet et al. 2005). CORT interferes with both emotional and nonemotional episodic memory, and variation in CORT influences on episodic memory is attributable to several factors, including gender, the type of stress (acute vs chronic), dose (typically as an inverted U-shaped function) and time of day relative to the circadian flux in endogenous CORT levels (McGaugh and Roozendaal 2002; Wolf et al. 2004; Het et al. 2005). Exogenous administration of CORT and/or stress-induced endogenous CORT release during episodic encoding enhance memory, but similar experimental manipulations during episodic retrieval impair memory (de Quervain et al. 2000; Wolf et al. 2004; Het et al. 2005; Kuhlmann et al. 2005a, b). The observation that a CORT-induced decrement in episodic retrieval is abolished by coadministration of *propranolol* (40 mg p.o.; de Quervain et al. 2007a) is consistent with findings in rodents. These findings suggest that the detrimental effects of CORT on hippocampal function during memory retrieval require concurrent NE-dependent activation of the BLA (Roozendaal et al. 2003, 2004; see also de Quervain et al. 1998).

However, reports of a positive correlation of endogenous CORT plasma levels with enhanced episodic memory formation only in those individuals who are emotionally aroused (Abercrombie et al. 2003) suggest that CORT and LC–NE coactivation could interact by potentiating amygdala–hippocampal responses during emotional episodic encoding. 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). In addition, studies in behaving rodents have demonstrated that NE-dependent activation of the BLA induced by emotional arousal is essential in enabling memory enhancement by CORT (Quirarte et al. 1997; Roozendaal et al. 2006). Extending this rodent-based model to the human, interactions of endogenous CORT plasma levels with increasing amygdala activation under *placebo* but not under *propranolol* administration (80 mg p.o.) have been shown to enhance emotional episodic encoding (van Stegeren et al. 2007). Consistent with these findings, CORT significantly contributes to peri-emotional amnesia only when combined with β-adrenergic activation. This role of CORT was identified in an oddball experiment, whereby the amnesiogenic potential of CORT was tested in the presence or absence of elevated NE levels (Fig. 2; Hurlemann et al. 2007c; see also Hurlemann et al.

2005). Under *hydrocortisone* (30 mg p.o.)–*reboxetine* (4 mg p.o.) dual challenge conditions, a linear dose–response relationship in the magnitude of emotion-induced retrograde amnesia was observed. This observation suggests that the phenotypic expression of amnesic responses varies as a function of NE–CORT interactions during emotional episodic encoding (Hurlemann et al. 2007c). Moreover, this study shows that the maladaptive consequences of emotional–cognitive interference can be modeled by a pharmacological manipulation of its putative neurochemical substrates.

Peri-traumatic amnesia and post-traumatic stress disorder

Interactions of emotion and episodic encoding may be of particular importance when it comes to adverse life events, where an individual is exposed to extreme stressors (e.g., emotional trauma).

Several lines of evidence suggest that the degree of mPFC top-down control is the variable that ultimately determines the magnitude of the autonomic stress response (Arnsten and Goldman-Rakic 1984; Jodo et al. 1998; Berridge and Waterhouse 2003; Aston-Jones and Cohen 2005a, b; Kim and Diamond 2002; Robbins 2005). Seminal findings in rodents indicate that, when a stressor is controllable, activation of autonomic brainstem nuclei is inhibited by descending connections from mPFC, and the behavioral sequelae of uncontrollable stress are blocked; experimental inactivation of mPFC eliminates stressor controllability and exerts deleterious effects on behavior (Amat et al. 2005). Given this empirical background, it is tempting to speculate about the potential contribution of disinhibited bottom-up autonomic responses to the pathogenesis of post-traumatic stress disorder (PTSD).

According to the *DSM-IV*, PTSD emerges after exposure to an inescapable stressor that elicits catastrophic fear, horror, or helplessness and involves bodily injury or threat of death to one's self or another person. Community-based studies in the USA estimate a lifetime prevalence of trauma exposure at 50% but only 5% of men and 10% of women will subsequently develop PTSD (Kessler et al. 1995). The conceptualization of PTSD as an acquired anxiety disorder derives by analogy from results of *Pavlovian* fear conditioning experiments in rodents and, thus, emphasizes the role of implicit emotional memory dysfunction (Rauch et al. 2006). Evidence in humans, however, suggests that emotional memory-related PTSD symptoms such as intrusive reexperiencing of the traumatic episode and avoidance of reminders of this episode transcend the traditional explicit–implicit distinction, thus, portraying PTSD as the quintessential emotional memory disorder (Yovell et al. 2003). In fact, the *Pavlovian* model of PTSD fails to account for persistent disturbances of episodic memory that are characteristic of PTSD in clinical experience, i.e., hypermnesia for the core traumatic event and peri-traumatic amnesia (PTA) for events temporally proximate to the traumatic event (Layton and Krikorian 2002).

As detailed in previous sections of this article, evidence from oddball experiments converges on a neurobiological mechanism, in which hypermnesia for the emotional oddball and peri-emotional amnesia for surrounding items

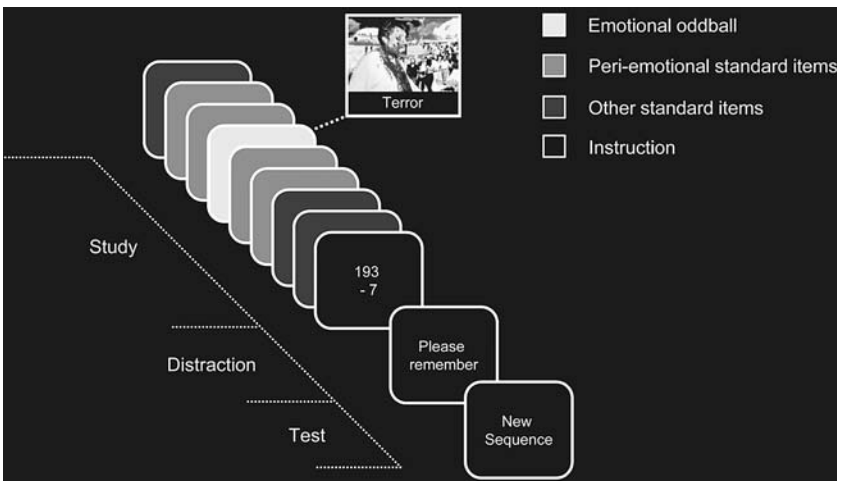

Fig. 2 Oddball memory test as devised by Hurlemann et al. (2007c). In this experiment, subjects were exposed to 24 study–distraction–test sequences. During each 40-s study phase, they were presented with a list of eight stimuli, including seven standard stimuli and one oddball inserted on list position 3, 4, 5, or 6. As exemplified, standard stimuli and oddballs were composed of a picture item and a verbal descriptor. After a 30-s arithmetic distraction task (e.g., count back in sevens), encoding strength for the eight list stimuli was tested by free recall. In each list, the oddball, either emotionally negative or neutral, was temporally flanked by at least two surrounding standard stimuli. Results from the 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 (reproduced from Hurlemann et al. 2007c)

are coupled (Strange et al. 2003; Hurlemann et al. 2005, 2007a, c). Specifically, the evidence suggests that the magnitude of peri-emotional amnesia varies as a function of CORT and NE coactivation during emotional episodic encoding (Hurlemann et al. 2007c). Given the phenomenological parallels in the effects of emotional oddballs and emotional trauma on episodic memory formation, a neurochemical model is proposed that posits a deleterious synergism of disinhibited NE and CORT signaling as a crucial etiological contributor to the pathogenesis of PTA and PTSD: Normally, both LC (Arnsten and Goldman-Rakic 1984; Jodo et al. 1998; Aston-Jones and Cohen 2005a, b) and hypothalamic–pituitary–adrenal (HPA) axis (Radley et al. 2006) activity are under top-down inhibitory control orchestrated by mPFC. Disinhibition of bottom-up CORT and LC–NE responses might result from relatively insufficient top-down inhibitory control under conditions of emotional trauma and be responsible for exaggerated amygdalar input to anterior hippocampus. As a consequence, hyperencoding (and hyperconsolidation) of the core traumatic event paralleled by PTA might occur, further augmenting decontextualization and dissociation of the traumatic memory from ordinary episodic memory. Cue-related reactivation of the traumatic memory might establish a self-perpetuating vicious cycle of episodic reconsolidation and low-threshold hyperretrieval because of cue generalization, which in turn, could cause intrusive reexperiencing in form of daytime recollections, traumatic nightmares, and flashbacks (Fig. 3).

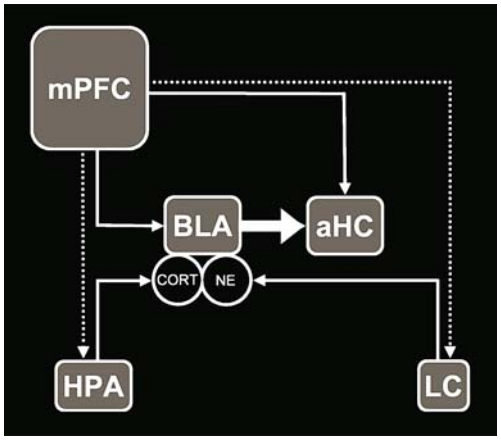

Fig. 3 Neurocircuitry model of peri-emotional amnesia. Whereas anterograde amnesic responses most likely result from a transient failure of attentional reorienting after emotion contact, retrograde amnesic responses appear to reflect a filter mechanism that controls episodic memory access based upon the 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 LC and HPA axis activity are under mPFC top-down inhibitory control. Prioritized encoding of emotional episodic memories in aHC is realized at the cost of ongoing encoding of non-emotional episodic memories, as indicated by robust retrograde amnesic responses. During uncontrollable stress (e.g., emotional trauma), mPFC top-down control is insufficent to inhibit CORT and LC–NE signaling (indicated by *dashed lines* in the diagram), resulting in exaggerated BLA responses to aHC. As a consequence, there is hyperencoding of the stressor event coupled with exacerbated peri-emotional amnesia (reproduced from Hurlemann et al. 2007c)

This neurochemical model allows PTA and dissociation to be framed as maladaptive consequences of emotion-encoding interactions mediated by disinhibited autonomic responses rather than avoidance of conditioned fear. Substantial support for the proposed model comes from findings that abnormally high initial adrenaline and CORT urinary levels predict subsequent PTSD in child trauma victims (Delahanty et al. 2005) as do abnormally low γ-aminobutyric acid plasma levels in road traffic accident victims (Vaiva et al. 2004, 2006), thus, implicating an imbalance between endogenous agonists and antagonists of emotional episodic encoding at the outset of the disorder. Moreover, PTA has been identified as a cardinal predictive risk factor for subsequent PTSD (Ozer et al. 2003; Briere et al. 2005; Gil et al. 2005). Furthermore, a genetically anchored alteration in NE neurotransmission is related to increased emotional episodic memory in healthy humans and predisposes to stronger traumatic memories in PTSD patients (de Quervain et al. 2007b).

The question raises about the therapeutic implications of the proposed neurochemical model. While exposure therapy and anxiety management training have been established as first-line treatments of PTA and PTSD (Keane et al. 2006), there has been little psychopharmacological research in this area. This is surprising given that the time of the insult that created PTA and PTSD is known—it is when the initiating trauma occurred (Ressler and Mayberg 2007). In PTSD patients, evidence points to LC–NE overdrive as a neurochemical substrate—and thereby, obvious therapeutic target—of hyperarousal (Southwick et al. 1993, 1997; Pitman et al. 2002; Vaiva et al. 2003; Debiec and LeDoux 2006). LC–NE overdrive appears to be paralleled by pathological reductions of baseline CORT plasma levels (Yehuda 2002). In medical–surgical patients undergoing ICU treatment, prolonged bolus/infusion administration of CORT (at doses of >300 mg/day) has been reported to reduce the risk of subsequent PTSD (Schelling et al. 2006). Moreover, low-dose CORT treatment (10 mg/day) has been used in clinical trials to attenuate core symptoms of established PTSD (Aerni et al. 2004; de Quervain 2006) and phobia (Soravia et al. 2006). These therapeutic effects of CORT have been suggested to involve inhibition of episodic hyperretrieval of traumatic memories (de Quervain 2006), as well as facilitation of extinction of conditioned fear (Cai et al. 2006).

However, observations of enhanced emotional episodic encoding under conditions of CORT and NE coactivation (Hurlemann et al. 2007c; van Stegeren et al. 2007; see also Quirarte et al. 1997; Abercrombie et al. 2003; Roozendaal et al. 2006) suggest that low-dose CORT treatment could be contraproductive during initial trauma encoding and consolidation, where further exogenous elevation of endogenous CORT signaling might augment rather than disrupt overlearning of the traumatic episode and, thus, increase vulnerability to PTA and PTSD. In contrast, immediate β-adrenergic blockade of initial trauma encoding and consolidation by *propranolol* seems effective in the secondary prevention of PTA and PTSD. In one clinical trial, individuals who presented to an emergency room immediately after motor vehicle accidents randomly received either *propranolol* (40 mg p.o.) or *placebo* four times daily for 10 days, followed by a taper period. The first dose of *propranolol* was administered, on average, 4 h after the traumatic event. One month after the trauma, PTSD measures trended lower in the 11 completers treated with *propranolol* compared to the 20 completers who received *placebo* (Pitman et al. 2002). A second open-label study examined 19 completers, 11 of whom took *propranolol* (40 mg p.o.), three times daily, beginning 2–20 h after the trauma for 7 days followed by a taper period. At 2 months after trauma, levels of PTSD symptoms were lower in individuals treated with *propranolol* (Vaiva et al. 2003). However, the ethics of these pharmacological interventions, as well as their precise empirical and theoretical basis, require further investigation in larger randomized clinical trials.

Acknowledgment The author gratefully acknowledges fruitful discussions with and excellent contributions by Raymond J. Dolan (London) and Wolfgang Maier (Bonn). This work was supported by a German Research Foundation (DFG) grant (HU1302/2-1), a German Federal Ministry of Education and Research (BMBF) grant (01GW0671), and a BONFOR fellowship.

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

Adolphs R, Cahill L, Schul R, Babinsky R (1997) Impaired declarative memory for emotional material following bilateral amygdala damage in humans. Learn Mem 4:291–300

Adolphs R, Tranel D, Buchanan TW (2005) Amygdala damage impairs emotional memory for gist but not details of complex stimuli. Nat Neurosci 8:512–518

Aerni A, Traber R, Hock C, Roozendaal B, Schelling G, Papassotiropoulos A, Nitsch RM, Schnyder U, de Quervain DJ (2004) Low-dose cortisol for symptoms of posttraumatic stress disorder. Am J Psychiatry 161:1488–1490

Amat J, Baratta MV, Paul E, Bland ST, Watkins LR, Maier SF (2005) Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. Nat Neurosci 8:365–371

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

Anghelescu I, Janen B, Schindler F, Lammers CH (2005) Worsening of borderline symptoms under reboxetine treatment. J Neuropsychiatry Clin Neurosci 17:9–560

Arnsten AF, Goldman-Rakic PS (1984) Selective prefrontal cortical projections to the region of the locus coeruleus and raphe nuclei in the rhesus monkey. Brain Res 306:9–18

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

Aston-Jones G, Cohen JD (2005b) Adaptive gain and the role of the locus coeruleus–norepinephrine system in optimal performance. J Comp Neurol 493:99–110

Berridge CW, Waterhouse BD (2003) The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Brain Res Rev 42:33–84

Briere J, Scott C, Weathers F (2005) Peritraumatic and persistent dissociation in the presumed etiology of PTSD. Am J Psychiatry 162:2295–2301

Brown R, Kulik J (1977) Flashbulb memories. Cognition 5:73–93

Burnham WH (1903) Retroactive amnesia: illustrative cases and a tentative explanation. Am J Psychol 14:382

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, Haier RJ, Fallon J, Alkire MT, Tang C, Keator D, Wu J, McGaugh JL (1996) Amygdala activity at encoding correlated with long-term, free recall of emotional information. Proc Natl Acad Sci U S A 93:8016–8021

Canli T, Zhao Z, Brewer J, Gabrieli JD, Cahill L (2000) Event-related activation in the human amygdala associates with later memory for individual emotional experience. J Neurosci 20:RC99

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

Christianson S-Å (1992) In: Christianson S-Å (ed) The handbook of emotion and memory: research and theory. Erlbaum, Mahwah, NJ, pp 307–340

Colegrove FW (1899) Individual memories. Am Psychol 10:228–255

Davis HP, Squire LR (1984) Protein synthesis and memory: a review. Psychol Bull 96:518–559

Debiec J, LeDoux JE (2006) Noradrenergic signaling in the amygdala contributes to the reconsolidation of fear memory: treatment implications for PTSD. Ann N Y Acad Sci 1071:521–524

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

Delahanty DL, Nugent NR, Christopher NC, Walsh M (2005) Initial urinary epinephrine and cortisol levels predict acute PTSD symptoms in child trauma victims. Psychoneuroendocrinology 30:121–128

de Quervain DJ (2006) Glucocorticoid-induced inhibition of memory retrieval: implications for posttraumatic stress disorder. Ann N Y Acad Sci 1071:216–220

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

de Quervain DJ, Aerni A, Roozendaal B (2007a) Preventive effect of beta-adrenoceptor blockade on glucocorticoid-induced memory retrieval deficits. Am J Psychiatry 164:967–969

de Quervain DJ, Kolassa IT, Ertl V, Onyut PL, Neuner F, Elbert T, Papassotiropoulos A (2007b) A deletion variant of the alpha2b-adrenoceptor is related to emotional memory in Europeans and Africans. Nat Neurosci 10(9):1137–1139

Detterman DK, Ellis NR (1972) Determinants of induced amnesia in short-term memory. J Exp Psychol 95:308–316

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

Dolcos F, McCarthy G (2006) Brain systems mediating cognitive interference by emotional distraction. J Neurosci 26:2072–2079

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

Duncan CP (1949) The retroactive effect of electroshock on learning. J Comp Physiol Psychol 42:32

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

Easterbrook JA (1959) The effect of emotion on cue utilization and the organization of behavior. Psychol Rev 66:183–201

Eichenbaum H (2000) A cortical–hippocampal system for declarative memory. Nat Rev Neurosci 1:41–50

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

Fertuck EA, Lenzenweger MF, Clarkin JF, Hoermann S, Stanley B (2005) Executive neurocognition, memory systems, and borderline personality disorder. Clin Psychol Rev 3:346–375

Gerard RW (1949) Physiology and psychiatry. Am J Psychiatry 106:161

Gil S, Caspi Y, Ben-Ari IZ, Koren D, Klein E (2005) Does memory of a traumatic event increase the risk for posttraumatic stress disorder in patients with traumatic brain injury? A prospective study. Am J Psychiatry 162:963–969

Goldstein A, Spencer KM, Donchin E (2002) The influence of stimulus deviance and novelty on the P300 and novelty P3. Psychophysiology 39:781–790

Grundemann D, Schechinger B, Rappold GA, Schomig E (1998) Molecular identification of the corticosterone-sensitive extra-neuronal catecholamine transporter. Nat Neurosci 1:349–343

Hamann S (2001) Cognitive and neural mechanisms of emotional memory. Trends Cogn Sci 5:394–400

Hamann SB, Ely TD, Grafton ST, Kilts CD (1999) Amygdala activity related to enhanced memory for pleasant and aversive stimuli. Nat Neurosci 2:289–293

Het S, Ramlow G, Wolf OT (2005) A meta-analytic review of the effects of acute cortisol administration on human memory. Psychoneuroendocrinology 30:771–784

Holland P, Lewis PA (2006) Emotional memory: selective enhancement by sleep. Curr Biol 17:R179–R181

Hu P, Stylos-Allan M, Walker MP (2006) Sleep facilitates consolidation of emotionally arousing declarative memory. Psychol Sci 10:891–898

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 Neuroci 25:6343–6349

Hurlemann R, Wagner M, Hawellek B, Reich H, Pieperhoff P, Amunts K, Oros-Peusquens AM, Shah NJ, Maier W, Dolan RJ (2007a) Amygdala control of emotion-induced forgetting and remembering: evidence from Urbach–Wiethe disease. Neuropsychologia 45:877–884

Hurlemann R, Hawellek B, Maier W, Dolan RJ (2007b) Enhanced emotion-induced amnesia in borderline personality disorder. Psychol Med 37:971–982

Hurlemann R, Matusch A, Klingmuller D, Hawellek B, Kolsch H, Maier W, Dolan RJ Emotion-induced retrograde amnesia varies as a function of noradrenergic–glucocorticoid activity. Psychopharmacology (2007c):194:261–269

Jodo E, Chiang C, Aston-Jones G (1998) Potent excitatory influence of prefrontal cortex activity on noradrenergic locus coeruleus neurons. Neuroscience 83:63–79

Keane TM, Marshall AD, Taft CT (2006) Posttraumatic stress disorder: etiology, epidemiology, and treatment outcome. Annu Rev Clin Psychol 2:161–197

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 U S A 101:3310–3315

Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB (1995) Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry 52:1048–1060

Kilpatrick L, Cahill L (2003) Amygdala modulation of parahippocampal and frontal regions during emotionally influenced memory storage. Neuroimage 20:2091–2099

Kim JJ, Diamond DM (2002) The stressed hippocampus, synaptic plasticity and lost memories. Nat Rev Neurosci 3:453–462

Kleinsmith LJ, Kaplan S (1963) Paired-associate learning as a function of arousal and interpolated interval. J Exp Psychol 65:190–193

Kuhlmann S, Kirschbaum C, Wolf OT (2005a) Effects of oral cortisol treatment in healthy young women on memory retrieval of negative and neutral words. Neurobiol Learn Mem 83:158–162

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

LaBar KS, Cabeza R (2006) Cognitive neuroscience of emotional memory. Nat Rev Neurosci 7:54–64

Lang PJ (1995) The emotion probe. Studies of motivation and attention. Am Psychol 50:372–385

Lang PJ, Bradley MM, Cuthberg BN (1997) International affective picture system. NIMH Center for the Study of Emotion and Attention, Gainesville, FL, USA

Layton B, Krikorian R (2002) Memory mechanisms in posttraumatic stress disorder. J Neuropsychiatry Clin Neurosci 14:254–261

Lechner HA, Squire LR, Byrne JH (1999) 100 years of consolidation—remembering Müller and Pilzecker. Learn Mem 6:77–87

Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M (2004) Borderline personality disorder. Lancet 364:453–461

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

Loftus EF, Loftus G, Messo J (1987) Some facts about "weapon focus.". Law Hum Behav 11:55–62

Losel R, Wehling M (2003) Nongenomic actions of steroid hormones. Nat Rev Mol Cell Biol 4:46–56

Markowitsch HJ, Calabrese P, Wurker M, Durwen HF, Kessler J, Babinsky R, Brechtelsbauer D, Heuser L, Gehlen W (1994) The amygdala's contribution to memory—a study on two patients with Urbach–Wiethe disease. Neuroreport 5:1349–1352

McDougall W (1901) Experimentelle Beitraege zur Lehre vom Gedaechtnis: von G.E. Mueller und A. Pilzecker. Mind 10:388–394

McGaugh JL (2000) Memory—a century of consolidation. Science 287:248–251

McGaugh JL (2002) Memory consolidation and the amygdala: a systems perspective. Trends Neurosci 25:456

McGaugh JL (2004) The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu Rev Neurosci 27:1–28

McGaugh JL, Roozendaal B (2002) Role of adrenal stress hormones in forming lasting memories in the brain. Curr Opin Neurobiol 12:205–210

Mitchell DGV, Luo Q, Mondillo K, Vythilingam M, Finger EC, Blair RJR (2007) The interference of operant task performance by emotional distracters: an antagonistic relationship between the amygdala and frontoparietal cortices. Neuroimage (in press). DOI 10.1016/j.neuroimage.2007.08.002

Müller GE, Pilzecker A (1900) Experimentelle Beiträge zur Lehre vom Gedächtnis. Z Psychol 1:1

Neisser U, Winograd E, Bergman ET, Schreiber CA, Palmer SE, Weldon MS (1996) Remembering the earthquake: direct experience vs. hearing the news. Memory 4:337–357

Nieuwenhuis S, Aston-Jones G, Cohen JD (2005) Decision making, the P3, and the locus coeruleus-norepinephrine system. Psychol Bull 131:510–532

O'Carroll RE, Drysdale E, Cahill L, Shajahan P, Ebmeier KP (1999) Stimulation of the noradrenergic system enhances and blockade reduces memory for emotional material in man. Psychol Med 29:1083–1088

Ozer EJ, Best SR, Lipsey TL, Weiss DS (2003) Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis. Psychol Bull 129:52–73

Paller KA, Wagner AD (2002) Observing the transformation of experience into memory. Trends Cogn Sci 6:93–102

Phelps EA (2006) Emotion and cognition: insights from studies of the human amygdala. Annu Rev Psychol 57:27–53

Pitman RK, Sanders KM, Zusman RM, Healy AR, Cheema F, Lasko NB, Cahill L, Orr SP (2002) Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. Biol Psychiatry 51:189–192

Quirarte GL, Roozendaal B, McGaugh JL (1997) Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala. Proc Natl Acad Sci U S A 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

Ranganath C, Rainer G (2003) Neural mechanisms for detecting and remembering novel events. Nat Rev Neurosci 4:193–202

Rauch SL, Shin LM, Phelps EA (2006) Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. Biol Psychiatry 60: 376–382

Rempel-Clower NL, Zola SM, Squire LR, Amaral DG (1996) Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. J Neurosci 16:5233–5255

Ressler KJ, Mayberg HS (2007) Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nat Neurosci 10:1116–1124

Richardson MP, Strange BA, Dolan RJ (2004) Encoding of emotional memories depends on amygdala and hippocampus and their interactions. Nat Neurosci 7:278–285

Robbins TW (2005) Controlling stress: how the brain protects itself from depression. Nat Neurosci 8:261–262

Roozendaal B, Griffith QK, Buranday J, de Quervain DJ, McGaugh JL (2003) The hippocampus mediates glucocorticoid-induced impairment of spatial memory retrieval: dependence on the basolateral amygdala. Proc Natl Acad Sci U S A 100:1328–1333

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 U S A 103:6741–6746

Russell JA (1980) A circumplex model of affect. J Pers Soc Psychol 39:1161–1178

Schelling G, Roozendaal B, Krauseneck T, Schmoelz M, De Quervain D, Briegel J (2006) Efficacy of hydrocortisone in preventing posttraumatic stress disorder following critical illness and major surgery. Ann N Y Acad Sci 1071:46–53

Sharot T, Martorella EA, Delgado MR, Phelps EA (2007) How personal experience modulates the neural circuitry of memories of September 11. Proc Natl Acad Sci U S A 104:389–394

Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20:11–21

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 U S A 103: 5585–5590

Southwick SM, Krystal JH, Morgan CA, Johnson D, Nagy LM, Nicolaou A, Heninger GR, Charney DS (1993) Abnormal noradrenergic function in posttraumatic stress disorder. Arch Gen Psychiatry 50:266–274

Southwick SM, Krystal JH, Bremner JD, Morgan CA 3rd, Nicolaou AL, Nagy LM, Johnson DR, Heninger GR, Charney DS (1997) Noradrenergic and serotonergic function in posttraumatic stress disorder. Arch Gen Psychiatry 54:749–758

Squire LR, Stark CE, Clark RE (2004) The medial temporal lobe. Annu Rev Neurosci 27:279–306

Stefanacci L, Buffalo EA, Schmolck H, Squire LR (2000) Profound amnesia after damage to the medial temporal lobe: a neuroanatomical and neuropsychological profile of patient EP. J Neurosci 20:7024–7036

Strange BA, Dolan RJ (2007) Beta-adrenergic modulation of oddball responses in humans. Behav Brain Funct 3:29

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

Talarico JM, Rubin DC (2003) Confidence, not consistency, characterizes flashbulb memories. Psychol Sci 14:455–461

Tasker JG, Di S, Malcher-Lopes R (2006) Minireview: rapid glucocorticoid signaling via membrane-associated receptors. Endocrinology 147:5549–5556

Teng E, Squire LR (1999) Memory for places learned long ago is intact after hippocampal damage. Nature 400:675–677

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

Vaiva G, Ducrocq F, Jezequel K, Averland B, Lestavel P, Brunet A, Marmar CR (2003) Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. Biol Psychiatry 54:947–949, 1471

Vaiva G, Thomas P, Ducrocq F, Fontaine M, Boss V, Devos P, Rascle C, Cottencin O, Brunet A, Laffargue P, Goudemand M (2004) Low posttrauma GABA plasma levels as a predictive factor in the development of acute posttraumatic stress disorder. Biol Psychiatry 55:250–254

Vaiva G, Boss V, Ducrocq F, Fontaine M, Devos P, Brunet A, Laffargue P, Goudemand M, Thomas P (2006) Relationship between posttrauma GABA plasma levels and PTSD at 1-year follow-up. Am J Psychiatry 163:1446–1448

van Stegeren AH, Everaerd W, Cahill L, McGaugh JL, Gooren LJ (1998) Memory for emotional events: differential effects of centrally versus peripherally acting beta-blocking agents. Psychopharmacology 138:305–310

van Stegeren AH, Everaerd W, Gooren LJG (2002) The effect of beta-adrenergic blockade after encoding on memory of an emotional event. Psychopharmacology 163:202–212

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. Psychologische Forschung 18:299–342

Wagner U, Hallschmid M, Rasch B, Born J (2006) Brief sleep after learning keeps emotional memories alive for years. Biol Psychiatry 60:788–790

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 Neurosci 24(7):57

Wolf OT, Kuhlmann S, Buss C, Hellhammer DH, Kirschbaum C (2004) Cortisol and memory retrieval in humans: influence of emotional valence. Ann N Y Acad Sci 1032:195–197

Yamasaki H, LaBar KS, McCarthy G (2002) Dissociable prefrontal brain systems for attention and emotion. Proc Natl Acad Sci U S A 99:11447–11451

Yehuda R (2002) Post-traumatic stress disorder. N Engl J Med 346:108–114

Yovell Y, Bannett Y, Shalev AY (2003) Amnesia for traumatic events among recent survivors: a pilot study. CNS Spectr 8:676–685

Zola-Morgan S, Squire LR, Amaral DG (1986) Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci 6:2950–2967