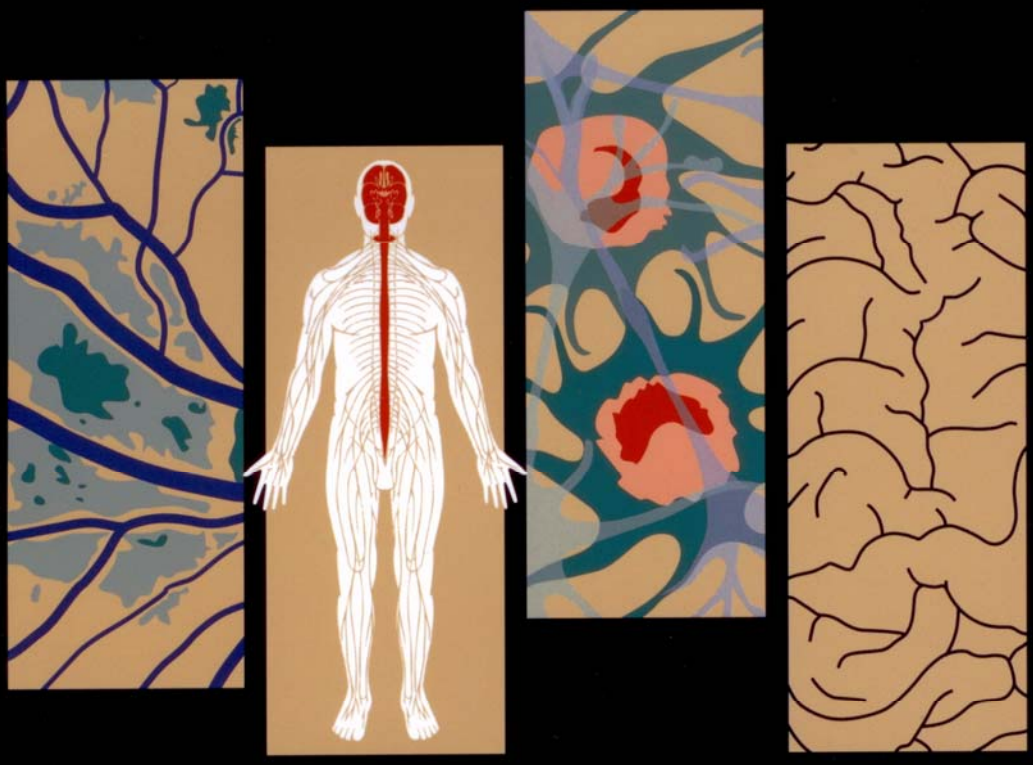
VOLUME 17, NO. 5, 2006 ISSN: 0334-1763

Reviews in the Neurosciences

Editor-in-Chief: **Joseph P. Huston**



FREUND & PETTMAN, U.K.

Reviews in the Neurosciences, 17, 525-532 (2006)

Noradrenergic Control of Emotion-induced Amnesia and Hypermnesia

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SYNOPSIS

Emotional memory encoding is associated with retrograde and anterograde episodic memory changes involving amnesia and hypermnesia, respectively. These effects are noradrenergic-dependent and reflect an interaction with emotional arousal and valence. Whereas anterograde amnesic effects most likely result from attentional capture by emotional arousal, retrograde amnesic and hypermnesic effects may reflect a valence-dependent filter mechanism that operates during emotional memory encoding and controls episodic memory access based upon behavioral significance. This filter mechanism may originnate in amygdala-hippocampal interactions that are modulated by both ascending locus coeruleus and descending prefrontal cortex inputs.

KEY WORDS

emotion, encoding, episodic memory, hippocampus, norepinephrine, propranolol, reboxetine

Accepted: 19 March, 2006

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INTRODUCTION

Through evolution, episodic memory formation, a function of the hippocampus /52/, is biased towards emotion /17/. This bias is evident in that what humans remember most is not the mundane but emotional events, an effect that has been confirmed in numerous psychological studies for a wide range of experimental stimuli /17/. An important neurochemical substrate of emotional memory has been identified in animal experiments that provide evidence of a noradrenergic (norepinephrine [NE]) modulation /9,35-37/. In a pioneering human study wherein subjects were exposed to an emotional story recall task, Cahill *et al.* /10/ found that prelearning administration of the β-adrenergic antagonist propranolol (40 mg p.o.) abolished the memory benefit for emotional events. This influence of propranolol was centrally mediated, as peripheral β-adrenoceptor blockade had no such effect /60/. These results provided an important link to those obtained in animal experiments, by suggesting that an emotion-induced enhancement of episodic memory formation depends on central β-adrenoceptor activation /10,61/ (but see /38,40/).

Augmenting the NE response to emotional stimuli with the α_2-adrenergic antagonist yohimbine boosted emotional memory /39,54/, adding further support to the hypothesis that the influence of emotion on episodic memory formation varies as a function of central NE signaling. The source of central NE signaling is the locus coeruleus (LC), a collection of noradrenergic neurons (~16,000 per hemisphere) located in the dorso-rostral pons /6-8/. Another striking feature of emotional memory is a dependence on the amygdala. Patients with selective bilateral amygdala calcification lesion due to Urbach-Wiethe disease (Fig. 1) do not display an advantage of emotion on episodic memory formation in the emotional story task /11/, a finding that closely mimics that observed with propranolol /10/.

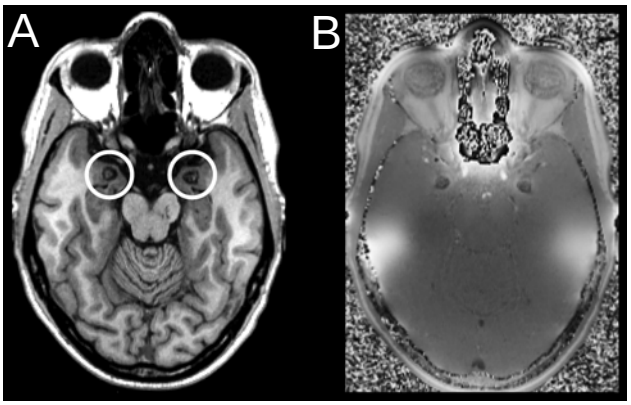

Fig. 1: Horizontal MRI sections of the anterior medial temporal lobe; the white circles index the selective bilateral amygdala calcification lesions in a patient with Urbach-Wiethe disease (hyalinosis cutis et mucosae, lipoproteinosis) (OMIM 247100). Shown are magnitude (A) and phase (B) images derived from a reconstructed 5-average MRI data set acquired with 0.8 mm isotropic resolution.

ENCODING VERSUS CONSOLIDATION EFFECTS

Encoding operations create initial memory representations, which require post-encoding modifications (consolidation) to become more stable and thereby resistant to disruption. Consolidation has been conceptualized as a re-organization process that transfers memory representations from hippocampal to neocortical circuits /58/. The time course of consolidation in humans is unclear. Estimates have extended up to decades, based on retrospective lesion and functional neuroimaging studies /23,52/. When investigated on a shorter time scale, prospective studies in rodents and non-human primates have revealed upper-bound estimates of a few weeks /48,66/. In humans, the behavioral outcome of declarative memory consolidation can be observed after a night of sleep /22/. Current hypotheses of emotional memory formation target consolidation rather than encoding stages /45/. These hypotheses state that emotional stimuli engage LC to release NE in the basolateral amygdala (BLA), an effect critical for potentiating hippocampus-dependent consolidation of these stimuli /35-37/. However, the proposed timescale of consolidation in this model cannot account for the immediate effects of emotion on episodic memory formation. Instead, there must be rapid mechanisms that operate during emotional memory encoding prior to consolidation /24,25/. One such mechanism is reflected by the amygdala's biasing of selective attention towards emotional stimuli that prioritizes emotional memory encoding /17,20,43-45/. Another relevant mechanism may originate in direct amygdala-hippocampal interplay during emotional memory encoding /18,30,49/.

AMYGDALA-HIPPOCAMPAL INTERACTIONS DURING EMOTIONAL MEMORY ENCODING

Several lines of evidence support a critical role of the amygdala in the modulation of hippocampal function during emotional memory encoding. Anatomical studies in rodents demonstrate reciprocal amygdalo-hippocampal connections /46/. Subseizure electrical stimulation of the rodent amygdala produces retrograde amnesia, which can be prevented by pre-treatment with propranolol /55/. Substantial evidence also comes from functional imaging experiments in humans. Positron emission tomography (PET) studies initially established that amygdala engagement during encoding correlates with later emotional memory /12/. Crucially, amplified amygdala activation to both positive and negative stimuli is predictive of later emotional memory recall /25/. Event-related functional magnetic resonance imaging (fMRI) experiments have replicated this correlation using the so-called subsequent memory paradigm /13/. This paradigm isolates the Dm (difference due to memory) effect /42/ by contrasting amygdala activation for stimuli that are subsequently remembered versus those that are subsequently forgotten. Enhanced encoding due to emotional influences can then be investigated by comparing the Dm effect for emotional versus neutral stimuli /31/.

Emotion-specific Dm correlations between the amygdala and the hippocampus /18,30/ suggest a functional coupling of these structures during emotional memory encoding. This is confirmed by a study of patients with temporal lobe epilepsy in whom hippocampal pathology predicted memory for neutral and emotional stimuli alike, while amygdala pathology predicted memory for emotional stimuli alone /49/. This indicates an amygdala-

hippocampal interactive response during emotional memory encoding. Such amygdala-hippocampal cross-talk appears to be susceptible to drug challenge with propranolol /56/, thus neutralizing the retrieval advantage of emotional stimuli, despite propranolol being no longer active during retrieval /61/. Together with behavioral evidence of facilitated emotional memory encoding by application of the selective NE reuptake inhibitor (SNRI) reboxetine /26,27/, these data favor a critical role of intra-amygdalar NE release in emotional memory encoding.

EMOTIONAL MEMORY ENCODING AND EMOTION-INDUCED AMNESIA

Tulving /59/ described experimental retrograde amnesia in a free-recall task of words lists, produced by inserting items (names of famous people such as 'Freud') having priority in recall. In similar studies, both retrograde and anterograde amnesic effects were demonstrated, particularly in response to negative emotion /4,14,16,34,51/. In contrast to emotional memory encoding *per se*, emotion's potential to evoke retrograde and anterograde episodic memory changes has attracted less attention from neurobiology. A landmark study in this regard is that of Strange *et al.* /57/, who combined psychological, pharmacological, and neuropsychological evidence to implicate mechanisms similar to those involved with emotional memory encoding in emotion-induced amnesia. Subjects were exposed to an oddball paradigm composed of word lists, in which enhanced encoding of oddballs (the von Restorff phenomenon /62,64/) interfered with the encoding of preceding standard items, if the oddball was emotional (aversive words such as 'massacre'). As a consequence, subjects subsequently recalled the emotional (*E*) items significantly better than the neutral items, while those items immediately preceding the *E* items (neutral *E-1* items) were forgotten, an emotion-induced amnesic effect up to several seconds /57/. Strange *et al.* /57/ asked whether the *E-1* amnesic effect in response to *E* items was triggered by NE- and amygdala-dependent mechanisms. They addressed the first question by administering propranolol (40 mg p.o) in a double-blind, placebo-controlled, randomized experiment, and addressed the second question by testing a patient with selective bilateral amygdala damage, resulting from Urbach-Wiethe disease (Fig. 1), and matched controls. The findings were similar: NE blockade and bilateral amygdala damage both abolished memory increments for *E* items and memory decrements for *E-1* items, demonstrating a significant coupling between the memory-enhancing and amnesic effects of negative emotion: the more likely an aversive item was remembered, the more likely the preceding neutral item was not. Thus, an emotion-induced amnesia is amygdala- and NE-dependent, implicating intra-amygdalar NE release as a critical substrate of emotional memory encoding and the modulatory effects driven by it.

DIFFERENTIAL ROLES FOR VALENCE AND AROUSAL IN EMOTION-INDUCED AMNESIA AND HYPERMNESIA

The aforementioned findings implicate emotional memory encoding in causing retrograde amnesia. In effect, these authors showed that episodic memory encoding of neutral stimuli temporally contiguous to an emotional stimulus is fragile and susceptible to disruption by encoding of an emotional stimulus. Psychological frameworks propose that emotional stimuli are best characterized along quantitative and qualitative dimensions corresponding to arousal (intensity) and valence (negative vs positive) /32,50/. Increasing evidence indicates neural organization of emotional memory according to these dimensions /19,29,30/. This suggests that there could be dissociable contributions of arousal and valence to the retrograde (and anterograde) episodic memory changes associated with emotional memory encoding.

To test the above hypothesis, Hurlemann *et al.* /28/ established an experimental procedure similar to that used by Strange *et al.* /57/. However, input lists were shorter and included picture items paired with their verbal descriptors to yield more intense emotion-episodic encoding interactions. Of 36 oddballs implemented in the paradigm, 12 were perceptual-neutral (*P*), and 24 were perceptual-emotional (E_xP), including 12 positive ($E_{pos}P$) and 12 negative ($E_{neg}P$) oddballs. $E_{pos}P$ and $E_{neg}P$ oddballs differed from each other in terms of valence,

but were matched for arousal. E_xP oddballs, however, differed from P oddballs in terms of valence and arousal. Recall profiles from each list were pooled according to the three oddball types, thus yielding a neutral (control), positive, and negative condition. As outcome parameter, episodic memory accuracy was determined condition-wise by calculating the percentage of correct recall (i.e. the output/input ratio) for 'oddball – 1', 'oddball', and 'oddball + 1' list positions. Contrasting the emotional conditions (E_xP) with the neutral condition (P) (according to $E_xP - P = E_x$) isolated retrograde and anterograde effects in response to positive and negative emotion on one adjacent standard item ($E_x \pm 1$) corresponding to a time window of ± 5 s (Fig. 2).

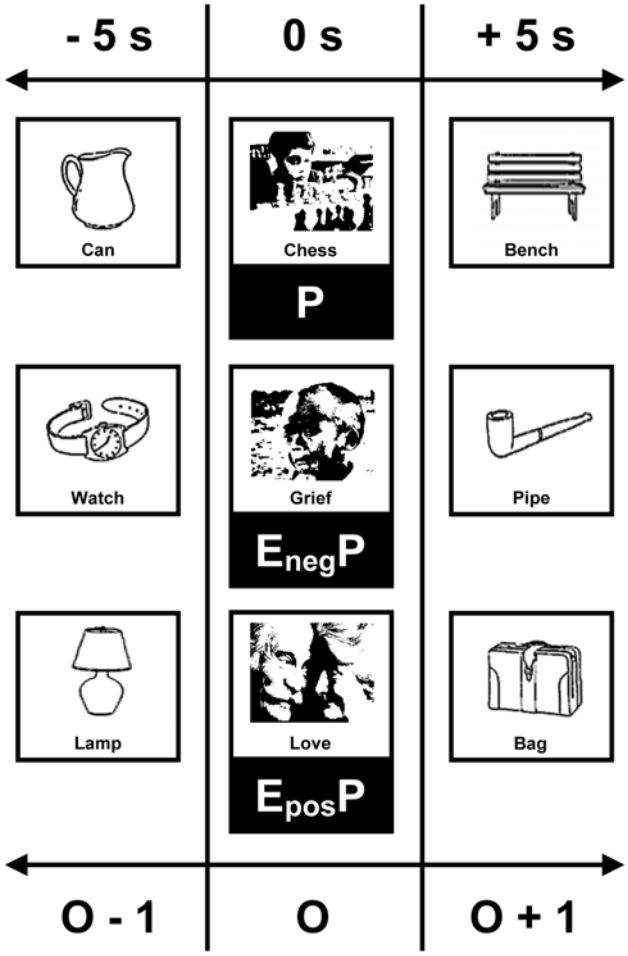

Fig. 2: Experimental design used by Hurlemann *et al.* /28/: In each input list, 1 oddball (O), either emotionally salient (E_x: positive, $E_{pos}P$; negative, $E_{neg}P$) or neutral (P), was temporally flanked by a preceding (O – 1) and following (O + 1) standard item. Results from list recall were pooled according to the three types of oddballs, thus yielding a positive, negative, and neutral condition. Contrasting the emotional conditions with the neutral condition (according to $E_xP - P = E_x$) allowed extraction of retrograde and anterograde effects of positive and negative emotion on episodic memory encoding within a time window of $E_x \pm 1$ items or ± 5 s.

With this subtractive design, Hurlemann *et al.* /28/ identified an organization of E_x-*1* retrograde and E_x+*1* anterograde episodic memory changes consistent with a taxonomy of emotion along the dimensions of valence and arousal. Thus, E_x-*1* effects are determined by valence, with negative emotion eliciting amnesia and positive emotion eliciting hypermnesia, while E_x+*1* effects are determined by arousal, with negative and positive emotion eliciting amnesia (Fig. 3). These distinct types of emotion-episodic encoding interactions can be eliminated by propranolol (40 mg p.o.) and enhanced by reboxetine (4 mg p.o.), pointing to NE as a control neurochemical substrate.

Anterograde effects of emotional arousal

The amnesic effect observed by Hurlemann *et al.* /28/ was not restricted to E_x-*1* encoding, but extended to E_x+*1* encoding, implicating a biological mechanism based upon an emotional arousal-dependent capture of attention /4/. According to Easterbrook's 'cue-utilization' theory /20/, the ability to attend to a to-be-remembered event is a primary factor influencing episodic memory encoding. Encoding rather than retrieval of episodic memories is fragile and vulnerable to attentional manipulation /15/. Emotional stimuli tend to capture attention /5,41,63/, thus enhancing the encoding of these stimuli /43-45/. Once an emotional stimulus has attracted attention, it is difficult to re-orientate attention to non-emotional stimuli /21/, illustrating costs and benefits to the emotional bias of attention. Thus, E_x+*1* effects most likely reflect the cost of devoting attentional resources to preferential encoding of E_x items, which transiently disrupts an attentional re-orienting that is a prerequisite for encoding a following E_x+*1* item. The above interpretation is in keeping with findings

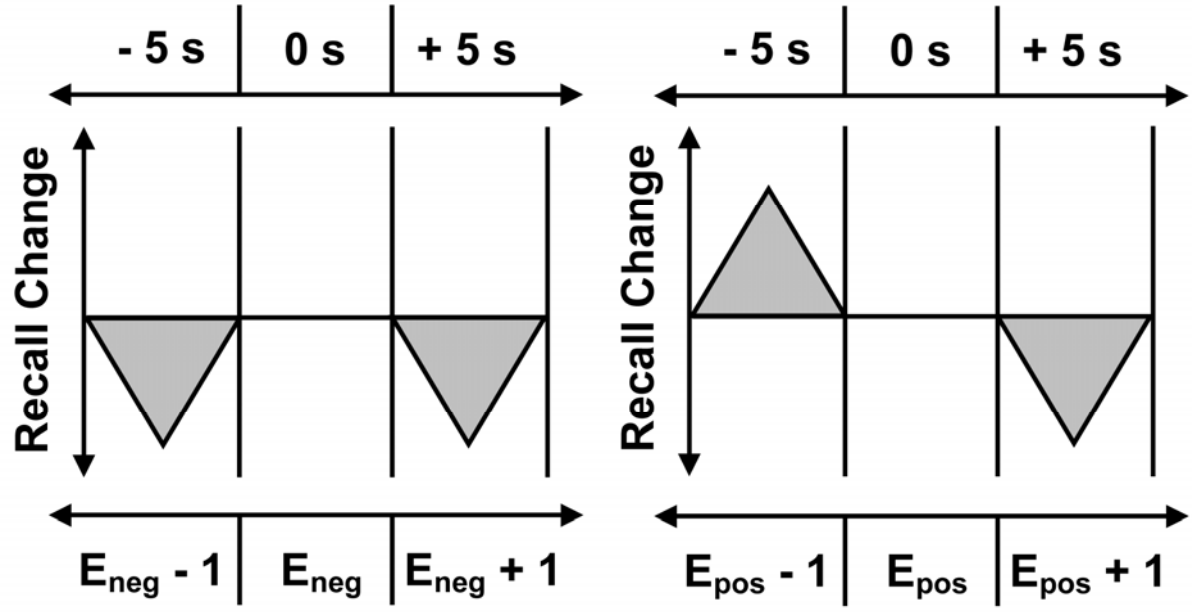

Fig. 3: Schema depicting emotion-induced recall changes (relative to the neutral condition) observed by Hurlemann *et al.* /28/. Equal (near-ceiling) von Restorff effects were obtained for emotional and neutral oddballs, such that subtraction yielded no difference on the emotion (E_x: positive, E_{pos}; negative, E_{neg}) position. In contrast, episodic memory for immediately preceding (E_x-*1*), but not for following (E_x+*1*) items depended on emotional valence. While negative emotion elicited retrograde amnesia, positive emotion elicited retrograde hypermnesia. Both positive and negative emotion elicited anterograde amnesia.

using the 'attentional blink' paradigm, in which detection of an initial target in a visual stimulus stream induces 'inattentional blindness' for a successive second target /47/. While the attentional blink is attenuated when the second target is emotional, this attenuation is abolished in patients with amygdala damage /2/. Further, these patients do not show a trade-off between memory for emotional gist and non-emotional details of complex visual stimuli /1/. Compatible with Easterbrook's hypothesis /20/ and the 'weapon-focus' phenomenon in eyewitness testimony research /29,33/, these patient data suggest a role for the amygdala in narrowing the attentional focus to E_x items, thus leaving less capacity available for processing competing E_x+*1* items. In view of NE as a key neurochemical factor in the amygdala's modulation of encoding /56,57,61/, reboxetine's amplification and propranolol's attenuation of E_x+*1* effects indicate a narrowing or broadening of episodic memory access as a function of intra-amygdalar NE release.

Retrograde effects of emotional valence

Tulving /59/ conjectured that retrograde amnesia in free recall could emerge from the premature termination of episodic memory encoding. Retrograde amnesia in response to intense negative emotion, and the enhancement of this effect with reboxetine, is consistent with an emotional arousal cost on ongoing encoding operations in the hippocampus /28/. This premature termination, however, is not expressed when an emotionally arousing stimulus is positive, and indeed there is an opposite effect of hypermnesia in response to intense positive emotion /28/. This calls for a more complex explanation that invokes an interaction between arousal and valence in the expression of E_x-*1* effects. The amygdala is known to integrate valence and arousal contingencies of emotional stimuli /65/ rather than code for arousal *per se* /3,53/. However, when it comes to emotional memory, neural segregation of arousal and valence has been reported /19,29,30/, which might underlie

dissociable contributions of arousal and valence to E_x-*1* effects.

Compatible with the model proposed by Kensinger and Corkin /30/, the quantity of E_x-*1* effects may vary as a function of emotional arousal, perhaps under the control of amygdala-hippocampal connectivity, while their quality (i.e. the occurrence of retrograde amnesia vs hypermnesia) may be related to valence-dependent activation of prefrontal cortex-hippocampal circuits. Thus, differential computation of valence and arousal likely determines whether an E_x-*1* item is subsequently remembered or forgotten /28/. Substantial support for this interpretation comes from functional imaging findings of a valence- and arousal-specific parcellation within the prefrontal cortex /19/. According to these findings, positively valenced arousing items might engage specific subdivisions of prefrontal cortex to inhibit emotional arousal-related disruption of E_x-*1* encoding in the hippocampus, thus augmenting ongoing encoding processes and inducing hypermnesia. Evidence for this mechanism is provided by neurophysiological and modeling studies in non-human primates, in which descending projections from prefrontal cortex areas represent the major top-down regulatory influence on LC function /6,7/.

CONCLUSIONS

Identification of the psychological indices and biological substrates of emotional memory encoding and the amnesic and hypermnesic effects driven by it extends understanding of the mechanisms that influence episodic memory formation. Accumulating evidence indicates that amygdala- and NE-dependent modulatory influences of emotion on hippocampal function are not restricted to consolidation, but already act during encoding of episodic memories. Amnesic and hypermnesic effects associated with emotional memory encoding suggest that the primary function of episodic memory may be to guide behavior rather than to accurately reproduce the past. Accordingly, up- and downregulation of hippocampal function during encoding in response to the presence or absence of intra-amygdalar NE release may represent an important filter mechanism that controls episodic memory access upon criteria of behavioral significance, with behaviorally significant items receiving privileged access to consolidation resources, and insignificant items being filtered out. This filter mechanism appears to be a function of amygdala-hippocampal interactions which receive bottom-up modulatory inputs from LC and top-down modulatory inputs from the prefrontal cortex. The prefrontal cortex, in turn, controls LC output and central NE signaling. This functional circuitry may be part of the architecture that has evolved to orchestrate forgetting and remembering (Fig. 4).

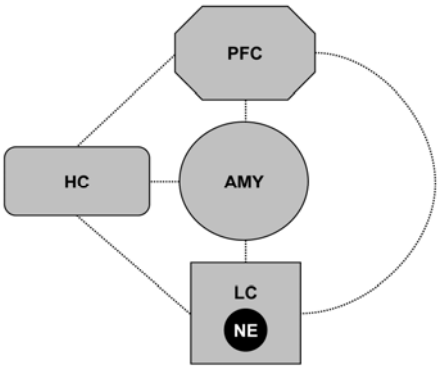

Fig. 4: Schematic outline of the functional circuitry hypothesized to underlie emotion-induced amnesia and hypermnesia. While anterograde amnesic effects most likely result from attentional capture by emotional arousal, retrograde amnesic and hypermnesic effects may reflect a filter mechanism that operates during emotional memory encoding and controls episodic memory access upon criteria of behavioral signifycance. This filter mechanism appears to be based on amygdala-hippocampal interactions which are modulated by ascending locus coeruleus (LC) and descending prefrontal cortex inputs. According to this model, the amygdala (AMY) - activated by noradrenergic (norepinephrine [NE]) input from the LC - communicates emotional arousal to the hippocampus (HC), to render it susceptible to valence transfer from the prefrontal cortex (PFC). PFC, in turn, controls LC output.

ACKNOWLEDGEMENTS

The author thanks Professor Raymond J. Dolan (London) and Professor Wolfgang Maier (Bonn) for inspiring discussions and critically reading the manuscript. R.H. was supported by BONFOR and the German Federal Ministry of Education and Research (BMBF).

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