Amygdala control of emotion-induced forgetting and remembering: Evidence from Urbach-Wiethe disease

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Abstract

When presented in a neutral context, emotional items interfere with episodic encoding of temporally contiguous non-emotional items, resulting in dissociable valence-dependent retrograde and arousal-dependent anterograde modulatory effects. By studying two rare patients with congenital lipoid proteinosis (Urbach-Wiethe) and a focal disease emphasis on the basolateral amygdala (BLA), we demonstrate that this bidirectional modification of episodic encoding by emotion depends on the integrity of the amygdala, as both retrograde and anterograde modulatory effects are absent. Our findings implicate the amygdala in a neural circuitry that orchestrates rapid retrograde and anterograde regulation of episodic memory access upon criteria of behavioral significance.

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Keywords: Emotion; Amygdala; Lesion; Episodic memory; Amnesia; Hypermnesia

1. Introduction

The hippocampus is critical for episodic memory formation (Scoville & Milner, 1957). In contrast, an enhancement of episodic memory formation by emotion is amygdala- and norepinephrine (NE)-dependent, being abolished by both bilateral amygdala lesion (Adolphs, Cahill, Schull, & Babinski, 1997; Cahill, Babinsky, Markowitsch, & McGaugh, 1995) and pharmacological blockade of central NE signaling with the β-adrenergic antagonist propranolol (Cahill, Prins, Weber, & McGaugh, 1994; van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998). Current hypotheses of emotional memory formation target post-encoding (consolidation) rather than encoding stages (Phelps & LeDoux, 2005). These hypotheses state that emotional stimuli evoke, via projections from locus coeruleus (LC) (Aston-Jones & Cohen, 2005), NE release in the basolateral amygdala (BLA), an effect critical for potentiating hippocampal consolidation of these stimuli (McGaugh, 2000, 2004). Consequently, emotional memory formation should increase with time, as the gradual process of consolidation proceeds.

However, this time-dependent mechanism cannot account for the instant effects of emotion on episodic memory formation. Instead, there must be rapid modulatory mechanisms related to emotional memory encoding (Hamann, 2001). Studies of amygdala-lesioned patients demonstrate that one such mechanism depends on the amygdala’s influence on perception and attention (Adolphs, Tranel, & Buchanan, 2005; Anderson & Phelps, 2001; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). Neuroimaging studies demonstrate that another mechanism depends on the amygdala’s modulation of hippocampal function during emotional memory encoding (Cahill et al., 1996; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000;
emotion-induced amnesia and hypermnesia. Pharmacological evidence indicates that this modulation is susceptible to antagonistic (Strange & Dolan, 2004; Strange, Hurlemann, & Dolan, 2003; van Stegeren et al., 2005) and agonistic (Harmer, Hill, Taylor, Cowen, & Goodwin, 2003; Harmer, Shelley, Cowen, & Goodwin, 2004) challenges of central NE signaling. Propranolol blocks emotional memory encoding in a manner akin to bilateral amygdala lesion (Strange et al., 2003), implying intra-amygdalar LC-NE release as a potent regulator of amygdala-hippocampal interactions during emotional memory encoding.

However, this regulation has costs and benefits. Free recall tests of episodic memory formation demonstrate that this enhanced encoding of oddballs (the von Restorff phenomenon: von Restorff, 1933; Wallace, 1965) critically interferes with the encoding of standard stimuli, an effect particularly evident for emotional oddballs (Angelini, Capozzoli, Lepore, Grossi, & Orsini, 1994; Strange et al., 2003; Tulving, 1969). Using an emotional oddball paradigm, we recently showed that emotional memory encoding is associated with retrograde and anterograde episodic memory changes involving an amnesia and hypermnesia, respectively. Consistent with a taxonomy of emotion along the orthogonal dimensions of arousal and valence (Russell, 1980; Lang, 1995), anterograde interference is determined by arousal, with negative and positive emotion eliciting amnesia, whereas retrograde interference is determined by valence, with negative emotion eliciting amnesia and positive emotion eliciting hypermnesia. Both amnesic and hypermnesic effects are propranolol-sensitive, pointing to LC-NE as the control neurochemical substrate (Hurlemann et al., 2005).

Neuropsychological studies of patients with bilateral amygdala lesion provide key mechanistic insights into emotional memory formation (LaBar & Cabeza, 2004a; Hamann, Eyl, Grafton, & Kilts, 1999; Kensinger & Corkin, 2004; Kilpatrick & Cahill, 2003; Richardson, Strange, & Dolan, 2004). In our study, BG suffered an epileptic grand-mal seizure aged 12, which led to diagnosis of LP and subsequent diagnosis of her twin sister. When tested in our study, BG was on anticonvulsive therapy with a 900-mg daily dose of valproate. AM and BG completed 10 years of school education and have been in fulltime employment since. Both are married and have children.

Sixteen female control volunteers matched for age (range 24.3–34.2 years; mean age 29.1 ± 2.4 years) and education served as the comparison group. Both controls and LP patients underwent psychiatric exploration to exclude either current or past DSM-IV (Diagnostic and Statistical Manual of Mental Disorders IV) axis I and axis II disorder. Controls had no current physical illness, and had not been on psychoactive medication for >3 months. The study was approved by the local ethical committee, and all participants gave written informed consent according to the 1964 Declaration of Helsinki.

2.2. Neuropsychological assessment

Neuropsychologically, LP patients show much less cognitive deviation from controls than initial studies of patients with this rare aetiology had suggested (Siebert, Markowitz, & Bartel, 2003). Previous neuropsychological testing showed AM (and BG) to be of normal verbal IQ (VIQ) and within normal limits for a wide range of cognitive functions, including attention and short-term memory (Strange et al., 2003). Therefore, LP patients and controls underwent restricted neuropsychological screening in the present study. This included the VLMT (Verbaler Lern- und Merkfähigkeits) (Helmstaedter, Lend, & Lux), 2001, a German version of the RAVLT (Rey Auditory Verbal Learning Test), to assess immediate verbal learning span, new learning, susceptibility to interference, and recognition memory. The ROCF (Rey-Osterrieth Complex Figure Test) (Osterrieth, 1944; Rey, 1941) was used to test incidental visual memory and the visuospatial constructional ability. Motor speed and visual attention were examined with the TMT (trail making tests) (Raitan, 1958). VIQ was determined with the HAWIE-R (Hamburg-Wechsler Intelligenztest für Erwachsene) (Tewes, 1991), a German Version of the WAIS-R (Wechsler Adult Intelligence Scale-Revised). A subtest of the RBMT (Rivermead behavioral memory test) (Wilson, Cockburn, Baddeley, & Horns, 1989) was used to investigate recognition of facial identity, whereas facial emotion recognition was assessed with the FEEST (facial expressions of emotions: stimuli and test) (Young, Perrett, Calder, Sprengelmeyer, & Ekman, 2002). As summarized in Table 1, neuropsychological screening showed that AM and BG have an average VIQ (HAWIE-R 100 and 105, respectively) and relatively normal cognitive skills as evident in most tasks, which replicates our previous findings (Strange et al., 2003). Interestingly, BG, but not AM, was significantly impaired in recognizing fearful facial expressions, with a recognition rate of 50% relative to 100% in controls.

2.3. Episodic memory test

Stimulus setup and experimental design have been detailed elsewhere (Hurlemann et al., 2005). The paradigm featured 36 von Restorff lists, each composed of one oddball and seven standard stimuli, presented as picture items in the paradigm, 12 were perceptual-neutral (Epos, Epos), including 12 positive (Epos, Epos) and 12 negative (Epos, Epos) oddballs. Epos, Epos oddballs differed from each other in terms of valence, but were matched for arousal. Epos oddballs differed from P oddballs in terms of valence and arousal.

All participants were presented with 36 study-distraction-test sequences. Episodic memory was tested by free recall. Recall profiles were pooled according to the three oddball categories, thus, yielding a neutral, positive, and negative condition. As outcome parameter, episodic memory performance was determined condition-wise by calculating the percentage of correct recall (i.e. the output/input ratio) for the following three list positions: oddball −1, oddball,
Table 1
Demographical and neuropsychological characteristics of female Lipoid Proteinosis (Urbach-Wiethe) patients AM and BG and controls (n = 16)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Max</th>
<th>Controls S</th>
<th>AM S.D.</th>
<th>BG S.D.</th>
<th>AM S</th>
<th>BG S</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.1</td>
<td>2.4</td>
<td>30</td>
<td>30</td>
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<td>30</td>
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<tr>
<td>Height (cm)</td>
<td>163.7</td>
<td>6.8</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160</td>
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<tr>
<td>Weight (kg)</td>
<td>61.3</td>
<td>5.5</td>
<td>60</td>
<td>49</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Education (years)</td>
<td>10.4</td>
<td>0.5</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>HAWIE-R VIQ</td>
<td>106</td>
<td>12.9</td>
<td>100</td>
<td>105</td>
<td>105</td>
<td>105</td>
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</table>

VLMTa

<table>
<thead>
<tr>
<th>Trial</th>
<th>15</th>
<th>7.9</th>
<th>1.4</th>
<th>9</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 5</td>
<td>15</td>
<td>10.9</td>
<td>2.1</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>52.6</td>
<td>6.7</td>
<td>49</td>
<td>55</td>
</tr>
<tr>
<td>Recognition</td>
<td>75</td>
<td>13.3</td>
<td>1.6</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

ROCFa

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<tr>
<th>Copy</th>
<th>36</th>
<th>32.4</th>
<th>3.9</th>
<th>30</th>
<th>32</th>
</tr>
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<tbody>
<tr>
<td>30 min recall</td>
<td>36</td>
<td>19.2</td>
<td>2.3</td>
<td>18</td>
<td>19</td>
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</tbody>
</table>

TMTa

<table>
<thead>
<tr>
<th>Part A (s)</th>
<th>26.9</th>
<th>5.7</th>
<th>29</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part B (s)</td>
<td>73.3</td>
<td>15.3</td>
<td>82</td>
<td>76</td>
</tr>
</tbody>
</table>

RBMTa

| Face recognition | 5 | 5 | 5 | 5 |

FEESTa

| Happiness | 12 | 12 | 11 | 12 |
| Surprise  | 12 | 12 | 9  | 11 |
| Fear      | 12 | 12 | 11 | 6 |
| Sadness   | 12 | 12 | 12 | 11 |
| Disgust   | 12 | 12 | 10 | 12 |
| Anger     | 12 | 12 | 11 | 12 |
| Total     | 72 | 72 | 64 | 64 |

Abbreviations: Max, maximum possible score; MS, mean score; S, individual score; S.D., standard deviation.
a Raw scores.

and oddball +1. Additionally, a standard item index (SI) based on the seven non-oddball list positions was calculated for each condition (e.g., SI1:). Contrasting the emotional conditions (E1/P1) with the neutral condition (P) (according to \(E1-P1 = E1\)) allowed us to isolate retrograde and anterograde effects of positive (\(E_{pos}\)) and negative (\(E_{neg}\)) emotion on one adjacent standard item (\(E1 \pm 1\)) corresponding to a time window of \(\pm 5\) s. While our previous paradigm was designed to demonstrate a coupling between the memory-enhancing (\(E_{neg}\) items) and memory-impairing (\(E_{neg}\) items) effects of negative emotion (Strange et al., 2003), the present paradigm was optimized to investigate \(E1 \pm 1\) anterograde effects by using a subtractive design. To assess potential effects of bilateral amygdala damage on the cognitive appraisal of emotion, patients and controls both performed valence and arousal ratings to \(E1, P\) and P oddballs on a nine-point scale after memory testing.

2.4. MRI scanning

A Siemens Sonata system (Siemens, Erlangen, Germany), operating at 1.5 T, was used to acquire T1-weighted MRI scans of AM and BG. The parameters of the MP-RAGE sequence (Mugler & Brookeman, 1991) were optimized to yield the best white matter-gray matter-CSF contrast for in vivo imaging: TR = 2200 ms, TE = 4.38 ms, TI = 1240 ms, \(\alpha = 20^\circ\). A total of six volumes were acquired for each patient. Volume 1 was a standard 3D anatomical scan with 0.8 mm isotropic resolution. The whole brain volume was covered by 160 axial slices. The field-of-view (FOV) was 256 mm \(\times\) 256 mm and the matrix size 256 \(\times\) 256 pixels. Volumes 2–6 were acquired with the higher isotropic resolution, we acquired five averages (in form of five separate one-average runs, subsequently co-registered and re-sliced) for the final image. To perform complex averaging, which leads to efficient noise suppression, the product MP-RAGE sequence was modified to output phase images in addition to the usual magnitude images. The real and imaginary parts were calculated for each of the five data sets and then used to obtain the complex average. The use of real and imaginary values instead of magnitude and phase has the advantage of avoiding phase wraps. Fig. 1 depicts the bilateral amygdala lesion in AM (Fig. 1A(i)) and (ii) and BG (Fig. 1B(i) and (ii)).

2.5. MRI analysis

To determine whether or not the BLA is affected in AM and BG, we used three-dimensional probabilistic maps based on cytoarchitectonic parcellations of the amygdala in histological sections of postmortem brains (Amunts et al., 2005), thus, enabling accurate anatomical labeling in the stereotaxic reference
2.6. Statistics

To determine whether each of the patients performed within or outside the normal range on the free recall task, we compared AM’s and BG’s individual recall scores by reference to the mean and standard deviation of scores of the control sample (Table 2). The $Z$ statistic indicated no performance difference between patients and controls in the neutral condition. Moreover, AM and BG performed similarly to controls on $E_n$ and SI recall in the emotional conditions. In contrast, each of the patients performed outside the normal range on $E_{neg} \pm 1$ recall and $E_{pos} \pm 1$ recall. Since no evidence was found for a differential contribution of scores of the control sample by calculating separate $Z$ scores. On the group level, two-factor within-subjects and three-factor mixed analyses of variance (ANOVA)s followed by two-tailed one-sample and two-sample $t$-tests served to determine whether $E_n - 1$ retrograde and $E_{pos} + 1$ anterograde memory changes were present or absent in patients as compared to controls. A significance threshold of $p < 0.05$ was adopted throughout. Effect sizes were quantified by calculating the values of partial Eta squared ($\eta^2_p$) and Cohen’s $d$.

3. Results

A condition (positive, negative, neutral) $\times$ position (oddball, oddball $\pm 1$) $\times$ condition (first, second, third) $\times$ position (odd-ball, oddball $\pm 1$) $\times$ condition (positive, negative, neutral) $\times$ position (first, second, third) $\times$ condition ANOVAs for oddballs ($F_{(2,30)} = 1.215; p < 0.05$) and standard items ($F_{(2,30)} = 1.344; p > 0.05$) indicated that performance remained unchanged throughout the experiment. Thus, our findings in controls replicated those reported previously (Hurlemann et al., 2005) and served as baseline for the subsequent analyses.

AM’s and BG’s individual recall scores were converted into $Z$ scores by reference to the mean and standard deviation of scores of the control sample (Table 2). The $Z$ statistic indicated no performance difference between patients and controls in the neutral condition. Moreover, AM and BG performed similarly to controls on $E_n$ and SI recall in the emotional conditions. In contrast, each of the patients performed outside the normal range on $E_{neg} \pm 1$ recall and $E_{pos} \pm 1$ recall. Since no evidence was found for a differential contribution of scores of the control sample by calculating separate $Z$ scores. On the group level, two-factor within-subjects and three-factor mixed analyses of variance (ANOVA)s followed by two-tailed one-sample and two-sample $t$-tests served to determine whether $E_n - 1$ retrograde and $E_{pos} + 1$ anterograde memory changes were present or absent in patients as compared to controls. A significance threshold of $p < 0.05$ was adopted throughout. Effect sizes were quantified by calculating the values of partial Eta squared ($\eta^2_p$) and Cohen’s $d$.

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Max Controls</th>
<th>AM</th>
<th>BG</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI $P$</td>
<td>84</td>
<td>50.9</td>
<td>7.3</td>
</tr>
<tr>
<td>$P - 1$</td>
<td>12</td>
<td>6.3</td>
<td>1.9</td>
</tr>
<tr>
<td>$P + 1$</td>
<td>12</td>
<td>11.5</td>
<td>0.7</td>
</tr>
<tr>
<td>SI $neg$</td>
<td>84</td>
<td>43.9</td>
<td>8.9</td>
</tr>
<tr>
<td>$E_{neg} - 1$</td>
<td>12</td>
<td>4.3</td>
<td>1.5</td>
</tr>
<tr>
<td>$E_{neg} + 1$</td>
<td>12</td>
<td>11.7</td>
<td>0.8</td>
</tr>
<tr>
<td>SI $pos$</td>
<td>84</td>
<td>52.3</td>
<td>8.9</td>
</tr>
<tr>
<td>$E_{pos} - 1$</td>
<td>12</td>
<td>8.1</td>
<td>1.4</td>
</tr>
<tr>
<td>$E_{pos}$</td>
<td>12</td>
<td>11.4</td>
<td>0.7</td>
</tr>
<tr>
<td>$E_{pos} + 1$</td>
<td>12</td>
<td>4.9</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Listed are the raw scores for the following list positions: oddball ($E_n$), oddball $\pm 1$ ($E_n \pm 1$), and standard items (SI, SI $\pm 1$). Abbreviations: Max, maximum possible score; MS, mean score; $S$, individual score; S.D., standard deviation.

Fig. 2. Superposition of BLA stereotaxic cytoarchitectonic probabilistic maps on the amygdala in Lipoid Proteinosis (Urbach-Wiethe) patients AM and BG. Equiprobability contours in blue indicate a 50% likelihood of a given voxel to be localized within the BLA. (A) Medial temporal lobe of patient AM in coronal (i) and horizontal view (ii). (B) Medial temporal lobe of patient BG in coronal (i) and horizontal view (ii). Abbreviations: BLA, basolateral amygdala constituted by the lateral, basolateral, and basomedial nuclei.

The localization of the BLA probabilistic map in relation to the amygdala lesions in AM (Fig. 2A(i) and (ii)) and BG (Fig. 2B(i) and (ii)).

2.6. Statistics

To determine whether each of the patients performed within or outside the normal range on the free recall task, we compared AM’s and BG’s individual accuracy scores to the corresponding normative scores derived from the control sample by calculating separate $Z$ scores. On the group level, two-factor within-subjects and three-factor mixed analyses of variance (ANOVA)s followed by two-tailed one-sample and two-sample $t$-tests served to determine whether $E_n - 1$ retrograde and $E_{pos} + 1$ anterograde memory changes were present or absent in patients as compared to controls. A significance threshold of $p < 0.05$ was adopted throughout. Effect sizes were quantified by calculating the values of partial Eta squared ($\eta^2_p$) and Cohen’s $d$.
5.25 ± 5.13 balls (5.19 × n)

Fig. 3. Recall profile of female Lipoid Proteinosis (Urbach-Wiethe) patients AM and BG as compared to controls (n = 16). (A) Percentage (%) correct recall as determined in controls (i) and patients (ii). Global task performance and perceptual von Restorff effects were unaffected by bilateral amygdala lesion. (B) Recall retrograde and arousal-related anterograde memory changes for the surrounding standard items. Positive emotion elicited retrograde hypermnesia (+14.58%) and changes (%) in controls (i) and patients (ii). In controls, but not in AM and BG, enhanced memory for emotional oddballs was associated with valence-related oddball. Error bars indicate 1 S.E.

4. Discussion

Organic syndromes rarely affect the amygdala selectively. If the brain lesion extends to adjacent temporal lobe memory structures, the patient is rendered amnesic, which complicates the study of amygdala-dependent episodic memory changes (LaBar & Cabeza, 2006). In the current neuropsychological experiment, we therefore focused on the LP phenotype in AM and BG as a rare model system of selective amygdala dysfunction to determine the amygdala’s role in amnesia-related Ex − 1 retrograde and arousal-related Ex + 1 anterograde episodic memory changes. The novel finding here is the absence of these specific changes in AM and BG, which mimics that observed after amygdala suppression with propranolol in controls (Hurlemann et al., 2005). In our paradigm, perceptual-neutral (P) and perceptual-emotional (E,P) oddballs were normalized for near-ceiling von Restorff effects to specify the influences of arousal and valence on Es-dependent effects by using a subtractive design. While the perceptual component (P) of the von Restorff effect is intact in AM and BG, the emotional component (Ex) is not (Strange et al., 2003), as indicated by the lack of retrograde Ex − 1 and anterograde Ex + 1 effects driven by this component (Fig. 3). We thus conclude that an intact amygdala is necessary for generating retrograde and anterograde episodic memory changes in response to positive and negative emotion.

The finding that AM and BG exhibit no arousal-related Ex + 1 anterograde amnesic effects is consistent with deficient Es emotional item processing at the amygdala level and parallels the distribution of the patients’ individual performance to these results, AM’s and BG’s data were collapsed to one diagnostic sample. A group (controls, patients) × condition × position 2 × 3 × 3 ANOVA yielded group (F(1,16) = 12.698; p = 0.003; ηp² = 0.442), position (F(2,32) = 107.598; p < 0.0001; ηp² = 0.871), and two-way position × group (F(2,32) = 3.765; p = 0.034; ηp² = 0.190) interaction effects. Post hoc two-sample t-tests revealed between-group differences in Epos − 1 (t(16) = −2.995; p = 0.009; d = 2.38), Epos + 1 (t(16) = −2.648; p = 0.018; d = 2.11) and Epos + 1 (t(16) = −2.437; p = 0.027; d = 1.94) recall. The absence of a between-group difference in Epos − 1 (t(16) = 0.535; p > 0.05) recall is not compatible with preserved Epos − 1 hypermnesic effects in AM and BG, as Epos − 1 recall was not better than P − 1 recall in either of the patients. Together, these findings indicate no global memory dysfunction in AM and BG, but a specific lack of emotion-induced memory increments and decrements, such that Ex ± 1 recall equated P ± 1 recall (Fig. 3A(ii) and B(ii)).

The oddball arousal and valence scores (mean ± S.D.) obtained after memory testing were as follows—controls: EposP oddballs (5.31 ± 0.60, 7.75 ± 0.78); EposP oddballs (5.25 ± 0.58, 2.31 ± 0.48); P oddballs (2.81 ± 0.66, 5.13 ± 0.72). Patients (5.44 ± 0.51, 7.69 ± 0.48); EposP oddballs (5.19 ± 0.54, 2.44 ± 0.51); P oddballs (2.94 ± 0.57, 5.25 ± 0.45). Separate group (controls, patients) × oddball type (positive, negative, neutral) 2 × 3 ANOVAs yielded no significant between-group effects on either arousal scores or valence scores (p values > 0.05).
failure of gist memory effects (Adolphs, Tranel, et al., 2005) and an emotional modulation of the attentional-blind effect (Anderson & Phelps, 2001) in amygdala-lesioned patients. Our results emphasize the pivotal role of the amygdala in devoting attention to preferential encoding of $E_x$ emotional items. We suggest that this allocation of attentional resources as a function of emotional arousal is adaptive and can provoke a transient refractory period, of at least 5 s duration, which disrupts attentional re-orienting that is a prerequisite for encoding a following $E_x + 1$ non-emotional item in the hippocampus.

Whereas arousal-related $E_x + 1$ anterograde effects appear to reflect the cost of an amygdala-dependent capture of attention, $E_x + 1$ retrograde effects most likely result from an interference of valence-specific input during emotional memory encoding with ongoing episodic encoding operations in hippocampus (Hurlemann et al., 2005). Our finding that an amygdala dependence of $E_{neg} - 1$ retrograde amnesia (Strange et al., 2003) extends to $E_{pos} - 1$ retrograde hypermnesia, raises the possibility that this input could be generated by the amygdala. However, both lesion and neuroimaging data (Hamann, Lee, et al., 1999; Kensinger & Schacter, 2006) indicate no differential amygdala engagement during encoding of emotionally positive and negative stimuli, which supports the hypothesis of a neural segregation of arousal and valence influences on emotional memory encoding. This hypothesis states that the amygdala communicates arousal to the hippocampus to render it susceptible to valence-specific top-down input from prefrontal cortex (PFC) (Dolcos, LaBar, & Cabeza, 2004b; Kensinger & Corkin, 2004). Given this background, we suggest that valence-related $E_x - 1$ retrograde effects require arousal-driven amygdala-hippocampal interactions.

In animal models, intra-amygdalar infusions of NE agonistic and antagonistic drugs demonstrate LC-NE release within the BLA as an important neurochemical factor in the amygdala’s control of emotional memory consolidation (McGaugh, 2000, 2004). Similarly, activation of the human amygdala during emotional memory encoding has been revealed to depend on a rise in intra-amygdalar LC-NE (Strange & Dolan, 2004; van Stegeren et al., 2005). Thus, emotional memory encoding and consolidation both appear to depend critically on LC-NE bottom-up activation of the BLA.

In this study, we used stereotaxic cytoarchitectonic probabilistic maps to verify that amygdala calcifications in AM and BG encompassed the BLA (Fig. 2). The absence of $E_x - 1$ retrograde effects in AM and BG as well as in controls treated with propranolol indicates that BLA dysfunction, whether due to anatomical lesion or pharmacological inhibition, can abolish an arousal-induced amygdala-hippocampal coupling that is a prerequisite for the modification of ongoing episodic encoding operations by valence-specific input from PFC. Our finding that $E_x$ emotional item valence predicts subsequent memory for $E_x - 1$ non-emotional items, suggests that amygdala- and LC-NE-dependent valence-arousal interactions during emotional memory encoding contribute to a filter mechanism that segregates behaviorally significant items from less significant items, thus, restricting the latter from consuming consolidation resources.

Whereas the memory-modulating effects of arousal and valence were absent in AM and BG, both patients performed similarly to controls on arousal and valence ratings to emotional oddballs. This result is in keeping with previous reports that bilateral amygdala lesion does not affect the way patients judge arousal and valence attributes of emotional stimuli (Anderson & Phelps, 2002; Adolphs et al., 1997; Cahill et al., 1995). Arousal and valence judgments have indeed been shown to engage PFC subregions rather than the amygdala (Dolcos & Cabeza, 2002; Dolcos, LaBar, & Cabeza, 2004b), which could explain why emotional oddball ratings are normal in AM and BG, but significantly changed in controls treated with NE agonistic and antagonistic drugs acting in these subregions (Hurlemann et al., 2005).

Although neuroimaging studies of the amygdala indicate responsiveness to a wide range of facial expressions (Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006), the amygdala plays a particular role in fear recognition (Phelps, 2006). Recognizing fear from facial expressions seems to depend primarily on the eye region (Whalen et al., 2004). Defective gaze monitoring has been identified as the critical pathomechanism for impaired fear recognition in patients with bilateral amygdala lesion (Adolphs et al., 2005b). However, in a large sample of nine amygdala-lesioned patients, the ability to recognize fear varied from severely impaired to relatively intact (Adolphs et al., 1999). In the present study, BG, but not AM, was compromised in recognizing fear. The fact that AM and BG are monozygotic twins both suffering from LP argues against a potential influence of dissociable aetiologies. In addition, there is no MRI evidence for significant differences in lesion size. The single clinical factor that distinguishes between the two cases, is that BG’s lesion is epileptogenic. While we cannot exclude that deficient fear recognition in BG could be related to epilepsy or anticonvulsive medication, we consider it more likely that the early onset of the disease during childhood and the slowly progressive amygdala degeneration with disease duration (Appenzeller et al., 2006) enables some LP patients, like AM, to develop an alternate fear recognition network sparing the amygdala or cognitive strategies compensating their deficit.

The present study of two monozygotic twins with bilateral amygdala lesion, although limited by its casuistic nature and the restrictedness of neuropsychological testing, lends credence to the hypothesis that the amygdala has an adaptive role in allocating processing resources during emotional memory encoding, with behaviorally significant items receiving privileged memory access and insignificant items being filtered out. In so doing, the amygdala appears to serve the guidance of behavior rather than an accurate reproduction of the past.

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References


