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ENGAGEMENT OF LATERAL AND MEDIAL PREFRONTAL AREAS IN THE ECPHORY OF SAD AND HAPPY AUTOBIOGRAPHICAL MEMORIES

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ABSTRACT

Autobiographic memory is usually affect-laden, either positively or negatively. A central question is whether the retrieval of both emotive forms of memory engages the same or a different neural net. To test this we studied 13 normal subjects with functional magnetic resonance imaging while they retrieved a number of distinct episodes, all of which were either rated as strongly positive (happy) or strongly negative (sad) in affect. Comparing the retrieval of sad with that of happy episodes revealed activation in both lateral orbital cortices symmetrically (extending into the ventrolateral prefrontal cortex as well), together with a small region in the right lateral temporal cortex and the left cerebellum. Vice versa, comparing the retrieval of happy with that of sad episodes revealed a major activation in the left hippocampal region, bilateral (though more right-sided) activation in the medial orbitofrontal/subgenual cingulate and a left sided activation in the dorsolateral prefrontal activation. These findings point to the importance of the orbitofrontal cortex for affect-laden information processing and to the existence of distinct neural nets for the re-activation of positively and negatively viewed autobiographic episodes.

INTRODUCTION

Memory is nowadays divided into several systems of which the episodic-autobiographic system is considered to be the most complex, requiring conscious reflection and allowing mental time travel into the past (Tulving and Markowitsch, 1998). Due to its complexity, autobiographic memory is vulnerable to diverse forms of focal as well as diffuse brain damage and to various psychiatric problems, frequently related to stress, trauma, and dissociative disorders (Markowitsch, 1999, 2000).

Results from brain damaged patients (Kroll et al., 1997; Levine et al., 1998) and functional imaging studies (Fink et al., 1996) have pointed to a special role of prefrontal regions in memory processing as well as in theory of mind (Stuss et al., 2001), consciousness (Knight and Grabowecky, 2000; Wheeler et al., 1997), emotion processing (Baker et al., 1997), self-recognition and personal identity (Keenan et al., 2000; Vogeley et al., 2001). This research ties to early studies, implicating particularly the orbitofrontal portion of the prefrontal lobes in personality dimensions (Harlow, 1848, 1869; Kleist, 1934; Welt, 1888). A further corroboration can be seen in discussions on metabolic reductions in the frontal lobes of affective murderers (Raine et al., 1998) and on gray matter

volume reductions in subjects with antisocial personality disorder (Raine et al., 2000). (Affective murderers are more impulsive, emotional and unplanned than predatory murderers.) Furthermore, morphological changes have been observed in the prefrontal and orbitofrontal regions of brains of patients with psychiatric diseases, and impairments in social and moral behavior have been noted in patients with damage to these regions (SW Anderson et al., 1999; Clark et al., 2001; Nies, 1999; Eslinger, 1999; Goldstein et al., 1999; Harrison, 1999; Nyffeler and Regard, 2001).

Orbitofrontal and adjacent subcallosal cortices receive input from (other) prefrontal and posterior cortical integration areas as well as from many limbic regions, representing the hierarchical apex of this system. It is involved in social, emotional, motivational, and self-regulatory processes and represents the site of convergence for extero- and interoceptive information (Bechara et al., 2000; Goel and Dolan, 2001; Rolls, 1999, 2000; Shammi and Stuss, 1999). Lateral and medial portions of this basal frontal cortex have different networks of connectivity. The medial sector is particularly related to hippocampal and parahippocampal regions, and the posterior cingulate and retrosplenial areas, while the lateral section has strong connections with the amygdala, sensory and premotor regions (Cavada et al., 2000).

Results of animal studies complement the findings on social functions of the (orbito-) frontal (and anterior temporal) cortex (Franzen and Myers, 1973). The ventral striatum may be seen as a subcortical extension of this anterior frontal-temporal circuit which Nauta (1979) termed the “expanded limbic system”. This region has been linked to emotional information processing as well (Davidson, 2000; Ohara et al., 1999; Thomas et al., 2001).

Elliot et al., (2000) suggested that the orbitofrontal cortex becomes active when there is insufficient information available to determine the appropriate course of action. Selection of stimuli, based on their familiarity and on a feeling of “rightness” are – according to these authors – related orbitofrontal functions. Further, decoding and readjusting the reinforcement value of stimuli seem to be an important function of the orbitofrontal cortex (Rolls, 1999), which therefore can be characterized as involved in high level judgement, implicating the anticipation of consequences, empathy and decision making (Bechara et al., 2000).

Autobiographical memories involve many of these processes attributed (among other regions) to the orbitofrontal cortex. They are inherently personal memories and therefore part of an individual’s personality – used to form the basis of the self (Conway and Pleydell-Pearce, 2000). Secondly, they are usually of an emotive character, having positive or negative valence. Thirdly, their retrieval or ephory requires consciousness. (The term ‘ephory’ is used to describe the process by which retrieval cues interact with stored information so that an image or a representation of the information in question appears, Tulving, 1983.)

A question of interest is, however, whether autobiographical memories of a positive (pleasant, happy) character recruit other portions of the frontal lobe than autobiographical memories of a negative (sad, unhappy) character. There is a huge literature on the influence of emotional valence on information encoding
and retrieval (Bower, 1992; Brewer, 1988; Holmes, 1970). It is also intriguing to ask whether, in addition to the likely engagement of frontal lobe regions, other brain areas are implicated differentially in the processing of sad versus happy old autobiographical memories, and whether processing episodes of a positive and of a negative character involve a difference in brain laterality.

Regions of the limbic lobe, in particular portions of the prefrontal/orbitofrontal cortex, the ventral striatum and the amygdala are considered to process emotional information (Davidson, 2000; Davidson and Irwin, 1999; Mesulam, 2000; Morris and Dolan, 2001). The amygdala receives preprocessed polysensory information and its left and right nuclear complexes respond differently to different aspects of emotional stimuli (Markowitsch, 1998/99), though frequently a bilateral activation can be measured with functional imaging methods such as functional magnetic resonance imaging (fMRI) (e.g., Royet et al., 2000; Sander and Scheich, 2001). There is evidence for a strong engagement of both amygdalae to fearful or negative as opposed to positive stimuli (Adolphs, 1999; Adolphs et al., 1999; Davidson and Irwin, 1999; Morris et al., 1998; Nader et al., 2000). Several careful analyses, however, challenged or specified (AK Anderson and Phelps, 1998; Davis, 1998) this view. Recent fMRI findings demonstrated significant and bilateral amygdala activations towards both positively and negatively valenced pictures and showed that the arousal level modulated the amygdala response for negative, but not for positive stimuli (Garavan et al., 2001). Furthermore it was found that the duration or frequency of exposure to emotional material may change amygdalar responses (Phillips et al., 2001). Wright et al., (2001) suggested from their fMRI findings to repeatedly presented emotional stimuli that the right amygdala is part of a dynamic emotional stimulus detection system and the left is specialized for sustained stimulus evaluations. (Related to their argumentation, Canli et al., 2000, suggested that amygdala activation reflects moment-to-moment subjective emotional experience.)

Aside from the relation of verbal material to the left and non-verbal to the right amygdala (Beauregard et al., 2001; Markowitsch, 1998/99), there are further laterality effects, some of which may have to do with the right hemispheric preponderance to attention mechanisms (Heilman and Van den Abell, 1980) and emotional expression (Borod et al., 1998; Cimino et al., 1991). Though there is some specific data in favor of lateralization effects between the amygdalae, results are not infrequently contradictory: Phelps et al. (2001) described, a specific activation of the left amygdala to the cognitive representation of fear, while Abercrombie et al. (1998) stated that the metabolic rate in the right amygdala predicts negative affect in depressed patients. Similarly, Drevets (1998) found that depressed patients had higher blood flow rates in the left amygdala, while Abercrombie et al. (1998) observed them in the right amygdala. Adolphs et al. (2001) compared 20 patients with unilateral amygdala damage and one with bilateral damage to two groups of control subjects. They found differences only for the subject with bilateral amygdala damage: she showed – compared to the controls – poorer memory for gist but superior memory for visual details.

Reviewing this literature, Markowitsch (1998/99) concluded that the left
amygdala is more closely related to affective encoding with a higher affinity for language and for detailed feature extraction, and the right amygdala to affective retrieval with a higher affinity for pictorial or image-related material. Furthermore, the right amygdala may be more strongly engaged than the left one in a fast, shallow or gross analysis of affect-related information.

Functional magnetic resonance imaging is used in normal human subjects to address these questions of interaction between memory, emotion, and functional neuroanatomy. We proposed that especially regions modulating memory by providing an affective flavor to it, would be activated. Furthermore, we assumed that in general regions similar as in our previous report (Fink et al., 1996) might be engaged. In the study of Fink et al. ventral prefrontal and temporal regions, including amygdalar and hippocampal areas were activated. Recently in an fMRI study Cadoret and co-workers (2001) also found that the ventrolateral prefrontal cortex was activated during the retrieval of previously stored visual representations. Other memory modulating regions, which might be activated within the present design include the cingulate gyrus (Fink et al., 1996; Markowitsch, 2000; Markowitsch et al., 2000; Shah et al., 2001), basal forebrain regions (e.g., septal region, ventral striatum) (Mesulam, 2000; Von Cramon and Markowitsch, 2000) and the precuneus – termed “the mind’s eye” by Fletcher et al. (1995) (Markowitsch et al., 2000; Shah et al., 2001).

The hippocampal region has also been consistently discussed, though more with respect to memory processing (Eichenbaum, 2000) than with respect to the processing of affect. The possible engagement of hippocampal regions in retrieval processes is thus controversial (Maguire et al., 2001) – especially as it seems to be impossible to distinguish between mere retrieval and retrieval accompanied by the re-encoding of the retrieved information (Tulving and Markowitsch, 1997, 1998). This is largely due to the unresolved nature of memory consolidation (McGaugh, 2000; Moscovitch and Nadel, 1998; Sara, 2000).

In the meantime, a considerable amount of literature on neuroimaging and emotion has accumulated. Because the central theme of the present investigation is on memory, only a short review will be given. Lane et al. (1997) reported in a PET study on pleasant and unpleasant emotions, elicited by pleasant, neutral, and unpleasant pictures, that unpleasant emotions activated the left amygdala and hippocampus. Other functional imaging studies also found increased neural activity in the left amygdala while negative emotions were being processed (Breiter et al., 1996; Ketter et al., 1996; Morris et al., 1996; Phelps et al., 2001; Schneider et al., 1995), whereas other authors reported the opposite pattern of lateralization: positive emotions leading to an increased left hemispheric amygdaloid activation, and negative emotions to an increased right hemispheric one (Canli et al., 1998; Tabert et al., 2001; Zalla et al., 2000). Gender effects might contribute to differences in results, as Schneider et al. (2000) recently found that only males demonstrated an amygdala activation during sadness, and Cahill and co-workers (2001) demonstrated activation with enhanced memory for emotional films in males on the right and in females in the left amygdala. Similarly, brain activations differed in part between sexes when viewing erotic film excerpts (Karama et al., 2002). In a developmental study on amygdala responses to affective faces, only females showed a progressive increase in
prefrontal relative to amygdala activation in the left hemisphere with increasing age (Killgore et al., 2001).

A specific aspect of emotions was the target of an fMRI study of Beauregard et al. (2001). They wanted to compare inhibition of sexual arousal, elicited by viewing erotic stimuli, with responding in a normal manner. Standard viewing resulted in activity of structures of the expanded limbic system – right amygdala, right anterior temporal pole, hypothalamus – while inhibition evoked activity in the right superior frontal and the right anterior cingulate gyri.

The present study was undertaken to study whether a person’s own biographical memories of different emotional valence (positive versus negative) lead to different metabolic changes on the brain level.

**METHODS**

**Subjects**

Subjects were 13 right-handed healthy volunteers (7 females) from the Universities of Cologne and Frankfurt am Main (average age: 30 years; range: 19-43 years). None had a history of previous neurological or psychiatric illnesses or syndromes. No gross brain abnormalities were found on magnetic resonance (MR) scans. All subjects were native German speakers. Informed consent was obtained from each subject prior to participation in this study.

**Procedure**

Subjects were told that psychologists have been studying memory for many years, but that there is still a need for research on the brain representation of autobiographical memory about pleasant and sad experiences. They were asked to retrieve autobiographic episodes of either a pleasant or a sad content, evoked by a fixed set of 36 key words, from the following periods of their life: (1) the first 12 years, (2) the period between years 12 and 18, (3) and from age 18 to the present. This division into three time periods was done (a) to obtain homogeneous episodes between subjects with respect to the past, and (b) in order to structure the retrieval of episodes. As there were not enough individual episodes to analyze per period, they were combined.

Subjects were encouraged to provide episodes with a degree of intensity as high as possible for both mood conditions. They were told that the investigators were not interested in particulars of the content, but in the general way in which different experiences are re-activated and memorized.

The episodes retrieved were sorted with respect to the two conditions. Subjects were asked to rate and comment on the intensity of their happy or sad emotion for each episode provided and on the easiness with which it came to their mind. Intensity and easiness had to be rated on scales between 1 and 10. Likewise, happiness or sadness had to be rated between 1 (neutral) and 10 for each given episode.

In spite of obviously differing in content between individuals, all episodes
were carefully selected with respect to their emotionality and their latency for evocation. While we attempted to maintain a balanced number of positive and negative episodes with respect to their intensity, this was not always possible. Likewise, it was not possible to maintain the same average of intensity across subjects. Some individuals rated nearly everything as very intensive, while others were more moderate in their ratings. We obtained a mean intensity level of 7.8 for the positive, and a mean intensity level of 6.7 for the negative condition.

These results correspond to those of previous reports studying positive and negative autobiographical episodes, in which positive compared to negative episodes tended to be more intense, elaborated, and more easily accessed (Larsen, 1998). In line with this result, Raspotnig (1997) found that the imagery associated with positive memories is more vivid than that related to negative memories. D’Argembeau et al. (2002) similarly found that positive autobiographical episodes were more easily accessed, tended to be more elaborated, and were more frequently rehearsed than negative autobiographical episodes. D’Argembeau et al. interpreted their findings as consistent with the general positive view most people possess from themselves.

After the interview phase, subjects practiced using a computer program to become familiar with the key words and the time-constraints of the procedure. Subjects received the key words on a computer screen for 5 s and checked whether each key word immediately evoked the appropriate episode.

Brain scanning was done on the day of the interview; subjects were instructed to re-imagine their original episodes. The key words used in the interview were presented for 5 s on a screen. The screen was completely darkened for the next 20 s while subjects retrieved the triggered episode. Following an alternation (‘boxcar’) design, every task (imagination) period of 25 s alternated with a rest condition of the same length (5 scans each for rest and task). During the two experimental conditions sad and happy episodes had to be ephorized, that is subjects retrieved previously elicited memories from their past. During REST, subjects had to fixate a small cross centered on the screen with a light gray background (similar to the one in the study of Fink et al., 1996). The higher luminance of the rest-screen indicated to the subjects that they were to immediately stop the imaginations from the complete darkness phase. All 36 cues (18 sad, 18 pleasant) were arranged in 2 blocks, consisting of 6 successive items of the same quality (first 6 sad, then 6 happy ones, in fixed order), and 3 time periods (childhood, adolescence, recent past). The sequence of sessions (120 scans each) was counterbalanced between subjects. Before starting a session, the display showed them the imaginative ‘life period’ to facilitate retrieval: “you are a child” (or ‘adolescent’, or ‘adult’).

After scanning, subjects were again asked to rate and comment on their retrieved episodes (easiness of retrieval, emotional intensity of the episode). The questions depicted in Table I were used.

fMRI procedure

Prior to the start of the experiment, subjects’ brains were scanned with MRI to exclude morphological-pathological abnormalities. All fMRI measurements
were performed on a 1.5 Tesla whole-body scanner (Siemens Vision) with standard head coil and using a standard EPI sequence (TR = 5 s, TE = 66 ms, FA = 90°, FoV = 220; matrix 128 × 128, voxel size=1.64 × 1.64 × 5, scan time 2 s for 15 slices, 5 mm slice thickness). All fMRI scans were realigned to the initial scan to correct for any head movement. Between each of the 3 sessions of 125 scans each (first 5 discarded) a short break was necessary for technical reasons to restart the EPI sequence for the next 125 measurements. Subjects were instructed to hold their position unchanged over sessions. Data analysis was performed using SPM (Worsley and Friston, 1997). After realignment of all 360 scans to the first scan, and spatial normalization to standard stereotactic space (Friston et al., 1995), images were smoothed applying a Gaussian kernel.

### TABLE I

**Questions Used to Trigger Emotive Episodes from the Past**

<table>
<thead>
<tr>
<th>Category</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. NEGATIVE REMEMBRANCES FROM CHILDHOOD</strong></td>
<td>1. The first negative memory in your life that you remember truly.</td>
</tr>
<tr>
<td></td>
<td>2. A situation in which you were very angry.</td>
</tr>
<tr>
<td></td>
<td>3. A situation in which you experienced anxiety.</td>
</tr>
<tr>
<td></td>
<td>4. A situation in which you were hurt.</td>
</tr>
<tr>
<td></td>
<td>5. A negative memory about a friend.</td>
</tr>
<tr>
<td></td>
<td>6. A sad memory</td>
</tr>
<tr>
<td><strong>B. POSITIVE REMEMBRANCES FROM CHILDHOOD</strong></td>
<td>1. The first positive memory in your life that you remember truly.</td>
</tr>
<tr>
<td></td>
<td>2. A positive event you can remember, for example a play situation.</td>
</tr>
<tr>
<td></td>
<td>3. A birthday in your childhood.</td>
</tr>
<tr>
<td></td>
<td>4. A positive memory about a good friend.</td>
</tr>
<tr>
<td></td>
<td>5. A pleasant memory in which you played with others.</td>
</tr>
<tr>
<td></td>
<td>6. A pleasant holiday situation.</td>
</tr>
<tr>
<td><strong>C. NEGATIVE REMEMBRANCES FROM ADOLESCENCE</strong></td>
<td>1. A negative experience from your school-time.</td>
</tr>
<tr>
<td></td>
<td>2. A close contact with another person, which evoked very awkward feelings.</td>
</tr>
<tr>
<td></td>
<td>3. A very awkward situation in which you were alone.</td>
</tr>
<tr>
<td></td>
<td>4. A negative experience evoking massive stress.</td>
</tr>
<tr>
<td></td>
<td>5. A shameful situation.</td>
</tr>
<tr>
<td></td>
<td>6. A conflict with someone close</td>
</tr>
<tr>
<td><strong>D. POSITIVE REMEMBRANCES FROM ADOLESCENCE</strong></td>
<td>1. Feelings of being in love.</td>
</tr>
<tr>
<td></td>
<td>2. A pleasant experience of success.</td>
</tr>
<tr>
<td></td>
<td>3. A cheerful amusing adventure.</td>
</tr>
<tr>
<td></td>
<td>4. A very agreeable situation with someone.</td>
</tr>
<tr>
<td></td>
<td>5. A happy holiday.</td>
</tr>
<tr>
<td></td>
<td>6. A very pleasant appointment.</td>
</tr>
<tr>
<td><strong>E. NEGATIVE REMEMBRANCES FROM ADULTHOOD</strong></td>
<td>1. A situation in which you were very worried.</td>
</tr>
<tr>
<td></td>
<td>2. A moment of deep sadness.</td>
</tr>
<tr>
<td></td>
<td>3. The death of a beloved person.</td>
</tr>
<tr>
<td></td>
<td>4. A situation in which you were exploited.</td>
</tr>
<tr>
<td></td>
<td>5. A situation in which you were hurt.</td>
</tr>
<tr>
<td></td>
<td>6. A situation in which you were jealous.</td>
</tr>
<tr>
<td><strong>F. POSITIVE REMEMBRANCES FROM ADULTHOOD</strong></td>
<td>1. One of your happiest moments in the last years.</td>
</tr>
<tr>
<td></td>
<td>2. A very motivating positive situation.</td>
</tr>
<tr>
<td></td>
<td>3. A happy moment.</td>
</tr>
<tr>
<td></td>
<td>4. A really joyful situation.</td>
</tr>
<tr>
<td></td>
<td>5. The memory of a very pleasant, intimate experience.</td>
</tr>
<tr>
<td></td>
<td>6. A situation which made you very enthusiastic.</td>
</tr>
</tbody>
</table>
of 12 mm FWHM. Statistical analysis was then carried out in two stages. First, a fixed effect (within-subject) model was applied to the time series of every individual subject. After filtering (high-pass: 100 s, low-pass: hrf), and proportional scaling the images to overall grand mean, t-statistic maps (height threshold: \( t = 3.12 \)) were generated for the contrasts (SAD > REST), (HAPPY > REST), (SAD > HAPPY) and (HAPPY > SAD) and a single contrast image was written out from the parameter estimates for each contrast and for every subject. Then, with one summary contrast ‘scan’ per subject, a second-level random effects analysis was conducted for these four contrasts, applying a one-sample-t-test model. This approach takes the between subjects variability into account and extends inferences from the subjects studied to the overall population effects. The resulting activation maps were superimposed to the MNI template brain of SPM 99 (Figures 1 and 2).

Statistical analysis

All possible permutations of any two of the three conditions SAD, HAPPY, REST were analyzed, applying contrast calculation within the general linear model approach provided by the SPM 99 software (two-level random effect analysis [Friston et al., 1995]). Performing a two-level random effects – second level – analysis implies to include inter-individual variances in the tests of significance. It further implies to report p-values uncorrected for the entire volume.

RESULTS

Subjects provided in general affect-based episodes with easiness: The average rating score was 7.2 for the intensity with which subjects rated the emotions on the scale ranging between 1 (lowest intensity) and 10 (meaning highest intensity). Easiness of remembrance of a specific episode was scored 6.6 on the average (10 meaning absolutely no effort necessary or that the episode came ‘automatically’ to mind).

The main results are a lateral orbitofrontal activation, when activating SAD memory episodes, and a subcallosal-anterior cingulate activation, when activating HAPPY ones. The terminology used for these regions differs: Sometimes, they are referred to as limbic frontal or frontolimbic cortex, sometimes as orbitofrontal or basal frontal regions, and some authors use the term prefrontal even when addressing anterior cingulate and subcallosal regions (e.g., Gusnard et al., 2001; Simpson et al., 2001). The cingulate sulcus and paracingulate gyrus are structurally variable, so that exact anatomical locations differ between subjects (cf. Paus et al., 1996).

The most revealing comparisons were those between sad and pleasant episodes (SAD > HAPPY; HAPPY > SAD). Figures 1 and 2 illustrate our main results.

The SAD > HAPPY contrast (after random effect analysis) revealed a major symmetrical activation of the lateral orbitofrontal cortices, possibly extending...
into the ventrolateral prefrontal cortices (see Table II for coordinates), together with smaller activated regions in the right lateral temporal cortex and the left cerebellum (Figures 1 and 2; Table II). Vice versa, the comparison of the retrieval of pleasant episodes with that of sad ones (HAPPY > SAD condition) revealed a major activation in the left hippocampal region, a bilateral activation (with a preponderance to the right hemisphere, however) in the subgenual cingulate (Brodmann area 25) and a left dorsolateral activation of the prefrontal area (Table II). The medial subcallosal activation was exactly below the genu of the corpus callosum (Figures 1 and 2). The levels of this activity were all highly significant (second-level random effects analysis; height threshold t = 3.93, \( p_{\text{uncorrected}} < .0001 \)).

Comparisons of the activation conditions with the condition REST uncovered...
Hans J. Markowitsch and Others

TABLE II
Activated Regions in the Comparisons Employed

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Region</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAD &gt; HAPPY COMPARISON</td>
<td>Lateral orbitofrontal cortex, left</td>
<td>−52</td>
<td>24</td>
<td>−2</td>
<td>3.52</td>
</tr>
<tr>
<td></td>
<td>Lateral orbitofrontal cortex, right</td>
<td>54</td>
<td>34</td>
<td>−6</td>
<td>3.79</td>
</tr>
<tr>
<td></td>
<td>Lateral temporal cortex, right</td>
<td>64</td>
<td>−28</td>
<td>−12</td>
<td>3.90</td>
</tr>
<tr>
<td></td>
<td>Cerebellum, left</td>
<td>−10</td>
<td>−60</td>
<td>24</td>
<td>3.99</td>
</tr>
<tr>
<td>HAPPY &gt; SAD COMPARISON</td>
<td>Medial orbitofrontal cortex, right</td>
<td>14</td>
<td>26</td>
<td>−10</td>
<td>3.77</td>
</tr>
<tr>
<td></td>
<td>Medial orbitofrontal, left</td>
<td>−24</td>
<td>24</td>
<td>48</td>
<td>3.79</td>
</tr>
<tr>
<td></td>
<td>Hippocampal region, left</td>
<td>−30</td>
<td>−28</td>
<td>−16</td>
<td>4.10</td>
</tr>
<tr>
<td></td>
<td>Dorsolateral prefrontal cortex, left</td>
<td>−24</td>
<td>24</td>
<td>48</td>
<td>3.79</td>
</tr>
<tr>
<td>SAD &gt; REST COMPARISON</td>
<td>Anterior cingulate gyrus (area 24/32), left</td>
<td>12</td>
<td>20</td>
<td>26</td>
<td>4.89</td>
</tr>
<tr>
<td></td>
<td>Lateral orbitofrontal cortex (area 47), left</td>
<td>−44</td>
<td>44</td>
<td>10</td>
<td>4.84</td>
</tr>
<tr>
<td></td>
<td>Lenticular nucleus, right</td>
<td>28</td>
<td>10</td>
<td>2</td>
<td>4.81</td>
</tr>
<tr>
<td></td>
<td>Cerebellum, medial</td>
<td>4</td>
<td>−48</td>
<td>−18</td>
<td>4.22</td>
</tr>
<tr>
<td>HAPPY &gt; REST COMPARISON</td>
<td>Posterior temporal gyrus (area 37), right</td>
<td>32</td>
<td>−56</td>
<td>2</td>
<td>5.99</td>
</tr>
<tr>
<td></td>
<td>Anterior cingulate gyrus (area 24/32), right</td>
<td>14</td>
<td>16</td>
<td>28</td>
<td>5.37</td>
</tr>
<tr>
<td></td>
<td>Medial frontal gyrus, left</td>
<td>−16</td>
<td>20</td>
<td>48</td>
<td>5.19</td>
</tr>
<tr>
<td></td>
<td>Superior frontal gyrus, left</td>
<td>−12</td>
<td>−45</td>
<td>4</td>
<td>5.12</td>
</tr>
<tr>
<td></td>
<td>Precuneus, left</td>
<td>−26</td>
<td>−58</td>
<td>16</td>
<td>5.09</td>
</tr>
<tr>
<td></td>
<td>Ventral pallidal/dorsal amygdalar region, left</td>
<td>−22</td>
<td>−4</td>
<td>−4</td>
<td>5.29</td>
</tr>
</tbody>
</table>

All these activations were highly significant, after second-level random effects analysis (height threshold $t = 3.93$, puncorrected < .0001).

Fig. 2 – Projections of activations onto representations of the standard stereotactic space as defined by Talairach and Tournoux (1988) (“SPM-99 glass brains”). The top three maps show the activations for the SAD > HAPPY, and the bottom tree for the HAPPY > SAD comparison.
(for second-level analyses) several significant activations for the comparisons HAPPY > REST and SAD-REST (Table II; Figure 2). For the HAPPY > REST comparison, regions in the right posterior temporal and anterior cingulate cortex, in the left dorsolateral cortex, the medial frontal cortex, the left precuneus and the left ventral pallidal – dorsal amygdalar region were activated; for the SAD-REST comparison, the left lateral orbital frontal cortex, the right anterior cingulate cortex, the right lenticular nucleus and the medial cerebellar region were activated.

**DISCUSSION**

This study is a further step in tracing the functional anatomy of episodic memory. It centers on old autobiographical information and emphasizes the link between emotion and memory. There are several important aspects of these results: the activity patterns are very distinct and differ considerably between negatively and positively experienced episodes. With the exception of the cerebellar one, all activations involve the cerebral cortex and are largely confined to limbic or paralimbic regions. Within limbic structures, the hippocampal region was only activated during the retrieval of happy memories (but not significantly in the HAPPY > REST condition), suggesting that at least under the circumstances of data analysis (e.g., combining the three time periods tested), ephorizing past episodes engages the hippocampal region only to a minor degree. This finding is in conformity with a recent study of our group, where we found a hippocampal engagement only for more recent, but not for remote old autobiographical memories (Piefke et al., 2003). As we combined in our present analysis memories from childhood and adulthood, a less prominent hippocampal activation remained which was only significant for the HAPPY > SAD condition. In line with our present findings of a left hippocampal activation for the HAPPY > SAD, Piefke et al. (2003) had observed a left medial temporal lobe and a left temporal pole activation for this same comparison, but – again in line with the present results – not for the other comparisons (e.g., not for SAD>HAPPY). Here, they observed activations in the right middle temporal gyrus which again corresponds to our present findings (cf. Table II). Also in the report of Liotti et al. (2000), no hippocampal activations were found in relation to generated sadness or anxiousness provoking autobiographical memories.

Alternatively, the selective hippocampal engagement for the HAPPY > SAD condition might reflect a more intense re-encoding, elaboration and rehearsal of aspects of the happy memories just retrieved, which would correspond to our finding of a higher level of intensity in association with the retrieval of positive memories (cf. Methods section and Buckner et al., 2001). Thirdly, future studies need to consider possible differences in neural activations related to gender (Cahill et al., 2001; Schneider et al., 2000; cf. below under the ‘amygdala’).

Differences in activation patterns between the HAPPY > SAD and the HAPPY > REST conditions possibly indicate the major visual and emotional components, which are seen in the comparison to rest, but not in that between the two emotional memory conditions. Similarly, the cingulate activation, found
in the HAPPY > REST and SAD > REST may be related to emotional as well as attentive mechanisms (George et al., 1995; Mayberg et al., 1999). Interestingly, this activation was right-hemispheric for the positive and left-hemispheric for the negative ones.

The orbitofrontal and subcallosal cortex thus appear to be a major hub for the retrieval of emotional memories. The orbitofrontal cortex and its immediately adjacent prefrontal and anterior ventral cingulate regions figure as major trigger stations for ephorizing emotionally colored episodes of the distant past. Within this area there is a clear distinction between regions engaged in the retrieval or ephory of positive and negative episodes of the distant past. We will comment on these findings.

The orbitofrontal-subcallosal area as a hub for emotional memory retrieval

The division of medial and lateral portions of the basal frontal cortex, as described by Cavada et al. (2000), corresponds (a) to the selective medial subgenual (and left hippocampal) activation when ephorizing positively valued episodes, and (b) to the selective lateral orbitofrontal activation, when remembering sad or unhappy episodes (it has repeatedly been stressed that the amygdala evaluates negative or particularly intense emotions to a higher degree than positive ones; Canli et al., 2000; Markowitsch, 1998/99). Related to this point are the findings of Frey et al. (2000) of area 13 involvement in the processing of unpleasant auditory information and that of Simpson et al. (2001) of medial orbitofrontal/subgenual involvement during anticipatory anxiety.

In the literature on conscious reflection (Wheeler et al., 1997), attribution within personal theory of mind (Stuss et al., 2001), and on self-recognition, personal identity and self-referential mental activity (Gusnard et al., 2001; Keenan et al., 2000; Kircher et al., 2000; Miller et al., 2001) there are proposals or links to the ventral (and medial) frontal lobe, and these proposals are fully in accordance with our present observation of activations in exactly this portion of the brain. The interaction between memory and emotion consequently seems to be central for the self (Markowitsch, in press).

We cannot determine whether the activation in the two disparate loci reflects the triggering of the respective episodes or is used to influence (e.g., suppress) the respective other circuit. In favor of this last hypothesis are observations of Zubieta et al. (1999), who found a medial frontal engagement in posttraumatic stress symptoms, and of Elliot et al. (2000), who suggested that activation of the lateral orbitofrontal cortex may reflect the suppression of previously rewarded responses. (However, they also referred to an activation of the lateral orbitofrontal cortex when viewing an angry face.) For the first hypothesis, on the other hand, the work of Blood et al. (1999) is relevant who found that emotional responses to pleasant music correlated with medial orbitofrontal activation. Price (1999) referred to PET data which showed increased blood flow in the lateral orbitofrontal cortex in patients with unipolar depression (compared to normals) and decreased blood flow in medial frontal regions in bipolar, manic-depressive patients, in their depressed phase, suggesting again a differential involvement of these two basal frontal sectors in emotional processing. Gusnard et al. (2001)
hypothesized from their findings with functional magnetic resonance imaging that the region they term medial prefrontal cortex (and which with respect to anatomical co-ordinates closely resembles our medial anterior orbital/subcallosal area) is engaged in aspects of the self (‘self-referential mental activity’), which they found by letting subjects determine which of presented pictures were pleasant or unpleasant.

There are a few results which may be viewed as at variance with our findings of a medial anterior cingulate/subcallosal activation when ecphorizing positively valued episodes and a lateral orbitofrontal activation when ecphorizing negatively valued ones: In a PET-study Mayberg and co-workers (Mayberg et al., 1999; Liotti et al., 2000) found increases in sadness related activity in the subgenual cingulate cortex, and Drevets et al. (1998) found that the volume of the subgenual prefrontal cortex is reduced in patients with major depressive disorders. These observations might, however, indicate that this cortical region, in fact, processes positively valued information in normal, non-depressed subjects. Alternatively, or in addition, it could process both positively and negatively valued episodes, but with varying strength or engagement. Evidence for this view was provided by Rolls (2000) and Ochsner et al. (2001). Rolls (2000) reviewed neuroimaging results which showed that “areas of the orbitofrontal cortex (and connected subgenual cingulate cortex) are activated by pleasant touch, by painful touch, by rewarding and aversive taste, and by odor” (p. 284). From their findings in a patient with bilateral anterior cingulotomy, Ochsner et al. suggested that one “of the anterior cingulate’s roles may be to monitor on-line processing and signal the motivational significance of current actions or cognitions” (p. 219), indicating a more general role of this cortex in information processing.

Recently, Lepage et al. (2000) also found anterior cingulate activations during memory retrieval tasks and proposed that neuronal activity in this region is correlated with the maintenance of the episodic memory retrieval mode, a condition necessary for remembering past episodes. In this article, they also provided a new interpretation of their HERA model (hemispheric encoding retrieval asymmetry) by writing that the previously assumed strict right hemispheric activation during episodic retrieval should be replaced by a bilateral, though more prominently right hemispheric activation – a revision fitting our present data.

In conclusion, spatially different and distinct portions of the human basal frontal cortex seem to work as hubs within wider and primarily cortical nets engaged in ecphorizing old autobiographic episodes of a positive or negative character.

Dorsal prefrontal cortex

As mentioned above, we found a left dorsolateral prefrontal activation (together with a left hippocampal one) during the retrieval of happy episodes. The left dorsolateral prefrontal cortex is engaged in numerous functions, above all, in encoding episodic and semantic information (Tulving et al., 1994; Nolde et al., 1998). It has also been suggested that this brain region is engaged in
‘working with meaning’ (Kapur et al., 1994), an interpretation fitting the present design. As the retrieval of episodes is accompanied by their re-encoding, this might be an explanation for the left dorsolateral activation. The selective activation under the condition ‘HAPPY > SAD’ is most likely related to the significance threshold set.

Reduced activation of the dorsolateral prefrontal cortex has been found in a variety of psychiatric diseases such as in schizophrenia (Selemon et al., 1998); furthermore, dysfunction to the left dorsolateral prefrontal cortex is associated with clinical depression (Baxter, 1989; Martinot et al., 1990; Robinson, 1996).

**Hippocampal formation**

The hippocampal formation is that brain structure which first comes to mind in connection with memory. The engagement of the hippocampus in autobiographic information processing (Vargha-Khadem et al., 1997), and in particular in conscious recollection (Heckers et al., 1998), and the fronto-hippocampal disconnection hypothesis in schizophrenia (Csernansky et al., 1998; Fletcher, 1998), all fit the combined prefrontal and hippocampal activation seen under the condition HAPPY > SAD. Vargha-Khadem et al. (1997) demonstrated that young patients without a hippocampus proper were unable to encode (and consequently also unable to retrieve) autobiographical episodes, while they could successfully retrieve world knowledge which is independent of conscious reflection (Markowitsch, in press). An interaction between ventral prefrontal and hippocampal regions has been proposed both from anatomical (Lavenex and Amaral, 2000) and functional (Mesulam, 2000; Seamans et al., 1998) points of view. It seems therefore possible to consider the principal activation pattern as reflecting neuronal circuitry for emotional evaluation of memorized episodes and possibly even more so of those with a positive affective background.

Alternatively, or in addition, the hippocampal activation could indicate that this region indeed is implicated in information retrieval – at least for a limited period of time (as we combined the three time periods we cannot determine whether there is a greater activation for the retrieval of more recent as opposed to more remote memories) (cf. Moscovitch and Nadel, 1998). If this were true, it might be that the selective – left hemispheric – activation just became significant, while the right hemispheric did not. Or, that retrieving old episodes (or old positively valued episodes) engages the hippocampal formation of the left hemisphere.

The issue of laterality, where initially a right-hemispheric dominance was seen (Fink et al., 1996; Tulving et al., 1994; Shallice et al., 1994) became much less clear-cut over the last years (cf. Ojemann et al., 2002, for temporal areas, discussed below). The recent review of Lee and co-workers (2002) discusses this issue extensively. These authors question the importance of language related material for a left hemispheric activation (both for encoding and retrieval) and suggest that a multitude of factors in various combinations will lead to a more pronounced left or right hemispheric activation. Similarly, Nolde et al. (1998) earlier had argued that more demanding or ‘reflective’ retrieval situations may activate regions of the left hemisphere to a greater extent than basic mnemonic
processes. Cabeza et al. (2002), on the other hand, stressed that it is not so much the reflection, but the generation of information during more demanding conditions (e.g., free recall as opposed to recognition) which activates the left hemisphere. Other authors found that the retrieval of specific perceptual information (‘picture-like memories’) engages left-hemispheric more than right-hemispheric regions (Ranganath et al., 2000).

Cerebellum

The significant left hemispheric cerebellar activation corresponds to the findings of others suggesting that the left cerebellum is particularly engaged in several nonmotor mental activities, including episodic memory retrieval (Andrease et al., 1999; Cabeza and Nyberg, 2000; Fink et al., 1996), and attribution or experience of emotion (Lane et al., 1997; Paradiso et al., 1999). In the study of Andreasen et al. (1999) subjects intentionally recalled a specific past personal episodic memory. The authors suggested the participation of the cerebellum in an interactive cortical-cerebellar network initiating and monitoring the conscious retrieval of episodic memory. Probably, therefore, cerebellar neurons provide a (sequencing) time code or a temporal programming to ephorized events.

Lateral temporal cortex

The selective engagement of a right-hemispheric region of the lateral temporal gyrus during the retrieval of sad episodes can be interpreted differently: it more likely reflects a more controlled, less emotional access to unpleasant as opposed to pleasant past experiences. Sad as opposed to happy episodes probably have different degrees of vividness, ‘mental visibility’, and self-attribute (Kircher et al., 2001; Kircher et al. (2001) suggested the right temporal cortex to be associated with the semantic processing of sentences. Distantly related old work of Flor-Henry (1963) on patients with epilepsy pointed out that psychotic (schizophrenic) behavior is more likely associated with dysfunction of the left (‘dominant’ in his words), than of the right temporal lobe region, while vice versa dysfunction of the right temporal lobe is associated with depressive behavior. The temporal region probably reflects the particular engagement of a possible storage place for engrams (Chen et al., 1996; Miyashita et al., 1998; Sakai and Miyashita, 1994).

While there is not much controversy with respect to the importance of lateral temporal regions for old memory processing (Phelps et al., 1997), the issue of left and right temporal lobe engagement and of a differential engagement during positively as opposed to negatively rated memories is a complex one. This becomes especially evident when comparing studies relying on different methodological approaches (e.g., studying of brain damaged patients, functional neuroimaging in healthy subjects, single-unit recordings in patients). Ojemann and co-workers (2002) recently discussed this issue, based on their results obtained from single cell recordings in the human lateral and inferior temporal cortex (see also Fletcher and Tyler, 2002). Ojemann et al. failed to find
hemispheric differences within lateral and inferior temporal cortices for encoding, storage, and retrieval processes of memory.

The tone of resignation formulated in the abstract of a recent functional imaging study on positive and negative emotional material seems nevertheless to reflect the still open issues on laterality and precise topographical assignments: “The outcomes of imaginal studies of emotions seem to be largely dependent on the conservativeness of the statistical analysis and very likely also on the method of emotion induction” (Aalto et al., 2002, p. 67).

**Amygdala**

The amygdala can be regarded as that structure that attaches emotional flavors to memories (Sarter and Markowitsch, 1985). Consequently, we might well expect it to be activated during the retrieval of old biographical memories (Dolan et al., 2000; Fink et al., 1996; Markowitsch, 1998/99; Markowitsch et al., 2000). Indeed, this was found when comparing retrieval of happy memories with the rest condition. However, the comparisons of principal interest, namely HAPPY > SAD and SAD > HAPPY, apparently cancelled out the amygdala’s activation. Alternatively, or in addition, one could speculate about a habituation effect (Wright et al., 2001). The male-female differences in amygdaloid activation during memory retrieval (Cahill et al., 2001) and during sadness (Schneider et al., 2000) complicate the picture further. Together, these factors may have resulted in an insignificant activation of the amygdala during all but one condition of comparison. Aalto et al. (2002) studied possible neuroanatomical substrates of amusement and sadness with PET. Similarly to our results, they failed to find amygdala activations in a strict explorative analysis and attributed the differences to earlier reports (who had observed amygdala activations) to differences in statistical and methodological approaches.

**Bi-hemispheric activations**

The bi-hemispheric activations in the orbitofrontal cortex in the two principal comparisons HAPPY>SAD and SAD>HAPPY may reflect the comparatively high demands of the task, requiring the activity of neurons in the respective areas of both hemispheres. Similar bi-hemispheric activations have been found in other memory retrieval paradigms (Ranganath and Paller, 2000). They may also be due to the combined visual and verbal portions of the retrieved episodes (Wagner et al., 1998).

**Conclusions**

This report provides evidence for an engagement of portions of the orbitofrontal/ventral prefrontal cortex in the retrieval of old, emotionally colored episodes. We demonstrate a differential activation towards past episodes that were viewed as clearly happy or otherwise positive in character and episodes
that were viewed as clearly of a sad or otherwise negative character. This study complements earlier ones in which it was found that the retrieval of old episodes activates a temporo-frontal network of structures for which the expression “expanded limbic system” (Nauta, 1979) can be used as umbrella (Fink et al., 1996; Markowitsch et al., 2000). Areas especially within the prefrontal lobe can be described as acting in a dynamic interplay between cognition and emotion (Simpson et al., 2001a, b).

From our findings it can be concluded that different anatomical networks engage in the ecphory of positively and negatively rated biographical events. It can furthermore be concluded that cortical structures provide a significant contribution to the processing of affective memories.

While we are quite confident about the reliability and validity of the results obtained, some cautious remarks have to be made. The possibilities for controlling and equalizing responses between subjects are limited; subjects provide different statements which vary in contents as everyone has his or her own, individual background of experiences. Furthermore, when one subject makes a specific intensity rating of his or her experience this does not imply that another subject would have made the same rating towards the same experience. Individual backgrounds, personality variables, mood conditions etc. influence ratings. Fresh experiences may have more detail and vividness, old experiences on the other hand may still be remembered exactly because of their emotional severity. Gender may contribute to enhancing or diminishing possible neural activation effects towards affect-related information (Cahill et al., 2001; Killgore et al., 2001; Schneider et al., 2000). Consequently, it cannot be excluded that different aspects of emotional and memory variables contribute differently in male and female subjects to our finding of an anatomical separation of positively and negatively valued autobiographical episodes.

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REFERENCES


GOLDSTEIN JM, GOODMAN JM, SEIDMAN LJ, KENNEDY DN, MAKRIS N, LEE H, TOURVILLE J, CAVINESS VS Jr, FARONE SV and TSUANG MR. Cortical abnormalities in schizophrenia identified by structural magnetic resonance imaging. *Archives of General Psychiatry, 56*: 537-547, 1999.


KETTER TA, ANDREASON PJ, GEORGE MS, LEE C, GILL DS, PAREKH PI, WILLIS MW, HERSCOVITCH P and...


MAGUIRE EA, HENSON RNA, MUMMERY CJ and FRITH CD. Activity in prefrontal cortex, not hippocampus, varies parametrically with the increasing remoteness of memories. *NeuroReport, 12*: 441-444, 2001.


MORRIS JS, FRISTON KJ, BüCHEL C, FRITH CD, YOUNG AW, CALDER AJ and DOLAN RJ. A


SANDER K and SCHIECH H. Auditory perception of laughing and crying activates human amygdala


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