Dissociable contributions within the medial temporal lobe to encoding of object-location associations

Tobias Sommer,1 Michael Rose, Jan Gläscher, Thomas Wolbers, and Christian Büchel

The crucial role of the medial temporal lobe (MTL) in episodic memory is well established. Although there is little doubt that its anatomical subregions—the hippocampus, peri-, entorhinal and parahippocampal cortex (PHC)—contribute differentially to mnemonic processes, their specific functions in episodic memory are under debate. Data from animal, human lesion, and neuroimaging studies suggest somewhat contradictory perspectives on this functional specialization: a general participation in declarative memory, an exclusive involvement in associative mnemonic processes, and a specific contribution to spatial memory are reported for the hippocampus, adjacent cortices, and the PHC. A functional lateralization in humans dependent on the verbalizability of the material is also discussed herein. To further elucidate the differential contributions of the various MTL subregions to encoding, we employed an object-location association memory paradigm. The memory for each of the studied associations was tested twice: by the object, and by the location serving as retrieval cue. The memory accuracy in response to both cue types was also assessed parametrically. Brain activity during encoding which leads to different degrees of subsequent memory accuracy under the two retrieval conditions was compared. We found the bilateral posterior PHC to participate in encoding of both the object associated with a location and the location associated with an object. In contrast, activity in an area in the left anterior PHC and the right anterior MTL was only correlated with the memory for the location associated with an object.

Results

Behavior

We employed a substantial modification of a previously introduced recognition-memory paradigm with a significantly prolonged recognition test and two different retrieval cue types. We were concerned about three issues: (1) difficulty of the task, (2) differences in both cue types, and (3) better understanding of the cognitive processes followed by both retrieval cues. A description of the task is given in Figure 1.

Response accuracy during the encoding task was high (98.8%, SD 1.2), and only objects that were categorized correctly
The task was to indicate, by selecting one or more objects depending on the accuracy of memory, which object was associated during the encoding phase. When retrieval was cued by the object, one of the studied objects appeared in the center of the screen, twice in randomly intermixed order: (1) by the object and (2) by the location serving as retrieval cue. When retrieval was cued by the location, the 16 locations appeared on the screen, one with a white question mark, followed by the same 16 objects randomly rearranged in two rows in the middle of the screen. The task was to indicate, by selecting one or more objects depending on the accuracy of memory, which object was associated with the location during the encoding phase.

by the subject were analyzed further. We found that 96.8% of all responses in the subsequent memory test in response to both cue types (object as well as a location retrieval cue) fell into the five categories 1 to 4 and 16 selected locations, where the latter one corresponds to the indication of a forgotten location. To simplify further analyses, only these responses’ categories (RCs) were included and will be referred to as RC1 to RC4 (one to four selected objects/locations) and RC 5 (indication of a forgotten object/location). The proportions of the various RCs are not equally distributed. A cue type \( \times \) RC ANOVA revealed a significant main effect of response-category \( [F_{4,56} = 22.2; P < 0.000] \) and a significant interaction \( [F_{4,56} = 10.1; P < 0.000] \). RC1 is more frequent than the remaining responses’ categories (post hoc Tukey HSD tests \( P < 0.000 \)) in response to both cue types. RC4 was more frequent after an object cue and RCs after a location cue (post hoc Tukey HSD tests \( P < 0.000, P = 0.01 \) respectively; Fig. 2).

A comparison with the behavioral results of a previous study (Sommer et al. 2005) using only object retrieval cues revealed no significant difference in the proportion of the RCs (design-complexity \( \times \) RC ANOVA, \( F_{4,112} = 0.46 \)).

In addition, the hit rate in RC1 is greater than in the remaining RCs, as a cue type \( \times \) RC ANOVA revealed \( [F_{4,112} = 14.3; P < 0.000] \); post hoc Tukey HSD \( P < 0.01 \) for RC 1 vs. 2, 3, 4; Table 1]. Although subjects were instructed to indicate in case of low confidence a forgotten object/location, they selected sometimes false objects/locations, which is defined as “guessing.” The likelihood of a “lucky guess” differs depending on the number of selected locations/objects (see Materials and Methods). Therefore the hit rates must be corrected for “lucky guesses” to test whether they are above chance in all RCs. Assuming that the misses provide a rough estimate of the guessing rate for hits in our paradigm (Snodgrass and Corwin 1988), we adopted the correction for guessing (Rugg et al. 1998) for our recognition task where subjects had to select from 16 alternative objects/locations, as follows: For one selected location, the probability for a lucky guess is 1/16. Therefore the miss rates represent 15/16 of the merely guessed responses, and 1/16 of lucky guesses is hidden in the hit rate. In other words, 1/16 of the miss rate is just by chance correct, and the hit rate must be corrected by this value to get a more valid behavioral measure of the accuracy. Following this rationale, the hit rates in the four categories were corrected for guessing. Importantly, the corrected hit rate in all categories significantly exceeded the particular chance level \( (P < 0.000 \) for all RCs).

In the further behavioral analysis, the relative proportion of the five RCs were entered because the relative composition is an indicator for the overall memory performance. The proportions of correct responses were lucky guess-corrected by the misses as outlined above to get a more valid behavioral measurement of memory accuracy.

There was no significant effect of the duration of the preceding or following interstimulus interval (ISI) (0–2 null events, min. 2.5 sec, max. 14.5 sec) for any of the RCs (ISI \( \times \) cue type \( \times \) RC ANOVAs \( F_{4,112} = 1.11 \), respectively \( F_{4,112} = 0.35 \)). The reaction time (RT) of the encoding task also had no influence on the

![Figure 1. Description of the task. In the encoding phase (left panel), each trial consisted of an orienting cue indicating the position of the next object in an array of 16 black boxes, and then (after a jittered ISI) the picture of a common object appeared. In the retrieval phase (right panel), each object-location association was tested twice in randomly intermixed order: (1) by the object and (2) by the location serving as retrieval cue. When retrieval was cued by the object, one of the studied objects appeared in the center of the screen, followed by the same array of black boxes. The task was to indicate, by selecting one or more locations depending on the accuracy of memory, which object was associated during the encoding phase. When retrieval was cued by the location, the 16 locations appeared on the screen, one with a white question mark, followed by the same 16 objects randomly rearranged in two rows in the middle of the screen.](https://www.learnmem.org/)
subsequent memory performance (cue type × RT × RC ANOVA \(F_{(4,64)} = 1.97\)). The effect of the spatial position in the array of boxes during the encoding phase was analyzed by comparing the influence of the amount of direct neighbors (2, 3, or 4) on the memory performance. RC1 was more frequent for the corner positions (two direct neighbors) during the encoding phase (position × RC × cue type ANOVA, \(F_{(8,112)} = 10.1\); post hoc Tukey HSD \(P < 0.00\)). The other RCs were equally distributed over the various spatial positions.

The serial position during retrieval had no significant impact on the memory performance (retrieval position × RC × cue type ANOVA, \(F_{(12,173)} = 1.17\)).

Given that in all 10 sessions the same locations were used in association with different pictures, the locations became more familiar over sessions, whereas the pictures were (despite the familiarization phase) relatively novel. To test the possibilities that (1) this disparity led to differences in the processing of both cue types over time, and (2) subjects became increasingly confused by the multiple former associated pictures, a time × cue type ANOVA for all five RCs was conducted. No significant interaction between cue type and time was observed in any of these analyses.

The frequency of RC1 increased over sessions independent of cue type [main effect session \(F_{(9,126)} = 4.5, P < 0.00\)].

Decision latencies were measured as the RT from the occurrence of the retrieval cue until the selection of the first object/ location. It took significantly longer to retrieve an object than a location [RT × RC × cue type ANOVA, main effect of cue type \(F_{(1,14)} = 80.49\)], and subjects were significantly faster when they selected only one item rather than two, three, or four [main effect of RC \(F_{(4,56)} = 15.33\); post hoc Tukey HSD RC 1 vs. 2, 3, and 4 \(P < 0.00\)].

Each association was tested twice, one time with the object and one time with the location as retrieval cue. The correlation between the memory performances in these two tests per item was calculated via a 6 × 6 contingency table (RCs 1,2,3,4, forgotten, and misses). The resulting coefficient of contingency over all subjects and items is \(C = 0.6124 \left( df = 25, \chi^2 = 1345, P < 0.0000 \right)\) at a maximal \(C_{\text{max}} = 0.9129\). This corresponds to a Cramer’s statistic \(V_c = 0.433\), which is comparable to the coefficient of a Pearson product moment correlation. The correlation in the individual subjects ranges from \(V_c = 0.36\) to \(V_c = 0.48\). In response to the second recognition test for each association (independent of the order of retrieval cue types), only the proportion of forgotten responses increased significantly [cue order × RC ANOVA, \(F_{(4,56)} = 4.66, P < 0.00\); post hoc Tukey HSD for RC 5 \(P < 0.00\)].

The relative hit rate in each category did not change over the two tests [cue order × RC ANOVA \(F_{(3,42)} = 0.37\)].

### Functional neuroimaging

#### Object retrieval cue

Brain areas showing a significant positive correlation of brain activity with the five categories of subsequent memory confidence are listed in Table 2. The results of Sommer and colleagues (2005) using an identical design but only an object retrieval cue were replicated. The activity clusters were—probably due to the improved signal to noise ratio using a 3 Tesla—more prominent. In particular, right V1/V2, right dorsal extrastriate area (DE), the bilateral inferior and superior parietal lobes, and the bilateral fusiform and lingual gyri revealed this relationship. In addition, activity in the bilateral PHC and anterior MTL correlated significantly with the accuracy of subsequent memory retrieval. The bilateral frontal eye fields, the superior rostral part of the left premotor cortex, the left anterior prefrontal cortex, left angular gyrus, and the bilateral superior colliculi also showed a significant correlation.

#### Location retrieval cue

For the location-retrieval cue, the network of areas where activity during encoding predicted the subsequent memory performance was less extended and also comprised the bilateral superior parietal lobe, bilateral posterior fusiform and parahippocampal gyri.

### Table 2. Brain regions showing a significant correlation between activity during encoding and subsequent memory performance when retrieval was cued by the object (upper part) or by the location (lower part)

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Hemisphere</th>
<th>Location (MNI coordinates)</th>
<th>Peak Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Object serving as retrieval cue</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Calcarine</td>
<td>Right</td>
<td>3 – 93 21 4.45</td>
<td></td>
</tr>
<tr>
<td>Dorsal extrastriate cortex</td>
<td>Right</td>
<td>39 – 72 24 4.94</td>
<td></td>
</tr>
<tr>
<td>Superior parietal cortex</td>
<td>Left</td>
<td>– 9 – 81 48 3.82</td>
<td></td>
</tr>
<tr>
<td>Angular gyrus</td>
<td>Left</td>
<td>– 30 – 57 45 4.57</td>
<td></td>
</tr>
<tr>
<td>Lingual gyrus</td>
<td>Left</td>
<td>21 – 63 3 9 4.38</td>
<td></td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>Right</td>
<td>45 – 45 18 3.88</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>45 – 48 – 18 3.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>– 42 – 63 24 3.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parahippocampal gyrus</td>
<td>Right</td>
<td>21 – 63 – 9 4.37</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>– 42 – 48 – 27 3.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal eye fields</td>
<td>Left</td>
<td>– 27 3 48 4.06</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>30 3 51 3.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior inferior prefrontal cortex</td>
<td>Left</td>
<td>– 45 27 15 4.80</td>
<td></td>
</tr>
<tr>
<td>Anterior MTL</td>
<td>Left</td>
<td>– 24 9 27 3.37</td>
<td></td>
</tr>
<tr>
<td>Colliculi superiori</td>
<td>Right</td>
<td>– 3 27 15 3.13</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>9 24 3 3.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location serving as retrieval cue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior parietal cortex</td>
<td>Right</td>
<td>27 – 69 57 3.29</td>
<td></td>
</tr>
<tr>
<td>FUSIFORM GYRUS</td>
<td>Right</td>
<td>24 – 51 18 3.34</td>
<td></td>
</tr>
<tr>
<td>Parahippocampal gyrus</td>
<td>Right</td>
<td>24 – 44 6 3.57</td>
<td></td>
</tr>
<tr>
<td>Inferior prefrontal cortex</td>
<td>Left</td>
<td>– 27 42 15 3.54</td>
<td></td>
</tr>
<tr>
<td>Lateral occipital cortex</td>
<td>Right</td>
<td>45 – 72 – 21 3.34</td>
<td></td>
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</tbody>
</table>

Activity was defined as significant at \(P < .05\) corrected for a spherical volume of interest (10 mm radius, see Materials and Methods).
rus, and the left occipital complex (Table 2). The left anterior inferior prefrontal cortex also showed this correlation.

Conjunction
To identify areas where activity during encoding is correlated with the retrieval success in response to both cue types, we conducted a conjunction analysis. This conjunction revealed a common activity pattern for both cue types consisting of the left fusiform gyrus, the bilateral parahippocampal cortex, and the inferior prefrontal cortex (Table 3). Lowering the statistical threshold by using an uncorrected p-value (p = 0.001) did not reveal more clusters of activity in the MTL. Each object-location association was assessed twice. This successive testing could theoretically exaggerate the size of overlapping effects in the conjunction analysis. Therefore we applied a second model where only the first retrieval occasion of each object-location association was included. The result of this additional analysis confirmed the foci that were already revealed in the first conjunction analysis. This subsequent testing could theo-

Interaction
An interaction analysis was conducted to identify areas that are preferentially involved in encoding a location associated with an object, and vice versa. The interaction analyses revealed only areas where activity during encoding predicts the subsequent memory performance in response to an object cue. This analysis exhibited such responses in areas of the dorsal and ventral visual stream, the PHC, and the left inferior prefrontal cortex. This is to say activity in these areas may not only predict the location of an object in memory, but also the object associated with a particular location. The opposite interaction (location cue over object cue) revealed no suprathreshold voxel. The same pattern of activity was found in the MTL when the statistical threshold was lowered to P = 0.001 uncorrected.

Discussion
In a previous experiment (Sommer et al. 2005) we characterized a network of brain areas where activity during encoding predicts the retrieval success for the former location of an object. In particular, activity in areas of the dorsal and ventral visual stream, the PHC, and the left inferior prefrontal cortex was correlated with the precision of the resulting memory trace. In the present study we were able to replicate and extend these findings with an improved paradigm that allows a direct comparison between areas involved in encoding two aspects of an object: object-identity and object-location. Statistical conjunction and interaction analyses revealed that activity in the fusiform gyrus, bilateral PHC, and left inferior prefrontal cortex predicts the accuracy of memory for both object-identity and object-location. Activity in the right anterior MTL, left PHC, left angular gyrus, left lingual gyrus, and the rostral precentral sulcus is specifically correlated with the precision of the memory trace for the associated location.

Behavioral data
The analysis of subsequent memory performance showed that the challenging retrieval task yielded valid estimates of the precision of the memory traces, and that there are no major performance differences dependent on the cue type. The retrieval of an object associated with a particular location seems to be slightly more difficult, as indicated by the higher forgetting rate. The prolonged decision latencies for the retrieval of objects is probably due to the tri
cue type. The retrieval of an object associated with a particular location seems to be slightly more difficult, as indicated by the higher forgetting rate. The prolonged decision latencies for the retrieval of objects is probably due to the trial-wise randomly rearranged array of objects, which demanded time to find the remembered pictures in the display.

The employed parametric measurement of memory accuracy shares two important features with classical confidence ratings, on a scale from 1 (low) to 6 (high confidence): (1) a correlation between decision latency and RCs (Murdock and Dufy 1972; Koppell 1977), and (2) a monotonically decreasing hit rate over RCs (Yonelinas 2001). These relationships are explained by signal detection models of memory where decision latency, hit rate, and confidence are reflections of the continuously distributed strength of the memory traces (McNicol and Stewart 1980; Hockley and Murdock 1987). In case of object-location associations, the term “memory trace strength” refers to the strength of the link between the mental representation for the two individual components of an association. Dual-process models hypothesize an additional process, namely recollection, which supports associative recognition (Yonelinas 1999).

Here, the moderate correlation between the performances in the two retrieval conditions indicates that the accessibility for a particular association differs depending on the cue type. Probably due to spontaneous fluctuations of the attentional focus between identity and location, in some associations the location is encoded deeper than the object identity and vice versa. This implies that domain-specific encoding processes exist for objects and locations. This has been shown before in behavioral experiments by explicit manipulations of the encoding tasks (Kohler et al. 2001).

No output encoding (Humphreys and Bowyer 1980) took place, as indicated by the equal performance at the first and second retrievals of each association. Consistent with previous reports, the equal reaction times during encoding for different degrees of subsequent memory indicate that the observed differences in brain activity are not related to differences in task difficulty or time on task (Cansino et al. 2002; Sommer et al. 2005).

Table 3. Conjunction and interaction analysis

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Hemisphere</th>
<th>Location (MNI coordinates)</th>
<th>Peak Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunction analysis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Parahippocampal cortex</td>
<td>Right</td>
<td>24 – 45 – 6</td>
<td>3.38</td>
</tr>
<tr>
<td>Left</td>
<td>– 24 – 42 – 9</td>
<td></td>
<td>3.24</td>
</tr>
<tr>
<td>Fusiform</td>
<td>Left</td>
<td>– 33 – 36 – 30</td>
<td>3.96</td>
</tr>
<tr>
<td>Left</td>
<td>– 27 – 51 – 18</td>
<td></td>
<td>3.78</td>
</tr>
<tr>
<td>Anterior inferior prefrontal cortex</td>
<td>Left</td>
<td>– 42 – 27 – 15</td>
<td>4.38</td>
</tr>
<tr>
<td>Interaction: object cue &gt; location cue</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Anterior MTL</td>
<td>Right</td>
<td>30 – 6 – 27</td>
<td>3.52</td>
</tr>
<tr>
<td>Parahippocampal cortex</td>
<td>Left</td>
<td>– 36 – 33 – 12</td>
<td>3.25</td>
</tr>
<tr>
<td>Rostral precentral sulcus</td>
<td>Left</td>
<td>– 27 – 6 – 45</td>
<td>3.28</td>
</tr>
<tr>
<td>Angular gyrus</td>
<td>Left</td>
<td>– 30 – 57 – 33</td>
<td>3.67</td>
</tr>
<tr>
<td>Lingual gyrus</td>
<td>Left</td>
<td>– 12 – 66 – 6</td>
<td>3.23</td>
</tr>
</tbody>
</table>

Activity was defined as significant at P < .05 corrected for a spherical volume of interest (10 mm radius, see Materials and Methods).

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jcts and locations compared to a perceptual baseline have been reported before (Moscovitch et al. 1995; Pihlajamaki et al. 2004).

In addition to areas that contribute to the processing of the item, it is well established that regions of the MTL are involved in episodic memory. The contributions of the various subregions to material-specific and general mnemonic processes are a matter of debate (Squire et al. 2004).

**Posterior MTL**

The PHC has been linked with two distinct cognitive processes: spatial cognition (Epstein et al. 2003) and mnemonic processing (Schacter and Wagner 1999). We found evidence of a functional specialization of neighboring areas within the PHC with respect to these cognitive domains (Fig. 3, upper panel).

The specific role in spatial coding of areas in the PHC was defined as processing spatial relationships in a visual scene independent of the exact object-identity (Rombouts et al. 1999; Kohler et al. 2002; Epstein et al. 2003), which parallels the association of a particular location to an object in our task.

Human lesion and neuroimaging studies revealed an important role of the posterior MTL in spatial encoding and/or the association of objects and location. Focal lesions in the parahippocampal gyrus lead to topographical amnesia (Aguiurre and D’Esposito 1999); lesions in the right MTL result in object-location memory deficits (Smith and Milner 1981, 1989; Pigott and Milner 1993), and neuroimaging studies confirmed the role of the PHC in spatial navigation (Aguiurre et al. 1996; Maguire et al. 1998; Janzen and van Turennout 2004).

A more general role in associative mnemonic processes of the PHC is suggested by neuroimaging studies of memory. Areas in that region were found to be active during encoding and retrieval of associative information (Henke et al. 1997, 1999; Rombouts et al. 1997; Krause et al. 1999; Eldridge et al. 2000; Kohler et al. 2002; Davachi et al. 2003; Dobbins et al. 2003; Duzel et al. 2003; Kirwan and Stark 2004; Ranganath et al. 2004). In addition, memory studies using nonassociative stimulus material found the PHC contributing to encoding and retrieval of items (Schacter and Wagner 1999; Kirchhoff et al. 2000; Strange et al. 2002; Morcom et al. 2003), where it is important to note that high-confidence recognition and free recall are mostly accompanied by the retrieval of contextual, associated information. Eichenbaum (2000) concluded from animal experiments that the parahippocampus is involved in the encoding of associations as fused, unitized, or configural representations, as is the case in our paradigm.

**Anterior MTL**

Although most animal, human lesion, and imaging studies investigating the functional role of the right MTL seem to agree on a contribution of this structure to various aspects of memory, they remain contradictory with respect to its exact nature. In short there exist reports emphasizing (1) a specific role in spatial memory (Maguire et al. 1999), (2) a contribution to all forms of declarative memory (Stark and Squire 2001a), and (3) a selective involvement in associative memory processes (Eichenbaum 2000).

In our paradigm, activity in the right anterior MTL during encoding correlated exclusively with spatial encoding processes: the more active this area was during encoding, the deeper a location is associated with an object, and the more accurately the former location is subsequently retrieved (Fig. 3, lower panel).

A crucial role in spatial memory of the hippocampus and adjacent areas was first described in the cognitive map theory of hippocampal function (O’Keefe and Nadel 1978) and later confirmed by many findings in rats and monkeys (Suzuki et al. 1997; Broadbent et al. 2004; Burwell et al. 2004; Hampton et al. 2004; Jenkins et al. 2004; Leutgeb et al. 2004; Ludwig et al. 2004).

Human lesions restricted to the right hippocampus result in a loss of spatial memory and imply that its spatial role is lateralized to the right hemisphere (Smith and Milner 1981, 1989; Pigott and Milner 1993; Abrahams et al. 1997; Nunn et al. 1999; Bohbot et al. 2000; Rombouts et al. 1999; Astur et al. 2002; Stepankova et al. 2004). Such a lateralization was supported by neuroimaging studies, which found a preferential processing of words in the left, locations in the right, and pictures in bilateral hippocampus (Schacter and Wagner 1999; Kirchhoff et al. 2000; Reber et al. 2002). A pronounced role in spatial processing of the right hippocampus comes also from navigation experiments (Burgess et al. 2002). Furthermore, right anterior MTL activity during retrieval of previously learned locations of objects was reported (Owen et al. 1996). This cognitive process seems very similar to the retrieval processes in our paradigm when the object served as cue and the location had to be retrieved.

Evidence of a more general role of the right anterior MTL in memory comes from many neuroimaging studies that did not explicitly contrast familiarity-based and associative memory (Schacter and Wagner 1999; Kirchhoff et al. 2000; Stark and Squire 2000; Fletcher and Henson 2001; Strange et al. 2002; Henson et al. 2003; Morcom et al. 2003). Nevertheless, recent studies...

Our finding that an area in the anterior MTL is specifically involved in encoding of spatial associations is not in contradiction to these studies. Animal and human data suggest that sub-regions of the hippocampus and entorhinal cortex participate in distinct cognitive processes. More specifically there is evidence that only parts of the anterior MTL cortex participate in navigation and spatial encoding in rats (Broadbent et al. 2004; Fynh et al. 2004). Two neuroimaging studies comparing face and name encoding and object-identity and spatial configuration processing showed a functional specialization within the hippocampus (Small et al. 2001; Pihlajamaki et al. 2004). It was suggested that a functional dissociation within the hippocampus is related to afferents from distinct neocortical areas through the parahippocampal gyrus (Veltman et al. 1989). Therefore there might exist subareas in the anterior MTL involved in spatial encoding, and others which are more general involved in mnemonic processing.

Materials and Methods

Subjects

Informed consent was obtained from 21 right-handed healthy subjects. Due to elevated error rates (>50%), six of the subjects were excluded after scanning from the further analysis; the final sample consisted of 15 subjects (seven female; age range 20–28 yrs; mean age 24.4 yrs; recruited by advertisement). Ethics approval was obtained from the local (Hamburg Board of Physicians) ethics committee.

Task

Each of the 10 sessions (+ two practice sessions outside of the scanner) consisted of four phases: “familiarization,” “encoding,” “distraction,” and “retrieval,” where the first three phases were identical to those of a previously published experiment (Sommer et al. 2005). The subjects were kept in the magnetic resonance (MR) scanner during all four phases of each session but were scanned only during the familiarization and encoding phases. In each session, a new subset of 16 pictures of common objects (Snodgrass and Vanderwart 1980) were used including eight natural and eight artificial objects. The order of subsets was randomized over subjects. Because the pictures of each session belong to two categories or semantic fields such as “African animals” and “musical instruments,” or “body parts” and “vehicles,” they are within one category semantically related, like neighboring locations are spatially related. At the beginning of each phase in each session, the instructions appeared on the screen to cue subjects to the task. The background was gray in all four phases, and instructions were presented in white.

Picture stimuli were presented controlled by a PC that ensured synchronization with the MR scanner using the software “Presentations” (http://www.neurobehavioralsystems.com). An LCD projector projected the stimuli on a screen positioned on the top of the head coil, and the stimuli were viewed by the subjects through a mirror (10 × 15° field of view). Participants entered the responses by pressing buttons on an MR-compatible response box (familiarization and encoding phase) and computer mouse (retrieval phase).

The familiarization phase was introduced after pilot studies showed that the pictures are not equally familiar and verbalizable for German subjects, which is confirmed by a German standardization study of the Snodgrass and Vanderwart pictures (Genzel et al. 1996). Thus the familiarization phase ensured that all subjects recognized all pictures in a comparable time frame. During this phase the pictures of the particular session were shown in the center of the screen for 2.3 sec in randomized order. Beneath the picture, the common German name for the object was presented. The subjects were instructed to press the response button as soon as they recognized the picture and read the name.

In the encoding phase (Fig. 1), the subjects were shown an irregular array of 16 black boxes with the hidden pictures of the particular subset. Each picture was shown for 2 sec sequentially in a randomized order while the subject had to make a natural/artificial judgment by pressing one of two response buttons. The ISI was jittered between 2.5 and 3.5 sec with 14% null events and a maximum of two consecutive null events. We indicated the location of the next picture in advance (after presenting the last picture) by changing the color of the relevant box to white for 500 msec. This was undertaken to avoid orienting reactions when presenting the images, which may otherwise interfere with spatial attention. Subjects were instructed to fixate on the cued box and keep it in the focus of attention until the picture appear. All cues were valid.

In the immediately following distraction phase (not scanned), subjects were instructed to count aloud backwards in steps of three from a random number between 80 and 100 displayed on the screen to overwrite working memory and minimize a recency effect.

In the retrieval phase, each of the previously encoded object-location associations were probed twice in randomly intermixed order: (1) by the object (picture) and (2) by the location serving as retrieval cue. In object-retrieval cue trials, one picture was presented in the center of the screen for 3 sec, followed by the empty array of 16 boxes. Subjects were instructed to select the remembered location of the picture in the study phase by moving the mouse cursor to that box and clicking with the mouse button. It was specifically emphasized to the subjects that they should not guess the location but select as many boxes as necessary in case of doubt, or indicate that they forgot the location. In trials with the location as retrieval cue, the empty array of 16 boxes were presented for 3 sec, where one box was marked as retrieval cue by a white question mark. This cue was followed by the 16 slightly downsized pictures of the particular subset randomly arranged in two rows in the center of the screen (Fig. 1). Subjects were instructed to select the object that was presented before at that location by moving the mouse cursor to that picture and clicking with the mouse button. Again it was emphasized to the subjects that they should not guess the picture but select as many as necessary in case of doubt, or indicate that they forgot the picture. At the end of each session a feedback for the overall memory performance in this session was given (total number of correct and “forgotten” responses in location- and object-retrieval cue trials in that session).

Image acquisition

Functional MRI was performed on a 3T system (Siemens Trio) with a gradient-echo EPI T2* sensitive sequence in 38 contiguous axial slices (2-mm thickness with 1-mm gap, TR 2.2 sec, TE 40 msec, flip angle 90°, field of view 210 × 210 mm², matrix 64 × 64).

Image analysis

The imaging series was realigned, slice-time corrected, normalized into standard anatomical space (MNI), and smoothed with a Gaussian kernel of 10 mm full-width half-maximum. A high-pass filter with a cut-off period of 120 sec was applied.

An event-related analysis of the imaging data was conducted using Statistical Parametric Mapping (SPM2) to compare encoding related activity of individual object-location associations during the study phase. Only trials in which subjects made the correct natural/artificial decision during encoding (98.8%) were analyzed.

These encoding trials were post-hoc classified in two separate analyses according to the subsequent memory performance as response to (1) the object retrieval cue and (2) the location retrieval cue. Both analyses revealed that 96.8% of all responses fell into the following five categories: subjects selected one, two, three, or four locations/objects or indicated the absence of any confident memory. Only encoding trials belonging to these categories were functionally analyzed.

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The analysis of the behavioral results showed an effect of the serial position during encoding. This effect was only significant for the first item, which was subsequently retrieved very accurately as indicated by a category 1 response (position × response category × cue type ANOVA, $F_{6,0,846} = 2.91; P < 0.000$; post hoc Tukey HSD $P = 0.05$ for response category 1 at position 1 vs. position 4, 7, 8, 9, 10, 11, 12, and 15). This was interpreted as a Primacy effect. For the following two items in each session, there was a statistical trend in the same direction. To avoid confounding of Primacy and the “normal” subsequent memory effect, the first three items of each session were therefore excluded in cases where only one location/object was subsequently selected (Stange et al. 2002).

These considerations have led to similar models for both types of retrieval cues: a total of seven regressors were created (i.e., stick functions convolved with a canonical hemodynamic response function as implemented in SPM) as the basis function of the following categories. Additionally, six subject-specific movement parameters from the rigid body registration were used as covariates. The first regressor accounted for the Primacy effect as described above. Regressor 2 consisted of the encoding events belonging to retrieval category 1 (subjects selected in the retrieval phase the correct location/object), regressor 3 comprised the events of category 2 (only when the correct location/object was among the selected), regressor 4 of category 3 (only when the correct location/object was among the selected), regressor 5 of category 4 (only when the correct location/object was among the selected), regressor 6 contained the forgotten encoding events, that is, when subjects indicated subsequently the absence of any memory, and regressor 7 the remaining events (errors during the encoding task, false responses during retrieval). In the first-level analysis, mean contrasts of each category were estimated over all memory, and regressor 7 the remaining events (errors during the encoding phase enter the model twice: for the spatial cue and for the object cue retrieval. In the case of the conjunction analysis, this could potentially lead to an exaggeration of the overlapping activity patterns. To validate the results of the conjunction analysis, we therefore conducted additional analyses in which each encoding event was only characterized by the memory performance in the first retrieval occasion.

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**References**


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