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ORIGINAL PAPER

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Anterior hippocampus orchestrates successful encoding and retrieval of non-relational memory: an event-related fMRI study

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Abstract Episodic memory encoding and retrieval processes have been linked to different neural networks. However, the common brain regions associated with non-relational memory processing during successful encoding (subsequent memory effect) and successful retrieval (recognition effect) have not yet been investigated. Further, the majority of functional imaging studies have been conducted in young subjects, whereas patients from lesion studies, where most neuropsychological models are still based upon, are usually older. Inferences from younger subjects cannot necessarily be applied to the elderly, an issue becoming particularly relevant with our ageing society. Using an event-related fMRI approach we studied 29 healthy elderly subjects (mean age 67.8, SD 5.4 years) with a non-associative task of intentional word list encoding and retrieval. For each subject, behavioural responses were individually classified into four event types (hits test, misses test, false alarms, correct rejections). Brain areas activated during successful memory encoding comprised the anterior left hippocampus extending into the surrounding parahippocampal gyrus. Regions associated with successful memory retrieval involved a widespread network of anterior left parahippocampal gyrus, bilateral temporal cortices and bilateral ventral and dorsal prefrontal areas. Regions contributing to both successful encoding and retrieval, evidenced by a conjunction analysis, revealed prominent left lateralized activations of the anterior hippocampus and the inferior parietal lobe. Our results indicate that the anterior left hippocampus plays an important role during successful memory encoding and during successful memory retrieval in a task of simple, non-associative wordlist learning in healthy elderly subjects.

Key words non-relational memory · hippocampus · er-fMRI

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Introduction

Episodic memory is a form of long-term memory that supports the conscious remembrance of everyday experiences [48]. This ability requires an initial successful encoding of experiences into long-term

memory and its subsequent successful retrieval. Further a number of factors modulate memory functions and its neural correlates such as age (elderly/young adults), type (verbal/spatial material) and meaningfulness of the material (novel/familiar items), task demands (incidental/intentional encoding), the mnemonic process involved (encoding/retrieval) and the way of information recovery (free recall/recognition).

During encoding, information of different modalities (visual, auditory, etc.) is integrated and linked to existing representations. Therefore, the ease and success of encoding is strongly related to prior knowledge of the to-be-encoded material. Distributed neocortical regions account for this processing, depending on the type of information, but the hippocampus proper is viewed as the binding and integration site that establishes a coherent memory trace [36, 47]. The cross-linkage of novel stimuli with information already stored in declarative memory operates via mismatch detection and a subsequent associative encoding [45]. While several sub-areas of the medial temporal lobe (MTL), especially the parahippocampal gyrus as the principal input pathway to the hippocampal region are important for successful memory encoding [52], the hippocampus proper serves as the key area to establish inter-item associations [21]. However, the MTL network not only contributes to associative learning, but also is engaged in tasks of simple, non-relational memorization of single items. Recent neuroimaging [21, 35, 47] and patient studies [16, 18, 43, 50] even discuss a functional dissociation within the medial temporal lobe with respect to relational and non-relational declarative memory formation. Thereafter relational memory functions have been associated with hippocampal/parahippocampal activity, whereas the role of the hippocampal formation during simple, non-relational memory remains somewhat elusive [21, 47].

On the other hand, successful recovery of information from episodic long-term storage requires both, successful encoding and retrieval. Functional imaging studies investigating retrieval processes document prominent dorsolateral/ventrolateral prefrontal cortex (DLPFC/VLPFC) activations [5, 6, 22]. However, based on patient and neuroimaging studies several authors propose that MTL structures, too, are strongly linked to retrieval processes [30, 32]. Several models concerning memory processes and their neural correlates have been proposed: the hippocampal encoding/retrieval (HIPER) model assumes an anterior–posterior hippocampal segregation with respect to the gradient of encoding- and retrieval related activity [27, 45]. On the other hand, Schacter and Wagner (1999) assume that anterior regions contribute to relational memory, whereas posterior portions are more likely engaged in non-relational memory [39].

Further, depending on the material to be processed, prefrontal and medial temporal regions are differentially involved. Verbal material primarily activates left lateralized VLPFC/DLPFC as well as left medial temporal structures including the hippocampus and parahippocampal gyrus [22, 23, 29]. Lateralization of activation related to the processing of spatial [4, 17, 23, 25, 51], pattern [17, 22, 51] or facial items [3, 17, 23, 28, 29] is not found to be that clear-cut, however right and/or bilateral hemispheric dominance is found in most studies.

Regarding the age of subjects Daselaar et al. (2003) documented mainly overlapping activation patterns in elderly and young adults while executing a semantic classification task (living/nonliving vs. uppercase/lowercase). The authors argue that, given the overlap of contributing cortical structures in both age groups, semantic retrieval processes are similar in both age groups [10].

Opposed to that, Cabeza (2002) proposed a reduced general hemispheric lateralization in elderly relative to young adults. His approach is conceptualized in the Hemispheric Asymmetry Reduction in Old Adults (HAROLD) model suggesting a more bilateral cortical engagement in elderly in order to compensate for a reduced processing efficiency of other regions of the brain [7]. Amplified overall activation in elderly relative to young adults or patients with mild cognitive impairments (MCI) relative to healthy controls, arguably compensating for a reduced processing efficiency, has been documented in a number of research studies [8, 9, 19, 24, 49].

Neuroimaging data on memory functioning should also be evaluated with respect to the success of encoding and retrieval of items [2, 4, 5, 26, 35, 52, 53]. Investigating activations related to a *successful encoding*, Brassen et al. [2] detected bilateral hippocampus, VLPFC/DLPFC and inferior temporal gyrus activations. Other groups derived predictions about the success of memory retrieval upon cortical activity during the process of encoding [4, 37, 52]. In summary, hippocampus/parahippocampal and prefrontal activity during encoding were found to predict subsequent declarative memory retrieval, lateralized with respect to the material type (verbal/spatial) to be processed [4, 52]. On the other hand, studies focusing on *successful retrieval* only yielded prominent activations in left anterior prefrontal and medial/lateral parietal regions, again lateralized with respect to the material type that had to be processed [5, 26].

The only study to date directly comparing activity related to successful verbal encoding *and* to successful verbal retrieval used associations between words or between words and fonts as task [35]. As noted above, relational memory is clearly associated with hippocampal activity. Extending this finding Prince and colleagues (2005) provided first evidence that cortical activity related to a *successful* encoding and a *successful* retrieval of relational items was associated with MTL structures (encoding = anterior hippocampus; retrieval = posterior hippocampus/parahippocampal

gyrus) as well as with prefrontal cortices (encoding = VLPFC; retrieval = DLPFC and anterior PFC).

The aim of the present study was to delineate the neural network engaged in successful memory encoding (subsequent memory effect) and successful memory retrieval (recognition effect) of non-relational material, as well as particularly the overlap of regions activated commonly during both successful encoding *and* successful retrieval. The vast majority of functional imaging studies have been conducted in young subjects, whereas most of the lesion studies stem from older subjects (usually with stroke lesions). To better integrate lesion and functional imaging studies and with an ageing society in industrialized countries, it is important to test hypotheses derived from young subjects in the elderly. We therefore investigated healthy, elderly subjects and applied a verbal memory task that enabled us to differentiate between successfully encoded and successfully retrieved single items. We hypothesize the hippocampus/parahippocapal region to be engaged in both successful encoding and retrieval, in a task of intentional, non-relational verbal learning.

Experimental procedures

Subjects

A total of 29 (17 females, 12 males) elderly subjects participated in the study. The mean age of the participants was 67.7 years, with a range from 60 to 81 years. All subjects had normal or corrected-to-normal vision and were right-handed according to the Edinburgh Handedness Index [33]. All subjects were interviewed, tested and given a medical and psychiatric examination by an experienced psychiatrist (D.L.). Subjects were screened to exclude history or evidence of neurological, medical, or psychiatric disorder including substance abuse. None of the subjects was taking psycho-pharmacologically active medication at time of study or within the last two months.

Subjects further underwent neuropsychological testing, including the SIDAM (Structured Interview for the Diagnosis of dementia of the Alzheimer type, multi-infarct dementia and dementia of other etiology according to ICD-10 and DSM-IV) which also includes the Mini Mental State Examination (MMSE) [13] to exclude the presence of MCI, dementia and evaluate global cognitive functioning. Further, the Verbal Learning and Memory Test (VLMT) [20] was administered to account for verbal encoding/immediate recall, delayed recall and recognition deficits in all participants.

The study was approved by the local ethical committee. All participants signed written informed consent prior to participation and were paid a fee for participation.

Stimuli and task

Stimuli consisted of 360 German nouns that were matched for imagery, concreteness and meaningfulness [1, 34]. Examples would be "house", "nurse", "apple". The experiment consisted of six runs: two encoding and four recognition runs. Each of the encoding runs (*study runs*) as followed by two recognition runs (*test runs*) so that all words learned during that run were shown in the two subsequent recognition runs.

During each of the encoding runs, 90 randomly selected words were presented for 2,000 ms each. Words were presented visually at a randomized interstimulus interval (ISI) of 2–22 s (mean 12 s). The jittering introduced by variable interstimulus intervals allowed for a complete mapping of the hemodynamic response function. During the ISI, a string of eight X was presented as a low level base line. Subjects were instructed to memorize the words for later recognition and to press the right of two response buttons once for every word.

During each of the recognition runs, 45 words from the preceding encoding run (targets) were randomly intermixed with 45 distracters (non-targets). Words were presented visually at the same presentation rate as during the study phase. During the ISI, a string of eight X was presented as a low level base line. Subjects were required to make an old/new decision for each presented word. By pressing the right button they indicated a previously learned word, while they used the left button for words that were considered new. Button presses were executed with two fingers of the right hand.

fMRI data acquisition

All scans were performed on a 1.5 T whole body scanner (Siemens Sonata, Erlangen, Germany) using standard gradients and an eight-channel head coil. Subjects lay in a supine position, while head movement was limited by foam padding within the head coil. Words were projected on a transparent screen which could be seen via a mirror attached to the head coil in front of the subjects head. If necessary, participants wore fMRI-compatible glasses to ensure optimal visual acuity. For each subject, we acquired six series of EPI-scans, two for the study runs and four for the test runs. Scans covered the whole brain, including five initial dummy scans parallel to the AC/PC line with the following parameters: number of slices (NS): 25; slice thickness (ST): 4.5 mm; interslice gap (IG): 1.00 mm; matrix size (MS): 64 × 64; field of view (FOV): 192 mm × 192 mm; repetition time (TR): 2 s; echo time (TE): 40 ms; flip angle (FA): 90°. Each of the six runs comprised 462 scans.

To rule out anatomic malformations which might affect regular brain organization, we acquired high resolution anatomic images with a T1-weighted 3D turbo flash sequence (MPRAGE; TR = 1,300 ms; TE = 3.22 ms; NS = 176 (sagital); MS: 256 × 256; ST = 1 mm; IG = 0 mm; FOV = 256 × 256 mm; voxel size = 1 × 1 × 1 mm).

fMRI data analysis

MR images were analyzed using Statistical Parametric Mapping (SPM2, http://www.fil.ion.ucl.ac.uk) implemented in MATLAB 6.5 (Mathworks Inc., Sherborn, MA, USA). After discarding the first five volumes, all images were realigned to the first image to correct for head movement. Unwarping was used to correct for the interaction of susceptibility artifacts and head movement. After realignment and unwarping, the signal measured in each slice was shifted relative to the acquisition time of the middle slice using a sinc interpolation in time to correct for their different acquisition times. Volumes were then normalized into standard stereotaxic anatomical MNI-space by using the transformation matrix calculated from the first EPI-scan of each subject and the EPI-template. Afterwards, the normalized data with a resliced voxel size of 3 × 3×3 mm were smoothed with a 10-mm FWHM isotropic Gaussian kernel to accommodate inter-subject variation in brain anatomy. The time series data were band-pass filtered to remove artifacts due to cardio-respiratory and other cyclical influences.

For each subject, stimuli were individually classified into the four event types (hits test, misses test, false alarms, correct rejections) according to the individual responses during recognition. Words that elicited no reaction were modeled separately but not considered in later analyses.

The expected hemodynamic response at stimulus onset for each event-type was modeled by two response functions, a canonical hemodynamic response function (HRF) and its temporal derivative. The temporal derivative was included in the model to account for the residual variance resulting from small temporal differences in the onset of the hemodynamic response, which is not explained by

Table 1 Demographic data and neuropsychological screening results

	Subjects (n = 29)
Female:male	17:12
Age (SD; range)	67.8 (5.4; 60–81)
SIDAM (SD; range)[a]	52.1 (2.0; 46–55)
MMSE (SD; range)[b]	28.8 (1.2; 27–30)
Verbal learning/immediate recall (SD; range)[c]	48.5 (6.6; 38–60)
Delayed recall (SD; range)[d]	9.9 (2.3; 5–15)
Recognition (SD; range)[e]	12.0 (2.4; 5–15)

[a]Structured interview for the diagnosis of dementia of the Alzheimer type, multi-infarct dementia and dementia of other etiology according to ICD-10 and DSM-IV, scores may range from 0 to 55
[b]Mini-Mental State Examination, scores may range from 0 to 30
[c]Immediate recall/sum of five learning trials à 15 words, scores may range from 0 to 75
[d]Delayed recall of the 15-words list after 20 min; scores may range from 0 to 15
[e]Correct recognitions of the 15 words out of a 50 words list less the false alarms

the canonical HRF alone. The functions were convolved with the event-train of stimulus onsets to create covariates in a general linear model. Six movement parameters (three translations, three rotations) were included in the model as covariates of no interest to capture residual movement-related artifacts. Subsequently, parameter estimates of the HRF regressor for each of the different conditions (subsequent hits during study, subsequent misses during study, hits test, misses test, correct rejections during test, false alarms during test) were calculated from the least mean squares fit of the model to the time series. Parameter estimates for the temporal derivative were not further considered in any contrast.

Single-subject contrast maps were determined for the main effects of all experimental conditions: subsequent hits during study, subsequent misses during study, hits test, misses test, correct rejections during test, false alarms during test. For the current research question the last two contrast maps were not necessary and therefore did not enter group analyses.

As a measure of successful memory encoding, we examined the subsequent memory effect [2, 4, 35, 52], the difference in brain activity during study between those words that were later remembered and those words that were later forgotten. To delineate areas involved with successful memory retrieval, we looked at the recognition effect [53], the difference in brain activation during recognition between hits and misses. To identify areas involved with both successful memory encoding and successful memory retrieval, we computed a conjunction analysis of the subsequent memory effect and the recognition effect [14, 31].

An SPM2 group analysis was performed by entering these contrast images into a random effects analysis using a within-subjects ANOVA approach. For the difference contrasts, we applied a voxel-wise threshold of $P < 0.001$, uncorrected for multiple comparisons and report only clusters of ten or more contiguous voxels. For the conjunction analysis, we applied a voxel-wise threshold of $P < 0.005$, uncorrected for multiple comparisons. Again, we only consider clusters of ten or more contiguous voxels. The reported voxel coordinates of activation peaks were transformed from MNI space to Talairach and Tournoux [46] atlas space by non-linear transformations (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) (Table 1).

Results

Behavioral results

Recognition memory performance and reaction times are listed in Table 2. Accuracy of recognition was assessed by the difference in probabilities of a correct old judgment and an old judgment for a new item (Pr = probability hit − probability false alarm). Recognition performance was well above chance level [mean Pr = 0.49 (SD = 0.15), $t_{28} = 17.54$; $P < 0.0001$].

Table 2 Behavioral data: recognition memory performance and reaction times (n = 29)

	Number (SD)	RT (SD)
Hits test	126.96 (28.77)	1486.58 (293.16)
Misses test	50.89 (28.16)	1896.76 (335.42)
Correct rejections	138.61 (26.61)	1665.43 (278.61)
False alarms	39.14 (25.77)	1808.97 (419.31)

RT reaction time, *SD* standard derivation

Reactions to hits were significantly faster than reactions to misses ($t_{28} = 7.75$; $P < 0.0001$), correct rejections ($t_{28} = 3.44$; $P < 0.002$) and false alarms ($t_{28} = 8.96$; $P < 0.0001$). Reactions to correct rejections were significantly faster than reactions to misses ($t_{28} = 9.71$; $P < 0.0001$) and false alarms ($t_{28} = 2.06$; $P < 0.05$).

Neuroimaging results

Subsequent memory effect (subsequent hits during study; i.e. later remembered words > subsequent misses during study; i.e. later forgotten words) Considering successful memory encoding (difference in brain activity during study between those words that were later remembered and those words that were later forgotten) we found activation in the left hippocampus, extending into the surrounding parahippocampal gyrus (BA 34, 37), in the right posterior middle temporal gyrus (BA 37), the right precuneus (BA 31) and the right cerebellum (Fig. 1; Table 3). There were no detectable differences between males and females in the intensity of activation as determined by the parameter estimates of the local maxima activations (later remembered words: $t_{27} = 0.581$; $P > 0.05$; later forgotten words: $t_{27} = .529$; $P > 0.05$). Furthermore, VLMT performance, age and intensity of cerebral activation as determined by the parameter estimates of the local maxima activations did not correlate significantly.

Recognition effect (hits test > misses test) Areas involved with successful memory retrieval (difference in brain activation during test between hits and misses) (Fig. 2; Table 3) comprised a wide-spread network of bilateral medial (BA 28, 34, 35) and lateral (BA 20, 21, 37) temporal cortices, bilateral ventral and dorsal prefrontal areas (BA 8, 9, 10, 11, 46, 47), bilateral medial frontal activations (BA 32), a left parietal area (BA 7, 39, 40) and bilateral occipital areas (BA 17, 18, 19). One large activation cluster centered in the right middle temporal gyrus (BA 37) extended into the precuneus and adjacent subcortical regions. At a more stringent statistical threshold

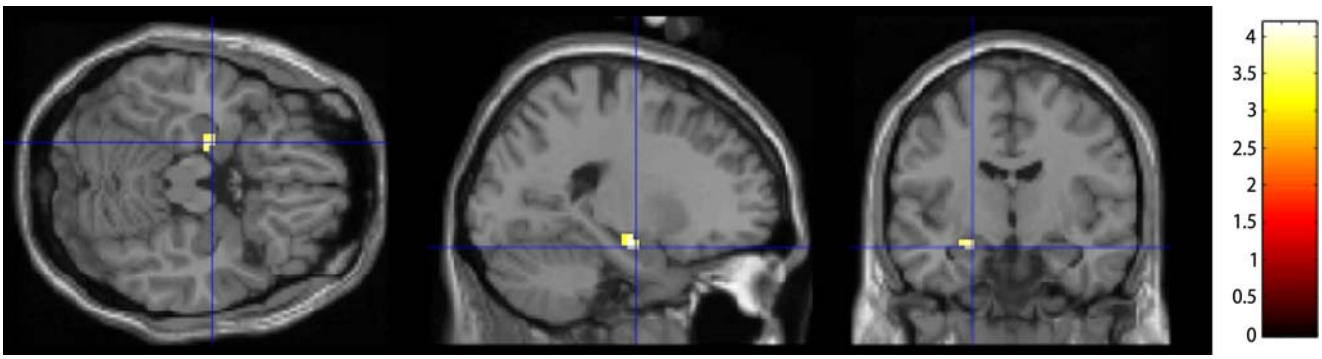

Fig. 1 Subsequent Memory Effect (later remembered words > later forgotten words). Regions activated more strongly for successful as opposed to unsuccessful memory encoding during the "study" condition. The activation map ($P < 0.001$, uncorrected; minimal cluster size ten voxels) is shown superimposed onto three-dimensional slices of the T1-weighted SPM-template

Table 3 Activation peaks with their localization

	BA	Coordinates			*t*-value	No. voxels
		x	*y*	*Z*		
Subsequent Memory Effect (later remembered words > later forgotten words)						
Left hippocampus		−21	−12	−12	4.16	30
Right middle temporal gyrus	37	30	−72	20	3.74	11
Right precuneus	31	15	−36	32	3.62	17
Right cerebellum		9	−51	−23	3.71	10
Recognition Effect (hits test > misses test)						
Left parahippocampal gyrus	35	−24	−24	−21	4.17	24
Left middle temporal gyrus	21	−59	−44	−5	5.53	181
Right middle temporal gyrus	37	56	−44	−5	5.26	1098
Left inferior temporal gyrus	20	−53	−10	−25	3.61	12
Right middle temporal gyrus	21	56	−21	−7	3.67	13
Left superior frontal gyrus	8	−18	46	42	4.09	22
Left superior frontal gyrus	10	−15	62	13	3.56	10
Left middle frontal gyrus	10	−39	52	−3	4.22	43
Left inferior frontal gyrus	46	−45	41	12	3.68	13
Left anterior cingulate	32	−9	38	9	3.56	14
Left precentral gyrus	9	−39	16	35	3.86	100
Right middle frontal gyrus	11	33	40	−12	4.00	28
Right inferior frontal gyrus	46	45	27	12	3.77	36
Left angular gyrus	39	−30	−54	36	4.43	103
Left inferior parietal lobule	40	−48	−56	44	3.91	24
Right precuneus	31	12	−60	25	4.85	663
Right precuneus	19	33	−74	42	3.95	61
Left lingual gyrus	18	−21	−71	−12	3.64	18
Right middle occipital gyrus	18	24	−90	7	3.64	32
Right lingual gyrus	18	21	−94	−5	4.06	27
Right declive		12	−80	−24	4.47	102
Right cuneus	18	3	−90	13	3.77	22
Conjunction of Subsequent Memory Effect and Recognition Effect						
Left hippocampus		−21	−9	−15	3.42	26
Left middle temporal gyrus	37	−53	−50	−8	3.06	11
Right fusiform gyrus	37	33	−36	−13	3.03	14
Left inferior parietal lobule	40	−45	−56	44	3.45	82
Right cingulate gyrus	23	6	−33	29	2.77	10

Significance level and the size of the respective activation cluster (number of voxels) for the subsequent memory effect, the recognition effect ($P < 0.001$, uncorrected, minimal cluster size ten voxels) and the conjunction analysis at $P < 0.005$, uncorrected, minimal cluster size ten voxels
Coordinates are listed in Talairach and Tournoux (1988) atlas space. BA is the Brodmann area nearest to the coordinate and should be considered approximate

($P < 0.0001$, uncorrected), however, the mentioned cluster splits up into several distinct activation clusters leading to an approximation of the cluster sizes of the left and right middle temporal gyri. There were no detectable differences between males and females in the intensity of activation as determined by the parameter estimates of the local maxima activation (hits test: $t_{27} = -0.392$; $P > 0.05$; misses test: $t_{27} = -.052$; $P > 0.05$). Furthermore, VLMT performance, age and intensity of cerebral activation as determined by the parameter estimates of the local maxima activations did not correlate.

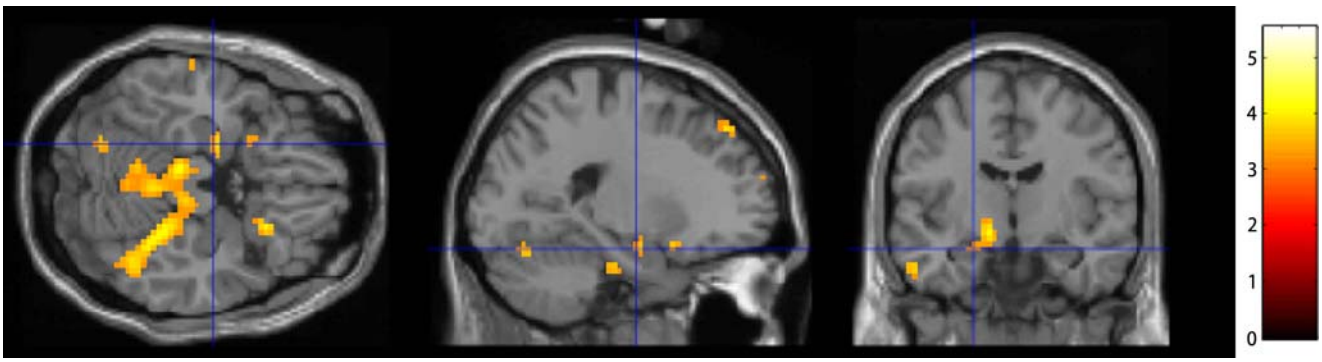

Fig. 2 Recognition Effect (hits test > misses test). Regions activated more strongly for hits as opposed to misses during the "test" condition. The activation map ($P < 0.001$, uncorrected; minimal cluster size ten voxels) is shown superimposed onto three-dimensional slices of the T1-weighted SPM-template

Conjunction analysis (subsequent memory effect and recognition effect) To identify areas involved with both successful memory encoding and successful memory retrieval, the overlap of activations of successfully encoded and successfully retrieved items was examined by computing a conjunction analysis. Most prominent activations were found in the left hippocampus and in the left inferior parietal lobule, extending into the angular gyrus (Fig. 3; Table 3). Some smaller activation clusters were further identified in the left middle temporal gyrus (BA 37), the right fusiform gyrus (BA 37) and the right cingulate gyrus (BA 23).

Discussion

In the present study, we investigated hippocampal contribution to non-relational verbal memory formation during successful encoding and successful retrieval in elderly subjects. Brain areas associated with successful encoding mainly comprised the anterior left hippocampus, extending into the surrounding parahippocampal gyrus. Activation linked to successful memory retrieval yielded a wide-spread network of bilateral medial and middle temporal cortices as well as bilateral VLPFC/DLPFC areas. Further, we identified areas commonly activated by successfully encoded (subsequent memory effect) and successfully retrieved (recognition effect) single items. This conjunction analysis revealed the anterior left hippocampus as the convergence structure for both processes of successful declarative memory.

Supported by both animal and human studies the critical role of the hippocampus proper for the encoding of episodic information is widely accepted [42]. However, functional neuroimaging studies controvert a dissociation within the medial temporal lobe with respect to relational and non-relational declarative memory formation [21, 43, 47, 50]. Pursuing this issue, Prince and colleagues (2005) detected pronounced left hippocampal involvement during *successful* associative memory formation. Remarkably, this finding was evident regardless of phase (encoding/retrieval) and content (verbal/perceptual). With the present study we could extend these findings to non-relational memory processes in a group of elderly subjects by investigating hippocampal involvement in simple, single item memorization of verbal material. Since we were mainly interested in MTL contributions to successful memory encoding and retrieval, we will focus our discussion mainly on these structures.

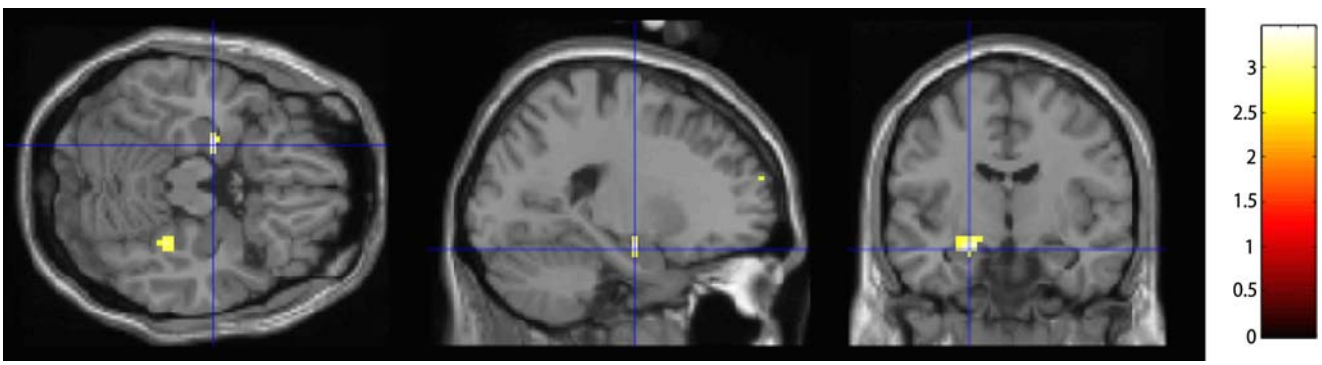

Fig. 3 Conjunction of the Subsequent Memory Effect and Recognition Effect. Regions activated more strongly during successful as opposed to unsuccessful memory encoding during "study" and more strongly for hits as opposed to misses during "test". The activation map ($P < 0.005$, uncorrected, minimal cluster size ten voxels) is shown superimposed onto three dimensional slices of the T1-weighted SPM-template

Activations associated with successful memory encoding (subsequent memory effect)

With various aspects of events being processed in distributed neocortical regions the hippocampus is considered as a binding and integration site that establishes a coherent memory [36, 47]. The parahippocampal gyrus acts as the principal neocortical input pathway to the hippocampal region and therefore is also viewed to play an important role in memory encoding [52]. Our findings of anterior left hippocampus/parahippocampal gyrus activation during successful non-relational verbal encoding perfectly agree with these predictions.

Anterior left hippocampus engagement in particular has been also implicated in studies examining the memorization of novel stimuli [12, 38, 45] and intentionality of memorization [45], both aspects playing a major role in the encoding task we applied in our study. However, associative encoding has been linked with anterior hippocampal function [21], too, whereas simple, single-item based encoding, comparable to the task demand of our study, elicited activations in perirhinal cortex [11, 53]. Thus, our results advocate an involvement of the anterior left hippocampus during intentional single-item encoding of verbal material. To note, differences in MTL involvement across studies speculatively could relate to the smoothing applied to the fMRI data during preprocessing. The amount of smoothing commonly applied affects spatial resolution in such a way that a distinction within small MTL structures might become difficult.

Furthermore, our results are in perfect agreement with the assumption of a material-specific view of MTL contribution to verbal encoding [17, 23, 25]. Following this line of reasoning, verbal material primarily activates left lateralized MTL structures including the hippocampus/parahippocampal gyrus [22, 23, 29].

Activations associated with successful memory retrieval (recognition effect)

Functional neuroimaging studies examining verbal memory retrieval exhibited profound lateral prefrontal cortex activations [5, 6, 22]. Other studies found MTL structures to be involved in retrieval processes [30, 32]. In the present study, successful retrieval of verbal items elicited activations in a widespread network of bilateral MTL, lateral temporal cortices, bilateral DLPFC/VLPFC as well as bilateral medial frontal activations. Hence, our data supports a more general contribution of memory related cortical regions in verbal retrieval. Contrary to the prediction derived from studies promoting a material-specific lateralization during retrieval [5, 26], the present data would advocate a bilateral involvement of memory relevant brain areas. A comparable activation pattern has been reported in a number of studies examining elderly relative to young adults and has been conceptualized in the HAROLD model [7]. According to this model, elderly subjects engage more bilateral cortical regions presumably to compensate for a reduced processing efficiency of other regions of the brain [7, 10]. Several other research studies support the view of such a compensatory mechanism in elderly, too [8, 9, 19, 49]. Likewise, a study assessing memory related activation in a group of MCI patients demonstrated an increased overall signal change in MTL regions, presumably reflecting a compensatory response to a beginning AD pathology [24].

As our sample consisted of a group of healthy elderly subjects the detected activation pattern during retrieval would perfectly agree with the assumption of the HAROLD model. However, the question remains why a bilateral involvement of memory relevant structures apparently has not been elicited during encoding as it would be also predicted by the HAROLD model [7].

Overlap of activations related to successful encoding and successful retrieval

The present study focused on the question of how the hippocampal formation contributes to successful encoding *and* successful retrieval of simple, non-relational verbal material. The results of the conjunction approach indicate that, within memory relevant brain regions, only the anterior left hippocampus is activated when successful encoding *and* retrieval are considered concomitantly. Prince et al. (2005) examined memory processes related to a successful encoding *and* to a successful retrieval of verbal/perceptual items in younger adults, which, in contrast to our study, were of relational (associatively linked) character. They found that the left hippocampus was the only brain region to be associated with successful memory formation regardless of phase (encoding vs. retrieval) and content (verbal vs. perceptual). These findings correspond well with our results, although the hippocampal activation detected in our study was located somewhat more anteriorly. The distinction between anterior and posterior MTL regions can be regarded as an encoding/retrieval gradient with a middle convergence region shared by both processes [35, 40]. From further literature on younger subjects, an involvement of the hippocampus in memory encoding and retrieval was mainly expected for associative memory (e.g. [15, 41]) as opposed to memory for single words as employed in our study. On the other hand, a role for the hippocampus in non-associative memory has also been shown in younger subjects [44] In summary, we could corroborate and extend these findings to non-relational material and in particular show that healthy elderly exhibit a similar pattern of activation as young subjects.

Somewhat intriguing, the activation pattern related to a successful encoding alone, as documented in the Prince et al. (2005) study could be clearly replicated by our data, though encoding processes differed with respect to the associative/non-associative nature of the stimuli. On the other hand, the activation pattern associated with a successful retrieval alone clearly differed between studies, although the character of the applied tasks (associative/non-associative) remained identical with the encoding phase. As mentioned above, successful encoding was associated with anterior left hippocampal activity in both studies. However, successful retrieval elicited significant activations in posterior left hippocampal/parahippocampal regions in the Prince et al. study, whereas the center of activation was located somewhat more anteriorly in our study. Most likely, the distinct activation pattern between studies that was observed during successful retrieval accounts for the different findings of the conjunction approaches.

Hence, the present data neither totally confirms the assumptions made by the HIPER model, which would assume an anterior/posterior hippocampal segregation with respect to the gradient of encoding- and retrieval related activity, nor does it fully support the suggestion of Schacter and Wagner whereupon anterior/posterior hippocampal regions contribute to relational/non-relational memory, respectively [27, 39, 45]. Our data would rather suggest a reversed hippocampal involvement in simple, non-relational memory. Based on findings of our study and the literature we would suggest that with respect to the task approach applied (associative vs. non-associative memory), nearly identical portions of the medial temporal lobe contribute to a successful formation of declarative memory. Thereafter, only a conjunction of successfully encoded and retrieved items uncovers a shift of the activation center from a more anterior portion (during non-associative memory formation) to a middle part (during associative memory formation) of the hippocampus.

Limitations

Given the high number of subjects in the present study, the applied statistical threshold was rather liberal ($P < 0.001$, uncorrected: subsequent memory effect and recognition effect; $P < 0.005$, uncorrected: conjunction analysis). However, as we had strong a-priori assumptions about the localization of cortical activity related to successful encoding and retrieval processes, i.e. the hippocampus proper, and taking into account the relatively small size of the hippocampus, we think that the applied threshold would suffice in order to derive meaningful and well interpretable results. Further, a sample of young healthy control subjects would have strengthened the interpretation of the findings.

Taken together, the present study yielded four major findings: first, successful encoding of non-associative verbal material (subsequent memory effect) involves the anterior left hippocampus, a region consistently implicated in intentional encoding of novel items. Second, successful retrieval of non-associative verbal material (recognition effect) relates to significant activation of a widespread cortical network including the memory relevant bilateral hippocampal/parahippocampal region and the bilateral DLPFC/VLPFC. Thus, our data neither clearly supports the supposition made by the HIPER model nor does it corroborate a pure material-specific point of view with respect to the encoding and retrieval of verbal items. Third, in line with the fact that our sample consisted of healthy elderly subjects, the prediction made by the HAROLD model comes closest to the observations derived in our study. However, a hemispheric asymmetry reduction in memory relevant cortical regions could only be demonstrated during successful retrieval, leaving an explanation for the observed laterality effect during successful encoding somewhat elusive. Lastly, a conjunction analysis of successfully encoded *and* successfully retrieved items revealed that only one memory relevant cortical structure contributes to both phases concomitantly: the anterior left hippocampus.

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