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Research report

Neural correlates of episodic memory: Associative memory and confidence drive hippocampus activations

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HIGHLIGHTS

- Higher levels of associations enhance OLD responses in recognition memory.
- Associative memory manipulation modulates left hippocampus activation.
- U-shaped confidence functions in MFG and PCG not affected by level of associations.

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ABSTRACT

The present study used a study-test recognition memory task to examine the brain regions engaged in episodic and associative memory processes. Participants evaluated on a six-point rating scale how confident they were on whether or not an item was presented in a previous study phase. Neural activations for high- and low-confidence decisions were examined in old and new items at two levels of between-item-associations. Items had different amounts of associations within the stimulus set, while associations were defined by co-occurrence statistics.

The medial frontal gyrus, the posterior cingulate gyrus, the superior temporal gyrus and the right hippocampus revealed U-shaped activation functions with greater activations for high-confidence OLD and NEW decisions. This was independent of the associative memory manipulation, which suggests that not episodic memory, but rather processes related to confidence account for the activation in these brain regions. In contrast, left hippocampus followed a different activation pattern that was modulated by the amount of associations. This provides evidence for the role of the left hippocampus in associative memory.

1. Introduction

In standard recognition memory tasks participants judge whether a presented item has been recently encountered during a learning session (OLD), or not (NEW). The literature converges on the view that memory relies on the functioning of a medial temporal lobe (MTL) network comprising the hippocampus and anterior and posterior parahippocampal brain regions [1]. Models of recognition memory propose that two components contribute to successful recognition, namely familiarity and recollection [1,2]. Whereas familiarity reflects the intuitive knowledge that something has been encountered before without the need to remember specific details, recollection refers to remembering specific contextual details of OLD items [3,4]. The exact contribution of these processes to recognition memory is still under debate [1,5,6]. Most notably, memory strength, i.e. the differentiation between weak and strong memories, has been identified as a likely confounding variable underlying recollection- and familiarity-based decisions in recognition memory [1,5]. In fact it is becoming hard to differentiate between both concepts and an adequate experimental paradigm is required to advance our knowledge, especially concerning the function of the hippocampus [7–11].

In this study, we will examine two variables that affect memory strength, confidence assessment and associative memory, and their interaction. First, associative activation can increase the memory strength of an item [12], also termed relational or associative memory processes [13,14]. Associations to other items in the task context were found to activate a context memory brain network at encoding ([15], see below) and to engage recollection at retrieval [14]. A high amount of associations is expected to drive recollection, because more specific details about the stimulus (i.e., associated

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items) can be remembered [16,1]. Such contextual between-item-associations, for example, elicit the 'false memory effect' in the DRM paradigm [17,18]: learning associated items (e.g., "table," "sit," "legs") to a non-learned target item (e.g., "chair") strengthens the erroneous recall or recognition of a target item. Thus, remembered contextual details and, in particular, a manipulation of the between-item-associations is known to enhance the strength of the episodic memory signal [12] and to drive recollection [4].

Second, memory strength is also indicated by the subjective confidence with which a studied item is remembered [19,4]. Familiarity- and recollection-based decisions differ with respect to the subjective level of confidence [20]. Recollection-based decisions are generally made with a higher level of confidence. Thus, the standard recognition memory paradigm can be extended by judgments of the confidence with which these decisions are made. For example, using a six-point rating scale ranging from surely NEW (1) over unsure new (3) to unsure (4) or sure OLD (6) provides a more continuous measure of the memory signal. Participants deliver most recollection-based judgments with high confidence, because of the remembered contextual details, whereas lower levels of subjective confidence accompany most familiarity-based judgments [20].

At the neural level, the hippocampus is the target region of a recognition memory network ([21,22,1], but see [23]). For example, Yonelinas et al. [21] examined recollection- and familiarity-based recognition memory judgments at a comparable level of confidence by asking their participants to provide either a recollective 'remember' response or a non-recollective 'know' response (at varying levels of confidence). Recollection-related brain activation was examined by contrasting the neural responses to confidently remembered items and highest confidence familiar items (see [22] for a similar approach). This contrast identified a network of brain regions associated with recollection: bilateral hippocampus, the medial frontal gyrus (MFG), the posterior cingulate gyrus (PCG), and the left superior temporal gyrus (STG; see Fig. 1 in [21]). Still, it is questionable whether memory strength differs between confidently remembered and high-confidence familiar items [5,24] emphasizing an overestimation of recollection-related activations in these brain regions. Of note is the high overlap between the recognition memory network and the context memory network, i.e. the same brain regions have been identified as supporting the processing of contextual associations [15,25]. The neural networks supporting familiarity and novelty in recognition memory have also been examined by means of a linear contrast of confidence: An increase in confidence for familiar OLD items is accompanied by activations in the lateral left inferior-frontal gyrus, a superior parietal region and the precuneus. High confidence NEW items, in contrast, elicit activations in the inferior temporal lobe, the anterior cingulate cortex, a left hippocampal region and the cerebellum [21]. Moreover, remembering familiar items has often been associated with brain activation in the anterior parahippoampal gyrus (= perirhinal cortex) [3].

Other recognition memory studies report that high-confidence decisions are associated with activations in the targeted recollection regions when compared to low-confidence judgments, i.e. MFG, PCG, and bilateral temporal lobes including the bilateral hippocampus [26,27,28]. Chua et al. [27] point out that little is known about the neural mechanisms supporting confidence judgments despite the fact that they are widely used in recognition memory tasks. They suggest that confidence judgments may involve both, the cognitive process of confidence assessment and the subjective feeling of confidence [27]. Thus, 'subjective level of confidence' subsumes a number of factors that may contribute to the differences between high- and low-confidence judgments, which could involve ease of retrieval, specific attributes of the test item, or heuristics about a subject's own memory ([19], cf. [27]). It is evident, that there exists conceptual overlap between recollection, memory strength and a high 'subjective level of confidence' and they appear to rely on similar networks. We therefore hypothesized that the 'subjective level of confidence' accounts for some of the above findings associated with recollection [21,22].

In particular, the shape of the 'oldness scales' (e.g., [21,22]) might provide additional evidence to differentiate between confidence-based activations and memory-related processes (recollection or memory strength). Such oldness-scales depict increases and decreases of event-related neural activation as a function of the perceived oldness ranging from 'sure new' to 'sure old' responses. As explored in [29], some of the oldness-scales follow a U-shaped function. For example, the inferior parietal cortex reveals strong activations for high-confidence OLD and high-confidence NEW decisions and weak activations for low-confidence ratings. Such U-shaped functions (Fig. 1) are difficult to explain with an assumption of pure memory-related processing, because NEW items have not been studied and are therefore less likely to activate memory-related brain regions. The more likely account for U-shaped oldness scales is the view of confidence being a part of the processes supporting memory decisions (so-called metamemory processes [30,31] and/or attentional processing [29]). Note, however that MFG, PCG, and STG oldness scales are U-shaped in [21] (also [22]). Activations in the hippocampal region, in contrast, follow an L-shaped function [21,22] that only increases for high-confidence OLD decisions (see Fig. 1). We expect such a L-shaped neural response pattern particularly for regions that specifically process memory strength, as NEW items are not expected to elicit such a signal.

Thus, the present study aimed to combine a manipulation of between-item-associations with a confidence-based approach in a recognition memory paradigm to examine the oldness-scales in the proposed target regions (bilateral hippocampi, PCG, MFG, STG [21]) of the memory network discussed to support recollection/memory strength. We expected to replicate the pattern of confidence-based U-shaped oldness scales in regions of the memory network outside the MTL, and L-shaped oldness scales in hippocampal and parahippocampal regions. Such a pattern would be in line with the notion of a support memory network dedicated to metamemory and attentional processing distinct from the MTL core memory network. In addition, we applied a novel manipulation of associative connections within the stimulus set. To measure the associative structure in the stimulus set, we used co-occurrence-statistics. This rationale is based on Hebbian learning [32]: Items that occur often together are likely to be associated. Thus, the manipulation of between-item-associations differentiates between words with a high (HIGH-A) or low (LOW-A) amount of associated items in the stimulus set. The manipulation of between-item-associations is thought to explicitly enhance episodic memory processes [12]. Using a similar manipulation, Hofmann et al. [12] were able to increase participants' memory performance in a behavioral and a simulation study. HIGH-A items elicited a higher proportion of 'OLD' responses to OLD items and NEW items. Thus, the manipulation of the between-item-associations can inform about the underlying memory functions. The availability of contextual associations during encoding, for example, has been shown to correlate with activations in the hippocampus, and superior and inferior parietal regions [15], i.e. the main target regions of the recognition memory network.

Brain regions where U-shaped oldness scales are not affected by this manipulation are likely to support confidence, not memory itself. In contrast, when a high amount of associations drives the activation of OLD items only, this supports the conclusion of actual memory processes. As HIGH-A items have increased memory strength [12], we expect a higher amount of associations to specifically engage hippocampal activation. This structure is known to bind contextual associations to the item information

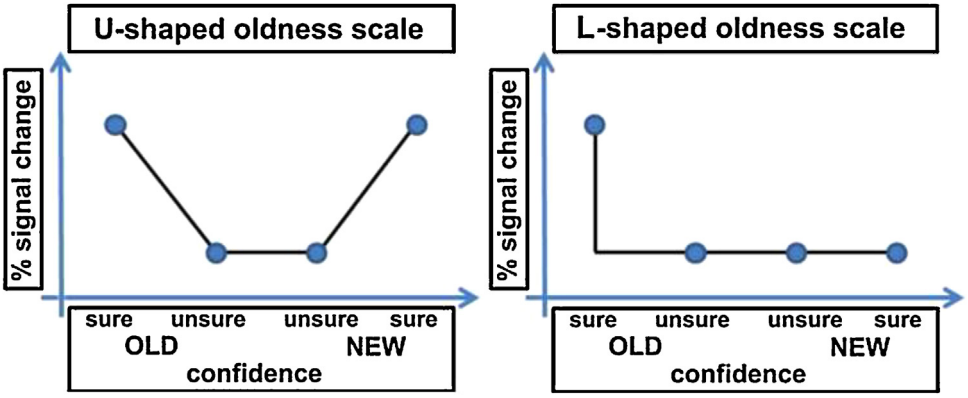

Fig. 1. Schematic representation of U-shaped and L-shaped oldness-scales.

[33]. As memory strength is indicated by subjective confidence and affected by contextual associations, an interaction between these factors in one brain region and the observation of L-shaped oldness scales would indicate a high memory strength signal. Thus, we predict greater activations for HIGH-A items in the hippocampus, with an L-shaped scale for HIGH-A and a lower or flattend L-shaped scale for LOW-A items.

2. Materials and methods

2.1. Stimuli

Stimuli were German nouns with a length of four to eight letters from the Berlin Affective Word List Reloaded (BAWL-R [34]), which includes ratings of emotional valence, arousal, and imageability, while the number of orthographic neighbors was derived from the CELEX Database [35]. Frequency classes were taken from the German Corpus of the Leipzig Wortschatz Projekt (http://corpora.informatik.uni-leipzig.de/) [36]. Token bigram frequencies were calculated with the SUBLEX software [37], using the frequency counts of a cleaned version of the Leipzig Corpus, from which word forms not contained in the CELEX lexical database were excluded [12]. All of the above properties were controlled for the 256 experimental stimuli in the four stimulus lists ($Fs \leq 1$, cf. Table 1). The manipulation of between-item-associations was achieved by varying the number of significantly co-occurring items of a target item to all other items in the whole stimulus set. Two words were regarded "associated" when they occur significantly more often together in one sentence of a large corpus than could be predicted by their single words' occurrence using the log-likelihood test ($p \leq 0.05$, $Chi^2 \geq 6.63$; [36,38]). The HIGH-A conditions contained words with at least 10 co-occurring items in the stimulus set, while LOW-A stimuli had less than 10. As a result, HIGH-A OLD items share on average more associates than LOW-A OLD items within the study list. For NEW items this effect extends to associates in both, OLD and NEW items. Of note is, that following this manipulation HIGH-A NEW items, that share many associates in the OLD item set, behave like 'critical lures' in the false memory paradigms, i.e. they increase the rate of false OLD responses [12].

2.2. fMRI study

2.2.1. Participants

Participants were 20 healthy right-handed native German speakers (6 male, 14 female) aged 18–45 years (mean = 24.5 years). Right-handedness was determined by the Edinburgh handedness inventory [39]. They were recruited from the Free University of Berlin and were paid or received course credits.

2.2.2. Procedure

Stimuli were presented on a desktop computer by Presentation software (Version 14.1, Neurobehavioral Systems Inc., Canada). The experiment started after a brief verbal instruction on the screen. Both, study and test period were conducted while participants were lying in the scanner. However, the present article focuses on the analysis of the test period. Both experimental periods began with practice trials to familiarize participants with the task. The study period consisted of the 128 randomly presented OLD items. These were accompanied by three filler items at the beginning and the end of the period, respectively, to avoid primacy and recency effects. These six items and the practice items were not significantly associated to other words in the set. During the test period all 128 OLD and 128 NEW items were presented to the participants in random order. Both periods were separated by a break of approximately ten minutes. Every trial began with the presentation of a fixation cross (+) in the middle of the screen for 500 ms and the presentation of an item for 1500 ms. The latter was followed by five pound signs (#####) in the study phase, whereas participants gave memory judgments on a six-point-rating scale (from (1) 'sure new' to 'unsure' to (6) 'sure old') in the test phase. All stimuli were presented in random order and memory judgment labels on the rating scales were reversed for half of the participants.

Participants used a trackball (Current Design; http://curdes.com/) for the memory judgments that was placed under their right hands, to move a virtual cursor vertically over the scales (with their middle finger). They indicated their decisions by clicking the trackball response button over one of the ratings (with their index finger). The cursor was restricted to only move vertically over the scale and to jump from one end of the scale to the other when being moved further. To get the participants used to the trackball, the number of practice trials of the test phase was increased in comparison to the study phase. After the presentation of either pound signs (study phase) or memory judgment scales (test phase) for 3000 ms respectively, jittered inter-trial-intervals were included by an optimized procedure, using an AFNI script (http://afni.nimh.nih.gov/afni/). The jitter lasted 2000 ms on average (maximum: 5000 ms). For anatomical localization, a high-resolution T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE, 176 slices, voxel size 1.0 mm × 1.0 mm × 1.0 mm) image was collected in the break between the two functional runs.

Scanning was performed on a 3T Siemens Tim Trio system (Siemens, Erlangen, Germany) with a standard 32 channel head coil and a standard EPI sequence (TR = 2000 ms, TE = 30 ms, flip angle = 70°, 37 axial slices oriented along the AC-PC plane, interleaved from bottom to top, 3 mm slices, no gap, 3 mm × 3 mm, in-plane). Susceptibility artifacts in blood-oxygen-level dependence fMRI were reduced using localized shimming. The initial six volumes were discarded to allow for scanner stabilization. The study period comprised 475 and the test period 906 volumes.

2.2.3. fMRI analysis

Imaging data were analyzed with SPM8 (Wellcome Department of Cognitive Neurology) for Matlab (Mathworks, Inc.). Images were slice time corrected, realigned, and unwarped. The resulting mean unwarped image was used to estimate normalization parameters relative to the standard MNI EPI template provided by SPM8 at a voxel size of 3 × 3 × 3, which were then applied to all EPI volumes. The normalized images were smoothed with an 10 mm full-width half-maximum Gaussian kernel for whole-brain analyses, whereas unsmoothed, normalized images were used in the region of interest (ROI) analysis. A GLM was modeled at the first level comprising stick functions convolved with the hemodynamic response function for the onsets of each item per condition and level of confidence. Only correctly answered items were modeled in the condition regressors. Confidence levels '2' to '3', and '4' to '5' were collapsed for each 'between-item-association' condition because of low numbers of correct answers or even no answers by some participants in these conditions. Thus, the design matrix was reduced to a 2 (HIGH-A/LOW-A) × 4 (Confidence) design plus regressors of no interest for missing or incorrect judgments, onsets of the rating scales following item presentation, and six regressors of movement parameters obtained from preprocessing. Because only correct responses were considered for this design, the number of trials corresponds directly to the absolute number of correct responses per each of the eight experimental conditions displayed in Table 2. For the group analysis, participants were treated as random effects and parameter estimates for the eight regressors were included in a full-flexible within-subjects ANOVA at the second level. An a priori Monte Carlo simulated extend threshold of 15 contiguous voxels (10.000 simulations using MATLAB scripts based on [40] at $p < 0.001$) was applied to correct for multiple comparison at $p < 0.05$ in the whole brain analyses [41] (if not otherwise stated).

Mean percent signal change in ROIs was extracted by growing spheres with a 4 mm radius around respective peak voxels of the recognition memory network identified in [21] using the MarsBAR toolbox (http://marsbar.sourceforge.net/; [42]). Five regions were selected as target ROIs based on the peak voxels of the recognition memory network reported in [21]: (1) left hippocampus (MNI [*x*, *y*, *z*]) [−24, −21, −21], (2) right hippocampus [30, −21, −21], (3) MFG [−6, 54, −6], (4) PCG [0,

Table 1
Manipulation and control of psycholinguistic variables in the stimulus set (means and standard deviations).

Condition	OLD HIGH-A	OLD LOW-A	NEW HIGH-A	NEW LOW-A
# Stimuli	64	64	64	64
# Co-occurring items	12.98 (3.29)	6.95 (1.84)	13.02 (3.39)	7.14 (1.91)
Frequency class	11.97 (1.37)	12.03 (1.37)	11.97 (1.22)	11.94 (1.30)
Emotional valence	−0.05 (1.22)	0.15 (1.03)	0.03 (1.31)	0.09 (1.28)
Arousal	2.79 (.76)	2.73 (.73)	2.81 (0.80)	2.76 (0.74)
Imageability	4.21 (1.17)	4.18 (1.20)	4.24 (1.38)	4.15 (1.28)
Letters	6.14 (1.23)	6.13 (1.16)	5.86 (1.42)	6.17 (1.16)
# Orthographic neighbors	1.58 (2.05)	1.23 (1.97)	1.78 (2.33)	1.64 (2.46)
Bigram frequency (token)	14 002 (7 366)	14 386 (8 159)	15 938 (8 642)	15 999 (8 780)

#: Number of. NEW/OLD: nonstudied/studied stimuli. HIGH-A/LOW-A: high/low amount of associated stimuli in the stimulus set. Emotional valence ranges from −3 to +3. Imageability and arousal range from 0 to +5.

−45, 30], and (5) STG [−42, −54, 15]. A 2 × 4 within-subjects ANOVA was computed for these ROIs comprising 'between-item-associations' and 'confidence' as factors. Significance level was set at $p < 0.05$.

2.2.4. Behavioral analysis

The confidence categories (2) and (3), and (4) and (5) were also collapsed for the behavioral analyses for each 'between-item-association' condition to form new low confidence categories, whereas (1) and (6) answers were taken as high confidence responses. Thus the design was reduced to a 2 (HIGH-A/LOW-A) × 2 (high confidence/low confidence) × 2 (OLD (1)(2)(3)/NEW) design. Three-way within-subjects ANOVAs were computed for the absolute number of correct answers per condition and for the corresponding response times.

3. Results

3.1. Behavioral data

The behavioral results are displayed in Table 2. The three-way ANOVA (comprising the factors associations, confidence, and old–new) of correctly classified answers revealed no significant main effect (all p's > 0.470), but significant two-way interactions between associations and old-new ($F(1,19) = 10.919$, $p = 0.004$), as well as between confidence and old-new ($F(1,19) = 39.871$, $p < 0.001$). The associations × confidence interaction ($p = 0.196$) and the three-way interaction ($p = 0.914$) are non-significant. The associations × old–new interaction effect is driven by a higher number of HITs (correctly classified OLD items) in the HIGH-A condition, compared to a higher number of Correct Rejections (correctly classified NEW items) in the LOW-A condition. Similarly, the confidence × old–new interaction is based on a higher number of high-confidence HITs compared to low-confidence HITs, whereas this effect is reversed in the NEW items (lower number of Correct Rejections in high-confidence items). This overall pattern is also visible in the analysis of the response times (RTs): No significant main effect (all p's > 0.410), but significant associations × old–new ($F(1,19) = 5.249$, $p = 0.034$) and confidence × old–new ($F(1,19) = 5.348$, $p = 0.032$) interactions, whereas associations × confidence ($p = 0.429$) and the three-way interaction remained (0.983) non-significant. The pattern of the associations × old–new interaction effects replicates that observed in [12] with higher 'OLD' responses in case of higher between-item-associations (corresponding to higher HITs and higher False Alarms/lower Correct Rejections, respectively).

3.2. Imaging data

3.2.1. Old vs. NEW

The whole-brain analysis revealed widespread activations in the recognition memory network greater for OLD items compared to NEW items covering bilateral inferior and superior parietal lobe regions, posterior left mid- and inferior temporal regions, midline structures in anterior and posterior cingulate cortex, medial frontal gyrus and precuneus, subcortically the caudate and thalamus, as well as left lateral frontal regions in addition to left-hemisphere MTL regions (anterior parahippocampus and hippocampus, amygdala). The reverse contrast revealed a greater activation to NEW items in the anterior left inferior temporal gyrus (see Table 3 for a complete list of activations).

3.2.2. Confidence

A network similar to that in the OLD vs. NEW contrast was also revealed when contrasting high-confidence vs. low-confidence items, although to a much greater extend and with higher overall activations (see Fig. 2a and Table 4). Notably, the effect was slightly more robust in the left hemisphere, probably due to the verbal nature of the stimuli. Strong high-confidence related activations were observed in parietal and occipital regions around the cuneus and large areas around the cingulate gyrus and the precuneus, extending to the supramarginal and the angular gyrus. The hippocampal formation and other parts of the temporal lobe, the limbic lobe, the cerebellum, and medial areas of the frontal lobe were also activated by this contrast. There were significant effects for high-confidence vs. low-confidence items in all five targeted regions of the memory network, i.e. MFG, PCG, STG, and bilateral hippocampus.

3.2.3. Interaction: OLD/NEW and confidence

The activations when contrasting high- and low-confidence items differ between OLD and NEW items in regions shown activated in the overall confidence contrast as revealed by the

Table 2
Behavioral Results (means and standard errors of the mean).

Condition	OLD (1) High confidence	OLD (2) (3) Low confidence	NEW (4) (5) Low confidence	NEW (6) High confidence
# correct (HIGH-A)	30.4 (2.9)	16.6 (1.5)	26.4 (2.2)	19.4 (2.7)
# correct (LOW-A)	28.8 (2.8)	16.5 (1.6)	28.2 (2.1)	20.1 (2.6)
RTs (HIGH-A)	992 (23)	967 (21)	1058 (23)	1005 (26)
RTs (LOW-A)	1039 (37)	984 (29)	978 (21)	957 (42)

correct: number of correctly responded items. NEW/OLD: nonstudied/studied stimuli. HIGH-A/LOW-A: high/low amount of associated stimuli in the stimulus set. RTs: response times in milliseconds. Note that correctly classified OLD items refer to measures of HITs and correctly classified NEW items to Correct Rejections if summed across the confidence categories.

Table 3
Brain regions showing significantly greater BOLD signal ($p < 0.001$) for OLD than for NEW items (and the reverse contrast).

brain regions	L/R	# voxel	*T*	*x*	*y*	*z*
OLD > NEW						
Inferior and superior parietal gyrus, angular gyrus, supramaginal gyrus, precuneus, mid-occipital gyrus, mid-temporal gyrus	L	2167	7.55	−34	−72	44
Caudate, putamen, thalamus, anterior parahippocampal gyrus, hippocampus, amygdala	L,R	3121	7.28	10	12	0
Inferior frontal gyrus, anterior insula, mid-frontal, gyrus, superior frontal gyrus, inferior orbitofrontal gyrus, mid-orbitofrontal gyrus	L	2478	6.57	−32	24	−4
Middle frontal gyrus, superior-orbitofrontal gyrus	L	41	3.68	−22	44	−16
Medial superior frontal gyrus, anterior cingulate, gyrus, suplementar motor area	L	231	4.63	−4	30	52
Precuneus	L	401	4.71	−10	−64	32
Posterior cingulate gyrus	L,R	315	4.32	−6	−32	38
Calcarine gyrus	L	50	3.69	−8	−94	6
Mid-temporal gyrus, inferior temporal gyrus	L	120	4.07	−64	−40	−14
Inferior + middle occipital gyrus	L	134	4.03	−26	−90	−6
Inferior + superior parietal lobule, angular gyrus	R	104	3.77	36	−68	40
Anterior cingulate gyrus, medial frontal gyrus	R	44	3.68			
Inferior frontal gyrus, anterior insula	R	76	3.90	34	24	−8
Inferior frontal gyrus	R	26	3.60	30	14	20
Cerebellum	R	491	5.58	12	−78	−28
Cerebellum	R	130	3.87	36	−70	−50
Cerebellum	R	17	3.51	10	−56	−36
NEW > OLD						
Inferior temporal gyrus	L	28	3.67	−48	6	−40

OLD/NEW × confidence contrast. In particular, activations in the bilateral posterior cingulate cortex in combination with the precuneus, anterior cingulate and medial frontal regions and left superior parietal regions are observed. But these differences are also visible in left hemisphere cluster in anterior hippocampus spreading into the neighboring parahippocampus and amygdala (Table 5 and Fig. 2b).

3.2.4. Between-item-associations

The manipulation of the amount of associations in the stimulus set only had a small significant activation cluster in the superior frontal gyrus with increased activations for items that share a higher number of activations (Table 6).

3.2.5. Interaction: OLD/NEW and between-item-associations

The examination of the interaction between the manipulation of associative connections within the stimulus set and OLD vs. NEW items points to differences in neural activation patters of HIGH-A and LOW-A OLD and NEW items in a superior frontal and a medial frontal regions, the thalamus and the cerebellum. Most importantly, a significant interaction was obtained in a left-hemispheric posterior hippocampal region that overlaps with the left

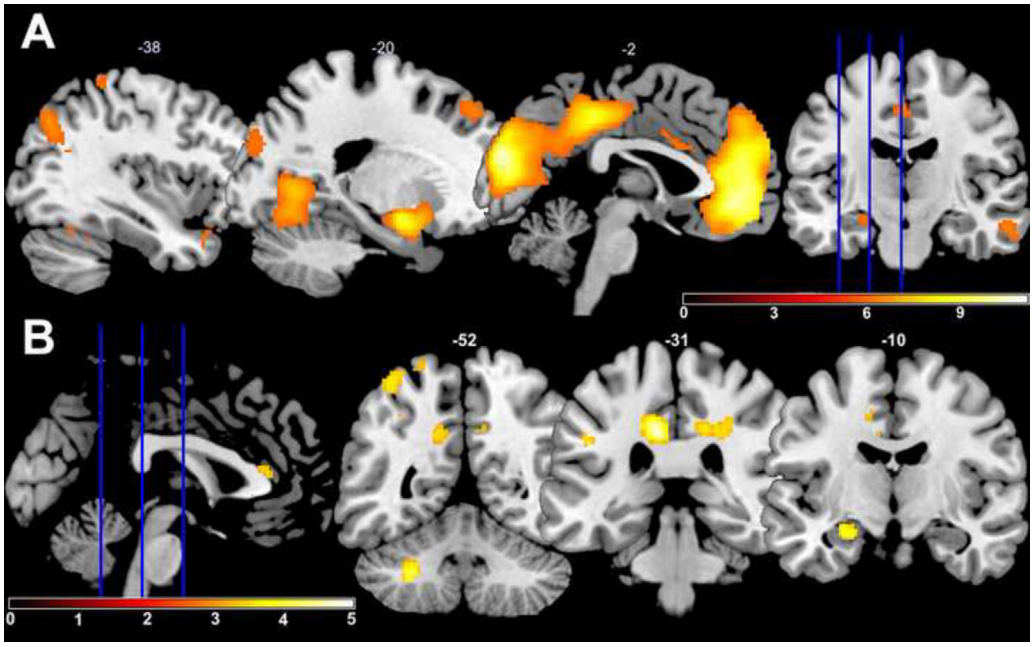

Fig. 2. High- versus low-confidence decisions reveal (A) large scale confidence processing networks including medial temporal lobe and anterior and posterior midline regions (displayed at $p < 0.001$, FEW corrected, $k = 15$). (B) Interaction between OLD/NEW and confidence indicating differential neural responses to confidence processing in OLD and NEW items in (left to right) left superior parietal cortex, posterior cingulate cortex and left hippocampus (at $p < 0.001$, $k = 15$).

Table 4
Brain regions showing significantly greater BOLD signal ($p < 0.01$, FWE corrected) for high-confidence than for low-confidence decisions.

Brain regions	L/R	# voxel	*T*	*x*	*y*	*z*
High-confidence > low-confidence						
Occipital cluster: precuneus, cuneus, lingual gyrus, posterior cingulate gyrus, fusifrom gyrus, posterior parahippocampal gyrus	L, R	9626	10.50	0	−88	20
Medial frontal cluster: medial frontal gyrus, anterior, cingulate gyrus, superior frontal gyurs, mid-frontal gyrus, orbitofrontal gyrus	L, R	5933	10.12	−2	44	−6
Parahippocampal gyrus, hipocampus, amygdala, temporal pole, insula, putamen	L	1014	8.93	−20	−4	−16
Inferior parietal lobule, posterior mid-temporal gyrus, angular gyrus, superior temporal gyrus, supramarginal gyrus	L	2464	8.13	−46	−68	38
Mid-temporal gyrus	R	344	7.04	66	−32	−12
Caudate, parahippocampal gyurs, anterior hippocampus, amygdala	R	349	7.09	8	8	−8
Inferior + mid-temporal gyrus	R	344	7.04	56	−18	−18
Mid-temporal gyrus	R	42	5.99	50	−66	10
Inferior + mid-temporal gyrus	L	145	6.38	−60	−26	−18
Postcentral parietal gyrus	L	46	6.32	−26	−48	68
Fusiform gyrus	L	56	6.43	−44	−58	−16
Precentral gyrus	L	40	6.33	−50	−6	52
Cerebellum	L	93	6.27	−28	−40	−28
Mid + superior temporal gyrus	R	51	6.01	60	−48	8
Inferior frontal gyrus, orbito-frontal gyrus	R	47	6.31	26	24	−18
Postcentral parietal gyrus	L	37	6.08	−40	−38	62
Cerebellum	L	57	6.12	−12	−82	−34
Supramarginal gyrus	R	29	5.92	58	−44	32

Please note that a more conservative significance threshold is used in this contrast ($p < 0.001$, FWE corrected). The reverse contrast of low-confidence vs. high-confidence decisions did not reveal activations above the a priori significance threshold of $p < 0.001$.

Table 5
Brain regions found active in the OLD/NEW × confidence interaction contrast ($p < 0.001$).

Brain regions	L/R	# voxel	*T*	*x*	*y*	*z*
Posterior cingulate gyrus	L	758	4.88	−14	−38	36
Posterior cingulate gyrus	R	280	4.58	14	−28	38
Cerebellum	L	88	4.21	−28	−50	−38
Cingulate gyrus	L	83	4.02	−14	−6	44
Inferior + superior parietal lobule	L	102	3.91	−38	−54	60
Supramarginal gyrus, inferior parietal gyrus	L	45	3.92	−46	−30	30
Hippocampus, parahippocampus, amygdala	L	99	3.98	−24	−10	−18
Anterior cingulate gyrus	L,R	39	3.65	2	34	12
Rolandic operculum, insula	L	25	3.56	−48	−6	10
Precuneus	R	103	3.57	12	−48	38
Inferior parietal lobule, supramarginal gyrus	L	111	3.53	−40	−42	40
Superior parietal gyrus	L	19	3.44	−24	−50	70
Inferior parietal lobule	L	16	3.43	−52	−26	42

Table 6
Brain regions showing significantly greater BOLD signal ($p < 0.001$) for high-association than for low-association items.

Brain regions	L/R	# voxel	*T*	*x*	*y*	*z*
Superior frontal gyrus	L	19	3.72	−12	50	26

Table 7
Brain regions found active in the OLD/NEW × associations interaction contrast ($p < 0.001$).

Brain regions	L/R	# voxel	*T*	*x*	*y*	*z*
Posterior parahippocampal gyrus, hippocampus	L	92	4.22	−26	−24	−20
Superior frontal gyrus	R	17	3.60	20	38	28
Medial frontal gyrus	L,R	37	3.56	−2	36	−20
Thalamus	L	27	3.65	−6	−6	2
Cerebellum	L	15	3.32	−14	−82	−50
Cerebellum	L	40	3.90	−46	−66	−46
Cerebellum	L,R	136	3.73	6	−48	−22
Cerebellum	R	30	3.73	46	−64	−50
Cerebellum	L	45	3.77	−20	−34	−34
Cerebellum, midbrain	R	26	3.54	6	−38	−6

hippocampal region reported by Yonelinas et al. [21] ([−24, −21, −21]) in their recollection contrast (Table 7).

3.2.6. Interaction: confidence and between-item-associations

Also, the contrast between high-confidence and low-confidence items was modulated by the association manipulation, revealing again, a significant activation cluster in the left hippocampus and an adjacent parahippocampal region and the cerebellum (Table 8).

3.3. Regions of interest analysis

To refine the whole brain analysis and to be able to more specifically examine the shape of the oldness scales a ROI analysis was conducted. Mean% signal change was computed for five target regions selected following the results of Yonelinas et al. [21]. Because of the high overlap between the target ROI and the left hippocampal activation in Section 3.2.5 only the latter will be reported here,[1] extended by the anterior left hippocampus ROI revealed in Section 3.2.6. All ROIs were created by a 4 mm radius sphere around the respective peak voxel. The shape of the oldness scales can be seen in Fig. 3. As is evident, non-MTL regions show U-shaped confidence functions in HIGH-A and LOW-A items (also evident in the right hippocampus) whereas the left hippocampal ROIs show U-shaped oldness scales only in LOW-A items. HIGH-A items with a greater associative structure instead reveal an L-shaped function in the posterior hippocampus and a parametric increase from 'sure new' items to 'sure old' items in the more anterior hippocampal ROI. This result pattern is confirmed by the ANOVA. In the medio-frontal, the posterior cingulate and the left superior temporal ROI only the main effect of confidence reached significance [MFG: $F(1,19) = 3.287$, $p = 0.027$; PCG: $F(1,19) = 10.588$, $p < 0.001$; STG: $F(1,19) = 9801$, $p < 0.001$], whereas all between-item association main effects and interactions did not reach significance threshold (all p's > 0.133). Of further interest may be that in these three ROIs the significant main effects of confidence are accompanied by significant quadratic post hoc contrasts at $p < 0.05$ indicating U-shaped oldness scales. This pattern with a significant confidence main effect and a significant quadratic post hoc contrast is also visible in the right hippocampus ($F(1,19) = 3.876$, $p = 0.014$). In both left hippocampal ROIs [11], instead, significant interactions between the association manipulation and confidence are visible [posterior left: $F(1,19) = 9.726$, $p < 0.001$; anterior left: $F(1,19) = 3.210$, $p = 0.030$] indicating that the left hippocampus is especially sensitive to associative memory and confidence in the present paradigm.

4. Discussion

In the present verbal recognition memory study we manipulated the amount of reverberant associative feedback from other items in the experimental context to the presented items. In addition, we examined confidence-based neural responses to test the proposal of a memory-processing network [1,21], a contrast that showed the highest activations in a wide-spread brain network including all target regions of the recognition memory network. Of particular interest were hemodynamic responses in a proposed recognition memory network that reflect U-shaped oldness scales. These likely indicate confidence-based metamemory processes, because episodic memory signals cannot account for increased activations in confident NEW items. In contrast to our initial hypotheses, the ROI analysis revealed that such U-shaped oldness scales are observed within and outside a MTL core memory network.

In addition, L-shaped oldness scales indicate a strong memory signal. The U-shape/L-shape distinction, thus, provides a promising analytical approach that allows to infer whether a region provides episodic memory signals, or not, and how that is affected by an experimental manipulation. The present associative memory findings suggest that in left hippocampal regions, transitions to L-shaped oldness-scales can be observed for verbal items with many associates in the stimulus set. These association-driven activations are well in line with a recollection-based memory process [4,14]. Hofmann et al. [12] proposed that a higher associative activation increases the episodic memory signal strength (also [1]). Thus, in particular for highly associated stimuli, a strong memory signal might account for the hippocampal activations. Only left hemisphere hippocampus activations were modulated by the amount of associated items in the stimulus set (cf. Fig. 3), which fits with assumptions of the left hippocampus supporting verbal memory [43] and in particular associative memory processing (e.g., [44,45]).

The results of the whole brain analysis reveal a remarkable overlap between the correct recognition of OLD items and the processing of high-confidence OLD and NEW items in a widespread network including midline structures in MFG, PCG and occipital regions around the cuneus and lateral regions in inferior and superior parietal regions as well as left frontal regions. These activations appear to be more likely linked to processes related to the subjective level of confidence, which replicates and extends previous findings [26,27,28]. Thus, confidence in recognition memory judgments requires a broad network of brain regions that have previously been discussed to support attentional (inferior and superior parietal regions, see [26,46]) and metamemory processing [47,48]. Please note, however that these confidence-related activations are also modulated by the OLD/NEW feature of the test items, as indicated by the observed interaction between OLD/NEW and confidence in core regions of this 'confidence' network (PCG, MFG, precuneus and superior and inferior partietal cortex). Thus, the possibility remains that these regions are specifically involved in the correct recognition of learned items and their contextual details, or that successful recognition induces additional attentional processing. However, high-confidence in recognition performance cannot account for all activations.

An examination of the associative memory manipulation intended to specifically enhance episodic memory processing by manipulating the availability of associated contextual details may help to answer this question. The manipulation of the between-item-associations did not affect brain activation nor the shape of the oldness scales in PCG or MFG (see also upper row of Fig. 3). This is in line with the proposed role of these regions in metamemory processes like attention guidance and the decision about subjective confidence [36,46,47,49]. A case study of the parieto-occipital lesioned patient D.H. suggests a role of posterior parietal areas in subjective memory states. Though patient D.H. had semantic memories of his life-time, he reported that he did not feel like having truly experienced these memories ([50], cited by [49]). Still these processes are likely to differ between OLD and NEW items.

For the analysis of the core recognition memory network, only activations in left MTL regions (comprising anterior and posterior hippocampus, adjacent parahippocampus and the amygdala) are affected by the associative memory manipulation. As mentioned above, right hippocampus might be less involved in verbal associative memory [43] due to a specialization for non-verbal material. Its U-shaped response pattern suggests that also right hippocampus supports metamemory functions based on verbal task context. In the left hippocampus, in particular HIGH-A items revealed the predicted L-shaped oldness scales as assumed by the proposed role of these regions to selectively support episodic memory

[1] An analysis of the left hippocampus ROI from [21] confirmed the results of the present analysis, no main effect of association $F(1,19) = 1.556$, $p = 0.226$, but a significant confidence × association interaction $F(1,19) = 6.525$, $p = 0.001$.

Table 8
Brain regions found active in the confidence × associations interaction contrast ($p < 0.001$).

Brain regions	L/R	# voxel	T	x	y	z
Anterior hippocampus, parahippocampal gyrus	L	21	3.81	−34	−8	−24
Cerebellum	L, R	174	3.94	−12	−46	−36
Cerebellum	L, R	27	3.46	2	−60	−32

processes like recollection [4,16,51] or memory strength processing [24,52]. Squire and colleagues [5] propose that the hippocampus is more adept at associating multiple attributes of differential forms of memory than other structures. And it has previously been shown that subjectively available associated details enhance posterior hippocampal and parahippocampal activation during memory encoding [15]. The study by Peters et al. [15] also revealed robust encoding-related activations for contextual associative processing in the other target regions of the recognition (or context) memory network (MFG, LPC; PCG), which were not visible in the present examination of retrieval-related activation differences between high and low-association items. This supports our notion that these regions are not directly involved in memory strength.

A rather unexpected result are the U-shaped oldness scales in the left-hemispheric anterior and posterior hippocampus ROIs for LOW-A items. These U-shaped oldness scales suggest that the processing of NEW items with only a few associations in the stimulus set requires hippocampal activation when participants are able to correctly classify them with high confidence. We can only speculate that such a U-shaped patterns reflect two memory processes in case of low-association items: encoding activity associated with novel items (those given high-confidence NEW ratings) and retrieval activity associated with well-remembered items (those given high-confidence OLD ratings) [21]. The discrepancy between HIGH-A and LOW-A NEW items seems best explained by their differential integration into the associative context within the stimulus set. Because previously unseen HIGH-A items are more like critical lures in a false memory paradigm, such items are predicted by the associative context (and require less effortful encoding activity). LOW-A items, in contrast, are not predicted by

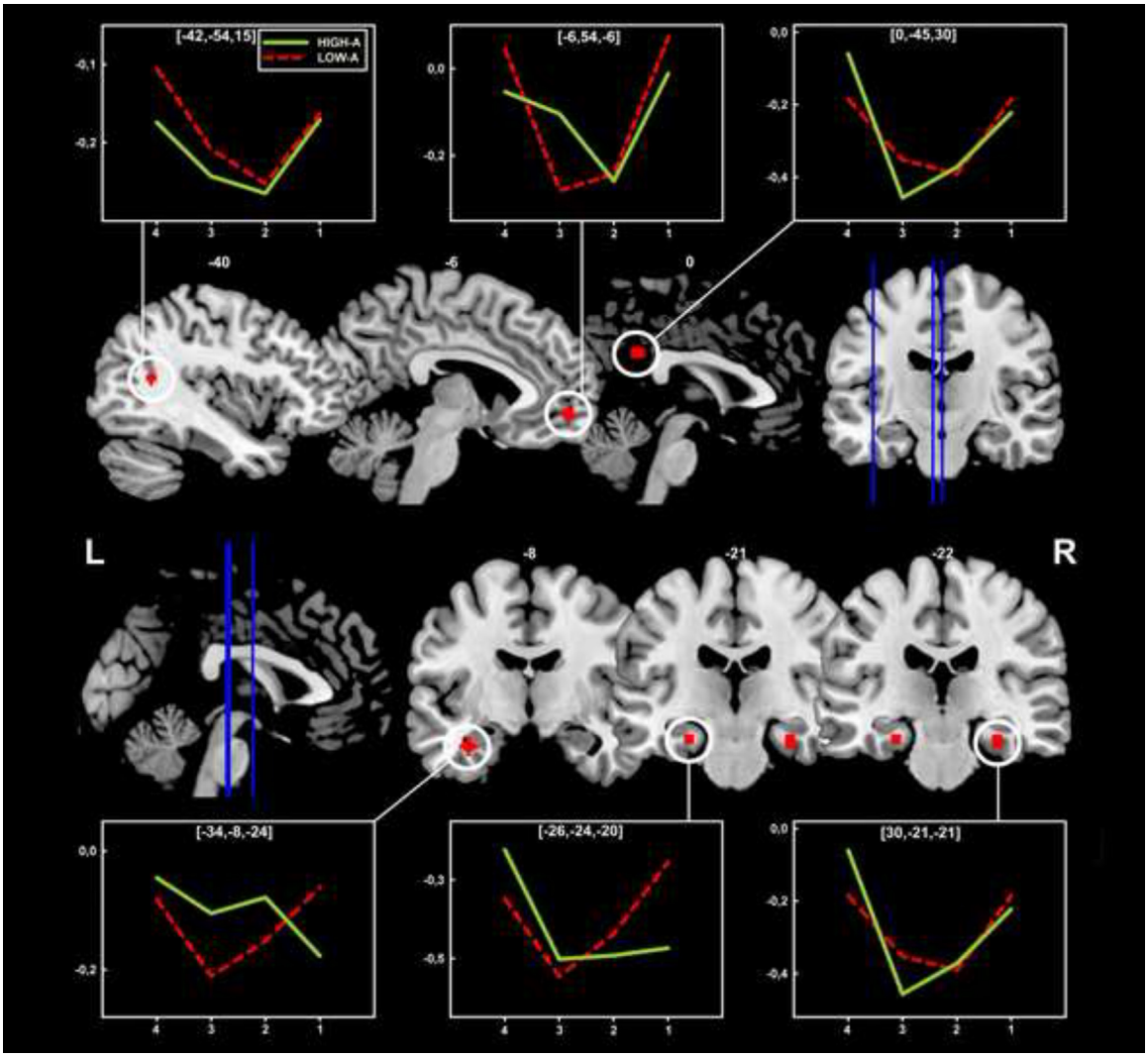

Fig. 3. Oldness-scales for six selected ROIs (spheres with 4 mm radius). Green lines = stimuli with a high amount of associates in the stimulus set. Red lines = stimuli with a low amount of associates in the stimulus set. ROIs of STG, MFG, PCG (upper row), left posterior and anterior Hippocampus, right anterior Hippocampus (lower row). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

the task context and need to be encoded as being NEW (to establish a greater associative structure for future processing). Novelty detection (and thus encoding) in recognition memory paradigms has previously been discussed to be supported by the anterior hippocampus and adjacent rhinal cortices [3,21,22], and the present results emphasize that these diverging memory signals are modulated by the associative structure an item has within the stimulus set and the subjective level of confidence it receives.

The whole-brain analyses' main effect of association level only revealed a small significant cluster in the superior frontal gyrus of the left hemisphere. This indicates that episodic memory decisions benefit from associative information, and fits well with our finding that associations elicit differential mediofrontal effects on NEW and OLD items, respectively (e.g., [25]). While associations help memory performance for OLD items [12], they hinder correct decisions for NEW items as was visible in the higher 'OLD' responses (=higher False Alarm rates in the behavioral data). Such 'false memories' have also been reported by Hofmann et al. [12] based on the same association manipulation (see [53]). The availability of associative activation inhibits the correct rejection of NEW high-association items, which might be visible in the activation of these control-related frontal activations.

In addition to interactions between association level and OLD/NEW in medial frontal regions, also cerebellum activations were obtained. This structure also revealed an interaction of associations with confidence. The role of the cerebellum in episodic and semantic memory [21,54] and language processing has been underestimated [55,56], as suggested by a recent review [57]. A close connection between posterior parietal cortices and the cerebellum is well documented [58], which would relate the present cerebellum activations more closely to the proposed metamemory functions of the posterior parietal lobe in support of successful memory retrieval [54]. Again, much further investigations, in particular lesion studies, seem necessary to reveal the particular role of cerebellum in recognition memory.

5. Conclusion

The present results support our initial hypotheses that regions of a proposed recollection network outside the MTL most likely process metamemory functions. Contrasting high- and low-confidence decisions in a recognition memory paradigm revealed a high overlap between the OLD/NEW contrast and activations related to high-confidence decisions. An examination of the activation functions based on the subjective level of confidence of the participants showed U-shaped oldness-scales in MFG, PCG and STG. These oldness functions consist of higher activations for high-confidence OLD and NEW decisions. As these functions are not affected by a manipulation of the associative structure of the test items, an episodic memory explanation seems unlikely. In contrast, anterior and posterior hippocampus activations in the left hemisphere were modulated by the association level of the test items. Particularly high-association items display an L-shaped activation function which pinpoints at the left hippocamus' pivotal role in verbal episodic memory performance. Somewhat surprisingly, this pattern does not hold for items with a smaller association level which also revealed U-shaped activation functions in the left hippocampus. When the memory signal is sufficiently low, the hippocampus may switch to an encoding-mode, in which greater neural activation to confidently judged NEW items indicates a novelty signal. This points at a more complex interaction between confidence and associative memory and a likely parallel availability of encoding- and retrieval-related activity in hippocampal regions for OLD and NEW items, which is based on the associative activation of an item by its context. Thus, based on these results, and because hippocampal confidence-based activity of low-association NEW items cannot be discriminated from that of OLD items, the examination of the associative structure (and thus the predictability of an item based on the task context) seems a useful condition of future recognition memory studies.

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