

Is a novel conceptual unit more than the sum of its parts?: fMRI evidence from an associative recognition memory study



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ABSTRACT

Recollection, an effortful process relying on the integrity of a brain network including the hippocampus, is generally required to remember arbitrary associations whereas a simple familiarity signal arising in the perirhinal cortex is sufficient to recognize single items. However, the integration of separate items into a single configuration (unitization) leads to reduced involvement of recollection and greater reliance on familiarity. This seems to imply that unitized associations are processed similar to single items. Here, using functional magnetic resonance imaging, we investigated the effects of unitization as encoding strategy on retrieval processes in a between-group-design. A definition was provided that allows combining two unrelated words into a novel conceptual unit (e.g., milk taxi = a delivery service, which is directly dispatched from a farm). We compared this to an encoding strategy in which the words were studied as parts of a sentence. We included pairs in reversed order at test because reversing a unitized word pair is assumed to disrupt the unit while leaving item familiarity for the single constituents intact. This enabled us to compare recognition memory for novel units and single items. Sentence encoding led to a flexible recruitment of brain areas previously associated with recollection, irrespective of the order of the test pair. Unitization encoding reduced the involvement of the recollection network and specifically engaged regions within the parahippocampal cortex and the medial prefrontal cortex for novel units. In contrast, recognition of reversed pairs involved activation of BA 45 in the left inferior frontal gyrus. This possibly suggests that familiarity for novel units and single items are associated with different brain networks.

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1. Introduction

Imagine that you were unable to remember the associations between the persons, objects, and locations that make up specific episodes. The constant experience of your life would be an incoherent mixture of familiar and novel situations. The ability to remember associations is essential for episodic remembering. A means of investigating this ability is the associative recognition memory paradigm requiring participants to recognize a previously encountered specific association or combination of items. Essential to this paradigm is that participants have to discriminate between

pairs reappearing in the same pairing as during study and new combinations of studied items, i.e. recombined pairs. Both types of pairs comprise constituents that were previously encountered and thus are equally familiar. Therefore, they can only be discriminated on the basis of associative information. According to traditional dual-process models of recognition memory (for a review see Yonelinas, 2002), an effortful recollection process is required to retrieve the link between distinct items, whereas a simple familiarity signal for studied items is sufficient in order to recognize single items. Neurocognitive models of recognition memory specify the brain regions supposedly being involved in recognition memory (Aggleton & Brown, 2006; Diana, Yonelinas, & Ranganath, 2007; Eichenbaum, Yonelinas, & Ranganath, 2007; Norman & O'Reilly, 2003; Skinner & Fernandes, 2007). The medial temporal lobes (MTL) have concordantly been ascribed a key role in memory encoding and retrieval. In more detail, the hippocampus has been linked to recollection because it is able to create pattern-separated

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representations of to-be-associated items. By this, it establishes novel associations between items and contextual information and enables the retrieval of contextually rich memories. By contrast, familiarity has been associated with activity modulation in the perirhinal cortex (PrC), which is the anterior part of the MTL cortices (MTLC). It is assumed to deal with representations of individual stimuli by enhancing the relative sharpness of item representations (Norman & O'Reilly, 2003). In line with these models and the traditional view on associative memory, functional magnetic resonance imaging (fMRI) studies have demonstrated enhanced hippocampal activity when arbitrary associations are encoded (Davachi & Wagner, 2002; Park & Rugg, 2008; Staesina & Davachi, 2006) and retrieved (Giovanello, Schnyer, & Verfaellie, 2004, 2009). Moreover, patients with lesions limited to the hippocampus and spared PrC have been found to exhibit selective impairment in memory for arbitrary associations (Mayes et al., 2001; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004; Vargha-Khadem et al., 1997).

Recent advancements of dual-process models of recognition memory, however, propose that an association between two or more items can be familiar if the parts are unitized (Diana et al., 2007; Ranganath, 2010; Yonelinas, 2002; Yonelinas, Aly, Wang, & Koen, 2010; Yonelinas, Kroll, Dobbins, & Soltani, 1999), i.e. integrated into one single configuration (Ceraso, 1985). Generally, unitized associations are embedded within an entity defining framework and are therefore perceived as one single whole (Mecklinger & Jäger, 2009). Units feature emergent properties, i.e. properties which cannot be directly inferred from the properties of their constituents (Ceraso, 1985; Graf & Schacter, 1989). For instance, the symmetry of a face cannot be predicted by the properties of the different face parts. Moreover, in contrast to arbitrary associations, which are bound in a relatively flexible manner, units exhibit a rigid configuration (Henke, 2010; Horowitz & Prytulak, 1969). As Yonelinas et al. (2010) noticed, unitization is rather a continuum than a dichotomy coming along with different forms and various ways of creating unitized associations. One important dimension on which unitized representations vary is whether they are pre-existing (i.e., stored in semantic memory) or newly created. Whereas the former holds for example for compound word pairs (e.g., motor-cycle), the latter can be induced by means of an encoding strategy such as creating a mental image of a unified interactive scene of two objects.

Evidence for stronger reliance on familiarity for pre-existing unitized word pairs such as compound pairs in contrast to semantically unrelated word pairs (e.g., poker-curl) has been found with various methodological approaches. Giovanello, Keane, and Verfaellie (2006) let amnesic patients with damage to the hippocampus perform an associative memory task with unitized as well as unrelated word pairs. Being forced to rely primarily on familiarity due to their impairment, these patients showed significantly better associative memory performance for unitized than for unrelated word pairs. Findings from an fMRI study suggest a shift in the relative contribution of familiarity and recollection in healthy participants as they showed a reduction of hippocampal activation and an enhancement of perirhinal involvement for pre-existing units in contrast to unrelated word pairs (Ford, Verfaellie, & Giovanello, 2010; for confirming evidence from event-related potentials (ERP) see Rhodes & Donaldson, 2007). This has been taken as evidence that pre-existing unitized associations are remembered in a similar way as single items.

An important question is whether this is also the case for previously unrelated items which are unitized not until encoding. Even though it has been suggested that one learning trial can be sufficient for unitization to induce subsequent familiarity-based remembering subserved by the PrC (Henke, 2010), this notion has not yet been tested with brain imaging techniques. Notably, a neuropsychological study by Quamme, Yonelinas, and Norman

(2007) showed that the hippocampus is not inevitable for recognition of arbitrary pairings when unitization is used as an encoding strategy. They found that amnesic patients with damage limited to the hippocampus, who exhibit severe recollection deficits, are much more likely to remember unrelated word pairs when the two words have been combined to a novel conceptual unit (definition encoding: CLOUD-LAWN = A yard used for sky-gazing) in contrast to when the two words are studied as distinct lexical items within the context of a sentence (sentence encoding: He watched the CLOUD float by as he sat on the LAWN.). In contrast, patients with damage to the hippocampus plus the surrounding MTLC did not show any difference between encoding instructions. This suggests an increased contribution of MTLC-mediated familiarity-based remembering for unitized associations. Using the same paradigm, Haskins, Yonelinas, Quamme, and Ranganath (2008) showed by means of fMRI increased engagement of the PrC during the encoding of previously unrelated word pairs as novel conceptual units. Moreover, activation in this region during encoding covaried with levels of subsequent familiarity for these units. This suggests an important role of the PrC for familiarity-based associative memory, comparable to familiarity for single items.

However, the brain structures involved in the retrieval of novel conceptual units cannot readily be inferred from these studies. As indicated by the results from two ERP studies from our laboratory, investigating the retrieval of such type of novel compounds (Bader, Mecklinger, Hopstädter, & Meyer, 2010; Wiegand, Bader, & Mecklinger, 2010), familiarity for novel conceptual units and single items is associated with different ERP signatures. Thus, the aim of the current study was two-fold. The first aim was to compare the brain regions generally involved in the retrieval of experimentally unitized associations to those involved in the retrieval of arbitrary associations. The second aim was to identify brain regions which are involved in recognition of single items and those involved in recognition of novel units. In the current report, we will refer to these two signals as item familiarity and unit familiarity, respectively. However, note that the present use of the two terms is solely motivated by the different kinds of representations the two types of familiarity processes operate on but the way these processes differ remains to be elucidated. Analogous to our previous ERP studies (Bader et al., 2010; Wiegand et al., 2010), we compared neural correlates of associative recognition memory for unrelated word pairs under two different encoding conditions. For this purpose, we contrasted definition and sentence encoding in a between-group design by means of fMRI. Encoding instruction was manipulated between subjects to avoid any strategy carry-over between the two instructions. Moreover, we opted for incidental encoding conditions because we wanted to reduce the probability that participants apply individual encoding strategies, which could obscure the intended effects of the instructions. During recognition, different word pairs were presented: same pairs, reversed pairs (studied pairings in reversed order), recombined pairs, and completely new pairs. Same and reversed pairs had to be classified as 'old' whereas recombined and new pairs had to be classified as 'new'.

Fig. 1 shows the pair types used in the test phase as well as the fMRI contrasts. In the fMRI analyses, we contrasted types of pairs that are most distinct with respect to the process of interest but very similar with respect to all other aspects of recognition (Henson, Hornberger, & Rugg, 2005). Generally, we expected associative recognition in the sentence group to be mainly driven by recollection. In contrast, in the definition group recollection should play a minor role in associative recognition memory as reduced engagement of regions normally associated with recollection has already been shown for pre-existing unitized pairs (Ford et al., 2010) and the putative ERP correlate of recollection is attenuated when novel conceptual units are retrieved (Bader et al., 2010). In line with previous studies (Ford et al., 2010; Giovanello et al.,

test phase						
pairs			contrasts			
pair type	example	correct response	general recognition	associative recognition	unit recognition	item recognition
same	A B	‘old’				
reversed	B A					
recombined	A D	‘new’				
new	E F					

Fig. 1. Schematic illustration of pairs used in the test phase and the fMRI contrasts for the example study pairs A B and C D. fMRI analyses contrasted types of pairs that are most distinct with respect to the process of interest but very similar with respect to all other aspects of recognition. Pair types which should be perceived as “old” are marked in dark gray and those which should be perceived as “new” are marked in light gray (note that this does not necessarily correspond with the correct response as in the case of unit recognition). For instance, associative recognition should lead to perception of “old” for same pairs and to perception of “new” for recombined pairs. Only pairs with correct responses were used for the fMRI analyses.

2009), brain regions involved in *associative memory* were examined by contrasting correct responses to same and recombined pairs as item familiarity should not be diagnostic to distinguish these pair types. In the sentence group, this contrast was assumed to reveal mostly brain regions associated with recollection including the hippocampus, the posterior cingulate cortex and the ventral posterior parietal cortex (Daselaar, Fleck, & Cabeza, 2006; Henson et al., 2005; Vilberg & Rugg, 2008; Yonelinas, Otten, Shaw, & Rugg, 2005). In contrast, the engagement of this network was expected to be smaller in the definition group. Here, familiarity-related regions should be more engaged. These should be limited to regions involved in unit familiarity (see below).

In addition, we conducted a *general recognition memory* contrast between same and new pairs as the former condition reflects recognized items in general and the latter condition is a memory free baseline condition. For the sentence group, we expected a similar pattern as in the same vs. recombined contrast. For the definition group, this contrast should have the maximal potential to disclose all the brain structures involved in both hypothesized familiarity processes. Thus, we generally predicted deactivation in the PrC as well as activation in other regions previously associated with familiarity such as the lateral prefrontal cortex (PFC; BA 45/46) and the dorsal PPC (Aly, Yonelinas, Kishiyama, & Knight, 2011; Daselaar et al., 2006; Henson et al., 2005; Montaldi, Spencer, Roberts, & Mayes, 2006; Vilberg & Rugg, 2008; Yonelinas et al., 2005).

Effects specific to *unit recognition* should only be present in the definition group and absent in the sentence group. As the exact configuration is a key feature of units (Haskins et al., 2008; Henke, 2010; Horowitz & Prytulak, 1969; Wiegand et al., 2010) and reversing the order of the pair disrupts this newly created unit in the definition group, we assume the effects of unitization to be present in this group for same pairs only while pure item recognition mechanisms should be diagnostic for reversed pairs. This should be indicated on the behavioral level as decreased performance and longer reaction times for reversed compared to same pairs in the definition group but not in the sentence group. Brain regions which are specific to unit familiarity were determined by contrasting same and reversed pairs. These two pair types are equal with respect to item familiarity for their constituents but differ with respect to their degree of unitization. Due to the lack of previous studies, we did not have any specific expectations with respect to the localization of these regions. From the data reported by Haskins et al. (2008), a familiarity signal should be expected in the PrC for same in contrast to new pairs. However, it is unclear whether this would be additional to the familiarity signal for the single items (in magnitude or spatial extent) and therefore visible in the same vs. reversed contrast.

In contrast, *item recognition* signals should be observable in both groups across both same and reversed word pairs. As reversed pairs are not assumed to evoke unit familiarity, they should be a more sensitive indicator of pure item familiarity than same pairs when contrasted to new pairs.¹ Given that recollection is assumed to play a minor role in the definition group, the reversed vs. new contrast is expected to reveal mostly activity modulation in regions previously associated with familiarity. In particular, given that a signal decrease in the PrC is usually associated with familiarity for single items (Henson, Cansino, Herron, Robb, & Rugg, 2003; Montaldi et al., 2006), we predicted decreased activation for reversed compared to new pairs in this region. As recollection-based processing in the sentence group should be flexible with respect to the order of the pair (Giovanello et al., 2009), the pattern of results in the sentence group was expected to be similar to the same vs. new contrast.

2. Methods

2.1. Participants

Forty native German speakers, all students from Saarland University, took part in the experiment and were randomly assigned to the two encoding groups. Mean age was 22.3 (19–28) and 23.2 (19–29) in the definition (10 female) and the sentence (10 female) encoding group, respectively. All participants had no known neurological problems, had normal or corrected-to-normal vision (contact lenses or MRI compatible goggles) and were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). One additional participant took part, but had to be excluded because of excessive motion artifacts during scanning. The experiment was approved by the local ethics committee of Saarland University. Participants gave informed consent and were reimbursed with course credit or payment (€ 8/hour) for participation.

2.2. Materials

Stimuli were built from 160 pairs of conceptually unrelated German 3–10 letter nouns with a mean lexical frequency of 54/million (Baayen, Piepenbrock, & Gulikers, 1995). Pairings had to fulfill the requirement of being suitable for a compound combination in German in original and reversed order. To this end, some of the words were used in plural form. Original and reversed pairs did not differ according to the frequency of plural words occurring in first and second position. Unrelatedness of word pairs (for original as well as reversed order and all recombined pairs) was assured by a pre-experimental rating study (each word pair was rated by 16 participants on average who belonged to the same student population as above but did not participate in the actual experiment). For definition encoding, a definition combined each word pair to denote a novel concept (e.g., MILK TAXI – a delivery service, which is directly dispatched from a farm). Only synonyms or associates of the words were used in the definitions. Likewise, there were no repetitions of the words in the sentences of the sentence group. Here, the words were part of a sentence as separate lexical items but were substituted by placeholders (e.g., MILK TAXI – The ____ was spilled inside the ____).

Study lists comprised 128 word pairs together with either the corresponding definitions or sentences. In the test phase, 32 of these pairs reappeared in the same combination and order as in the study phase. Another 32 were in the original combination but in reversed order. The remaining 64 pairs were used to build 32 recombined pairs consisting of new combinations of studied words whereby only one word of each original pair was used. First and second positions of the single words were maintained from original to recombined pairs. Additional 32 word pairs served as new pairs. Assignment of word pairs to the 4 pair types (same, reversed, recombined, and new) was counterbalanced across participants.

2.3. Procedure

The experiment was designed and presented using E-Prime Professional 2.0 (Psychology Software Tools, Inc.). The experiment consisted of three parts: a study phase, a motor response task in the retention interval, and a test phase. All three

¹ We chose reversed pairs and not recombined pairs for this contrast because the requirement to classify recombined pairs as ‘new’ allows that not recognized unfamiliar recombined pairs are correctly rejected. This makes recombined pairs more heterogeneous in terms of familiarity and therefore less suitable for the item recognition contrast.

parts were run in the scanner. Participants responded via two 2-button response grips using their thumbs and index fingers of both hands. Participants were not aware of the final memory test.

Participants' head movements were minimized using cushions and a headrest. Stimuli were viewed through a mirror attached to the head coil on which they were projected via a translucent screen. All stimuli were presented in white on a black background. Word pairs were presented next to each other separated by four blank spaces. In the study phase, word pairs and definitions/sentences were displayed one above the other, slightly above and below the center of the screen. In the test phase, word pairs were presented in central vision.

Encoding instruction was manipulated between subjects. The definition group had to give a subjective rating on a scale from 1 ('very badly') to 4 ('very well') according to how well the definition combined the meanings of the two words into a novel compound. To facilitate the rating, they were told to create a mental image of the new concept. In the sentence group, participants were supposed to rate the plausibility of the sentence on a 4-point-scale after having mentally inserted the two words into the placeholders in the given order. To prevent unitization, participants were told to imagine each single object separately. Assignment of fingers and ratings was counterbalanced across subjects. In both encoding groups, a trial started with a 500 ms fixation cross followed by 300 ms blank screen. Then, the stimulus appeared on the screen for 4000 ms after which participants were given a 1500 ms response window for the rating judgment indicated by a question mark. The inter-stimulus interval (ISI) was jittered in steps of 1000 ms following an approximately exponential distribution (mean: 7000 ms, range: 4000–12000 ms). It included the response window and a blank screen. In the middle of the study phase, there was a break of 46.2 s.

After the study phase, there was a retention interval of about 10 min in which a simple motor response task had to be performed. Participants were then informed about the upcoming memory test. In the test phase, both encoding groups saw exactly the same stimuli and had the same task. Participants had to classify same and reversed pairs as 'old' and recombined and new pairs as 'new'. They were instructed to indicate if they were sure or unsure about their classification resulting in four possible responses. Mapping of responses and fingers was counterbalanced across subjects. Trials started with a 500 ms fixation cross followed by a 300 ms blank screen. Word pairs were presented for 1000 ms. The response window expanded additional 1750 ms with a blank screen. If participants failed to respond until then, they saw a warning 'Too slow!' for 500 ms. The ISI included the response window and the warning if applicable. The remaining time was filled with a blank screen. ISI duration was jittered in steps of 1000 ms following an approximated exponential distribution (mean: 4000 ms, range: 3000–9000 ms). In the middle of the test phase, there was a break of 46.2 s.

2.4. Data acquisition and processing

A Siemens Skyra 3T system was used for MRI data acquisition. For functional MR scans T2-weighted gradient-echo planar imaging sequences were used (matrix: 94, FOV=192 mm, TR=2200 ms, TE=30 ms, flip angle=90°). Thirty axial slices with a thickness of 3 mm, an inter-slice gap of .75 mm, and an in-plane resolution of 2.04 × 2.04 mm were acquired parallel to the AC–PC plane covering the whole brain. In order to allow for T1 equilibration, the first four volumes of each functional run were discarded. Prior to the experiment, high resolution (9 × 9 × 9 mm) T1-weighted anatomical brain scans (MP-RAGE) were obtained. In order to foster the co-registration of these anatomical images with the functional images, 3 mm thick T1-weighted images (TR=250 ms, TE=2.5 ms, flip angle=70°, in-plane resolution of .6 × .6 mm) in plane with the functional images were acquired.

MRI data was processed using Brain Voyager QX (Brain Innovation; Goebel, Esposito, & Formisano, 2006). First, the 366 functional volumes of the test phase were slice scan time corrected to the beginning of each volume scan using cubic spline interpolation. Second, all images were motion corrected to the first volume of the run applying a trilinear detection and sinc interpolation rigid-body-transformation. There were no group differences in all six motion parameters (p -values > .27). Following spatial smoothing (Gaussian kernel with a full width at half maximum of 4 mm), low-frequency signal changes and baseline drifts were removed by a high-pass filter at .004 Hz. Transformation parameters gained by co-registration of functional and anatomical images were applied to the preprocessed fMR images to create a representation of the functional time series in 3D space which was subsequently normalized into stereotactic Talairach space (Talairach & Tournoux, 1988) and re-sampled to a resolution of 2 × 2 × 2 mm.

2.5. Data analysis

Only data of the test phase was analyzed for the current report. Behavioral data was analyzed using SPSS 18. Accuracy as indicated by the percentage of correctly classified items and reaction times for correct items were entered into a 4 × 2 multivariate analysis of variance (MANOVA, Pillai's trace) with the within-subjects factor of Pair Type (same, reversed, recombined, new) and the between-subjects factor of Encoding Group (definition, sentence). Proportion of high confidence judgments of correct items was analyzed in a Confidence (high, low) × Encoding

Group (definition, sentence) MANOVA. The significance level of the aforementioned analyses was set to $\alpha = .05$. P -values in post-hoc comparisons were corrected for Type-I-error accumulation using Holm's sequential Bonferroni correction method (Holm, 1979).

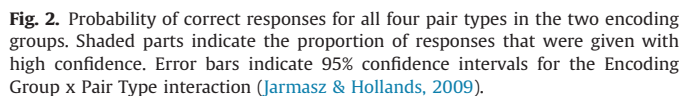
The functional time series were analyzed with least-squares estimation using a mixed effects general linear model. The event-related design matrix was created by modeling the hemodynamic response function for each predictor using a box-car function with a 1 s event duration convolved with a 2-gamma function model (onset: 0, time to response peak: 5 s, time to undershoot peak: 15 s) starting at the onset of the critical events. Correctly responded to items were used to build four levels of Pair Type which entered the GLM as predictors (same, reversed, recombined, and new). Mean/minimum numbers of analyzed trials were 25.8/19 (same), 21.9/16 (reversed), 23.7/13 (recombined), and 30.1/26 (new) in the definition group and 26.7/22 (same), 25.7/17 (reversed), 25.3/18 (recombined), and 30.5/21 (new) in the sentence group. All incorrectly classified items, key presses as well as 3-D motion parameters estimated during motion correction were added as predictors of no interest. Because of high susceptibility in the MTL resulting in low signal intensities, no intensity threshold (usually employed to segregate intracranial from extracranial voxels) was applied. Baseline was calculated as the average of all non-modeled time points. Second-level analysis determined active clusters for four contrasts of interest. Generally, clusters of voxels were considered as active when the t -test for the contrast exceeded a threshold of $p < .001$ for at least 10 contiguous voxels in a statistical map using non-interpolated data (see Lieberman & Cunningham, 2009, for arguments in favor of using a voxel extent threshold). Due to the lower signal-to-noise-ratio in the MTL, the threshold was set to $p < .005$ for at least 5 contiguous voxels (Schacter & Wagner, 1999; Staresina & Davachi, 2006).

In order to get an overview of the regions being generally involved in recognition of the word pairs, we first examined the general recognition memory contrast between correctly recognized same and new pairs. Regions involved in associative recognition were identified by contrasting correctly identified same and recombined pairs. Item recognition regions were defined as regions which were more active for correctly recognized reversed than for new pairs. Brain regions specific to unit recognition were determined by the same vs. reversed pairs contrast. For all four contrasts, we conducted three different analyses to disentangle effects specific to each group and common for the two groups. In the first analysis, common group effects were revealed by a conjunction analysis identifying the overlap between active regions in both groups (Friston, Penny, & Glaser, 2005). In the other two analyses, we identified group specific effects for each group by exclusively masking active regions in the other group. Exclusion masks were thresholded at a liberal threshold of $p < .05$ in order to reduce the probability of missing a truly active region. Note that a liberal threshold in the exclusion mask is equivalent to a conservative procedure to detect group specific effects (see Desseilles et al., 2009; Uncapher, Otten, & Rugg, 2006, for a similar rationale).

3. Results

3.1. Behavioral results

As can be seen in Fig. 2, performance in the sentence group seemed to be generally better than in the definition group. A MANOVA of accuracy as indicated by percentage of correctly classified items with the factors Pair Type and Encoding Group revealed a significant main effect of Pair Type ($F(3,36)=67.07$, $p < .001$), a significant main effect of Encoding Group ($F(1,38)=6.30$, $p=.016$), and a marginally significant interaction ($F(3,36)=2.75$, $p=.057$). Dissolving the interaction, post-hoc comparisons between encoding groups for each pair type separately yielded only one significant difference, namely higher accuracy for reversed pairs in the sentence group ($M=.80$, $SE=.12$) than in the definition group ($M=.68$, $SE=.10$; $t(38)=3.48$, $p=.005$). Comparisons of same pairs (definition: $M=.80$, $SE=.11$; sentence: $M=.83$, $SE=.09$), recombined pairs (definition: $M=.74$, $SE=.15$; sentence: $M=.79$, $SE=.13$), and new pairs (definition: $M=.94$, $SE=.06$; sentence: $M=.95$, $SE=.08$) across encoding groups were not significant (p -values > .62). These results show that the overall difference is mainly driven by the lower performance for reversed pairs in the definition group. Furthermore, testing our specific hypotheses regarding accuracy for same pairs and reversed pairs, planned t -tests revealed that reversed pairs were remembered significantly worse than same pairs in the definition group ($t(19)=4.22$, $p < .001$), but not in the sentence group ($p=.276$) suggesting processing difficulties for disrupted units in the definition group.



	Same	Reversed	Recombined	New
Definition	1401 (53)	1512 (56)	1677 (72)	1476 (66)
Sentence	1567 (49)	1554 (41)	1910 (52)	1770 (52)

The proportion of high confidence judgments of all correct responses shows that participants in both groups were highly confident (Fig. 2), but consistently higher in the sentence group than in the definition group for same pairs (definition: $M=.85$, $SE=.03$; sentence: $M=.93$, $SE=.02$), reversed pairs (definition: $M=.80$, $SE=.05$; sentence: $M=.94$, $SE=.02$), recombined pairs (definition: $M=.56$, $SE=.05$; sentence: $M=.68$, $SE=.06$), and new pairs (definition: $M=.63$, $SE=.05$; sentence: $M=.68$, $SE=.06$). A Pair Type $\times$ Encoding Group MANOVA yielded a significant main effect of Pair Type ($F(3,36)=22.54$, $p<.001$) and of Encoding Group ($F(1,38)=4.31$, $p=.045$), the latter reflecting

In order to see the general pattern of active regions underlying successful associative recognition, active regions contrasting correctly classified same vs. new pairs were explored. The results are listed in [Table 2](#). Activation clusters common to both groups were found on the left medial and lateral surface of the parietal lobe. Specifically in the sentence group, activation on the medial surface was generally more widespread, also including the right hemisphere, and the activation in

Region of activity	Hemi	BA	Size	x	y	z	t-value
Both groups							
<i>Same > new</i>							
Posterior cingulate	L	31	520	-5	-46	27	
Inferior parietal lobule	L	40	88	-41	-56	37	
Angular gyrus	L	39	136	-50	-60	32	
Angular gyrus	L	39	416	-42	-68	32	
<i>New > same</i>							
No clusters							
Sentence group							
<i>Same > new</i>							
Medial frontal gyrus	L	6	96	-6	39	34	5.51
Superior frontal gyrus	L	8	80	-21	23	49	4.89
Superior frontal gyrus	L	6	88	-18	13	56	5.45
Middle frontal gyrus	L	8	136	-47	11	39	5.21
Middle frontal gyrus	L	6	176	-39	0	45	5.25
Thalamus	L		88	-4	-13	10	7.14
Cingulate gyrus	L	31	216	-14	-47	26	5.50
Posterior cingulate	L	30	752	-3	-47	14	6.64
Superior temporal gyrus	R	22	88	53	-51	11	4.47
Posterior cingulate	R	23	80	5	-53	20	4.90
Angular gyrus	L	39	168	-55	-59	37	5.06
Superior temporal gyrus	L	39	1640	-52	-62	19	8.03
Precuneus	L	31	88	-13	-64	23	5.33
Middle temporal gyrus	L	19	120	-38	-78	20	5.50
Superior occipital gyrus	L	19	152	-39	-80	28	5.36
Hippocampus/entorhinal cortex	L	28	176	-17	-21	-12	4.65
<i>New > same</i>							
No clusters							
Definition group							
<i>Same > new</i>							
Inferior parietal lobule	L	40	152	-39	-52	44	5.59
Precuneus	L	19	160	-32	-72	36	6.29
<i>New > same</i>							
No clusters							

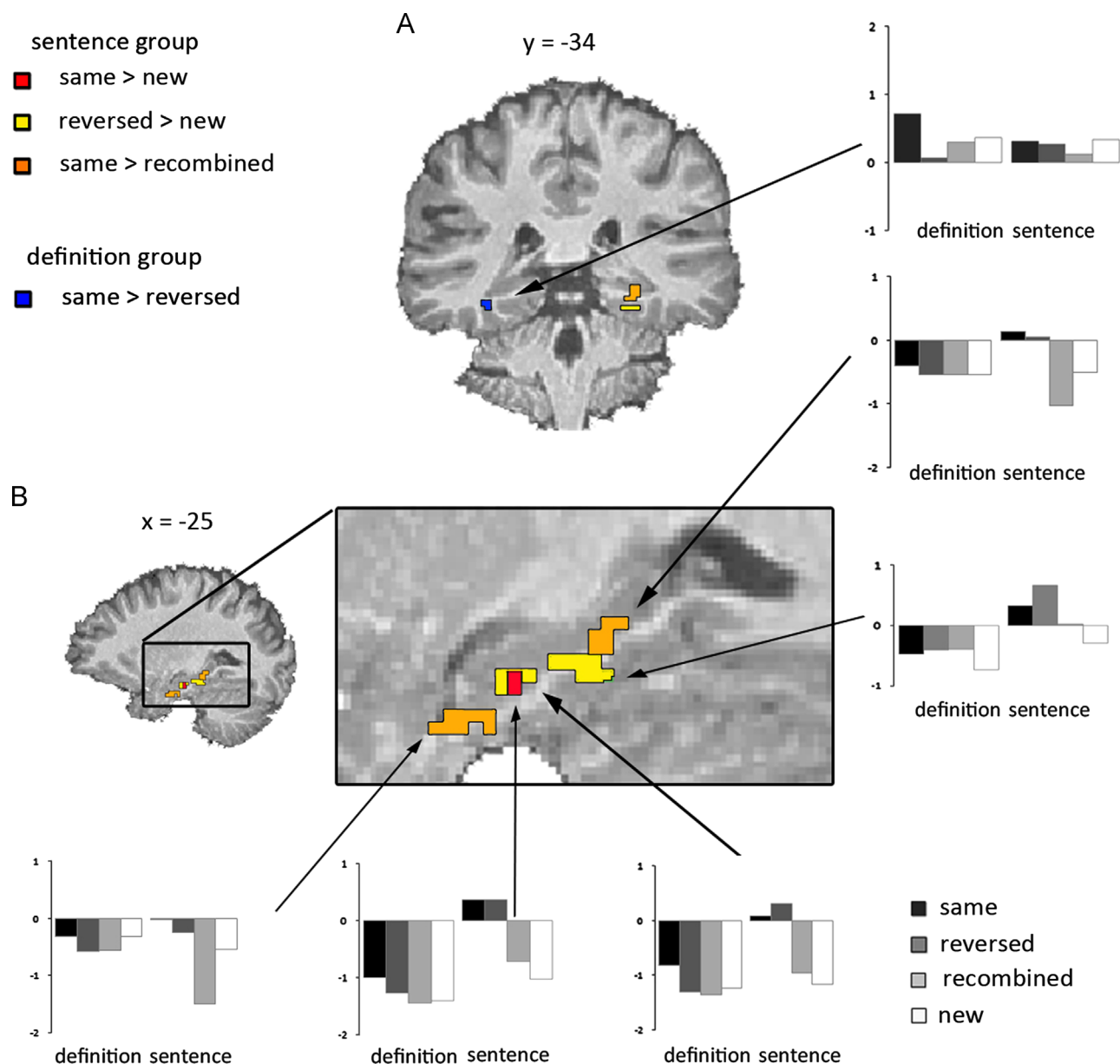


Fig. 3. Activation clusters in the MTL revealed by three different contrasts in the sentence group and one contrast in the definition group. The clusters are overlaid on a T1-weighted image of one participant and coordinates indicate slice position. Note that left hemisphere is depicted on the right side. For descriptive purpose, bar graphs show mean beta values averaged for the indicated clusters for all four pair types in both encoding groups.

the PPC extended further ventral. In addition, there were activation clusters in the left middle frontal gyrus, the left superior frontal gyrus, left and right superior temporal gyrus, the thalamus, and in a region at the border of the left hippocampus and entorhinal cortex (Fig. 3B). In the definition group, the activation in the PPC spread further dorsal and medial. No clusters were identified in the new > same contrast.

3.2.2. Same vs. recombined pairs: associative recognition

In order to identify regions specific to associative recognition, same and recombined pairs were compared. As listed in Table 3, whole brain analysis revealed activation common to both groups in regions on the medial surfaces of the PFC and the parietal lobe. In the sentence group, there was additional activation on the medial and lateral surfaces of the PFC, the cingulate gyrus, the superior temporal gyrus, the posterior cingulate, the ventral PPC, the amygdala, and the hippocampus (Fig. 3B). Specific to the definition group was an anterior extension of the common

activation in the left anterior cingulate, additional clusters in the right anterior cingulate, and the caudate nucleus. Clusters showing a higher activation for recombined than same pairs were not revealed.

3.2.3. Reversed vs. new pairs: item recognition

The results of the reversed vs. new pairs contrast are listed in Table 4. Activation in this contrast common to both groups was found in the left PPC. This activation pattern spread more ventral in the sentence group. In addition, there was activation specific for the sentence group in the left lateral and medial surfaces of the PFC, the insula, the thalamus, the posterior cingulate, the lingual gyrus, the amygdala, the left hippocampus, and the left parahippocampal gyrus (BA 36; Fig. 3B). Regions exclusively activated in the definition group were found in the left IFG (BA 45), the left claustrum, the caudate nucleus, and in a more dorsal and more medial extension of the common activation in the PPC.

Table 3

Brain regions showing significantly different BOLD signals for **same vs. recombined** pairs (associative recognition). See Table 2 for details.

Region of activity	Hemi	BA	Size	x	y	z	t-value
Both groups							
<i>Same > recombined</i>							
Medial frontal gyrus	L	10	144	-7	50	15	
Anterior cingulate	L	24	88	-2	38	3	
Posterior cingulate	L	23	80	-2	-49	25	
<i>Recombined > same</i>							
No clusters							
Sentence group							
<i>Same > recombined</i>							
Superior frontal gyrus	R	8	152	8	50	38	5.42
Medial frontal gyrus	R	9	88	4	47	33	5.20
Medial frontal gyrus	L	8	88	-7	45	37	6.18
Anterior cingulate	L	32	272	-6	34	20	6.96
Anterior cingulate	L	24	160	0	33	6	6.75
Superior frontal gyrus	L	6	80	-9	27	58	5.95
Superior frontal gyrus	R	6	104	17	19	60	6.15
Superior frontal gyrus	L	6	88	-16	19	61	4.80
Middle frontal gyrus	L	6	80	-37	12	49	5.40
Superior temporal gyrus	R	21	152	53	-3	-9	5.58
Cingulate gyrus	L	23	152	0	-23	30	5.53
Cingulate gyrus	L	24	176	0	-23	39	5.25
Cingulate gyrus	R	31	136	5	-31	35	5.35
Posterior cingulate	R	23	488	11	-47	25	7.08
Posterior cingulate	L	31	96	-8	-50	24	4.77
Inferior parietal lobule	R	40	496	47	-51	35	6.01
Posterior cingulate	L	30	1064	-6	-51	13	6.64
Superior temporal gyrus	L	39	520	-50	-60	27	7.05
Superior temporal gyrus	L	22	744	-58	-60	17	8.36
Inferior parietal lobule	L	39	192	-47	-62	42	5.54
<i>Recombined > same</i>							
No clusters							
Definition group							
<i>Same > recombined</i>							
Anterior cingulate	L	32	304	-3	44	7	6.18
Anterior cingulate	R	32	80	5	36	-6	4.86
Anterior cingulate	R	32	88	13	33	20	6.30
Caudate nucleus	R		104	7	11	7	5.79
<i>Recombined > same</i>							
No clusters							

3.2.4. Same vs. reversed pairs: unit recognition

In search for regions specific to unitization, we contrasted same and reversed pairs. Clusters being more activated by same than reversed pairs were found neither exclusively for the sentence group nor in the conjunction analysis. However, in the definition group, the whole-brain analysis revealed one cluster in the left claustrum (peak voxel: $x = -32$, $y = 4$, $z = -2$; $t = 6.48$; size = 88 voxels) and the MTL analysis revealed one cluster in the right parahippocampal gyrus (BA 36; peak voxel: $x = 35$, $y = -33$, $z = -10$; $t = 4.01$; size = 72 voxels, Fig. 3A). No clusters were revealed in the reversed greater than same pairs contrast.

3.2.5. Unit vs. item recognition

In the same vs. reversed pairs contrast, which was intended to identify clusters specific to unit recognition, the whole-brain analysis revealed only one relatively small cluster in the claustrum. However, there were different patterns of activation for same and reversed pairs when each of them was compared to the same

Table 4

Brain regions showing significantly different BOLD signals for **reversed vs. new** pairs (item recognition). See Table 2 for details.

Region of activity	Hemi	BA	Size	x	y	z	t-value
Both groups							
<i>Reversed > new</i>							
Angular gyrus	L	39	104	-45	-62	35	
Precuneus	L	39	80	-37	-66	35	
<i>New > same</i>							
No clusters							
Sentence group							
<i>reversed > new</i>							
Medial frontal gyrus	L	9	128	-4	52	18	5.87
Medial frontal gyrus	L	6	208	-6	39	22	7.17
Anterior cingulate	L	32	104	-7	35	24	5.89
Medial frontal gyrus	L	9	216	-10	31	32	6.24
Superior frontal gyrus	L	6	144	-23	17	60	5.36
Insula	L	13	80	-38	1	-3	6.87
Precuneus	L	6	96	-49	1	46	6.72
Thalamus	L		208	-4	-16	10	7.40
Posterior cingulate	R	23	216	11	-47	24	6.25
Inferior parietal lobule	L	40	80	-47	-47	20	5.20
Posterior cingulate	L	31	2176	-11	-55	19	7.93
Lingual gyrus	L	18	96	-18	-55	4	4.76
Middle temporal gyrus	L	19	4016	-38	-77	21	9.13
Hippocampus	L		208	-22	-19	-13	5.20
Parahippocampal gyrus	L	36	184	-25	-31	-12	5.24
Amygdala	L		96	-16	-7	-9	6.06
<i>New > reversed</i>							
No clusters							
Definition group							
<i>Reversed > new</i>							
Inferior frontal gyrus	L	45	240	-48	23	20	5.94
Clastrum	L		88	-30	15	1	5.01
Caudate nucleus	L		112	-10	4	10	5.03
Inferior parietal lobule	L	39	624	-36	-63	41	6.98
Precuneus	L	19	96	-32	-71	35	4.90
<i>New > reversed</i>							
No clusters							

Table 5

Brain regions which were selectively activated for same > new and reversed > new in the definition group. In this analysis, each contrast was exclusively masked by the other contrast and by the same contrast in the sentence group. See Table 2 for details.

Region of activity	Hemi	BA	Size	x	y	z	t-value
<i>Same > new masked by reversed > new</i>							
Medial frontal gyrus	L	10	80	-12	51	7	6.62
Posterior cingulate	L	31	112	-10	-50	22	5.34
Precuneus	L	7	96	-4	-59	31	5.97
Middle temporal gyrus	L	39	176	-41	-70	28	5.24
<i>Reversed > new masked by same > new</i>							
Inferior frontal gyrus	L	45	96	-44	19	12	4.87

memory free baseline (new pairs) in the definition group. This suggests that there are subtle differences in the processing of same and reversed pairs which might not have been revealed when directly contrasting the two pair types. Therefore, we conducted two additional, more exploratory, sets of analyses for the definition group that might be more sensitive to detect regions specific to unit and item recognition. In order to isolate unit recognition regions, the same > new contrast was masked by the reversed > new contrast (exclusive mask thresholded at $p < .05$). Thus, this analysis revealed regions which are activated by same pairs contrasted with new pairs, but not for reversed pairs contrasted with new pairs. To ensure that the outcome of this contrast is

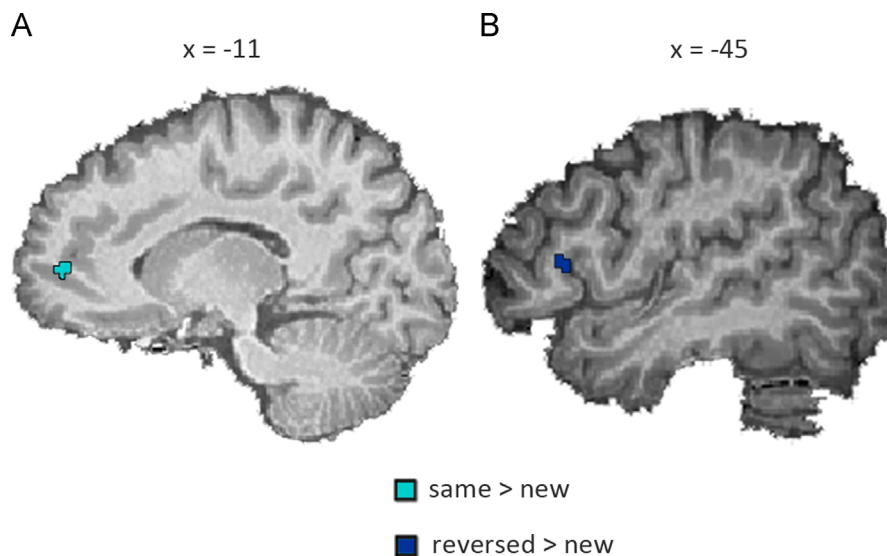


Fig. 4. Selected clusters in the left hemisphere which were selectively activated for same > new and reversed > new, respectively, in the definition group. In this analysis, each contrast was exclusively masked by the other contrast. The clusters are overlaid on a T1-weighted image of one participant and coordinates indicate slice position.

specific to the definition group, we exclusively masked it also by the same contrast in the sentence group ($p < .05$). Activation clusters were found in the left medial frontal gyrus, the left posterior cingulate, the left precuneus as well as the left PPC (Table 5 and Fig. 4A). In order to identify regions specific to item recognition, the reversed > new contrast was masked by the same > new contrast. This analysis revealed regions which show greater activation for the reversed compared to new pairs but not for same compared to new pairs (again also masked by the same contrast in the sentence group). Only one activation cluster in the left IFG (BA 45) was found in this analysis (Table 5 and Fig. 4B).

4. Discussion

The current study compared neural activity during associative retrieval for unrelated word pairs which were either encoded in a unitized or in a non-unitized manner. We wanted to explore which brain regions are generally involved in retrieval of unrelated word pairs when they have been unitized in only one study trial compared to non-unitized word pairs. Importantly, our design allowed to directly compare brain regions associated with unit recognition to those associated with recognition of single items within one experiment. Unitization was manipulated between subjects. In the definition group, participants encoded word pairs together with a definition combining the two words to a novel conceptual unit. In the sentence group, participants were provided with a sentence frame in which they had to fill in the two words of the pair separately minimizing the degree of unitization. At test, participants had to discriminate same, reversed, and recombined versions of the studied pairs as well as completely new pairs.

4.1. Behavioral evidence for effects of unitization in the definition group

Assessment of behavioral data revealed that participants in the two groups generally performed at the same level but differed according to how well they could deal with reversed pairs. Consistent with our assumption, the definition group recognized reversed pairs significantly worse than the sentence group. This is in line with a less flexible retrieval processing being engaged after definition encoding relying on a familiarity signal for novel conceptual units, which is sensitive to the exact configuration of

the pair and is disrupted by reversed test cues. Thus, the missing unit familiarity signal for reversed pairs makes the participants falsely rejecting these item pairs. Also consistent with greater reliance on unit familiarity in the definition group was the speed advantage for the definition group, which was found for all except for reversed pairs. This speed advantage can also be observed for new and recombined pairs as the attempt to recollect study details, even if unsuccessful, should always take more time than merely assessing the presence or absence of a familiarity signal. Within-group comparisons between same and reversed pairs complement this pattern. Decreased performance and slower reaction times for recognition of reversed pairs compared to same pairs were shown only in the definition group but not in the sentence group. In the case of reversed pairs, participants in the definition group probably perceive interference when item familiarity indicates that the two items are old but missing unit familiarity indicates that the pair is new. In line with our hypothesis of a reduced reliance on recollection for unitized word pairs is the lower confidence with which participants gave their responses because recollection-based responses are thought to be associated with on average higher confidence (see Yonelinas, 2002).

4.2. Flexible recollection in the sentence group

Analyses revealed greater activation for studied pairs (same and reversed) than non-studied pairs (recombined and new) in the posterior cingulate, the ventral PPC, and the hippocampus which was more extended in the sentence group than in the definition group or even exclusive as in the case of the hippocampus. In addition, one cluster in the parahippocampal cortex was revealed only in the reversed > new contrast with an activation pattern that is very similar to the one observed in the hippocampus. All these regions were previously identified as being associated with recollective processing (Dobbins, Rice, Wagner, & Schacter, 2003; Henson et al., 2005; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Vilberg & Rugg, 2009; Yonelinas et al., 2005). Thus, these results are in line with the prediction that associative recognition of word pairs which were studied as separate lexical items within sentence frames recruits a network typically associated with recollection. Joining the low number of fMRI studies examining the retrieval phase of associative recognition memory for arbitrary word-word associations (Ford et al., 2010; Giovanello et al., 2004, 2009), the current experiment

provides further evidence that in healthy young participants recognition of arbitrary word pairs strongly engages the recollection network including the hippocampus.

Under the assumption that activation in this network reflects recollective processing also in the current study, this pattern of brain activation highlights flexibility as a core characteristic of the recollection process complementing the behavioral results. Such flexibility is needed when word pairs encoded in a specific configuration (word order in the sentence) have to be retrieved regardless of whether retrieval is initiated by a specific (same pairs) or unspecific (reversed pairs) retrieval cue. This view is supported by our finding of overlapping activity in the anterior hippocampus (see Fig. 4B) for both, the same vs. new and the reversed vs. new contrast. This extends behavioral findings from recall paradigms implicating that recollection is less reliant on the precise configuration of the association (Kahana, 2002) and one other fMRI study showing flexibility of the anterior hippocampus with respect to order of the association (Giovanello et al., 2009). The current results extend the findings of Giovanello et al. (2009) showing flexibility also for other regions in the recollection network such as the posterior cingulate and the ventral PPC.

4.3. Reduced recollection in the definition group

Assuming that the lack of an involvement of the hippocampus and substantially reduced activity in the posterior cingulate and the ventral PPC in the same vs. new pairs contrast indicates diminished recollection, the definition group exhibited less recollection as compared to the sentence group which is in line with our prediction. However, the residual activity in the posterior cingulate and the PPC either suggests some minor contribution of recollection in the definition group or another functional role of these regions after definition encoding. Notably, recollection-related activation in the definition group was primarily found when same pairs were presented as test cues. Thus, recollection in the definition group was dependent on the exact repetition of the study cue. This speaks in favor of successful integration during encoding and a less flexible retrieval process than after sentence encoding. The lower performance for reversed pairs in the definition group is also consistent with this view. In sum, these results imply an attenuated contribution of recollection to recognition memory when word pairs have been unitized in contrast to non-unitized word pairs. Although evidence for reduced recollection for unitized associations has been reported before in ERP (Bader et al., 2010; Jäger, Mecklinger, & Kipp, 2006; Kriukova, Bridger, & Mecklinger, 2013) as well as fMRI studies (Ford et al., 2010), this finding has until now received only little attention. Reduced recollection for unitized representations could reflect that more effortful recollective retrieval processes are less recruited if unit familiarity provides a sufficiently diagnostic signal as in the definition condition. Note that some ERP studies did not find evidence for reduced recollection for unitized associations when study conditions promoted the contribution of recollection. For example in the Wiegand et al. (2010) study, all word pairs were studied twice, a condition which is known to increase recollection (Jacoby, Jones, & Dolan, 1998; Opitz, 2010a) while in the Rhodes and Donaldson studies (2007, 2008) multiple short study-test-cycles were used. The exact boundary conditions of when unitization attenuates recollection still have to be determined (see below).

4.4. Familiarity-related regions activated in the definition group

Whereas activation within the PPC extended into more ventral areas in the sentence group (for same > new, same > recombined, and reversed > new), activation spread more dorsal and medial into the vicinity of the intra-parietal sulcus in the definition group

(for same > new and reversed > new). This corresponds well with a dissociation which has previously been reported associating ventral PPC regions around the angular gyrus with recollection and more dorsal areas near the intra-parietal sulcus with memory strength/familiarity (Henson et al., 2005; Hutchinson et al., 2014; Vilberg & Rugg, 2008). Although the dorsal area has often been associated with familiarity-based responses, there are doubts about the memory-specificity of its function (see Vilberg & Rugg, 2008). However, irrespective of the exact functional interpretation, the differential activation patterns across the sub-regions of the PPC suggest stronger reliance on recollection in the sentence group and more familiarity-based responding in the definition group. As the pattern of activation was comparable for same and reversed pairs which are thought to engage unit and item familiarity, respectively, when contrasted to new pairs, this familiarity-related processing seems to be general and neither specific to unit nor item familiarity.

One region in the left IFG (BA 45) was more activated for reversed than new pairs selectively in the definition group. This region has previously been associated with increased activation during familiarity-based retrieval (Angel et al., 2013; Yonelinas et al., 2005) and damage to this region leads to a selective deficit in familiarity (Aly et al., 2011). Thus, the finding of activation in the left IFG supports the notion that there was a tendency to base decisions on familiarity signals in the definition group. In support of this view, a cluster within this region was selectively activated by the reversed vs. new contrast and not by the same vs. new contrast suggesting a specific role of this region in item familiarity. An alternative explanation for this activation pattern, however, could be that it reflects stronger engagement during the specification of the retrieval cue (Dobbins, Foley, Schacter, & Wagner, 2002). Cue specification might be more demanding for reversed pairs when participants choose the strategy to mentally reverse the test cue whenever they do not immediately recognize it as 'old' or 'new'. Although the consistent use of a reversal strategy by all participants under the reversed condition would also be consistent with our behavioral data, we consider a significant employment of such a specific strategy as rather unlikely because of the following reasoning: On the one hand, if all participants in the definition group had employed this strategy consistently during the experiment, performance under the reversed condition should be more comparable to performance under the same condition as reversing a reversed pair renders it equal to a same pair test cue. On the other hand, if only some participants had applied this strategy, we would assume that slower participants should be more accurate than faster participants. However, across participants in the definition group, there was no correlation between reaction time and percentage of correct responses for reversed pairs (Pearson's $r = -.03$, $p = .913$). Yet another possibility is that the reversal strategy was employed by all participants but only during some trials. In this case longer reaction times in each individual participant would more likely be associated with an accurate response than shorter reaction times. The opposite pattern was revealed by a point-biserial correlation analysis: Longer reaction times were associated with inaccurate (accuracy = 0) responses rather than accurate (accuracy = 1) responses (mean $r = -.16$, $p < .01$). However, as we cannot completely rule out this alternative interpretation, future research is warranted to better understand the role of the inferior frontal gyrus in familiarity processing.

In the same > reversed contrast, which should reflect activation specific for unit recognition, we found one cluster in the definition group located in the parahippocampal cortex extending to fusiform gyrus and is characterized by activation that is selective for same pairs studied as novel conceptual units. Binder, Desai, Graves, and Conant (2009) propose that this region constitutes "an interface between lateral semantic memory and medial episodic memory encoding networks" (p. 2777). In line with this proposal we assume that the activity in the parahippocampal

cortex reflects the process of linking the novel conceptual unit to pre-existing knowledge about the constituents (see also [Opitz, 2010b](#), for a related view). The increase in activation found here stands in opposition to the familiarity-related activation decrease in more anterior parts of the MTLC, i.e. in the PrC, which is usually observed for single items (see [Diana et al., 2007](#)). The increase as opposed to a decrease in activation might be explained by a still ongoing integration process as normally observed during encoding ([Haskins et al., 2008](#); [Meyer, Mecklinger, & Friederici, 2010](#)). The recruitment of the semantic system during recognition is thus more important for novel conceptual units than for pre-experimentally known items. Lastly, it is also possible that the activation reflects recollection as the parahippocampal cortex has often been associated with recollection. However, we consider this latter view as unlikely because there were no condition differences in this cluster in the sentence group, in which recollection is thought to play a major role. Furthermore, the same > reversed contrast did not reveal any other clusters in a brain network indicative for recollection.

In contrast to our predictions, we did not observe activation related to item familiarity in the PrC. One possible reason of this null finding is that fMRI signals in the MTL can suffer from susceptibility-induced signal loss ([Asano, Mihara, Kirino, & Sugishita, 2004](#)) leading to a poor signal-to-noise ratio. This might differentially affect anterior and posterior regions of the MTLC. As we could not directly contrast activation patterns for item and unit familiarity within the MTLC, future studies will have to further follow up the hypothesis that item and unit familiarity are associated with signals in the anterior and posterior parts of the MTLC, respectively.

The whole-brain analysis contrasting same and reversed pairs did not reveal activation clusters except for the claustrum. It is conceivable that the differences in memory-related brain activation for the two types of familiarity signals are too subtle to be detected by this contrast. The situation is even changed for the worse by a less optimal signal-to-noise ratio for the reversed pairs due to the poor performance for this pair type in the definition group. However, we conducted an additional contrast which might be more sensitive to detect brain regions which are specific to unit recognition, namely, regions which were selectively activated in the same vs. new contrast, but not in the reversed vs. new contrast. Most notably, one region specific to the same vs. new contrast was found in BA 10 in the mPFC. Moreover, this region was also activated in the same > recombined contrast in the definition group and the same holds for the same > new contrast when the voxel extent threshold was reduced to five contiguous voxels. A recent model forwarded by [Preston and Eichenbaum \(2013\)](#) ascribes an important role to the mPFC in the retrieval of information which is congruent with pre-existing (schema) knowledge. Similarly, according to [van Kesteren, Ruiters, Fernández, and Henson \(2012\)](#), the mPFC detects if incoming information is congruent to information stored in memory. In this case, mPFC inhibits hippocampal processing. Grounded on the increased mPFC activation and lack of hippocampal activation for unitized pairs in the present study, it could be speculated that unitization encoding renders word pairs congruent with pre-existing memories, as for example FOREST-BEER and TANK-SOUP can be integrated as novel instances of 'beer' and 'soup'. This integration might be performed and still ongoing in the parahippocampal cortex (see above), which is in turn detected by the mPFC. In support of this hypothesis, post-hoc analyses revealed that activation differences between same and reversed pairs in the mPFC cluster and the parahippocampal cortex cluster are correlated across participants in the definition group (Pearson's $r = .49$, $p < .05$) but not in the sentence group ($r = .09$, $p = .704$). This suggests that these two regions might be involved concertedly in the retrieval of novel conceptual units.

With respect to the functional differences between recognition of items and units, one possible explanation is that single items and newly created units might be recognized on the basis of two different but interwoven familiarity signals as suggested by our previous ERP studies ([Bader et al., 2010](#); [Wiegand et al., 2010](#)). Single items with pre-existing meanings undergo an increment in familiarity relative to their pre-experimental baseline familiarity ([Bridger, Bader, & Mecklinger, 2014](#); [Mandler, 1980](#); [Stenberg, Hellman, Johansson, & Rosén, 2009](#)) reflecting whether an item has recently been encountered (relative familiarity). In our previous ERP studies, item familiarity was associated with the mid-frontal old/new effect (FN400) ([Wiegand et al., 2010](#)). It is possible that the left IFG, as one of the possible generators of the mid-frontal old/new effect (see [Bridger, Bader, Kriukova, Unger, & Mecklinger, 2012](#), for a discussion), is involved in assessing the increment in familiarity relative to a pre-experimental baseline as it was suggested for the mid-frontal old/new effect ([Bridger et al., 2014](#); [Stenberg et al., 2009](#)). Consistent with this notion, studies relating this region to familiarity used pre-existing single items ([Aly et al., 2011](#); [Angel et al., 2013](#); [Yonelinas et al., 2005](#)). In contrast, for newly created units an absolute familiarity signal is more diagnostic when compared to new pairs which, as a whole, are completely unfamiliar ([MacKenzie & Donaldson, 2007](#)). Thus, an absolute familiarity signal reflects whether the unit has been encountered ever before. The schema-related interpretation of the mPFC activation for novel units would be consistent with an absolute familiarity account: Successful integration into pre-existing knowledge implies that something is familiar in an absolute sense and this is signaled by the concerted activation of the mPFC and parahippocampal cortex. However, future studies will have to establish a link between activation in these brain areas and behavioral measures of unit and item familiarity.

4.5. Conclusions

The current results show that recognition of arbitrary associations encoded within sentence frames recruits a network of brain regions that has previously been associated with recollection. This is in line with the importance of recollection in memory for arbitrary associations. Moreover, large parts of this network were shown to be highly flexible with respect to the order of the retrieval cue. Concordantly, memory performance for reversed pairs was comparable to same pairs in the sentence group. In contrast, using unitization as an encoding strategy as in the definition group leads to a limited involvement of this network. Consistent with this, we found faster reaction times and less confident responses in the definition group, which is commensurate with reduced reliance on recollection. This suggests that effortful recollection is recruited only if it yields additional diagnostic value for an associative memory task. Possibly, this is already determined during encoding which is why recollection could not be recruited for reversed pairs during the test although it would have been advantageous. In contrast, recognition of novel conceptual units was associated with increased activation in the parahippocampal cortex. Moreover, an additional set of exploratory analyses suggests that BA 10 in the mPFC was also activated during the retrieval of novel conceptual units whereas activation in BA 45 was specific for reversed pairs, i.e. is possibly associated with item recognition. Hence, unit recognition and item recognition recruit qualitatively different networks in the brain which are possibly associated with unit and item familiarity, respectively.

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References

- Aggleton, J. P., & Brown, M. W. (2006). Interleaving brain systems for episodic and recognition memory. *Trends in Cognitive Sciences*, 10, 455–463.
- Aly, M., Yonelinas, A. P., Kishiyama, M. M., & Knight, R. T. (2011). Damage to the lateral prefrontal cortex impairs familiarity but not recollection. *Behavioural Brain Research*, 225, 297–304.
- Angel, L., Bastin, C., Genon, S., Baiteau, E., Phillips, C., Luxen, A., et al. (2013). Differential effects of aging on the neural correlates of recollection and familiarity. *Cortex*, 49, 1585–1597.
- Asano, S., Mihara, B., Kirino, T., & Sugishita, M. (2004). Anatomical constraints on visualization of the human hippocampus using echo-planar imaging. *Neuroradiology*, 46, 535–540.
- Baayen, R. H., Piepenbrock, R., & Gulikers, L. (1995). *The CELEX lexical database [weblex]*. Philadelphia, PA, USA: University of Pennsylvania, Linguistic Data Consortium.
- Bader, R., Mecklinger, A., Hoppstädter, M., & Meyer, P. (2010). Recognition memory for one-trial-united word pairs: Evidence from event-related potentials. *NeuroImage*, 50, 772–781.
- Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cerebral Cortex*, 19, 2767–2796.
- Bridger, E. K., Bader, R., Kriukova, O., Unger, K., & Mecklinger, A. (2012). The FN400 is functionally distinct from the N400. *NeuroImage*, 63, 1334–1342.
- Bridger, E. K., Bader, R., & Mecklinger, A. (2014). More ways than one: ERPs reveal multiple familiarity signals in the word frequency mirror effect. *Neuropsychologia*, 57, 179–190.
- Ceraso, J. (1985). Unit formation in perception and memory. *Psychology of Learning and Motivation: Advances in Research and Theory*, 19, 179–210.
- Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2006). Triple dissociation in the medial temporal lobes: Recollection, familiarity, and novelty. *Journal of Neurophysiology*, 96, 1902–1911.
- Davachi, L., & Wagner, A. D. (2002). Hippocampal contributions to episodic encoding: Insights from relational and item-based learning. *Journal of Neurophysiology*, 88, 982–990.
- Desseilles, M., Baiteau, E., Sterpenich, V., Dang-Vu, T. T., Darsaud, A., Vandewalle, G., et al. (2009). Abnormal neural filtering of irrelevant visual information in depression. *The Journal of Neuroscience*, 29.
- Diana, R. A., Yonelinas, A. P., & Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: A three-component model. *Trends in Cognitive Sciences*, 11, 379–386.
- Dobbins, I. G., Foley, H., Schacter, D. L., & Wagner, A. D. (2002). Executive control during episodic retrieval: Multiple prefrontal processes subserve source memory. *Neuron*, 35, 989–996.
- Dobbins, I. G., Rice, H. J., Wagner, A. D., & Schacter, D. L. (2003). Memory orientation and success: Separable neurocognitive components underlying episodic recognition. *Neuropsychologia*, 41, 318–333.
- Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annual Review of Neuroscience*, 30, 123–152.
- Ford, J. H., Verfaellie, M., & Giovanello, K. S. (2010). Neural correlates of familiarity-based associative retrieval. *Neuropsychologia*, 48, 3019–3025.
- Friston, K. J., Penny, W. D., & Glaser, D. E. (2005). Conjunction revisited. *NeuroImage*, 25, 661–667.
- Giovanello, K. S., Keane, M. M., & Verfaellie, M. (2006). The contribution of familiarity to associative memory in amnesia. *Neuropsychologia*, 44, 1859–1865.
- Giovanello, K. S., Schnyer, D. M., & Verfaellie, M. (2004). A critical role for the anterior hippocampus in relational memory: Evidence from an fMRI study comparing associative and item recognition. *Hippocampus*, 14, 5–8.
- Giovanello, K. S., Schnyer, D., & Verfaellie, M. (2009). Distinct hippocampal regions make unique contributions to relational memory. *Hippocampus*, 19, 111–117.
- Goebel, R., Esposito, F., & Formisano, E. (2006). Analysis of FIAC data with BrainVoyager QX: From single-subject to cortically aligned group GLM analysis and self-organizing group ICA. *Human Brain Mapping*, 27, 392–401.
- Graf, P., & Schacter, D. L. (1989). Unitization and grouping mediate dissociations in memory for new associations. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 15, 930–940.
- Haskins, A. L., Yonelinas, A. P., Quamme, J., & Ranganath, C. (2008). Perirhinal cortex supports encoding and familiarity-based recognition of novel associations. *Neuron*, 59, 554–560.
- Henke, K. (2010). A model for memory systems based on processing modes rather than consciousness. *Nature Reviews Neuroscience*, 11, 523–532.
- Henson, R. N., Cansino, S., Herron, J. E., Robb, W. G. K., & Rugg, M. D. (2003). A familiarity signal in human anterior medial temporal cortex? *Hippocampus*, 13, 301–304.
- Henson, R. N., Hornberger, M., & Rugg, M. D. (2005). Further dissociating the processes involved in recognition memory: An fMRI study. *Journal of Cognitive Neuroscience*, 17, 1058–1073.
- Henson, R. N., Rugg, M. D., Shallice, T., Josephs, O., & Dolan, R. J. (1999). Recollection and familiarity in recognition memory: An event-related functional magnetic resonance imaging study. *Journal of Neuroscience*, 19, 3962–3972.
- Holm, S. (1979). A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics*, 6, 65–70.
- Horowitz, L. M., & Prytulak, L. S. (1969). Redintegrative memory. *Psychological Review*, 76, 519–531.
- Hutchinson, J. B., Uncapher, M. R., Weiner, K. S., Bressler, D. W., Silver, M. A., Preston, A. R., et al. (2014). Functional heterogeneity in posterior parietal cortex across attention and episodic memory retrieval. *Cerebral Cortex*, 24, 49–66.
- Jacoby, L. L., Jones, T. C., & Dolan, P. O. (1998). Two effects of repetition: Support for a dual-process model of knowledge judgments and exclusion errors. *Psychonomic Bulletin & Review*, 5, 705–709.
- Jäger, T., Mecklinger, A., & Kipp, K. H. (2006). Intra- and inter-item associations doubly dissociate the electrophysiological correlates of familiarity and recollection. *Neuron*, 52, 535–545.
- Jarmasz, J., & Hollands, J. G. (2009). Confidence intervals in repeated-measures designs: The number of observations principle. *Canadian Journal of Experimental Psychology*, 63, 124–138.
- Kahana, M. J. (2002). Associative symmetry and memory theory. *Memory & Cognition*, 30, 823–840.
- Kriukova, O., Bridger, E., & Mecklinger, A. (2013). Semantic relations differentially impact associative recognition memory: Electrophysiological evidence. *Brain and Cognition*, 83, 93–103.
- Lieberman, M. D., & Cunningham, W. A. (2009). Type I and Type II error concerns in fMRI research: Re-balancing the scale. *Social Cognitive and Affective Neuroscience*, 4, 423–428.
- MacKenzie, G., & Donaldson, D. I. (2007). Dissociating recollection from familiarity: Electrophysiological evidence that familiarity for faces is associated with a posterior old/new effect. *NeuroImage*, 36, 454–463.
- Mandler, G. (1980). Recognizing: The judgment of previous occurrence. *Psychological Review*, 87, 252–271.
- Mayes, A. R., Isaac, C. L., Holdstock, J. S., Hunkin, N. M., Montaldi, D., Downes, J. J., et al. (2001). Memory for single items, word pairs, and temporal order of different kinds in a patient with selective hippocampal lesions. *Cognitive Neuropsychology*, 18, 97–123.
- Mecklinger, A., & Jäger, T. (2009). Episodic memory storage and retrieval: Insights from electrophysiological measures. In: F. Rösler, C. Ranganath, B. Röder, & R. H. Kluwe (Eds.), *Neuroimaging of human memory: Linking cognitive processes to neural systems* (pp. 357–381). New York, NY, US: Oxford University Press.
- Meyer, P., Mecklinger, A., & Friederici, A. D. (2010). On the processing of semantic aspects of experience in the anterior medial temporal lobe: An event-related fMRI study. *Journal of Cognitive Neuroscience*, 22, 590–601.
- Montaldi, D., Spencer, T. J., Roberts, N., & Mayes, A. R. (2006). The neural system that mediates familiarity memory. *Hippocampus*, 16, 504–520.
- Norman, K. A., & O’Reilly, R. C. (2003). Modeling hippocampal and neocortical contributions to recognition memory: A complementary-learning-systems approach. *Psychological Review*, 110, 611–646.
- Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia*, 9, 97–113.
- Opitz, B. (2010a). Context-dependent repetition effects on recognition memory. *Brain and Cognition*, 73, 110–118.
- Opitz, B. (2010b). Neural binding mechanisms in learning and memory. *Neuroscience & Biobehavioral Reviews*, 34, 1036–1046.
- Park, H., & Rugg, M. D. (2008). The relationship between study processing and the effects of cue congruency at retrieval: fMRI support for transfer appropriate processing. *Cerebral Cortex*, 18, 868–875.
- Preston, A. R., & Eichenbaum, H. (2013). Interplay of hippocampus and prefrontal cortex in memory. *Current Biology*, 23, R764–R773.
- Quamme, J. R., Yonelinas, A. P., & Norman, K. A. (2007). Effect of unitization on associative recognition in amnesia. *Hippocampus*, 17, 192–200.
- Ranganath, C. (2010). A unified framework for the functional organization of the medial temporal lobes and the phenomenology of episodic memory. *Hippocampus*, 20, 1263–1290.
- Rhodes, S. M., & Donaldson, D. I. (2007). Electrophysiological evidence for the influence of unitization on the processes engaged during episodic retrieval: Enhancing familiarity based remembering. *Neuropsychologia*, 45, 412–424.
- Rhodes, S. M., & Donaldson, D. I. (2008). Electrophysiological evidence for the effect of interactive imagery on episodic memory: Encouraging familiarity for non-unitized stimuli during associative recognition. *NeuroImage*, 39, 873–884.
- Schacter, D. L., & Wagner, A. D. (1999). Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus*, 9, 7–24.
- Skinner, E. L., & Fernandes, M. A. (2007). Neural correlates of recollection and familiarity: A review of neuroimaging and patient data. *Neuropsychologia*, 45, 2163–2179.
- Staresina, B. P., & Davachi, L. (2006). Differential encoding mechanisms for subsequent associative recognition and free recall. *The Journal of Neuroscience*, 26, 9162–9172.
- Stenberg, G., Hellman, J., Johansson, M., & Rosén, I. (2009). Familiarity or conceptual priming: Event-related potentials in name recognition. *Journal of Cognitive Neuroscience*, 21, 447–460.
- Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: An approach to cerebral imaging*. Stuttgart, Germany: Thieme.
- Turiziani, P., Fadda, L., Caltagirone, C., & Carlesimo, G. A. (2004). Recognition memory for single items and for associations in amnesic patients. *Neuropsychologia*, 42, 426–433.

- Uncapher, M. R., Otten, L. J., & Rugg, M. D. (2006). Episodic encoding is more than the sum of its parts: An fMRI investigation of multifeature contextual encoding. *Neuron*, 52, 547–556.
- van Kesteren, M. T. R., Ruiter, D. J., Fernández, G., & Henson, R. N. (2012). How schema and novelty augment memory formation. *Trends in Neurosciences*, 35, 211–219.
- Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., Van Paesschen, W., & Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science*, 277, 376–380.
- Vilberg, K. L., & Rugg, M. D. (2008). Memory retrieval and the parietal cortex: A review of evidence from a dual-process perspective. *Neuropsychologia*, 46, 1787–1799.
- Vilberg, K. L., & Rugg, M. D. (2009). Functional significance of retrieval-related activity in lateral parietal cortex: Evidence from fMRI and ERPs. *Human Brain Mapping*, 30, 1490–1501.
- Wiegand, I., Bader, R., & Mecklinger, A. (2010). Multiple ways to the prior occurrence of an event: An electrophysiological dissociation of experimental and conceptually driven familiarity in recognition memory. *Brain Research*, 1360, 106–118.
- Yonelinas, A. P. (2002). The nature of recollection and familiarity: A review of 30 years of research. *Journal of Memory and Language*, 46, 441–517.
- Yonelinas, A. P., Aly, M., Wang, W.-C., & Koen, J. D. (2010). Recollection and familiarity: Examining controversial assumptions and new directions. *Hippocampus*, 20, 1178–1194.
- Yonelinas, A. P., Kroll, N. E., Dobbins, I. G., & Soltani, M. (1999). Recognition memory for faces: When familiarity supports associative recognition judgments. *Psychonomic Bulletin & Review*, 6, 654–661.
- Yonelinas, A. P., Otten, L. J., Shaw, K. N., & Rugg, M. D. (2005). Separating the brain regions involved in recollection and familiarity in recognition memory. *Journal of Neuroscience*, 25, 3002–3008.