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Structure-function associations of successful associative encoding

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A B S T R A C T

Functional magnetic resonance imaging (MRI) studies have demonstrated a critical role of hippocampus and inferior frontal gyrus (IFG) in associative memory. Similarly, evidence from structural MRI studies suggests a relationship between gray-matter volume in these regions and associative memory. However, how brain volume and activity relate to each other during associative-memory formation remains unclear. Here, we used joint independent component analysis (jICA) to examine how gray-matter volume and brain activity would be associated during associative encoding, especially in medial-temporal lobe (MTL) and IFG. T1-weighted images were collected from 27 young adults, and functional MRI was employed during intentional encoding of object pairs. A subsequent recognition task tested participants' memory performance. Unimodal analyses using voxel-based morphometry revealed that participants with better associative memory showed larger gray-matter volume in left anterior hippocampus. Results from the jICA revealed one component that comprised a covariance pattern between gray-matter volume in anterior and posterior MTL and encoding-related activity in IFG. Our findings suggest that gray matter within the MTL modulates distally distinct parts of the associative encoding circuit, and extend previous studies that demonstrated MTL-IFG functional connectivity during associative memory tasks.

1. Introduction

Episodic memory, the remembrance of events situated in time and place (Tulving, 1972), requires the ability to link together elements of an event and to integrate them into a cohesive memory episode (i.e., associative memory; Davachi, 2006). Functional magnetic resonance imaging (MRI) studies have provided a bulk of evidence for the differential roles of hippocampus and inferior frontal gyrus (IFG) in associative memory processes (Jackson and Schacter, 2004; Prince et al., 2005; Staresina and Davachi, 2006; Becker et al., 2017). The hippocampus is known for its key role in rapidly forming associations between relational information in episodic memory (Eichenbaum and Cohen, 2001). That is, in accordance with its anatomical position the hippocampus is attributed the role of a hub (Backus et al., 2016; Geib et al., 2017), i.e., it is thought to act as a mnemonic convergence zone in which distributed information are integrated into coherent episodic memory representations (Sperling et al., 2003; Backus et al., 2016). Several previous studies have suggested a dichotomy for functional role of the HC longitudinal axis (Fanselow and Dong, 2010; Brickman et al., 2011; but also see Strange et al., 2014). For example, it has been suggested that anterior hippocampus is more engaged during associative memory encoding (Salami et al., 2012; Becker et al., 2017), whereas the posterior HC is more active during item memory retrieval (Sheldon and Levine, 2015). Inferior frontal regions are suggested to be involved in strategic and control processes that support binding in the hippocampus (Addis and McAndrews, 2006; Murray and Ranganath, 2007; Qin et al., 2009). In contrast to studies using functional MRI, most structural MRI studies focus on the medial temporal lobes (MTL) when investigating the relationship between gray-matter volume and associative memory. Some studies observed negative or zero correlations between hippocampal volume and associative memory (Van Petten, 2004). Others reported larger hippocampal volume (Rajah et al., 2010; Poppenk and Moscovitch, 2011; Nordin et al., 2017) to reliably predict higher associative-memory accuracy. As such, the exact contribution of hippocampal volume to associative memory over and above memory for single items still remains unresolved. Moreover, it remains unknown if task-related brain activity patterns found in the hippocampus are attributable to its underlying brain structure. It is reasonable to expect that if associative memory is linked to functional and volumetric measures, functional activity induced by an associative memory task might be related to features of gray matter. Investigating the relationship

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between gray-matter volume and brain activity will further our understanding of how different brain modalities relate to each other during associative-memory formation (Kalpouzos et al., 2012).

Associations between gray matter and brain activity can be measured with local or distal multimodal approaches. Previous studies that investigated structure-function associations within the same localized brain area commonly used correlational analysis or entered gray matter at a given voxel in the analysis of voxelwise functional data (Siegle et al., 2003; Oakes et al., 2007; Salami et al., 2012). For example, episodic encoding activity in anterior hippocampus has been associated with larger local gray-matter volume (Maillet and Rajah, 2011). Similarly, Brassen et al. (2009) found a positive correlation between activity in prefrontal cortex (PFC) and local gray-matter volume during item retrieval. Although most previous studies investigated local structure-function associations within MTL and/or IFG, these two regions are structurally connected (i.e., via the uncinate fasciculus; see Poppenk et al., 2013), hence volumetric characteristics of one region might affect functional characteristics of the respective other, more distant region (Michael et al., 2010; Salami et al., 2014). Most studies that have looked into distal structure-function relationships between MTL and prefrontal regions during memory encoding used a sample of older adults and found volumetric decline associated with age-related changes in brain activity (Rosen et al., 2005; Düzel et al., 2011; Kalpouzos et al., 2012; see Maillet and Rajah, 2013). In young adults, two studies found a positive association between hippocampal volume and activity in IFG during episodic memory tasks (Brassen et al., 2009; Maillet and Rajah, 2011). Moreover, Harms et al. (2013) found a positive relationship between hippocampal volume and activity in IFG during a working memory task. However, only Maillet and Rajah (2011) acknowledged the functional dissociation of the anterior and posterior hippocampus (Poppenk et al., 2013). That is, the authors investigated brain volume in anterior hippocampus as opposed to measuring volume of the entire hippocampus, thus could provide further evidence for the relevance of this hippocampal portion for associative memory (Rajah et al., 2010).

In a previous publication on the same experiment, we showed that the activation in the left anterior hippocampus and left IFG were engaged in successful associative-memory formation, likely reflecting a binding process accomplished by these regions (Becker et al., 2017). Here, we expand our previous functional MRI study by additionally looking at volumetric data in anterior hippocampus and IFG, and their associations with associative-memory performance. Further, we used joint independent component analysis (jICA) to examine if larger gray-matter volume in MTL would be locally or distally associated with brain activation in MTL or IFG respectively during successful associative-memory formation. jICA takes into account all voxels in selected regions of interest of the first (structural MRI, i.e., gray-matter volume) and of the second brain dataset (functional MRI, i.e., associative encoding activity) simultaneously, and combines them to create components ("joint sources") that represent systematic inter-subject covariation between patterns of gray-matter volume and activity. Hence, volume-activity covariation can be detected both locally and distally.

2. Methods

Functional MRI results from this experiment have been reported previously (Becker et al., 2017). A more detailed description of the behavioral task material and results of the fMRI analysis can be found there (Becker et al., 2017). Here, we focused exclusively on the associative memory part of the study.

2.1. Materials

Stimuli consisted of gray scale photographs of common objects from 25 categories (e.g., kitchen tools, clothing, animals). Stimuli were partly taken from the Bank of Standardized Stimuli (BOSS; Brodeur et al., 2010), and partly from freely available pictures on the internet. All stimuli were processed so that image properties from both image sources were identical. All trials contained object pairs. Stimuli were of equal size and presented on white background in the upper left and right corners of a squared box (Fig. 1). Presentation positions were randomly assigned to the stimuli. To match the visual input to other task conditions not described here, all trials also comprised a gray circle that was presented in the middle lower part of the square.

2.2. Participants

Written informed consent was obtained from 27 healthy, right-handed adults with normal or corrected-to-normal vision, who were eligible for MRI (16 females, $M_{age} = 24.89 \pm 1.63$ years, $M_{education} = 15.17 \pm 2.09$ years). All participants lived in the area of Stockholm, Sweden, and were paid for participation. The investigation was approved by the Regional Ethical Review Board in Stockholm.

2.3. Experimental procedure

Experimental Design. Participants were scanned while completing blocks of encoding. The scanning session consisted of three runs, each entailing three blocks of associative encoding among experimental blocks not described here. Each block comprised ten trials. Trials were shown for 3 *s* followed by a white fixation cross, presented on a black background (Fig. 1). The inter-stimulus fixation varied from 1.5 *s* to 5.5 *s* (mean = 3.28 *s*).

Encoding Task. The encoding task consisted of 90 object pairs. Participants were instructed to press one button as soon as an object pair appeared on the screen. Button presses were performed with the right index- and middle fingers and counterbalanced across participants. Participants were instructed to memorize the objects and their combinations for a subsequent recognition task.

Retrieval Task. Immediately after fMRI scanning, recognition of object pairs was tested outside of the scanner. The recognition task consisted of 108 object pairs. Among those were 63 *old* trials, 18 *new* trials, and 27 *rearranged* trials (i.e., one object image from an original encoding pair was alternated with another object from a different pair previously presented). The positions of the objects within a pair remained the same to ensure that participants would not identify rearranged pairs based on changes in object locations. The recognition task contained more old trials than rearranged trials as only old trials lead to a production of hits and misses, which allow for subsequent memory analyses. In addition, we added a number of *new* trials to increase the number of "no" trials without decreasing the number of hit trials important for subsequent memory analyses by rearranging objects across them. Recognition trials were shown for 3 *s* and within this time participants were instructed to indicate with a button press whether or not they had seen the object pairs during encoding.

2.4. Behavioral measures

Individual recognition performance was measured as proportion of hits minus false alarms (discrimination index Pr (p(hits) - p(false alarms)); Snodgrass and Corwin, 1988). This measure did not include *new* associative foils, since they could have been identified as foils by relying on memory of one single object, not the pair. Some subjects' associative memory performances were below zero. These individuals were still kept in the analysis, as they could reflect solving associative memory processes with familiarity, hence a true failure of remembering an item combination rather than guessing, which reflected individual differences we were interested in investigating.

2.5. Imaging acquisition

Participants were scanned with a 3T GE750 scanner using a 32-channel head coil. T1-weighted MRI scans were collected from each subject

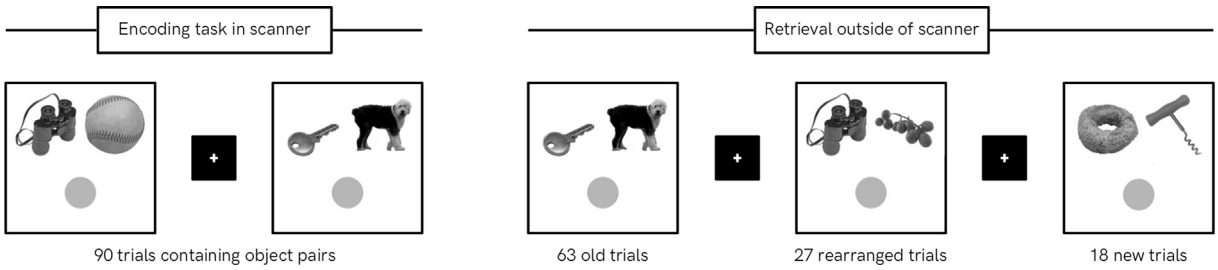

Fig. 1. Experimental design and exemplar trials from the in-scanner encoding and off-scanner retrieval task. During encoding participants were presented with 90 trials containing object pairs. Participants were instructed to remember the single objects and their combination. Trials were shown for 3 *s*, followed a fixation cross that lasted between 1.5 *s* and 5.5 *s* (mean = 3.28 *s*). The recognition task took place outside of the scanner and consisted of 63 *old* trials, 18 *new* trials, and 27 *rearranged* trials (i.e., one object image from an original encoding pair was alternated with another object from a different pair previously presented). Trials were shown for 3 *s* and participants had to indicate whether or not they had seen the object pair during encoding.

using the SAG FSPGR BRAVO sequence (TR = 8.20 m s, TE = 3.22 m s, FOV = 24, in-plane resolution = 0.94 × 0.94 mm, 172 adjacent sagittal slices, slice thickness = 1 mm). Functional data were collected using a gradient echo pulse sequence (TR = 2.2 *s*, TE = 30 m s, flip angle = 70°, FOV = 22, in-plane resolution = 1.72 × 1.72 mm). Forty-six slices (slice thickness = 3 mm) were collected in axial orientation covering the whole brain. Prior to image acquisition, ten dummy scans were performed to allow for MR stabilization. In total, 500 vol were collected for each of the three functional runs.

2.6. Imaging preprocessing

2.6.1. Functional MRI: event-related analysis

Functional images were slice-time corrected and realigned for motion correction with reference to the first slice. Images were co-registered to their respective structural T1 scan, spatially normalized to the group-specific DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra; Ashburner, 2007) template and to MNI space, resampled into 2 mm cubic voxels, and finally smoothed with a Gaussian kernel of 8 mm FWHM (see Becker et al., 2017).

2.6.2. Structural MRI: voxel-based morphometry

T1-weighted images were preprocessed and analyzed in SPM12 (Statistical Parametric Mapping, Wellcome Department of Imaging Science, Functional Imaging Laboratory, http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab R2014b (Mathworks Inc, MA, US). Images were segmented into gray matter, white matter and cerebrospinal fluid using the unified segmentation approach (Ashburner and Friston, 2005). Total intracranial volume was computed as the sum of gray matter, white matter and cerebrospinal fluid. Gray-matter images were further processed with DARTEL with a voxel resolution of 2 × 2 × 2 mm.

Gray-matter images were spatially normalized and further registered to Montreal Neurological Institute (MNI) space. Volumetric information that was lost during spatial normalization was re-integrated by modulating the images using Jacobian determinants from the deformations for the signal to be as close as possible to the signal of the native T1 images. Finally, gray-matter images were smoothed with a Gaussian FWHM (full width at half maximum) convolution kernel of 8 mm in the 3 directions.

2.7. Imaging analysis

2.7.1. Functional MRI analysis: subsequent memory effect

Statistical parametric maps were generated for each individual within the framework of the general linear model (GLM) in SPM12. Event onsets were modeled with a stick function and convolved with the hemodynamic response function. Events were specified as occurring at the presentation of the stimuli that participants responded to with a button press and labeled according to subsequent memory in the post-scanning recognition task (hit or miss). Trials that were rearranged for the post-scanning recognition task, trials that participants did not respond to during encoding, and trials that belonged to other experimental conditions not discussed here were modeled as events of no interest. We concatenated runs treating all three to a single time series, because there were too few events in one or more runs for some participants (<6; Murphy and Garavan, 2005). Covariates of no-interest also included six realignment parameters to account for motion artifacts and two dummy regressors to control for effects between runs. The subsequent-memory effect contrast that was used in subsequent analysis compared encoding activity of trials that were subsequently remembered to those that were later forgotten (hits > misses, on average 35 hit and 26 miss trials; Brewer et al., 1998; Wagner et al., 1998; Paller and Wagner, 2002).

2.7.2. Structural MRI: analyses of gray-matter volume correlates of associative memory

To identify gray-matter volume correlates of associative memory we applied multiple regression within the framework of the GLM in SPM12. Associative recognition performance (H-FA) was added into the regression as covariate of interest. Additional covariates of no interests included total intracranial volume (calculated as gray matter + white matter + cerebrospinal fluid), age, gender, and education. Gray-matter images were explicitly masked with the left anterior hippocampal region and left IFG (comprising pars opercularis, pars triangularis, and pars orbitalis; Ridgway et al., 2008), areas we previously reported to be related to subsequent associative memory (Becker et al., 2017). We chose these left-lateralized ROIs because we hypothesized to find a gray matter association to associative memory in regions, in which we previously found a functional association. An MNI-based mask of the left anterior hippocampal region including foci at and anteriorly to $y = -21$ mm (Poppenk et al., 2013) was created using the Automated Anatomic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Results were considered significant at a Family-Wise Error (FWE)-corrected cluster-extent threshold of $p < .05$ with a peak-voxel threshold of $p < .001$ (uncorrected).

2.8. Joint independent component analysis

jICA was performed using the Fusion ICA Toolbox (http://mialab.mrn.org/software). This data fusion method (Calhoun et al., 2006; Sui et al., 2014) assesses mutual information of multiple imaging modalities in one joint analysis, in contrast to traditional regression analysis, in which one brain modality is constrained by features of another brain modality (Sui et al., 2014). The underlying assumption behind ICA is that source signals are based on independent processes and therefore statistically independent from each other. At each data point, the signal is considered as a neuronal mixture of underlying independent components. JICA as applied to different modalities extracts maximally spatially independent source signals that are coupled together by a shared loading parameter.

First, a normalized and smoothed gray-matter image (structural image) and a subsequent-memory effect contrast image (functional

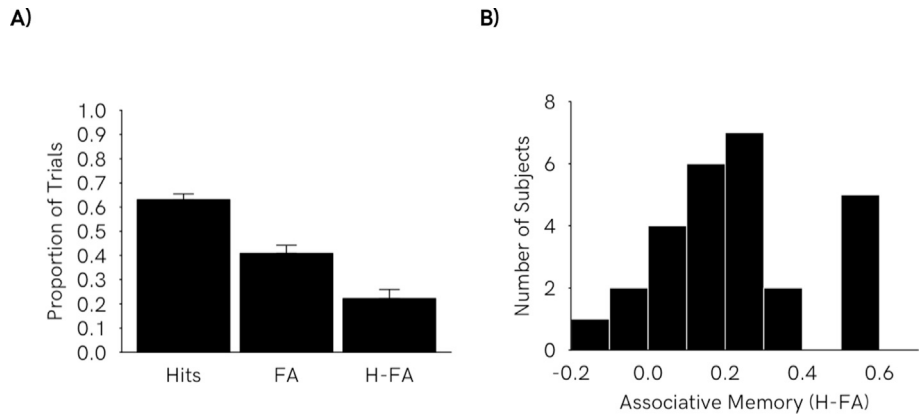

Fig. 2. A) Proportion of hits and false alarms (FA) and hits minus false alarms (H-FA) in the recognition task. Error bars represent standard errors around the means. B) Distribution of participant performance (H-FA).

image) were computed for each individual with a voxel size of 2 cubic mm. Images were normalized to have the same average sum-of-squares across all subjects and voxels for each modality. After normalization, the two modalities (i.e., features) were organized into a feature matrix that places the features side by side. This feature matrix is further modeled as containing spatially maximally independent component images and subject-specific loading parameters. Because in this analysis we were primarily interested in structure-function interactions of the MTL and IFG but had no a-priori hypothesis where exactly in MTL and IFG we would find structure-function covariances, jICA was performed masking the data with an MNI-based mask that was created with the AAL atlas that included bilateral hippocampus and parahippocampal gyrus as well as bilateral IFG as defined above. The validity of ICA analysis on a pre-selected region of interest was investigated before (Blessing et al., 2016). Dimensionality of the feature matrix was estimated using the Minimum Description Length (MDL) criteria (Li et al., 2007), which revealed a maximum of two components the data could be decomposed into. Principal component analysis (PCA) served as a pre-processor of jICA. More precisely, it was applied to reduce the dimensionality of the feature matrix based on the maximum value of the MDL criteria. This served to increase performance of jICA by minimizing pair-wise dependencies while higher-order dependencies can be separated by jICA (Bartlett et al., 2002). The reduced feature matrix was decomposed into maximally independent component images and subject specific loading parameters using the Infomax algorithm (Bell and Sejnowski, 1995). Only joint components that entailed the hippocampus were further examined, which was our main region of interest. Structural and functional images were converted to z-values and thresholded at $z > 2$ for display. Localization of gray matter was obtained by reference to MNI labels. To examine the functional relevance of the jICA we correlated the loading parameters of resulting components with associative memory performance.

3. Results

3.1. Behavioral results

A more detailed description of the behavioral results can be found in Becker et al. (2017). The average proportion of hits was 0.63 ± 0.12. The mean false-alarm rate was 0.41 ± 0.18. Overall performance, i.e., averaged hits minus false alarms (H-FA) rate, was 0.22 ± 0.20 (Fig. 2).

When exploring the sample, we identified three potential statistical outliers by applying the Outlier Labeling Rule (Tukey, 1977) on associative recognition performance (H-FA), i.e., we multiplied the interquartile range by a factor of 1.5. This resulted in three outliers ($H\text{-}FA_{outlier1} = 0.57$; $H\text{-}FA_{outlier2} = 0.58$, $H\text{-}FA_{outlier3} = 0.59$). However, given that these outliers where still within a normal performance range, they were kept in all brain analyses. To investigate whether these outliers had any leverage on the results, we re-ran all analyses with the three outliers removed. Results can be found in the Supplementary material.

3.2. Imaging results

3.2.1. Gray-matter volume related to associative-memory performance

Analysis of gray-matter volume in relation to H-FA rates revealed one significant cluster located in left anterior hippocampus. Larger gray-matter volume in this region was related to higher H-FA rates, i.e., better performance in the associative-memory task (peak voxels at [-32 -12 -14] and [-27 -13 -21], 209 voxels; Fig. 3).

3.2.2. Joint independent component analysis

According to the MDL criterion, two joint ICs were estimated. With regard to our main region of interest (i.e., the hippocampus), only one component entailed a regional signal in anterior hippocampus and was thus examined further. Fig. 4 shows the spatial maps of the joint IC

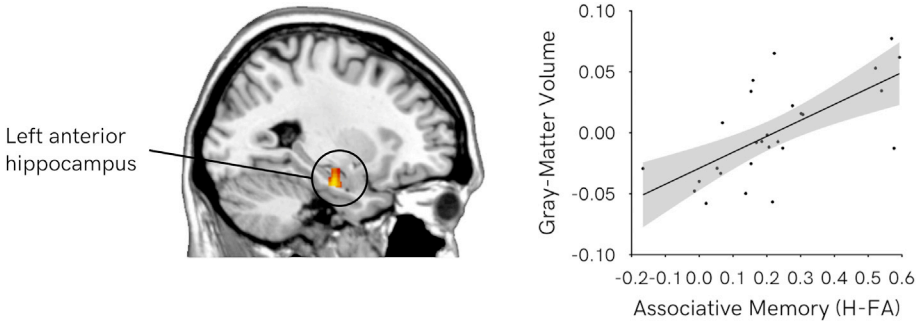

Fig. 3. Results of the VBM analysis. Left: Gray-matter volume in left anterior hippocampus correlated positively with associative memory performance (H-FA) when controlling for age, gender, TIV, and education. Effects are significant at a cluster-extent threshold of $p < .05$ (FWE-corrected). Right: Scatter plot showing significant positive relationship between associative memory performance (H-FA) and residuals of gray-matter volume after controlling for age, gender, TIV, and education. Each dot represents one participant. Shaded area represent 95% confidence interval.

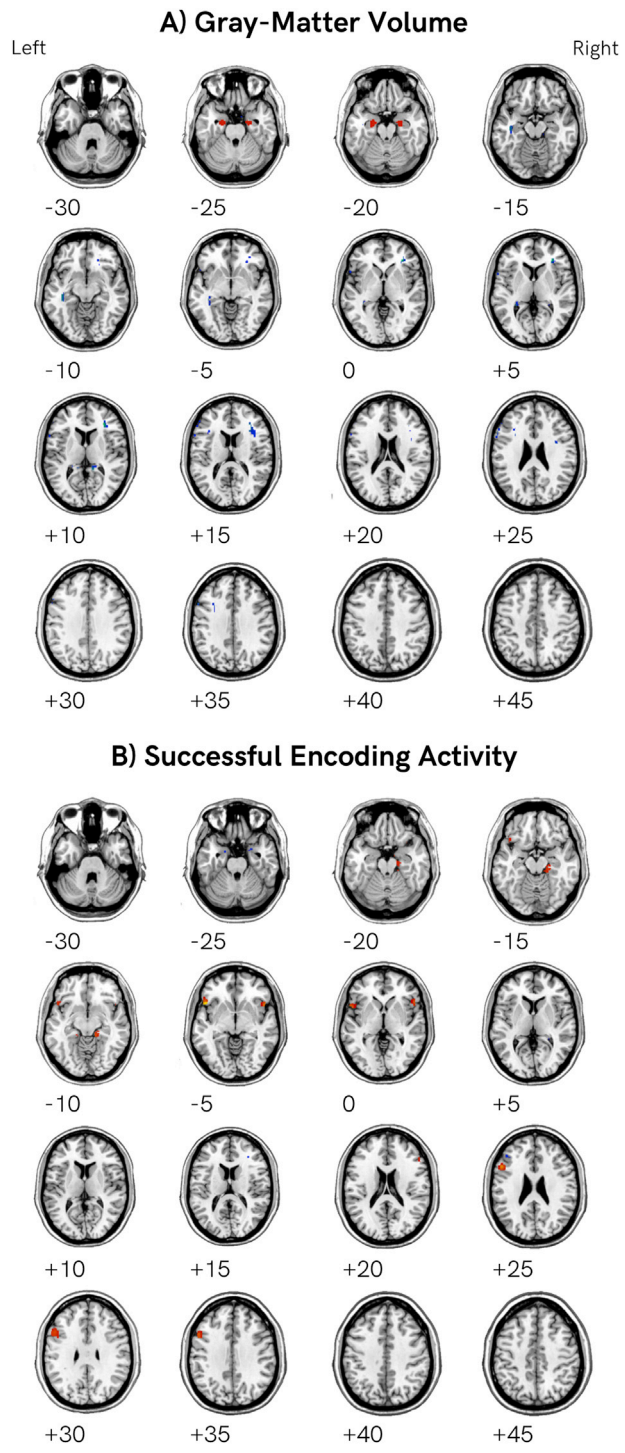

Fig. 4. Spatial structure of joint component thresholded at $z > 2$. A) Brain regions in which gray-matter volume was either larger (yellow-red) or smaller (blue-green) with higher encoding activity for subsequently remembered associations. B) Brain regions in which successful encoding activity was either higher (yellow-red) or lower (blue-green) with larger gray-matter volume.

features of gray matter volume and activity related to successful associative encoding. Spatial maps of the second joint IC not discussed here can be found in the supplementary material.

We found some structural-functional specificity along the longitudinal axis of the medial temporal lobe, such that larger gray-matter volume in bilateral anterior and smaller gray-matter volume in bilateral posterior hippocampus/parahippocampus together with bilateral IFG (Brodmann areas 44, 47, and 48) was related to (a) higher encoding activity in neighboring but non-overlapping areas of bilateral ventral IFG (Brodmann areas 44, 45, 47, 48) and right parahippocampal gyrus and (b) lower encoding activity in entorhinal cortex (Brodmann area 28) and non-overlapping regions in bilateral dorsal IFG (Brodmann area 45). A list of all regions can be found in Table 1. Pearson correlation between the component's loading parameter and associative-memory performance showed a positive but non-significant relationship between the two ($r = 0.25$, $p = .20$).

4. Discussion

In this study we investigated the joint contributions of gray matter volume and successful encoding-related brain activation in regions of the MTL and IFG to associative memory in healthy young adults. In a previous study, we observed the involvement of the left anterior hippocampus and left IFG in successful associative-memory formation (Becker et al., 2017). Here, using VBM we found larger gray matter volume in left anterior hippocampus predictive of better associative-memory performance. Further, using jICA we identified a relationship between gray-matter volume and activity during successful associative encoding in regions of the MTL and IFG.

4.1. Larger anterior hippocampal volume relates to better associative memory

In the current study, we observed that larger volume of the anterior portion of the left hippocampus predicted better memory for item-item associations. This finding fits well with the functional role of the hippocampus that is critically involved in forming coherent memory representations between relational information (Diana et al., 2007; Eichenbaum et al., 2007). Our finding is in line with other studies that reported positive relationships between hippocampal head volume and episodic memory (Hackert et al., 2002; Chen et al., 2010; Rajah et al., 2010). However, evidence on how associative memory relates to features of gray-matter volume is still controversial. For example, in a recent study, less volume of anterior hippocampus in healthy young adults predicted better associative binding performance (Schlichting et al., 2017). Similarly, DeMaster et al. (2014) and Poppenk and Moscovitch (2011) observed better source memory in individuals with smaller hippocampal head sizes. These seemingly contradicting findings might relate to the distinct functional characteristics the hippocampus exhibits along its longitudinal axis (Ranganath and Ritchey, 2012; Poppenk et al., 2013; Ritchey et al., 2015; Salami et al., 2016). For example, studies that reported negative correlations used either source-memory paradigms or memory tasks containing abstract stimuli. In comparison to our paradigm, associative memory in these tasks might be based on specific details of the stimuli represented in posterior hippocampus (Poppenk and Moscovitch, 2011). On the other hand, item-item associations in our task that entail concrete objects might rely on more gist-like representations located in anterior hippocampus (Gutchess and Schacter, 2012; Poppenk et al., 2013). Furthermore, the anterior portion of the hippocampus comprises a larger proportion of CA1-3 subfields than its posterior part (Poppenk et al., 2013) as well as portions of the dentate gyrus (Duvernoy et al., 2013). The CA3/dentate gyrus subfields are thought to promote pattern separation, i.e., the orthogonalization of overlapping inputs into separate outputs that enables the discrimination among similar memories (Bakker et al., 2008; Lacy et al., 2011; Deuker et al., 2014). CA1 has further been identified as detecting mismatches when incoming stimuli deviate from memory (Deuker et al., 2014). Both processes are specifically important for associative memory. Synaptic proliferation in these subfields might allow for coding of distinct, non-overlapping traces (Travis et al., 2014; Schlichting et al., 2017) and could potentially be explanatory why increased volume of the anterior hippocampus is positively related to associative memory in our study. Together, these findings underline the importance of acknowledging the differential

Table 1
Brain regions within joint component depicted in Fig. 4.

Modality	Loading	Region	BA	volume (cc)	z.value	mni.x	mni.y	mni.z
GMV	Volume greater	Anterior hippocampus/parahippocampal gyrus		0.6	2.5	−22	−8	−22
				0.1	2.3	−22	−6	−26
				0.1	2.0	−18	−6	−26
				0.4	2.5	22	−6	−22
				0.1	2.0	22	−6	−26
	Volume less	Parahippocampal gyrus	37, 20	1.7	2.7	−42	−18	−14
		Posterior hippocampus/parahippocampal gyrus	27	0.3	2.7	−30	−40	6
			27	0.2	2.6	−28	−36	8
			27	0.3	2.7	14	−40	10
		Posterior hippocampus	27	0.1	2.2	−22	−36	10
			37	0.1	2.2	26	−40	6
		Inferior Frontal Gyrus	48	0.1	2.1	−36	24	14
			44, 48	0.1	2.4	−60	16	8
			47	0.1	2.2	−52	18	−8
			44	1	2.7	−58	16	30
			44	0.8	2.5	−56	14	36
			47	2.0	2.7	30	34	10
			47, 48	0.4	2.7	26	32	−4
			47, 48	0.3	2.5	32	40	−4
			48	0.2	2.1	32	24	14
			48	0.1	2.4	36	2	28
SM activity	Activity greater	Inferior Frontal Gyrus	47	0.2	3.9	−50	18	−8
			44, 48	0.8	3.6	−52	18	30
			44, 48	1	3.3	−52	20	26
			48	0.1	3.9	30	14	−22
			45	0.1	3.6	52	32	20
			47, 45	0.7	3.3	50	18	−6
		Parahippocampal Gyrus	27	0.1	3.0	−16	−32	−12
			30	0.8	3.0	20	−26	−16
	Activity less	Inferior Frontal Gyrus	46, 48	0.1	2.5	−38	34	24
			45, 48	0.1	2.2	−42	36	16
			48	0.1	2.5	34	8	16
		Enthorinal cortex	28	0.1	2.1	−18	4	−24
			28	0.1	2.1	22	4	−26

Note. BA = Brodmann area. GMV = gray-matter volume. SM activity = activity during successful associative encoding (subsequent memory contrast associative hits > associative misses).

contributions of hippocampal subfields to associative memory. However, our voxel-by-voxel analysis required data smoothing, which is one reason why we cannot make exact statements about the contribution of particular subfields. Another limitation inherent when investigating brain structure is that we cannot disentangle the processes that underlie memory performance. That is, we cannot tear apart whether variance in anterior hippocampal volume relates to variance at encoding or retrieval or both.

The hippocampal cluster reported here is overlapping with the hippocampal portion involved in successful memory encoding in the same task (Becker et al., 2017). Thus, the findings of the current study extend our previous findings and underscore the relevance of left anterior hippocampus in successful associative-memory formation on both a functional and structural level. Future studies should investigate the importance of hippocampal subfield volumes beyond the separate contributions of anterior and posterior hippocampal portions to associative memory.

4.2. Structure-function interplay during successful associative encoding

The jICA produced one component that represented a relationship between larger gray matter volume in bilateral hippocampus and greater activity in bilateral IFG in Brodmann areas 44, 45, 47, and 48 and less activity in entorhinal cortex. Further, less gray matter volume in IFG corresponded to greater activity partly in neighboring but not overlapping areas of IFG. Across individuals, greater expression of this structure-function relationship was associated with better associative memory performance, and was thus functionally meaningful.

Our study provides novel evidence for a long-distance structure-function relationship between MTL and IFG underlying associative-memory formation. In line with our previous results, the jICA produced one component that entailed activity during successful associative encoding in the IFG (Becker et al., 2017). Interestingly, activity in IFG voxels did not relate to features of gray-matter volume in the same but adjacent voxels in this component. Similarly, we did not find evidence for a covariant relationship between gray-matter volume and activity in the hippocampus during associative-memory formation. This might seem counterintuitive given that activity in an overlapping hippocampal cluster previously predicted successful associative encoding in the same task (Becker et al., 2017). One potential reason for this discrepancy in findings might be that in our previous study we investigated subsequent memory effects within individuals, while here we observed covariance relationships between brain structure and function across individuals. As such, our findings underscore the necessity of multimodal analyses in understanding complex network properties of the brain that are dependent on both gray-matter volume and regional activity. Moreover, and in line with previous studies, our findings suggest that brain volume and function are not intuitively linked, i.e., larger gray-matter volume does not necessarily result in more brain activity in the same region (Kalpouzos et al., 2012; Persson et al., 2012; Harms et al., 2013); rather, their interaction is complex and stretches across different regions in the brain. Yet, it remains difficult to make assumptions about the causality of this relationship, in particular, as MRI provides only indirect measures for tissue properties and neural activity.

Our findings are in line with observations from correlational studies that reported a positive relationship between hippocampal volume and encoding-related activity in IFG during episodic memory tasks (Maillet and Rajah, 2011). Harms et al. (2013), who observed a similar

structure-function relationship during a working memory task suggested two possible biological mechanisms: local gray-matter in the hippocampus might serve as a morphological substrate (Calhoun et al., 2006) that affects the functional output released from this region, which in turn could affect the quantity of synaptic input arriving at a distal cortical region, i.e., the IFG. Alternatively, functional activity in the IFG could influence the structural volume of a distant region, i.e., the hippocampus through for example neurotrophic factors (Harms et al., 2013). Another factor that could mediate the relationship between gray-matter volume and activity in MTL and IFG could be microstructural integrity. For example, the uncinate fasciculus, which has been implicated in episodic memory before (Lockhart et al., 2012), connects the anterior portion of the hippocampus to IFG (Aggleton, 2012; Catani and Thiebaut de Schotten, 2012; Poppenk et al., 2013). In particular, CA1 receives input anteriorly through the entorhinal and perirhinal cortices that have strong connections to orbitofrontal cortex (i.e., perforant pathway; Cavada et al., 2000; Sperling et al., 2003; Schott et al., 2011). In line with the anatomical positions of regions in the IFG produced by the jICA, Leng et al. (2016), identified the pars triangularis and pars orbitalis as cortical areas of termination of the uncinate fasciculus white matter tractography. While our findings do not provide evidence for a direct connection between these regions, the uncinate fasciculus could be one potential pathway underlying the observed relationship between MTL and IFG.

To our knowledge, this is the first study investigating structure-function relationships in associative memory in young adults using jICA. Interestingly, the observed opposing association between anterior and posterior MTL volume and IFG activity supports previous observations of separate contributions of these segments to memory, which might speak for divergent roles of these regions in associative encoding, e.g., their relative contribution to associative memory encoding (more anterior) and retrieval (more posterior; Salami et al., 2012; Poppenk et al., 2013; Sheldon and Levine, 2015; Becker et al., 2017).

Moreover, our findings extend well-established observations of functional connectivity between the hippocampus and IFG during associative memory formation (Addis and McAndrews, 2006; Gagnepain et al., 2011; Becker et al., 2017). For example, activity in anterior hippocampus and IFG was significantly correlated during successful formation of face-name associations (Sperling et al., 2003). Similarly, subsequent recall effects in IFG (BA 45) correlated with subsequent recall activity in left hippocampus (Long et al., 2010). Together, these results suggest that the interaction between IFG and hippocampus promotes strong encoding, a prerequisite for successful recollection and associative memory (DuBrow and Davachi, 2016). Interestingly, the association between associative memory performance and the structure-function relationship between MTL and IFG was not significant. Hence, this structure-function relationship seems to primarily underlie proficient encoding processes and to not promote overall memory performance, which also relies on consolidation and retrieval processes. When re-running the analyses on the sample with three outliers removed, all results remained stable, while additionally, the MTL and IFG structure-function relationship positively and significantly correlated with associative-memory performance (see Supplementary material). This could indicate a potential relevancy for this relationship in memory processes beyond encoding. However, the association between associative memory performance and the structure-function relationship between MTL and IFG needs to be interpreted with utmost caution and requires further investigation by future studies as this relationship did not hold when running the analysis on the full sample (see Supplementary material).

To conclude, our study provides novel insights into structure-function interactions between distant brain regions that contribute to associative memory. While previous studies have shown that gray-matter volume and activity in hippocampus and IFG relate to associative memory, we extend these findings and provide evidence that the interaction between these two brain regions and different brain modalities promote successful associative encoding. Future studies should try to elucidate the biological underpinnings of such long-distance structure-function relationships by including e.g., diffusion tensor imaging.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.116020.

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