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Sex differences in volume and structural covariance of the anterior and posterior hippocampus

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ABSTRACT

Sex differences in episodic and spatial memory are frequently observed, suggesting that there may be sex-related structural differences in the hippocampus (HC). Earlier findings are inconsistent, possibly due to a known variability along the hippocampal longitudinal axis. Here, we assessed potential sex differences in hippocampal volume and structural covariance with the rest of the brain in young men and women (N = 76), considering the anterior (aHC) and posterior (pHC) hippocampus separately. Women exhibited a larger pHC than men adjusted for brain size. Using partial least squares, we identified two significant patterns of structural covariance of the aHC and pHC. The first included brain areas that covaried positively and negatively in volume with both the aHC and pHC in men, but showed greater covariance with the aHC than pHC in women. The second pattern revealed distinct structural covariance of the aHC and pHC that showed a clear difference between men and women: in men the pHC showed reliable structural covariance with the medial and lateral parietal lobes and the prefrontal cortex, whereas in women the aHC showed reliable structural covariance with the anterior temporal lobe bilaterally. This pattern converges with resting state functional connectivity of the aHC and pHC and suggests that these hippocampal sections interact with different brain regions, consistent with a division of labor with regards to episodic and spatial memory. Our findings lend support to a division of the HC into an anterior and posterior part and identify sex as a potential moderating factor when investigating hippocampal structure and connectivity.

Introduction

Sexual dimorphism in brain anatomy has been researched for quite some time now, and some differences are consistently observed. Overall, men have larger brains by approximately 10% and exhibit a larger proportion of white matter compared to women who have relatively greater gray matter volume (Giedd et al., 2012; Sacher et al., 2013). There is also evidence of sex differences in anatomical connectivity, such that women exhibit more connectivity overall and have more efficiently organized anatomical networks compared to men, as assessed using graph theoretical approaches on diffusion tensor imaging (DTI) data (Gong et al., 2009; see Gong et al., 2011 for a review on sex differences in both structural and functional connectivity). Considering laterality, there is evidence of higher asymmetry in men than in women, both structurally in terms of volume (Rentería, 2012) and functionally as measured during resting state (Liu et al., 2009) as well as during some cognitive tasks (Kansaku et al., 2000; Persson et al., 2013; Rilea et al., 2004; but see Sommer et al., 2008). Based on DTI, a higher regional efficiency (a measure of connectivity for a specific network node) has been observed predominantly in left hemisphere nodes in women, while a higher efficiency has been observed in right hemisphere nodes in men (Gong et al., 2009).

In terms of regional sex differences in brain volume, the hippocampus (HC) is a structure that has been well studied (Filipek et al., 1994; Giedd et al., 1996; Gogtay et al., 2006; Maller et al., 2007; Murphy et al., 1996). This structure is crucial for episodic memory (Schacter et al., 1996; Scoville and Milner, 1957; Vargha-Khadem et al., 1997),

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the memory for personally experienced events (Tulving, 1983, 2002), as well as for spatial memory (Maguire et al., 1996a, 1996b; O'Keefe and Nadel, 1978). These functions frequently show sex differences, where women are usually superior in episodic memory (Herlitz and Rehnman, 2008), and men excel in spatial memory (Astur et al., 1998; Lawton and Morrin, 1999). Given these sex differences in performance and evidence of distinct neural correlates of these memory systems within the HC (Kühn and Gallinat, 2013), regionally varying sex differences in HC volume might also be expected.

When considering overall HC volume, sex differences have sometimes been reported, suggesting a larger hippocampus in women than in men after correcting for total intracranial volume (Filipek et al., 1994; Giedd et al., 1996; Murphy et al., 1996), but a large number of studies report no difference in volume (Bueller et al., 2006; Jack et al., 1989; Lange et al., 1997; Mu et al., 1999; Pruessner et al., 2001; Tisserand et al., 2000). Sex differences in functional lateralization in the hippocampus could be expected considering the sex difference in episodic and spatial memory — functions that sometimes show hippocampal lateralization (e.g. Burgess et al., 2002; e.g. Golby et al., 2001). Such differences have also been reported (Frings et al., 2006; Persson et al., 2013), but no corresponding sex difference in structural laterality has been observed (Giedd et al., 1996, 1997; Maller et al., 2007).

One reason that findings of sex differences in hippocampal volume are equivocal may be that the above studies considered overall HC volume while there is evidence that the HC is not a homogeneous structure, with both structural and functional differences along its longitudinal axis (Poppenk et al., 2013). In rodents, the dorsal and ventral HC (corresponding to the posterior (pHC) and anterior (aHC) hippocampus in humans) vary in cell densities, receptors and electrochemical features (Moser and Moser, 1998), as well as in gene expression (Fanselow and Dong, 2010). Similarly, in humans, there is evidence of variation in pyramidal cell density in the subiculum (Babb et al., 1984) and in metabolites (King et al., 2008) between the aHC and pHC. Thus, there is much evidence to support a meaningful division of the HC into at least two parts along its longitudinal extension. As alluded to above, spatial and episodic memory have at least partly separate neural correlates in the hippocampus (Kühn and Gallinat, 2013) and it is possible that potential sex differences in hippocampal volume are local rather than global, obscuring these potential differences when considering this structure as a whole. In one study comparing children (8–11 years) and young adults (18–26 years), the volumetric differences in the hippocampus varied regionally, with greater volume in the hippocampal body and smaller volume in the right hippocampal head and tail in adults (DeMaster et al., 2013). Furthermore, the relationship between volume and episodic memory performance depended on hippocampal segment, with young adults exhibiting a negative correlation in the head and a positive correlation in the body of the right hippocampus, and children a positive correlation in the left hippocampal tail. Another study considered the development of the aHC and pHC in boys and girls between 4 and 25 years old, observing decreased volume in the posterior-most part in girls, and in the anterior part in boys, though they did not directly assess sex differences (Gogtay et al., 2006). Together, these findings indicate that different subsections of the hippocampus follow different developmental trajectories, which may differ for men and women. However, to our knowledge, no previous study has examined potential sex differences in volumes of hippocampal subsections in young adults.

Another feature that distinguishes the aHC from the pHC is the neural pathways that connect them to the neocortex and other subcortical regions (Fanselow and Dong, 2010). The pHC predominantly projects to the mammillary nuclei and anterior thalamic complex as well as the retrosplenial and anterior cingulate cortex. Meanwhile, the aHC is primarily connected to the amygdala and the hypothalamic–pituitary–adrenal (HPA) axis via the bed nucleus of the stria terminalis (Fanselow and Dong, 2010). While not making a distinction between the pHC and aHC, Duvernoy (2005) describes two intrahippocampal pathways, the polysynaptic pathway and the direct hippocampal pathway, with distinct extrahippocampal projections. This structural architecture corresponds well with the two resting state functional connectivity patterns of the pHC and aHC, respectively, observed previously (Kahn et al., 2008; Poppenk and Moscovitch, 2011). The polysynaptic pathway sends its projections via the fornix to the anterior thalamic nucleus and mammillary bodies, further extending into the posterior and anterior cingulate and the retrosplenial cortex (Duvernoy, 2005), much like the pHC projections described by Fanselow and Dong (2010). The posterior parietal cortex (PPC) and its surrounding occipital and temporal cortex also provide the input to the polysynaptic pathway (Duvernoy, 2005). The direct hippocampal pathway sends its projections via the uncinate fasciculus to the inferior temporal cortex, the temporal pole and the prefrontal cortex while also receiving projections from the inferior temporal cortex. Thus, the anterior and posterior segments are situated to interact with distinct regions, raising the possibility that they covary in size with different areas of the brain. Such coordinated variation in volume between brain regions across the population, referred to as structural covariance, has been observed in networks of regions that show functional connectivity and are known to subserve the same cognitive functions (Alexander-Bloch et al., 2013a).

Considering the lack of consensus regarding potential sex differences in HC size, and the evidence of variation along the HC axis in terms of function, structure and connectivity, the aim of this study was to assess potential sex differences in the aHC and pHC size and structural covariance. To date, this issue has not been investigated, and may explain the inconsistent findings regarding sex differences in hippocampal size, and shed light on potential sex differences in how the aHC and pHC are related to volume patterns in the rest of the brain. Additionally, we assessed episodic and spatial memory, and whether performance was related to the aHC and pHC volume or the structural covariance of these areas. We studied a sample of young adults, using a multivariate approach to assess patterns of structural covariance of the hippocampus. This approach identifies patterns of whole brain covariance across subjects with hippocampal gray matter volume. Identifying potential sex differences in whole brain–HC covariance may contribute to explaining frequently observed sex differences in episodic and spatial memory and can be informative of sex-differences in overall cerebral organization and function.

Methods

Participants

Seventy-six participants (38/38 men and women) between 20 and 35 years of age (see Table 1 for subject characteristics) were recruited from the student population at Uppsala University. Participants were right-handed with no history of brain injury or neurological disease and all had Swedish as their first language. Men and women did not

Table 1
Demographic characteristics and cognitive performance of the study sample (means, standard deviations in parentheses).

	Men (N = 38)	Women (N = 38)
Demographics		
Age, yrs	24.4 (3.4)	23.5 (3.6)
Education, yrs	15.0 (1.6)	14.7 (2.0)
Cognitive function		
TMT A (time, s)	26.6 (9.8)	30.8 (10.2)
TMT B (time, s)	54.5 (17.4)	57.6 (18.3)
Letter Digit Substitution	37.9 (5.0)	37.8 (6.1)
SRB (synonyms)	23.0 (4.1)	22.5 (4.5)
FAS, total	50.5 (11.2)	50.5 (10.9)

There was no significant difference between men and women in the demographic or cognitive measures.

differ in age, level of education, or overall cognitive ability (see Table 1). All participants provided written informed consent, which, along with the study, was approved by the regional ethical review board in Uppsala.

Behavioral assessment

Participants performed a set of cognitive tests to ensure comparable cognitive function in the groups. Trail Making Tests A and B (TMT-A and TMT-B) were included to measure visuomotor speed and cognitive flexibility (Lezak, 2004), Letter Digit Substitution test (LDS; Jolles et al., 1995) to assess cognitive speed, and Synonyms from the Dureman-Sälde Battery (SRB; Dureman, 1960) to measure verbal ability. No sex differences were found on any of the tests (see Table 1).

Episodic memory tasks

Two episodic and two spatial memory tasks were included in the study. The episodic memory tasks consisted of a word list recognition test (WL) and an object location test (OL), including memory for item and location. Briefly, the WL task consisted of 80 nouns to be memorized for a subsequent recognition test and 80 additional nouns serving as distractors during the recognition phase. Half of the targets and distractors consisted of concrete nouns. During encoding, participants made a concrete/abstract decision for each noun as it appeared for 2 s centered on a computer screen. Recognition memory was tested using an old/new decision task. During the retention interval, TMT-A and B were administered.

The OL task consisted of line-drawings of objects (Snodgrass and Vanderwart, 1980), 88 targets and 44 distractors. Objects were presented one at a time for 1.5 s in one of four quadrants of a computer screen. Participants were asked to memorize the object and its location on the screen for subsequent item and location memory tests. During encoding, participants made a man-made/naturally-occurring classification of the objects as they appeared. Recognition memory was tested with an old/new decision task and location memory with a forced-choice task that followed for each object that was classified as old. LDS was administered during retention. For both episodic tasks, participants were informed of the subsequent memory tests. The duration of each trial was fixed during encoding while the memory tests were self-paced. Participants registered their responses during encoding and testing using the keyboard. D-prime was calculated as a measure of recognition memory performance by subtracting the z-transform of false alarms from the z-transform of hits. Due to missing WL data from one female participant, results from this task are reported for 75 participants only.

Spatial memory tasks

The spatial memory tests consisted of a so-called pointing task and a virtual version of the Morris Water Maze (vWM). The pointing task has been described in detail elsewhere (Persson et al., 2013). In short, it consisted of virtual three-dimensional mazes which participants traversed, and at the end they were asked to indicate their starting position. No alternative routes existed and the mazes only contained 90° left and right turns that were equally spaced throughout the maze. The task contained mazes of 2, 4 and 6 turns. The outcome measure was deviation in degrees from the correct pointing angle when indicating the origin.

The vWM task consisted of a virtual quadratic room with a circular pool of water centered within it. Participants were to search for a hidden platform in the pool over several trials, starting randomly at one of three different positions. The position of the platform remained constant over trials allowing participants to gradually acquire knowledge of its position relative to distal cues (e.g., paintings, windows), placed at each of the four walls. Once the platform was found, participants were allowed a brief time window during which they could look around the environment before the onset of the next trial. Both tasks were self-paced, displayed on a computer monitor, and performed using the arrow buttons on a keyboard. Performance was measured as the average time taken to reach the platform and the average distance traveled to reach it.

Potential differences between men and women on the cognitive measures were assessed using independent samples *t*-test and considered significant at $p < .05$.

Data acquisition

Scanning was performed on a Philips Achieva clinical whole-body 3 T scanner with an 8 channel head coil (Achieva X-series, Philips Medical Systems, Best, The Netherlands). Anatomical T1-weighted images were acquired with a 3D magnetization prepared rapid gradient echo sequence (repetition time = 9 ms; echo time = 4 ms; inversion time = 900 ms; shot interval = 3000 ms; flip angle = 9°; field of view = 240 × 240 mm^2; voxel size = 1 mm^3 isotropic voxels; 170 slices).

Preprocessing

The data were preprocessed using Statistical Parametric Mapping 8 (SPM8; www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 8.0.0 (The Mathworks, Natick, MA). First, the T1-weighted images were segmented using the routine *New segment* as implemented in SPM8 (Ashburner and Friston, 2005). After visually inspecting the segmented images for errors, the gray and white matter segmentations were used to create a study specific template with the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) tools. The individual gray matter images were subsequently warped to this template, aligned with the Montreal Neurological Institute (MNI) space and resliced to 1.5 mm isotropic voxels. Finally, the voxel values were weighted by the Jacobian determinants to preserve regional volume information and a smoothing kernel of 8 mm full-width at half-maximum was applied.

To account for individual differences in overall brain size, total intracranial volume (TIV) was calculated for each participant by summing the voxel values of the gray matter, white matter and cerebrospinal fluid segmentations, and used to scale the voxel intensities of the normalized image. The voxels of the final images thus represent proportional regional gray matter volume.

Volumetric comparisons of the aHC and pHC

To assess the volumes of the aHC and pHC in men and women, the hippocampus definition from the Automated Anatomical Labeling (AAL) library (Tzourio-Mazoyer et al., 2002) from the Wake Forest University PickAtlas (WFUPickatlas) toolbox (Maldjian et al., 2003) was used. The anatomical marker for delineating the anterior and posterior hippocampus was the appearance of the uncal apex on coronal slices, based on a recent definition of the aHC and pHC (Poppenk et al., 2013). This delineation was made after superimposing the anatomical label onto an average of the normalized individual images in this study. To avoid contamination between the regions due to misregistration or partial volume effects, a 2 mm coronal slice was removed from each of the two adjacent ends. The final definitions of the aHC and pHC spanned from −2 to −18 and from −24 to −42 along the y-axis, respectively. For each individual preprocessed gray matter image, the voxels identified as belonging to the respective region were summed and multiplied by the voxel volume to quantify the volume of that region, relative to TIV. This was done on unsmoothed images to further avoid contamination from adjacent brain regions.

To assess regionally varying sex differences in HC volume, the resulting volume estimations were entered into a 2 (segment) × 2 (laterality) × 2 (sex) repeated measures ANOVA.

Covariance of the aHC and pHC in men and women: partial-least-squares

To contrast the covariance patterns of the aHC and pHC in men and women we used a multivariate approach, partial least squares (PLS; McIntosh and Lobaugh, 2004; McIntosh et al., 1996; see Spreng and Turner, 2013 for structural covariance analysis in PLS), implemented in MATLAB 8.0.0. This method can be used to identify patterns of voxels that covary with an exogenous measure (e.g. behavior or a seed). PLS identifies a set of latent variables (LVs) that optimally relate the exogenous data and the imaging data (similar to eigenvectors in principal component analysis). The statistical significance of the LVs is assessed using permutations, and the reliability of the voxel weights, that reflect the whole brain pattern captured by each LV, is estimated using a bootstrapping procedure. The reliability is expressed as a voxel-wise bootstrap ratio (BSR; the ratio of the salience to the bootstrap standard error). For each LV, a brain score is obtained for each participant by taking the dot product of the group result image and the individual gray matter image. Brain scores reflect the extent to which the voxel pattern captured by an LV is expressed in each participant. In the case of structural seed PLS, brain scores represent the weighted sum of the gray matter volume identified in the structural covariance image.

Here, seed PLS was used to identify volumetric patterns that relate to the gray matter volume of the aHC and pHC, respectively, and how these patterns differ as a function of sex. The warped, modulated, smoothed and TIV-scaled gray matter images were entered into a PLS analysis, with the aHC and pHC volumes, as calculated above, defining the seed regions. Men and women were entered as different groups. The analysis was performed using 1,000 permutations and 500 bootstraps. An LV was considered significant at a threshold of $p < .05$ and a voxel BSR of 3 or more (corresponding to a p-value of .003) was considered reliable (Krishnan et al., 2011; McCormick et al., 2013). No corrections for multiple comparisons were necessary since the PLS analysis was performed in a single analytic step.

Assessment of structure–behavior relationship

To assess the relationship between HC volume and behavior, the aHC and pHC volumes were correlated with the respective memory performance measure. Further, to assess the relationship between identified structural covariance patterns and behavior, individual brain scores for each significant LV were correlated with memory performance. Correlations were calculated for the whole sample, as well as separately for men and women, and considered significant at $p < .05$.

Results

Hippocampal volume

TIV was significantly greater for men than women by approximately 13% ($t(74) = 8.15$, $p < .001$; 1.67 ± .10 and 1.47 ± .10 l, respectively), in line with earlier findings (Giedd et al., 2012). Adjusted for TIV, the segment × laterality × sex ANOVA did not reveal a main effect of sex on HC volume ($F(1,74) = 2.34$, *n.s.*; 2,317.5 ± 139.1 mm^3 for men, 2,361.6 ± 110.3 mm^3 for women), a sex × laterality interaction ($F(1,74) = .24$, *n.s.*) or a sex × segment × laterality interaction ($F(1,74) = 2.14$, *n.s.*). However, sex interacted with segment ($F(1,74) = 4.33$, $p < .05$), showing that pHC volume was greater in women than in men (1,058.5 ± 75.5 and 1,014.0 ± 89.5 mm^3, respectively, a 4.3% difference), while aHC volume was comparable in men and women (1,303.5 ± 78.6 for men, 1,303.1 ± 68.7 for women).

There were also main effects of segment ($F(1,74) = 611.92$, $p < .001$), where the aHC was larger than the pHC, and laterality ($F(1,74) = 585.92$, $p < .001$), with the left HC being larger than the right HC, and a segment × laterality interaction ($F(1,74) = 41.02$, $p < .001$), such that the left > right HC difference was larger in the aHC than the pHC.

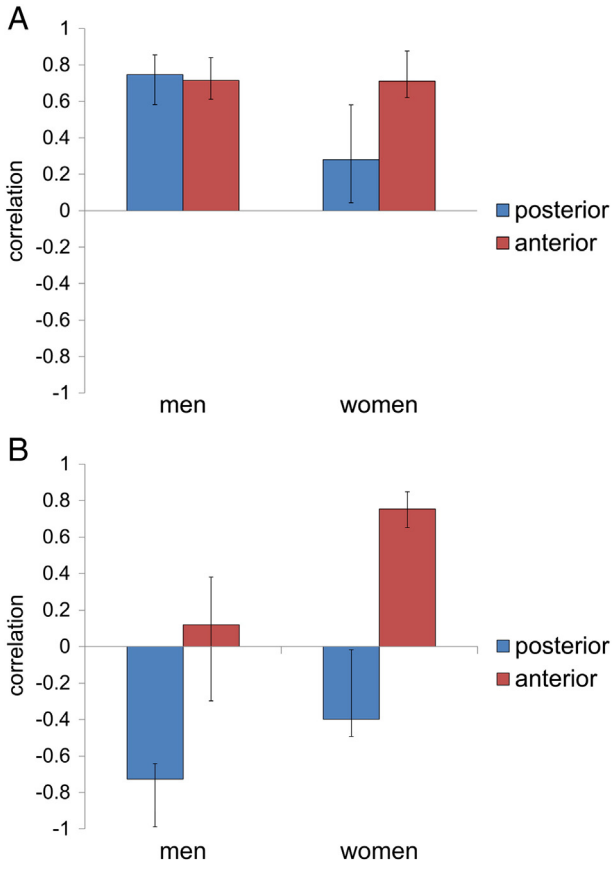

Fig. 1. Brain score–seed correlation patterns for the latent variables (LVs). The bars represent the extent to which the seeds relate to the voxel salience pattern captured by the LV for the anterior and posterior seeds, as a function of sex. (A) The first latent variable ($p < .001$) shows similar structural covariance patterns of the posterior and anterior hippocampus in men. This covariance pattern is shared by women in the anterior hippocampus, and less so in the posterior hippocampus. (B) The second latent variable ($p = .003$) shows a structural covariance pattern of the posterior hippocampus which is mainly present in men, and which differs from a structural covariance pattern of the anterior hippocampus only present in women.

Structural covariance of the hippocampus

An initial seed PLS analysis did not distinguish between the left and right aHC and pHC (as indicated by overlapping confidence intervals; see Supplementary Fig. 1 for these results), and we therefore averaged the left and right seeds into overall aHC and pHC seeds. The PLS analysis produced two significant LVs (see Fig. 1 for the bootstrapped correlation between the seed value and a composite score of the covariance pattern (i.e. brain score) and Table 2 for a cluster report of reliable voxels). The first LV ($p < .001$) reflected structural covariance common to the aHC and pHC in both men and women, though the pHC in women was significantly less related to this pattern than the other seed regions (see Fig. 1A). The spatial pattern of positive covariance related to this LV extended through the entire length of the hippocampus and to the adjacent neocortex, bilaterally, including the thalamus, insula and posterior cingulate (see Fig. 2). Negative covariance was observed bilaterally in the middle frontal gyrus, supramarginal gyrus, superior parietal lobule, and middle occipital gyrus, among other areas.

The second LV ($p = .003$) showed a significant sex × segment interaction that dissociated the covariance pattern of the pHC in men and the aHC in women (see Fig. 1B). A specific pattern of covariance was found for the aHC in women only, extending bilaterally in the anterior

Table 2
Clusters of reliable voxel saliences for the two significant latent variables (LVs). Coordinates and bootstrap ratio (BSR) reported for the peak voxel of each cluster.

Location	Voxels	MNI coordinates			BSR
		X	Y	Z	
LV1					
Positive saliences					
Insula (R; bordering on putamen)	220	32	20	14	4.20
Superior frontal gyrus (R)	57	20	3	63	3.26
Hypothalamus/mammillary bodies	241	−3	0	−15	4.13
Middle cingulate cortex (R)	99	2	−5	38	3.43
Thalamus, at ventricular border (L)	73	−2	−11	−5	3.31
Middle temporal gyrus (L)	60	−60	−15	−5	3.48
Hippocampus (R; extending into parahippocampal gyrus and amygdala)	6238	30	−18	−11	16.24
Hippocampus (L; extending into parahippocampal gyrus and amygdala)	5178	−27	−18	−15	12.09
Posterior cingulate (R)	237	2	−33	26	3.36
Cerebellum (R)	60	51	−44	−42	3.57
Lingual gyrus (R)	133	21	−59	−6	3.73
Lingual gyrus (R)	57	24	−78	−2	3.89
Negative saliences					
Middle frontal gyrus (R)	550	30	57	26	−5.40
Middle frontal gyrus (L)	305	−39	41	36	−4.15
Postcentral gyrus (L)	200	−53	−17	54	−3.48
Supramarginal gyrus (R)	792	69	−27	32	−5.20
Superior parietal lobule (R)	114	38	−48	66	−3.35
Inferior temporal gyrus (R)	358	57	−57	−9	−5.60
Angular gyrus (R)	238	48	−60	36	−4.49
Superior parietal lobule (L)	563	−23	−77	53	−4.54
Middle occipital gyrus (R)	528	30	−84	3	−5.38
Middle occipital gyrus (R)	96	35	−84	23	−3.79
Middle occipital gyrus (L)	1337	−23	−92	2	−5.48
LV2					
Positive saliences					
Anterior temporal lobe[a] (L; lateral)	2727	−54	5	−27	6.42
Anterior temporal lobe (R)	5945	35	−3	−30	6.41
Anterior temporal lobe (L; ventromedial)	4061	−35	−6	−27	6.87
Middle temporal gyrus (R)	100	68	−23	−3	3.80
Negative saliences					
Superior orbital gyrus (L)	79	−27	62	−5	−3.92
Superior frontal gyrus (L)	66	−21	56	15	−3.78
Middle orbital gyrus (R)	247	39	50	−9	−4.13
Superior frontal gyrus (L)	55	−20	38	29	−3.33
Precentral gyrus (L)	454	−35	−11	48	−4.37
Posterior hippocampus (R; extending into parahippocampal gyrus)	1227	23	−38	2	−7.19
Posterior hippocampus, parahippocampal and lingual gyrus (L)	1466	−18	−41	−3	−6.45
Cerebellum (L)	104	−20	−44	−44	−4.10
Cerebellum (R)	268	48	−50	−56	−5.56
Middle temporal gyrus (R)	175	60	−51	15	−4.10
Superior parietal lobule (R)	104	17	−57	62	−3.95
Inferior parietal lobule (L)	250	−35	−62	51	−4.41
Precuneus (L)	58	−2	−66	60	−4.18
Lingual gyrus (R)	192	12	−69	0	−4.19

[a] Covers the fusiform and parahippocampal gyrus, hippocampus and amygdala medially, and the middle and inferior temporal gyrus and temporal pole laterally. Bootstrap ratios (BSRs) indicate the reliability of the voxels and are proportional to *z* scores. Voxels with BSR > 3 are considered reliable. Clusters exceeding 50 voxels are reported.

temporal lobe (ATL), including the amygdalae, the anterior parahippocampal and fusiform gyri, and the anterior aspects of inferior and middle temporal gyri (see Fig. 3A). Also reflected in this LV, both men and women showed covariance between the pHC and the lingual gyri, the medial and lateral parietal lobes, the prefrontal cortex and cerebellum bilaterally (see Fig. 3B). However, this pattern of covariance was expressed to a greater extent in men.

As mentioned above, the initial analysis did now show any laterality effect, but since episodic and spatial memory sometimes show functional lateralization we ran an additional non-rotated PLS analysis which allowed us to enter contrasts to explicitly assess potential laterality effects. Specifically, we included two contrasts to test the main effect of laterality, as well as a sex × laterality interaction. While there was no main effect of laterality ($p = .121$) there was a small but significant sex × laterality interaction ($p = .016$), reflecting a different structural covariance of the right HC (both the aHC and pHC) in men and women (see Fig. 4). In men, the right HC covaried with the insula and lateral orbitofrontal cortex bilaterally, with the middle and superior frontal gyrus ipsilaterally, and with the cerebellum, precuneus and parahippocampal gyrus contralaterally. In women, ipsilateral covariance was present in the middle temporal and fusiform gyrus while contralateral covariance was found in occipital areas and superior parietal gyrus (see Table 3 for a summary).

Episodic and spatial memory

Men were more accurate than women in estimating the starting location in the pointing task ($t(74) = 7.43$, $p < .001$) and solved the vWM task faster than women ($t(74) = 5.26$, $p < .001$). No other performance differences were found (see Table 4).

When correlating performance in the memory tasks with the pHC and aHC volumes, significant correlations were found for the WL task in men only, with a negative correlation between pHC volume and task performance ($r = -.46$, $p = .003$; see Table 5). There was also a non-significant trend of error in the pointing task to correlate positively with pHC volume ($r = .21$, $p = .06$), such that a larger volume was

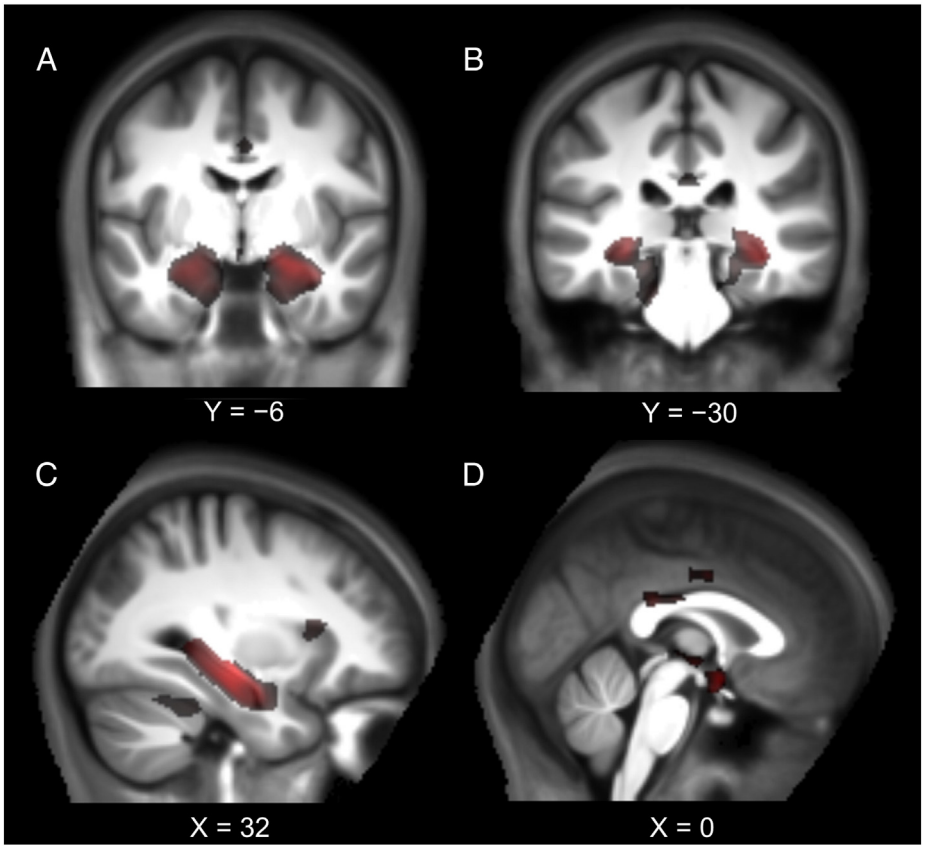

Fig. 2. Structural covariance captured by the first latent variable. A) Anterior hippocampus; (B) posterior hippocampus; (C) right hippocampus, insula and cerebellum; (D) thalamus and mid-posterior cingulate cortex.

associated with worse performance. Further, correlating memory performance with individual brain scores for each LV revealed significant correlations for the WL task only, with a negative relationship between the gray matter volume captured by the first LV's pattern of structural covariance, and WL performance in the whole sample ($r = -.28$, $p = .016$) and separately in men ($r = -.40$, $p = .014$) but not in women ($r = -.01$; see Table 6). Thus, the greater the volume within the structural covariance pattern common to the aHC and pHC in men, the lower the WL performance tended to be.

Discussion

Sex differences in hippocampus-dependent memory functions suggest differences in hippocampal structure and function between men and women. Earlier research on sex differences in hippocampal volume has yielded inconsistent findings (e.g. Giedd et al., 1996; Jack et al., 1989; Murphy et al., 1996; Pruessner et al., 2001), possibly due to the hippocampus being considered as a whole. Here we have shown that young men and women do not differ in their overall hippocampal volume corrected for total intracranial volume, but that when considering the anterior and posterior hippocampus separately, women have larger posterior hippocampi than men by about 4%. Further, these subsections of the hippocampus show distinct whole-brain structural covariance patterns, which differ between men and women. It is therefore important to consider both subsections and sex when studying hippocampal structure and function.

There was a local sex difference in the hippocampus, with women having a somewhat larger posterior hippocampus than men. Considering the male advantage in spatial memory, a function frequently associated with the posterior hippocampus, this finding was somewhat unexpected. We have previously observed a sex difference in engagement of the posterior hippocampus while performing a spatial memory task, where men tended to right-lateralize activity whereas women activated more bilaterally, which was paralleled by worse performance (Persson et al., 2013). If women in everyday life tend to engage the hippocampus more bilaterally than men, this could perhaps explain an increase in volume in this area.

The way the volume in the anterior and posterior hippocampus covaried with the volume in the rest of the brain also differed between men and women. There were two significant patterns of such hippocampal structural covariance. The first pattern expressed similar structural covariance for the anterior and posterior hippocampus with the rest of the brain in men, and greater anterior than posterior hippocampal–whole-brain covariance in women. Positive covariance associated with this pattern was found bilaterally throughout the hippocampal region, as well as in the insula, thalamus, and posterior cingulate, while negative covariance was evident in the bilateral middle frontal gyrus, supramarginal gyrus, superior parietal lobule, and middle occipital gyrus. This suggests that both anterior and posterior hippocampal volumes covary (positively and negatively) with volumes of these brain regions in men, while mainly the anterior hippocampus covaries with these areas in women.

There was a second qualitatively different pattern of structural covariance associated with the anterior and posterior hippocampus, as well as a gender effect. Here, structural covariance of the anterior hippocampus was only evident in women and comprised the bilateral anterior temporal lobe, including the middle and inferior temporal, fusiform and parahippocampal gyri as well as the amygdalae. This overlaps well with the structural connections of the direct hippocampal pathway (Duvernoy, 2005), as well as with the anterior functional network

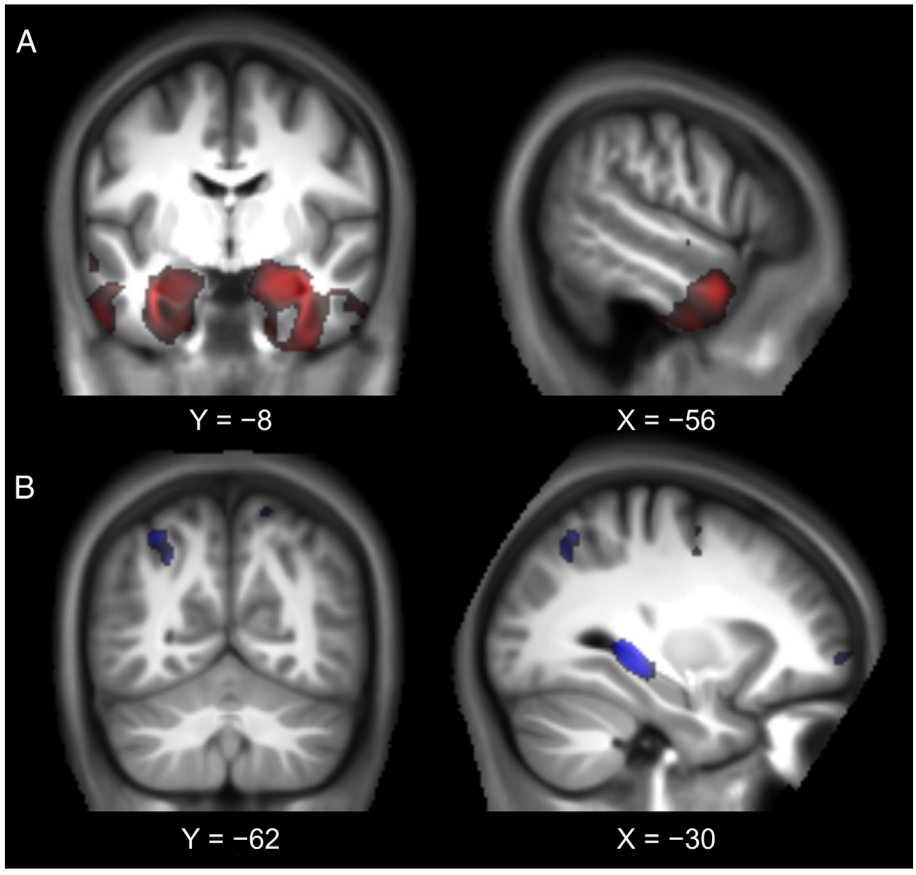

Fig. 3. Structural covariance captured by the second latent variable. Red color indicates areas that covary positively with the anterior hippocampus and negatively with the posterior hippocampus, and blue color areas that covary positively with the posterior hippocampus and negatively with the anterior hippocampus. (A) Structural connectivity of the anterior hippocampus in women; (B) structural connectivity of the posterior hippocampus, predominantly in men.

observed by Kahn et al. (2008) during resting state. Conversely, the structural covariance associated with the posterior hippocampus was mainly evident in men. It included areas within the medial and lateral parietal lobes, the prefrontal cortex and cerebellum and again shows overlap with the findings of Kahn et al. (2008) who reported that dorsolateral prefrontal and posterior parietal regions were functionally connected to the posterior hippocampus during resting state.

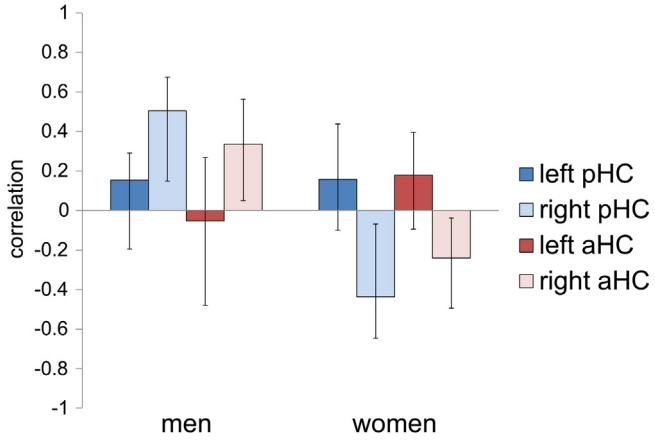

Fig. 4. Brain score–seed correlation patterns for the latent variable (LV) reflecting a sex × laterality interaction in the non-rotated PLS ($p = .016$). The bars represent the extent to which the seeds relate to the voxel salience pattern captured by the LV for the left and right, anterior and posterior seeds, as a function of sex. The latent variable shows structural covariance of the right hippocampus that differs significantly between men and women.

Earlier studies on hippocampal structural covariance with the rest of the brain are sparse, but suggest hippocampal volume as a whole covaries with that in surrounding regions, such as the amygdala and

Table 3
Brain areas where volume covaries positively with right hippocampal volume in men (positive saliences) and women (negative saliences) in the non-rotated PLS analysis explicitly contrasting the left and right hippocampal seeds in men and women. Coordinates and bootstrap ratios (BSR) are reported for the peak voxel of each cluster.

	Voxels	MNI coordinates			BSR
		X	Y	Z	
Positive saliences					
Insula (R)	451	44	17	−8	4.76
Middle frontal gyrus (R)	145	30	21	41	3.75
Orbital inferior frontal gyrus (R)	425	29	27	−23	3.82
Superior medial frontal gyrus (R)	239	5	26	57	3.46
Medial orbitofrontal gyrus (L)	115	−2	63	−6	3.86
Precuneus (L)	79	−17	−35	56	3.29
Cerebellum (L)	145	−20	−72	−45	3.58
Parahippocampal gyrus (L)	81	−33	−27	−18	3.23
Insula (L; extending into orbital inferior frontal gyrus and temporal pole)	1,766	−44	8	−6	4.67
Negative saliences					
Middle temporal gyrus (R)	109	50	−47	−2	−3.55
Fusiform gyrus (R)	91	44	−18	−42	−3.59
Fusiform gyrus (R)	86	33	−3	−44	−3.88
Precuneus (R)	60	15	−38	3	−3.46
Calcarine sulcus (L)	169	0	−99	0	−3.52
Superior occipital gyrus (L)	143	−12	−89	18	−3.69
Superior parietal gyrus (L)	115	−32	−48	56	−3.72
Middle occipital gyrus (L)	60	−39	−77	9	−4.00

Bootstrap ratios (BSRs) indicate the reliability of the voxels and are proportional to *z* scores. Voxels with BSR > 3 are considered reliable. Clusters exceeding 50 voxels are reported.

Table 4
Performance on the episodic and spatial memory tasks as a function of gender.

	Men	Women
Pointing, pointing error (degrees)*	21.7 (10.8)	43.6 (14.6)
Water maze, latency (s)*	20.2 (7.4)	30.8 (10.0)
Word list, d′[a]	2.1 (.6)	2.0 (.4)
Object location		
Object recognition, d′	2.2 (.5)	2.2 (.4)
Location memory, hit ratio	.5 (.2)	.4 (.1)

* The groups differed at $p < .001$, two-sample t-test.
[a] One female participant excluded due to missing data.

the parahippocampal, perirhinal, entorhinal, and orbitofrontal cortices (Bohbot et al., 2007). Here we have shown that hippocampal covariance differs between the anterior and posterior hippocampus. We also extend earlier functional findings of distinct anterior and posterior resting state functional connectivity (Kahn et al., 2008) to brain morphology, and show that men and women differ in the strength of the respective patterns of structural covariance. Indeed, the anterior hippocampal connectivity pattern was unique to the women in our sample. This was in contrast to the posterior hippocampal network which was predominantly driven by men, while the association with the posterior seed for women was only marginally significant. The finding of a more marked anterior hippocampal network in women and posterior network in men can be related to reported sex differences in the developmental trajectories of the hippocampus, where girls show a decrease in the posterior-most aspect of the hippocampus, while boys show a decrease in the anterior-most aspect, between 4 and 15 years of age (Gogtay et al., 2006). Although the posterior hippocampus being larger in women than in men in our sample might seem at odds with these findings, the decrease in volume for women was only found in the posterior-most part, while the overall part of the posterior hippocampus showed an increase with age that was seemingly larger in women than in men (Gogtay et al., 2006).

The underlying causes of structural covariance are still unclear (Alexander-Bloch et al., 2013a). Just as our findings are in line with observed functional covariance during resting state (Kahn et al., 2008; Poppenk and Moscovitch, 2011), other studies have found a convergence between structural covariance and functional connectivity (Kelly et al., 2012; Spreng and Turner, 2013) as well as white matter tracts (Gong et al., 2012), and a significant portion of structural covariance can be attributed to synchronized maturation of brain regions (Alexander-Bloch et al., 2013b). As for sources of sex differences in structural covariance, there are various brain areas that differ in volume between men and women (Sacher et al., 2013), at least partly due to variation in sex hormone concentrations (Witte et al., 2010). On top of this, men and women may recruit the brain differently throughout life, as reflected during various tasks (e.g. Gong et al., 2011; Sacher et al., 2013; Stevens and Hamann, 2012), including during resting state (Azari et al., 1992; Biswal et al., 2010; Kilpatrick et al., 2006). As brain volume often increases with use (Draganski et al., 2006; Maguire et al., 2000), repeated co-use of certain regions is likely to increase the volumetric covariance between these regions.

Table 5
Correlations between spatial and episodic memory performance and volume of the anterior and posterior hippocampus in men and women.

	aHC		pHC	
	Men	Women	Men	Women
Pointing, pointing error (degrees)	−.14	.12	−.06	.16
Water maze, latency (s)	−.09	−.09	.02	.00
Word list, d′ [a]	−.20	−.10	−.46*	.31
Object location				
Object recognition, d′	−.20	−.06	.00	.12
Location memory, hit ratio	−.22	−.08	−.05	.06

[a] One female participant excluded due to missing data. aHC = anterior hippocampus; pHC = posterior hippocampus.
* $p < .01$.

Here, the hippocampus covaried with a region anterior of the thalamus, likely including the mammillary bodies, as well as the posterior cingulate cortex and retrosplenial cortex. These areas receive projections from the hippocampus via fornix (Duvernoy, 2005) and have been implicated in both episodic and spatial memory (Epstein, 2008; Vandekerckhove et al., 2005; Vann, 2010). In women, the anterior hippocampus covaried with the adjacent parahippocampal gyrus, which comprises the entorhinal and perirhinal cortex, anteriorly, providing input to the hippocampus (Duvernoy, 2005). The perirhinal cortex is implicated in item memory (Davachi, 2006) and coactivates with the hippocampus during associative retrieval (Staresina et al., 2013), implicating it in episodic memory. Additionally, the anterior temporal lobe has been implicated in semantic memory (Rogers et al., 2006). In contrast, and more prominently in men, the posterior hippocampus covaried with regions such as the parahippocampal cortex and the posterior parietal cortex. The posterior parahippocampal cortex is known to represent the spatial layout of the local scene (Epstein, 2008) while the posterior parietal cortex holds an egocentric representation of space (Ciaramelli et al., 2010). Consequently, these regions, together with the hippocampus, are implicated in spatial cognition and navigation (Burgess, 2008; Spiers and Maguire, 2007). In line with this, it has recently been shown that the resting state functional connectivity of the anterior and posterior medial temporal lobe reflects functional differences such that regions that are part of the posterior network are involved in encoding spatial associations while the anterior network is activated during associative encoding overall (Ritchey et al., 2013). These results, together with our findings, make plausible a division of labor between the anterior and posterior hippocampus with regards to episodic and spatial memory.

We did not initially in our data-driven analyses observe any difference in laterality between men and women in terms of structural covariance or volume of the hippocampus, but instead it was location within the hippocampus (anterior vs. posterior) that mattered. When explicitly testing the potential effect of laterality, structural covariance associated with the right hippocampus differed significantly between men and women. In men, the right hippocampus covaried with large regions within the bilateral insula, extending into orbital frontal areas. The insula and hippocampus have been shown to be corecruited in the left hemisphere during mental navigation, possibly reflecting a role of the insula in mentally representing the body in space (Ghaem et al., 1997). Of note was also contralateral covariance with the parahippocampal cortex, a region involved in spatial representations (Epstein, 2008). In women, the right hippocampus covaried positively with right ventral temporal areas, probably reflecting the anterior temporal lobe regions we found to covary with the anterior hippocampus. Both men and women showed structural covariance with the precuneus, albeit within different subregions. This structure is involved in both navigation and episodic memory retrieval, through its role in mental imagery (Cavanna and Trimble, 2006; Hirshhorn et al., 2012). The laterality effects found here may be reflective of the commonly observed sex differences in spatial and episodic memory performance, and may suggest that the way the right hippocampus interacts with the rest of the brain differs between men and women.

In terms of behavior, men excelled in the spatial tasks in this study, replicating earlier findings (Astur et al., 1998; Lawton and Morrin, 1999; Persson et al., 2013). However, the frequently observed female advantage on episodic tasks was not replicated. Both groups performed at a rather moderate level, which may have contributed to the lack of a sex difference. Although often observed, the female advantage in episodic memory is usually smaller than the male spatial advantage (Herlitz and Rehnman, 2008) and is more robust when using free recall rather than recognition to assess memory (Herlitz et al., 1999). Only the episodic word list task showed a relationship with hippocampal volume and structural covariance, and this effect was only present in men,

Table 6
Correlations between brain scores and spatial and episodic memory performance for the latent variables (LVs) from the seed (LVs 1–2) and non-rotated PLS (sex × laterality contrast LV).

	LV1[a]		LV2[b]		Sex × laterality contrast LV[c]	
	Men	Women	Men	Women	Men	Women
Pointing, pointing error (degrees)	−.07	.25	−.01	−.07	.03	−.03
Water maze, latency (s)	−.07	−.03	−.18	−.03	−.16	−.01
Word list, d′ [d]	−.40*	−.01	.20	−.23	.18	−.10
Object location						
Object recognition, d′	−.06	.03	−.20	−.06	−.16	.01
Location memory, hit ratio	−.08	.21	−.17	−.03	−.14	.03

[a] Seed PLS; LV reflecting structural covariance of both anterior and posterior hippocampus in men, and mainly the anterior hippocampus in women.
[b] Seed PLS; LV reflecting structural covariance of the posterior hippocampus in men, and mainly the anterior hippocampus in women.
[c] Non-rotated PLS explicitly contrasting laterality in men and women; LV reflecting structural covariance of the right hippocampus in men and women.
[d] One female participant excluded due to missing data.
* $p < .05$.

where a smaller posterior hippocampus was beneficial to performance. Further, a negative association with hippocampal volume covariance was found for the first latent variable, reflecting that this covariance pattern is not beneficial for episodic memory. Negative associations between volume and performance have been observed previously. In a meta-analysis, Van Petten (2004) did not find any support for a simple bigger-is-better relationship. Instead, the nature of the hippocampus volume–memory performance association depended on the age group under study, where a smaller hippocampus was beneficial for memory in children and younger adults. Similarly, DeMaster et al. (2013) recently found a negative association between the right hippocampal head volume and episodic memory. Such a negative relationship could also potentially explain the present finding of a large posterior hippocampus in women compared to men, if greater volume in this region is associated with worse spatial performance. No such relationship was found, however. Note that the negative associations that we did observe here should be interpreted with caution, since the large number of comparisons increases the risk of spurious findings.

Except for these negative associations, no correspondence between the structural covariance of the hippocampus and memory performance was found. This suggests that the clear sex difference observed on the structural level does not relate directly to sex differences in behavior, and likely implies that it is not how the brain is structured per se that matters for performance, but rather how this structure is used on a functional level. The structural covariance patterns may reflect more general neuronal organization, and it is likely the specific functional recruitment of this neuronal organization that explains performance on a given task, thus mediating the relationship between structural covariance and memory. As mentioned above, there is evidence of a significant relationship between structural covariance and functional connectivity (Alexander-Bloch et al., 2013a), and the overlap between our findings and the intrinsic connectivity of the medial temporal lobe reported by Kahn et al. (2008) similarly suggests a structure–function coupling that could act as a mediator between structural covariance and behavior.

It should be noted that the template-based approach used here to define hippocampal volume is always susceptible to error due to misregistration of the individual brains. This could potentially have an influence on the results in this study, although the relatively large number of participants increases the reliability of the volume estimates. Furthermore, the structural covariance patterns observed here are in line with earlier findings (Duvernoy, 2005; Kahn et al., 2008), speaking to the validity of the current approach. Still, it would be worthwhile to replicate these results using manual tracing to define the seed volumes.

Conclusions

Here, using a novel approach to study structural covariance, we demonstrate distinct structural patterns associated with the anterior and posterior hippocampi, respectively. Furthermore, we show that these covariance patterns differ as a function of sex, with the anterior pattern found in women and the posterior pattern in men. The results show high similarity to the intrinsic functional coupling of the hippocampus and suggest that sex is an important factor to take into account when studying brain morphology. Future studies should focus on disentangling the undoubtedly complex structure–function–behavior relationship in general, as well as the relationship between hippocampal structure, function and memory.

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