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ABSTRACT

The hippocampus is a brain region critical for learning and memory, and is also implicated in several neuropsychiatric disorders that show sex differences in prevalence, symptom expression, and mean age of onset. On average, males have larger hippocampal volumes than females, but findings are inconclusive after adjusting for overall brain size. Although the hippocampus is a heterogenous structure, few studies have focused on sex differences in the hippocampal subfields – with little consensus on whether there are regionally specific sex differences in the hippocampus after adjusting for brain size, or whether it is important to adjust for total hippocampal volume (HPV). Here, using two young adult cohorts from the Queensland Twin IMaging study (QTIM; N = 727) and the Human Connectome Project (HCP; N = 960), we examined differences between males and females in the volumes of 12 hippocampal subfields, extracted using FreeSurfer 6.0. After adjusting the subfield volumes for either HPV or brain size (brain segmentation volume (BSV)) using four controlling methods (allometric, covariate, residual and matching), we estimated the percentage difference of the sex effect (males versus females) and Cohen's *d* using hierarchical general linear models. Males had larger volumes compared to females in the parasubiculum (up to 6.04%; Cohen's $d = 0.46$) and fimbria (up to 8.75%; $d = 0.54$) after adjusting for HPV. These sex differences were robust across the two cohorts and multiple controlling methods, though within cohort effect sizes were larger for the matched approach, due to the smaller sub-sample. Additional sex effects were identified in the HCP cohort and combined (QTIM and HCP) sample (hippocampal fissure (up to 6.79%), presubiculum (up to 3.08%), and hippocampal tail (up to −0.23%)). In contrast, no sex differences were detected for the volume of the *cornu ammonis* (CA)2/3, CA4, Hippocampus-Amygdala Transition Area (HATA), or the granule cell layer of the dentate gyrus (GCDG). These findings show that, independent of differences in HPV, there are regionally specific sex differences in the hippocampus, which may be most prominent in the fimbria and parasubiculum. Further, given sex differences were less consistent across cohorts after controlling for BSV, adjusting for HPV rather than BSV may benefit future studies. This work may help in disentangling sex effects, and provide a better understanding of the implications of sex differences for behaviour and neuropsychiatric disorders.

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1. Introduction

Males, on average, have larger total brain volumes than females. Regional brain volumes also show size differences in this direction, but these findings are inconsistent once intracranial or total brain volume is used as a correction factor (Kaczkurkin et al., 2019; Ritchie et al., 2018). As such, both smaller (Malykhin et al., 2017; Nordenskjöld et al., 2015) and larger total hippocampal volumes in males versus females have been reported (Lotze et al., 2019; Pintzka et al., 2015; Raz et al., 2004), as well as no differences at all (Ritchie et al., 2018). Studies of young adults (Gur et al., 2002; Narr et al., 2004; Neufang et al., 2009; Satterthwaite et al., 2014; Schriber et al., 2017; Takahashi et al., 2006; Tamnes et al., 2018; Wierenga et al., 2017) show similar inconsistencies to those in middle-aged and older adults with regard to sex differences in overall hippocampal volume. This inconsistency may be due to the small effect size of hippocampal volume differences between males and females, as well as heterogeneity across samples and the use of different methods to adjust for brain size across studies. Further, while total hippocampal volume might not differ between males and females, sex differences at the regional level might be more pronounced and may account to some extent for functional differences, as well as differences between males and females observed in subfield-specific hippocampal cognition tasks and prevalence rates or symptom expression for disorders involving the hippocampus. Even so, an important question is whether it is more relevant to adjust for total hippocampal volume as opposed to total brain size. Prior work has not examined sex differences in the hippocampal subfields after adjusting for differences in total hippocampal volume. Even after controlling for brain size, hippocampal subfield volumes may still be driven by sex differences in overall hippocampal volume. Thus, to gain a clearer understanding of region-specific sex differences in the hippocampus we adjusted for total hippocampal volume (HPV), as well as overall brain size (Brain Segmentation Volume; BSV). We also restricted our focus to sex differences that were robust across controlling methods and replicated across two large young adult imaging cohorts.

Animal work shows consistent evidence for hippocampal subregion-specific sex differences in morphology – in the dentate gyrus, *cornu ammonis* (CA) 1, and CA3 (see review Yagi and Galea, 2018). Human imaging studies, with no adjustment for brain size, report larger volumes for males than females (Krogsrud et al., 2014; Malykhin et al., 2017; Tamnes et al., 2014, 2018) in all subfields, with the exclusion of the hippocampal fissure (Krogsrud et al., 2014; Tamnes et al., 2014, 2018) and fimbria (Krogsrud et al., 2014). However, only a few studies, often using small samples, have examined sex differences in the hippocampal subfield volumes adjusted for brain size. An earlier study using a small sample and wide age range (Mueller et al., 2007) (N = 42, 33% female, aged 21–85 yrs) found females had larger volumes for the CA2. Two more recent studies (Kurth et al., 2017; Malykhin et al., 2017) (N = 129, 54% female, aged 18–85 yrs; N = 96, 50% female, aged 18–69 yrs) also found females had larger volumes than males for total CA, as well as volumes of the dentate gyrus and subiculum. These sex differences in subfield volumes may reflect differences in functions associated with these subfields, such as neuroplasticity, memory formation and retrieval, and spatial and object-based memory (Aggleton and Christiansen, 2015; Krogsrud et al., 2014; Lewis, 2017). However, a recent developmental study in a large sample (N = 270, scanned three times; 53.7% females; aged 8–28.7 yrs) (Tamnes et al., 2018) showed that while there are parallel developmental trajectories of the subfields for males and females, the volume of the Hippocampus-Amygdala Transition Area (HATA) was larger for males than for females (adjusted for brain size). The HATA is part of the hippocampal-amygdala network involved in contextual fear learning (Fudge et al., 2012), and differences in volume may reflect behavioural differences found on emotional learning and memory (Whittle et al., 2011).

In addition to sex differences in subfield volumes, reduced functional connectivity of brain networks that include the hippocampus have been reported in males compared to females (Scheinost et al., 2015). After adjusting for total brain size, the posterior hippocampus showed greater structural covariance with the medial and lateral parietal lobes and the prefrontal cortex in males than in females (Persson et al., 2014), and the anterior hippocampus showed structural covariance with the anterior temporal lobes in females but not in males (Persson et al., 2014). Similarly, sex differences have been found in white matter microstructure pathways to and from the hippocampus, as reflected by higher fractional anisotropy (FA) in males than females (Chou et al., 2011).

Several fMRI studies have linked activity in specific subfields to specific memory processes, for example relating CA1 to match/mismatch detection (Duncan et al., 2012) and allocentric spatial computations (Suthana et al., 2009), as well as CA2/3 and the dentate gyrus to differentiating contextual representations (Copara et al., 2014) and pattern separation (Bakker et al., 2008). However, others have not found evidence for differentiated task activity across subfields (Kyle et al., 2015). Further, the volume of CA3 and the dentate gyrus has been associated with encoding and early retrieval of information, while the volume of CA1 has been associated with consolidation and late retrieval (Mueller et al., 2011). More recent neuroimaging studies of older adults further showed that volume size of the dentate gyrus predicted pattern separation performance (Dillon et al., 2017), while CA3 volume predicted object recognition memory (Dillon et al., 2017). Also, smaller volumes of CA1 and subiculum have been associated with poorer episodic memory retrieval (Zammit et al., 2017). The link between task activity and volume remains unclear; however, recent work (Carr et al., 2017) showed that including structural (i.e. subfield thickness) and functional measures (i.e. task activity) explained differences in memory performance better than measures derived from one modality. Sex differences in subfield volumes could be associated with sex differences observed in hippocampal-dependent tasks, such as on average, better performance for males than females on visuospatial processing (Parsons et al., 2004), and on average, better performance for females than males on episodic memory (Herlitz et al., 1997). In addition, there is some evidence linking volume changes in specific hippocampal subfields to a particular disorder (Burkert et al., 2015; Cao et al., 2017; Haukvik et al., 2018) – although results across studies are inconsistent. For example, Cao et al. (2017) found reduced volumes in specific subfields to be associated with bipolar disorder (left CA4, granule cell layer, molecular layer, and bilateral hippocampal tail) but not with major depressive disorder (MDD). For many of these disorders (e.g. anorexia nervosa, schizophrenia, mood disorders), there are sex differences in symptom expression, time of onset, or prevalence rates (McCarthy, 2016). Thus, a clearer understanding of sex differences in hippocampal subfield volumes in young adults may provide insights into sex differences observed at a behavioural level.

Recently, it has been shown that adjusting versus not adjusting for brain size (Brun et al., 2009; Luders et al., 2006a, 2006b, 2014), as well as different adjusting methods (Fjell et al., 2009; Nordenskjöld et al., 2015; Pintzka et al., 2015; Sanchis-Segura et al., 2019) can lead to different results when assessing regional sex differences in the brain, and are a contributing factor to the mixed findings of sex differences reported in the literature. The most common approaches to brain normalization are the proportion, residual, covariate, and matching methods (Nordenskjöld et al., 2015). Recently, the proportion method has been shown to lead to systematic errors (Nordenskjöld et al., 2015; O'Brien et al., 2011; Pintzka et al., 2015), and as brain structures vary in how they scale to brain size (de Jong et al., 2017), an allometric scaling method is recommended (Mankiw et al., 2017; Reardon et al., 2016). This uses a log-log regression to define the scaling relationship between each brain region and brain size to regress out brain size. Even so, all approaches – allometric, covariate, residual, and matching methods have their own limitations (Sanchis-Segura et al., 2019). In particular, differences between log-transformed and original data (Feng et al., 2014; Rodríguez-Barranco et al., 2017), highly correlated variables in the model (Nordenskjöld et al., 2015; Pintzka et al., 2015), unbalanced groups (Nordenskjöld et al., 2015) or different regression slopes (O'Brien et al.,

2011), and reduced sample sizes (Nordenskjöld et al., 2015) are known to influence results. Not one controlling method is ideal, and discrepancy between methods resulting in differences in effect sizes could lead to mixed findings.

Previous inconsistent findings may also be explained by differences in total hippocampal volume. Here, using data from two large independent imaging cohorts with a similar age range (N = 727; N = 960), we tested for region-specific sex differences in the hippocampus by adjusting for HPV, as well as BSV. We used four common statistical methods (i.e. allometric, covariate, residual, and matching) to adjust for HPV (and BSV). Based on evidence from animal work and human imaging studies, we expect some subfield volumes (i.e. CA, dentate gyrus, subiculum, and HATA) to show sex differences. In particular, we hypothesize that these volumes are larger in females than males (except for the HATA) after adjusting for BSV, but the effect may be in the opposite direction once accounting for differences in HPV.

2. Materials and methods

2.1. Participants

This study examined data from two independent imaging cohorts: the Queensland Twin IMaging (QTIM) study, and the Human Connectome Project (HCP). The QTIM sample comprised 727 young adult twins (mean age = 23.94 ± 2.45 yrs; ranging from 21 to 30, 63.5% female) from South-East Queensland, Australia. All twins were right-handed. Those with developmental, neurological or psychiatric disorders, impaired intellectual functioning, or head trauma were excluded. The Human Connectome Project (HCP) release S1200 (Van Essen et al., 2012) comprised 960 right-handed twins and their non-twin siblings (mean age = 28.78 ± 3.73 yrs; range 22–36, 55.5% female), primarily from Missouri, United States (Van Essen et al., 2013). Exclusion criteria included neurodevelopmental, neuropsychiatric or neurological disorders, as well as severe health conditions, such as diabetes, multiple sclerosis and cerebral palsy, and premature birth (Van Essen et al., 2013). For consistency, as the QTIM cohort only included right-handed individuals, we further excluded left-handed individuals from HCP. All QTIM and HCP participants gave written informed consent, and both studies were approved by the relevant institutional review boards.[1]

2.2. MRI acquisition and image processing

QTIM structural scans were obtained at 4-T (Siemens Bruker), acquiring a coronal 3D-structural T1-weighted image (T1/TR/TE = 700/1500/3.35 ms; flip angle = 8°, FOV = 256 x 256, voxel size = 0.9375 × 0.9375 × 0.9 mm). A further 194 participants acquired with a sagittal acquisition were excluded from these analyses due to vascular pulsation phase-encoded motion artefacts in the temporal lobe, which affected hippocampal subfield segmentation. Test-retest scans were available for 66 individuals (mean age = 23.45 ± 2.27 yrs; ranging from 21 to 29, 62.12% female). For HCP, the scans were obtained at 3-T (Siemens Connectome Skyra), acquiring a 3D-structural T1-weighted image (T1/TR/TE = 1000/2400/2.14 ms; flip angle = 8°, FOV = 224 x 224, voxel size = 0.7 x 0.7 × 0.7 mm), and a 3D-structural T2-weighted image (TR/TE = 3200/565 ms; flip angle: variable, FOV = 224 x 224, voxel size = 0.7 x 0.7 × 0.7 mm). Test-retest scans were available for 40 individuals (mean age = 30.25 ± 3.26 yrs; ranging from 22 to 35, 67.50% female).

BSV (including grey and white matter and cerebrospinal fluid) was already available, processed with FreeSurfer 5.3 (Fischl, 2012). Detailed post-processing quality checks were performed in line with procedures used in the ENIGMA consortium (http://enigma.ini.usc.edu/protocols/imaging-protocols/). Then, we used FreeSurfer's 6.0 hippocampal subfield segmentation module (Iglesias et al., 2015). Version 6 is an improvement on FreeSurfer's version 5.3 hippocampal subfield module (Iglesias et al., 2015; Whelan et al., 2016), as the probabilistic atlas is based on manual labels from ex-vivo data (Iglesias et al., 2015). Using the T1-weighted images for the QTIM cohort, and both the T1-and T2-weighted images for HCP, we extracted 12 hippocampal subfields from each hemisphere, including (in size order from smallest to largest): the parasubiculum, HATA, fimbria, hippocampal fissure, CA3 (includes both CA2 and CA3 as these regions have indistinguishable MRI contrast – named CA2/3 in further analyses), CA4, presubiculum, granule cell layer of dentate gyrus (GCDG), subiculum, molecular layer, hippocampal tail, and CA1. We computed a measure of total HPV by summing over the subfields, but excluding the hippocampal fissure, which is a measure of cerebrospinal fluid (Tamnes et al., 2018). We then averaged over left and right subfields, after finding little evidence of a sex by hemisphere effect (Appendix A, Tables A1 and A2). Test-retest reliability of these averaged subfield volumes was computed with the Intraclass Correlation Coefficient (ICC) (absolute agreement) between measures derived from two different timepoints, for the QTIM and HCP cohort separately.

2.3. Statistical analyses

We examined associations between sex and hippocampal subfield volumes while accounting for genetic relatedness of participants (twins and siblings from the same family), using hierarchical general linear models (HGLM) (Rönnegård, 2010) in the R Statistics package version 3.4.4 (R Core Team, 2018). Sex was included as a fixed effect and relatedness as a random effect, with individuals weighted for relatedness using a pedigree-based kinship matrix (QTIM: 727 x 727, HCP: 960 x 960) (Therneau, 2015). For the combined QTIM and HCP sample we included a cohort variable, which was used as a covariate in the HGLM, or as an additional regression variable.

We estimated both the percentage difference of the sex effect and Cohen's *d*, based on the fixed effect estimates for sex derived from the HGLM. The latter measure of effect size is the standardized difference between male and female means, which allows comparison across the different subfield volumes as well as with other studies (Del Giudice, 2019). As the 12 hippocampal subfield volumes were correlated with one another (Appendix B), we used a Matrix Spectral Decomposition (MatSpD) algorithm (Nyholt, 2004) and estimated the number of independent variables to be 9.24 in QTIM, 8.12 in HCP, and 9.24 in the combined sample, with Bonferroni-corrected significance thresholds of $p \leq .0054$, $p \leq .0062$ and $p \leq .0054$ respectively.

Sex differences were examined using four adjusting methods. For the allometric scaling method, we applied a log-log regression (Mankiw et al., 2017; Reardon et al., 2016) – regressing out either HPV or BSV for each subfield volume by using the logs for the respective volumes, and using the residuals of the subfield volumes as dependent variables in the HGLM. In addition, we examined whether there were any sex differences in allometric scaling by testing the following model in the HGLM: $\log_{10}(\text{subfield volume}) = ß_0 + ß_1(\log_{10}(\text{BSV})) + ß_2(\text{Sex}) + ß_3(\log_{10}(\text{BSV})*\text{Sex})$ (as has previously been done by Mankiw et al., 2017; Reardon et al., 2016). This was performed separately for HPV and BSV. In the covariate method we adjusted results by including either HPV or BSV as a covariate in the model. In the residual method, we regressed out the effect of the covariate(s) on regional volumes (Nordenskjöld et al., 2015; Pintzka et al., 2015) by removing the estimated linear association between the raw subfield volumes and the covariate(s) (Nordenskjöld et al., 2015), and used the residuals of the subfield volumes as dependent variables in the HGLM. Finally, in the matched sample method, we matched females and males for HPV or BSV. As has been done previously (Pintzka et al., 2015), we used a maximum 10 ml (10,000 mm) volume difference to match an individual BSV for a male to a female, with a

[1] The QTIM study was approved by the Human Research Ethics Committees of The University of Queensland and the QIMR Berghofer Medical Research Institute. Approval for the HCP was obtained from the Institutional Review Board (IRB) # 201204036; Title: 'Mapping the Human Connectome: Structure, Function, and Heritability'.

balanced direction of difference across sex. For HPV, we used a maximum 30 mm volume difference, as HPV was approximately 0.30% of BSV in our two samples. Matching was done within each cohort using the FUZZY command in the program SPSS (IMB SPSS Statistics 25.0); script provided in Appendix C. This procedure finds all potential (opposite-sex) matches for an individual, with a maximum 30 mm (HPV) or 10 ml (BSV) difference, and randomly chooses a match from this list (i.e. a match is not based on the smallest difference). This sampling is done without replacement, making the individuals that are already matched unavailable for further matches (Peck, 2011). For the QTIM cohort, 368 individuals (286 families) could be matched to a member of the opposite sex for HPV, and 262 individuals (207 families) for BSV. For the HCP cohort, 546 individuals (333 families) were matched for HPV and 372 individuals (251 families) for BSV (Appendix D). No age-by-sex interactions were observed ($p \leq .0054$) (Appendix E), hence age was not considered a variable to control or match for in our final analyses.

To further explore indications of sex differences, we conducted a *post hoc* analysis to compute the ICC between measures derived in monozygotic (MZ, identical: N = 160 complete pairs) and dizygotic (DZ, fraternal) twins (same sex DZ: N = 112 complete pairs; opposite-sex DZ: N = 84 complete pairs) in the full QTIM sample. Sex differences are indicated if DZ opposite sex correlations are lower than DZ same-sex correlations.

3. Results

Table 1 shows the Mean ± SD (range) for the 12 hippocampal subfields, HPV, and BSV, for the QTIM and HCP cohorts, separately for males and females. As expected, unadjusted volumes were larger, on average, in males than in females for all hippocampal subfields (QTIM: between 7.37 and 14.84% larger in males; $d = 0.74$ to 0.87; HCP: 6.58–15.06% larger in males; $d = 0.61$ to 1.00), HPV (QTIM: 8.61% larger in males; $d = 1.18$; HCP: 9.72% larger in males; $d = 1.22$) as well as BSV (QTIM: 11.06% larger in males; $d = 1.58$; HCP: 12.69% larger in males; $d = 1.79$).

After adjusting for HPV, in both the QTIM and HCP cohorts, we found larger volumes in males than females for the parasubiculum (up to 6.04% larger in males; $d = 0.46$) and fimbria (up to 8.75% larger in males; $d = 0.54$) (Table 2, and Fig. 1). Additional sex effects were found in the HCP cohort, and also the combined (QTIM and HCP) sample, in the hippocampal fissure (up to 6.79% larger in males; $d = 0.58$), presubiculum (up to 3.08% larger in males; $d = 0.33$), and hippocampal tail (up to 2.23% smaller in males; $d = 0.20$) (Table 2, Appendix F). There was no evidence for sex differences for four of the subfields: HATA, CA2/3, CA4, and GCDG (Table 2, and Fig. 1) across cohorts after adjusting for either HPV or BSV. Across the four controlling methods there was strong consistency (Table 2, Fig. 1). Even so, we note that not all sex differences were below the cut-off (*p*-value controlled for multiple testing, $p < .0054$) across cohorts and across the four controlling methods. In particular, using the matched method the sex effect for the parasubiculum in the QTIM cohort showed a similar direction of effect, but failed to reach the threshold ($p < .0054$). Also, the sex effect for the hippocampal fissure was greater in HCP than QTIM.

Adjusting for BSV (Table 2; Appendix G), also revealed, in both cohorts, that males have larger volumes for the fimbria and hippocampal fissure. However, whereas in the QTIM cohort the parasubiculum, presubiculum, subiculum, hippocampal tail, and CA1 subfield volumes were

Table 1
Mean ± SD (range), Cohen's *d* and percentage difference (males versus females) for hippocampal subfields, total hippocampal and brain segmentation volumes (mm^3; unadjusted for Brain Segmentation Volume (BSV)) for the QTIM and HCP cohorts.

	QTIM (N = 727)[a]		*d*	*% diff*	HCP (N = 960)[a]		*d*	*% diff*
	Females (N = 462) (23.94yrs ± 2.45)	*Males* (N = 265) (23.93yrs ± 3.64)			*Females* (N = 533) (29.51yrs ± 3.64)	*Males* (N = 427) (27.88yrs ± 3.64)		
	mean ± SD	*mean ± SD*			*mean ± SD*	*mean ± SD*		
Parasubiculum	59.23 ± 6.59 (40.54–79.23)	66.19 ± 8.07 (37.55–92.31)	0.90**	10.17	63.83 ± 8.64 (38.41–88.72)	72.08 ± 10.48 (47.75–105.92)	0.92**	12.07
HATA	65.14 ± 7.06 (45.80–85.71)	71.38 ± 7.49 (52.79–94.68)	0.81**	8.57	66.12 ± 8.52 (43.41–90.03)	73.44 ± 9.80 (43.02–102.71)	0.84**	10.39
Fimbria	67.18 ± 12.41 (34.65–107.26)	79.29 ± 13.99 (44.83–121.86)	0.87**	14.84	98.51 ± 15.76 (52.90–145.01)	115.87 ± 19.09 (60.07–175.26)	1.00**	15.06
Hippocampal Fissure	149.52 ± 20.34 (103.87–210.15)	163.5 ± 20.58 (110.50–215.15)	0.65**	8.46	113.18 ± 14.27 (76.62–163.38_	130.13 ± 16.29 (88.30–182.09)	1.10**	12.93
CA2/3	214.03 ± 22.02 (155.75–280.62)	233.86 ± 27.17 (154.89–306.10)	0.79**	8.41	212.39 ± 23.59 (139.99–289.90)	231.28 ± 27.45 (163.91–319.36)	0.84**	9.09
CA4	259.69 ± 21.06 (206.60–320.46)	282.38 ± 24.73 (208.76–347.90)	0.95**	7.87	255.43 ± 24.30 (188.33–323.27)	282.59 ± 27.00 (213.99–364.19)	1.14**	10.19
Presubiculum	293.10 ± 26.04 (234.14–366.43)	323.45 ± 28.92 (245.25–420.75)	1.02**	9.00	286.33 ± 29.78 (213.11–384.45)	318.79 ± 35.15 (220.56–420.73)	1.08**	10.83
GCDG	299.27 ± 23.88 (237.33–373.89)	326.28 ± 27.75 (242.20–398.35)	1.00**	8.08	315.09 ± 30.21 (232.66–398.20)	348.99 ± 33.78 (264.79–446.11)	1.12**	10.17
Subiculum	399.72 ± 35.98 (303.48–513.02)	440.18 ± 38.58 (352.27–555.19)	1.03**	9.03	431.39 ± 42.81 (331.04–559.34)	476.16 ± 49.05 (362.31–622.62)	0.98**	9.46
Molecular Layer	553.52 ± 43.30 (445.25–677.36)	607.08 ± 47.35 (478.62–732.03)	1.11**	8.58	437.06 ± 46.30 (318.15–590.56)	481.68 ± 50.40 (368.19–631.77)	0.97**	9.68
Hippocampal Tail	574.17 ± 57.70 (407.87–766.59)	618.32 ± 63.14 (426.58–801.66)	0.74**	7.37	526.86 ± 56.93 (352.66–712.23)	559.63 ± 65.13 (368.12–759.09)	0.61**	6.58
CA1	608.24 ± 51.77 (478.29–774.86)	671.65 ± 54.64 (516.64–838.22)	1.11**	9.16	680.71 ± 67.84 (507.08–854.62)	758.17 ± 78.69 (550.18–968.31)	1.07**	10.28
HPV	3393.3 ± 252.98 (2791.83–4148.21)	3720.06 ± 268.76 (2990.12–4492.72)	1.18**	8.61	3373.73 ± 285.37 (2672.78–4176.70)	3718.67 ± 318.04 (2883.87–4580.37)	1.22**	9.72
BSV	1080623.63 ± 74982.12 (876654–1275680)	1217924.95 ± 90930.00 (991247–1426970)	1.58**	11.06	1107406.61 ± 85142.81 (859947–1388501)	1262830.37 ± 98002.89 (989751–1580143)	1.79**	12.69

**$p \leq .0001$.

[a] After excluding participants with poor hippocampal segmentation (QTIM: N = 6; HCP: N = 22), or one or more outlying values (>3.29SD) for hippocampal subfields (QTIM N = 14; HCP: N = 38) or brain segmentation volume (HCP: N = 2). Outliers were calculated within each sex. Subfields are listed from small to large. HPV reflects the total hippocampal volume in mm^3, summing up all subfields except the hippocampal fissure. *Abbreviations: CA = Cornu Ammonis; HATA = hippocampus-amygdala-transition-area; GCDG = granule cell layer of dentate gyrus; HPV = total hippocampal volume; BSV = brain segmentation volume; SD = standard deviation; QTIM = Queensland Twin IMaging study; HCP = Human Connectome Project.*

Table 2
Sex differences (Cohen's *d*, percentage difference, and *p*-value) in hippocampal subfield volumes, after adjusting for total hippocampal volume (HPV) or brain segmentation volume (BSV), using four controlling methods (Allometric, Covariate, Residual, and Matched), in the QTIM, HCP, and combined samples.

	Adjusted for HPV									Adjusted for BSV								
	QTIM (N = 727[a]; 368[b])			HCP (N = 960[a]; 546[b])			Combined (N = 1,687[a]; 914[b])			QTIM (N = 727[a]; 262[b])			HCP (N = 960[a]; 372[b])			Combined (N = 1,687[a]; 634[b])		
	d	% diff	p	d	% diff	p	d	% diff	p	d	% diff	p	d	% diff	p	d	% diff	p
Parasubiculum																		
Allometric	0.23†	2.35	.003	0.29†	3.56	.000	0.26†	2.96	.000	0.23†	2.62	.003	0.09	1.08	.201	0.11*	1.59	.025
Covariate	0.28†	3.42	.000	0.33†	4.65	.000	0.27†	3.84	.000	0.38†	4.62	.000	0.15*	2.10	.048	0.18†	2.51	.001
Residual	0.23†	2.23	.003	0.29†	3.42	.000	0.26†	2.83	.000	0.23†	2.41	.003	0.09	1.06	.181	0.13*	1.44	.009
Matched	0.20	2.15	.058	0.46†	6.04	.000	0.28†	3.65	.000	0.45†	4.98	.001	0.19	2.51	.077	0.20*	2.59	.008
HATA																		
Allometric	0.01	0.09	.886	0.04	0.45	.502	0.03	0.28	.533	0.16*	1.63	.040	−0.03	−0.36	.635	0.04	0.44	.418
Covariate	0.00	0.02	.973	0.05	0.67	.360	0.04	0.48	.334	0.21*	2.39	.015	−0.05	−0.67	.486	0.05	0.68	.307
Residual	0.01	0.05	.933	0.06	0.54	.392	0.03	0.30	.486	0.16*	1.53	.045	−0.03	−0.32	.657	0.04	0.36	.483
Matched	0.09	0.80	.434	0.13	1.60	.137	0.05	0.59	.417	0.33*	3.35	.013	−0.01	−0.12	.929	0.07	0.83	.364
Fimbria																		
Allometric	0.36†	6.26	.000	0.33†	4.57	.000	0.36†	5.54	.000	0.21*	3.66	.008	0.14*	2.05	.035	0.05	2.99	.238
Covariate	0.45†	8.23	.000	0.37†	6.06	.000	0.27†	6.57	.000	0.30†	5.54	.001	0.21†	3.51	.004	0.18†	4.26	.000
Residual	0.36†	5.83	.000	0.33†	4.32	.000	0.35†	4.86	.000	0.21*	3.33	.008	0.14*	1.93	.032	0.18†	2.50	.000
Matched	0.54†	8.75	.000	0.51†	7.54	.000	0.31†	7.17	.000	0.38†	6.48	.004	0.32†	4.76	.004	0.22†	5.14	.000
Hippocampal Fissure																		
Allometric	0.12	1.46	.125	0.41†	4.27	.000	0.29†	3.28	.000	0.21*	2.85	.006	0.33†	3.95	.000	0.27†	3.65	.000
Covariate	0.14	1.86	.080	0.42†	5.52	.000	0.22†	4.00	.000	0.36†	4.83	.000	0.52†	6.75	.000	0.33†	5.88	.000
Residual	0.12	1.40	.127	0.40†	4.00	.000	0.27†	3.00	.000	0.22†	2.80	.005	0.33†	3.70	.000	0.28†	3.44	.000
Matched	0.17	2.15	.114	0.58†	6.79	.000	0.24†	4.43	.000	0.49†	6.24	.000	0.72†	8.63	.000	0.40†	7.08	.000
CA2/3																		
Allometric	−0.03	−0.25	.691	0.01	0.06	.914	−0.05	−0.44	.274	0.07	0.68	.382	0.00	0.00	.995	0.00	−0.15	.953
Covariate	−0.03	−0.30	.670	0.02	0.23	.709	−0.04	−0.42	.352	0.11	1.27	.189	−0.06	−0.69	.422	−0.01	−0.07	.916
Residual	−0.02	−0.17	.782	0.01	0.11	.829	−0.04	−0.35	.365	0.08	0.78	.295	0.00	0.03	.961	−0.01	−0.07	.879
Matched	0.06	0.65	.571	0.07	0.70	.445	−0.01	−0.08	.906	0.16	1.78	.220	−0.02	−0.22	.845	−0.01	−0.14	.873
CA4																		
Allometric	−0.17*	−0.70	.029	0.07	0.27	.304	−0.05	−0.21	.301	0.07	0.50	.378	0.04	0.27	.576	0.04	0.20	.373
Covariate	−0.09*	−0.78	.025	0.03	0.28	.340	−0.02	−0.24	.282	0.10	0.90	.197	0.01	0.07	.916	0.04	0.39	.388
Residual	−0.15*	−0.60	.046	0.07	0.27	.283	−0.04	−0.16	.382	0.08	0.53	.325	0.04	0.26	.580	0.03	0.19	.582
Matched	−0.02	−0.13	.873	0.16	1.16	.086	0.00	−0.01	.992	0.23	1.80	.087	0.08	0.64	.467	0.06	0.51	.420
Presubiculum																		
Allometric	0.12	0.72	.107	0.20†	1.46	.002	0.16†	1.08	.001	0.21†	1.78	.005	0.12	1.07	.072	0.16†	1.22	.001
Covariate	0.11*	1.13	.021	0.17†	1.93	.000	0.13†	1.41	.000	0.32†	3.09	.000	0.16*	1.82	.018	0.19†	2.03	.000
Residual	0.12	0.68	.107	0.20†	1.36	.003	0.16†	1.03	.001	0.21†	1.69	.005	0.12	1.01	.074	0.14†	1.17	.004
Matched	0.07	0.53	.500	0.33†	3.08	.000	0.15*	1.29	.023	0.52†	4.18	.000	0.22*	2.09	.047	0.28†	2.59	.000
GCDG																		
Allometric	−0.14	−0.53	.063	0.04	0.18	.502	−0.03	−0.13	.498	0.09	0.64	.241	0.01	0.11	.830	0.01	0.24	.803
Covariate	−0.06	−0.58	.061	0.02	0.19	.518	−0.02	−0.16	.453	0.13	1.15	.088	−0.01	−0.13	.833	0.04	0.41	.358
Residual	−0.13	−0.46	.088	0.05	0.18	.484	−0.03	−0.11	.536	0.10	0.65	.213	0.01	0.09	.844	0.03	0.20	.557
Matched	0.00	0.03	.973	0.13	0.94	.167	0.00	−0.18	.974	0.25	1.93	.062	0.08	0.63	.478	0.07	0.62	.321
Subiculum																		
Allometric	0.00	−0.01	.978	−0.08	−0.38	.256	−0.01	−0.04	.867	0.23†	1.92	.003	0.01	0.11	.844	0.08	1.00	.081
Covariate	0.01	0.14	.727	−0.02	−0.24	.526	−0.01	−0.08	.761	0.33†	3.21	.000	0.05	0.54	.448	0.14†	1.57	.002
Residual	0.01	0.07	.848	−0.07	−0.35	.279	−0.01	−0.04	.868	0.24†	1.87	.002	0.01	0.11	.832	0.11*	0.90	.022
Matched	−0.04	−0.30	.696	0.10	0.84	.275	−0.02	−0.18	.729	0.57†	4.53	.000	0.13	1.20	.227	0.21†	2.06	.003

(*continued on next page*)

Table 2 (*continued*)

	Adjusted for HPV									Adjusted for BSV								
	QTIM (N = 727[a]; 368[b])			HCP (N = 960[a]; 546[b])			Combined (N = 1,687[a]; 914[b])			QTIM (N = 727[a]; 262[b])			HCP (N = 960[a]; 372[b])			Combined (N = 1,687[a]; 634[b])		
	d	% diff	p	d	% diff	p	d	% diff	p	d	% diff	p	d	% diff	p	d	% diff	p
Molecular Layer																		
Allometric	−0.16*	−0.28	.038	−0.06	−0.31	.406	−0.06	−0.28	.191	0.19*	1.28	.015	0.04	0.35	.551	0.13†	0.68	.004
Covariate	−0.03*	−0.30	.043	−0.04	−0.46	.274	−0.02	−0.29	.217	0.24†	2.14	.001	0.05	0.54	.475	0.09*	1.30	.008
Residual	−0.15*	−0.26	.049	−0.06	−0.31	.389	−0.05	−0.19	.346	0.19*	1.23	.015	0.04	0.31	.579	0.10*	0.73	.050
Matched	−0.04	−0.24	.722	0.00	−0.03	.970	−0.03	−0.46	.350	0.48†	3.54	.001	0.02	0.16	.869	0.10*	1.39	.033
Hippocampal Tail																		
Allometric	−0.07	−0.50	.393	−0.20†	−1.71	.003	−0.19†	−1.53	.000	0.26†	2.64	.001	−0.01	−0.07	.915	0.09	0.59	.052
Covariate	−0.10	−1.04	.112	−0.20†	−2.23	.000	−0.16†	−1.83	.000	0.36†	3.73	.000	−0.03	−0.37	.682	0.10	1.15	.073
Residual	−0.07	−0.51	.364	−0.19†	−1.55	.004	−0.18†	−1.38	.000	0.26†	2.51	.001	0.00	−0.04	.953	0.06	0.63	.196
Matched	−0.11	−1.00	.305	−0.14	−1.44	.122	−0.17†	−1.83	.004	0.58†	5.74	.000	−0.01	−0.15	.897	0.16*	1.78	.030
CA1																		
Allometric	0.01	0.03	.909	−0.06	−0.23	.393	0.02	0.07	.705	0.22†	1.67	.004	0.02	0.20	.710	0.07	1.00	.168
Covariate	0.01	0.06	.806	−0.01	−0.12	.685	0.00	0.05	.789	0.30†	2.79	.000	0.07	0.76	.274	0.13†	1.59	.001
Residual	0.01	0.03	.883	−0.05	−0.18	.491	0.01	0.04	.817	0.23†	1.63	.004	0.03	0.21	.681	0.12*	0.89	.017
Matched	0.03	0.21	.773	0.12	0.98	.187	0.02	0.17	.741	0.54†	4.39	.000	0.15	1.36	.166	0.19†	1.95	.005
HPV																		
Allometric	–	–	–	–	–	–	–	–	–	0.25†	1.64	.001	0.05	0.32	.444	0.13*	0.78	.006
Covariate	–	–	–	–	–	–	–	–	–	0.32†	2.65	.000	0.07	0.61	.252	0.15†	1.31	.001
Residual	–	–	–	–	–	–	–	–	–	0.25†	1.57	.001	0.05	0.30	.454	0.12*	0.72	.017
Matched	–	–	–	–	–	–	–	–	–	0.58†	3.97	.000	0.15	1.07	.169	0.23†	1.63	.003

† = p survived controlling for multiple testing (QTIM $p \leq .0054$; HCP $p \leq .0062$; Combined $p \leq .0054$); *$p \leq .05$ (not controlled for multiple testing); Subfields are listed from small to large. HPV reflects the total hippocampal volume in mm^3, summing up all subfields except the hippocampal fissure.

Abbreviations: CA = Cornu Ammonis; HATA = hippocampus-amygdala-transition-area; GCDG = granule cell layer of the dentate gyrus; HPV = total hippocampal volume; BSV = brain segmentation volume; QTIM = Queensland Twin IMaging study; HCP = Human Connectome Project.

[a] Allometric, covariate and residual.

[b] Matched method.

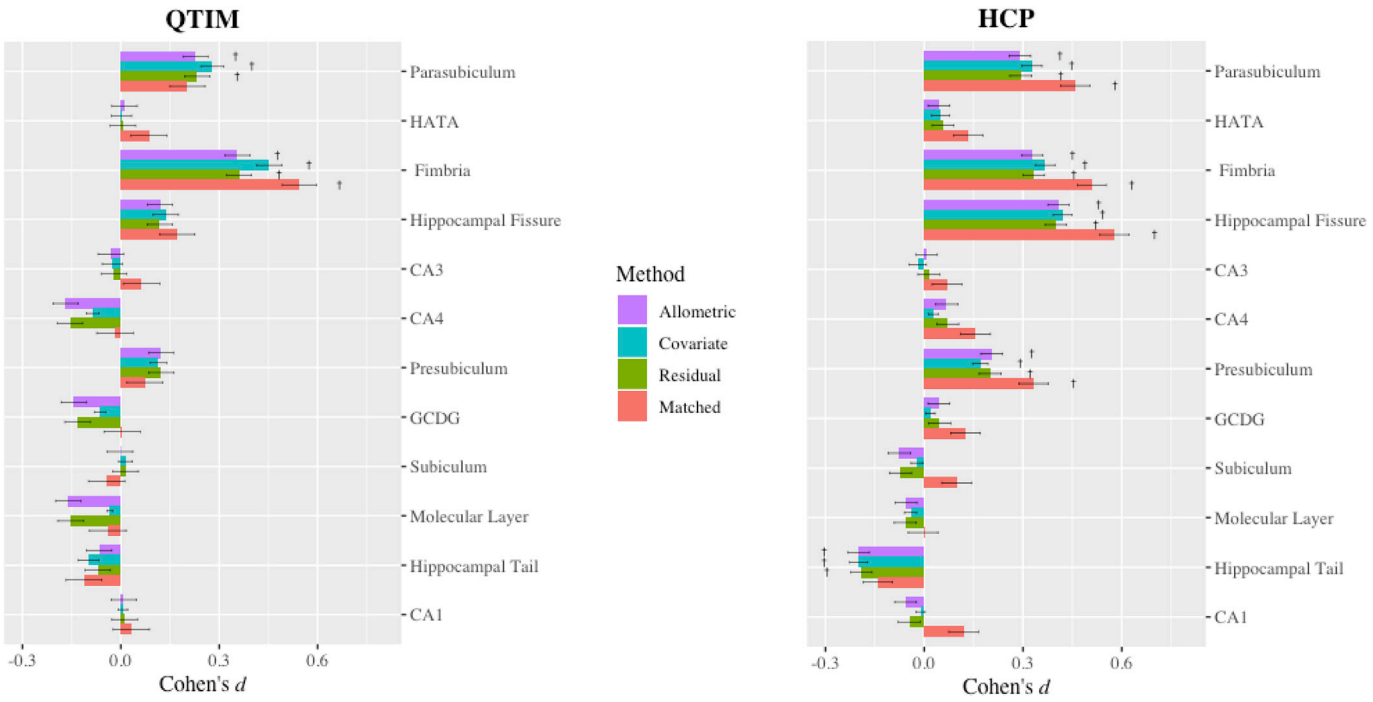

Fig. 1. Sex difference (Cohen's *d*) in hippocampal subfield volumes after adjusting for total hippocampal volume (HPV) (with the Allometric, Covariate, Residual, and Matched methods) in the QTIM (left) (N = 727) and HCP (right) (N = 960) cohorts. † $p \leq .0054$ (controlled for multiple testing). Sex differences in the parasubiculum and fimbria were consistent across cohorts and across three of the four methods adjusting for total hippocampal volume. Additional sex effects were observed for the HCP cohort (right), including the parasubiculum, fimbria, hippocampal fissure, presubiculum, and hippocampal tail. Effect sizes were generally larger for the matched method compared to the allometric, covariate, and residual method. Subfields are listed from small to large. HPV reflects the total hippocampal volume in mm^3, summing up all subfields except the hippocampal fissure. *Abbreviations: CA = Cornu Ammonis; HATA = hippocampus-amygdala-transition-area; GCDG = granule cell layer of dentate gyrus; HPV = total hippocampal volume; QTIM = Queensland Twin IMaging study; HCP = Human Connectome Project.*

larger in males compared to females, and this finding was consistent across the four controlling methods, in the HCP cohort the only sex difference found was in the volume of hippocampal fissure (Table 2; Appendix G). In addition, in the HCP cohort we found no difference between males and females in HPV, after adjustment for BSV, whereas in QTIM, HPV (adjusted for BSV) remained larger in males compared to females (up to 3.97% larger; $d = 0.58$).

After adjusting for either HPV or BSV, effect sizes were generally consistent across controlling methods. Notably, the matching method showed larger effect sizes compared with the allometric, covariate, and residual method. This was observed in both the QTIM and HCP cohorts (Fig. 1, Table 2), but less so in the combined (QTIM and HCP) sample (Table 2, Appendix F), in particular after adjusting for HPV.

We found little evidence of a sex by hemisphere effect (Appendix A; Table A1-A2), except for the hippocampal tail in the HCP cohort, where we found a sex difference in the left but not the right (Appendix A; Table A3). In addition, sex differences in allometric scaling were found in both cohorts (Appendix H), but results were not consistent across cohorts. In the QTIM cohort, sex differences in scaling ($p < .05$) were found for CA3, CA4, and GCDG subfield volumes, while in HCP, sex differences were found for the parasubiculum and fimbria (Appendix H). Test-retest reliability for the subfield volumes was moderate to excellent (Appendix I). In the QTIM cohort, we found moderate consistency for the hippocampal fissure and fimbria, and good consistency for all other subfields, while in HCP, we found excellent reliability for all subfields.

In a *post-hoc* analysis using the QTIM cohort, we found lower twin pair correlations for opposite-sex compared to same-sex DZ twins for the parasubiculum, fimbria, hippocampal fissure, and presubiculum (Appendix J), which is suggestive of sex differences. However, except for the parasubiculum, the confidence intervals for the opposite-sex and same-sex DZ twin pairs overlapped (Appendix J). In contrast, opposite-sex and same-sex DZ twin pair correlations were similar for CA2/3, CA4, and GCDG (Appendix J). We could not compare the DZ twin pair correlations for HCP as this cohort included only one opposite-sex (DZ) twin pair.

4. Discussion

In the present study, using data from two large cohorts, we identified robust, reproducible sex differences in the volumes for two of the twelve hippocampal subfields after adjusting for HPV. Volumes of the parasubiculum and fimbria were up to 6.04 and 8.75% larger in males compared to females, with effects showing consistency across allometric, covariate, residual, and matched sample approaches. Additional sex effects, after adjusting for HPV, were found in both the HCP cohort and combined (QTIM and HCP) sample. These included larger volumes for males than females in the hippocampal fissure (up to 6.79%) and presubiculum (up to 3.08%), and smaller volumes for males than females in the hippocampal tail (up to 2.23%). In contrast, in both the QTIM and HCP cohorts, there was little evidence for sex differences in the HATA, CA2/3, CA4, and GCDG – subfields previously identified to show sex effects in earlier human imaging (Kurth et al., 2017; Malykhin et al., 2017; Mueller et al., 2007; Tamnes et al., 2018), and animal studies (Yagi and Galea, 2018)). Similarly, when we adjusted for BSV, volumes of the fimbria (QTIM: 6.48%, HCP: 4.76%) and hippocampal fissure (QTIM: 6.24%, HCP: 8.63%) were again larger for males than females. However, several sex differences were found in the QTIM cohort, which were not evident in HCP, including a larger HPV for males (up to 3.97% larger than females), after adjustment for BSV. Across both cohorts, unadjusted subfield volumes were 7–15% larger in males than in females. Together, these findings build on prior work by disentangling sex effects in both the total hippocampus and its subfields in healthy young adults, while adjusting for HPV and BSV and comparing consistency across allometric, covariate, residual, and matched controlling methods.

The subfields including the parasubiculum, fimbria and presubiculum are part of the angular bundle (of the perforant pathway) and forniceal pathway respectively (Zeineh et al., 2017); the parasubiculum and presubiculum directly connect with other brain regions such as the temporal, frontal, and parietal cortex (Ding et al., 2000; Insausti et al., 2017), while the fimbria, as part of the fornix, connects with the hippocampal commissure, basal forebrain, hypothalamus, and brain stem regions (Amaral and Lavenex, 2007). As such, all of these subfields contain myelin (Zeineh et al., 2017) (Ábrahám et al., 2010), so it is possible that some of the sex-differences in volume reflect connectivity differences between males and females. Larger white matter volumes have been found in males compared with females (Gur and Gur, 2016), and remained in several brain regions after adjusting for brain size (Bourisly et al., 2017). For most white matter tracts, with the exception of the corpus callosum, males also have higher FA (Gur and Gur, 2016), including the hippocampus (Chou et al., 2011; Hsu et al., 2008). In future work, multi-modal analyses incorporating diffusion weighted imaging will be important in assessing hippocampal subfield-cortical connectivity similarities and differences between males and females.

More work is needed to establish how these sex differences at the subfield-level relate to differences on subfield-specific tasks such as for fMRI task activity, cognition, and psychiatric disorders. Animal work (Dalton and Maguire, 2017) has linked the parasubiculum and presubiculum to spatial processing, and a large human imaging study (Evans et al., 2018) (Rotterdam Study; N = 5,035) found smaller volumes of the fimbria and presubiculum (but not the parasubiculum) to be associated with poorer executive functioning. Our findings of differences in subfield volumes between males and females may relate to sex differences in visuospatial processing and executive functioning (whether or not driven by differences in strategy (Grissom and Reyes, 2018)). In addition, sex differences in subfield volumes may relate to subfield volume differences found for psychiatric disorders which have shown sex differences (Yagi and Galea, 2018) (e.g. anorexia nervosa, schizophrenia, mood disorders, and Alzheimer's disease). For example, a failing hippocampus-fornix connection (fimbria) and atrophy of the presubiculum are one of the early markers for Alzheimer's Disease (Carlesimo et al., 2015; Metzler-Baddeley et al., 2012), and volume size of the presubiculum (and subiculum) has been associated with memory performance in patients with mild cognitive impairment (Carlesimo et al., 2015). Longitudinal studies are crucial to map sex differences in the developmental trajectories of hippocampal subfield volumes to determine whether changes in volume precede or predict these disorders.

The larger hippocampal fissure volume (a cerebrospinal fluid structure), after adjusting for HPV, in males compared with females in the HCP cohort and combined (QTIM and HCP) sample, is in line with work showing sex differences in cortical folding (Awate et al., 2010; Fish et al., 2017; Gautam et al., 2015; Kochunov et al., 2005; Luders et al., 2004, 2006c; Mutlu et al., 2013). Sex differences in the hippocampal fissure were also evident in both the QTIM and HCP cohort after adjusting for BSV. There is some evidence for larger sulcal lengthening in males versus females independent of brain size (Fish et al., 2017), and greater gyrification in males versus females for the superior temporal lobe once adjusting for brain size (Gautam et al., 2015). Folding of the hippocampal fissure occurs due to the growth of the neocortex as well as unequal growth of the hippocampal subfields (Dekeyzer et al., 2017), so that some of the variation in hippocampal fissure volume could reflect differences in developmental processes for males and females.

The hippocampal tail was the only subfield where there was evidence of a sex by hemisphere interaction. The hippocampal tail is an umbrella label – including hippocampal volume of remaining slices from the first coronal slice where the fornix is fully connected to the hippocampus (Iglesias et al., 2015). A smaller volume for males than females in the left but not in the right hippocampal tail (Appendix A) was evident in HCP, as well as the combined sample, and replicates a previous study (Maller et al., 2006). In addition, it aligns with a large mega-analysis by the ENIGMA consortium (N = 17,141) (Kong et al., 2018) that showed sex differences in cortical asymmetry for both surface area and cortical thickness in several regions of the brain, including the medial temporal regions.

In contrast, we found no evidence for a sex difference in volume of the HATA, CA2/3, CA4, and GCDG subfields. These subfields are involved in neuroplasticity, memory formation and retrieval, response to stressors, as well as contextual fear learning (Aggleton and Christiansen, 2015; Fudge et al., 2012; Krogsrud et al., 2014; Lewis, 2017; Yagi and Galea, 2018). Our finding of very similar volumes for males and females in these subfields may suggest that any sex differences in such behaviour are not the result of differences in subfield volumes.

Previously, human imaging studies reported sex differences for the CA, dentate gyrus, subiculum, and/or the HATA (Kurth et al., 2017; Malykhin et al., 2017; Mueller et al., 2007; Tamnes et al., 2018), although inconsistent across studies, with some showing larger volumes in males (Tamnes et al., 2018) while others found larger volumes in females (Kurth et al., 2017; Malykhin et al., 2017; Mueller et al., 2007). Three of the previous studies (Kurth et al., 2017; Malykhin et al., 2017; Tamnes et al., 2018) found sex differences in HPV, either larger in females than males (Kurth et al., 2017; Malykhin et al., 2017), or larger in males than females (Tamnes et al., 2018), and thus previous sex differences found in the subfields may reflect sex differences in HPV, showing the need to adjust for HPV instead of BSV. However, we have not found evidence for sex differences in these subfields, irrespective of adjusting for BSV or HPV. Further, we have not found sex differences in subfields for which animal studies have showed sex differences in the morphology of CA3 and the dentate gyrus (Yagi and Galea, 2018), and neurogenesis in the dentate gyrus (Chow et al., 2013; Yagi and Galea, 2018). However, the work in rodents has not examined whether differences in morphology and neurogenesis are associated with differences in volume.

Across the allometric, covariate, residual, and matching methods adjusting for HPV (and BSV), we showed that sex differences were in the same direction, but with some differences in effect sizes. A recent study (Sanchis-Segura et al., 2019) which compared sex differences in regional grey matter volumes across controlling methods, found similar results, as have studies examining how different adjusting methods affect results for HPV (Fjell et al., 2009; Nordenskjöld et al., 2015; O'Brien et al., 2011; Pintzka et al., 2015). In general, at the individual cohort level, sex effects were larger, with larger standard deviations, for the matched compared to the allometric, covariate, and residual method. This was less evident in the larger combined (QTIM and HCP) sample, where effect sizes and standard deviations were similar across controlling methods. Although the matched approach, which does not involve a correction, may reflect true sex differences (Luders et al., 2014), the matched sample is both smaller and atypical – only a subsample of females with a larger brain size can be matched to males with a relatively smaller brain size. Also, with a smaller sample there is reduced power, reflected in the larger standard deviations for the matched method. Further, we found little evidence suggesting that the effect sizes for the allometric, covariate, and residual methods were underestimated. Specifically, across cohorts we found no robust sex differences in allometric scaling; estimates may be reduced if the scaling relationship is different for males compared to females. We also found little evidence for the more highly correlated variables (i.e. larger subfields – which are more highly correlated with HPV) influencing the effect size estimates. Prior work has indicated that highly correlated variables may both deflate and inflate effect sizes in the covariate method (Nordenskjöld et al., 2015; Pintzka et al., 2015). Further, both the QTIM and HCP cohorts were balanced for sex; similar numbers of males and females in each cohort reduces the possibility of an overcorrection in the largest group that can lead to an underestimate of the effect size in the residual method (Nordenskjöld et al., 2015).

We note four main limitations to this study. First, we used an automatic segmentation method trained on older adults (Iglesias et al., 2015). Although we carefully visually inspected the segmentation of the HPV and removed participants with extreme outliers in the subfields, we did not visually inspect the segmentation of each subfield (from a total of 1,

687 scans). However, except for the hippocampal fissure and fimbria, there was strong test-retest reliability for hippocampal subfield volumes in the QTIM cohort (Appendix I), and excellent reliability for all subfield volumes in HCP (Appendix I), in line with findings of improved segmentation once a T2 scan is included (Iglesias et al., 2015; Mueller et al., 2018). Second, the lower image resolution, and the lack of a T2-weighted scan in the QTIM sample may have resulted in greater segmentation errors, especially in the molecular layer, as the segmentation will mostly rely on the statistical atlas than image intensities (Iglesias et al., 2015). Further, it is unclear how the T2-weighted scan influenced results, in particular in comparison to the use of a scan with a high in-plane resolution coronally. Measurement error is likely to influence smaller volumes more than larger volumes, and thus may more greatly affect smaller female volumes instead of larger male volumes, in particular in smaller subfields. However, we found additional sex differences in the HCP sample in both smaller and larger subfields (hippocampal fissure, presubiculum, hippocampal tail) suggesting that most of these additional sex differences are not driven by measurement error alone, but are possibly the result of the higher image resolution and the use of an additional T2-scan improving the segmentation (Iglesias et al., 2015; Tamnes et al., 2018). To mitigate differences across cohorts, we extracted the subfield volumes with the same software version, and discussed sex differences for each cohort separately. Lastly, while we found no robust evidence for sex differences in allometric scaling for the hippocampus and its subfields across samples, within the HCP cohort sex differences in scaling for the parasubiculum and fimbria volumes may explain some of the sex differences in these volumes. Previous research has found some evidence for sex differences in scaling for certain brain regions – e.g. the anterior cerebellar lobe (Mankiw et al., 2017) and thalamus (Reardon et al., 2016) – but a recent large study (N = 2,904) (Reardon et al., 2018) found no evidence for a different scaling relationship for males and females. As sex differences in the parasubiculum and fimbria were found across cohorts, but sex differences in allometric scaling were only observed in the HCP cohort, it is unlikely that sex differences in scaling can fully account for sex differences found in these subfields.

In conclusion, we found regional-specific sex differences in two hippocampal subfields – the fimbria and parasubiculum, with larger volumes for males than females after adjusting for HPV, which were consistent across multiple controlling methods adjusting for HPV, and across two large young adult cohorts. Additional sex effects were identified in the HCP cohort and combined sample (presubiculum, hippocampal fissure, and hippocampal tail). Differences in effect sizes across the controlling methods within cohorts, suggest the matched approach may overestimate the effect size when the matched sample is too small. Further, accounting for HPV instead of BSV may benefit future studies, as our findings were more similar across cohorts after adjusting for HPV. This work may help in disentangling sex effects, which could contribute towards our understanding of the implications of sex differences for behaviour and psychiatric disorders.

Data and code availability statement

The QTIM dataset used in this manuscript is available through the following link: https://doi.org/10.14264/uql.2019.465. Access to the HCP dataset should be requested through the Human Connectome Project team. We have included the matching method script in Appendix C.

Contribution to authorship

Contributor	Statement of contribution
Liza van Eijk	Conception and design (40%)
	Analysis and interpretation (40%)
	Drafting and reviewing (20%)
Narelle K. Hansell	(*continued on next column*)
	Conception and design (40%)
	Analysis and interpretation (20%)
	Drafting and reviewing (10%)
Lachlan T. Strike	Analysis and interpretation (30%)
Baptiste Couvy-Duchesne	Analysis and interpretation (10%)
	Drafting and reviewing (5%)
Greig I. de Zubicaray	Drafting and reviewing (5%)
Paul M. Thompson	Drafting and reviewing (10%)
Katie L. McMahon	Drafting and reviewing (10%)
Brendan P. Zietsch	Drafting and reviewing (10%)
Margaret J. Wright	Conception and design (20%)
	Drafting and reviewing (30%)

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Declaration of competing interest

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Appendix A-J and Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116781.

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