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The human hippocampus is not sexually-dimorphic: Meta-analysis of structural MRI volumes

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ABSTRACT

Hippocampal atrophy is found in many psychiatric disorders that are more prevalent in women. Sex differences in memory and spatial skills further suggest that males and females differ in hippocampal structure and function. We conducted the first meta-analysis of male–female difference in hippocampal volume (HCV) based on published MRI studies of healthy participants of all ages, to test whether the structure is reliably sexually dimorphic. Using four search strategies, we collected 68 matched samples of males' and females' uncorrected HCVs (in 4418 total participants), and 36 samples of male and female HCVs (2183 participants) that were corrected for individual differences in total brain volume (TBV) or intracranial volume (ICV). Pooled effect sizes were calculated using a random-effects model for left, right, and bilateral uncorrected HCVs and for left and right HCVs corrected for TBV or ICV. We found that uncorrected HCV was reliably larger in males, with Hedges' g values of 0.545 for left hippocampus, 0.526 for right hippocampus, and 0.557 for bilateral hippocampus. Meta-regression revealed no effect of age on the sex difference in left, right, or bilateral HCV. In the subset of studies that reported it, both TBV ($g = 1.085$) and ICV ($g = 1.272$) were considerably larger in males. Accordingly, studies reporting HCVs corrected for individual differences in TBV or ICV revealed no significant sex differences in left and right HCVs (Hedges' g ranging from $+0.011$ to -0.206). In summary, we found that human males of all ages exhibit a larger HCV than females, but adjusting for individual differences in TBV or ICV results in no reliable sex difference. The frequent claim that women have a disproportionately larger hippocampus than men was not supported.

Introduction

As neuroimaging research has exploded over the past quarter century, it has become evident that males and females show certain group-level differences in brain structure. Adult male brains are some 14% larger than female brains, with bigger ventricles, a higher ratio of white:gray matter, and a longer period of growth during adolescence (e.g., Lenroot et al., 2007). These differences are reliable enough that most brain morphometry studies now use sex as a covariate when analyzing mixed-sex samples.

With regard to specific brain structures, however, the evidence for sexual dimorphism has been less compelling (Fjell et al., 2009). The hippocampus has been extensively studied due to its importance in memory, spatial navigation, and stress regulation. Meta-analysis has demonstrated reduced HCV in many neuropsychiatric disorders, including depression (McKinnon et al., 2009; Videbech and Ravnkilde, 2004), post-traumatic stress disorder (PTSD; Smith, 2005; Woon and Hedges, 2011), schizophrenia (Adriano et al., 2012), borderline personality disorder (BPD; Ruocco et al., 2012), Alzheimer's disease (Barnes et al., 2009), and mild cognitive impairment (MCI; Shi et al., 2009). Since many of these disorders show higher prevalence in women (Breslau, 2009; Johnson et al., 2003; Kessler et al., 2003; McLean et al., 2011; Moschetti et al., 2012), it is reasonable to suspect that a pre-morbid sex difference in HCV—i.e., smaller in females—contributes to this differential vulnerability.

Indeed, research in rats and voles has led to the hypothesis that sexual selection for spatial ability produced an expansion of male HCV in polygynous species, including humans (Sherry et al., 1992). The hippocampus is rich in androgen receptor-expressing cells, especially CA1 pyramidal neurons, whose spine density in male rats peaks at puberty under the influence of testosterone (Leranth et al., 2008). Prenatal testosterone is also implicated, since neonatal castration has been found to eliminate male rats' advantage on hippocampus-dependent spatial navigation tasks (Isgor and Sengelaub, 2003; Williams and Meck, 1991). Human studies similarly suggest that prenatal testosterone enhances spatial skills (Puts et al., 2008; Vuoksimaa et al., 2010) although post-pubertal testosterone fluctuations do not (Puts et al., 2010). It is possible, then, that early androgen exposure enhances HCV and later spatial and navigational skills in males.

On the other hand, female rats exhibit an increase in dendritic spine density in hippocampal neurons in response to estrogen, an effect associated with changes in spatial learning and synaptic plasticity across the

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estrous cycle (Cooke and Woolley, 2005). High levels of estrogens in females have been associated with greater spine density in rhesus monkeys (Hao et al., 2003) and with the size and synaptic density of hippocampal subregions in both rats (Galea et al., 1999) and humans (Protopopescu et al., 2008), all findings suggesting HCV may be specifically enhanced in reproductive-aged women.

In fact, most reviews of sex difference in the human brain state that the hippocampus is larger in *females*. For example, Gur et al. (2010, p.80) write that "imaging studies consistently find that the hippocampus is larger in women compared to men when adjusted for brain size," with similar statements appearing in other reviews (Cahill, 2006; Hines, 2010), and in recent primary research articles (e.g., Knickmeyer et al., 2014; Lentini et al., 2013). In addition to spatial skills, the hippocampus participates in verbal and episodic memory, so a larger volume could contribute to female advantage in these abilities (Andreano and Cahill, 2009). It is important to note, however, that most references to a larger HCV in females cite the same few early MRI studies (Filipek et al., 1994; Giedd et al., 1996; Goldstein et al., 2001).

Separate lines of research have thus led to opposing hypotheses about gender and HCV. However, one factor that may reconcile these differences is age. Specifically, some studies suggest that the hippocampus is larger in females, but only during childhood (Cosgrove et al., 2007) or adolescence (Neufang et al., 2009). By contrast, other work suggests greater hippocampal growth in males during adolescence (Bramen et al., 2011; Suzuki et al., 2005). Aging, too, is said to be a time of increased sex difference, with several studies finding that HCV declines more rapidly in men than women over late life (e.g., Knoops et al., 2012; Pruessner et al., 2001; Raz et al., 2004a), but others (Murphy et al., 1996) finding greater decline in females, as might be expected after menopause based on estrogen's effect on synaptic density.

We therefore undertook a meta-analysis of HCV difference between healthy males and females, exploiting the many hippocampal morphometry studies published over the past quarter century. We hypothesized that HCV differs between the sexes, but did not specify the direction of the difference. We further hypothesized that age would be a significant moderator of hippocampal sex difference, but again, did not specify the direction of this possible effect.

Materials and methods

This study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

Search strategy

Several strategies were used to find MRI studies reporting HCVs in matched samples of healthy male and female participants (Fig. 1). First, we searched PubMed through April 2013 for English-language articles using the terms: [(hippocamp*) AND (magnetic resonance OR MRI) AND (sex OR gender)]. Second, we used the same terms to perform full-text searches in the journals *Hippocampus, Human Brain Mapping,* and *Cerebral Cortex* and the first 200 hits sorted by "relevance" in the journals *NeuroImage* and *Biological Psychiatry*. Third, we searched the Internet Volume Brain Database for studies of normal subjects in which male and female HCVs were reported separately. Fourth, we hand-searched all primary studies cited in ten prior meta-analyses of hippocampal volume not related to sex differences (Adriano et al., 2012; Fusar-Poli et al., 2012; McKinnon et al., 2009; Molendijk et al., 2012; Pedraza et al., 2004; Ruocco et al., 2012; Shi et al., 2009; Smith, 2005; Videbech and Ravnkilde, 2004; Woon and Hedges, 2011).

These four searches yielded 2224 citations from which we were able to identify 88 initial studies that reported HCV measurements (mean ± SD) separately for age-matched samples of healthy males and females (Fig. 1). We further identified 31 studies that reported statistical comparisons, qualitative findings, or graphical comparisons, without publishing actual male and female HCVs; for such studies published in 2005 or later, we emailed the authors to request the mean ± SD volumes in their published samples of healthy males and females. Of 28 such requests, authors of 11 different studies sent HCVs for 15 age-matched samples of males and females.

Excluded and overlapping studies

Initially, we collected studies with any sample size, but due to the greater variance of smaller samples, we set a minimum threshold of ten participants in each age-matched gender group. This eliminated 14 studies (15 samples; Fig. 1) plus four samples in studies (Bramen et al., 2011; Mouiha and Duchesne, 2011; Smith et al., 1999; Uematsu et al., 2012) that also included larger samples (Supp. Table 1). For studies reporting corrected HCVs (Table 2), we excluded four (Briellmann et al., 1998; den Heijer et al., 2004; Free et al., 1995; Knoops et al., 2012) that normalized males and females separately—that is, based on the average TBV or ICV of the sex of the subject—because this precludes correction for sex difference in overall brain size.

Overlapping samples were identified and eliminated based on either authors' report or when samples of similar size and demographic profile were noted among studies that shared any authors. Nine studies were excluded on this basis (Supp. Table 2). Seven other pairs of studies with overlapping samples were retained because the samples were incorporated into separate meta-analyses (see Tables 1 and 2) where they did not overlap.

Further exclusions are detailed in the Supplementary Material.

Data extraction

HCVs of healthy age-matched males and females were sorted according to whether they were "raw" or corrected for individual differences in overall brain size. After eliminating small and overlapping samples, 58 studies remained that reported uncorrected HCVs in 68 matched samples of healthy males and females (Table 1). Most studies reported left and right HCVs separately; a smaller number reported total (bilateral) HCV. Similarly, after eliminating small and overlapping samples, we identified 33 studies reporting HCVs corrected for overall brain volume (ICV or TBV) in 36 age-matched samples of males and females (Table 2). In total, 76 primary studies reported either raw, corrected, or both types of HCV in matched male and female samples and were included in the analyses below.

For the moderator, "age of participants," we either used the reported mean age of the total sample or calculated the weighted mean age of male and female groups. If range, but not mean age was reported, we used its midpoint.

Bias and quality assessment

Meta-analytic findings are only valid if the literature from which they derive is free from systematic bias. For analyses of sex differences, the "file drawer" problem leans toward the omission of negative findings (Song et al., 2010)—that is, data that find no significant difference between males and females (Halpern, 2012, p. 76). We observed evidence of this bias in the 22 studies we identified that stated only qualitative sex comparisons or graphed male and female volumes without publishing numeric data; 15 of these 22 stated there was "no difference" between males and females (Supp. Table 3), indicating that studies that do include numeric male and female volumes lean toward finding a significant difference. Of these 22 qualitative studies, we were able to obtain volumetric data directly from the authors of ten, helping to reduce considerable "file drawer" omission from our analysis.

Another reason this study is less vulnerable to publication bias is because most data were collected from studies not explicitly studying gender. The vast majority of studies were evaluating HCV as it relates to

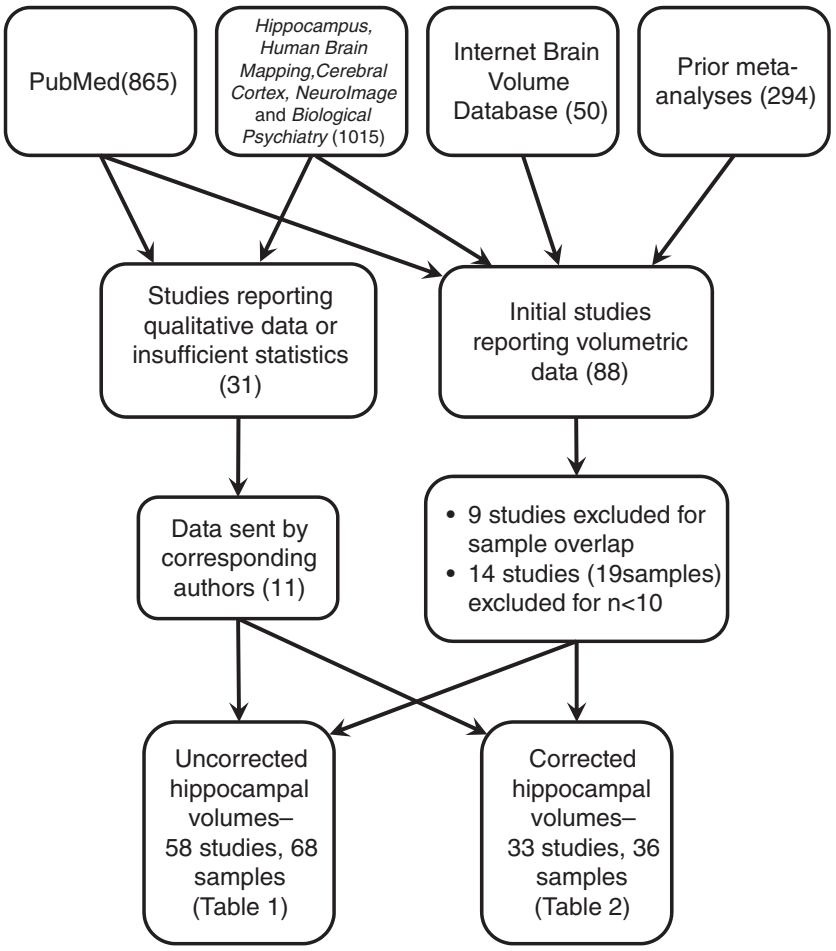

Fig. 1. Search strategies and results, with parentheses indicating number of studies at each step. The Internet Brain Volume Database (http://www.cma.mgh.harvard.edu/ibvd) includes 672 studies, but selection by structure (hippocampus), diagnosis (normal), species (human), and sex (male and female) limited this to 50 unique studies.

either normal aging or psychiatric diagnosis, so gender was essentially a nuisance variable. Thus, out of 76 final studies, only 19 included any of the following words in their titles: "sex," "gender," "male," "female," "women," "men," "boys," or "girls."

Over the quarter-century that MRI has been used to measure brain volumes, imaging devices and analysis methods have advanced enormously. Earlier studies used scanners with weaker magnets and employed cruder analytic methods, with a steady trend toward greater automation in image processing and measurement. Also, as resolution has improved, hippocampal boundaries can be defined with greater precision. We thus used "year of study" as a proxy for improving quality and accuracy of measurements over this period, and ran meta-regression on effect size versus publication year to assess the impact of cumulative methodological advances on estimates of sex difference. Nonetheless, we note that among the 14 studies that were excluded for sample sizes < 10, six employed presumably lower quality methods (MRI magnet strength < 1.5 T or slice thickness > 3 mm). By contrast, only two (Lloyd et al., 2004; Mouiha and Duchesne, 2011) of the 76 studies that were included in our meta-analyses employed MRI scanners with magnet strength < 1.5 T, and all studies except five (Greenberg et al., 2006; Gur et al., 2002; Jack et al., 1989; Li et al., 2007; Murphy et al., 1996) reported a slice thickness < 3 mm.

Statistical analysis

Meta-analytic calculations were performed using Comprehensive Meta-Analysis Version 2.0 (Borenstein, 2009). For both raw (Table 1) and corrected (Table 2) measures, all HCV differences between male and female groups were converted to standardized mean difference effect sizes (Hedges' g). We used a random-effects model to calculate overall effect size and 95% confidence interval (CI) for each sex difference. Statistical significance of the pooled effect size was evaluated using a *z* test, with significance set at $p < 0.05$. Heterogeneity was estimated using the Q statistic, which reflects the ratio of observed variance to within-study error, and its associated I^2 index, which estimates the proportion of variability due to real, or non-random differences between studies. I^2 values less than 40% are considered unimportant; I^2 values between 30% to 60% represent moderate heterogeneity, and I^2 values above this level indicate substantial heterogeneity (Higgins and Green, 2011).

Results

The hippocampus is reliably larger in males

Among the 76 studies, including 104 matched samples of male and female HCV that we collected, the largest dataset was for uncorrected (raw) left HCV: 50 matched samples of healthy males and females ($n = 4418$) with mean ages ranging from birth to 79 years. As shown in Fig. 2A and Table 5, meta-analysis indicates a medium-sized pooled sex difference, larger in males (Hedges' $g = 0.545$, $p < 0.001$), corresponding to a mean volume difference of 0.207 cm^3 (7.1%). In this and all of the forest plots presented, studies are ordered according to the mean age of participants, to better visualize any lifespan changes in

Table 1
MRI studies reporting raw volumes (mean ± SD cm^3) included in meta-analyses.

Study	Subgroup	#M/#F	Mean Age	Left HCV		Right HCV		Bilateral HCV		Comments
				M	F	M	F	M	F	
Aas et al. (2012)		26/37	28.0	nr	nr	nr	nr	4.05 + 0.86	4.37 + 0.78	
Abbs et al. (2011)		27/21	40.5	nr	nr	nr	nr	8.33 ± 0.91	7.89 ± 0.64	Same sample as Goldstein et al. (2002) (left HCV).
Agartz et al. (1999)		17/19	19.8	3.61 ± 0.46	3.53 ± 0.41	3.94 ± 0.36	3.73 ± 0.47	nr	nr	
Allen et al. (2005) [a]		43/44	48.2	3.35 ± 0.45	3.21 ± 0.35	3.62 ± 0.47	3.47 ± 0.38	6.98 ± 0.89	6.68 ± 0.71	
Bhatia et al. (1993)		15/14	34.2	3.78 ± 0.55	3.38 ± 0.39	3.77 ± 0.61	3.40 ± 0.36	nr	nr	
Bigler et al. (1997)		37/59	40.5	2.58 ± 0.32	2.39 ± 0.26	2.65 ± 0.29	2.45 ± 0.24	5.23 ± 0.59	4.85 ± 0.48	
Bleich et al. (2003)		16/14	48.2	3.87 ± 0.42	3.67 ± 0.36	3.99 ± 0.47	3.87 ± 0.33	nr	nr	
Bonilha et al. (2004)		11/19	33.0	1.63 ± 0.28	1.51 ± 0.23	1.58 ± 0.27	1.47 ± 0.25	nr	nr	
Bramen et al. (2011)	Late puberty	23/29	12.6	4.53 ± 0.34	4.13 ± 0.39	4.90 ± 0.47	4.34 ± 0.36	nr	nr	Matched for pubertal stage
Briellmann et al. (1998)		15/15	29.0	nr	nr	nr	nr	4.47 ± 0.44	3.93 ± 0.38	
Buss et al. (2012)		30/35	7.5	3.85 ± 0.40	3.88 ± 0.29	3.91 ± 0.43	4.02 ± 0.29	nr	nr	
Caviness et al. (1996)		15/15	9.2	nr	nr	nr	nr	8.90 ± 1.40	8.60 ± 0.07	
Cherbuin et al. (2008)		197/233	46.7	nr	nr	nr	nr	5.54 ± 0.76	5.06 ± 0.57	Sample includes Maller et al., 2007a (left & right HCV).
Filipek et al. (1994)		10/10	27.2	nr	nr	nr	nr	9.60 ± 1.40	10.40 ± 1.00	
Fjell et al. (2009) [a]		467/676	46.8	nr	nr	nr	nr	8.44 ± 1.14	7.67 ± 0.99	
Flaum et al. (1995)		45/42	30.4	2.70 ± 0.35	2.63 ± 0.36	2.72 ± 0.36	2.56 ± 0.44	5.42 ± 0.67	5.18 ± 0.75	
Free et al. (1995)		19/13	27.0	2.89 ± 0.24	2.53 ± 0.22	2.93 ± 0.27	2.60 ± 0.25	nr	nr	
Goldstein et al. (2002)		27/21	40.5	4.24 ± 0.49	4.00 ± 0.33	nr	nr	nr	nr	Same sample as Abbs et al. (2011) (bilateral HCV).
Greenberg et al. (2006)	Females non-HRT	33/51	71.0	3.17 ± 0.59	2.86 ± 0.40	3.37 ± 0.46	3.10 ± 0.47	nr	nr	Overlaps Greenberg et al. (2008), Table 2.
Gur et al. (2002)		57/59	26.0	4.32 ± 0.85	4.08 ± 0.44	4.60 ± 1.17	4.32 ± 0.44	8.92 ± 1.72	8.40 ± 1.03	
Head et al. (2005) [a]	Younger	26/24	22.5	3.31 ± 0.41	2.96 ± 0.33	3.34 ± 0.38	2.96 ± 0.33	nr	nr	
	Older	14/36	76.5	3.25 ± 0.63	2.81 ± 0.39	3.32 ± 0.66	2.85 ± 0.35	nr	nr	
Hempel et al. (2012)		25/23	60.0	nr	nr	nr	nr	3.09 ± 0.33	3.02 ± 0.31	
Irle et al. (2011)		23/23	33.6	3.28 ± 0.34	2.95 ± 0.46	3.41 ± 0.40	3.06 ± 0.35	nr	nr	
Karnik et al. (2010) [a]	All BDNF genotypes	59/70	49.3	2.42 ± 0.38	2.22 ± 0.33	2.90 ± 0.45	2.64 ± 0.34	nr	nr	
Knoops et al. (2012) [a]		514/122	62.0	nr	nr	nr	nr	6.05 ± 0.71	5.51 ± 0.65	
Kronmuller et al. (2009)		11/19	42.4	3.19 ± 0.25	2.72 ± 0.30	3.30 ± 0.29	2.79 ± 0.41	6.49 ± 0.49	5.51 ± 0.66	
Laakso et al. (1998)	Younger	10/10	28.0	3.48 ± 0.47	3.12 ± 0.41	3.70 ± 0.62	3.41 ± 0.59	nr	nr	
	Older	19/23	72.0	3.44 ± 0.54	2.99 ± 0.45	3.46 ± 0.55	3.34 ± 0.50	nr	nr	
Lange et al. (1997)		65/50	11.4	4.57 ± 0.47	4.35 ± 0.51	4.75 ± 0.56	4.69 ± 0.55	9.32 ± 0.93	9.05 ± 0.97	
Li et al. (2007)		29/32	37.8	2.42 ± 0.20	2.36 ± 0.14	2.63 ± 0.24	2.53 ± 0.14	5.41 ± 0.41	4.88 ± 0.20	
Li et al. (2012)		139/188	20.4	4.14 ± 0.35	3.96 ± 0.29	4.31 ± 0.35	4.08 ± 0.31	nr	nr	

(continued on next page)

Table 1 (*continued*)

Study	Subgroup	#M/#F	Mean Age	Left HCV		Right HCV		Bilateral HCV		Comments
				M	F	M	F	M	F	
Li et al. (2014)			38/38	43	nr	nr	nr	nr	8.77 ± 0.89	8.37 ± 0.69
Lopez-Larson et al. (2009) [a]		16/12	10.5	nr	nr	nr	nr	7.78 ± 0.87	7.97 ± 0.78	
Maller et al. (2007a)		13/17	37.3	3.27 ± 0.43	2.99 ± 0.25	3.20 ± 0.49	2.96 ± 0.28	nr	nr	Subsample of Cherbuin et al. (2008) (bilateral HCV)
Maller et al. (2007b)		238/214	62.6	2.98 ± 0.42	2.71 ± 0.40	3.03 ± 0.45	2.75 ± 0.40	nr	nr	Overlaps with Sachdev et al. (2006) , Table 2
Mouiha and Duchesne (2011)	30–40 yrs	29/31	35.0	2.83 ± 0.36	2.62 ± 0.38	2.96 ± 0.39	2.78 ± 0.35	nr	nr	
	40–50 yrs	45/76	45.0	2.88 ± 0.33	2.61 ± 0.37	3.03 ± 0.36	2.78 ± 0.37	nr	nr	
	50–60 yrs	40/50	55.0	2.82 ± 0.41	2.66 ± 0.40	2.97 ± 0.42	2.79 ± 0.44	nr	nr	
	60–70 yrs	26/51	65.0	2.84 ± 0.42	2.66 ± 0.35	3.03 ± 0.48	2.81 ± 0.41	nr	nr	
	70+ yrs	14/30	75.0	2.74 ± 0.46	2.76 ± 0.35	2.78 ± 0.66	2.87 ± 0.38	nr	nr	
Nardelli et al. (2011)		32/24	11.3	nr	nr	nr	nr	9.10 ± 0.80	8.40 ± 0.90	
Narr et al. (2004)		30/30	26.4	2.66 ± 0.28	2.60 ± 0.28	2.76 ± 0.27	2.59 ± 0.26	nr	nr	
Neumeister et al. (2005) [a]		21/35	38.0	3.66 ± 0.33	3.52 ± 0.34	3.74 ± 0.34	3.64 ± 0.36	7.41 ± 0.65	7.16 ± 0.69	
Patwardhan et al. (2002)		10/10	28.5	nr	nr	nr	nr	8.70 ± 1.06	8.10 ± 0.74	
Paus (2010)		281/298	15.0	nr	nr	nr	nr	4.40 ± 0.35	4.10 ± 0.36	
Pearlson et al. (1997)		43/17	31.6	0.39 ± 0.09	0.38 ± 0.10	0.42 ± 0.11	0.42 ± 0.13	nr	nr	
Piven et al. (1998)		20/16	20.2	2.82 ± 0.35	2.68 ± 0.35	2.95 ± 0.34	2.76 ± 0.28	nr	nr	
Razi et al. (1999)		18/13	29.9	2.56 ± 0.70	2.53 ± 0.58	2.63 ± 0.76	2.63 ± 0.66	nr	nr	
Savic and Arver (2011)		24/24	34.0	3.20 ± 0.30	3.20 ± 0.40	3.40 ± 0.40	3.10 ± 0.50	nr	nr	
Smith et al. (1999)	Young	13/13	27.0	2.66 ± 0.42	2.46 ± 0.23	2.76 ± 0.36	2.77 ± 0.28	nr	nr	
Smitka et al. (2012)	Under 45	31/35	32.0	nr	nr	nr	nr	6.78 ± 0.75	6.44 ± 0.94	
	Over 45	24/27	62.0	nr	nr	nr	nr	6.23 ± 0.95	6.22 ± 0.83	
	Total	55/62	37.0	3.20 ± 0.47	3.10 ± 0.46	3.34 ± 0.47	3.25 ± 0.47	nr	nr	
Staff et al. (2012)[a]		125/110	68.7	4.21 ± 0.43	3.93 ± 0.42	4.15 ± 0.43	3.93 ± 0.41	nr	nr	
Suzuki et al. (2005)	Younger adolescent	10/13	13.4	2.91 ± 0.34	2.85 ± 0.30	3.01 ± 0.30	2.95 ± 0.37	nr	nr	
	Older adolescent	15/15	19.7	3.29 ± 0.34	2.80 ± 0.21	3.49 ± 0.32	3.02 ± 0.31	nr	nr	
Takahashi et al. (2006)		35/28	24.3	3.21 ± 0.40	2.75 ± 0.23	3.38 ± 0.35	2.98 ± 0.25	nr	nr	
Tanskanen et al. (2005)		62/42	34	3.43 ± 0.31	3.25 ± 0.42	3.51 ± 0.35	3.32 ± 0.36	nr	nr	
Thompson et al. (2009)[a]		18/14	0.0	1.15 ± 0.13	1.18 ± 0.14	1.18 ± 0.11	1.21 ± 0.14	nr	nr	Full-term infants only; preterm sample in Thompson et al. (2008) , Table 2
Tupler and De Bellis (2006)		62/60	11.7	4.24 ± 0.51	3.84 ± 0.47	4.32 ± 0.60	3.99 ± 0.49	8.56 ± 1.03	7.83 ± 0.92	
Uematsu et al. (2012)	2–9 yrs	17/17	6.0	nr	nr	nr	nr	5.80 ± 0.58	5.57 ± 0.51	
	> 10 yrs	22/26	15.9	nr	nr	nr	nr	6.46 ± 0.54	5.94 ± 0.52	
Verma et al. (2009)		14/15	27.7	1.83 ± 0.46	1.57 ± 0.18	1.84 ± 0.23	1.67 ± 0.28	3.67 ± 0.66	3.25 ± 0.36	
Watson et al. (1997)		30/31	34.0	4.23 ± 0.42	3.60 ± 0.35	4.27 ± 0.41	3.66 ± 0.35	nr	nr	
Wolf et al. (2004)		14/21	78.7	1.53 + 0.12	1.51 + 0.2	1.62 + 0.22	1.62 + 0.17	nr	nr	
Ystad et al. (2009)		50/120	62.2	3.50 ± 0.42	3.43 ± 0.33	3.77 ± 0.43	3.66 ± 0.36	nr	nr	
Zhang et al. (2010)		226/318	71.3	3.46 ± 0.50	3.21 ± 0.44	3.53 ± 0.48	3.29 ± 0.43	6.99 ± 0.94	6.49 ± 0.84	

M, males; F, females; HCV, hippocampal volume; nr, not reported, TBV, total brain volume; ICV, intracranial volume.

[a] Data obtained directly from authors.

Table 2
MRI studies reporting corrected hippocampal volumes or ratios included in meta-analyses.

Study	Subgroup	#M/#F	Mean Age	Correction Method	Left HCV		Right HCV		Bilateral HCV	
					M	F	M	F	M	F
Abbs et al. (2011)		27/21	40.5	TBV ratio	nr	nr	nr	nr	7.50 ± 0.80[b]	7.80 ± 0.80[b]
Bai et al. (2009)		12/11	71.2	ICV ratio	1.45 ± 0.36	1.22 ± 0.13	1.36 ± 0.27	1.23 ± 0.14	nr	nr
Bhatia et al. (1993)		15/14	34.2	TBV ratio	3.00 ± 0.40[b]	3.00 ± 0.50[b]	3.00 ± 0.40[b]	3.00 ± 0.50[b]	nr	nr
Bigler et al. (1997)		37/59	40.5	ICV covariance	2.43 ± 0.28	2.60 ± 0.28	2.50 ± 0.24	2.66 ± 0.25	4.92 ± 0.51	5.27 ± 0.51
Callen et al. (2004)		20/20	70.5	ICV ratio	nr	nr	nr	nr	3.10 ± 0.48	3.14 ± 0.47
Filipek et al. (1994)		10/10	27.2	TBV ratio	nr	nr	nr	nr	8.00 ± 1.00[b]	9.00 ± 1.00[b]
Gao et al. (2012)		13/12	31.3	ICV ratio	2.91 ± 0.24	3.05 ± 0.02	3.02 ± 0.25	3.14 ± 0.26	nr	nr
Goldstein et al. (2002)		27/21	40.5	TBV ratio	3.80 ± 0.50[b]	3.90 ± 0.40[b]	nr	nr	nr	nr
Greenberg et al., 2008		16/66	71	ICV ratio	2.60 ± 0.40[b]	2.60 ± 0.40[b]	2.80 ± 0.40[b]	2.70 ± 0.40[b]	nr	nr
Head et al. (2005)[a]	Young	26/24	22.5	ICV atlas	3.62 ± 0.34	3.74 ± 0.38	3.65 ± 0.32	3.75 ± 0.35	nr	nr
	Old	14/36	76.5	ICV atlas	3.51 ± 0.46	3.59 ± 0.43	3.59 ± 0.49	3.64 ± 0.40	nr	nr
Jack et al. (1989)		27/25	30	ICV covariance	2.50 ± 0.10	2.50 ± 0.10	2.80 ± 0.10	2.80 ± 0.10	nr	nr
Li et al. (2007)		29/32	37.8	ICV covariance	2.38 ± 0.19	2.39 ± 0.13	2.59 ± 0.23	2.56 ± 0.14	4.97 ± 0.39	4.95 ± 0.20
Li et al. (2012)		38/38	43	TBV ratio	nr	nr	nr	nr	6.78 ± 0.46[b]	7.27 ± 0.51[b]
Lloyd et al. (2004)		10/29	73.1	TBV ratio	2.90 ± 0.20	2.90 ± 0.40	3.10 ± 0.30	3.10 ± 0.40	nr	nr
Maller et al. (2006)	TBV-corrected	76/74	62.3	TBV ratio	2.70 ± 0.32[b]	2.82 ± 0.33[b]	2.74 ± 0.33[b]	2.85 ± 0.35[b]	nr	nr
Maller et al. (2007a)	ICV-corrected[c]	13/17	37.3	ICV ratio	2.20 ± 0.25[b]	2.08 ± 0.24[b]	2.15 ± 0.23[b]	2.06 ± 0.24[b]	nr	nr
	TBV-corrected	13/17	37.3	TBV ratio	2.68 ± 0.35[b]	2.53 ± 0.33[b]	2.62 ± 0.33[b]	2.50 ± 0.32[b]	nr	nr
Maller et al. (2007b)		238/214	62.6	ICV ratio	1.88 ± 0.26[b]	1.94 ± 0.28[b]	1.91 ± 0.26[b]	1.97 ± 0.29[b]	nr	nr
McHugh et al. (2007)		12/28	70.6	ICV covariance	3.52 ± 0.56	3.46 ± 0.38	3.66 ± 0.44	3.70 ± 0.42	nr	nr
Murphy et al. (1996)	Young	13/11	25.9	ICV ratio	1.60 ± 0.20 [b]	2.20 ± 0.30[b]	1.70 ± 0.30[b]	2.20 ± 0.40[b]	3.30 ± 0.50[b]	4.30 ± 0.60[b]
	Old	12/12	70	ICV ratio	1.40 ± 0.30[b]	1.40 ± 0.30[b]	1.40 ± 0.30[b]	1.40 ± 0.30[b]	2.90 ± 0.50[b]	2.80 ± 0.60[b]
Narr et al. (2004)		30/30	26.4	ICV atlas	0.99 ± 0.25[b]	0.48 ± 0.22[b]	0.32 ± 0.26[b]	0.89 ± 0.27[b]	nr	nr
Nosarti et al. (2002)		31/17	14.9	ICV (not specified)	2.90 ± 0.70	2.26 ± 0.41	2.73 ± 0.69	2.32 ± 0.59	nr	nr
Paus (2010)		281/298	15	ICV atlas	nr	nr	nr	nr	4.30 ± 0.29	4.30 ± 0.31
Rodrigue et al. (2013)[a]		37/76	54	ICV covariance	1.98 ± 0.30	1.98 ± 0.27	2.03 ± 0.28	2.02 ± 0.27	nr	nr
Sachdev et al. (2006)		230/214	62.5	ICV ratio	nr	nr	nr	nr	3.78 ± 0.48[b]	3.92 ± 0.54[b]
Szabo et al. (2003)		15/19	28	ICV atlas	2.81 ± 0.32	3.01 ± 0.46	2.84 ± 0.29	3.10 ± 0.44	nr	nr
Thompson et al. (2008)	Pre-term infants	93/91	0	ICV covariance	1.12 ± 0.14	1.13 ± 0.13	1.14 ± 0.14	1.15 ± 0.12	nr	nr
Thompson et al. (2009)[a]	Full-term infants	18/14	0	ICV covariance	1.14 ± 0.11	1.20 ± 0.12	1.17 ± 0.09	1.22 ± 0.11	nr	nr
Tupler and De Bellis (2006)		62/60	11.7	TBV covariance	4.01 ± 0.51	3.99 ± 0.47	4.05 ± 0.60	4.14 ± 0.49	8.06 ± 1.03	8.12 ± 0.92
Whittle et al. (2011)		58/55	12.5	ICV covariance	2.81 ± 0.32	2.72 ± 0.32	2.95 ± 0.35	2.91 ± 0.35	nr	nr
Wolf et al. (2004)		14/21	78.7	ICV ratio	0.99 ± 0.10[b]	1.00 ± 0.12[b]	1.00 ± 0.15[b]	1.10 ± 0.14[b]	nr	nr
Yap et al. (2008)		55/51	12.5	TBV covariance	2.82 ± 0.32	2.73 ± 0.33	2.96 ± 0.36	2.91 ± 0.35	nr	nr
Yurgelun-Todd et al. (2003)		13/24	14.6	TBV ratio	4.61 ± 0.65[b]	4.40 ± 0.77[b]	4.44 ± 0.72[b]	4.35 ± 0.83[b]	nr	nr
Zhang et al. (2012)[a]		14/10	7.28	ICV covariance	2.06 ± 0.06	2.05 ± 0.05	2.08 ± 0.06	2.07 ± 0.09	nr	nr

[a] Data supplied directly by authors.
[b] Ratio data scaled to match order of magnitude.
[c] Omitted from Fig. 5 analysis (to avoid duplication with TBV-corrected values from this study) but included in analyses of ICV-corrected volumes(Suppl. Figs. 3 and 4).

HCV sex difference. However, meta-regression revealed no linear effect of age ($z = 0.407$, $p = 0.684$) and sub-group analysis by age category also failed to identify a specific age of heightened sex difference (Supp. Table 4). With regard to imaging methodology, we found no effect of year of study on the magnitude of this sex difference ($z = -0.836$, $p = 0.403$), and a sub-group comparison of manual ($\kappa = 41$, $g = 0.563$) versus automated ($\kappa = 9$, $g = 0.490$) hippocampal segmentation methods was not significantly different ($Q_{bet} = 0.468$, $p = 0.494$).

Raw right HCV was reported for matched male and female groups for all but one (Goldstein et al., 2002) of the same samples. Fig. 2B and Table 5 show the meta-analysis for these 49 samples ($n = 4370$): a medium-sized effect, larger in males ($g = 0.526$, $p < 0.001$), corresponding to a pooled volume difference of 0.203 cm^3 (6.7%). Again, neither age ($z = 0.027$, $p = 0.978$; Supp. Table 4) nor year of study ($z = 0.293$, $p = 0.770$) appeared to influence this effect size, and sub-group analysis showed no difference between manual ($\kappa = 40$, $g = 0.530$) and automated ($\kappa = 9$, $g = 0.517$) segmentation methods ($Q_{bet} = 0.012$, $p = 0.915$) in magnitude of the sex difference.

Bilateral uncorrected HCVs were reported in 29 samples ($n = 4749$) between 6 and 71 years of age. Again, male volumes are clearly larger ($g = 0.557$, $p < 0.001$; Table 5 and Suppl. Fig. 1), corresponding to a pooled volume difference of 0.397 cm^3 (6.2%). Meta-regression revealed no linear effect of age on this sex difference ($z = -0.035$, $p = 0.972$) although subgroup analysis indicated a smaller male advantage in the 19-29 year-old group. Also for this dataset, year of study was significantly correlated with effect size ($z = 2.161$, $p = 0.031$), indicating larger differences in more recent studies.

ICV and TBV are substantially larger in males

Larger male HCV is not surprising, considering that men's overall brain volume is some 8–14% larger across the lifespan (Paus, 2010; Ruigrok et al., 2014). To compare the HCV sex difference to global brain measures, we performed meta-analysis on the sex difference in both ICV and TBV, using all such values that were reported in the 76 final studies included in our hippocampal meta-analyses.

Mean ± SD of male and female ICV was reported for 22 of the samples ($n = 3057$; Table 3). The pooled difference in ICV was 155.8 cm^3 (10.7%) larger in males, corresponding to a Hedges' g of 1.272 ($p < 0.001$; Fig. 3 and Table 5). Both age ($z = 3.513$, $p < 0.001$; Supp. Table 4) and year of study ($z = 2.078$, $p = 0.038$) were associated with the ICV sex difference, indicating a larger difference among older participants and in more recent studies.

The findings were similar for TBV, based on the 21 studies ($n = 1669$) that reported its volume in addition to HCVs (Table 4). The mean difference was 116.8 cm^3 (10.6%) larger in males, an effect size of $g = 1.085$ ($p < 0.001$; Fig. 4 and Table 5). Both meta = regression ($z = 4.420$, $p < 0.001$) and sub-group (Suppl. Table 4) analyses indicate that the magnitude of the sex difference increases with age, but it was not affected by study date ($z = -0.258$, $p = 0.797$).

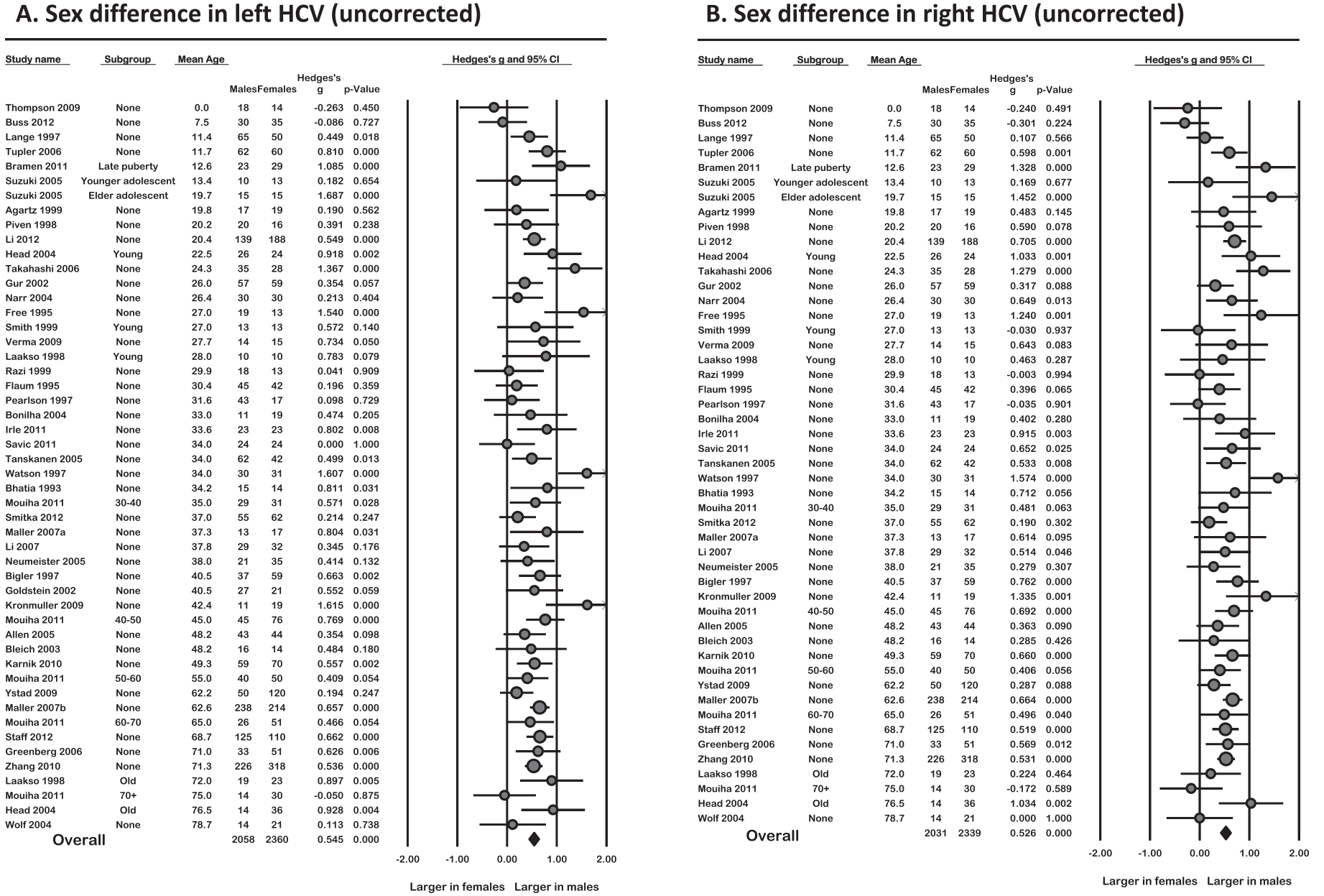

Fig. 2. Sex difference effect sizes (Hedges' g) and 95% confidence intervals (CI) for 50 samples (43 studies) reporting left (A) and 49 samples (42 studies) reporting right (B) uncorrected hippocampal volumes, where negative effect sizes indicate larger volumes in females. Studies are ordered by the mean age of all participants and the number of participants are listed under the headings "Males" and "Females" in this and subsequent figures. Pooled effect sizes correspond to roughly 7% larger volumes in males. Study details appear in Table 1.

HCV does not differ between males and females after correcting for TBV or ICV

The fact that raw HCV, like ICV and TBV, are all larger in males suggests that the hippocampus is not specifically sexually dimorphic. However, the smaller pooled effect size (~0.5) for the sex difference in HCV compared to the effect sizes (~1.1) for TBV and ICV sex difference does raise the possibility that the structure is proportionally larger in women, as commonly stated (Cahill, 2006; Hines, 2010; Knickmeyer et al., 2014; Lentini et al., 2013). To test either possibility, we performed meta-analyses on male and female HCVs that were already corrected for individual differences in ICV or TBV.

Altogether, 26 of the studies we identified reported ICV- or TBV-corrected left HCVs from 29 matched samples of healthy males and females (n = 2183). Fig. 5A illustrates that there is no significant sex difference in these corrected left HCVs (g = −0.063, p = 0.398). Neither age (z = −0.587, p = 0.557; Supp. Table 4) nor year of study (z = 1.634, p = 0.102) influenced the pooled effect size. The results were nearly identical for corrected right HCVs (Fig. 5B): a small, non-significant sex difference (g = −0.112, p = 0.070) based on 28 matched samples (n = 2135), with neither age (z = 0.158, p = 0.974; Supp. Table 4) nor year of study (z = 1.803, p = 0.071) moderating the sex effect.

Given the wide variety of methods used to correct for individual differences in overall brain volume (Table 2), we further analyzed left and right HCV sex differences according to whether ICV or TBV was the correcting factor. In all cases, the pooled effect size for HCV sex difference remained small and statistically non-significant (Table 5 and Supp. Figs. 2 and 3). Hedges' g was slightly negative (indicating larger corrected volume in females) for three of the four analyses, but slightly positive (g = 0.011, larger in males) for left HCV corrected by TBV.

As a last way of assessing the effect of correction method on HCV sex difference, we separated the ICV-corrected samples according to whether HCVs were reported as unit-less ratios (individual HCV/individual ICV) or as actual volumes after a covariance adjustment based on the linear relationship between ICV and HCV across the full sample (Jack et al., 1989; Perlaki et al., 2014). Of the 22 sex-matched samples of ICV-corrected left and right HCV samples in our data capture, eight used ratio correction, nine used covariance correction, and five used other methods that were not analyzed further (see Table 2).

Once again, for both left and right hippocampi, the pooled effect sizes for sex difference were small and not statistically significant (Hedges' g between − .074 and −0.206; Table 5). The effect sizes were larger using ratio correction (Table 5, Supp. Fig. 4), but not significantly different from null and these samples were considerably more heterogeneous than those using covariance correction (Fig. 6), which has been shown to be a better method for reducing variance in hippocampal (Free et al., 1995) and other (Sanfilipo et al., 2004) brain volume measurements. For samples using the covariance method, it was possible to calculate a pooled volume difference, amounting to 0.012 cm^3 larger left HCV in females (0.5% difference), and 0.015 cm^3 larger (0.7%) right HCV in females.

Finally, our search also captured 11 samples reporting male and female bilateral HCVs corrected by TBV or ICV. In both of these analyses, the pooled effect size showed larger volumes in females (Table 5 and Supp. Figs. 5 and 6), although the effect was not significant for ICV-corrected volumes. However, the small number of samples and high heterogeneity in these analyses indicate less reliability than the unilateral corrected HCVs.

Discussion

HCV has been extensively studied in relation to various psychiatric disorders, but less attention has been paid to the influence of sex. Several reviews of brain sex difference (Cahill, 2006; Durston et al., 2001; Gur et al., 2010; Hines, 2010) state that the hippocampus is proportionally larger in females, a difference thought to underlie women's advantage on certain verbal and memory tasks (Andreano and Cahill, 2009).

However, we found that for uncorrected volumes, the hippocampus is actually some 6–7% larger in males, amounting to a roughly 0.4 cm^3 bilateral difference. In studies that corrected for individual differences in ICV or TBV, this effect was reduced to a non-significant 0.6% (~0.013 cm^3) larger HCV in females. We did observe a somewhat larger effect size (favoring females) in studies reporting corrected bilateral HCV. However, this sex difference was based on fewer, more heterogeneous samples, and its significance varied with correction method.

A similar conclusion about bilateral HCV emerged from a study by Fjell et al. (2009), who combined data from seven subsamples (n = 1143) and found a small but significant sex difference in bilateral HCV that switched sign depending on whether ICV or TBV was used as the correcting factor: ICV-corrected bilateral HCV was slightly larger in males (d = 0.169), whereas TBV-corrected volume was slightly larger in females (d = −0.125). Taken together with our findings, these results indicate that any sex difference in HCV is modest and highly

Table 3
Studies reporting intracranial volumes (ICV) in male and females (mean ± SD cm^3).

Study (1st Author, Year)	Subgroup	#M/#F	Mean Age	Male ICV	Female ICV
Agartz et al. (1999)		17/19	19.8	1368.1 ± 87.6	1248.4 ± 113.1
Cherbuin et al. (2008)		197/233	46.7	1550.0 ± 110.0	1370.0 ± 100.0
Flaum et al. (1995)		45/42	30.4	1598.0 ± 138.0	1427.0 ± 123.0
Head et al. (2005)[a]	Younger	26/24	22.5	1573.5 ± 111.0	1394.5 ± 114.8
	Older	14/36	76.5	1581.0 ± 152.2	1378.2 ± 110.6
Irle et al. (2011)		23/23	33.6	1599.0 ± 103.0	1427.0 ± 92.0
Knoops et al. (2012)[a]		514/122	62.0	1489.0 ± 112.0	1311.0 ± 93.0
Lopez-Larson et al. (2009)[a]		16/12	10.5	1239.0 ± 67.3	1179.3 ± 57.7
Maller et al. (2007a)		13/17	37.3	1488.0 ± 1350.0	1446.0 ± 1127.0
Maller et al. (2007b)		238/214	62.6	1590.0 ± 150.0	1400.0 ± 130.0
McHugh et al. (2007)		12/28	70.6	1485.7 ± 115.2	1364.5 ± 108.7
Murphy et al. (1996)	Young and Old	35/34	70	1557.0 ± 119.0	1403.0 ± 114.0
Nardelli et al. (2011)		32/24	11.3	1620.0 ± 136.0	1448.0 ± 154.0
Narr et al. (2004)		30/30	26.4	1271.7 ± 96.4	1150.1 ± 66.8
Nosarti et al. (2002)		31/17	14.9	1428.6 ± 102.0	1304.7 ± 96.3
Rodrigue et al. (2013)[a]		37/76	53.96	2201.8 ± 119.1	2044.8 ± 152.8
Suzuki et al. (2005)	Older adolescent	10/13	13.4	1540.0 ± 196.5	1400.0 ± 135.5
	Younger adolescent	15/15	19.7	1541.0 ± 107.5	1355.0 ± 103.5
Wolf et al. (2004)		14/21	78.7	1548.0 ± 107.0	1492.0 ± 133.0
Ystad et al. (2009)		50/120	62.2	1585.7 ± 159.3	1381.3 ± 118.5
Zhang et al. (2010)		226/318	71.3	1611.9 ± 130.3	1402.7 ± 105.3
Zhang et al. (2012)[a]		14/10	7.28	2783.4 ± 178.4	2834.9 ± 120.0

[a] Data supplied directly by authors.

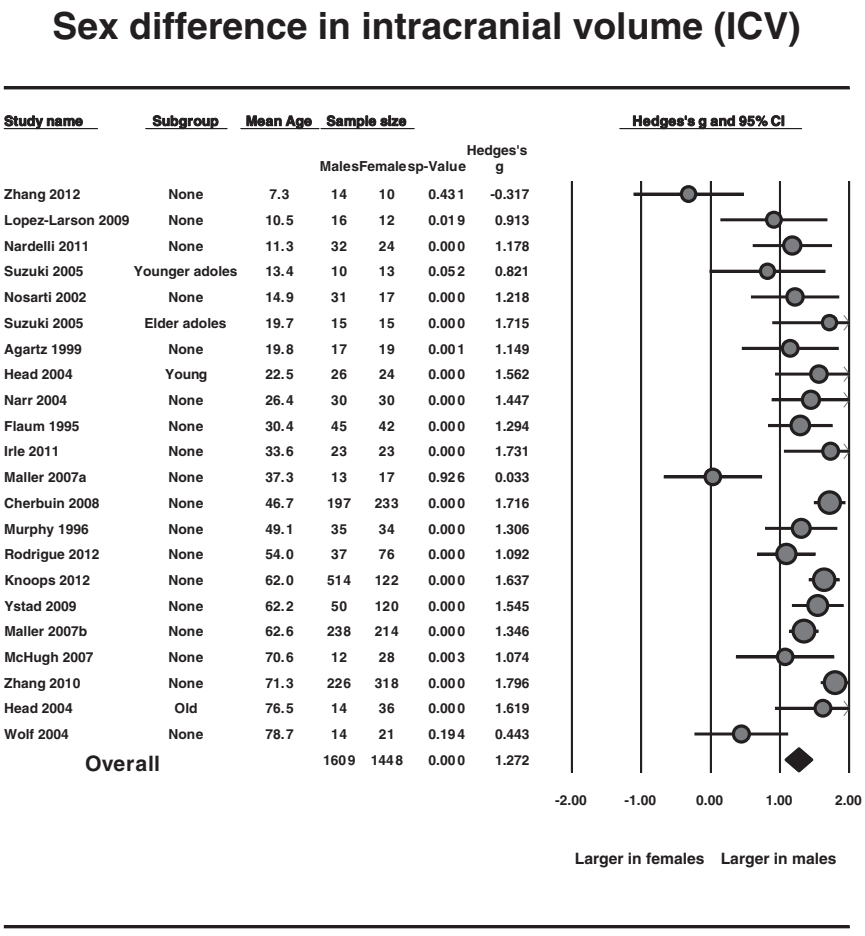

Fig. 3. Sex difference in intracranial volume (ICV), based on the 22 samples from 20 hippocampal studies that included this data, ordered by mean age of participants. The pooled effect size corresponds to a nearly 11% larger volume in males. Study details appear in Table 3.

sensitive to the method used for brain size correction. ICV is generally regarded as a better correction factor than TBV, since the former stays more stable throughout life (Ystad et al., 2009). For both unilateral and bilateral HCV, we found no significant sex difference based on ICV-corrected measures, and Fjell et al. (2009) reported a modestly larger volume in males, opposite the trend we observed.

Our results should also be interpreted in light of a recent meta-analysis of brain sex differences by Ruigrok et al. (2014). At the

Table 4
Studies reporting total brain volumes (TBV) in males and females (mean ± SD cm^3).

Study	Subgroup	#M/#F	Mean age	M	F
Abbs et al. (2011)		27/21	40.5	1116.2 ± 92.1	1023.6 ± 89.7
Bhatia et al. (1993)		15/14	34.2	1313.9 ± 89.5	1135.1 ± 101.2
Caviness et al. (1996)		15/15	9.2	1356.9 ± 80.6	1267.7 ± 81.7
Filipek et al. (1994)		10/10	27.2	1434.8 ± 116.2	1325.4 ± 85.4
Gur et al. (2002)		57/59	26.0	1365.2 ± 106.2	1195.1 ± 99.5
Irle et al. (2011)		23/23	33.6	1294.0 ± 83.0	1159.0 ± 91.0
Karnik et al. (2010)[a]	All BDNF genotypes	59/70	49.3	1045.1 ± 106.4	938.1 ± 87.3
Li et al. (2014)		38/38	43.0	1294.4 ± 98.8	1152.6 ± 80.7
Maller et al. (2006)	TBV-corrected	76/74	62.3	1260.0 ± 110.0	1110.0 ± 90.0
Maller et al. (2007a)		13/17	37.3	1227.0 ± 1294.0	1192.0 ± 967.0
Neumeister et al. (2005)[a]		22/35	38.0	1253.2 ± 11.1	1121.9 ± 97.4
Patwardhan et al. (2002)		10/10	28.5	1267.1 ± 111.3	1196.0 ± 40.6
Pearlson et al. (1997)		43/17	31.6	1469.0 ± 148.0	1328.0 ± 99.0
Savic and Arver (2011		24/24	34.0	1657.0 ± 123.0	1425.0 ± 146.0
Smitka et al. (2012)	Total	55/62	37.0	1445.0 ± 112.3	1270.0 ± 113.4
Staff et al. (2012)[a]		125/110	68.7	1203.7 ± 97.0	1069.5 ± 90.6
Thompson et al. (2008)[a]	Preterm infants	93/91	0.0	452.8 ± 67.0	424.2 ± 60.9
Thompson et al. (2009)[a]	Full-term infants	18/14	0.0	461.7 ± 57.5	437.4 ± 46.7
Wolf et al. (2004)		14/21	78.7	1088.0 ± 100.0	1069.0 ± 113.0
Ystad et al. (2009)		50/120	62.2	1119.4 ± 104.6	966.3 ± 84.2
Yurgelun-Todd et al. (2003)		13/24	14.6	1425.3 ± 113.5	1341.4 ± 108.4

[a] Data supplied directly by authors.

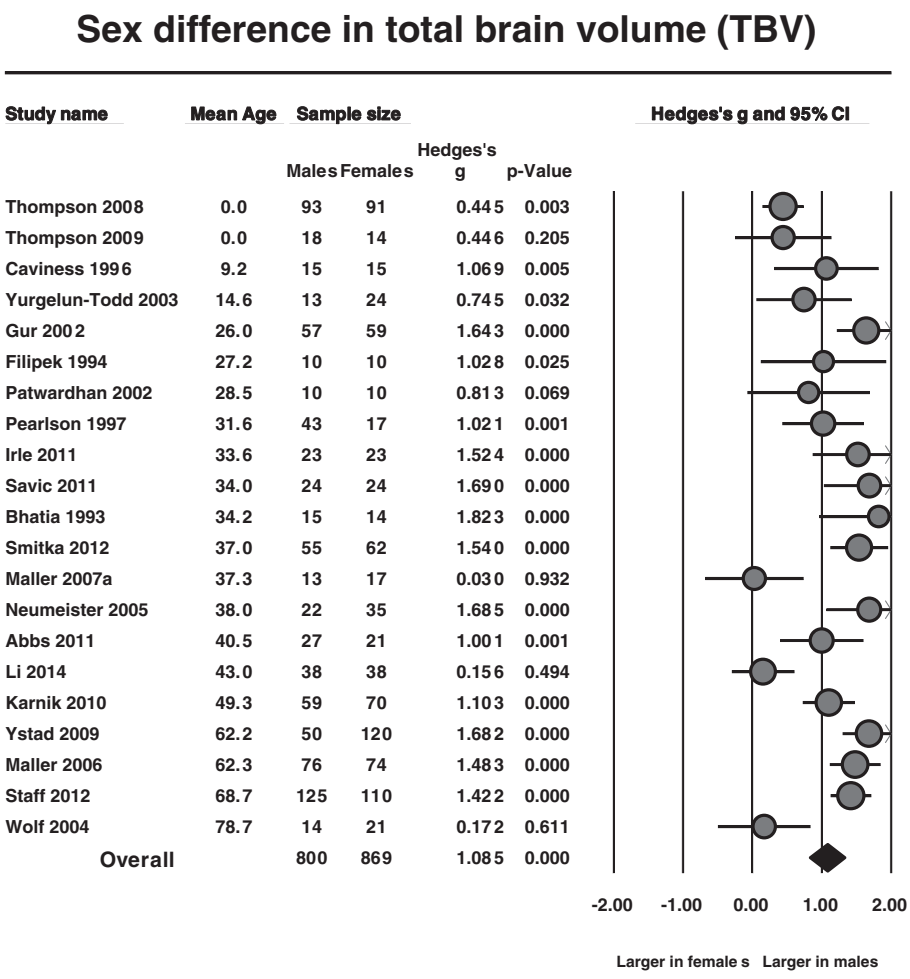

Fig. 4. Sex difference in total brain volume (TBV), based on the 21 hippocampal studies that included this data, ordered by mean age of participants. The pooled effect size corresponds to a nearly 11% larger volume in males. Study details appear in Table 4.

whole-brain level, these authors found sex differences comparable to our observations: for ICV, they reported a 135.3 cm^3 (12%) larger volume in males, similar to our 155.8 cm^3 (10.7%) difference; for TBV, they found a 131 cm^3 (10.8%) larger volume in males, close to the 116.8 cm^3 (10.6%) pooled difference we observed. Then, in their subregion analysis based on 16 voxel-based morphometry studies,

Table 5
Summary of meta-analyses.

Brain region	Hedges g	95% CI	p value	Volume difference in cm^3 (%)	I^2	κ	# M/F
Left HCV uncorrected	**0.545**	0.449 to 0.640	<**0.001**	0.207 (7.1)	51.4%	50	2058/2360
Right HCV uncorrected	**0.526**	0.428 to 0.625	<**0.001**	0.203 (6.7)	53.3%	49	2031/2339
Total HCV uncorrected	**0.557**	0.433 to 0.681	<**0.001**	0.397 (6.2)	66.2%	29	2377/2372
Intracranial volume (ICV)	**1.272**	1.089 to 1.455	<**0.001**	155.8 (10.7)	72.7%	22	1609/1448
Total brain volume (TBV)	**1.085**	0.839 to 1.331	<**0.001**	116.8 (10.6)	79.7%	21	800/869
Left HCV corrected (all methods)	−0.063	−0.210 to 0.084	0.398	*	59.1%	29	1030/1153
Left HCV corrected (by TBV)	0.011	−0.201 to 0.224	0.918	*	31.2%	8	271/290
Left HCV corrected (by ICV)	−0.081	−0.267 to 0.104	0.391	*	64.9%	22	772/880
Left HCV corr. by ICV ratio	−0.206	−0.638 to 0.227	0.351	*	76.2%	8	331/364
Left HCV corr. by ICV covariance	−0.074	−0.266 to 0.119	0.454	−0.012 (0.5)	34.0%	9	325/390
Right HCV corr. (all methods)	−0.112	−0.234 to 0.009	0.070	*	38.8%	28	1003/1132
Right HCV corrected (by TBV)	−0.078	−0.253 to 0.096	0.377	*	0%	7	244/269
Right HCV corrected (by ICV)	−0.123	−0.275 to 0.030	0.116	*	47.8%	22	772/880
Right HCV corr. by ICV ratio	−0.172	−0.516 to 0.171	0.326	*	62.5%	8	331/364
Right HCV corr. by ICV covariance	−0.089	−0.276 to 0.099	0.354	−0.015 (0.7)	30.9%	9	325/390
Total HCV corr. (all methods)	**−0.361**	−0.603 to −0.118	**0.004**	*	74.7%	11	759/802
Total HCV corrected (by TBV)	**−0.447**	−0.778 to −0.115	**0.008**	*	68.3%	5	367/370
Total HCV corrected (by ICV)	−0.300	−0.708 to 0.109	0.151	*	77.6%	6	392/432

HCV, hippocampal volume; I^2, proportion of non-random heterogeneity; κ, # of matched M/F samples.
All effect sizes (Hedges g or difference in mean volumes) calculated using a random effects model.
*Unable to calculate because some or all volumes were reported as unitless ratios, not in cm^3.

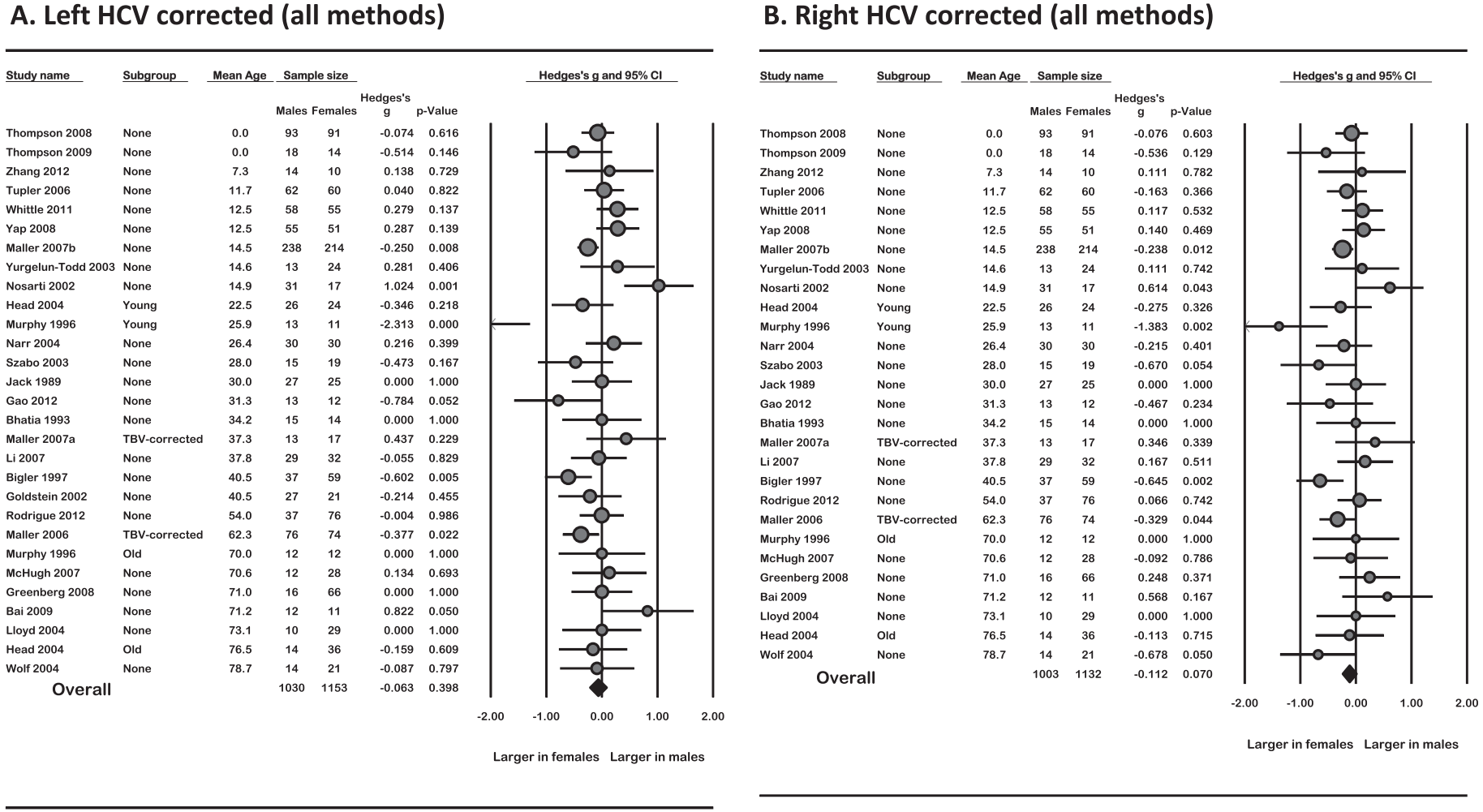

Fig. 5. Sex difference effect sizes and 95% CI for 29 samples (26 studies) reporting left (A) and 28 samples (25 studies) reporting right (B) hippocampal volumes corrected for individual differences in TBV or ICV and ordered by mean age of participants. Neither pooled effect size indicates a significant sex difference. Study details appear in Table 2.

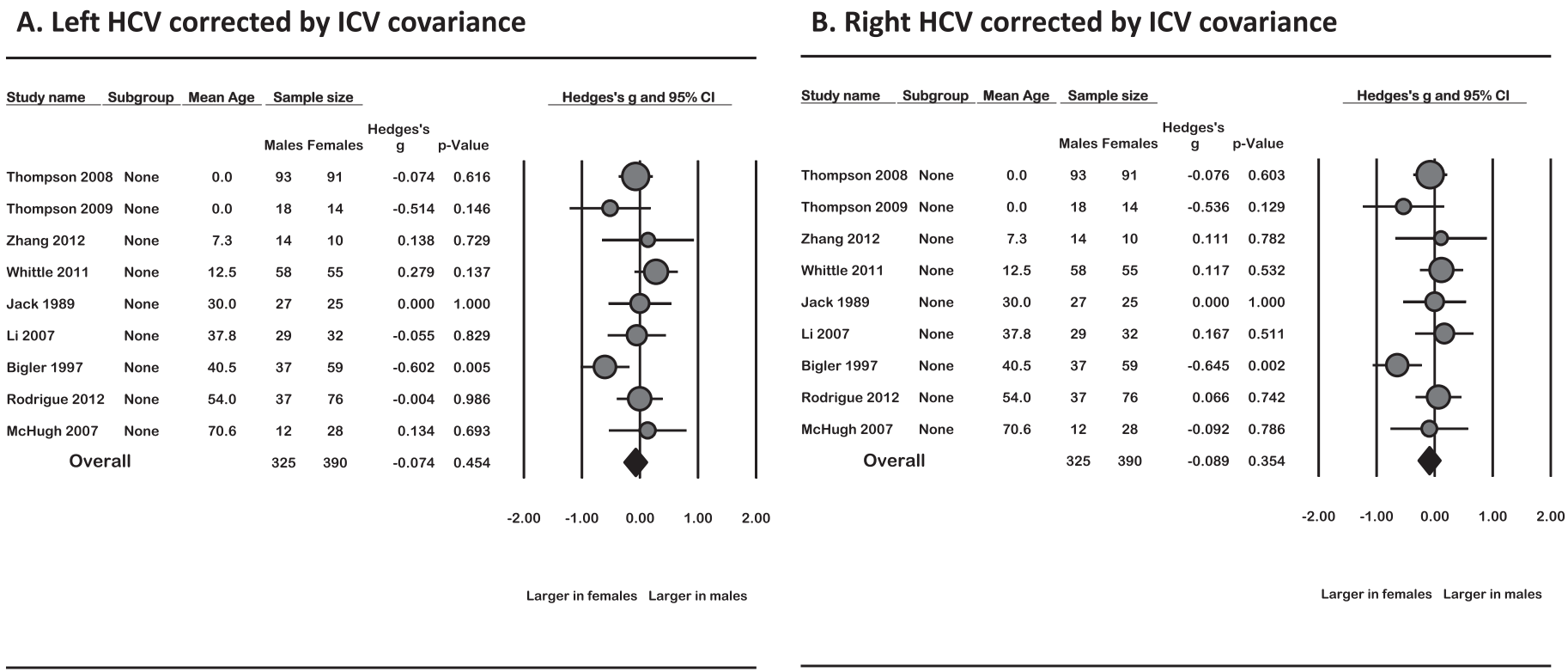

Fig. 6. Sex difference effect sizes and 95% CI for the subset of 9 studies reporting left (A) and right (B) hippocampal volumes corrected by individual ICV using a covariance method, ordered by mean age of participants. See Table 2 for study details. Neither pooled effect size indicates a significant sex difference.

Ruigrok et al. (2014) reported larger volumes in males for regions that included both left and right hippocampi, amygdalae, anterior parahippocampal gyri, temporal poles, and putamina. However, these authors did not disaggregate the sex effect for individual brain structures, so it is unclear whether the hippocampus contributed to the sex difference in this large brain region.

Age and hormonal effects on HCV sex difference

Among prior studies that have commented on hippocampal sex differences, several have suggested that such differences are constrained to either juvenile (Bramen et al., 2011; Cosgrove et al., 2007; Neufang et al., 2009; Suzuki et al., 2005) or aging (Knoops et al., 2012; Murphy et al., 1996; Pruessner et al., 2001; Raz et al., 2004a) phases of life. We thus ordered all forest plots according to average participant age of each sample, which are comprised of male and female groups that were statistically matched in age. Visual inspection reveals no obvious drift in magnitude of the HCV sex difference over the age span, nor did meta-regression or age subgroup analyses (Supp. Table 4) reveal a phase in which the HCV sex difference is reliably different from other ages. By contrast, both TBV and ICV sex differences were found to be larger in older samples; whether this reflects a true aging effect or results from cohort differences cannot be determined from this data, but the increases in TBV and ICV sex difference over the lifespan were not sufficient to induce age-related change in corrected HCV sex differences.

Our ability to detect an age effect on the HCV sex difference is subject to several limitations. First, in studies that included a wide age range of participants, the mean age obscures possible HCV changes over that range. A more meaningful analysis might have resulted using participants' median age, a better estimate of central tendency that unfortunately few studies currently report. Second, by using the weighted average of male and female ages, this factor is influenced by the ratio of males and females in a particular study. Third, there were relatively few studies of children and adolescents in either the raw or corrected HCV collection. Although subgroup analysis (Supp. Table 4) of raw left and right HCV hints at a smaller sex difference in children (ages 0–11) compared to adolescents and adults, there were just four studies in this subgroup, whereas the sex difference in raw bilateral HCV within the same 0–11 year-old subgroup was of considerable magnitude ($g = 0.445$) and based on six studies.

A key reason why the HCV sex difference has been suspected to change with age is based on gonadal hormone effects on hippocampal structure and function (e.g., Cooke and Woolley, 2005; Leranth et al., 2008). Since gonadal hormones fluctuate through the lifespan, exhibiting notable sex differences in both prenatal and post-pubertal phases, it is plausible that sex differences in the hippocampus might be more pronounced at these ages.

However, existing MRI studies do not provide strong evidence that gonadal hormones affect HCV. Prenatal testosterone variations do not appear to influence sexually-dimorphic brain structures, according to a large study of neonates (Knickmeyer et al., 2014). At the pubertal transition, Neufang et al. (2009) found that hippocampal gray matter volume correlated with circulating testosterone levels, but Peper et al. (2009) failed to find such a relationship. Savic and colleagues were similarly unable to correlate circulating testosterone levels with hippocampal sex differences (Lentini et al., 2013; Savic and Arver, 2011). Moreover, in a study of young adults, Witte et al. (2010) identified several brain regions whose gray matter volume covaries with circulating testosterone, estrogen, or progesterone levels, but the hippocampus was not among them.

In contrast to these largely negative findings, two studies of menstrual fluctuations have suggested that gray matter volume in the right anterior hippocampus (Protopopescu et al., 2008) or right parahippocampal/fusiform gyri (Pletzer et al., 2010) is greater in women during the higher-estrogen, compared to lower-estrogen phase of the cycle. Similarly, two studies of post-menopausal women found associations between hormone replacement therapy (HRT) and larger right HCV (Eberling et al., 2003; Lord et al., 2008). However, these results could be explained by "healthy user bias," a significant confound in many observational studies of HRT (Gleason et al., 2012), and they are also contradicted by another study (Raz et al., 2004b), which found that HCV in aging women was not related to HRT.

In sum, the evidence that estrogen exerts a trophic effect, particularly on right HCV, is more compelling than evidence regarding testosterone. Nonetheless, the weakness of existing hormonal data, coupled with the general lack of significant sex difference in corrected HCVs at any age, indicates that gonadal hormones do not exert a notable influence on global HCV.

Limitations, heterogeneity, and plasticity

Like all meta-analyses, this study is subject to publication bias, which for brain volume abnormalities skews toward the under-reporting of negative results (Ioannidis, 2011). Our analysis is less vulnerable to this bias than most, since sex difference was not a target hypothesis in most of the studies. Only 19 of the 76 studies included "sex," "gender," or related terms in their titles, so it is unlikely that publication bias is a significant factor in this study.

A greater limitation is the difficulty of proving a negative result. Based on the number of samples and average sample sizes we collected for left and right corrected HCV, our random effects meta-analyses of moderately heterogeneous samples have 80% power to detect a sex difference effect size of ± 0.156 (Borenstein, 2009). For the effect sizes we actually observed (-0.063 for left HCV, -0.112 for right HCV) the power was 21% and 52%, respectively. Thus, our study indicates an upper limit on a statistically resolvable sex difference in HCV, in the range considered "very small" by Cohen's convention. Although it remains possible that a significant, ~0.6% volume difference could be detected with 2–3 times more studies, it seems reasonable to conclude that the term sexual "dimorphism" (literally, "two different forms") does not apply (Ball et al., 2014) to the male–female difference in hippocampal volume.

The ability to detect a small sex difference in HCV is further limited by the moderate-to-high level of heterogeneity we observed across studies. This heterogeneity likely reflects both technical and demographic factors. Meta-regression did not reveal a significant influence of age or year of study in most of our analyses. Year of study can be considered a proxy for changes in MRI equipment and image processing technology over the past quarter-century, which could influence the precision of hippocampal measurement and thereby, the chance of detecting a significant sex difference. We did not detect any change over time in the sex effect size for either left or right raw HCV, although studies reporting raw bilateral HCV and ICV showed a larger male advantage in more recent years. However, the TBV sex difference was not affected by year of study, nor were most measures of the sex difference in corrected HCVs.

Of the many technical factors that could influence the heterogeneity of sex difference effect sizes, hippocampal segmentation seems the likeliest (Adriano et al., 2012). The studies we captured used a wide range of manual and automated methods to demarcate hippocampal boundaries—too many to feasibly code in meta-analysis. We note that anatomical boundaries were not identical in all studies; measurements were not always performed by blind raters; and inter-rater reliability was often not reported or was not always high. Of these several methodological variables, we were able to compare only the effect of automated versus manual segmentation; sex differences were slightly smaller for raw left and right HCVs measured using automated, as compared to manual segmentation, but the difference was not statistically significant.

As a complex, three-dimensional structure, the human hippocampus is challenging to segment from surrounding tissues. Konrad et al. (2009) reviewed 71 published protocols for delineating hippocampal

boundaries in MRI, identifying five areas of particular ambiguity. Of these, the posterior or "tail" portion of the hippocampus, which includes up to 11% of total HCV, has been especially variable across studies. Since the tail region has been singled out as the basis for hippocampal sex difference in studies of adolescents (Gogtay et al., 2006), early middle-age (Wellington et al., 2012), and older adults (Maller et al., 2006), this ambiguity could contribute to the heterogeneity in sex effect sizes we observed.

Measurement variability is further compounded in studies reporting ICV- or TBV-corrected volumes. First, there is the issue that HCV does not scale perfectly with either ICV or TBV. In a large meta-analysis of the genes associated with HCV, Stein et al. (2012) found a wide range of correlations between HCV and both of these global measures, with pooled correlations of just 0.50 for ICV and 0.58 for TBV, respectively. Second, heterogeneity is presumably enhanced by the fact that the normalizing factor itself is subject to measurement variability (Guadalupe et al., 2014). Indeed, Nordenskjold et al. (2013) demonstrated that two different automated segmentation programs both overestimate ICV, resulting in smaller sex effect sizes for corrected HCV relative to manual ICV segmentation. Nonetheless, we observed the lowest heterogeneity for sex effect sizes in HCVs corrected using either individual TBV (ratio or covariance) or ICV covariance methods. Since these analyses also showed some of the smallest pooled effect sizes for sex difference, the low heterogeneity raises confidence in the conclusion that sex difference in HCV is minor, after accounting for individual differences in brain size.

A similar conclusion was reached by Perlaki et al. (2014) in a recent paper that compares ratio ("proportion") and covariance ("general linear model") corrections on both the sex- and ICV-related differences in HCV. In an elegant analysis, Perlaki et al. (2014) showed for both MR volumetry and voxel-based morphometry that ratio correction resulted in relatively larger HCV for participants with a smaller ICV (male or female), whereas covariance correction eliminated both the sex and ICV influences on HCV. Thus, for purposes of both reducing heterogeneity and correcting for individual differences in overall brain size, ICV covariance method appears the optimal method. It is therefore notable that in both our hands and in Perlaki et al. (2014), this method resulted in the least significant HCV sex difference.

Finally, it is important to consider the many demographic factors that likely also contribute to sex effects on HCV. Although we found little evidence for an age effect on HCV sex difference, we were unable to assess the influence of ethnicity, SES, education, or IQ, since these were not consistently reported. Of all brain structures, the hippocampus is the best known to be influenced by experience and lifestyle (Fotuhi et al., 2012; Sullivan et al., 2001). In addition to the several psychiatric disorders associated with hippocampal atrophy—depression (McKinnon et al., 2009; Videbech and Ravnkilde, 2004), PTSD (Smith, 2005; Woon and Hedges, 2011), schizophrenia (Adriano et al., 2012), BPD (Ruocco et al., 2012), Alzheimer's disease (Barnes et al., 2009), and MCI (Shi et al., 2009)—HCV appears to be negatively impacted by obesity (Raji et al., 2010; Shefer et al., 2013), diabetes, hypertension, hypoxic brain injury, obstructive sleep apnea, head trauma, alcohol abuse (Fotuhi et al., 2012) and low childhood SES (Noble et al., 2012b; Staff et al., 2012). On the positive side, larger HCVs have been associated with mental and physical training regimens including meditation (Luders et al., 2013), aerobic exercise (Erickson et al., 2011) balance training (Hufner et al., 2011), spatial navigation (Woollett and Maguire, 2011), and high-stakes exam preparation (Draganski et al., 2006). Similarly, HCV in later life has been positively associated with educational attainment (Noble et al., 2012a) and with supervisory responsibilities in mid-career (Suo et al., 2012). Considering the many lifestyle factors that can influence HCV, and the possibility that these differ systematically between males and females in specific cohorts (Eliot, 2011), it is likely that the heterogeneity in sex effect sizes for HCV reflects true variation across different populations.

Conflict of interest

All of the authors report no biomedical financial interests or other conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.08.050.

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