

Individual differences in the dominance of interhemispheric connections predict cognitive ability beyond sex and brain size

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ABSTRACT

Global structural brain connectivity has been reported to be sex-dependent with women having increased interhemispheric connectivity (InterHc) and men having greater intrahemispheric connectivity (IntraHc). However, (a) smaller brains show greater InterHc, (b) larger brains show greater IntraHc, and (c) women have, on average, smaller brains than men. Therefore, sex differences in brain size may modulate sex differences in global brain connectivity. At the behavioural level, sex-dependent differences in connectivity are thought to contribute to men-women differences in spatial and verbal abilities. But this has never been tested at the individual level. The current study assessed whether individual differences in global structural connectome measures (InterHc, IntraHc and the ratio of InterHc relative to IntraHc) predict spatial and verbal ability while accounting for the effect of sex and brain size. The sample included forty men and forty women, who did neither differ in age nor in verbal and spatial latent components defined by a broad battery of tests and tasks. High-resolution T₁-weighted and diffusion-weighted images were obtained for computing brain size and reconstructing the structural connectome. Results showed that men had higher IntraHc than women, while women had an increased ratio InterHc/IntraHc. However, these sex differences were modulated by brain size. Increased InterHc relative to IntraHc predicted higher spatial and verbal ability irrespective of sex and brain size. The positive correlations between the ratio InterHc/IntraHc and the spatial and verbal abilities were confirmed in 1000 random samples generated by bootstrapping. Therefore, sex differences in global structural connectome connectivity were modulated by brain size and did not underlie sex differences in verbal and spatial abilities. Rather, the level of dominance of InterHc over IntraHc may be associated with individual differences in verbal and spatial abilities in both men and women.

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Introduction

Sex differences in neuroanatomical features, such as brain size and structural connectivity, have been consistently reported. On average, men have a larger brain size than women as denoted by a higher intracranial volume and total brain volume (Ruigrok et al., 2014), higher tissue-specific volume (Burgalata et al., 2012; Gong et al., 2011; Ruigrok et al., 2014), a greater amount of neurons, increased global cortical thickness and total cortical surface area (Escorial et al., 2015; Luders et al., 2009; Pakkenberg and Gundersen, 1997). Men also have higher fractional anisotropy (FA) values [a Diffusion Tensor Imaging (DTI)-metric] in major white matter tracts (Clayden et al., 2012; Herting et al., 2012; Hsu et al., 2008), while women have increased FA in the corpus callosum (Kanaan et al., 2012). Using a structural connectome-based approach, Ingahalikar et al. (2014) reported coherent findings: increased interhemispheric connectivity (InterHc) in women and, for both hemispheres, increased intrahemispheric connectivity (IntraHc) in men (Ingahalikar et al., 2014). However, this men-women difference in the dominant pattern of hemispheric connectivity may be primarily driven by brain size and not by sex per se, as demonstrated by Hanggi et al. (2014). Larger brains may compensate their increased conduction delay in transcallosal information transfer, due to the increased size transfer, by over-proportionally enhancing IntraHc (Ringo et al., 1994) and this occurs regardless of the individual's sex (Hanggi et al., 2014). On a functional level, this compensation effect might lead to larger brains (more likely in men) to show stronger lateralization or functional asymmetry of several brain functions than smaller brains (more likely in women). These functions include visual and language processing, spatial orientation, attention, face recognition, motor control of the hands, sense of body ownership and memory (Ageaoglu et al., 2015; Hausmann, 2017; Hiscock et al., 1994; Hiscock et al., 1995; Josse et al., 2006; Ocklenburg et al., 2016; Shaywitz et al., 1995; Tomasi and Volkow, 2012; Tzourio-Mazoyer et al., 2010).

Nevertheless, the direct influence of sex-related differences in brain size and connectome organization for explaining sex differences at the cognitive level is still unclear. Men and women show, at the group level, average differences in cognitive abilities: men outperform women in specific spatial abilities, while women outperform men in specific verbal abilities (Brody, 1992; Dolan et al., 2006; Hunt, 2011; Miller and Halpern, 2014; van der Sluis et al., 2006; Voyer et al., 1995). Although there is no concluding evidence regarding the causes underlying these average differences, reported sex differences in neuroanatomical features, such as brain size and connectivity, are reasonable candidates (Ingahalikar et al., 2014). Larger brain size has been consistently associated with higher full-scale IQ, performance IQ and verbal IQ scores across a wide age range (children and adults) (McDaniel, 2005; Pietschnig et al., 2015). But specific cognitive abilities, such as specific verbal and visuospatial skills, have shown distinguishable correlation patterns depending on the individual's sex (Burgalata et al., 2012; Witelson et al., 2006). Therefore, brain size should be taken into account when assessing the relationship between structural brain connectivity and spatial and verbal ability.

To the best of our knowledge, no study has assessed the relationship between sex differences in global connectome organization measurements and spatial-verbal ability at the individual level. Ingahalikar et al. (2014) proposed that average sex differences in the organization of the structural connectome might contribute to observed average sex differences in verbal and spatial performance (Ingahalikar et al., 2014). However, this hypothesis has not been tested. The current study addresses the complex link between sex-related differences in the structural connectome and cognitive differences at the individual level. For this purpose, men and women were matched by age and performance on two broad spatial-based and verbal-based latent components estimated from a large battery of fourteen tests and tasks. They also underwent MRI scanning for reconstructing the structural connectome

and obtaining two estimations of brain size, intracranial volume (ICV) and total brain volume (TBV). Firstly, we evaluated sex-related differences in InterHc, IntraHc, and the ratio InterHc/IntraHc (for measuring the level of dominance of InterHc over IntraHc), and also whether these differences were mediated by sex-related differences in brain size [as suggested by Hanggi et al. (2014)]. Then, we assessed whether individual differences in structural connectome measures were associated with spatial and verbal latent components in men and women, considering the potential influence of brain size on these relationships. Additionally, we probed these relationships using specific spatial and verbal tasks in which men and women systematically differ: Rotation of Solid Figures test (Yela, 1969) for assessing 3D mental rotation of object (in which men typically outperform women) and Keep Track task (Colom et al., 2008) for tapping verbal updating – working memory – (in which women typically outperform men) (Miller and Halpern, 2014).

We expected average sex differences in IntraHc, InterHc and the ratio InterHc/IntraHc, as well as in the two skill-specific measurements of spatial and verbal ability. Also, we predicted that sex differences in connectivity measures would disappear after controlling for brain size. Ingahalikar et al. (2014) suggested that a greater IntraHc would facilitate spatial processing in men (who outperform women, on average, in complex spatial tasks). Furthermore, greater InterHc in women would facilitate their better average performance in verbal tasks (Ingahalikar et al., 2014). Moving one step further, we tested these hypotheses at the individual level under the expectation that: verbal abilities would be positively associated with InterHc (specially in women) regardless of brain size, while spatial abilities would be positively associated with IntraHc (specially in men) independently of brain size.

Method

Participants

Fifty-eight young women (mean age = 19.5, SD = 1.3) and forty-four young men (mean age = 20.2, SD = 1.9) with no history of psychiatric or neurological illness (including a history of head injury and substance abuse) underwent cognitive assessment and MRI acquisition. All these participants were psychology undergraduate paid volunteers. Written informed consent following the Helsinki guidelines (World Medical Association, 2008) was obtained. The local ethical committee approved the study.

From the original sample, we selected forty women (mean age = 19.6, SD = 1.4, range 18 to 26 years) and forty men (mean age = 20.2, SD = 2.0, range 18 to 27 years) matched for their spatial and verbal ability, and age.

Psychological measures

A comprehensive cognitive battery of tests and tasks with different processing requirements (reasoning, working memory or attention control, among others) was administered. Two broad spatial-based and verbal-based latent components were estimated using principal component analysis (PCA) based on the tests and tasks displayed in Fig. 1a. More specifically, the spatial component was defined by seven measures: (1) DAT-SR [spatial relations subtest from the differential aptitude test battery (Bennett et al., 1990)]; (2) PMA-S [mental rotation subtest from the primary mental abilities battery (Thurstone and Thurstone, 1968)]; (3) Rotation of Solid Figures test (Yela, 1969); (4) Dot Matrix task (Colom et al., 2010); (5) 2-Back task (Colom et al., 2008); (6) a spatial variant of the Simon task (Colom et al., 2010); (7) Simple Recognition spatial task (Colom et al., 2008). The verbal component was estimated based on seven measures: (1) DAT-VR [verbal reasoning subtest from the differential aptitude test battery (Bennett et al., 1990)]; (2) PMA-V [vocabulary subtest from the

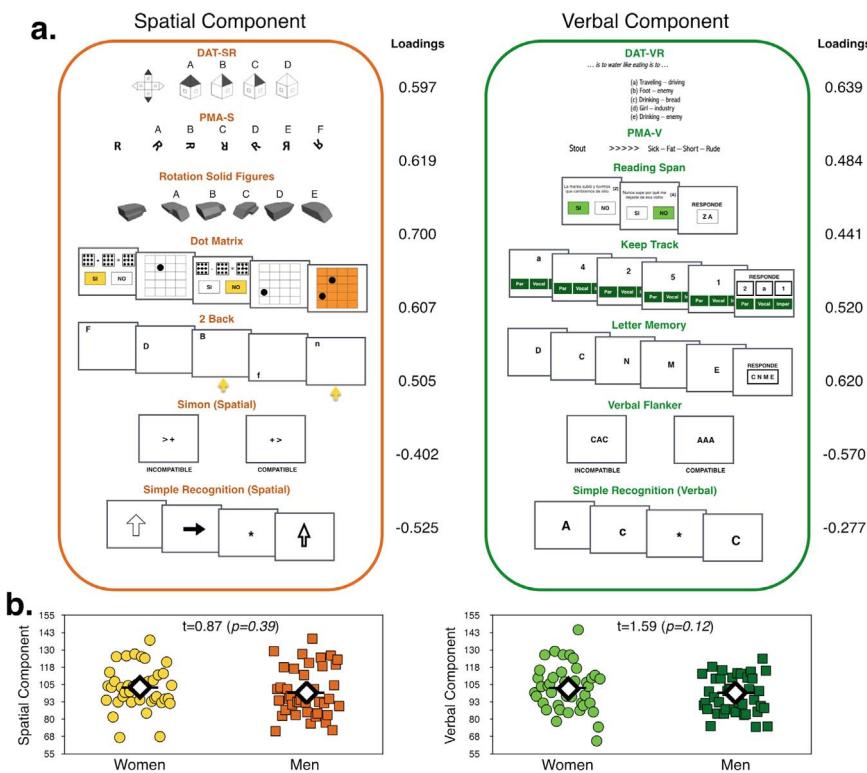


Fig. 1. (a.) Loadings obtained for the fourteen cognitive tests and tasks used for defining the two broad spatial-based and verbal-based latent components. (b.) Dispersion and mean values per component and sex. Student's *t* and *p* values obtained for the mean difference between men and women on spatial and verbal components are provided.

primary mental abilities battery (Thurstone and Thurstone, 1968)], (3) Reading span task (Colom et al., 2010); (4) Letter Memory task (Colom et al., 2008); (5) Keep Track task (Colom et al., 2008); (6) verbal and numerical versions of the Flanker task (Colom et al., 2010); (7) Simple Recognition verbal task (Colom et al., 2008).

Residual scores were computed after regressing out the general spatial and verbal component scores from Rotation of Solid Figures test and Keep Track task respectively. These residual scores capture specific skills, orthogonal to general spatial or verbal ability, that contribute to performance (Burgaleta et al., 2012).

MRI data acquisition

Participants were scanned on a General Electric Signa 3 T magnetic resonance (MR) scanner, using a whole-body radiofrequency coil for signal excitation, and a quadrature 8-channel coil for reception. Anatomical 3D T1-weighted images were acquired with a spoiled gradient echo (SPGR) sequence with the following parameters: TR/TE/PrepTime = 6.8/3.1/750 ms; flip angle 12°; 1 mm slice thickness, a 288×288 acquisition matrix and a 24 cm FOV yielding a voxel size of 0.83×0.83×1 mm³. Diffusion weighted images (DWI) were acquired with single-shot echo planar sequence with the following parameters: 24 cm FOV, TE/TR 78.2/11000 ms, 128×128 acquisition matrix, 2.4 mm slice thickness resulting in 2.5×2.5×2.4 mm³ voxels, 1 image with no diffusion sensitization (i.e., T2-weighted b_0 images) and 15 DWI ($b=1000$ s/mm²) with gradient directions uniformly distributed on the unit hemisphere, for unbiased angular sampling of diffusion.

Brain parcellation and reconstruction of the structural connectome

The FreeSurfer software suite (v5.1) was used to segment each subject's T₁-weighted image in 66 cortical and 16 subcortical regions and to obtain two estimations of brain size: intracranial volume [Gray Matter (GM) + White Matter (WM) + Cerebrospinal Fluid (CSF)] and

total brain volume (GM + WM) (Desikan et al., 2006; Fischl et al., 2004). As in previous studies (Aleman-Gomez et al., 2013; Janssen et al., 2014), image quality was determined with the support of two tools. (1) The “Check sample homogeneity” tool in the SPM-VBM8 toolbox (v.r435, <http://dbm.neuro.uni-jena.de/vbm/check-sample-homogeneity/>). This tool calculates the standard deviation by the sum of the squared distance of each image from the sample mean. (2) The FreeSurfer QA tool (v5.3, <http://surfer.nmr.mgh.harvard.edu/fswiki/QATools>) generates snapshots of anatomically-labeled surfaces which were checked for topological defects and high label accuracy. No images and output of the final sample were deemed of insufficient quality.

Diffusion weighted images (DWI) were pre-processed using the FMRIB's Diffusion Toolbox (FDT – <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT>). Correction for motion and geometrical distortion due to eddy currents was performed with the *eddycorrect* tool in FDT, taking as the reference image the b_0 volume. The matrix of gradient directions was rotated using the resulting matrices from the motion correction routine. Non-brain tissue from the b_0 images was removed using the FMRIB's Brain Extraction Toolbox, BET (Smith, 2002). The obtained brain mask was applied to the rest of the DWI. The masked b_0 images were registered to the masked T₁-weighted images using a rigid body transformation. The inverse of this transformation was applied to the cortical and subcortical regional masks obtained from the FreeSurfer pipeline. The Diffusion Toolkit (DTK – <http://www.trackvis.org>) was used to fit the diffusion tensor model using a least squares approach. FACT Tractography (Mori et al., 1999) was employed to estimate the fiber tracts connecting each pair of the 82 regions. Ten streamlines per voxel at random sub-voxel starting locations were generated, using as stopping criteria a maximum curvature angle of 60° between consecutive steps and a lower threshold of fractional anisotropy (FA) of 0.1 (Mori and van Zijl, 2002). Only tracts with a length shorter than 250 mm and larger than 15 mm were retained. The structural connection, SC_{ij}, between any pair

of regions (i,j) was defined as the number of streamlines connecting these two regions. Thus, structural connectivity networks were represented as symmetric weighted matrices of 82 nodes.

Finally, the weights corresponding to inter- and intrahemispheric connections were summed. Thus, InterHc mainly corresponds to connections of the corpus callosum, but also connections of the hippocampal commissure, and anterior and posterior commissure, whereas IntraHc includes all connections within the right and left hemispheres. The ratio InterHc/IntraHc was then computed for quantifying the dominance of intra- or interhemispheric connections in the individual structural connectivity networks.

Statistical analysis

Independent samples t-tests were used for assessing sex differences in both general cognitive components (spatial and verbal), the skill-specific scores (Rotation of Solid Figures test and Keep Track task before and after regressing out the latent component scores), age, brain size (ICV and TBV) and the structural connectome measures (InterHc, IntraHc and ratio InterHc/IntraHc). These latter differences were also assessed after controlling for brain size, by regressing out ICV and TBV from each structural connectome measures and submitting the unstandardized residuals to independent samples t-tests.

Within-sex Pearson correlations were computed for assessing whether brain size and the structural connectome measures explained individual differences in general and specific spatial and verbal abilities in women and men. Next, correlations among cognitive scores and the structural connectome measures, controlling for the effect of brain size,

were computed to assess whether the structural connectome measures predicted spatial and verbal performance in men and women regardless of brain size. Finally, a bootstrap sampling technique for validating these latter findings in 1000 random samples ($n=80$; with replacement) was implemented using the MATLAB's (R2015b) functions 'bootstrap' and 'bootci'. The bootstrap method allows to assess the stability of the results in relatively small sample sizes, since it can account for distortions in the findings due to sample specificities (Adèr et al., 2008). Mean, standard error, confidence interval (alpha=0.95) and percentiles 5th and 95th for the correlation values computed in the 1000 bootstrap samples were obtained and reported.

Fig. 2 summarizes the methods for obtaining the whole-brain, InterHc and IntraHc matrices, as well as the main statistical analyses for testing the hypotheses.

Results

Sex differences in general and specific spatial-verbal abilities and age

There were not sex-related differences in spatial [$t=0.87$ ($p=0.39$)] and verbal [$t=1.59$ ($p=0.12$)] general components. Also, men and women were matched by age [$t=1.50$ ($p=0.14$)]. **Fig. 1a** shows the loadings for each psychological measure obtained after a principal component analysis (PCA). **Fig. 1b** displays the dispersion and mean per cognitive component and sex.

Men outperformed women in Rotation of Solid Figures, but this difference was significant for the residual scores [$t_{\text{Raw Score}}=1.11$ ($p=0.27$); $t_{\text{Residual Score}}=2.49$ ($p=0.02$)]. However, women outper-

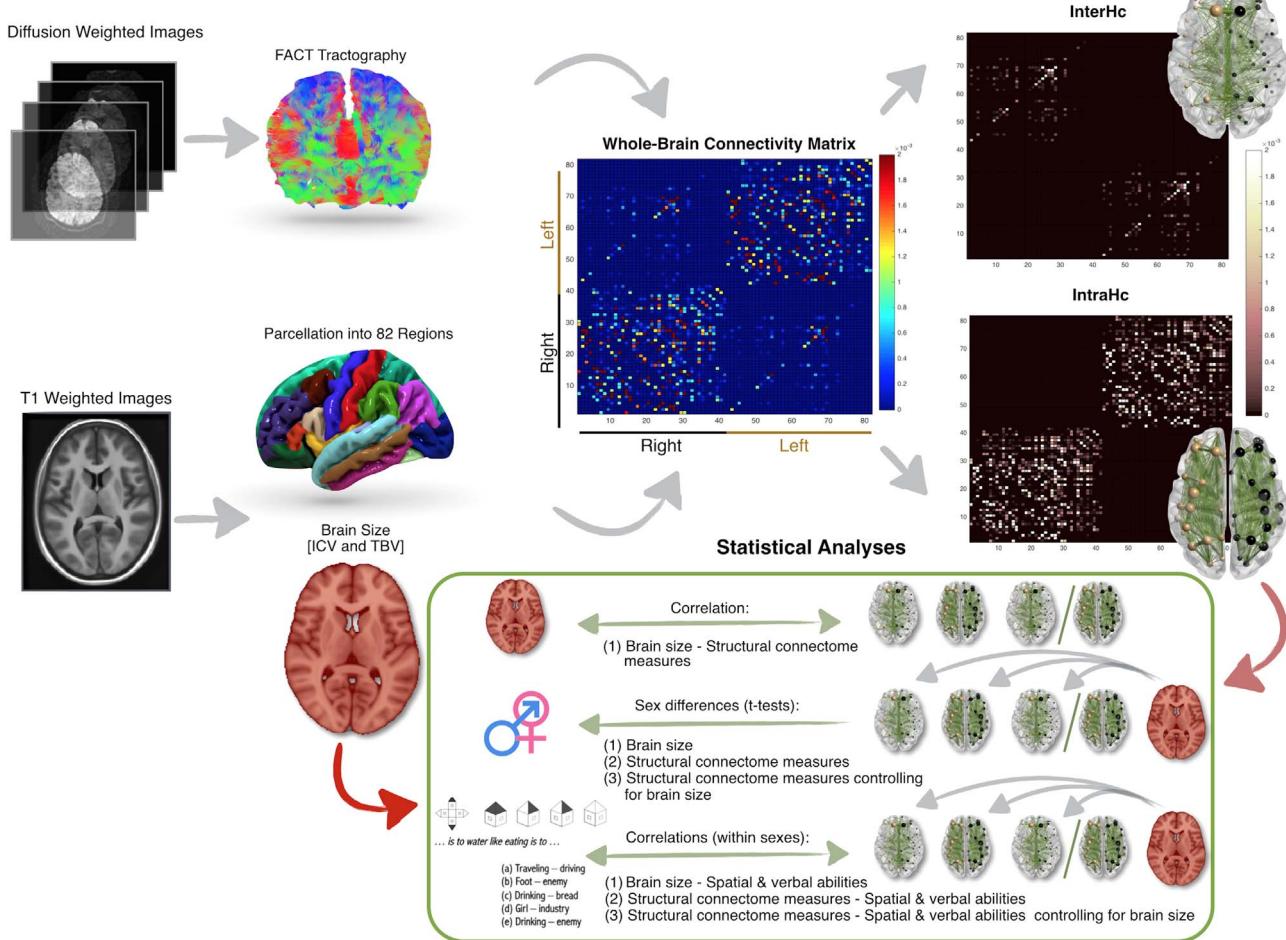


Fig. 2. Graphical workflow displaying the construction of whole-brain, interhemispheric (InterHc) and intrahemispheric (IntraHc) connectivity matrices as well as the main statistical analyses. ICV: Intracranial volume. TBV: Total brain volume.

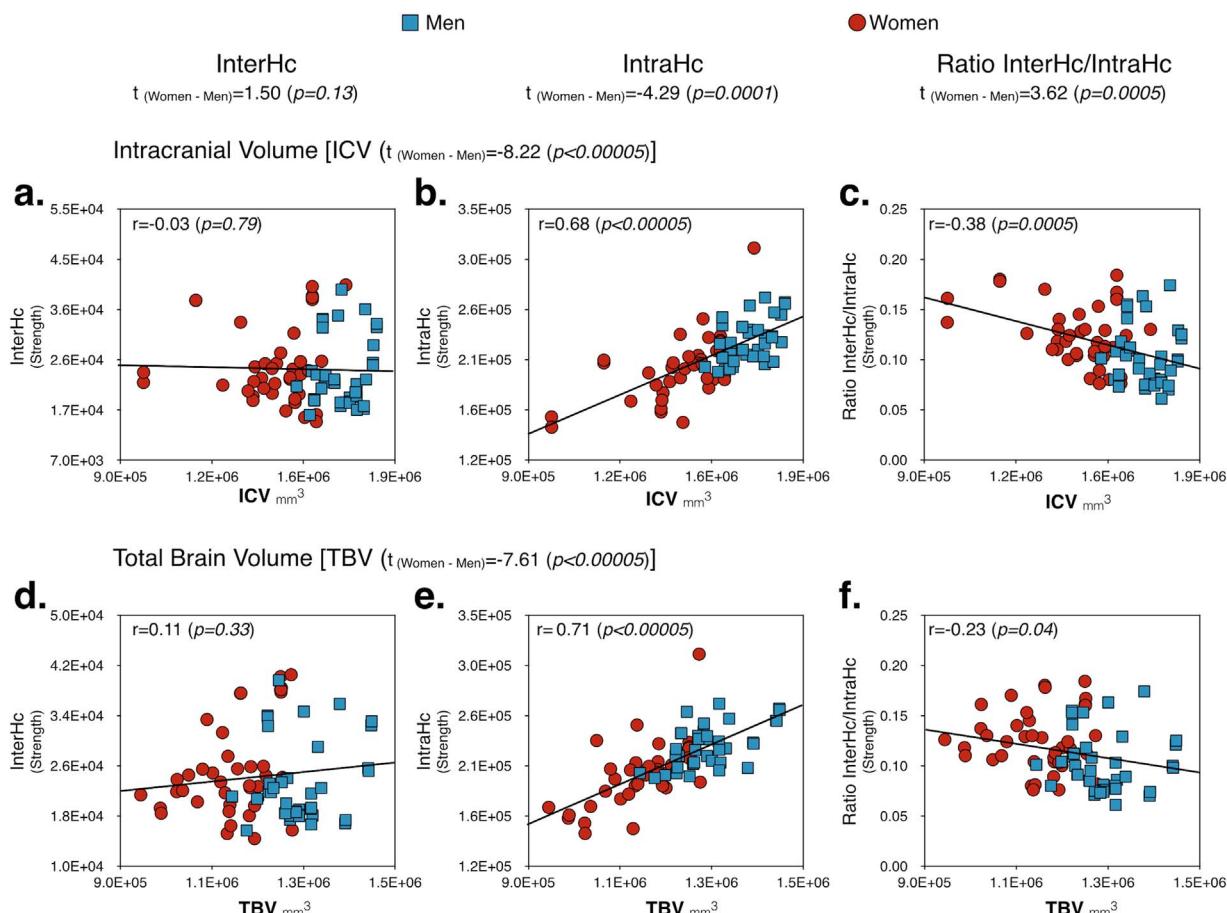


Fig. 3. Scatter plots for the relationships between the structural connectome measures and brain size [(a.) InterHc-ICV; (b.) IntraHc-ICV; (c.) ratio InterHc/IntraHc-ICV; (d.) InterHc-TBV; (e.) IntraHc-TBV; (f.) ratio InterHc/IntraHc-TBV]. Pearson's correlations (r) and their level of significance (p) are displayed. Student's t and p values obtained for the mean difference between men and women on the structural connectome measures and brain size (ICV and TBV) are provided. ICV: Intracranial volume. TBV: Total brain volume. InterHc: Interhemispheric connectivity. IntraHc: Intrahemispheric connectivity.

formed men in the Keep Track task before and after regressing out the effect of the latent component [$t_{Raw Score} = 4.00 (p=0.0001)$; $t_{Residual score} = 4.19 (p < 0.00005)$].

Sex differences in brain size and structural connectome measures

As shown in Fig. 3, brain size was positively related to IntraHc [$r_{ICV} = 0.68 (p < 0.0001)$; $r_{TBV} = 0.71 (p < 0.0001)$] and negatively correlated with the ratio InterHc/IntraHc [$(r_{ICV} = -0.38 (p=0.0005))$; $r_{TBV} = -0.23 (p=0.04)$]. The absolute number of streamlines computed for interhemispheric connections did not significantly correlate with brain size [$r_{ICV} = -0.03 (p=0.79)$; $r_{TBV} = 0.11 (p=0.33)$].

Men had larger brain size [$t_{ICV} = 8.22 (p < 0.0001)$; $t_{TBV} = 7.61 (p < 0.0001)$] and higher IntraHc than women [$t_{IntraHc} = 4.29 (p < 0.0001)$], whereas women had increased ratio InterHc/IntraHc [$t_{Ratio InterHc/IntraHc} = 3.62 (p=0.0004)$] compared to men. There was not an average sex difference in the absolute number of interhemispheric connections [$t_{InterHc} = 1.50 (p=0.13)$].

Sex differences in the IntraHc disappeared after controlling for the effect of brain size [$t_{IntraHc controlling ICV} = 0.40 (p=0.69)$; $t_{IntraHc controlling TBV} = 0.40 (p=0.69)$]. Also, sex-related differences in the ratio InterHc/IntraHc were not significant after controlling for ICV [$t_{Ratio InterHc/IntraHc controlling ICV} = 1.61 (p=0.11)$]; but remained significant after controlling for TBV [$t_{Ratio InterHc/IntraHc controlling TBV} = 2.90 (p=0.005)$]. However, the effect size for this latter difference was reduced [from a large effect (Cohen $d = 0.82$) to a medium effect (Cohen $d=0.66$)].

Predicting general and specific verbal and spatial abilities from brain size and structural connectome measures

As observed in Table 1, ICV and TBV were not significantly related to general verbal ability in both sexes, nor with specific spatial and verbal skills (i.e. Rotation of Solid Figures and Keep Track). General spatial ability was related to TBV in women [$TBV: r_{Women} = 0.39 (p=0.02)$] but no relationship was found in men.

An increased number of interhemispheric connections, as well as a greater ratio InterHc/IntraHc, predicted better general spatial and verbal ability in men and women (Table 2 and Fig. 4). These relationships remained significant, with similar effect sizes after controlling for the effect of ICV or TBV (Table 2 and Fig. 4). Table 2 shows a similar pattern of correlations for Rotation of Solid Figures and Keep Track (raw scores), but with reduced effect sizes that led to a number of non-significant correlations. However, the observed relationships were not significant for the residual scores, except for the positive association between Keep Track and the ratio InterHc/IntraHc in women. There were no significant correlations between IntraHc and general and specific spatial and verbal abilities.

The positive within-sex correlations between the ratio InterHc/IntraHc and the general spatial and verbal ability after controlling for brain size were replicated in the 1000 random samples (see Fig. 5).

Discussion

In the current study we assessed whether sex differences in global structural connectome organization were driven by sex differences in

Table 1

Correlations between the brain size measures and spatial-verbal abilities in men and women. Pearson's correlations (r) and their level of significance (p) are displayed. Bold numbers correspond to significant correlations ($p < 0.05$).

	ICV		TBV		
	WOMEN	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
General Spatial Ability		0.101	0.535	0.386	0.014
Rotation Solid Figures (Raw Scores)		0.035	0.831	0.246	0.125
Rotation Solid Figures (Residual Scores)		-0.065	0.691	-0.080	0.624
General Verbal Ability		0.149	0.359	0.281	0.079
Keep Track (Raw Scores)		0.035	0.831	0.246	0.125
Keep Track (Residual Scores)		-0.065	0.691	-0.08	0.624
MEN	<i>r</i>		<i>p</i>		
	General Spatial Ability	0.182	0.260	0.237	0.142
Rotation Solid Figures (Raw Scores)		-0.064	0.696	-0.039	0.813
Rotation Solid Figures (Residual Scores)		-0.273	0.088	-0.296	0.064
General Verbal Ability		-0.020	0.904	-0.040	0.808
Keep Track (Raw Scores)		-0.064	0.696	-0.039	0.813
Keep Track (Residual Scores)		-0.273	0.088	-0.296	0.064

brain size. We also investigated if individual differences in InterHc and IntraHc, as well as in the level of dominance of InterHc over IntraHc (or vice versa), predicted general spatial and verbal ability in men and women regardless of their brain size. As expected, men showed greater brain size and IntraHc, while women had higher ratio InterHc/IntraHc. These sex differences in the connectome organization were modulated by brain size. Reported findings do not provide support for a sex-dependent difference in global connectome wiring driving the average sex differences in verbal and spatial abilities. Rather, greater dominance of InterHc over IntraHc was associated with better spatial and verbal ability, for men and women and regardless of brain size.

Crucially, our methodological approach addressed three important issues. First, due to the modulatory effect of task specificities on sex-related differences in spatial and verbal skills (Miller and Halpern, 2014), we computed broad spatial and verbal latent components. Spatial and verbal ability defined at the latent level summarize what spatial-based and verbal-based tasks had in common beyond the specific skills and processing requirements (reasoning, working memory or attention control, among others). Second, men and women were matched by these two broad spatial and verbal components. Previous research showed that brain size and structural connectivity are related to performance on cognitive tests (Li et al., 2009; McDaniel, 2005; Pietschnig et al., 2015; Zalesky et al., 2011). Therefore, group-differences in connectivity and brain size in samples matched by cognitive ability may clarify the sole contribution of biological sex, as any observed group difference at the brain level should indicate an effect of sex instead of cognitive level. Finally, we tested within-sex relationships between general spatial and verbal ability and brain features in groups of men and women with the same general cognitive range. This helps to avoid misunderstandings about the functional relevance of sex-dependent differences at the brain level. Arguable attributions may occur by assuming that simultaneous group-differences in brain features and cognitive performance are associated before testing whether they are related at the individual level. Therefore, we tested whether the connectivity measures considered might be relevant for predicting performance in general spatial and verbal ability in men and women matched by their cognitive performance, but not in brain connectivity and size.

Sex differences in global structural connectome organization as a function of sex differences in brain size

In agreement with previous studies examining sex differences in structural connectivity with diffusion tensor imaging (Duarte-Carvalhalino et al., 2012; Ingallhalikar et al., 2014; Jahanshad, 2011; Tunc et al., 2016), the present study shows that women had an increased ratio InterHc/IntraHc while men had greater IntraHc. However, these global sex differences in connectivity were mediated by sex differences in brain size. These findings are in line with previous research using corpus callosum morphometry as a proxy for InterHc, as well as with more recent findings based on brain tractography methods (Hanggi et al., 2014; Jancke et al., 1997; Leonard et al., 2008). A larger corpus callosum size is thought to represent greater InterHc (Hanggi et al., 2014). Another morphological feature, larger callosal mid-sagittal area, is accompanied by shorter transcallosal fiber length, whereas increased fiber length is associated with a lower degree of InterHc (Lewis et al., 2009). The size of the corpus callosum and whole brain have a counterintuitive relationship: *absolute* corpus callosum volume is higher in larger brains than in smaller brains, but the *relative* corpus callosum volume (*absolute* corpus callosum volume / whole brain volume) is higher in smaller compared to larger brains (Jancke et al., 1997; Leonard et al., 2008). In addition, the ratio between the size of the corpus callosum and the whole brain decreases with increasing brain size across species; suggesting a decrease of InterHc as brain size increases (Hanggi et al., 2014). Meta-analytic evidence demonstrates that group average sex differences in the size of the corpus callosum disappear after adjusting for differences in brain size and group-level sex differences in corpus callosum thickness vanishes as well when women and men had the same brain size (Bishop and Wahlsten, 1997; Gong et al., 2011; Luders et al., 2014). Researchers have therefore argued that the apparent larger relative corpus callosum volume in women is in fact a result of their smaller brains.

Recently, a study using brain tractography methods extended these previous findings by demonstrating an interaction between brain size and the organization of the structural connectome (Hanggi et al., 2014). The authors concluded that the average sex differences in human structural connectome wiring -increased IntraHc in men and

Table 2

Correlations between the structural connectome measures and spatial-verbal abilities in men and women. Pearson's correlations (r) and their level of significance (p) are displayed. Bold numbers correspond to significant correlations ($p < 0.05$).

WOMEN		A		B		C	
		<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
General Spatial Ability	InterHc	0.520	0.0006	0.510	0.0008	0.390	0.011
	IntraHc	0.180	0.279	0.140	0.377	-0.090	0.571
	InterHc/IntraHc	0.500	0.001	0.55	0.0003	0.470	0.002
Rotation of Solid Figures (Raw Scores)	InterHc	0.315	0.047	0.313	0.049	0.236	0.142
	IntraHc	0.198	0.221	0.219	0.174	0.052	0.749
	InterHc/IntraHc	0.268	0.095	0.288	0.072	0.251	0.119
Rotation of Solid Figures (Residual Scores)	InterHc	-0.129	0.427	-0.123	0.449	-0.106	0.515
	IntraHc	0.091	0.577	0.160	0.324	0.185	0.254
	InterHc/IntraHc	-0.181	0.263	-0.206	0.202	-0.176	0.277
General Verbal Ability	InterHc	0.406	0.009	0.393	0.012	0.320	0.044
	IntraHc	0.110	0.498	0.028	0.865	-0.090	0.580
	InterHc/IntraHc	0.403	0.01	0.46	0.003	0.384	0.015
Keep Track (Raw Scores)	InterHc	0.342	0.031	0.329	0.038	0.260	0.106
	IntraHc	-0.027	0.869	-0.136	0.404	-0.250	0.120
	InterHc/IntraHc	0.415	0.008	0.470	0.002	0.397	0.011
Keep Track (Residual Scores)	InterHc	0.224	0.164	0.213	0.187	0.170	0.295
	IntraHc	-0.082	0.613	-0.193	0.232	-0.249	0.121
	InterHc/IntraHc	0.310	0.051	0.357	0.024	0.299	0.061
MEN		<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
General Spatial Ability	InterHc	0.517	0.001	0.494	0.001	0.486	0.001
	IntraHc	0.138	0.396	0.046	0.778	-0.009	0.956
	InterHc/IntraHc	0.492	0.001	0.492	0.001	0.499	0.001
Rotation of Solid Figures (Raw Scores)	InterHc	0.301	0.059	0.316	0.047	0.311	0.051
	IntraHc	-0.022	0.893	0.015	0.925	0.002	0.989
	InterHc/IntraHc	0.336	0.034	0.336	0.034	0.335	0.034
Rotation of Solid Figures (Residual Scores)	InterHc	-0.130	0.425	-0.086	0.597	-0.086	0.600
	IntraHc	-0.171	0.290	-0.027	0.869	0.012	0.940
	InterHc/IntraHc	-0.057	0.726	-0.057	0.726	-0.065	0.691
General Verbal Ability	InterHc	0.436	0.005	0.446	0.004	0.448	0.004
	IntraHc	-0.196	0.226	-0.221	0.171	-0.217	0.178
	InterHc/IntraHc	0.519	0.001	0.519	0.001	0.518	0.001
Keep Track (Raw Scores)	InterHc	0.275	0.086	0.243	0.130	0.229	0.154
	IntraHc	0.270	0.092	0.183	0.258	0.097	0.551
	InterHc/IntraHc	0.214	0.184	0.214	0.184	0.222	0.168
Keep Track (Residual Scores)	InterHc	0.176	0.278	0.147	0.366	0.133	0.412
	IntraHc	0.263	0.101	0.191	0.239	0.109	0.502
	InterHc/IntraHc	0.115	0.480	0.115	0.480	0.123	0.451

A. Correlations before controlling for brain size.

B. Correlations controlling for ICV.

C. Correlations controlling for TBV.

increased InterHc in women as proposed by Ingallalikar et al. (2014)– is driven by sex differences in brain size and not by sex *per se*. Interestingly, in coherence with our findings, Hänggi et al. (2014) reported a high increment of structural intrahemispheric connectivity in larger brains, whereas only a marginal increment in interhemispheric connectivity in larger compared with smaller brains. Also, they showed a negative correlation between brain size and the ratio InterHc/IntraHc. Our results show that these prior findings were not merely a proof of concept and provide support for the hypothesis that sex differences in global hemispheric connectivity are dependent on the sex differences in brain size.

The sex-by-brain size interaction effect on structural brain connectome measures is consistent with prior research suggesting that between-subject variability in brain size is associated with a non-linear increase in intrahemispheric and interhemispheric connections (Im et al., 2008; Jancke et al., 1997; Leonard et al., 2008). Specifically, the transcallosal conduction delay in larger brains might be compensated by an over-proportionally increase of intrahemispheric white matter fibers connecting local information processing units. This effect could explain why interhemispheric information transfer is shorter and more symmetrical in women (typically with smaller brains) compared to men (frequently with larger brains), or the increased occurrence of verbal

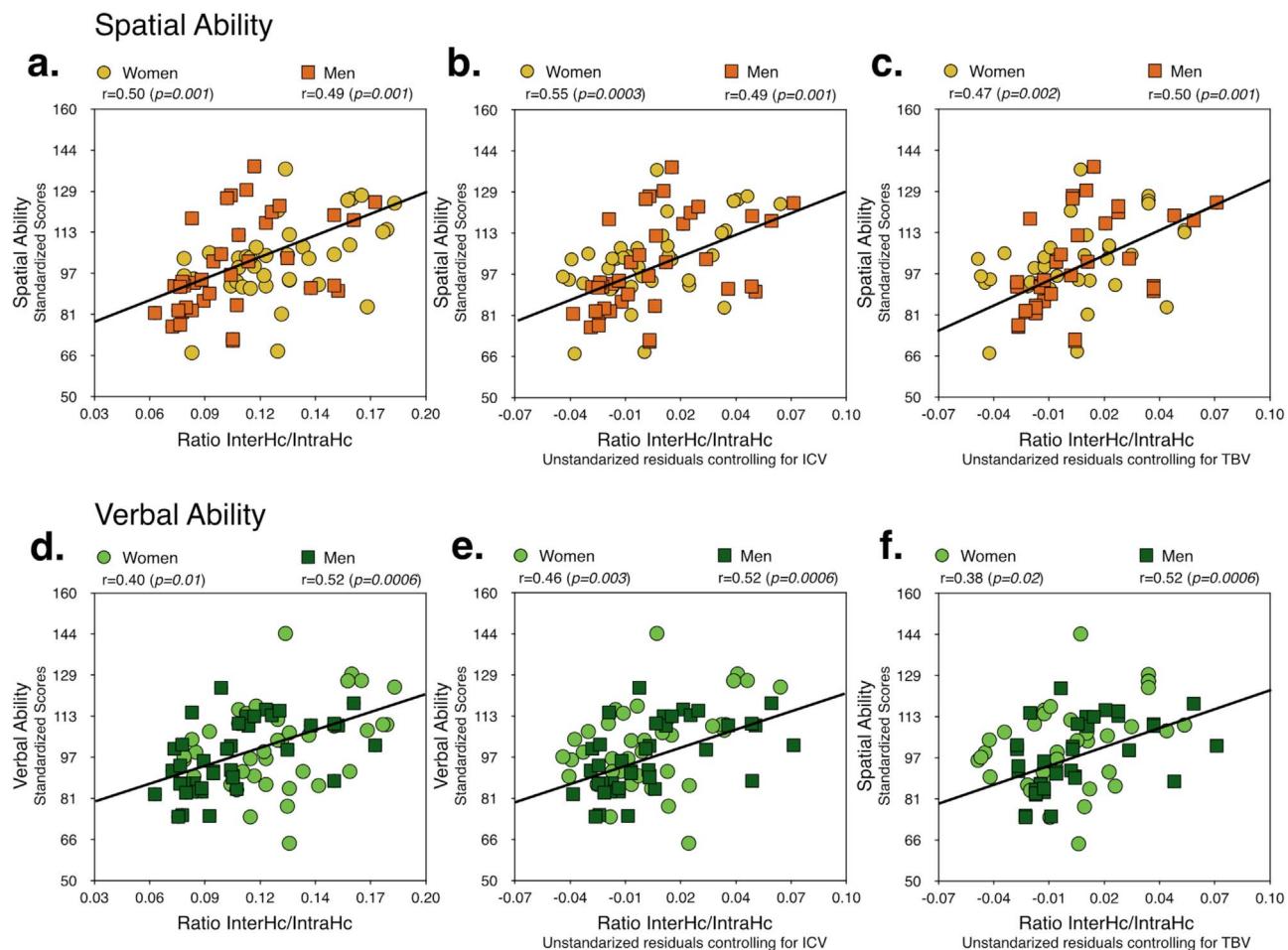


Fig. 4. Scatter plots for the relationship between the ratio InterHc/IntraHc and spatial-verbal ability in men and women before [(a.) and (d.)] and after controlling for ICV [(b.) and (e.)] or TBV [(c.) and (f.)]. Pearson's correlations (r) and their level of significance (p) are displayed. ICV: Intracranial volume. TBV: Total brain volume. InterHc: Interhemispheric connectivity. IntraHc: Intrahemispheric connectivity.

and non-verbal deficits after left and right hemispheric lesions in men (Hausmann, 2017).

Stronger interhemispheric connectivity enhances spatial and verbal ability regardless of sex and brain size

A stronger hemispheric lateralization of brain functions in men and larger brains compared to women and smaller brains provides a context for interpreting average sex differences in specific cognitive abilities (Hiscock et al., 1994; Hiscock et al., 1995; Jordan et al., 2002; Josse et al., 2006; Miller and Halpern, 2014; Shaywitz et al., 1995; Stoet and Geary, 2013; Tzourio-Mazoyer et al., 2010). A number of cognitive functions including spatial orientation, attention, face recognition, motor control of the hands, sense of body ownership, memory and language processing, have demonstrated more functional asymmetry or lateralization in men compared to women (Hausmann, 2017; Hiscock et al., 1994; Hiscock et al., 1995; Ocklenburg et al., 2016; Shaywitz et al., 1995). Resting state functional connectivity studies have suggested that men's brain may have stronger global lateralization of short-range connections (Tomasi and Volkow, 2012), and more pronounced lateralization of specific subnetworks, such as visual and frontal networks (Agcaoglu et al., 2015). A recent study (Tunc et al., 2016) investigated sex-related differences in functionally defined subnetworks (based on fMRI evidence), as well as their relation to cognitive sex differences. Men demonstrated greater connectivity in predominantly intrahemispheric subnetworks, whereas women exhibited higher connectivity when subnetworks included mainly interhemispheric connections. Also, greater

connectivity among subnetworks associated with motor, visual and executive control functions (frontoparietal and cingulo-opercular) were found for men, while women had higher connectivity among subcortical, sensory, and attention subnetworks. At the cognitive level, women outperformed men on non-verbal reasoning, whereas men did better in spatial, verbal and motor tasks. Finally, using multivariate classification analyses, they were able to distinguish men and women based on both brain structure and cognition. They also showed a significant correlation between classification scores computed for individual structural and cognitive patterns, suggesting a relationship between brain structure and cognition. However, as noted by the authors, more direct analyses of individual differences are still required for establishing conclusions at the individual level.

Ingalhalikar et al. (2014) argued that the observed increased IntraHc in men and the increased InterHc in women is the structural backbone for the sex differences in cognitive performance. Our study empirically tested this hypothesis at the individual level and found unexpected relationships. The reported results indicated that greater dominance of InterHc over IntraHc was associated with better spatial and verbal ability regardless of an individual's brain size and sex. Also, we observed that this pattern was especially strong for spatial and verbal ability defined at the latent level for which men and women did not differ. But also it was present when specific 'sex-biased' measurements (i.e. Rotation of solid Figures and Keep Track raw scores) were considered.

InterHc is highly dependent on the microstructural qualities of the corpus callosum as this is the main structure for information transfer

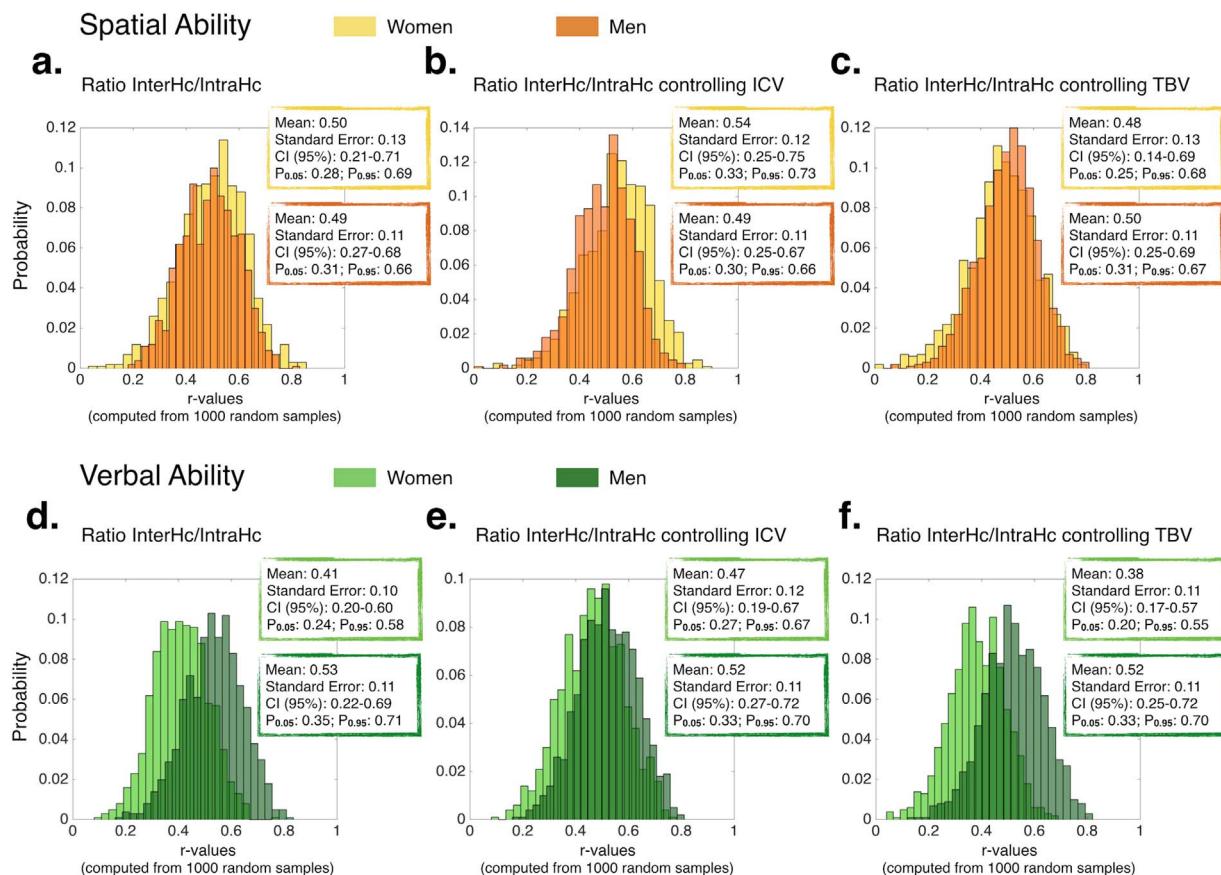


Fig. 5. Probability distributions for the correlations between ratio InterHc/IntraHc and spatial-verbal ability in men and women before [(a.) and (d.)] and after controlling for ICV [(b.) and (e.)] and TBV [(c.) and (f.)] computed from 1000 random samples. Mean, standard deviation, confidence interval and percentiles 5 and 95 for each distribution are provided. ICV: Intracranial volume. TBV: Total brain volume. InterHc: Interhemispheric connectivity. IntraHc: Intrahemispheric connectivity.

between homologous regions of the cerebral hemispheres (Hofer and Frahm, 2006). The microstructural properties of the corpus callosum, such as fractional anisotropy (FA), and morphological features such as thickness of the corpus callosum, have been positively related to performance measured by several tests of visuospatial cognition, language, and psychomotor ability (Fryer et al., 2008), as well as general intelligence (Clayden et al., 2012; Dunst et al., 2014; Luders et al., 2007; Navas-Sánchez et al., 2014; Tang et al., 2010; Yu et al., 2008). Additionally, increased FA has been reported in the corpus callosum of math-gifted children and adolescents who typically present high spatial abilities compared to non-gifted individuals of the same age (Navas-Sánchez et al., 2014). The increase in FA may be reflective of an increased bilateral involvement of brain regions observed in math-gifted subjects (Desco et al., 2011) and may be a central part of the mechanistic explanation of math giftedness (Desco et al., 2011; O'Boyle et al., 1995; Prescott et al., 2010; Singh and O'Boyle, 2004).

Whether an individual's sex and brain size have a moderating effect on the associations between corpus callosum structure and cognition is still unclear (Clayden et al., 2012; Dunst et al., 2014; Fryer et al., 2008; Navas-Sánchez et al., 2014; Prescott et al., 2010; Tang et al., 2010; Yu et al., 2008). Alternative study designs, e.g. focusing on one sex (Prescott et al., 2010; Singh and O'Boyle, 2004) or controlling for sex during analyses (Clayden et al., 2012; Navas-Sánchez et al., 2014; Yu et al., 2008) have not resolved this issue. Studies modeling the effect of sex by assessing the relevance of corpus callosum volume for predicting cognitive performance within-sex have yielded contradictory results: significant associations might or might not be generalized to men and women (Dunst et al., 2014; Luders et al., 2007; Tang et al., 2010). Regarding brain size, it may not have an effect on the relationship

between cognition and corpus callosum structure (Luders et al., 2007) although this finding needs replication.

Taken together, our results are in line with Dubois and Adolphs (2016), who underscore that we must move from the group to the individual level to improve the characterization of brain structure and function (Dubois and Adolphs, 2016). We have shown that, regardless of sex and brain size, spatial and verbal ability benefited from higher InterHc over IntraHc. This suggests that higher spatial and verbal performance benefits from increased global communication between hemispheres rather than functional lateralization. Importantly, we also demonstrated the relevance of testing the functional role of sex-dependent brain differences at the individual level. This must be done before interpreting any brain-difference as underlying a given cognitive-difference. Specifically, we have shown that even when men had higher IntraHc and better performance in a 3D mental rotation task than women, both variables were not related at the individual level. Also, men outperformed women in Rotation of Solid Figures, while women outperformed men in Keep Track, two measurements of specific skills in which men and women tend to differ (Miller and Halpern, 2014). The pattern of correlations between connectivity measurements and Rotation of Solid Figures and Keep Track was similar to the pattern observed for the spatial and verbal components. Interestingly, after removing the effect of the corresponding latent components: (a) group differences in Rotation of Solid Figures and Keep Track remained, and (b) the correlations with the connectivity measures vanished (except for the positive correlation between Keep Track and the ratio InterHc/IntraHc in women). This might imply that specific spatial-unrelated skills recruited by Rotation of Solid Figures are not predicted by the connectivity measures. The same might apply to Keep Track in men.

Limitations

Caution is warranted when interpreting the reported results. First of all, this study included a relative small young sample of university undergraduates, which warrants caution when generalizing these results to populations with larger age ranges, lower general intellectual performance or disease. Secondly, non-significant correlations between brain size and cognitive performance were found (except for the spatial ability-TBV relationship in women), which might be influenced by sample homogeneity or other characteristics of the sample. Future studies with larger sample sizes, as well as covering different stages of youth, adulthood and senescence, must be welcome for exploring the relationship between sex differences in brain size and structural connectivity and sex differences in cognitive abilities. Finally, the reconstruction of crossing fibers (and further complex configurations such as kissing or benching) benefits from an increased number of diffusion directions during acquisition. Nevertheless, the current study replicated previous findings of sex differences in brain connectivity from studies using improved scan acquisition protocols (Hanggi et al., 2014; Ingallalikar et al., 2014). Future studies using improved scan acquisition protocols may assess whether more local than global connectivity indices adhere to the same rules as observed in the present study. Our work may be considered a framework for those future studies.

Conclusions

Our findings are in line with the hypothesis of global sex differences in hemispheric connectivity as a function of brain size. After accounting for sex differences in brain size, sex-related differences in structural connectome measures were reduced. The level of dominance of interhemispheric over intrahemispheric connectivity was crucial for predicting individual differences in cognition in both men and women: higher interhemispheric over intrahemispheric connectivity predicted better spatial and verbal ability regardless of brain size. Therefore, we did not find empirical support for the hypothesis that sex differences in the global structural connectome organization underlie enhanced spatial ability in men and verbal ability in women. Thus, the reported results highlight the crucial relevance of testing the functional role, at the individual level, of sex-dependent differences in brain features for avoiding arguable interpretations.

The authors declare that they have no conflict of interest.

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