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Human sexual dimorphism of the relative cerebral area volumes in the data of the human connectome project

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SUMMARY

The average human brain volume of males is larger than that of females. Several MRI voxel-based morphometry studies show that the gray matter/white matter ratio is larger in females. Here we have analyzed the recent public release of the Human Connectome Project, and by using the data of 511 subjects (209 men and 302 women), we have found that the volumes of numerous subcortical areas and most cortical areas, normalized by the total brain mask volume, are significantly larger in women than in men. Additionally, we have discovered that, for multiple brain regions, the correlation of the size of the left and right part is different between the sexes.

Key words: Morphometry – FreeSurfer – Human Connectome Project – Sexual dimorphism – Cerebral area volumes

INTRODUCTION

It has been known for a long time that women, on the average, have smaller brains than men (see Witelson et al., 2006). If every brain structure was smaller proportionally to the total brain volumes of the females then there would be no differences in the relative volumes of the brain structures between men and women.

Surprisingly, this is not the case: there are significant differences between not only the absolute, but also the relative brain volumes between men and women. With the advance of MR imaging techniques, more and more datasets have been examined and evaluated for the relative sex differences in the brain anatomy.

Data from forty men and forty women of ages 18-45 were analyzed in Gur et al. (1999). By computing the relative volumes by dividing the brain area volumes and the intracranial volumes, it was found that men have a larger relative volume of the white matter and the cerebrospinal fluid than women, while the relative volume of the gray matter was greater in women than in men.

In a smaller study of 23 males and 23 females, Allen et al. (2002) investigated the gray- and white matter distributions in the cerebral lobes between the sexes. They have found that the volumes of the cerebral areas are larger in men, but the gray matter/white matter ratio is higher in women.

In Chen et al. (2007), 411 subjects of ages 44-48 were examined for white matter and gray matter ratios, compared to intracranial volume. It was found that women have higher gray matter to intracranial volume than men.

After a controlling process, involving age, years of education, handedness and intracranial volume, some areas were found with higher gray matter relative volume in men and other areas with higher gray matter relative volume in women.

In the work of Taki et al. (2011), the MRI data of 1460 healthy volunteers were examined: the regional gray matter volume differences between age and sex groups were evaluated on 34 brain areas and on the whole brain. The white matter

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ratio was found larger in women in all age groups while the CSF space ratio was larger in men. The gray matter ratio was found to be greater in young men than in young women; then it became larger in older women than in older men.

In the present study we are using the dataset of one of the largest and perhaps one of the most reliable human brain study to date, the NIH-sponsored Human Connectome Project's (McNab et al., 2013) Subject-500 Data Release http://www.humanconnectome.org/documentation/S500. The set contains the MRI data of 511 subjects of ages 22-35, comprising 302 women and 209 men.

In our study, we have compared the sizes of the brain areas between the sexes, normalized by the FreeSurfer's (Fischl, 2012) Total Brain Mask Volume (FS Mask Vol), without any "controlling" steps for age, handedness or education. We have found that women have larger normalized volumes for many cerebral areas.

While other studies have attempted to make conclusions about brain functions from these statistically proven anatomical dimorphisms, we feel that such conclusions require more elaborate studies than just the volume comparisons (e.g. functional- and anatomical connectomics as in Szalkai et al. (2015, 2016a, 2017), and comparisons with psychological test results as in Szalkai et al. (2016b). Therefore, those conclusions related to brain functions are outside of the scope of the present work.

Table 1. The correlations of the normalized volumes with the sex of the subjects. Positive correlations show that the value is greater at females, negative correlations correspond to larger relative volumes at males. The third column contains the p-values, fourth column the Holm-Bonferroni correction of the p-values (Holm, 1979), and the last two columns the averages for male and female subjects. This table contains data with Holm-Bonferroni corrected p-values of less, than 0.05. Table S2 at http://uratim.com/relvol/tables.zip contains the data of both Tables 1 and 2 together with more rows and standard deviation columns. The abbreviations are resolved at https://wiki.humanconnectome. org/display/PublicData/HCP+Data+Dictionary+Public-+500+Subject+Release

Name of area	Correlation	p-value	p (corr.)	Average (males)	Average (females)
FS SubCort GM RelVol	0.3564	0	0	0.0364	0.03797
FS L Superiorparietal RelVol	0.311	0	0	0.00734	0.00781
FS R Temporalpole RelVol	0.2787	0	0	0.00094	0.00101
FS L Temporalpole RelVol	0.2766	0	0	0.001	0.00108
FS Total GM RelVol	0.2749	0	0	0.41307	0.4218
FS L Caudate RelVol	0.2704	0	0	0.00226	0.0024
FS R Hippo RelVol	0.2665	0	0	0.00266	0.00277
FS CC Posterior RelVol	0.2599	0	0	0.00057	0.00062
FS R ThalamusProper RelVol	0.2561	0	0	0.00442	0.00461
FS R Caudate RelVol	0.248	0	0	0.00234	0.00247
FS L ThalamusProper RelVol	0.2461	0	0	0.00506	0.00526
FS L Hippo RelVol	0.2376	0	0	0.00262	0.00273
FS R Pallidum RelVol	0.2258	0	0	0.00089	0.00094
FS CC Anterior RelVol	0.2149	0	0.0001	0.00053	0.00057
FS CC MidPosterior RelVol	0.2146	0	0.0001	0.00027	0.0003
FS R Superiorparietal RelVol	0.2117	0	0.0002	0.00757	0.00789
FS LCort GM RelVol	0.2024	0	0.0005	0.15162	0.15468
FS TotCort GM RelVol	0.2014	0	0.0005	0.30691	0.31254
FS R VentDC RelVol	0.1934	0	0.0012	0.00254	0.00263
FS BrainStem RelVol	0.1929	0	0.0013	0.0131	0.01357
FS R Putamen RelVol	0.188	0	0.0021	0.00336	0.0035
FS L VentDC RelVol	0.1872	0	0.0023	0.00251	0.0026
FS R Medialorbitofrontal RelVol	0.1863	0	0.0025	0.00303	0.00314
FS RCort GM RelVol	0.1861	0	0.0025	0.15529	0.15786
FS L Paracentral RelVol	0.1849	0	0.0028	0.002	0.0021
FS L Pallidum RelVol	0.165	0.0002	0.0182	0.00081	0.00086
FS 3rdVent RelVol	-0.164	0.0002	0.0196	0.00048	0.00044
FS L Superiorfrontal RelVol	0.1572	0.0004	0.0355	0.01254	0.01286
FS L Putamen RelVol	0.1566	0.0004	0.0369	0.00331	0.00345

METHODS

The volume of different brain areas was computed as follows. For subcortical areas the HCP data release table already contained a single Volume which did not have to be post-processed. Cortical gray matter volumes were computed by multiplying the Thickness and Area data, which were available in the HCP database (McNab et al., 2013). We

Table 2. The correlations of the normalized volumes with the sex of the subjects. For these values the Holm-Bonferroni corrected p-values are greater than 0.05. Positive correlations show that the value is greater at females, negative correlations correspond to larger relative volumes at males. The third column contains the p-values, and the last two columns the averages for male and female subjects. Table S2 at http://uratim.com/relvol/tables.zip contains the data of both Tables 1 and 2 together with more rows and standard deviation columns. The abbreviations are resolved at https://wiki.humanconnectome. org/display/PublicData/HCP+Data+Dictionary+Public-+500+Subject+Release.

Name of area	Correlation	p-value	Average (males)	Average (females)
FS CC Central RelVol	0.1525	0.0006	0.000294	0.000313
FS R Postcentral RelVol	0.1522	0.0006	0.005333	0.005495
FS R Frontalpole RelVol	0.1511	0.0006	0.000476	0.000499
FS L Postcentral RelVol	0.1503	0.0007	0.005500	0.005656
FS L Parsopercularis RelVol	0.1463	0.0010	0.002797	0.002914
FS R Parsorbitalis RelVol	0.1367	0.0020	0.001346	0.001390
FS L Lateralorbitofrontal RelVol	0.1331	0.0027	0.004481	0.004578
FS BrainSeg RelVol	0.1299	0.0034	0.716413	0.721421
FS OpticChiasm RelVol	-0.1266	0.0043	0.000149	0.000141
FS CC MidAnterior RelVol	0.1247	0.0049	0.000292	0.000307
FS L Posteriorcingulate RelVol	0.1231	0.0055	0.001871	0.001929
FS L Parsorbitalis RelVol	0.1228	0.0056	0.001058	0.001089
FS L Frontalpole RelVol	0.1227	0.0056	0.000343	0.000357
FS R Lingual RelVol	0.1199	0.0068	0.004066	0.004186
FS L Rostralanteriorcingulate RelVol	-0.1131	0.0107	0.001641	0.001586
FS L Parahippocampal RelVol	0.1122	0.0114	0.001181	0.001216
FS L Pericalcarine RelVol	0.1114	0.0119	0.001750	0.001813
FS R LatVent RelVol	-0.1101	0.0130	0.003885	0.003478
FS R Caudalanteriorcingulate RelVol	0.1080	0.0148	0.001221	0.001280
FS R Pericalcarine RelVol	0.1075	0.0153	0.001930	0.001996
FS R Bankssts RelVol	0.1071	0.0156	0.001633	0.001683
FS R WM RelVol	-0.1069	0.0159	0.137525	0.135985
FS Tot WM RelVol	-0.1052	0.0177	0.273035	0.270053
FS L WM RelVol	-0.1024	0.0209	0.135510	0.134068
FS L Precentral RelVol	0.1014	0.0222	0.007940	0.008070
FS L Lingual RelVol	0.1011	0.0226	0.004012	0.004117
FS R Precentral RelVol	0.0994	0.0250	0.008054	0.008179
FS R Lateralorbitofrontal RelVol	0.0953	0.0316	0.004419	0.004487
FS WM Hypointens RelVol	-0.0950	0.0321	0.000546	0.000503
FS L LatVent RelVol	-0.0937	0.0345	0.004137	0.003736
FS R Posteriorcingulate RelVol	0.0937	0.0345	0.001898	0.001944
FS R Rostralanteriorcingulate RelVol	-0.0912	0.0397	0.001267	0.001226
FS L Precuneus RelVol	0.0896	0.0432	0.005863	0.005961
FS R Paracentral RelVol	0.0895	0.0435	0.002356	0.002411
FS R Parsopercularis RelVol	0.0881	0.0470	0.002414	0.002475
FS L Isthmuscingulate RelVol	-0.0877	0.0479	0.001520	0.001475

then divided these volumes by the Freesurfer's Total Brain Mask Volume (denoted by FS Mask Vol) (Fischl, 2012) and defined the relative volume of an ROI as this ratio.

The anonymized subject-level data of the normalized volumes can be downloaded as a large Table S1 from http://uratim.com/relvol/tables.zip. The first column of Table S1 contains the subject ID, the sex is given in column 2. Every further column contains the relative volumes of brain parts for each subjects, compared to their Total Brain Mask Volumes. The third column of Table S1 contains the quotients of the FreeSurfer's InterCranial Volume and the Total Brain Mask Volume. We remark that in this column one can find a few values larger than 1. The reason for this could be that these values depend on FreeSurfer's InterCranial Volume quantity, which is computed by the FreeSurfer's Talairach transform (Talairach and Bancaud, 1973; Talairach and Szikla, 1980) , which sometimes produces unreliable results. Because of this minute unreliability we have chosen the more straightforward Freesurfer's Total Brain Mask Volume (FS Mask Vol, Fischl, 2012) for quantifying the "whole" brain volume, in the computation of the relative volumes.

Table S1 describes the subject-level normalized volumes of 115 brain areas (Regions of Interests, or ROIs, and larger areas as well); the brain areas are named and abbreviated as given in the documentation of the Human Connectome Project: https://wiki.humanconnectome.org/display/PublicData/HCP+Data+Dictionary+Public-+500+Subject+Release.

It is not difficult to translate the column names in Table S1, without any reference: every column name begins with letters FS (referring to FreeSurfer), and ends with RelVol, referring to relative volume. The L and R letters stands for left and right, WM abbreviates white matter, GM gray matter, and the anatomical names are mostly clearly denoted, sometimes with a straightforward abbreviation.

In cortical regions the gray matter volume is considered.

Statistical analysis

We calculated Pearson's correlation coefficient (Wonnacott and Wonnacott, 1972) for sex and the relative volume of each ROI. We then calculated the two-tailed p-value from this correlation coefficient *r* and the number of subjects by using Student's t-test (Wonnacott and Wonnacott, 1972). After that, we sorted the p-values from smallest to largest and used the Holm-Bonferroni method (Holm, 1979) to correct for multiple comparisons. We have applied a threshold of 5% for these corrected p-values.

Data availability

The public release of the Human Connectome Project data is available at http://www.humanconnectome.org/documentation/S500. The subject-level data is available as Table S1 and the results of the statistical analysis as the Table S2 at http://uratim.com/relvol/tables.zip.

RESULTS

Our Table 1 summarizes the most significant findings of ours: very probably, all of these correlations with sex holds (i.e., the statistical second degree error for multiple comparisons, approximated by the Holm-Bonferroni method, is also small, i.e., it is less than 0.05). Table 2 lists those correlations that one-by-one have p-values less than 0.05, but their corrected p-values are larger than 0.05; that is, every single correlation in Table 2 probably holds, but it is improbable that all of them hold.

DISCUSSION

In Tables 1 and 2 the positive correlations show that the relative volume of the cerebral area is larger in women than in men.

In Table 1, the highest correlation with the female sex is shown with the relative volume of the subcortical gray volumes. This phenomenon was described, for example, in Sowell et al. (2002), our contribution here is the quantification of this correlation.

The left superior-parietal relative gray matter volume correlates stronger with the female sex than the right superior-parietal gray matter volume. This asymmetry is missing in the right- and left temporal pole relative volumes: both are larger in women. The normalized size-advantage in the temporal lobes was described in Sowell et al. (2002), too; we show here that there are no difference in correlations in the left- and the right hemispheres in the temporal area.

The normalized volumes of the parts of basal ganglia are also significantly larger in women in both hemispheres. In the case of putamen, the correlation with sex is stronger in the right hemisphere than in the left, while in the caudate nucleus, the correlation with sex is larger in the left hemisphere than in the right one.

The normalized volume of the right pallidum is stronger correlated with the sex than the left pallidum.

The normalized volume of the hippocampus is more definitely correlated with the female sex in the right hemisphere than in the left. As it was recognized by many previous studies (Allen et al., 2002; Chen et al., 2007; Gur et al., 1999), the normalized volume of the total gray matter is larger in females. Now we have found that this correlation in the left hemisphere is stronger.

In Table 1 only the normalized volume of the third ventricle is larger in males than in females.

In Table 2 those results are summarized that have larger than 0.05 Holm-Bonferroni corrected p -values: that is, they could hold one-by-one with a fairly high probability (i.e., > 0.95), but it is unlikely that *all of them* hold true. In Table 2 the total and the right- and the left white matter normalized volumes are larger in men than in women, as well as the normalized volumes of optic chiasm, and the rostral anterior cingulate cortex, the isthmus of cingulate gyrus, the right and the left lateral ventricles.

Conclusions

We have analyzed the sexual dimorphisms of cerebral areas, applying the data of the Human Connectome Project (McNab et al., 2013). We have found that for most cortical and sub-cortical areas, the brain-size normalized volumes are significantly larger in women. Additionally, we have discovered differences in the strengths of the correlations between the same structures in different hemispheres.

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