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Sex differences in the brain are not reduced to differences in body size

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ABSTRACT

In their comprehensive review of sex differences in the brain, Eliot et al. (2021) conclude that (1) men and women significantly differ in global brain size, but this "mostly parallels the divergence of male/female body size during development" and that (2) "once we account for individual differences in brain size, there is almost no difference in the volume of specific cortical or subcortical structures between men and women". In sum, almost all brain differences would directly or indirectly follow from differences in body size. In a recent study that does not have the same limitations as most studies reviewed by Eliot et al., we find that sex differences in total brain volume are not accounted for by sex differences in height and weight, and that once global brain size is taken into account, there remain numerous regional sex differences in both directions (Williams et al., 2021).

In their comprehensive review of sex differences in the brain, Eliot et al. (2021) survey a large number of neuroimaging studies comparing men and women, highlight their limitations and inconsistencies, and draw several conclusions. In particular, they conclude that (1) men and women significantly differ in global brain size, but this "mostly parallels the divergence of male/female body size during development" and that (2) "once we account for individual differences in brain size, there is almost no difference in the volume of specific cortical or subcortical structures between men and women". In sum, almost all brain differences would directly or indirectly follow from differences in body size.

In a recent study that does not have the same limitations as most studies reviewed by Eliot et al., we reach different conclusions (Williams et al., 2021). Many of the studies mentioned in the review suffer from two main limitations: small sample size, which together with publication bias, leads to an excess of false positive results, and inadequate adjustment for global brain size. Our study rests on the UK Biobank, the largest neuroimaging database currently available with 40,028 participants. And it uses the state-of-the-art method to adjust for global brain size: the well-known covariate method, but in a log-log scale to account for the allometric (non-linear) relationship between the brain and body, and between regional and global brain measures.

Although the sex difference in brain size seems to parallel the sex difference in body size, it does not follow that it is entirely accounted for by body size. It is not, by a long shot, at least with height and weight as proxies of body size. This was previously noticed by Ankney (1992), although without proper allometric adjustment. Indeed, the (within-sex) correlation between height and total brain volume (TBV) is only about 0.29. Moreover, whereas the unadjusted sex difference in TBV is $d = 1.14$, the sex difference in TBV adjusted on height remains $d = 0.7$. Similar results were obtained with total surface area and other global brain measures. Body weight did not explain any additional variance in TBV.[1] [2]

These results show that the sex difference in height only accounts for 39 % of the sex difference in TBV, and that men have a disproportionately large brain compared to women of the same height (Fig. 1).

Using the same log-log covariate method, we regressed every single

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[1] All analyses are available in Williams et al. (2021), on https://osf.io/s4qc5/ and in Supplemental Tables S1−9.

[2] Ordinal least squares regression of brain on body size has been criticised, and other approaches have been proposed (Forstmeier, 2011; Schluter, 1992). The corresponding analyses are reported in the Supplemental Information, as are analyses including both height and weight. It remains of course conceivable that another body measure might be a better correlate of TBV and therefore a better adjustment variable, but no other was available to us in the UK Biobank.

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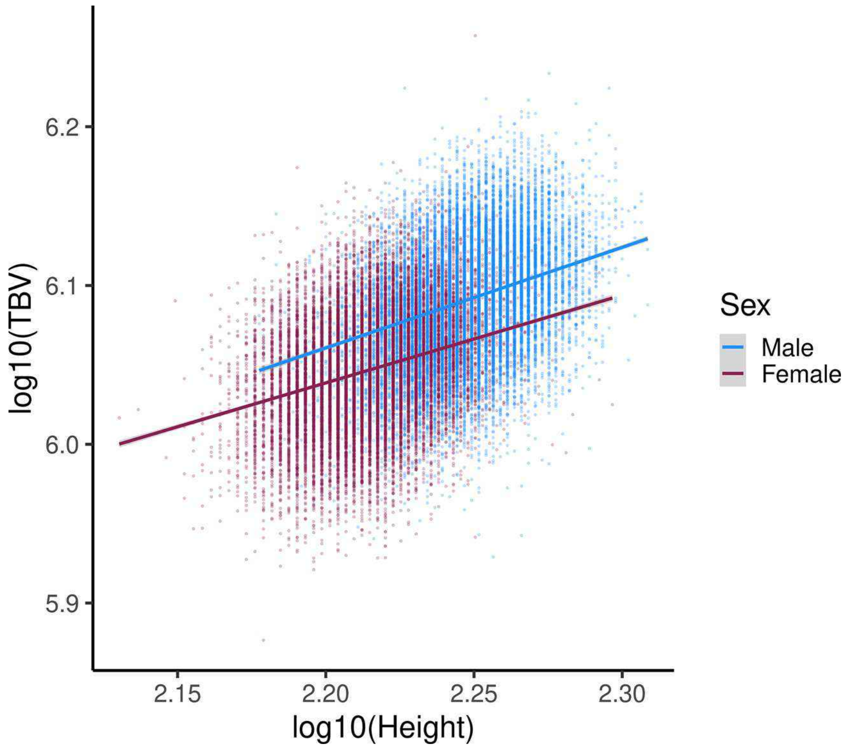

Fig. 1. Ordinal least squares regression of Total Brain Volume (TBV) on Height, on a log-log scale to take allometry into account, by sex. For the purpose of better visualisation, 0.5 cm was added to male height.
Analysis from Williams et al. (2021), Supplemental information.

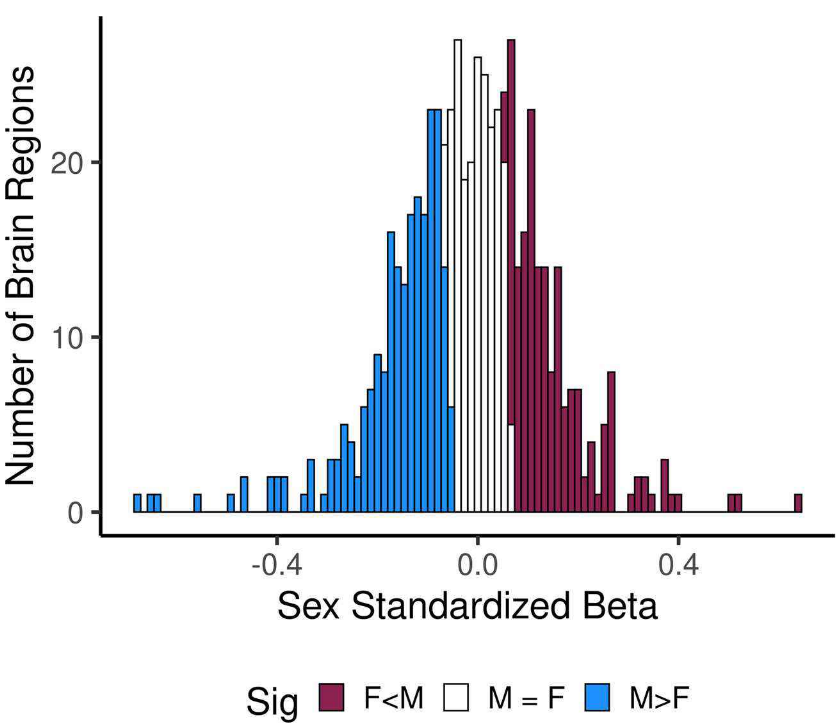

Fig. 2. Distribution of the residual effect size of sex differences across 620 regional brain measures, in a statistical model where log10(regional brain measure) is regressed on log10(total cerebral measure), sex, age, age^2, and their interactions, and scanner site. Blue bars reflect the number of regions with a significant sex difference where the region is larger in males than in females ($p < 7.33\ 10^{-6}$). Purple bars reflect the number of regions with a significant sex difference where the region is larger in females than in males. White bars reflect non-significant differences.
Results from Williams et al. (2021).

regional brain measure (a total of 620 volumes, surfaces and thicknesses) on its corresponding global measure (TBV, Total Surface Area or Total Mean Cortical Thickness), as well as on sex, age, and scanner site and their interactions. We applied an extremely stringent significance threshold of alpha = 0.05 / (620 brain regions of interest * 11 coefficients in the model).

We found that two thirds (409/620) of all brain measures showed a significant sex difference (36 % larger in males, 29 % larger in females), once total cerebral measure was properly adjusted. Effect sizes ranged from -0.67 (right choroid plexus) to 0.64 (cerebellar vermis X), with a median absolute effect size of d = 0.13. Although most of those differences were small, 46 % of regions (286/620) had an absolute effect size above 0.1 (Fig. 2).

Overall, our results provide the most robust estimation to date of neuroanatomical sex differences. Contrary to Eliot et al.'s assertions, we find that sex differences in total brain volume are not accounted for by sex differences in height and weight, and that once global brain size is taken into account, there remain numerous regional sex differences in both directions. We agree with these authors that these differences are small, although this does not necessarily make them insignificant. We also agree that both their causes and their consequences remain unclear. Future studies will tell. But these differences do exist and cannot be dismissed lightly.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.09.015.

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