

**Review:** Ingalhalikar, M. et al. (2014). Sex Differences in the Structural Connectome of the Human Brain. *Proceedings of the National Academy of Sciences of the United States of America*, 111(2), 823–828 (doi:10.1073/pnas.1316909110)

Ingalhalikar et al.'s paper is the first laboratory study investigating sex differences in the human connectome with diffusion tensor imaging (DTI) based on a large number of participants. As the title suggests, the authors report significant sex differences in the structural connections within the brains of male and female participants respectively. In a nutshell, the brains of female subjects were found to have strong interhemispheric connections, whereas the intrahemispheric connections appeared stronger in males. These results have not been reported before and the authors argue that they are in line with earlier findings of structural brain sex differences. Furthermore, Ingalhalikar et al. propose that the measured differences provide an explanation for functional differences in the brains of females and males as well as for the developmental process of the constitution of these differences.

The manuscript is well-written and the evidence compelling. As becomes clear in the following section-by-section review, a few revisions on the presentation of the data and its relation to earlier research would be advantageous. Addressing the growing body of literature on sex and gender differences that originates from the social sciences may be beneficial to the authors' argument regarding the relation of their findings to behavioral differences.

The abstract is very clear and provides a concise overview over the study and its results. The very first sentence gives insight into the authors' motivation to carry out the study; however, the reference to behavioral differences in males and females may create a false expectation in some readers. This manuscript stems from a neurostructural study and does not provide data about behavior or cognitive function. The inference towards the end of the abstract that "male brains [may be] structured to facilitate connectivity between perception and coordinated action, whereas female brains [may be] designed to facilitate communication between analytical and intuitive processing modes" (p. 1) seems neither to derive from the manuscript itself nor from any of the referenced works. It may be more in line with the scope of the project to save inferences on behavioral implications of the study's results for the discussion section of the paper.

The introduction summarizes important questions in the field of neuroscientific sex difference research very effectively: First, the reader is provided with a general overview of neuroanatomical sex differences that may potentially underlie behavioral differences in males and females. Second, the authors provide an overview of studies using DTI to investigate sex differences in human brains. It becomes clear that maturation may play an important role in the structural differentiation of female and male brains. Third, the authors make explicit the research gap that makes a whole-brain study with a large number of participants of different age groups desirable.

Despite the clarity, the manuscript would benefit from stronger references in the introductory section. The suggestion that behavioral sex differences derive "from complementary roles in procreation and social structure" (p. 1), for instance, seems to rest on two studies that are rather limited regarding the age group of participants (8–22 years) and the subject matter (science and mathematics) respectively. To give another example, the manuscript points to evidence from "[r]ecent studies" (p. 1), but the three papers in question were published between 1994 and 2002.

Sub-headings structure the clear results section very well. For the reader unfamiliar with DTI, some parameters and terms are not evident from the short overview at the beginning of the results section (p. 2). This limitation is due to the journal format style, and the ambiguities are resolved in the methods section at the end of the paper. As determined by a T statistic, the evidence for males' bilaterally higher intrahemispheric connections is very strong ( $P < 0.0001$ ) for the bilateral frontal, temporal, and parietal lobes. Similarly significant findings suggest the higher degree of modularity and transitivity in males as compared to females. The results regarding the lobar connectivity weight and the participation coefficients of individual nodes in the structural connectome would benefit from mentioning the P values instead of only referring the reader to Tables 2, 3, and Figure 3.

Noteworthy is the manuscript's emphasis of the developmental aspect of the study's results. Ingalhalikar et al. mention that they are presenting "a comprehensive study of developmental sex differences in brain connectivity" (p. 2). Accordingly, children, adolescents, and young adults were subject to the investigation. But despite this focus, the results are sometimes phrased as general sex differences, and not as gradually changing dimorphisms in maturing brains (e.g., p. 2). Even though the connection-wise analysis accounts for a sex-age interaction with structural connectivity, the manuscript does not supply data regarding the change of structural connectivity over time regardless of sex; every analysis is split in female/male. The absence of significant sex differences over the trajectory of the observed youth stages, for example, is reported in the discussion (p. 3), but the data was not included in the results section. It is not clear if Ingalhalikar et al. were aiming at a strong developmental perspective to their study as the above-mentioned quote suggests. If so, the recorded difference between adolescent and young adult female brains regarding their degree of interhemispheric connections (p. 2), for instance, could be expanded upon.

The discussion section restates the question of how integral the developmental perspective is to this project. It is reported that interhemispheric connections become stronger in the adult brain. This observation is attributed to the fact that intrahemispheric connections are not maintained as long as interhemispheric connections. With this in mind, it would be interesting to elaborate more on the implication for recorded sex differences in mature and maturing brains (p. 3).

The manuscript sometimes suggests functional outcomes of the obtained structural results; these interpretations do not directly follow from the data acquired. The study suggests, for instance, that brains "optimize into adulthood" (p. 3; see also p. 4). This formulation may imply the question of whether male or female brains are more "optimize[d]." In this connection as well as in the discussion section more broadly, the manuscript mentions some studies to back the authors' functional claims. At least one of these studies, however, has already been contested (Kaiser, Haller, Schmitz, & Nitsch, 2009).

The manuscript points to and explains seemingly contradictory measurements in the cerebellum: it is more intrahemispherically connected in males than in females due to its association with ipsilateral motor behavior (p. 3f). In this connection, it may be beneficial to provide more context deriving from recent structural or functional studies that illuminate the relationship between the cerebellum, sex differences, and hemispheric connectivity. The discussion section could also address the question of why a previous study with 439 participants (i.e., the ratio of participants is 0.46 in favor of Ingalhalikar et al.) did not find significant differences in the structural connectomes of male and female brains (p. 1).

Regarding the figures and tables, it is unclear why Table 1 contains such a meticulous account of the racial background of participants although further analysis does not draw on

this characteristic. Figure 1 is very helpful to visualize the process of data analysis, and Tables 2, 3, and Figure 3 provide valuable overviews of the results. Only Figure 2 does not offer a clear depiction of results. It is unclear which of the brains in Figures 2B, 2C, and 2D are male and female respectively. Furthermore, the “GM, gray matter” in the caption should be omitted, since this abbreviation is not used in Figure 2.

The methods section is overall very clear. DTI is well-suited for answering the question of structural differences in female and male brains. The data was acquired using standard parameters for the age range of subjects using a 3T scanner (Crossley et al., 2014; Tymofiyeva et al., 2013; Verstraete, Veldink, Mandl, Rene C W, van den Berg, Leonard H, & van den Heuvel, Martijn P, 2011). The connectivity analysis was performed with an unusually high number of randomizations and the correction for multiple comparisons rests on established statistical methods (p. 5). A clarification is needed in the formula for the weighted modularity of a network: the divisor of one of the coefficients, “l,” is not defined (p. 6). After the definition is added, maybe a different letter could be chosen, since the journal font does not allow a distinction between the coefficient “l” and the region “l” mentioned a few lines down.

The biggest concern regarding the methods section is the lack of information regarding the nearly 1,000 study participants. The heterogeneity of the sample regarding age is acknowledged by the authors (p. 2), but the manuscript does not provide any information concerning the participants’ educational background, cognitive abilities, etc. The reader is only provided with the participants’ racial background, their sex, and the information that the subjects were healthy. The reader does not learn about how participants were recruited.

A more substantial revision than the section-wise suggestions provided thus far seems advisable if the authors wish to maximize their study’s impact on the discourse within the social sciences. The authors themselves suggest that the manuscript is of interest to an audience much broader than the neuroscientific community (p. 1). Ingalhalikar et al. aim at providing a biological foundation for how various cognitive and behavioral differences between females and males come into being. In doing so, they propose a scientific explanation for the neural bases of social phenomena. In order to speak to social scientists on matters of sex and gender, however, the manuscript would benefit from addressing the concerns of social scientists working on sex and gender, in particular the “neurofeminists” (Bluhm, Jacobson, & Maibom, 2012). One limitation of the manuscript is, for example, that it uses the terms “sex” and “gender” interchangeably. Moreover, the way of reporting the differences in the manuscript is noticeably male-centric; it does not become clear whether the male characteristics are regarded as the norm or whether the findings for females showed less significance (e.g., the non-provided P in the connection-wise analysis for females; p. 2). In particular regarding the developmental aspects of the study, it may be beneficial to clarify to what extent the data suggests that sex differences increase in older age. Since the brain is structurally plastic, it would be suitable if the discussion section of the manuscript addressed the question of whether sex differences may be amplified due to gendered education and social experience, as it has been suggested by feminist scholars both from the neuro- and social sciences (Kaiser et al., 2009).

In conclusion, this is a solid study with important and significant findings regarding the structural connectome in female and male brains. In order to make functional inferences and speak to more behavioral and social topics, however, the manuscript would benefit from some revisions. References to a broader selection of scholarship within and beyond the neurosciences as well as a consideration of structural plasticity in connection with the developmental aspect of the authors’ argument would be particularly valuable.

## References

- Bluhm, R., Jacobson, A. J., & Maibom, H. L. (Eds.). (2012). *Neurofeminism: Issues at the Intersection of Feminist Theory and Cognitive Science*. New York: Palgrave Macmillan.
- Crossley, N. A., Mechelli, A., Scott, J., Carletti, F., Fox, P. T., McGuire, P., & Bullmore, E. T. (2014). The Hubs of the Human Connectome Are Generally Implicated in the Anatomy of Brain Disorders. *Brain*, *137*(Pt 8), 2382–2395. doi:10.1093/brain/awu132
- Kaiser, A., Haller, S., Schmitz, S., & Nitsch, C. (2009). On Sex/Gender Related Similarities and Differences in fMRI Language Research. *Brain Research Reviews*, *61*(2), 49–59. doi:10.1016/j.brainresrev.2009.03.005
- Tymofiyeva, O., Hess, C. P., Ziv, E., Lee, P. N., Glass, H. C., Ferriero, D. M., ... (2013). A DTI-Based Template-Free Cortical Connectome Study of Brain Maturation. *PloS one*, *8*(5), e63310. doi:10.1371/journal.pone.0063310
- Verstraete, E., Veldink, J. H., Mandl, Rene C W, van den Berg, Leonard H, & van den Heuvel, Martijn P. (2011). Impaired Structural Motor Connectome in Amyotrophic Lateral Sclerosis. *PloS one*, *6*(9), e24239. doi:10.1371/journal.pone.0024239