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Sex/gender differences in the brain are not trivial—A commentary on Eliot et al. (2021)

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ABSTRACT

In this commentary to the comprehensive review by Eliot et al. (2021), we fully comply with rejecting the 'sexual dimorphism' concept in its extreme, binary form. However, we criticise the authors' extreme position and argue that sex/gender differences in the brain are far from being 'trivial' and 'unlikely to be meaningful'. Our key arguments refer to the importance of small effects which can have meaningful behavioural consequences, and to several non-binary sex/gender-related factors which might explain individual differences better than sex/gender per se and which have shown to play important roles as risk factors in the aetiology of many mental and neurodevelopmental disorders. We conclude that the biopsychosocial approach is key to understanding sex/gender differences in the brain better than we currently do.

In their comprehensive review, Eliot et al. (2021) argued to "dump" the notion that the human brain is "sexually dimorphic" and that the brain as a whole does not come in two completely distinct, male and female versions. The authors are not the first to make this point, but the first who systematically reviewed a large body of literature and data on this matter. Like many other researchers working in this field, we completely agree with rejecting the "sexual dimorphism" concept in its extreme, binary form. However, the authors went a step further and argued that, in general, *sex/gender differences* in the brain (= a continuum on which males and females differ on average) are either "trivial", "negligible", "very weak", or "unlikely to be meaningful". This diametrically opposed view is similarly extreme and throws the baby out with the bathwater: It neglects that some sex/gender differences reliably exist and that they are not trivial, while at the same time they are not "sexual dimorphisms".

1. The importance of balanced phrasing

The authors correctly point out that especially in this research arena careful wording is important (e.g., when conceptualising "dimorphism" and "difference"). We recently aimed to debunk another myth according to which sex/gender differences in hemispheric specialization give rise to sex/gender differences in cognitive abilities (Hirnstein et al., 2019). This systematic review revealed less lateralization in men, but the effect is very small (d = 0.05–0.15) and therefore unlikely to account for sex/gender differences in certain verbal and spatial skills. Hiscock et al. (2001), whose work is also referenced in Eliot et al., came to a similar conclusion by finding evidence for the existence of a "small but reliable population-level sex difference in human laterality" (p. 137). This is markedly different to Eliot et al.'s conclusion that "the collective data do not support the widespread belief that males' brains are meaningfully more lateralized than females" (p. 678).

2. The importance of small effects and meta-analyses

Small effect sizes have, indeed, little meaning for a single event, but can become very meaningful over repeated events (Funder and Ozer, 2019). For example, a small sex/gender difference on the order of 1–5 % in the hippocampus or amygdala may have little impact, if any, on the single performance in a memory test. However, since these structures process emotional and spatial memories over and over again across lifetime, this may very well lead to profound behavioural effects in the medium to long run. Moreover, when multiple small differences are combined into multivariate analyses, computer algorithms can predict an individual's sex/gender with an accuracy between 60 % (Sanchis-Segura et al., 2020) to 70 % (Chekroud et al., 2016) – even if the large sex/gender difference in brain size is dropped as a factor from the algorithm. Eliot et al. correctly pointed out other potential issues with

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computer algorithms, such as difficulties when applying an algorithm to a different dataset from a different scanning environment, but it should be noted that such approaches are still in its infancy (Sanchis-Segura et al., 2020).

Meta-analyses are an important tool to identify small effects and Eliot et al. cited those that are available to date. Whenever they were missing, Eliot at al. filled the gaps by presenting tables (nine in total) with the "largest and most highly-cited studies" (p. 668). These studies are then classified as either showing a significant effect towards men/women or no significant sex/gender effect. Several studies yielded non-significant and/or inconsistent significant effects favouring either men or women. Although this clearly argues *against* the notion of a sexually dimorphic brain, it is no evidence *for* the notion that sex/gender differences do not exist or are trivial: A non-significant finding does not imply that there is no effect, and the included studies represent a limited selection – understandably given the wealth of studies that had to be covered. Properly conducted meta-analyses based on systematic literature searches are needed to approximate the magnitude of sex/gender differences and thus allow conclusions about whether they exist and their meaningfulness.

Simply lumping data together in meta-analyses, however, is also insufficient. Several factors can impact sex/gender differences in the brain such as age, socioeconomic status, education, sexual orientation and identity, gender roles, sex hormones etc. Eliot et al. acknowledge the relevance of those non-binary factors but hardly took them into account when summarising findings from the literature. For example, while there is enormous variance in age range and mean age in several summary tables, there is no distinction between samples during and after puberty or between pre- or postmenopausal samples. Modern meta-analyses tools allow regressions and examining moderator variables, which are necessary to discern the impact of those factors on sex/gender differences in the brain.

3. Brain/behaviour relationship unclear

A small sex/gender effect in the brain *might* have meaningful behavioural consequences, as described above. In contrast, large sex/gender differences in the brain do not necessarily lead to large behavioural differences. For example, male brains are undisputedly larger then female brains, but this does not seem to affect men's and women's average general IQ (Colom et al., 2002). Some sex/gender differences in the brain have even been assumed to reduce or compensate for behavioural sex/gender differences (De Vries, 2004). The relationship between sex/gender differences in the brain and behaviour does not simply follow a linear logic, where small differences in the brain lead to small differences in behaviour, and large differences in the brain lead to large differences in behaviour (see also Cahill, 2006).

4. Clinical disorders and the biopsychosocial approach

In their conclusion, Eliot et al. (2021) question generally whether studying sex/gender differences in the brain could aid understanding the aetiology of mental or neurodevelopmental disorders. We take a different stance: Several sex/gender-related factors are well-known to play important roles as risk factors in the aetiology of many mental and neurodevelopmental disorders, such as genetics (Kang et al., 2020), epigenetics (Hodes et al., 2017), sex hormones (Georgakis et al., 2016), socialization (Hyde and Mezulis, 2020), and life experiences (Shore et al., 2018) in depression. We will probably never fully understand sex/gender differences in brain and behaviour in the healthy and clinical context, if research does not take sex/gender-related biological, psychological, *and* social factors (as well as their complex interactions) more into account. In fact, these non-binary sex/gender-related factors might explain individual differences better than sex/gender per se. Recent technological progress made hormone assays increasingly feasible for every neuroimaging study to include. If, in addition, information about participants' age, education, socioeconomic status, sexual identity, and orientation was routinely collected, this would advance progress in this fascinating research area. The biopsychosocial approach offers promising opportunities in this context (Hausmann, 2020) and will certainly contribute to "dump the dimorphism".

Declaration of Competing Interest

The authors report no declarations of interest.

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References

Cahill, L., 2006. Why sex matters for neuroscience. Nat. Rev. Neurosci. 7, 477–484.
Chekroud, A.M., Ward, E.J., Rosenberg, M.D., Holmes, A.J., 2016. Patterns in the human brain mosaic discriminate males from females. Proc. Natl. Acad. Sci. U. S. A. 113. E1968–E1968.
Colom, R., García, L.F., Juan-Espinosa, M., Abad, F.J., 2002. Null sex differences in general intelligence: evidence from the WAIS-III. Span. J. Psychol. 5, 29–35.
De Vries, G.J., 2004. Minireview: sex differences in adult and developing brains: compensation, compensation, compensation. Endocrinology 145, 1063–1068.
Eliot, L., Ahmed, A., Khan, H., Patel, J., 2021. Dump the "dimorphism": comprehensive synthesis of human brain studies reveals few male-female differences beyond size. Neurosci. Biobehav. Rev. 125, 667–697.
Funder, D.C., Ozer, D.J., 2019. Evaluating effect size in psychological research: sense and nonsense. Adv. Methods Pract. Psychol. Sci. 2, 156–168.
Georgakis, M.K., Thomopoulos, T.P., Diamantaras, A.A., Kalogirou, E.I., Skalkidou, A., Daskalopoulou, S.S., Petridou, E.T., 2016. Association of age at menopause and duration of reproductive period with depression after menopause: a systematic review and meta-analysis. JAMA Psychiatry 73, 139–149.
Hausmann, M., 2020. Sex/gender differences in brain activity – it's time for a biopsychosocial approach to cognitive neuroscience. Cogn. Neurosci. 1–2.
Hirnstein, M., Hugdahl, K., Hausmann, M., 2019. Cognitive sex differences and hemispheric asymmetry: a critical review of 40 years of research. Laterality Asymmetries Body Brain Cogn. 24, 204–252.
Hiscock, M., Perachio, N., Inch, R., 2001. Is there a sex difference in human laterality? IV. An exhaustive survey of dual-task interference studies from six neuropsychology journals. J. Clin. Exp. Neuropsychol. 23, 137–148.
Hodes, G.E., Walker, D.M., Labonté, B., Nestler, E.J., Russo, S.J., 2017. Understanding the epigenetic basis of sex differences in depression. J. Neurosci. Res. 95, 692–702.
Hyde, J.S., Mezulis, A.H., 2020. Gender differences in depression: biological, affective, cognitive, and sociocultural factors. Harv. Rev. Psychiatry 28.
Kang, H.-J., Park, Y., Yoo, K.-H., Kim, K.-T., Kim, E.-S., Kim, J.-W., Kim, S.-W., Shin, I.-S., Yoon, J.-S., Kim, J.H., Kim, J.-M., 2020. Sex differences in the genetic architecture of depression. Sci. Rep. 10, 9927.
Sanchis-Segura, C., Ibañez-Gual, M.V., Aguirre, N., Cruz-Gómez, Á.J., Forn, C., 2020. Effects of different intracranial volume correction methods on univariate sex differences in grey matter volume and multivariate sex prediction. Sci. Rep. 10, 12953.
Shore, L., Toumbourou, J.W., Lewis, A.J., Kremer, P., 2018. Review: longitudinal trajectories of child and adolescent depressive symptoms and their predictors – a systematic review and meta-analysis. Child Adolesc. Ment. Health 23, 107–120.