LETTER

REPLY TO GLEZERMAN:

Why differences between brains of females and brains of males do not "add up" to create two types of brains

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As Marek Glezerman (1) rightly points out, there are differences between females and males in brain and behavior. Glezerman overlooks, however, the fact that such differences may be different and even opposite under different environmental conditions. That is, what is typical under some conditions in a brain composed of cells with an XX chromosomal complement residing in a body with low levels of testosterone, may be typical under other conditions in a brain composed of cells with an XY chromosomal complement residing in a body with high levels of testosterone. Such "reversals" of sex effects have also been reported when the manipulation of environmental conditions was done in utero (by manipulating the dam) and the offspring were tested in adulthood (reviewed in refs. 2 and 3). These observations led to the hypothesis that brains are composed of a "mosaic" of "male" and "female" features rather than of only "male" features or only "female" features, as expected of a "male brain" and a "female brain," respectively (2, 3). Our study (4) is the first to empirically test whether brains are "male" or "female" by assessing internal consistency in the degree of "maleness-femaleness" of different elements within a single brain. We found that brains with both "female-end" and "male-end" characteristics were more prevalent than brains with only "female-end" or only "male-end" characteristics. This was true for both the volume of brain regions and the strength of connections between regions (assessed in a similar way to ref. 5), in contrast to Glezerman's assumption that "Other imaging methods might have yielded different results." To corroborate our analysis of different aspects of brain structure assessed using MRI, we also analyzed brain function, as revealed in people's behaviors, personality characteristics, preferences, and attitudes. Also here there were many more people with both "feminine" (i.e., more common in females compared with males) and "masculine" (i.e., more common in males compared with females) characteristics than people with only feminine or only masculine characteristics (4).

There is no doubt that sex affects the structure and function of brain cells. However, the fact that sex can affect brain cells does not necessarily entail that the form and function of brain cells are either "male" or "female" nor that the brains comprised of these cells can be divided into two distinct categories. For such claims to be true it is necessary that the effects of sex are dimorphic, resulting in the formation of distinct "male" and "female" types, as well as internally consistent (2, 3, 6). Hopefully, future studies looking at the relations between sex and other systems in which sex differences have been documented (e.g., the immune system, the cardiovascular system) will assess both internal consistency and degree of overlap, to reveal whether the relations between sex and other systems are more similar to the relations between sex and the brain (mosaicism) or to the relations between sex and the genitalia (dimorphism).

1 Glezerman M (2016) Yes, there is a female and a male brain: Morphology versus functionality. *Proc Natl Acad Sci USA*, 10.1073/pnas.1524418113.
2 Joel D (2011) Male or female? Brains are intersex. *Front Integr Neurosci* 5:57.
3 Joel D (2012) Genetic-gonadal-genitals sex (3G-sex) and the misconception of brain and gender, or, why 3G-males and 3G-females have intersex brain and intersex gender. *Biol Sex Differ* 3(1):27.
4 Joel D, et al. (2015) Sex beyond the genitalia: The human brain mosaic. *Proc Natl Acad Sci USA* 112(50):15468–15473.
5 Ingalhalikar M, et al. (2014) Sex differences in the structural connectome of the human brain. *Proc Natl Acad Sci USA* 111(2):823–828.
6 Joel D, Fausto-Sterling A (2016) Beyond sex differences: New approaches for thinking about variation in brain structure and function. *Philos Trans R Soc Lond B Biol Sci* 371(1688):20150451.

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