

REPLY TO DEL GIUDICE ET AL., CHEKROUD ET AL., AND ROSENBLATT:

# Do brains of females and males belong to two distinct populations?

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We are glad that our paper (1) raised discussions on the relations between sex and the brain and on our new methodological approach. Clearly, sex affects the brain, as evidenced in differences between brains from females and brains from males in both macroscopic and microscopic features. However, the fact that sex affects the brain does not necessarily entail that there are two distinct types of brains, “male brains” and “female brains,” as there are two distinct types of genitalia (2–4). Answering this question was the aim of our study.

## Assessing Internal Consistency and Substantial Variability

The rational for our method of analysis was derived from animal studies demonstrating that in contrast to sex effects on genital organs, sex effects on brain features may be opposite under different environmental conditions. That is, what is typical in one sex category (e.g., females) under some conditions may be typical in the other sex category under other conditions (reviewed in refs. 2 and 3). As a result, brains are expected to be composed of both features more common in males compared with females and features more common in females compared with males, a situation that rarely occurs in genitalia. When it does occur, the genitalia are classified as “intersex” and not as “male” or “female” (5). Our analysis was designed to assess how common this “mixture” of features is in the human brain.

We found that there are many more “substantially variable” brains, that is, brains with both features that are more common in males compared with females (“male-end” features) and features more common in females compared with males (“female-end” features), than “internally consistent” brains, that is, brains with only “male-end” or only “female-end” features. The finding that substantial variability is more prevalent than internal consistency was robust across different samples, age groups, type of magnetic resonance imaging, method of analysis, and the cutoff used to define the “male-end” and “female-end” zones

(table S2 in ref. 1) and led to the conclusion that human brains do not belong to one of two distinct categories: “male brain”/“female brain”.

Del Giudice et al. (6) provide an elegant validation of our method of analysis, by demonstrating that internal consistency is higher than substantial variability when distinct populations (facial morphology of different primate species) are assessed. Thus, with a cutoff of 33%, internal consistency was found in 1.1–5.1% of profiles (depending on the pair of primates assessed) and substantial variability in 0% (6), compared with 0–8.2% internally consistent brains and 23–53% substantially variable brains [depending on the dataset (1)]. This comparison also reveals a degree of “mosaicism” in brains that is much higher than that found in primate species and provides further support to our conclusion that human brains do not belong to two distinct populations.

Using simulations in which they systematically varied the size of sex/gender differences and of correlations between variables, Del Giudice et al. (6) further demonstrated that our method of analysis returns more substantially variable profiles than internally consistent profiles, unless correlations and/or sex/gender differences become extremely large. These simulations corroborate our simulations (1), in which we systematically varied the mean random noise added to an otherwise internally consistent “brain.” Although the correlations between variables change as random noise is added, the multivariate distribution of variables created this way differs from that of the variables created by Del Giudice et al. (6). Indeed, for similarly sized correlations ( $0.7 < d \leq 0.84$ ) and sex differences ( $0.70 < d \leq 0.84$ ) our simulation revealed more internally consistent “brains” than substantially variable “brains” (1), whereas Del Giudice et al. (6) found the reverse (less internally consistent “brains” than substantially variable “brains”). Together, these simulations demonstrate that our method of analysis can differentiate between an

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internally consistent system with some degree of random noise (our simulated data) and a system in which there are similar correlations between variables but with no underlying internal consistency [the simulated data of Del Giudice et al. (6)].

We hope future studies on the effects of sex on additional systems in which sex/gender differences were found (e.g., the immune system) will use our method to reveal whether the relations between sex and other systems are more similar to the relations between sex and the brain (substantial variability more prevalent than internal consistency under several cutoffs) or to the relations between sex and the genitalia (internal consistency more prevalent than substantial variability under several cutoffs).

### Do Brains Belong to Two Distinct Types?

The high degree of overlap in the form of brain features between females and males combined with the prevalence of mosaicism within brains are at variance with the assumption that sex divides human brains into two separate populations. Moreover, the fact that the large majority of brains consist of unique mosaics of “male-end,” “female-end,” and intermediate (i.e., common in both females and males) features precludes any attempt to predict an individual’s unique brain mosaic on the basis of sex category (2–4). However, the existence of group-level differences between brains of females and brains of males is sufficient to make the reverse prediction, that is, to predict with accuracy above chance an individual’s sex category on the basis of the individual’s brain mosaic (2). For example, in the two voxel-based morphometry (VBM) datasets, one’s sex category can be predicted with ~70% accuracy by comparing the number of “male-end” and “female-end” features (figures 1F and 2A in ref. 1). This also means that one’s sex category predicts with ~70% accuracy whether s/he has more “female-end” than “male-end” characteristics, or vice versa. However, the reduction of the original 10-dimensional space (volume of each of 10 brain regions) to a 2D space (number of “female-end” and “male-end” features) results in the loss of information about the identity of the “female-end,” “male-end,” and intermediate features of each brain. As a result, sex category cannot predict a person’s number and specific combination of “male-end,” “female-end,” and intermediate characteristics. Moreover, “similarity” in the 2D space may have no biological meaning. Consider, for example, three individuals: A with a large (“female-end”) left hippocampus and all other regions in the intermediate form; B with a large (“female-end”) left hippocampus, small (“male-end”) left and right caudate, and all other regions in the intermediate form; and C with a small (“male-end”) left hippocampus, large (“female-end”) left and right caudate, large (“female-end”) left and right gyrus rectus, and all other regions in the intermediate form. In the 2D space (number of “female-end” and

“male-end” features), A and C fall on the “female” side, whereas B falls on the “male” side. However, by the details of their brain mosaic, A seems to be more similar to B than to C.

Del Giudice et al. (6), Rosenblatt (7), and Chekroud et al. (8) achieved better accuracy in predicting an individual’s sex category on the basis of brain form, using supervised learning over all brain measures to find the space in which brains of females and brains of males are most separated. Specifically, using linear discriminant analysis on our different datasets, Del Giudice et al. (6) correctly identified an individual’s sex category about 69–77% of the time (depending on the dataset); using linear support vector machines (SVM) on our VBM data, Rosenblatt (7) correctly identified an individual’s sex category about 80% of the time (depending on the random split); using penalized logistic regression on cortical thickness and subcortical volume calculated using FreeSurfer (a technique that does not “correct” for differences in brain size), Chekroud et al. (8) correctly identified an individual’s sex category about 89.5–95% of the time, but accuracy dropped to 65–74% when head-size-related measurements were regressed out. This latter finding is in line with previous reports that observed sex/gender differences are largely attributed to differences in brain size (9, 10) (see also figure S4 in ref. 1). Although the different supervised learning methods achieve better accuracy in predicting sex category than the simple method described above, they have the same conceptual problem, namely, it is unclear what the biological meaning of the new space is and in what sense brains that seem close in this space are more similar than brains that seem distant. Moreover, it is unclear whether the brain variability that is represented in the new space is related to sex or rather to physiological, psychological, or social variables that correlate with sex (e.g., weight, socioeconomic status, or type of education) or to a chance difference between the males and females in the sample (2, 4). One way to answer this question is by checking whether a model created to predict sex category in one dataset can accurately predict sex category in another dataset. Using SVM, we found that accuracy may drop dramatically (sometimes to less than 50%) when a model created using a dataset from one geographical region (Tel-Aviv, Beijing, or Cambridge) was tested on the other datasets.

### Conclusion

Sex affects the brain, but the prevalence of mosaicism does not support the view that sex effects on the brain produce two distinct types of brains. Current data are not sufficient, however, to fully characterize the relations between sex and the brain (4). Such characterization is necessary for studying sex effects on the brain as well as for studying brain structure, function, and dysfunction in general (4). We hope future studies will soon fill in this gap.

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