LETTER

# Patterns in the human brain mosaic discriminate males from females

Adam M. Chekroud[a,1,2], Emily J. Ward[a,1], Monica D. Rosenberg[a], and Avram J. Holmes[a,b]

In their PNAS article, Joel et al. (1) demonstrate extensive overlap between the distributions of females and males for many brain characteristics, measured across multiple neuroimaging modalities and datasets. They pose two requirements for categorizing brains into distinct male/female classes: (*i*) gender differences should appear as dimorphic form differences between male and female brains, and (*ii*) there should be internal consistency in the degree of "maleness–femaleness" of different elements within a single brain. Based on these criteria, the authors convincingly establish that there is little evidence for this strict sexually dimorphic view of human brains, counter to the popular lay conception of a "male" and "female" brain. This finding has broad implications not only for the ontology of gender, but also for the statistical treatment of sex in morphometric analyses.

Critically, however, the conclusion that human brains cannot be categorized into two distinct classes depends largely on the level of analysis. Although the set of properties that distinguish one category from another is rich and flexible, there is rarely a diagnostic form (e.g., what singular physical characteristic reliably distinguishes cats from dogs?) and there is often substantial within-category variability (e.g., breeds of dogs) (2). The failure of the brain to meet these two requirements does not mean that "human brains cannot be categorized into two distinct classes: male brain/female brain." In fact, an individual's biological sex can be classified with extremely high accuracy by considering the brain mosaic as a whole.

To demonstrate this, we acquired T1-weighted structural MRI scans for 1,566 individuals, aged 19–35 y (57.7% female), from the freely available Brain Genomics Superstruct Project (3). Cortical thickness and subcortical volume estimates were calculated using the FreeSurfer automatic segmentation algorithm (v5.3; surfer.nmr.mgh.harvard.edu/fswiki). First, 400 subjects were retained as a held-out validation set. Next, penalized logistic regression [elastic net (4, 5)] was used to predict the sex of each individual based on their mosaic, or pattern, of morphometric brain data. Within the training set ($n = 1{,}166$), a regression model was built using three repeats of 10-fold cross-validation. The model was then used, without modification, to predict the sex of each individual in the held-out sample. Classification accuracy was extremely high [accuracy: 93%, 95% confidence interval (CI) 89.5–94.9%, $P < 10^{-16}$] and remained significant if head-size-related measurements were excluded [92% (CI 88.9–94.5%), $P < 10^{-16}$] or regressed out [70% (CI 65.0–74.2%), $P < 10^{-6}$]. To borrow the framing of Joel et al. (1), the human brain may be a mosaic, but it is one with predictable patterns.

Despite the absence of dimorphic differences and lack of internal consistency observed by Joel et al. (1), multivariate analyses of whole-brain patterns in brain morphometry can reliably discriminate sex. These two results are not mutually inconsistent. We wholly agree that a strict dichotomy between male/female brains does not exist, but this does not diminish or negate the importance of considering statistical differences between the sexes (e.g., including sex as a covariate in morphometric analyses).


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2 Hampton JA (2012) Thinking intuitively: The rich (and at times illogical) world of concepts. *Curr Dir Psychol Sci* 21(6):398–402.
3 Holmes AJ, et al. (2015) Brain Genomics Superstruct Project initial data release with structural, functional, and behavioral measures. *Sci Data* 2:150031.
4 Zou H, Hastie T (2005) Regularization and variable selection via the elastic net. *J R Stat Soc, B* 67(2):301–320.
5 Chekroud AM, et al. (2016) Cross-trial prediction of treatment outcome in depression: A machine learning approach. *Lancet Psychiatry* 366(15):1–8.


[a]Department of Psychology, Yale University, New Haven, CT 06520; and [b]Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114

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[1]A.M.C. and E.J.W. contributed equally to this work.

[2]To whom correspondence should be addressed. Email: adam.chekroud@yale.edu.



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