

### **What is novel in the new paper?**

1. We use a very simple mathematical illustration to explain why the existence of sex differences is not sufficient to conclude that there are two types of brain or to characterize the population of brains.

2. We review current data, including my recent PNAS study (Sex beyond the genitalia: The human brain mosaic), to suggest that human brains belong to a single highly heterogeneous population, in which there may be differences between females and males in the frequencies of rare brain mosaics (e.g., brains with only “female-end” characteristics although rare in the population, are more common in females compared to males). Describing the population of brains this way, one can account for the existence of group-level sex/gender differences in brain structure; the observation that different studies (i.e., using different samples of females and males) report different structural and functional differences between brains of females and brains of males; and the existence of differences between females and males in the prevalence of specific behaviors and psychopathologies (e.g., extreme physical aggression, autism) – this is accounted for by the existence of differences between females and males in the frequencies of rare brain mosaics.

### **If brain dimorphism is a myth, how do we explain differences in behavior?**

Behavior is also not dimorphic, that is, there are many ways to be human, not just two, a “male way” and a “female way”.

As we show in the recent PNAS study, human behavior is also characterized by mosaic rather than by two distinct forms.

### **In the new framework you are suggesting, how do you explain sex differences in psychopathology?**

Differences between females and males in the prevalence of specific behaviors and psychopathologies (e.g., extreme physical aggression, autism) are accounted for by the existence of differences between females and males in the frequencies of rare brain mosaics (e.g., brains with only “male-end” characteristics although rare in the population, are more common in males compared to females).

**You suggest NOT to use sex category as a variable when studying brain structure and function in humans. Why?**

We believe that current data are better explained by the assumption that human brains belong to a single heterogeneous population rather than to two distinct populations. If we are correct, then using sex category as a variable is both unnecessary and misleading, because comparing brains of females to brains of males would be analogous to comparing two samples randomly drawn from a single population of brains, rather than to comparing two samples, one randomly drawn from a population of “male brains” and the other from a population of “female brains”. As a result, although such comparisons may well yield significant differences between females and males (due to the high heterogeneity of the population), these differences would probably reflect a false-positive finding resulting from a chance difference between the two samples included in a specific study. This concern is emphasized by our and others' findings that different structural and functional differences between brains of females and brains of males are often found in different samples.

**You suggest to use sex category as a variable when studying brain structure and function in laboratory animals. Why?**

In contrast to humans, genetic, developmental, and environmental conditions can be highly controlled in laboratory animals. Thus, the variability of factors that might interact with sex to affect the brain (such as age, stress, housing conditions, nutrition, etc.) is greatly reduced. Consequently, brains of laboratory animals in a specific experiment are

expected to be less heterogeneous compared to brains of humans in a single study, and observed differences between the sex categories may indeed reveal the effects of sex rather than the effects of some chance difference between the sample of females and the sample of males in the study. On the other hand, the controlled genetic, developmental, and environmental conditions limit our ability to generalize from the specific experimental conditions to other conditions and other species, especially humans. Moreover, in order to obtain a better understanding of the effects of sex on the phenomena under study, these effects should be studied using varied environments and on different genetic backgrounds (e.g., using different strains of inbred animals).

**Do you think one should use gender as a variable instead of sex?**

I think we should not aim to replace sex with gender as a factor analyzed in studies of brain and behavior. This is because gender has several meanings (a social system, a set of psychological characteristics, a type of performance), each multilayered and probably unmeasurable. For example, how can we measure the forces exerted on an individual by her/his gendered society? How can we measure one's gender characteristics when we already know that gender characteristics are not correlated and that each person has a unique mosaic of gender characteristics that cannot be aligned on a masculine-feminine continuum? How can we measure gender performance in view of the fact that behavior is highly dependent on the situation? Thus, although it would be wise to consider psychological and social variables (e.g., socio-economical status, stress, education, personality characteristics) in studies of brain and behavior, we should not attempt to integrate these variables into a 'gender' variable, even if some of these variables show sex/gender differences.