How sex and gender shape functional brain networks

Gloria Matte Bon[1,2], Dominik Kraft[1], Tobias Kaufmann[1,3,4]*

Sex and gender differences exist in the prevalence and clinical manifestation of common brain disorders. Identifying their neural correlates may help improve clinical care.

For many years, the neurosciences have operated with a blind spot when it comes to investigating the roles of sex and gender in study samples (*1*). This might be particularly harmful in the clinical neurosciences, as we know that substantial sex differences exist in the prevalence, timing, and clinical presentation of many common brain disorders across the life span (*2*). For example, autism spectrum disorder and Parkinson's disease are more common in males than in females, whereas depression, migraine, and Alzheimer's disease are more common in females than in males (*2*). Because the sources of sex differences are poorly understood, basing research and clinical care on a one-sex-fits-all approach calls into question the validity of such an approach.

Sex differences exist across a range of brain phenotypes, from brain anatomy (e.g., differences in brain size) to brain function (e.g., differences in the functional interplay between large-scale brain networks) (*3*, *4*). Some of these differences have previously been linked to clinical characteristics (*3*), but there is a high degree of uncertainty when it comes to robustness and generalizability because a deep, system-level understanding is lacking. A period of particular interest might be adolescence as this is a time of high brain plasticity that largely influences trajectories for higher cognitive function, social skills, and mental health, all critical for framing a unique personality.

This time is also one of individual pubertal development, with profound differences between individuals assigned male at birth and individuals assigned female at birth, but also substantial variance between individuals of the same biological sex. Whereas some of this variance may be explained by individual differences in biology (e.g., genetic makeup), other components also factor into the equation, such as individual environmental conditions and sociocultural factors. The latter includes gender, a complex construct that defines an individual's identity and behavior, largely determined by social norms. Importantly, time is a key modulator in the interplay of all these factors. For example, socially imposed gender roles may become stronger over the course of adolescence, and likewise, this factor may become more important over time in individual brain development. Understanding how these factors dynamically interact and their effects on the brain is integral if we want to make normative predictions about individual brain development such as, for example, signs that require clinical support.

Most research so far has looked at sex differences in terms of binary biological sex assigned at birth, ignoring variance related to gender. In fact, gender is sometimes confused with sex, as they oftentimes map onto each other (i.e., female social roles are often imposed on female biological individuals and male roles are often imposed on male biological individuals). However, gender is a multifactorial construct that is not binary, and the variance in gender within each biological sex might, to some degree, be relevant when characterizing individual brain development (*5*).

In this issue of *Science Advances*, Dhamala *et al.* (*6*) present results from a study in which they attempted to disentangle effects of sex from effects of gender in individual functional brain networks of children (Fig. 1). Derived from functional magnetic resonance imaging data, such brain networks characterize the functional interplay of a set of large-scale brain regions (e.g., between limbic and parietal brain areas) (*7*). Dhamala *et al.* analyzed functional brain networks from 2315 female and 2442 male children aged 9 to 10 years old, available as part of the Adolescent Brain and Cognitive Development (ABCD) study resource (*8*). Because of the high dimensionality of the data (they estimated 153 unique connections between 18 large-scale brain networks), they used machine learning to assess the degree to which all connections together predict if a given brain is from a male or female individual, as indicated by sex assigned at birth. They then applied the same technique to gender data to see whether differences in gender identity are also predictable from brain network data. For gender, they used a self-assessment by the children as well as an assessment by the parents.

In line with earlier work, the authors found that sex can be classified from brain network data with a high degree of certainty. It is much more complicated when it comes to gender, as for most individuals, gender identity is congruent with the sex assigned at birth (most individuals of biological male sex will also have a male-like gender and vice versa for females). This can result in sex bias when analyzing gender data. The authors therefore looked at the gender data within males and the gender data within females, again assessing to what degree gender can be predicted from the brain network data of females or males, respectively. Performances of the machine learning models dropped to chance level for the self-reported gender data of the children. For parent-reported gender, model performance was very low as well, but predictions were significantly above chance. This allowed the authors to assess whether the brain networks predictive of sex were the same as those predictive of gender. They found that this was not the case, potentially indicating that sex and gender may be encoded differently in the brain.

[1]Department of Psychiatry and Psychotherapy, Tübingen Center for Mental Health, University of Tübingen, Tübingen, Germany. [2]Department of Women's and Children's Health, Science for Life Laboratory, Uppsala University, Uppsala, Sweden. [3]German Center for Mental Health (DZPG), partner site Tübingen, Tübingen, Germany. [4]Centre for Precision Psychiatry, Division of Mental Health and Addiction, Institute of Clinical Medicine, University of Oslo, Oslo, Norway.
*Corresponding author. Email: tobias.kaufmann@med.uni-tuebingen.de

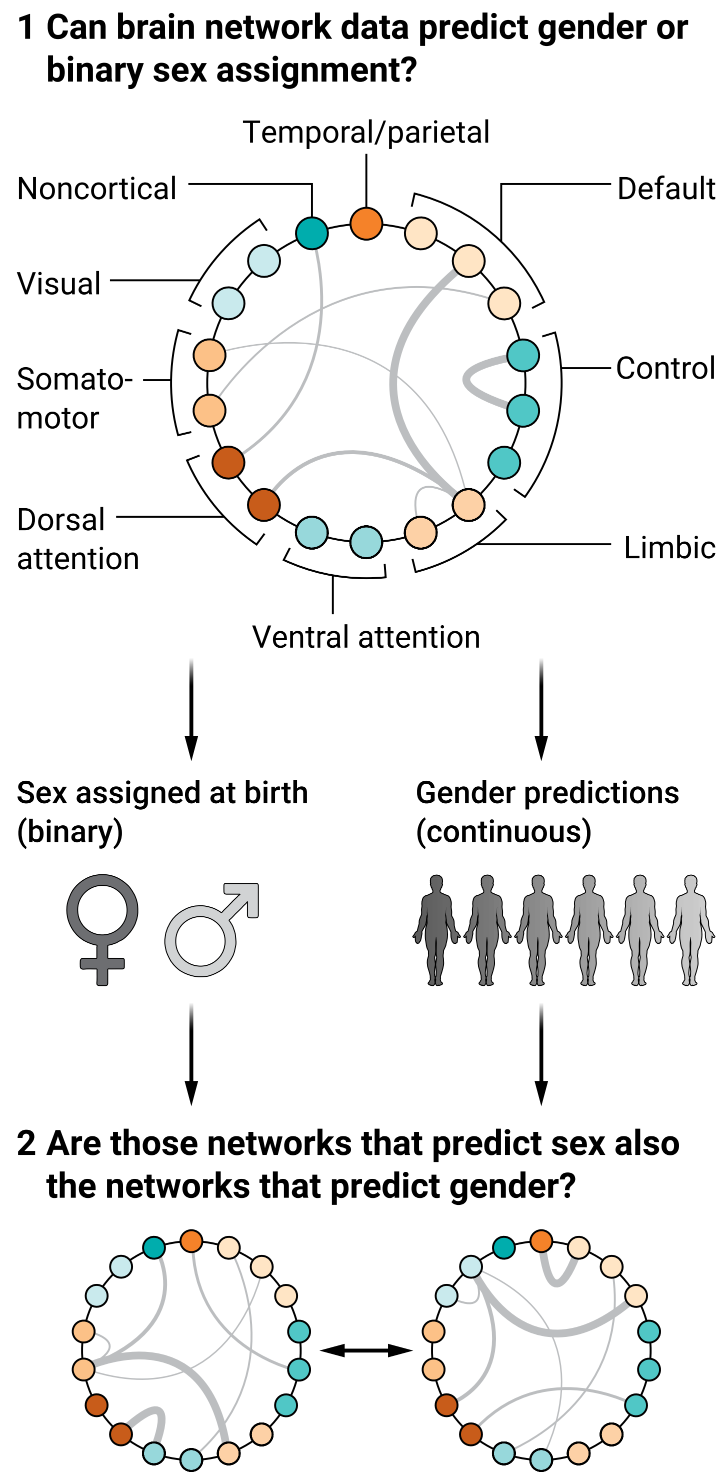

Fig. 1. Deciphering the interplay of sex and gender in shaping the developing brain. Conceptual illustration of the methods used in Dhamala *et al.* (*6*). The colored circles reflect nodes of a functional brain network, where gray lines indicate connection strengths between two network nodes. Illustration credit: Ashley Mastin/*Science Advances*.

One of the limitations of the current study is the restricted age range of the study sample. It is likely that gender data map closely to biological sex in young children because many of the social roles and norms may only be imposed on these individuals later in life. Fortunately, the ABCD study is a longitudinal effort. Since the authors conducted their initial analysis, the study participants have become older and meanwhile many individuals in this sample have undergone pubertal maturation. Therefore, it will be interesting to repeat this study as the children grow into adults and see how the ability to predict gender from neuroimaging data evolves once more variance factors into the gender assessment.

It must also be noted that gender norms can vary with ethnic, religious, and other social contexts, and therefore, it will be important to investigate different study populations in future research. Finally, scholars are just starting to explore this terrain and an array of opportunities by which the framework can be extended exist. These include investigations in other neuroimaging modalities, integration of hormonal markers, and, importantly, an integrative approach that allows the study of interactions between biological sex, environmental factors, and gender in a longitudinal context.

Regardless of these limitations, the study by Dhamala *et al* provides an important glimpse into potentially different encoding of sex and gender in the developing brain. If these results are confirmed by future studies, it will be clear that the neurosciences have to account for sex and gender differences alongside additional research to elucidate how sex and gender are encoded in the brain. Only by providing answers to questions of generalizability, biological and social mechanisms, and aspects of timing and dynamics may we one day be able to integrate a sex and gender perspective into brain-based clinical decision-making.

Several challenges lie ahead that need to be tackled to advance this field in the landscape of biomedical research: (i) Sex and gender are complex constructs, defined heterogeneously and often used interchangeably. To overcome this, appropriate sex and gender description and reporting are of utmost importance ideally leading to community-wide standards (*9*). (ii) Some aspects of sex and gender research will require large-scale studies whereas others will require carefully characterized samples and well-designed experimental work. A good balance of both will be key. To this end, the open sharing of data and the formation of international collaboration initiatives on focus topics around sex and gender neuroscience have started to transform the field. (iii) Although most studies focus on sex-specific effects, the interplay between gender and sex effects is still often overlooked. A holistic perspective will be key as isolated views of single factors may lead to wrong conclusions in a multifactorial puzzle. (iv) Researchers need to be aware that results in this domain might be misinterpreted and misused. Therefore, careful communication of research findings will be necessary. (v) Sustainable progress toward how sex and gender encode the brain is only possible with long-term commitment. Productive communities with regular scientific meetings such as the Organization for the Study of Sex Differences have already formed and will fuel the ongoing progress in the field. Scientific outreach programs such as podcasts and public events will be instrumental in communicating this progress to the broader research community and the public.

The neurosciences are beginning to shed light on the role sex and gender play in shaping the human brain. This task is long overdue, but it is also one that has the potential to transform the status quo of a one-sex-fits-all approach in many clinical processes.

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