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NEUROSCIENCE

Functional brain networks are associated with both sex and gender in children

Elvisha Dhamala[1,2]*, Dani S. Bassett[3,4], B.T. Thomas Yeo[5], Avram J. Holmes[6]

Sex and gender are associated with human behavior throughout the life span and across health and disease, but whether they are associated with similar or distinct neural phenotypes is unknown. Here, we demonstrate that, in children, sex and gender are uniquely reflected in the intrinsic functional connectivity of the brain. Somatomotor, visual, control, and limbic networks are preferentially associated with sex, while network correlates of gender are more distributed throughout the cortex. These results suggest that sex and gender are irreducible to one another not only in society but also in biology.

INTRODUCTION

Over the last two decades, the interactions between sex, neurobiology, and behavior have been extensively researched (*1*–*9*). However, these studies often report contradictory findings and fail to replicate (*7*, *10*). The growing literature on sex differences (*11*) and the lack of reproducibility of many of those reported differences (*7*) suggest a potential bias and/or misunderstanding in how we study, interpret, and report findings related to sex. More recently, researchers have begun to question whether these observed differences between males and females are driven by biology (e.g., sex) or whether they are a manifestation of social constructs (e.g., gender) (*7*, *10*). The reality is more complicated in that sex and gender are both influenced by biological and social factors (*12*, *13*). Critically, associations between biological and social factors are intertwined and reciprocal in nature. As an example, personal experiences across the life span are shaped by an individual's sex and gender as well as the sociocultural environment they are embedded within; complex relationships converge to influence brain organization and function. Here, we use the term "sex" to indicate features of an individual's physical anatomy, physiology, genetics, and/or hormones at birth, and we use the term "gender" to indicate features of an individual's attitude, feelings, and behaviors (*14*). For a detailed discussion of these terms and the complex relationships that can exist between sex and gender, we refer readers to our Supplementary Text. Biomedical research thus far has principally focused on understanding the influence of sex on brain and behavior. As such, the contributions of gender are largely unknown.

A fundamental aspect of our human experience is our sex and gender, how we perceive them, and how they are perceived by others. Sex and gender can explain our behavior, and influence our health and disease throughout the life span. Women, people assigned female at birth (AFAB), and sex/gender minorities have historically been excluded from biomedical research (*15*, *16*). Consequently, this group of individuals is more likely to be underdiagnosed or misdiagnosed for common brain disorders [e.g., attention-deficit/hyperactivity disorder (ADHD)] and experience adverse effects from treatment interventions (e.g., medications). In the brain sciences, there exist sex and gender differences in the prevalence and expression of psychiatric illnesses and treatment-seeking behaviors. AFAB people are more likely to meet criteria for mood and anxiety disorders, while people assigned male at birth (AMAB) are more likely to be diagnosed with substance use and attention deficit disorders (*17*). AFAB people are more likely to report mood problems and seek treatment for mental illnesses (*18*). In recent years, researchers have sought to relate these differences in the presentation of psychiatric illnesses to patterns of functional brain organization (*5*, *19*–*24*). However, work in this area has largely operated with the assumption that the observed differences are a product of sex, not gender. Moreover, studies examining the neuroscience of sex and gender have historically sought to identify basic biological differences between (binary) sexes. Sex and gender are often conflated in biomedical research based on the incorrect assumption that they are determined by the same factors and that the two are directly related to one another (*25*). However, sex and gender are complex multidimensional constructs associated with a host of biological, social, and environmental factors. An understanding of the unique functional brain correlates of sex and gender is essential for the study of brain-related illnesses that exhibit differences across males and females.

Here, we sought to characterize and disentangle the neurobiological underpinnings of sex and gender in children. To do so, we quantified the functional networks associated with assigned sex and gender in a large sample of children from the Adolescent Brain Cognitive Development (ABCD) Study ($n = 4757$) using brain-based predictions. Of note, we use the term "prediction" here in a machine learning context to refer to the output of the algorithms that estimate an individual's sex or gender. First, using brain-based predictive modeling approaches, we demonstrate that both sex and gender are associated with individual variability in functional connectivity. Next, evaluating whether shared or distinct functional connections are associated with sex and gender, we determine that although there is some overlap in the associations, sex and gender are uniquely represented in the brain. Finally, characterizing the functional network correlates of sex and gender, we reveal that sex is preferentially associated with somatomotor, visual, control, and limbic networks, while the network correlates of gender are more distributed throughout the brain. Collectively, these results suggest that sex and gender are both associated with individual functional connectivity and these associations may underlie the sex and gender differences that exist in brain-related illnesses.

[1]Institute of Behavioral Science, Feinstein Institutes for Medical Research, Manhasset, NY, USA. [2]Department of Psychiatry, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Uniondale, NY, USA. [3]University of Pennsylvania, Philadelphia, PA, USA. [4]Santa Fe Institute, Santa Fe, NM, USA. [5]Yong Loo Lin School of Medicine and College of Design and Engineering, National University of Singapore, Singapore, Singapore. [6]Department of Psychiatry, Brain Health Institute, Rutgers University, Piscataway, NJ, USA.
*Corresponding author. Email: elvisha@gmail.com

RESULTS

Children AMAB exhibit greater sex congruence in their genders than children AFAB

Leveraging neuroimaging data from the ABCD Study (*26*) (4757 children, 2315 females, 9 to 10 years old) at baseline, and self- and parent-reported gender data at the 1-year follow-up time point, we first evaluated sex differences in gender scores (Fig. 1A for all participants, fig. S1 for data split by site). Self-reported gender scores measured felt-gender, gender expression, and gender contentedness, while parent-reported gender scores measured sex-typed behavior during play and gender dysphoria (table S1). Across both self-report and parent-report gender measures, higher scores indicate greater sex congruence, which refers to the extent to which an individual's gender aligns with their assigned sex. Self- and parent-reported gender scores were more similar in AFAB children (Spearman correlation, $\rho = 0.173$, $P < 1.00 \times 10^{-10}$) than in AMAB children ($\rho = 0.108$, $P = 8.97 \times 10^{-5}$), and AMAB children exhibited greater sex congruence than AFAB children for both parent-report (Mann-Whitney U statistic, $U = 1.36 \times 10^6$, $P < 1.00 \times 10^{-10}$) and self-report ($U = 2.13 \times 10^6$, $P < 1.00 \times 10^{-10}$) measures. These trends are in line with those previously reported in the entire ABCD sample (*14*), indicating that the subsample with neuroimaging data used in these analyses is representative of the full cohort. Extant literature suggests that AMAB children feel more pressure to conform to gender norms than AFAB children (*27*, *28*). This may, in part, explain our results, in which AMAB children report stronger sex-congruent genders than AFAB children.

Sex and gender are associated with individual variability in functional connectivity

Using cross-validated linear ridge regression models, we quantified the associations between functional connectivity and sex as well as gender. Across all individuals, 59.27% ($P < 1.00 \times 10^{-10}$; prediction accuracy, $r = 0.77$, $P < 1.00 \times 10^{-10}$) of the variance in sex, 55.37% ($P < 1.00 \times 10^{-10}$; $r = 0.75$, $P < 1.00 \times 10^{-10}$) of the variance in self-reported gender, and 56.30% ($P < 1.00 \times 10^{-10}$; $r = 0.75$, $P < 1.00 \times 10^{-10}$) of the variance in parent-reported gender were associated with functional connectivity (Fig. 1B). These predictions

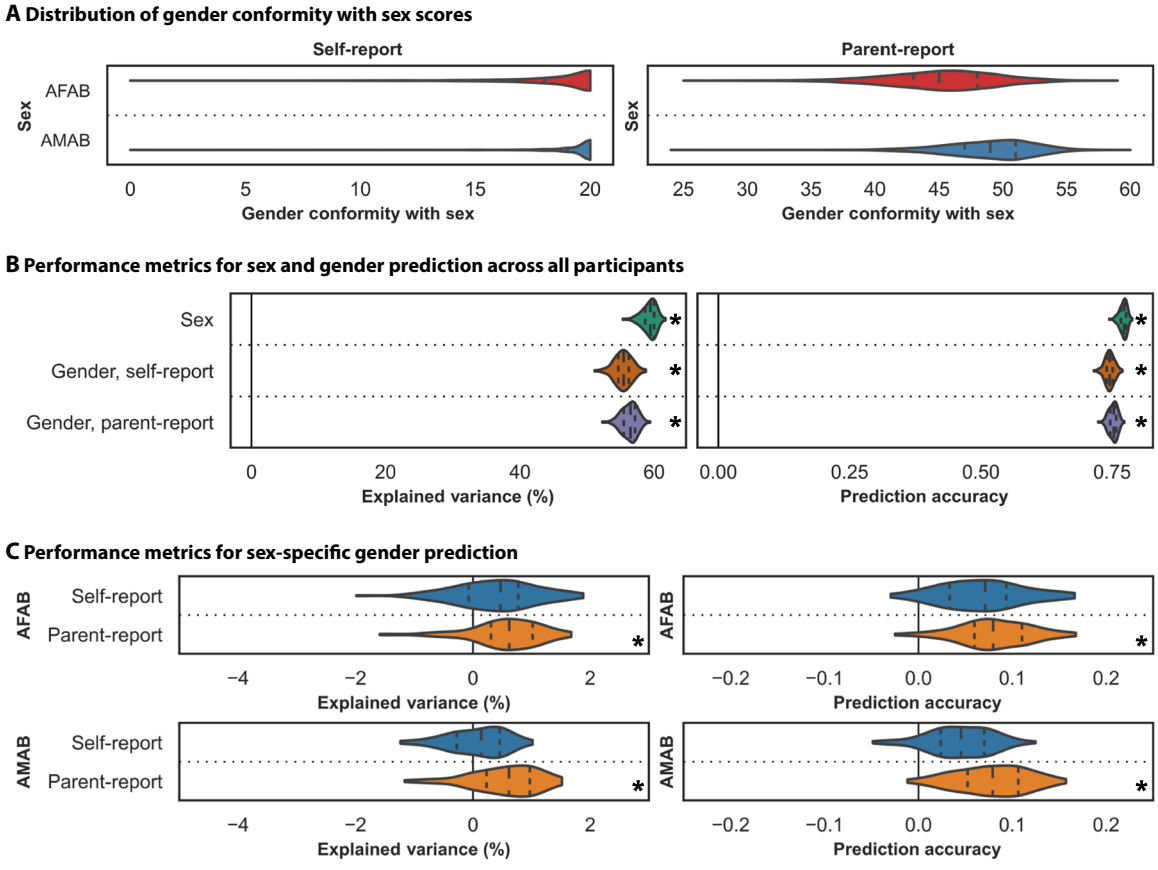

Fig. 1. Functional connectivity is associated with assigned sex and gender. (**A**) Violin plots display the distribution of the self- and parent-reported gender conformity with sex scores for AFAB (red) and AMAB (blue) children. (**B**) Explained variance (%) and prediction accuracy (correlation between observed and predicted values) obtained from the models trained to predict sex (green) and gender (orange, purple) across all participants. Black asterisks (*) indicate that the model performed significantly better than the null models ($P < 0.05$). (**C**) Explained variance (%) and prediction accuracy (correlation between observed and predicted values) obtained from the models trained to predict self- (blue) and parent-reported (orange) gender. Black asterisks (*) denote that the model performed significantly better than the null models (corrected $P < 0.05$). For all violin plots, the shape indicates the entire distribution of values; the dashed lines indicate the median; and the dotted lines indicate the interquartile range. AFAB, assigned female at birth; AMAB, assigned male at birth.

of gender across all individuals are likely to be confounded by sex (and vice versa), as sex and gender were associated with functional connectivity are undeniably related to one another.

To further disentangle the functional correlates of sex from those of gender, we quantified sex-specific associations between functional connectivity and gender. These models were trained separately in AFAB or AMAB children to predict gender. Our models did not successfully predict the self-reported gender scores in either sex (all corrected P values >0.05). On the other hand, 0.56% (corrected $P = 0.037$; $r = 0.08$, corrected $P = 0.033$) and 0.55% (corrected $P = 0.037$; $r = 0.08$, corrected $P = 0.033$) of the variance in parent-reported gender scores in AFAB and AMAB individuals, respectively, were associated with functional connectivity (Fig. 1C). Detailed model performance metrics and corrected P values are reported in Table 1. As a control, we also evaluated the extent to which functional connectivity was associated with sex in approximately half of the participants (corresponding roughly to the sample size used for the sex-specific gender analyses). Here, 54.14% ($P < 1.00 \times 10^{-10}$; $r = 0.74$, $P < 1.00 \times 10^{-10}$) of the variance in sex was associated with functional connectivity. This suggests that the differences in reported results between the sex and gender predictions are not driven by sample size alone. Moreover, multiple studies have shown that functional connectivity is influenced by sex (*20*, *29*, *30*). Here we replicate those findings in children and further demonstrate that functional connectivity is also associated with parental reports of their children's gender.

Shared and unique functional networks are associated with sex and gender in children

The Haufe transformation (*31*) was applied to the feature weights extracted from the models to increase their interpretability and reliability (*32*), and the absolute Haufe-transformed weights were averaged to compute a mean absolute feature importance score (at the regional pairwise level). We evaluated the correlations between the features extracted from the different prediction models (Fig. 2A). For the sex-independent gender prediction models, functional connections associated with sex largely overlapped with those associated with gender ($r_{\text{self-report}} = 1.00$, $r_{\text{parent-report}} = 0.99$), suggesting that models trained to capture variability in gender are capturing variance related to sex, and vice versa. For the sex-specific models, functional connections associated with sex were distinct from the functional connections associated with gender in AFAB ($r_{\text{self-report}} = 0.15$, $r_{\text{parent-report}} = 0.13$) and AMAB ($r_{\text{self-report}} = 0.12$, $r_{\text{parent-report}} = 0.11$) children. Functional connections associated with gender were weakly correlated across the sexes for the self-report measures ($r = 0.30$) but distinct for the parent-report measures ($r = 0.18$). Finally, functional connections associated with gender were moderately correlated across the self-report and parent-report measures in AFAB children ($r = 0.46$) but uncorrelated in AMAB children ($r = 0.19$). These results suggest that sex and gender, although strongly correlated, are uniquely represented in functional networks.

Finally, we established the network-level functional correlates of sex and gender by mapping regional feature weights onto 17 large-scale cortical networks (*33*) and one noncortical network (Fig. 2B). Here, we focus our analyses on the overlap between the functional correlates of sex and of sex-specific parent-reported measures of gender, as the sex-independent correlates of self- and parent-reported measures of gender (fig. S2) were nearly identical to those of sex, and the functional correlates of sex-specific self-reported measures (fig. S3) correspond to models that did not perform better than chance. We evaluated the correlations between the network-level feature weights shown in Fig. 2B. The network-level connections associated with gender were moderately correlated across the sexes ($r = 0.55$). This relationship was stronger than those observed between the network correlates of sex and gender in AFAB ($r = 0.31$) or AMAB ($r = 0.15$) children. This further demonstrates that the functional network correlates of sex are distinct from those of gender. These results also suggest that there are both shared and unique correlates of gender across the sexes.

Functional network correlates of sex were largely found in the somatomotor, visual, control, and limbic networks, while the network correlates of gender were more dispersed throughout the cortical networks. In AFAB children, network correlates of gender largely involved connections within and between temporal parietal, limbic, dorsal/ventral attention, and somatomotor networks. In AMAB children, network correlates of gender included connections within and between temporal parietal, default mode, limbic, dorsal/ventral attention, somatomotor, and visual networks. On the basis of these findings, we can speculate that distinct functional connections within/between unimodal and heteromodal networks are associated with sex and gender.

DISCUSSION

Sex and gender differences in biology and behavior are tied to health outcomes throughout the life span (*34*). An understanding of the neurobiological underpinnings of sex and gender is crucial for the

Table 1. Detailed performance metrics from models trained to predict sex and gender. Performance metrics from models trained to predict sex or gender based on functional connectivity. For explained variance (%) and prediction accuracy (correlation between observed and predicted measures), mean ± SD performance measured in the hold-out test set across the 100 train/test splits are shown. Model performance metrics were compared to those obtained from null distributions using an exact test for differences to evaluate whether they performed better than chance. Corrected P values for those comparisons are denoted in parentheses. Models that performed better than chance are indicated by bold type. AFAB, assigned female at birth; AMAB, assigned male at birth.

	Explained variance (%)		Prediction accuracy	
Data	**AFAB**	**AMAB**	**AFAB**	**AMAB**
Assigned sex	**59.273 ± 1.077 ($<1.00 \times 10^{-10}$)**		**0.771 ± 0.007 ($<1.00 \times 10^{-10}$)**	
Gender, self-report	**55.373 ± 1.300 ($<1.00 \times 10^{-10}$)**		**0.745 ± 0.009 ($<1.00 \times 10^{-10}$)**	
Gender, parent-report	**56.297 ± 1.170 ($<1.00 \times 10^{-10}$)**		**0.752 ± 0.008 ($<1.00 \times 10^{-10}$)**	
Gender, self-report	0.393 ± 0.693 (0.162)	0.077 ± 0.483 (0.198)	0.068 ± 0.044 (0.136)	0.044 ± 0.033 (0.147)
Gender, parent-report	**0.563 ± 0.596 (0.037)**	**0.551 ± 0.557 (0.037)**	**0.081 ± 0.038 (0.033)**	**0.078 ± 0.037 (0.033)**

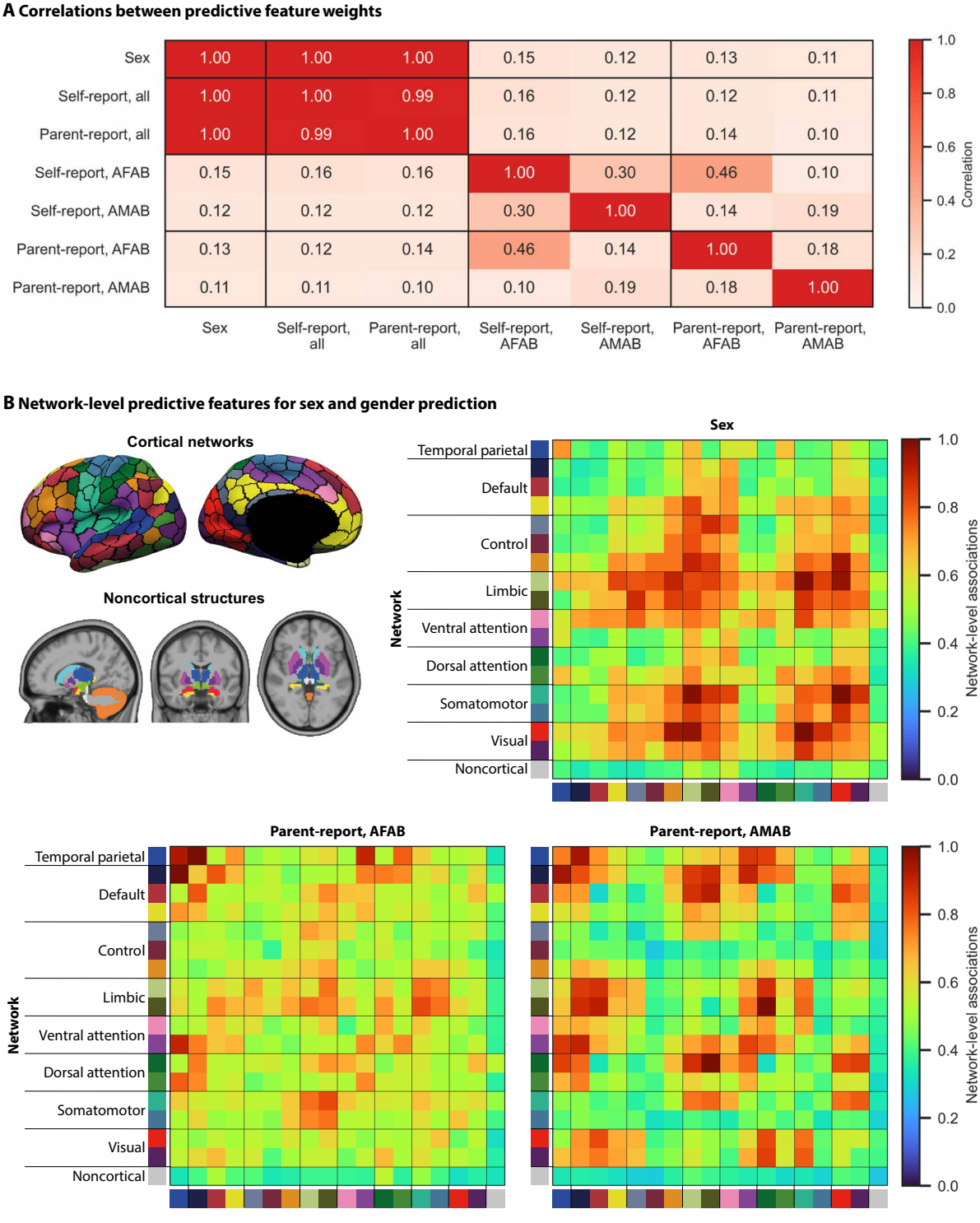

Fig. 2. Distinct functional networks are associated with assigned sex and gender. (**A**) Full correlation coefficient between Haufe-transformed absolute pairwise regional feature weights from distinct models trained to predict assigned sex and gender. Models trained to predict gender were either trained across all participants (all), only in AFAB children (AFAB), or only in AMAB children (AMAB). Warmer colors indicate a stronger correlation between the feature weights. (**B**) Regional pairwise feature weights were summarized to a network level by mapping the Schaefer 400 cortical parcels to 17 large-scale cortical networks and assigning the noncortical regions to a single noncortical network (top left). Cortical network image reproduced with permission from https://doi.org/10.6084/m9.figshare.10062482.v1 and noncortical network image reproduced with permission from https://doi.org/10.6084/m9.figshare.10063016.v1 under a CC BY 4.0 license. Associations between functional network connectivity and sex (top right) and parent-reported gender expression (bottom) are shown as per the color map, where warmer colors indicate stronger correlations and cooler colors indicate weaker correlations. AFAB, assigned female at birth; AMAB, assigned male at birth.

subsequent identification of how sex and gender influence health and illness and the development of sex-specific and gender-oriented diagnostic and prognostic tools (*13*, *35*). Here, we demonstrate that functional connectivity is associated with both sex and parent-reported gender.

Our predictions of gender (beyond sex) are far less accurate than predictions of sex or gender alone, suggesting that gender may be a more complex construct that is not as clearly represented in functional connectivity patterns. Gender is a multidimensional construct that encompasses an individual's internal identity and their external interactions and behaviors, both of which are extremely difficult to quantify. Critically, the self-report measure used here assesses sex-congruent and sex-incongruent felt-gender, along with gender expression and gender contentedness, while the parent-report measure assesses sex-congruent and sex-incongruent behavior during play and gender dysphoria in youth. As such, they seek to capture distinct aspects of an individual's gender. Here, we observe limited population-level variability in the self-reported scores relative to the parent-reported scores. However, the two measures are significantly, albeit weakly, correlated. Our inability to capture meaningful associations between self-reported gender and functional connectivity may be due to the limited variability in those measures and/or due to inherent differences in the dimensions of gender captured in the self- and parent-reported measures. However, several other factors may also contribute to these results. Sex and gender are highly correlated in this dataset; thus, it is unsurprising that the proportion of variance in gender (unrelated to sex) that is associated with functional connectivity is rather small. An alternative explanation is that the influences of sex on the brain are more stable across individuals whereas the influences of gender are more variable. Gender identity and expression are fluid, and this fluidity may be especially pronounced in nonbinary and transgender individuals. This dynamic nature in gender may be reflected in the network correlates, thus making it difficult to capture using cross-sectional predictive modeling approaches. Nonetheless, our detection of significant associations between functional connectivity and parent-reported gender demonstrates that gender does influence the organization of brain networks in children.

Functional brain networks mature nonuniformly across cortical networks (*36*–*38*) and sexes (*2*) during adolescence. Unimodal sensory networks (e.g., visual, auditory, and somatosensory) responsible for responding to stimuli within one sensory modality mature first, followed by heteromodal association networks (e.g., dorsal attention, ventral attention, and control) involved in higher-order cognitive and social processes. Here, we find that both unimodal and heteromodal networks are involved in sex and gender predictions, suggesting that the influences of sex and gender on the brain are widespread. Moreover, a distinct set of functional connections is associated with gender (after accounting for sex). Sex is more strongly associated with connectivity within/between somatomotor, visual, control, and limbic networks while the network correlates of gender are more dispersed throughout the cortex. Associations between functional connectivity and gender somewhat overlap between the sexes but also exhibit critical differences. In AFAB children, the strongest associations were observed in the temporal parietal and attention networks, whereas in AMAB children, we see a more dispersed pattern of association involving several heteromodal networks as well as visual and somatomotor networks. Together, these findings suggest that the functional correlates of sex are distinct from the functional correlates of gender, and the unique multidimensional constructs that comprise gender are differentially associated with functional connectivity patterns in AFAB and AMAB children. As such, sex and gender must both be studied concurrently to fully capture the differences and similarities that exist between males and females, between boys and girls, and between other genders.

These findings are subject to several limitations. First, sex is not binary. However, in the ABCD sample analyzed here, all participants reported their sex as either *female* or *male*. As such, we only considered the neural correlates of binary sex and the correlates of gender in AFAB and AMAB children. Additional analyses in a more sex- and gender-diverse sample may reveal further insights. Second, we considered gender on a continuum, rather than a binary variable, to represent its true nature and to prevent the loss of valuable information pertaining to individual differences in gender (*39*). However, there was limited variability in the self-reported gender data. This may, in part, have restricted our ability to capture accurate relationships between functional connectivity and gender and to disentangle the network correlates of sex and gender. Subsequent analyses in a dataset enriched in individuals who exhibit greater gender nonconformity are likely to have higher power to detect these relationships. Relatedly, analyses of subgroups of individuals with varying levels of gender conformity could reveal the extent to which functional network correlates of gender are consistent across the population. Third, these analyses were performed in a relatively young cohort. As these children undergo puberty, their understanding and expression of their gender can change appreciably. This change will be paralleled by structural and functional brain maturation (*37*, *38*, *40*). As such, it will be critical to consider how the interplay between brain maturation and puberty influence individual differences in gender. Future analyses should seek to evaluate how these functional network representations of sex and gender change during puberty and throughout the transition from childhood to adolescence as well as across adulthood. Fourth, gender was assessed at a single time point, using a set of questions that assumed a static form of gender identity and expression. Future work across multiple time points could instead use questions that allow for the assessment of gender fluidity over a range of time scales. Fifth, gender is influenced by local cultural norms and shared societal experiences. The ABCD dataset was collected entirely in the United States and is not representative of the global population (*41*). Subsequent analyses should investigate whether similar relationships exist in other countries. Finally, we used a whole brain approach consistent with previous work (*19*, *22*, *23*, *42*–*50*). However, the limbic network, which exhibits sex differences (*51*–*53*) and is implicated in complex behaviors (*54*), is prone to signal dropout and has lower test-retest reliability than other networks (*55*). Although we implemented strict quality control measures, we cannot rule out that inherent differences in the signal-to-noise ratio throughout the brain did not influence our predictions and/or interpretations, and this should be assessed in future analyses.

Our analyses reveal potential neurobiological correlates for sex and gender in children, suggesting that complex and nuanced biological and environmental factors jointly influence brain organization. However, these results do not provide evidence for gender essentialism, and we strongly caution against any simplifications or (mis)interpretations of this work to suggest otherwise. We refer readers to our Supplementary Text for more information.

A comprehensive understanding of the neurobiological correlates of sex and gender is necessary if we are to understand health

and disease in sex- and gender-diverse samples. Here, we identify the distinct functional network correlates of assigned sex and gender expression in the developing human brain. How these correlates may be maintained or altered during development and adulthood, and how they may relate to genderfluid experiences at any age, remains to be established.

MATERIALS AND METHODS

Dataset

The ABCD dataset is a large community-based sample of children and adolescents who were assessed on a comprehensive set of neuroimaging, behavioral, developmental, and psychiatric batteries (*26*). Here, we used minimally preprocessed neuroimaging data acquired at the baseline time point along with self- and parent-reported gender data at the 1-year follow-up time point from the National Institutes of Mental Health (NIMH) Data Archive for ABCD Release 2.0.1. Magnetic resonance (MR) images were acquired across 21 sites in the United States using harmonized protocols for GE and Siemens scanners. In line with our previous work (*44*, *45*), we used exclusion criteria to ensure quality control (fig. S4). For the T1 data, we removed individuals who did not pass recon-all quality control (*56*). For the functional connectivity data, we excluded functional runs with boundary-based registration (BBR) costs greater than 0.6. Further, we censored volumes with framewise displacement (FD)> 0.3 mm or voxel-wise differentiated signal variance (DVARS) > 50, along with one volume before and two volumes after. We also removed uncensored segments of data containing fewer than five contiguous volumes (*57*, *58*). We removed functional runs with more than half of their volumes censored and/or max FD > 5 mm. We also excluded individuals who did not have at least 4 min of data. As recommended by the ABCD consortium, we excluded individuals who were scanned using Philips scanners due to incorrect preprocessing (https://github.com/ABCD-STUDY/fMRI-cleanup). We also excluded individuals who did not have all behavioral (e.g., gender) data or were related to one another to prevent unintended biases due to inherent heritability in neurobiological and/or behavioral measures. Finally, we removed data from sites with fewer than 50 individuals. Our final sample comprised 4757 children (2315 AFAB, ages 9 to 10 years) from the ABCD 2.0.1 release (*26*). The research protocol for the dataset was reviewed and approved by a central Institutional Review Board (IRB) at the University of California, San Diego, and, in some cases, by individual site IRBs. Parents or guardians provided written informed consent, and children assented before participation.

Sex and gender data

We included sex assigned at birth (referred to as "sex") and gender data from the Youth Self-Report and Parent-Report Gender Questionnaires (*14*). All participants included in these analyses completed the Youth Gender Survey, which includes four questions that measure felt-gender, gender expression, and gender contentedness. In addition, their parents/caregivers completed an adapted Gender Identity Questionnaire (*59*, *60*) that included 12 questions that measure sex-typed behavior during play and gender dysphoria. A list of all questions asked in the self-report and parent-report surveys can be found in table S1. We computed summary self-report and parent-report gender scores for all participants by computing the sum across all questions within each questionnaire, respectively, and used these summary scores in our analyses. We used nonparametric Mann-Whitney *U* rank tests to evaluate sex differences in the gender scores. We corrected all *P* values for multiple comparisons using the Benjamini-Hochberg false discovery rate ($q = 0.05$) procedure (*61*). We also computed nonparametric correlations between the gender scores for each assigned sex to evaluate any underlying relationships that may exist.

Image acquisition and processing

We processed the minimally preprocessed MRI data as previously described (*45*, *62*). Briefly, we further processed minimally preprocessed T1 data using FreeSurfer 5.3.0 (*63*–*66*) to generate cortical surface meshes for each individual, which we then registered to a common spherical coordinate system (*65*, *66*). We also processed the minimally preprocessed functional Magnetic Resonance Imaging (fMRI) data with the following steps: (i) removal of initial frames, with the number of frames removed depending on the type of scanner (*56*), and (ii) alignment with the T1 images using BBR (*67*) with FsFast. We computed FD (*68*) and DVARS (*69*) using fsl_motion_outliers. We filtered out respiratory pseudomotion using a bandstop filter (0.31 to 0.43 Hz) before computing FD (*70*–*72*). We also regressed a total of 18 nuisance covariates from the fMRI time series: global signal, six motion correction parameters, averaged ventricular signal, averaged white matter signal, and their temporal derivatives. We estimated regression coefficients from the noncensored volumes. We performed global signal regression as we are interested in behavioral prediction, and global signal regression has been shown to improve behavioral prediction performance (*49*, *73*). Finally, we interpolated the brain scans across censored frames using least-squares spectral estimation (*74*), applied band-pass filtering ($0.009\ \text{Hz} \leq f \leq 0.08\ \text{Hz}$), projected them onto FreeSurfer fsaverage6 surface space, and smoothed them using a 6-mm full width at half maximum kernel. Once processed, we extracted regional time series for 400 cortical (*75*) and 19 noncortical (*76*) parcels. We computed full correlations between those time series yielding a 419×419 pairwise regional functional connectivity matrix. All processing as described was completed on a local server.

Predictive modeling

Linear ridge regression models avoid overfitting, are interpretable, and are relatively computationally inexpensive compared to deep learning algorithms for brain-based behavioral predictions (*47*, *50*). Here, using a similar framework as those previously used by our research team (*22*, *23*, *42*, *43*), we perform analyses to establish the functional brain correlates of assigned sex and gender. We used cross-validated ridge regression models to predict sex and gender based on functional connectivity. To facilitate comparisons of model performance and feature contributions across sex and gender predictions, we implemented the linear ridge regression framework for sex predictions instead of a classification model. Here, we use the term "prediction" in a machine learning context to refer to the output of the algorithms that estimate an individual's sex or gender. For further discussion on our use of this term, we refer readers to our Supplementary Text. For models predicting sex, we included all individuals (AMAB and AFAB), while for models predicting gender, we either included all individuals or used a sex-specific approach (i.e., trained and tested separately for each sex). For models predicting gender that included all individuals, we reversed gender scores in AFAB children such that they ranged from 0 to 20 for self-report scores (with 0 indicating more feminine gender identities and expressions and 20 indicating more masculine gender identities and expressions) and 0 to 60 for parent-report scores (with 0 indicating

more feminine gender identities and expressions and 60 indicating more masculine gender identities and expressions). For each model, we split the data into 100 distinct train and test sets (at approximately a 4:1 ratio) without replacement. We considered imaging site when splitting the data such that we placed all participants from a given site either in the train or test set but not split across the two. Within each train set, we optimized the regularization parameter using threefold cross-validation while similarly accounting for imaging site as in the initial train-test split. Once optimized, we evaluated models on the corresponding test set. We repeated this process for each of the 100 distinct train-test splits to obtain a distribution of prediction accuracy and explained variance. To evaluate model significance, for each set of predictive models, we generated a corresponding set of null models as follows: the output variable was randomly permuted 1000 times, and each permutation was used to train and test a null model using a randomly selected regularization parameter from the set of selected parameters from the original model. We then compared prediction accuracy from each of the null models to the average accuracy from the corresponding distribution of model accuracies of the original (true) models. The P value for each model's significance is defined as the proportion of null models with prediction accuracies or explained variances greater than or equal to those corresponding to the original (true) distributions. We corrected all P values for multiple comparisons across the gender measures using the Benjamini-Hochberg false discovery rate ($q = 0.05$) procedure (*61*).

Feature weights

We used the Haufe transformation (*31*) to transform feature weights obtained from the linear ridge regression models to increase their interpretability and reliability (*45*, *62*, *77*). For each train split, we used feature weights obtained from the model, W, the covariance of the input data (functional connectivity), Σ_x, and the covariance of the output data (behavioral score), Σ_y, to compute the Haufe-transformed feature weights, A, as follows: $A = \Sigma_x W \Sigma_y^{-1}$. We then averaged the absolute Haufe-transformed feature weights across the 100 splits to obtain a mean feature importance value. We computed full correlations between mean feature importance obtained from the different models to evaluate whether they relied on shared or unique features to predict sex/gender. For all models, we also summarized pairwise regional feature importance at a network-level to support interpretability as previously described (*22*). Briefly, we assigned cortical parcels to 1 of 17 networks from the Yeo 17-network parcellation (*33*) and subcortical, brainstem, and cerebellar parcels to a single noncortical network for convenience. We then averaged regional pairwise absolute feature weights to yield network-level estimates of associations between functional connectivity and sex/gender. Finally, we computed full correlations between these network-level estimates to evaluate the extent to which the network correlates of sex and gender were shared.

Supplementary Materials

This PDF file includes:

Supplementary Text
Figs. S1 to S4
Table S1
References

Correction (16 September 2024): A few sentences in the Results and Discussion have been slightly reworded to avoid confusion regarding the analyses that were completed. The PDF and XML have been updated.

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