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# Sex differences in the functional network underpinnings of psychotic-like experiences in children

**Elvisha Dhamala**

elvisha@gmail.com

Feinstein Institutes for Medical Research https://orcid.org/0000-0002-8253-6962

**Sidhant Chopra**

Yale University

**Leon Ooi**

National University of Singapore

**Jose Rubio**

Feinstein Institutes for Medical Research

**Thomas Yeo**

**Anil Malhotra**

Feinstein Institutes for Medical Research

**Avram Holmes**

Rutgers University https://orcid.org/0000-0001-6583-803X

## Article

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# Abstract

Psychotic-like experiences (PLEs) include a range of sub-threshold symptoms of psychosis which may not necessarily indicate the presence of psychiatric illness. While not all youth who report PLEs develop psychosis, many will develop other psychiatric illnesses during adolescence and adulthood, suggesting PLEs may represent early markers of poor mental health. Here, we sought to determine the neurobiological correlates of PLEs and evaluate the extent to which they differ across the sexes using a sex-specific brain-based predictive modeling approach. The ABCD Study includes a large community-based sample of children and adolescents who were assessed on a comprehensive set of neuroimaging, behavioral, developmental, and psychiatric batteries. For these analyses, we considered a sample of 5,260 children (2,571 females; ages 9-10) from the baseline timepoint with complete imaging and behavioral data. Brain-based predictive models were used to quantify sex-specific associations between functional connectivity and PLE Total and PLE Distress scores. Assigned males reported more PLEs (2.55±3.54) and greater resulting distress (5.84±10.06) relative to females (2.31±3.43 Total and 5.74±10.40 Distress scores). Functional connectivity was significantly associated with PLE Total and Distress scores in both females (prediction accuracy, $r_{Total}$=0.09, $p_{FDR}$<0.01 and $r_{Distress}$=0.08, $p_{FDR}$ <0.01) and males ($r_{Total}$= 0.10, $p_{FDR}$ <0.01 and $r_{Distress}$=0.11, $p_{FDR}$ <0.01). Functional connections associated with Total and Distress scores were highly similar within females (cosine distance, d=0.04) and males (d=0.04) and considerably different across the sexes ($d_{total}$=0.54, $d_{distress}$= 0.55). PLEs were associated with functional connections across dispersed cortical and non-cortical networks in females, whereas in males, they were primarily associated with connections within limbic, temporal parietal, somato/motor, and visual networks. These results suggest that early transdiagnostic markers of psychopathology may be distinct across the sexes, further emphasizing the need to consider sex in psychiatric research as well as clinical practice.


# Introduction

Psychiatric illnesses are often preceded by premorbid and/or prodromal states that emerge months to years before the onset of a diagnosable illness[1]. These states include subtle changes in mood, behavior, thought, and cognition that do not meet the threshold for a formal diagnosis. Psychotic disorders manifest across a spectrum ranging from psychotic-like experiences (PLEs) to clinical high-risk states, first episode psychosis, and chronic psychotic disorder[2]. PLEs represent the earliest potential manifestations of psychosis and tend to emerge during childhood and adolescence. PLEs include a range of sub-clinical symptoms that resemble aspects of psychosis, such as perceptual distortions (i.e., hallucinations), false beliefs (i.e., delusions), and disorganized thinking or speech. As many as 60% of youth report PLEs[2, 3], and these experiences are associated with distress and can hinder social, academic, and emotional development[4]. While only a subset of children with PLEs develop psychosis, many develop other forms of psychiatric illnesses, including affective disorders (e.g., depression) and post-traumatic stress disorder[5]. This suggests that PLEs may represent early markers of not only psychosis, but transdiagnostic psychiatric illness more broadly.

Sex and gender differences exist in the development and expression of psychiatric illnesses[6], including psychosis[7]. Women (as per their gender, hereafter referred to as 'women') and individuals assigned female sex at birth (hereafter referred to as 'females') are more likely to exhibit internalizing problems (e.g., loneliness), while men (as per their gender, hereafter referred to as 'men') and individuals assigned male sex at birth (hereafter referred to as 'males') are more likely to exhibit externalizing problems (e.g., aggression) [8]. Psychosis tends to have an earlier onset in men and males along with more several clinical features relative to women and females[9]. PLEs also differ across sexes and genders such that delusions are more common in women and females while hallucinations are more common in men and males[10]. Some recent studies have examined the neurobiological underpinnings for these phenomenological differences. Functional magnetic resonance imaging is used to indirectly estimate neuronal activation based on changes in blood oxygenation. Regional functional activation signals can be correlated to assess the functional connectivity (or coupling) between brain regions. Disruptions in functional connectivity within the frontoparietal control and default networks have been implicated in a wide range of psychiatric illnesses and mental health traits[11–13]. These networks are involved in sustained attention, goal-directed cognition, working memory [12, 14–16]. Critically, these functional networks exhibit sex differences[17, 18] and they are uniquely related to transdiagnostic psychiatric symptom domains (e.g., internalizing and externalizing problems) across the sexes in youth[19]. However, it remains to established whether PLEs map onto shared or distinct functional networks across the sexes. An analysis of the sex-specific functional network correlates of PLEs in children will reveal early brain-based markers indicative of potential future onset of psychiatric illness that can be used to develop targeted preventative strategies.

Here, we sought to characterize the sex-specific functional network correlates of PLEs in children. To do so, we used multivariate analyses to quantify the functional networks associated with the PLEs in a large sample of children from the Adolescent Brain Cognitive Development (ABCD) Study (n = 5620, 2671 females, ages 9–10) in a sex-specific manner. First, using a brain-based predictive modeling approach, we demonstrate that functional connectivity is significantly associated with the total number of PLEs and the resulting distress in females and males. Next, evaluating whether the functional networks underlying PLEs are shared or distinct across the sexes, we find that there are notable differences in the networks implicated in PLEs in females and males. Finally, characterizing the functional networks that predicted PLEs, we reveal that, in females, a diffuse set of cortical and non-cortical functional connections are associated with PLEs, whereas in males, PLEs predominantly map onto limbic, temporal parietal, somato/motor, and visual networks.

# Methods

The analyses described here use a similar framework as in our prior work [19–22] to perform novel analyses to establish the functional network correlates of psychotic-like experiences in a sex-specific manner.

Dataset: The Adolescent Brain Cognitive Development (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[23]. Here, we used minimally preprocessed neuroimaging data and behavioral data acquired at the baseline from the NIMH Data Archive for ABCD Release 2.0.1. Details about our imaging quality control and processing can be found in the supplementary methods. Our final sample comprised 5260 children (2571 females, ages 9–10 years). 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: We considered sex in terms of sex assigned at birth (referred to as 'sex').

Psychotic-Like Experiences: We considered the number and severity of psychotic-like experiences (PLEs) as measured by the self-report Prodromal Questionnaire–Brief Child Version. This questionnaire has previously been validated in the ABCD sample [3], and is considered to be a useful measure of early risk for psychosis. Moreover, psychotic-like experiences in the ABCD sample, as measured by this questionnaire, have been shown to be associated with a similar set of familial, cognitive, and emotional factors as in adults with psychosis[3]. Consistent with prior literature[3, 24, 25], we considered Total and Distress scores in these analyses. Details about the scores can be found in the supplementary methods. Non-parametric Mann-Whitney U rank tests were used to evaluate sex differences in the Total and Distress scores. Resulting p-values were corrected for multiple comparisons across the two scores using the Benjamini-Hochberg False Discovery Rate ($q = 0.05$) procedure[26]. Head motion, age, and race/ethnicity were not related to PLEs in either sex (see Tables S1-S3). Therefore, they were not considered as covariates in these analyses.

Predictive Modeling: Linear ridge regression models capture robust, reliable, and interpretable associations between neuroimaging and phenotypic data while avoiding data leakage and minimizing overfitting[27, 28]. Here, we used sex-specific cross-validated linear ridge regression models to predict the Total and Distress scores based on functional connectivity in a sex-specific manner. Details about our predictive modeling framework can be found in the supplemental methods. Briefly, for each sex, we trained 100 distinct models (using 100 distinct train sets) and evaluated the performance in corresponding test sets. Model performance from these models was compared to performance distributions generated from null models. The p-value for each model's performance is defined as the proportion of null models with prediction accuracies greater than or equal to those corresponding to the original distributions. All p-values were corrected for multiple comparisons across the two scores using the Benjamini-Hochberg False Discovery Rate ($q = 0.05$) procedure[26].

Feature Weights: We used the Haufe transformation[29] to transform feature weights obtained from the linear ridge regression models to increase their interpretability and reliability[13, 30, 31]. Once transformed, cosine distances between the feature importance values were computed to evaluate differences across sexes as well as Total and Distress scores. Next, features were summarized onto a

network-level to support interpretability as previously described[21]. Details about the transformation and the network-level summarization can be found in the supplementary methods.

# Results

Males report more PLEs and greater distress relative to females: We assessed sex differences in PLEs in children. PLEs were assessed using the Prodromal Questionnaire-Brief Child Version, which is comprised of 21 questions. Total and Distress scores were computed, consistent with prior literature[3, 24, 25]. In our sample, 57% of females and 60% of males reported one or more PLEs (out of 21), with 18% of females and 20% of males reporting five of more PLEs. Across all females, an average Total score of 2.31 ± 3.43 and Distress score of 5.74 ± 10.40 was reported. Across all males, an average Total score of 2.55 ± 3.54 and Distress score of 5.84 ± 10.06 was reported. Although higher Total (Mann Whitney U statistic, $U = 3.31x10^6$, $p_{FDR}<0.01$) and Distress ($U = 3.36x10^6$, $p_{FDR}=0.03$) scores were reported in males relative to females, the observed differences in the distribution of the Total and Distress scores were minimal (Fig. 1A). These results are in line with those previously reported in the ABCD Study[32], indicating that the subsample included here with complete resting-state functional MRI and behavioral data is representative of the larger ABCD cohort. Of note, these data indicate that PLEs are not uncommon in children.

Functional network connectivity is significantly associated with PLEs: Using sex-specific cross-validated linear ridge regression models, we quantified the sex-specific associations between functional network connectivity and the Total and Distress scores for PLEs. As in similar studies using brain-based predictive models to study associations between functional connectivity and behavioral measures in the ABCD sample[13, 19, 33, 34], model performance was evaluated using measures of prediction accuracy (i.e., correlation between observed and predicted scores). Across both sexes, individual variability in functional connectivity was associated with the Total and Distress scores (Fig. 1B). Although, these observed associations were numerically higher in males for both Total (prediction accuracy, $r_{Total}= 0.10$) and Distress ($r_{Distress}=0.11$) scores compared to females ($r_{Total}=0.09$; $r_{Distress}=0.08$), all brain-based prediction models yielded significant results ($p_{FDR}<0.01$ for all models relative to null models). These results demonstrate that individual variations in functional connectivity can predict both the endorsement of PLEs and the associated distress in youth. As such, functional network connectivity may serve as a potential early marker of transdiagnostic psychiatric illness risk.

Overlapping and distinct functional networks underlie PLEs across the sexes: We applied the Haufe transformation[29] to the model feature weights to increase their interpretability and reliability[33]. As in prior work[18, 19], we averaged the transformed weights across the multiple train/test splits to obtain a mean feature importance score. To assess sex differences in the functional connections associated with PLEs, we computed the cosine distance between the features extracted from each sex to predict Total and Distress scores. Across the distinct train/test splits, functional connections associated with Total and Distress scores were highly similar within each sex (cosine distance, $d_{females}=0.04 \pm 0.01$,

$d_{males}$=0.04 ± 0.01), while functional connections associated with each score exhibited considerable differences across the sexes ($d_{total}$=0.54 ± 0.11, $d_{distress}$=0.55 ± 0.09) (Fig. 2A). The mean absolute associations between functional connectivity and the Total and Distress scores were summarized to a network-level by mapping the absolute regional pairwise feature weights onto 17 cortical networks[35] and one non-cortical network to facilitate interpretation and visualization. In females, while the strongest associations were observed in temporal parietal, default, limbic, and ventral attention networks, dispersed functional connections throughout the brain were associated with PLEs (Fig. 2B **for Distress and S2 for Total scores**). In males, limbic networks exhibited the strongest associations with PLEs followed by weaker associations in temporal parietal, somatomotor, and visual networks (Fig. 2B **for Distress and S2 for Total scores**). Summarized network-level associations were also computed (Fig. 3) and demonstrate similar results. Prior work in this area has identified associations between resting-state network connectivity in control, default mode, and cinguloparietal networks and PLEs[36]. Here, we find that while those networks are implicated to some extent, other networks (e.g., limbic, ventral attention, somatomotor, visual) also contribute to PLEs, and these associations between connectivity and PLEs differ across males and females. Taken together, this suggests that the functional networks that underlie PLEs overlap to some extent across the sexes in children but also include distinct network contributions.

# Discussion

PLEs represent one of the earliest markers of transdiagnostic psychopathology[37]. An understanding of the neural correlates of PLEs is critical for the subsequent development of targeted prevention strategies to mitigate the potential negative sequelae of these experiences in at-risk youth. Here, we demonstrate that individual variations in functional network connectivity are significantly and uniquely associated with PLEs across the sexes in children. First, examining the prevalence in PLEs, we confirm prior work[2], showing that approximately 3 in 5 children report PLEs, and the number of experiences and the resulting distress is largely comparable across females and males. Next, quantifying the relationships between functional connectivity and PLEs, we demonstrate that individual differences in functional connectivity are significantly associated with PLEs in both sexes. Finally, comparing the network correlates of PLEs across the sexes, we find that they exhibit notable differences. In females, dispersed functional connections throughout cortical and non-cortical structures are implicated in PLEs, whereas in males, PLEs are primarily associated with functional connections in limbic, temporal parietal, somatomotor, and visual networks. Collectively, our results suggest that there are sex differences in the neurobiological underpinnings of PLEs in children.

Extant literature has shown that PLEs are related to changes in neurobiological structure and function. PLEs have previously been linked to lower cortical gyrification in left fronto-temporal regions and higher cortical gyrification in right parietal cortex[38]. Reduced cortical and subcortical volumes have also been reported in youth with more distressing PLEs[39]. In the functional domain, connectivity between cerebellar and control networks, between cerebellar and cingulo-parietal networks, and within the control network have been implicated in distressing PLEs[39]. A separate study found that connections within

the control, default, and cingulo-parietal networks were associated with PLEs[36]. A third study reported associations between corticostriatal networks and PLEs[40]. Unfortunately, these studies only considered assigned sex as a covariate, if at all, restricting their ability to capture critical sex differences in the functional networks that underlie PLEs[41]. Our present analyses demonstrate that the overlapping and unique individual variations in functional networks underlie PLEs across the sexes. Specifically, we observe significant associations between functional connectivity and Total and Distress PLE scores in the range of $0.08 < r < 0.11$. PLEs are phenomenologically heterogeneous, so it is not surprising that these effect sizes, while significant, are relatively small in magnitude. Notably, our observed effect sizes are comparable to those reported between gender and risk-taking behavior ($r = 0.09$) as well as combat exposure and PTSD ($r = 0.11$)[42].

Self-reported PLEs are highly prevalent in children and are associated with parent-report psychopathology[3], delayed functional development[39], and future development of psychiatric illnesses[5]. Although not all youth who report PLEs develop psychosis, the risk of conversion is 3.5 to 4 times higher than individuals without PLEs[43, 44]. Moreover, many of them experience other mental health problems, including anxiety, depression, PTSD, substance dependence, and suicide attempts[5]. In fact, a New Zealand birth cohort study suggests more than 90% of children with strong PLEs have some form by clinically diagnosable psychiatric disorder by age 38[5]. This suggests that childhood PLEs may be predictive of poor mental health during adolescence and adulthood. As such, children who experience PLEs may benefit from early interventions directed at improving their mental well-being[45]. Here, we establish the sex-specific neural bases of PLEs in a large sample, providing a critical foundation for subsequent research on the neurobiological mechanisms driving the future emergence of transdiagnostic psychopathology in these individuals. Importantly, the network associations captured here are, for the most part, unique from those previously reported between functional connectivity and other psychiatric illness-linked behaviors (e.g., internalizing and externalizing) in this sample[19]. This suggests the brain-behavior associations captured here are specific to PLEs and do not represent general psychopathology in children. The neurobiological markers of PLEs identified here can subsequently be validated in smaller, disease-specific samples (e.g., NAPLS [46–48]). The present findings can also be used to guide the development of targeted intervention strategies that may modulate these functional connections, ultimately improving resilience.

Sex differences in the neurobiological underpinnings of PLEs, and psychosis more broadly, have been largely understudied to date. In schizophrenia, men and males have a greater risk of developing negative symptoms (e.g., avolition, anhedonia, alogia), while women and females tend to display more affective symptoms (e.g., depression, impulsivity, emotional instability)[9, 49]. Women and females also exhibit stronger cognitive functioning along executive, verbal, and processing domains, while men and males outperform females along memory and attention domains[49]. Women and females are at a particularly elevated risk of developing psychosis during critical hormonal transition periods (e.g., pregnancy, post-partum, menopause)[50], and earlier menarche is associated with a later onset of schizophrenia[51]. Here, we observe critical sex differences in the associations between functional brain networks and PLEs, providing an insight into the neural bases that may, in part, underlie sex differences in psychosis

and schizophrenia. The sex differences observed here may be influenced by a number of sex- and gender-related factors, including differences in functional network maturation trajectories across the sexes[52–54]. Additional analyses using the longitudinal ABCD data and other datasets will inform whether the associations observed here remain consistent throughout adolescence and adulthood.

Importantly, the reported findings are subject to several limitations. First, these results were obtained using a single dataset. Although, our sample is relatively large (n = 5,260) and we used a cross-validated, sex-specific brain-based predictive modeling approach known to generate reliable results[19], we cannot rule out the possibility that these results may be limited in their generalizability[55]. Future research in global open-access datasets with comparable neuroimaging and behavioral data could analyze whether the reported findings are specific to the ABCD sample considered here. Second, we only considered the influences of binary assigned sex in these analyses. Although sex is not binary, participants in this sample reported their assigned sex as Female or Male, and as such we were only able to compare the network correlates of PLEs between the binary sexes. Additionally, gender has been shown to influence functional network organization[18] and the manifestation of psychiatric illness[56]. Unfortunately, gender identity data was not acquired in this sample at the baseline time point and thus was not considered here. It is possible that our results are, in part, driven by gender rather than sex. Subsequent analyzes considering both sex and gender could disentangle their independent and intersecting influences on the neural bases of PLEs. Third, we considered summary scores of PLEs in line with prior literature[3, 24, 25] that did not distinguish between delusion-like PLEs and hallucination-like PLEs. However, there may be sex differences in the expression and neural underpinnings of these distinct types of PLEs. Subsequent work considering specific types of PLEs can address these issues. Fourth, although head motion, age, and race/ethnicity were not related to PLEs, other biological and environmental factors (e.g., pubertal maturation, family history, urbanicity) may influence PLEs in one or both sexes. Finally, we assessed the relationships between functional connectivity and PLEs at a single time-point from the baseline acquisition as we sought to identify the earliest neurobiological markers of transdiagnostic psychopathology. However, the networks implicated in these findings mature throughout adolescence[52]. Therefore, it is possible that the brain markers of PLEs, and poor mental health more broadly, shift throughout the transition from childhood to adolescence to adulthood. Future work incorporating multiple time points and a longitudinal analytical framework will be able to assess these potential changes.

Sex is a fundamental part of human identity and can influence both neurobiology and mental health. An understanding of how sex shapes the relationships between neurobiology and mental health is necessary for the advancement of mental health prevention and intervention strategies that are tailored to each sex. Here, we identify unique functional network markers of PLEs across the sexes, revealing sex-specific early markers that may be broadly indicative of poor mental health and forecast the development of transdiagnostic psychopathology.

# Declarations

### Data Availability Statement

Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development[SM] (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children aged 9-10 and follow them over 10 years into early adulthood. The ABCD Study® is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members/. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators.

### Code Availability Statement

All code used the generate the results can be found on GitHub (https://github.com/elvisha/PLE_Predictions).


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# Figures

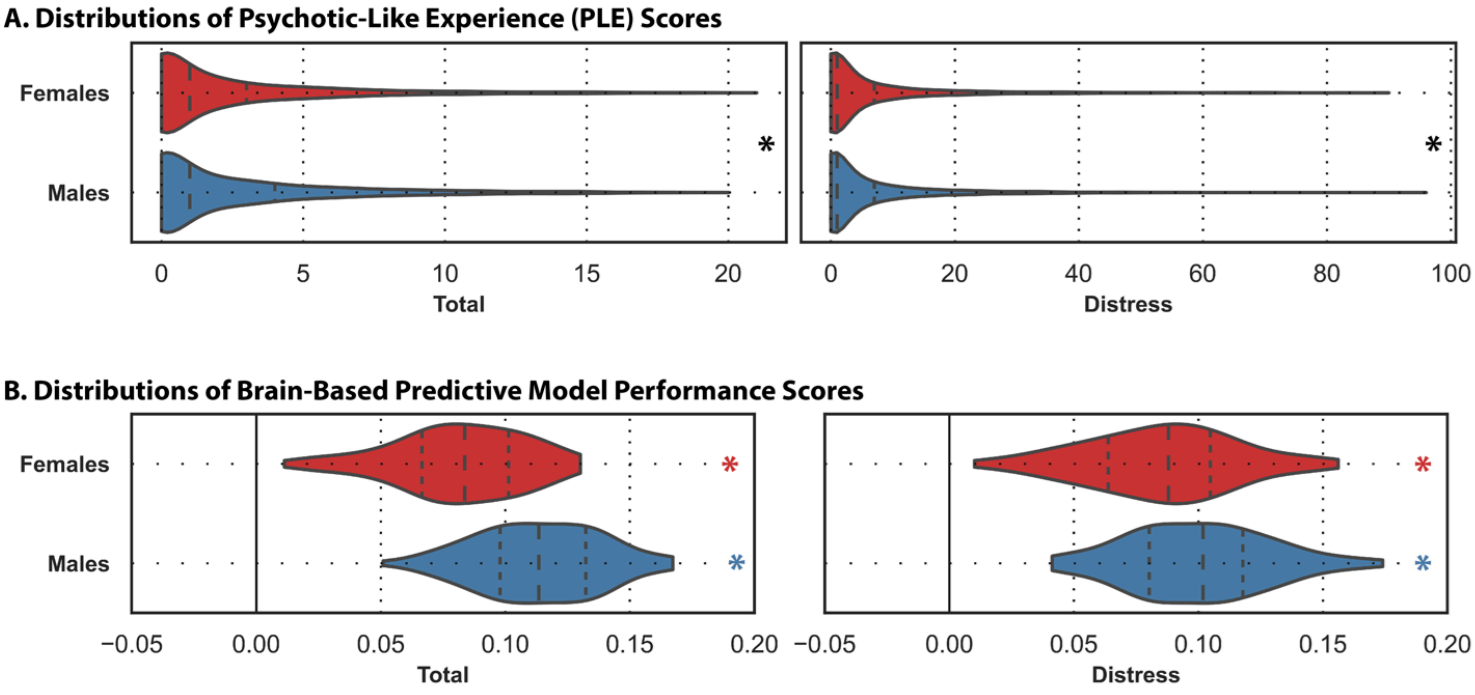
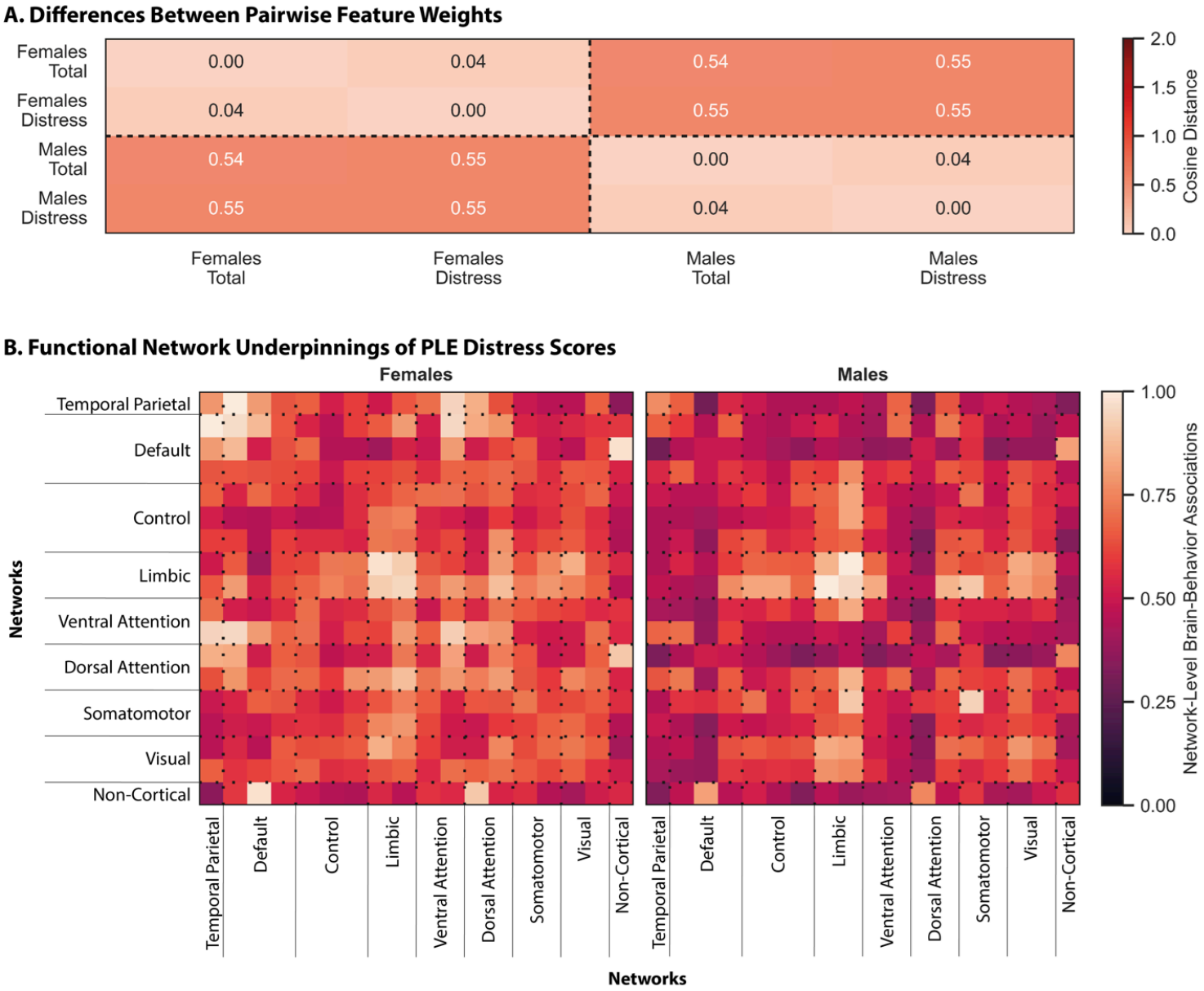



**Figure 1**

**Functional connectivity is associated with PLEs.**
(A) Violin plots display the distribution of the Total (left) and Distress (right) PLE scores for assigned females (red) and males (blue). Total and Distress scores, although significantly different across the sexes, as denoted by the asterisks (*), exhibited largely overlapping distributions.
(B) Prediction accuracy (correlation between observed and predicted values) obtained by the brain-

based predictive models trained to predict Total (left) and Distress (right) PLE scores in assigned females (red) and males (blue). Predictions for Total and Distress scores in both sexes were significantly better than chance ($p_{corrected}$<0.05), as denoted by the asterisks (*).

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.




## Figure 2

**Overlapping and distinct functional networks underlie PLEs across the sexes.**

(A) Mean cosine distance between the Haufe-transformed pairwise regional feature weights from models trained to predict Total and Distress PLE scores in assigned females and males. A value of 0 indicates perfect similarity while a value of 2 indicates perfect dissimilarity. Warmer colors indicate a greater difference between the feature weights.

(B) Absolute associations between functional network connectivity and PLE Distress scores in assigned

females (left) and males (right) are shown as per the colormap. To facilitate visualization, values within each matrix were divided by the maximum value within that matrix.

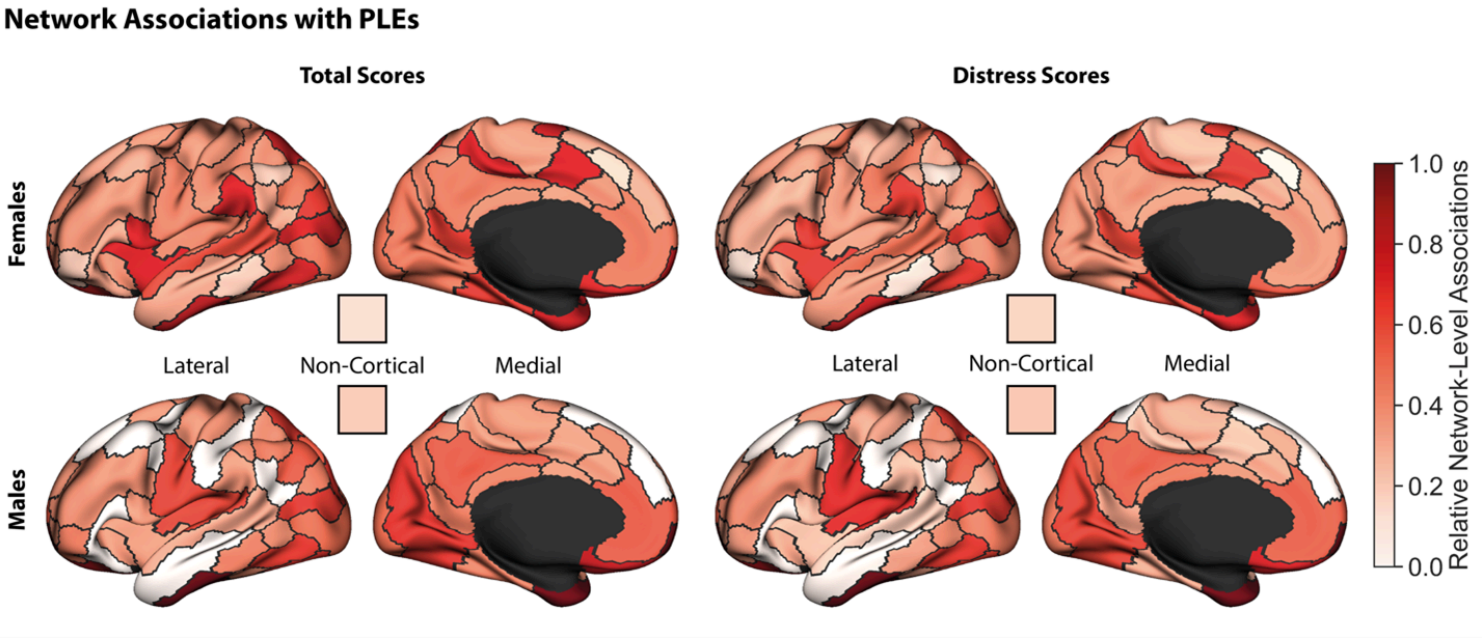



**Figure 3**

**Overlapping and distinct networks are associated with PLEs across the sexes.**
Summarized relative network-level associations between functional networks and PLE Total (left) and Distress (right) scores in assigned females (top) and males (bottom). Cortical networks are shown along lateral and medial surfaces, and non-cortical networks are visualized as a single square as per the colormap. Warmer colors indicate a stronger relative absolute association between the networks and the scores.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SexDiffsPLEsSupp240921.docx
- epced.pdf