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Regular Article

The default mode network is associated with changes in internalizing and externalizing problems differently in adolescent boys and girls

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Abstract

Internalizing and externalizing problems that emerge during adolescence differentially increase boys' and girls' risk for developing psychiatric disorders. It is not clear, however, whether there are sex differences in the intrinsic functional architecture of the brain that underlie changes in the severity of internalizing and externalizing problems in adolescents. Using resting-state fMRI data and self-reports of behavioral problems obtained from 128 adolescents (73 females; 9–14 years old) at two timepoints, we conducted multivoxel pattern analysis to identify resting-state functional connectivity markers at baseline that predict changes in the severity of internalizing and externalizing problems in boys and girls 2 years later. We found sex-differentiated involvement of the default mode network in changes in internalizing and externalizing problems. Whereas changes in internalizing problems were associated with the dorsal medial subsystem in boys and with the medial temporal subsystem in girls, changes in externalizing problems were predicted by *hyperconnectivity* between core nodes of the DMN and frontoparietal network in boys and *hypoconnectivity* between the DMN and affective networks in girls. Our results suggest that different neural mechanisms predict changes in internalizing and externalizing problems in adolescent boys and girls and offer insights concerning mechanisms that underlie sex differences in the expression of psychopathology in adolescence.

Keywords: adolescence; brain functional connectivity; externalizing; internalizing; sex differences

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Introduction

Adolescence is a developmental period during which there is a high risk for the onset of psychiatric disorders. Indeed, a recent meta-analysis of epidemiological studies estimated that in almost two-thirds of cases, mental disorders emerge before the age of 25 years; specifically, the onset of anxiety and fear-related disorders peaks at 15 years of age, alcohol/substance use disorders at 19 years, and mood and personality disorders at 20 years (Solmi et al., 2022). Individuals with early-onset mental disorders develop functional impairments that increase their risk for experiencing long-lasting difficulties in mental and physical health, academic performance, financial management, and interpersonal relationships (Balázs et al., 2013). Although early identification and preventive approaches can alter the course of disease progression and improve mental health outcomes in youth (Burke et al., 2019), most studies in this area have been conducted with individuals in whom disorders are already present (Fusar-Poli et al., 2021). Thus, it is crucial that we identify adolescents who are at risk for developing emotional difficulties as early as possible in order to prevent the progression of disorder.

Internalizing and externalizing problems in youth have been found to predict later mental health difficulties (Achenbach et al., 2016). Internalizing problems are characterized by internal expression of distress, in the form of depression or anxiety, withdrawal from the external environment, and somatic complaints, and are related to subsequent mood and personality disorders. In contrast, externalizing problems are directed outward through rule-breaking or aggressive behaviors, and are associated with subsequent conduct and substance use disorders (Cosgrove et al., 2011). Adolescents with internalizing and externalizing problems share neuroanatomical characteristics with adults who are diagnosed with various forms of psychopathology. For example, investigators have reported that, like adults diagnosed with depression and anxiety-related disorders, typically developing youth with internalizing problems have reduced hippocampal volume (Koolschijn et al., 2013). Similarly, like adults with attention-deficit/hyperactivity disorder (ADHD; Makris et al., 2007), adolescents with externalizing problems have less cortical thinning of the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) (Oostermeijer et al., 2016). Findings of longitudinal studies indicate that internalizing and externalizing problems that persist across childhood and adolescence are associated with poorer mental health outcomes later in life (Colman et al., 2007), highlighting the importance of elucidating neural mechanisms that might contribute to the developmental course of these problems.

Previous investigations of associations between resting-state functional connectivity (RSFC) and adolescent internalizing and externalizing problems have documented aberrant patterns of FC in resting-state networks across the brain. For example, in a longitudinal study of typically developing youth, Thijssen et al.

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(2021) found that increased amygdala connectivity with the ACC and orbitofrontal cortex (OFC) was associated with more severe externalizing problems. Using the NCANDA dataset, Silveira et al. (2021) also reported a significant relation between FC of the dorsal ACC and externalizing problems. Using the ABCD dataset, Lees et al. (2021) found that adolescents who reported higher externalizing problems had hyperconnectivity between the salience and ventral attention networks; in contrast, internalizing problems were associated with hypoconnectivity between the DMN and cingulo-opercular network, as well as with aberrant FC in the salience and cognitive control networks (Burkhouse et al., 2019). In a longitudinal study, Chahal et al. (2020) found that hyperconnectivity between the regions of the affective and default mode network were associated with both concurrent and subsequent internalizing problems. Overall, therefore, both internalizing and externalizing problems in adolescents have been found to be associated with brain-wide alterations in intrinsic functional architecture.

We do not yet fully understand, however, how these alterations are affected by pubertal maturation or the precise nature of sex differences in adolescent neurodevelopment. Most of the studies examining the relation between RSFC and internalizing and externalizing problems in adolescence either have controlled for sex or did not find that sex moderated their findings. There is now accumulating evidence of sex differences in structural and functional brain development in adolescence that extend to sex-differentiated risk for the development of psychopathology. For example, Kaczkurkin et al. (2019) reviewed the literature examining sex differences in gray matter, white matter, and cerebral blood flow in the context of the onset of puberty and noted implications of these difference for sex-differentiated risk for the development of psychopathology, including depression, anxiety, and ADHD. Similarly, Dorfschmidt et al. (2021) recently examined large-scale resting-state networks in adolescence and reported sex differences in the trajectory of brain-wide RSFC, such that females had more disrupted depression-related development of the default mode, limbic, and subcortical networks than did their male peers.

Importantly, researchers have documented sex differences in symptoms of psychopathology even at a nonclinical level: whereas girls are characterized by increasing symptoms of internalizing problems over adolescence, boys exhibit increasing symptoms of externalizing problems (Nivard et al., 2017; Zahn-Waxler et al., 2008). In addition, whereas white matter microstructural alterations have been found to be associated with internalizing problems more strongly in adolescent girls than in boys (Andre et al., 2020; Chahal, Ho, et al., 2022), reduced gray matter volume in the ventromedial prefrontal cortex and reduced cortical thickness in the supramarginal gyrus have been found in adolescent boys, but not in girls, with externalizing problems (Ibrahim et al., 2021). In another study using resting-state fMRI, Padgaonkar et al. (2020) found that the amygdala had heightened connectivity with different brain regions in adolescent boys than in girls with high levels of internalizing problems. Despite these promising findings, few studies have examined sex-differentiated neural characteristics that underlie changes in internalizing and externalizing problems in adolescence. Further, previous studies have limited the scope of their investigation to a priori regions of interest or to specific brain networks that were defined using atlases derived from adults.

To address this issue, in the present study we conducted multivoxel pattern analysis (MVPA) of resting-state fMRI data from adolescent boys and girls to identify sex-specific patterns of RSFC that are associated with change in internalizing and externalizing problems. We chose to examine RSFC for two primary reasons: (a) intrinsic organization of functional networks has been shown to be reproducible and stable across adolescents (Jalbrzikowski et al., 2019; Marek et al., 2019); and (b) variability in RSFC has been posited to be largely attributable to personal characteristics that have been found to predict adolescents' brain maturity and executive functioning (Cui et al., 2020). To capture more precisely substrates of change in internalizing and externalizing problems, we used a data-driven approach to examine the whole brain on a voxel-by-voxel basis.

MVPA is a powerful data-driven procedure that complements a priori seed-based and traditional group-level methods and utilizes the wealth of information available in neuroimaging data. For each voxel, MVPA identifies the multivariate pattern of functional connections with the rest of the brain that predicts properties of participants (e.g., cases vs. controls; boys vs. girls) or experimental conditions (e.g., pre- vs. post-intervention). Since the pioneering work of Craddock et al. (2009) examining the clinical applicability of using MVPA with resting-state fMRI data, investigators have used this procedure to identify biomarkers of psychiatric conditions (Kambeitz et al., 2017). To date, however, few studies have conducted MVPA or related forms of machine learning with neuroimaging data from adolescents to predict the development or progression of disorder (Chahal et al., 2020; Chahal, Miller, et al. 2022; Foland-Ross et al., 2015; Tymofiyeva et al., 2019); further, none of these studies has examined sex differences. Therefore, in this study we used MVPA to identify patterns of RSFC that predict change in internalizing and externalizing problems differentially in adolescent boys and girls over a 2-year interval.

Conducting MVPA separately in boys and girls can yield new insights into sex-specific neural mechanisms that might have been overlooked in previous studies that have examined group-level associations between network-level or *a priori* defined single regions of the brain and behavior and then tested for interactions with sex. Indeed, because MVPA involves voxel-by-voxel associations, it has the advantage of identifying discrete brain regions, rather than entire networks, that are related to specific behaviors. Given the sex-differential risk for the development of various psychiatric disorders, we predict that change in internalizing and externalizing problems will involve regions within the affective and default mode networks in girls and within the salience and attention networks in boys.

Material and methods

Participants

Two hundred and twenty five adolescents (132 females) were recruited in 2013–2016 from the San Francisco Bay Area for a larger longitudinal study assessing the effects of early life stress on psychobiology across puberty. Exclusion criteria included an inability to participate in neuroimaging scans (e.g., nonremovable metal), intellectual delay, non-fluency in English, and self-reported onset of menses for females. 8% of the sample was Black, 9% Hispanic, 11% Asian American, 20% two or more races, 44% White, and 8% other than what was listed. All adolescents and their parent(s)/legal guardian(s) provided informed assent and consent, respectively. This study was approved by the Stanford University Institutional Review Board. Given the longitudinal design of this study, we analyzed data from a final sample of 128 participants; participants were excluded from analyses if they did not have resting-state data that passed quality assurance criteria ($n = 27$) and if they did not have two timepoints of neural and behavioral data ($n = 67$). In the final sample, participants were 9.19–13.81 years

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of age ($M = 11.40 + 1.01$ years) at the first timepoint (T1) and 11.15–15.85 years of age ($M = 13.40 + 1.06$ years) at the second timepoint (T2). Because participants were matched on pubertal status at T1, males were older than females at T1 by an average of 9.24 months.

Behavioral problems

We administered the Youth Self-Report (YSR; Achenbach & Rescorla, 2001) at T1 and T2 to assess internalizing and externalizing problems. The YSR is a widely used measure of behavioral problems in adolescents ages 7–18 years. It has high test-retest reliability and is sensitive to change ($a = 0.88$; Ebesutani et al., 2011; Ferdinand, 2008; Smucker et al., 1986). In our sample, the reliability of participants' scores on the YSR internalizing and externalizing subscales at T1 and T2 ranged from .89 to .94. To assess change in the severity of internalizing and externalizing problems, T1 scores were subtracted from T2 scores and were entered into the analyses with T1 scores, age, and motion during fMRI scans (mean framewise displacement) as covariates. We performed corrections for multiple comparisons to control for false discovery and family-wise error.

MRI acquisition

MRI scans were conducted on a GE Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI) equipped with a 32-channel head coil (Nova Medical). We collected spoiled gradient echo (SPGR) T1-weighted sagittal anatomical images (repetition time [TR] = 6.24 ms; echo time [TE] = 2.34 ms; flip angle = 12°; FOV = 230 mm; voxel size = 0.8984 × 0.8984 × 0.9000 mm; scan time = 5:15). Resting-state BOLD fMRI data were acquired using aT2*-weighted echo planar imaging sequence with 37 axial slices (180 volumes, repetition time [TR] = 2.0 s; echo time [TE] = 30 ms; flip angle = 77°; FOV = 224 mm; voxel size = 3.2 mm^3, total scan time = 6 min). Participants were instructed to keep their eyes closed but remain awake. The raw functional images were quality checked prior to preprocessing.

Functional MRI preprocessing

Data were preprocessed using the automated fMRIPrep pipeline v20.2.1 (Esteban et al., 2019; RRID:SCR_016216), which is based on Nipype 1.5.1 (Gorgolewski et al., 2011; RRID:SCR_002502). We excluded scans based on visual inspection of imaging quality ($n = 4$), motion constraints (functional data that exceeded .25 mm framewise displacement (FD) on greater than 20 volumes or mean FD values that were greater than two standard deviations from the sample mean; $n = 23$), retaining 169 scans of unique participants. The BOLD time-series were then resampled into the standard pediatric template, MNIPediatricAsym:cohort-6, which matched the age range of our sample.

Functional MRI postprocessing

We discarded the first six volumes of the resting-state fMRI data to allow the MR signal to achieve T1 equilibrium. We then applied simultaneous band-pass filtering of .008–.10 Hz and nuisance regression using 32 regressors which included WM, CSF, translation and rotation in each directional axis (x,y,z), the temporal derivatives and quadratic terms, and framewise displacement. Finally, we applied 2 mm smoothing to the data.

Multi-Voxel Pattern Analysis (MVPA)

We conducted whole-brain connectome-wide MVPA as an agnostic, data-driven approach to identify seed regions for standard seed-to-voxel analysis using the CONN toolbox (Nieto-Castanon, 2022; Whitfield-Gabrieli & Nieto-Castanon, 2012). In this pipeline, a multivariate representation of the RSFC pattern for each voxel is estimated by computing the pairwise connectivity between each voxel and the rest of the brain and is characterized by reducing dimensions through two rounds of principal component analysis (PCA). First, 64 components are retained for each participant's voxel-to-voxel correlation structure. Then, the first four components are retained from the second PCA across all participants, which capture between-subjects variability in voxel-to-voxel connectivity maps across the entire brain. This approach enables resulting RSFC patterns to be used in General Linear Model (GLM) to make classical statistical inferences about individual voxels in the brain in the context of the shape of their functional connectivity patterns, and about the entire pattern regarding the experimental paradigm. An *F*-test was performed on all four MVPA components, which explain the maximum inter-subject variability, to identify voxels whose connectivity patterns show significant associations with the change in YSR scores (a height-level threshold of $p < 0.001$ and a false discovery rate (FDR)-corrected cluster threshold of $p < 0.05$). The voxel clusters were then used as the seed for a secondary seed-to-voxel analysis to confirm the direction in which they are associated with changes in YSR scores. This method has been used with both clinical and nonclinical samples of children and adolescents (Cahart et al., 2022; Mateu-Estivill et al., 2021; Walsh et al., 2022); more technical details can be found in Nieto-Castanon (2022). In regression analyses using MVPA-derived FC values to predict change in internalizing and externalizing problems in boys and girls, power was >.99 for all analyses.

Results

Participant characteristics

Demographic and clinical characteristics of the participants are presented in Table 1. Males and females were matched on pubertal status at entry into the study; as expected, therefore, they differed significantly in age at T1 and T2. Boys and girls did not differ in their levels of internalizing and externalizing problems at T1 and T2, nor did they differ in their changes in problem scores from T1 to T2. We should note, however, that almost half of the participants reported an increase in internalizing and externalizing problems from T1 to T2, although there were no significant sex differences in the proportion of participants who reported higher internalizing or externalizing problems at T2 than at T1 (see Figure 1 and Table 1).

MVPA

We found that different patterns of whole-brain connectivity were associated with change in internalizing and externalizing problems from T1 to T2 in girls and boys (see Figure 2 and Table 2). A whole-brain height-threshold of $p < 0.001$ and an FDR-corrected cluster-threshold of $p < 0.05$ were used to identify significant clusters. Change in internalizing problems was associated in girls with a voxel cluster located in the right ventrolateral prefrontal cortex (VLPFC), and in boys with voxel clusters located in right parahippocampal gyrus (PHG), the inferior parietal lobule (IPL), right temporal pole (TP), right insular cortex, and right ventromedial prefrontal cortex (VMPFC). Change in externalizing problems

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Table 1. Participant demographic and clinical characteristics

	Male	Female	*p*-value
Participants	55 (43.0%)	73 (57.0%)	
Age at T1 (years)	11.81 ± 0.87	11.04 ± 0.99	*p* < .001
Age at T2 (years)	13.83 ± 0.90	13.09 ± 1.06	*p* < .001
YSR internalizing problems at T1	10.80 ± 8.66	12.90 ± 9.58	*p* = .196
T-score above 65	6/55 (10.9%)	9/73 (12.3%)	
YSR externalizing problems at T1	10.25 ± 6.49	9.13 ± 6.89	*p* = .350
T-score above 65	2/55 (3.6%)	7/73 (9.6%)	
YSR internalizing problems at T2	9.65 ± 8.62	10.19 ± 8.50	*p* = .726
T-score above 65	4/55 (7.2%)	5/73 (6.8%)	
YSR externalizing problems at T2	10.11 ± 6.91	7.74 ± 5.62	*p* = .040
T-score above 65	1/55 (1.8%)	2/73 (2.7%)	
Increase in internalizing problems at T2	24 (43.6%)	26 (35.6%)	*p* = .46
Increase in externalizing problems at T2	24 (43.6%)	32 (43.8%)	*p* = 1

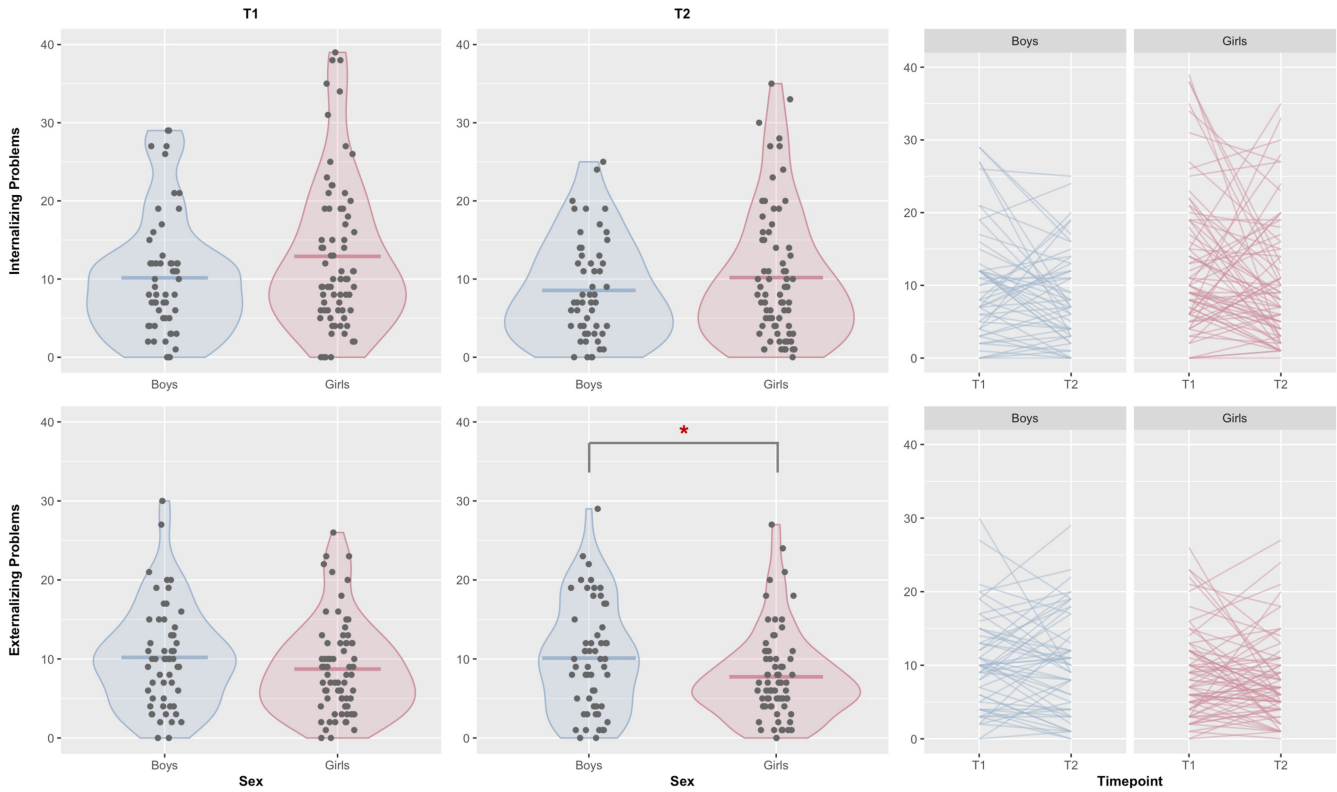

Figure 1. Sex differences on the Youth Self Report (YSR) internalizing and externalizing problems scores at Time 1 and Time 2, and changes from Time 1 to Time 2. T1 = Time 1; T2 = Time 2; *$p < .05$.

was associated in girls with voxel clusters located in the left OFC, left TP, and left occipital cortex, and in boys with a voxel cluster in the right posterior cingulate cortex (PCC).

We then characterized the directionality of the connectivity patterns by seeding from the MVPA-derived spatial patterns in the secondary seed-to-voxel analyses (see Figure 3 and Table 3). We used a height threshold of whole-brain $p < 0.001$ and FDR-corrected cluster threshold of $p < 0.05$ with non-parametric (1000 permutations) statistics to reduce Type 1 error from multiple comparisons. We found that in girls, the MVPA pattern that was associated with change in internalizing problems was negatively correlated with the PCC/precuneus and parahippocampal gyrus (PHG), and the pattern associated with change in externalizing problems was negatively correlated with medial prefrontal cortex

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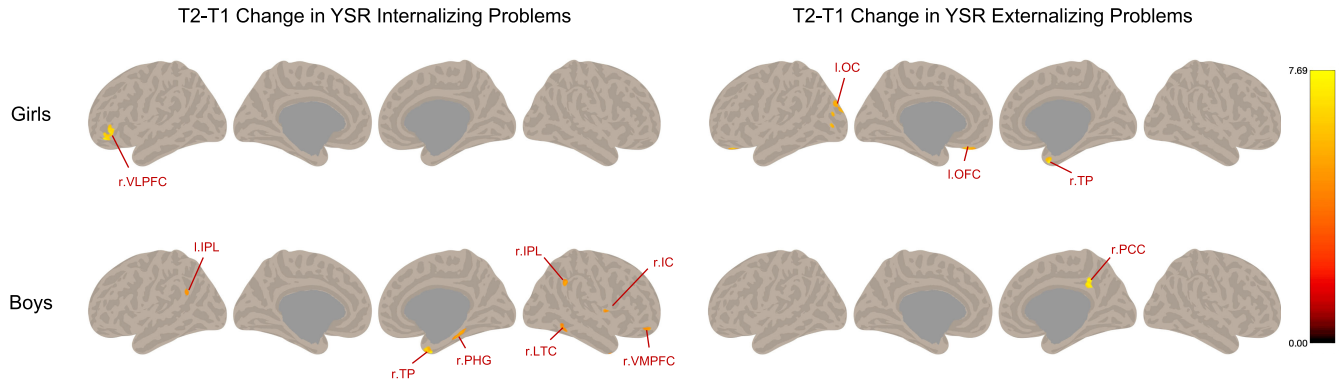

Figure 2. MVPA-derived spatial pattern associated with changes in internalizing and externalizing problems in boys and girls. (top left – internalizing in girls) r.VLPFC = Right Ventrolateral Prefrontal Cortex; (top right – externalizing in girls) l.OC = Left Occipital Cortex; l.OFC = Left Orbitofrontal Cortex; r.TP = Right Temporal Pole; (bottom left – internalizing in boys) l.IPL = Left Inferior Parietal Lobule; r.TP = Right Temporal Pole; r.PHG = Right Parahippocampal Gyrus; r.IPL = Right Inferior Parietal Lobule; r.LTC = Right Lateral Temporal Cortex; r.IC = Right Insula Cortex; r.VMPFC = right Ventromedial Prefrontal Cortex; (bottom right – externalizing in boys) r.PCC = Right Posterior Cingulate Cortex.

Table 2. MVPA result

Peak coordinate (MNI)	Brain region	Voxels
Girls: T2–T1 change in internalizing problems		
−50, 38, −4	L. Ventrolateral prefrontal cortex	33
−40, 44, −12	L. Ventrolateral prefrontal cortex	32
Boys: T2–T1 change in internalizing problems		
34, −32, −14	R. Parahippocampal gyrus	39
46, −42, 44	R. Inferior parietal lobule	26
52, −50, −14	R. Lateral temporal cortex	24
38, 4, 10	R. Insula cortex	21
24, 12, −42	R. Temporal pole	21
−52, −56, 28	L. Inferior parietal lobule	20
26, 52, −14	R. Ventromedial prefrontal cortex	20
Girls: T2–T1 change in externalizing problems		
−12, 40, −28	L. Orbitofrontal cortex	27
−32, −22, −24	L. Hippocampus	24
−16, −90, 26	L. Occipital cortex	22
20, 8, −38	R. Temporal pole	22
−42, −82, 14	L. Occipital cortex	18
Boys: T2–T1 change in externalizing problems		
10, −40, 34	R. Posterior cingulate cortex	21

(MPFC) and PCC. In boys, the pattern that was associated with change in internalizing problems was negatively correlated with postcentral gyrus, and the pattern that was associated with change in externalizing problems was positively correlated with dorsomedial (DMPFC) and dorsolateral prefrontal cortex (DLPFC). Thus, an increase in internalizing problems at T2 was predicted in girls by negative connectivity at T1 between the right VLPFC and PCC/precuneus/PHG and in boys by negative connectivity between multiple nodes of the default mode network (DMN) and the postcentral gyrus. Similarly, an increase in externalizing problems at T2 was predicted in girls by negative connectivity at T1 between nodes of the affective network and nodes of the default mode network, and in boys by positive connectivity between the PCC and DLPFC/Pre-SMA. We also tested the moderation effect of sex across all participants and specificity of each FC pattern, presented in the Supplement.

Discussion

The present study was conducted to examine sex differences in RSFC that predicted change in internalizing and externalizing problems in adolescents over a 2-year period. Using an agnostic whole-brain data-driven approach, we identified different patterns of FC that predicted the progression of internalizing and externalizing problems in boys and girls. Specifically, change in internalizing and externalizing problems was associated with different subsystems of the DMN in boys and girls. These findings suggest that there are sex-dependent neurodevelopmental trajectories of internalizing and externalizing problems in adolescents.

Change in internalizing problems was predicted by the medial temporal subsystem in girls and the dorsal medial subsystem in boys (see Andrews-Hanna et al., 2010, 2014). Girls who exhibited an increase in internalizing problems from T1 to T2 had negative FC at T1 between the right VLPFC and the medial temporal subsystem, which has been implicated in contextual retrieval of emotional stimuli (Leech et al., 2012; Ward et al., 2013). Given that the right VLPFC is important for decreasing negative emotions and for response selection and inhibition in adolescents (Ochsner et al., 2012; Somerville et al., 2011), it is possible that dysfunction in contextual processing and appraisal of emotion contributes to the increase in internalizing problems in girls, a formulation that is consistent with previous reports of stronger associations between difficulties in emotion regulation and depressive symptoms in girls than in boys (Chaplin et al., 2019; Gonçalves et al., 2019).

In boys, an increase in internalizing problems may be related more closely to aberrant self-reflective processing of somatosensory stimuli. The MVPA-derived pattern, which was negatively connected with the postcentral gyrus in boys who showed an increase in internalizing problems, included voxel clusters in the PHG, IPL, TP, and VMPFC that overlap substantially with the dorsal medial subsystems of the DMN, which have been implicated in mentalizing and processing of external stimuli (Alves et al., 2019; Andrews-Hanna et al., 2014). Furthermore, FC within this dorsal medial subsystem has been found to be positively correlated with rumination in young adults with MDD, suggesting that co-

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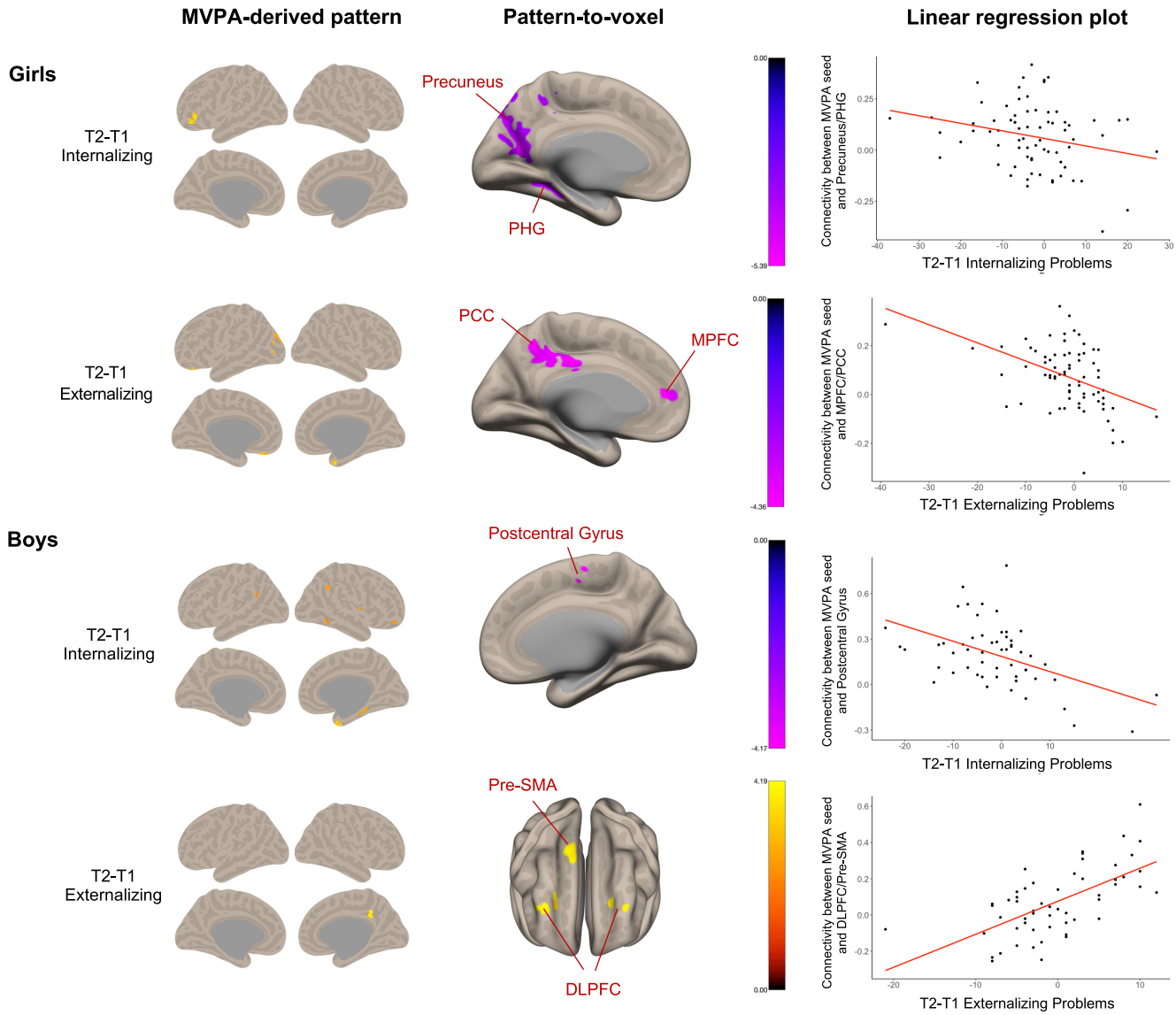

Figure 3. MVPA-derived functional connectivity patterns associated with changes in internalizing and externalizing problems in boys and girls. Left panel: spatial patterns identified using MVPA; Center panel: whole-brain functional connectivity of MVPA-derived patterns; Right panel: Linear regression plot of association between change score and brain FC. Brain FC value was calculated by averaging the connectivity value between the MVPA-derived pattern and resultant clusters from secondary seed-to-voxel analyses.

activation of these regions is related to maladaptive self-focus (Zhu et al., 2017). Given our relative lack of understanding of RSFC of the postcentral gyrus in the context of psychopathology, it is not yet clear precisely *how* these DMN nodes interact with the postcentral gyrus. Nevertheless, we posit that the increase in internalizing problems in boys is related to their aberrant self-reflective processing of somatosensory stimuli.

We found that the core nodes of the DMN, the MPFC and PCC are associated with an increase in externalizing problems from T1 to T2 differentially in boys and girls. Researchers have consistently noted the strong coactivation of the MPFC and PCC during self-referential processing and mentalizing; however, their functional characteristics in the context of adolescents' externalizing problems have received less attention. Weissman et al. (2018) reported reduced activation of the PCC during sadness introspection in adolescents with high levels of externalizing problems; from a different perspective, Perino et al. (2019) showed that adolescents who reported engaging in bullying behaviors had greater activation of the MPFC when viewing social exclusion.

In girls, the MPFC and PCC have been found to have negative connectivity with the OFC, hippocampus, TP, and visual areas, which collectively support socio-affective processing and decision making (Mızrak et al., 2021; Pehrs et al., 2018; Urbain et al., 2017). Importantly, researchers have reported alterations in the structure and function of these regions in a range of psychiatric disorders. For example, children with conduct disorder and/or externalizing problems have been found to have abnormal structural and functional connectivity in the OFC and hippocampus (Ameis et al., 2014; Bos et al., 2018; Oostermeijer et al., 2016). Reduced connectivity of these structures with DMN nodes has been found in patients with obsessive-compulsive disorder (Geffen et al., 2021) and in cocaine users with high rates of relapse (Geng et al., 2017). Thus, our observation that negative connectivity in these regions predicts a subsequent increase in externalizing problems in girls implicates difficulties in socio-emotional processing.

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Table 3. MVPA-derived pattern-to-voxel analysis result

Peak coordinate (MNI)	Brain region	Voxels
Girls: T2–T1 change in internalizing problems		
18, −54, 14	Precuneus cortex	869
−28, −46, −4	L. Parahippocampal gyrus	150
−4, −42, 52	L. Posterior cingulate cortex	132
Boys: T2–T1 change in internalizing problems		
−2, −10, 54	Postcentral gyrus	47
Girls: T2–T1 change in externalizing problems		
−12, −52, 44	Posterior cingulate cortex	139
−4, −24, 34	Posterior cingulate cortex	94
Boys: T2–T1 change in externalizing problems		
32, 62, 20	R. Dorsolateral prefrontal cortex	127
16, 18, 56	R. Pre-supplementary motor area	87
−30, 48, 30	L. Dorsolateral prefrontal cortex	64

In contrast, in boys, increases in externalizing problems was associated with positive connectivity between the PCC and DLPFC and pre-SMA region at T1. As part of the frontoparietal/central executive network (FPN/CEN), the DLPFC is implicated in cognitive control and is anticorrelated with the DMN, an association that strengthens over development as efficient switching between task-positive and task-negative states becomes increasingly important for various cognitive tasks (Avelar-Pereira et al., 2017; Chai et al., 2014). Lack of anticorrelation between these regions underlies not only cognitive deficits in MDD (Hamilton et al., 2011) and ADHD (Posner et al., 2014), but is also associated with a higher risk for developing depressive problems (Posner et al., 2016) and attentional problems in adolescence (Whitfield-Gabrieli et al., 2020). In this context, in a recent meta-analysis Wong et al. (2021) reported that pre-SMA is one of the most consistently identified regions in studies of ADHD, and also noted its FC with the FPN in relation to inattention and delinquency. Thus, we posit that the increase in externalizing problems in boys is more strongly related to a lack of attention, which is consistent with the higher prevalence of ADHD in adolescent boys than in girls.

We should note three limitations of this study. First, although we identified FC in brain areas that predicted increases in internalizing and externalizing problems over a 2-year period in adolescent boys and girls, few studies have examined sex-related divergence in the developmental trajectories of resting-state connectivity in adolescence; therefore, we cannot draw firm conclusions concerning the mechanisms that underlie the increase in these problems. Recently, however, researchers have begun to elucidate sex differences in the development of larger resting-state networks such as the DMN, limbic, and attentional networks (Dorfschmidt et al., 2021; Dumais et al., 2018; Ernst et al., 2019), as well as the neurodevelopmental trajectory of internalizing and externalizing problems across childhood and adolescence (Blok et al., 2022; Chahal et al., 2020; Chahal, Miller, et al., 2022; Whitfield-Gabrieli et al., 2020). Future studies that bridge these trajectories more explicitly and systematically are needed to replicate our findings. Second, although there was not a significant sex difference in internalizing and externalizing problems in our participants, at both timepoints girls reported nonsignificantly higher levels of internalizing problems and boys reported nonsignificantly higher levels of externalizing problems. It is important to note that our participants were just entering puberty at the baseline assessment, and we anticipate that sex differences in the progression of internalizing and externalizing problems will strengthen as our participants advance through puberty. Finally, we assessed a typically developing community sample of adolescents in this study, only a small number of whom met the cut-off criteria for clinical levels of internalizing and externalizing problems. Therefore, the brain areas we identified are not necessarily biomarkers of clinically significant symptoms. It is important to note, however, that in previous studies these brain regions have been implicated in cognitive and affective processes that are often disrupted in patients with depression (Gonçalves et al., 2019), OCD (Geffen et al., 2021), and ADHD (Makris et al., 2007). Further, our findings that change in internalizing problems in girls was related to FC of brain regions involved in emotion regulation, and that change in externalizing problems in boys was related to FC of brain regions involved in attentional control, are consistent with findings of sex differences in the prevalence of disorders that are characterized by dysfunction in these constructs. Thus, our findings help to elucidate sexually divergent neural mechanisms that may lead to increased risk for psychopathology in adolescence.

Despite these limitations, we were able to identify patterns of FC that, even after correction for multiple comparisons, were associated significantly and differentially with change in internalizing and externalizing problems in adolescent boys and girls. We observed that subnetworks within the DMN were differentially associated with each problem domain. Although researchers have examined the involvement of the DMN in a range of cognitive processes and clinical problems, they have tended to focus primarily either on the main nodes of the DMN or on the entire network. In contrast, we used a whole-brain data-driven approach and identified, as expected, brain regions that have previously been implicated in internalizing and externalizing problems, but also other brain areas in which patterns of FC have received less attention. In particular, whereas change in internalizing and externalizing problems in girls was associated with patterns of FC in the DMN subnetworks and brain regions that are involved in socio-emotional processing, change in internalizing and externalizing problems in boys involved the DMN subnetworks and brain regions that have been implicated in self-focus and cognitive control. These results are consistent with stress exposure theory, which posits that whereas girls are more sensitive to interpersonal stressors, boys are more sensitive to self-relevant stressors (Hankin, 2008; Oldehinkel & Bouma, 2011). Our findings point to neural correlates of the differential development of stress reactivity in adolescent boys and girls; these brain-wide signatures might be precursors to more severe forms of psychiatric disorder and negative life outcomes, and underscore the importance of examining sex differences in neurodevelopment and stress processing in investigations of adolescent psychopathology.

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