Another dimensional framework, the Research Domain Criteria[8], was developed to advance the investigation of neurobiological foundations of dimensional psychopathology. However, the research progress in uncovering the stratified neural bases of externalizing and internalizing disorders has remained slow[9,10]. This sluggishness is partly due to the historical emphasis on localizing brain abnormalities at the regional level in psychiatric disorders[11–13]. It is crucial to recognize that different brain regions do not function or develop independently; instead, they work in distributed and anatomically interconnected systems[14,15]. The above evidence hence suggests that distinct regionalized brain markers of psychiatric disorders might be located within a common psychopathological brain network. This hypothesis has recently gained support from normative network mapping and connectivity-based transdiagnostic studies[16,17], emphasizing the importance of network-based approaches in unifying region-level heterogeneous neural underpinnings of psychiatric disorders[18,19].

Furthermore, previous transdiagnostic neuroimaging studies have predominantly used a cross-sectional approach[20–22], thereby overlooking the developmental perspective on how the general and stratified neural substrates manifest and evolve longitudinally[3], especially during critical developmental periods such as adolescence. Utilizing a longitudinal large-scale imaging dataset, we can further elucidate the nuanced interplay between the enduring and phasic neural mechanisms of psychiatric comorbidity[23]. This approach will substantially advance our understanding of the onset and progression of psychiatric comorbidity.

The present study addresses three major questions regarding the specific transdiagnostic neural bases of externalizing and internalizing symptoms: (1) Can we identify stratified cross-disorder neural factors for externalizing and internalizing symptoms, respectively? (2) Do the two stratified neural factors exhibit distinct characterizations regarding neurobiological risk factors and clinical conditions? (3) How can we synthesize the general and stratified neural factors into a hierarchical neurocognitive model of comorbid psychopathology (NeuroHiP)?

Results

Summary of research approach

Our analytic approach consisted of five key steps to identify and characterize the specific neural factors underlying externalizing and internalizing symptoms. First, we used connectome-based predictive modeling[24] to estimate brain signatures of individual psychiatric symptoms using multiple task-based functional magnetic resonance imaging conditions from the IMAGEN cohort (age 14, $N = 1{,}750$). Specifically, we parcellated task-based imaging data from the stop-signal task (SST), monetary incentive delay task (MID) and emotional face

Stratified neural factors of externalizing and internalizing symptoms

Our previous study found significant predictive effects of task-based connectomes on 8 psychiatric symptoms in 14-year-old participants from the IMAGEN study[7] (Fig. 1a and Supplementary Tables 1 and 2; $N = 1{,}750$). For each psychiatric symptom, we generated a brain-predicted measure. Interestingly, we observed that there were significantly higher similarities between brain-predicted symptoms than the observed psychiatric symptoms (externalizing symptoms, brain-predicted $r_{mean} = 0.91$, observed $r_{mean} = 0.37$, $P_{perm} < 0.001$ for the difference; internalizing symptoms, brain-predicted $r_{mean} = 0.52$, observed $r_{mean} = 0.28$, $P_{perm} < 0.001$ for the difference) (Fig. 1b,c). The results thus suggested substantial shared neural bases within externalizing and internalizing symptoms.

We next aimed to identify specific neural factors, termed as 'stratified neural factors', comprising cross-disorder edges that predicted two or more symptoms from a single psychiatric domain (externalizing or internalizing), while not predicting any symptoms from the other domain (Fig. 1d). We found that stratified cross-disorder edges were consistently and reliably identified from task conditions relating to inhibitory control and reward sensitivity (that is, stop success, stop failure, positive reward feedback and reward anticipation; all $P_{perm} < 0.01$; Supplementary Table 3). We further ascertained the neural mechanisms of the stratified cross-disorder edges in terms of their predictive effects (Fig. 1d). Intriguingly, we observed a double dissociation effect: externalizing symptoms were reliably associated with positive–positive cross-disorder edges ($n_{edge} = 1{,}268$, $P_{perm} < 0.001$, showing positive correlations with externalizing symptoms), whereas internalizing symptoms were reliably associated with negative–negative cross-disorder edges ($n_{edge} = 469$, $P_{perm} < 0.001$, showing negative correlations with internalizing symptoms) (Supplementary Table 4). Therefore, in the following analyses, the summed FC strength of positive–positive cross-disorder edges will be referred to as the externalizing neural factor, and the summed strength of negative–negative cross-disorder edges as the internalizing neural factor.

Longitudinal analysis of stratified neural factors

As previous research has highlighted the stability of internalizing and externalizing behaviors over time[6], we next examined the longitudinal predictive performance of the two stratified neural factors from adolescence to early adulthood over a 10-year span (Fig. 1e). The externalizing factor demonstrated consistent performance for longitudinal prediction across ages 14, 19 and 23. To elaborate, the externalizing neural factor estimated at age 14 could significantly predict external-

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Hierarchical neurocognitive model of externalizing and internalizing comorbidity

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Mounting evidence suggests that hierarchical psychopathology factors underlie psychiatric comorbidity. However, the exact neurobiological characterizations of these multilevel factors remain elusive. Here, leveraging the brain-behavior predictive framework with a 10-year longitudinal imaging-genetic cohort (IMAGEN, ages 14, 19 and 23, $N = 1{,}750$), we constructed 2 neural factors underlying externalizing and internalizing symptoms, which were reproducible across 6 clinical and population-based datasets (ABCD, STRATIFY/ESTRA, ABIDE II, ADHD-200 and XiNan, from age 10 to age 36, $N = 3{,}765$). These two neural factors exhibit distinct neural configurations: hyperconnectivity in impulsivity-related circuits for the externalizing symptoms and hypoconnectivity in goal-directed circuits for the internalizing symptoms. Both factors also differ in their cognitive-behavior relevance, genetic substrates and developmental profiles. Together with previous findings, we propose a hierarchical neurocognitive model of comorbid psychopathology (NeuroHiP) from preadolescence to adulthood, comprising a general neuropsychopathological factor (manifested as inefficient executive control) and two stratified factors of externalizing (deficient inhibition control) and internalizing (impaired goal-directed function) symptoms, respectively. These holistic insights are crucial for the development of stratified therapeutic interventions for mental disorders.

Psychiatric comorbidity is prevalent and often leads to more severe prognoses[1], posing a major challenge to the current mental health diagnostic system[2]. In response, the Hierarchical Taxonomy of Psychopathology was proposed to categorize the complex psychiatric comorbidities into a general factor alongside multiple stratified transdiagnostic spectra, for instance, the externalizing (aggressive and hyperactive-impulsive) versus internalizing (anxious and depressive) spectrum[3,4]. This hierarchical dimensional approach has greatly advanced psychiatric research by better representing psychopathology and revealing neurobiological mechanisms across traditional diagnostic boundaries[5].

Among the various spectra identified in the Hierarchical Taxonomy of Psychopathology framework, externalizing and internalizing symptoms commonly manifest during adolescence—a critical neurodevelopmental period characterized by notable brain maturation and heightened vulnerability to psychopathology. The early manifestation of these two transdiagnostic spectra could reliably predict future psychopathology and functional impairment into adulthood[6]. Recently, our research team identified a prefrontal-related general neuropsychopathological (NP) factor underlying both externalizing and internalizing symptoms from preadolescence to early adulthood[7]. However, the neurobiological mechanisms of externalizing and internalizing disorders and the interaction of general-stratified factors during development remain elusive. Understanding these shared and distinct neural underpinnings of externalizing and internalizing spectra could provide crucial insights into the development and maintenance of psychiatric comorbidity from preadolescence to adulthood.

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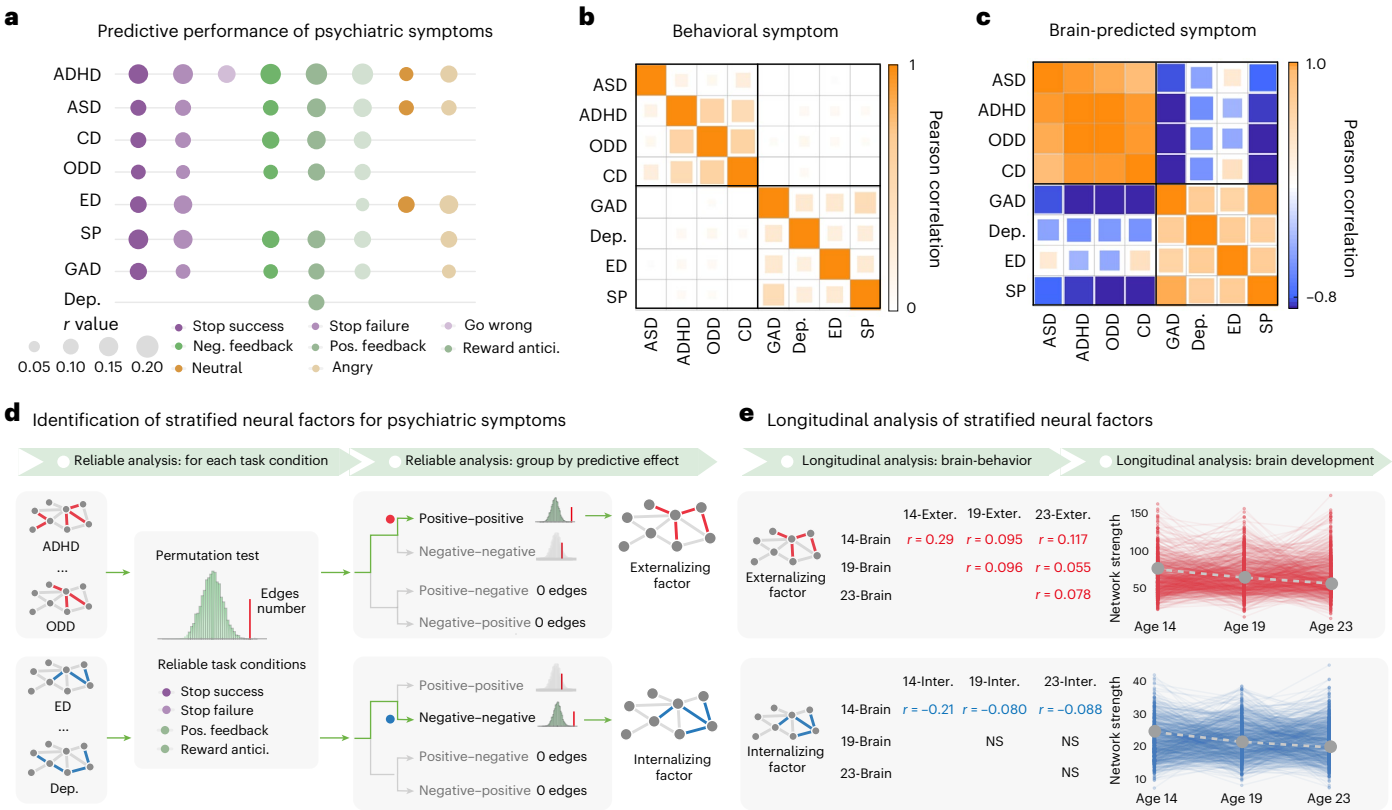

Fig. 1 | Identification of the stratified neural factors. a, The predictive performance of behavioral symptoms related to psychiatric symptoms with the task-based connectivity model. Task-based connectivity was estimated from the EFT (angry and neutral conditions), the MID task (reward anticipation, positive reward feedback and negative reward feedback conditions) and the SST (go-wrong, stop-success and stop-failure conditions). **b**, The correlation matrix of the behavioral symptoms. The externalizing and internalizing symptoms showed high intra-correlations within their respective psychiatric domain, but low correlations between each other. Externalizing symptoms consisted of ASD, ADHD, CD and ODD. Internalizing symptoms comprised GAD, Dep., ED and SP. **c**, The correlation matrix of the brain-predicted symptoms. **d**, With a two-step reliable analysis, we identified two stratified neural factors for externalizing and internalizing symptoms, respectively. We first identified task conditions with reliable stratified cross-disorder edges, which are defined as predictive edges that only predict externalizing but not internalizing symptoms and vice versa. We found that only conditions from the SST and MID task had significantly more stratified cross-disorder edges than a random observation. Then, we further identified which type of cross-disorder edges reliably predict externalizing or internalizing symptoms, which were termed the stratified factors. We discovered that the externalizing neural factor consisted of positive–positive cross-disorder edges (positively predicted at least two externalizing symptoms), while the internalizing neural factor comprised negative–negative cross-disorder edges (negatively predicted at least two internalizing symptoms). **e**, We checked the longitudinal predictive effects and developmental trajectories of the stratified factors across ages 14, 19 and 23. Abbreviations: CD, conduct disorder; ODD, oppositional defiant disorder; GAD, general anxiety disorder; Dep., depression; ED, eating disorder; SP, specific phobia; Neg. feedback, negative feedback; Pos. feedback, positive feedback; Reward antici., reward anticipation; NS, not significant; 14-brain, brain at age 14; 19-brain, brain at age 19; 23-brain, brain at age 23; 14-exter., externalizing symptoms at age 14; 19-exter., externalizing symptoms at age 19; 23-exter., externalizing symptoms at age 23; 14-inter., internalizing symptoms at age 14; 19-inter., internalizing symptoms at age 19; 23-inter., internalizing symptoms at age 23.

We next examined the longitudinal changes of the two stratified neural factors across ages 14, 19 and 23 (Fig. 1e). While both the externalizing and internalizing neural factors maintained consistently high FC strengths throughout ages 14, 19 and 23 (all $t > 100$, Cohen's $d > 3.1$, $P < 0.001$; note: the FC strength refers to the sum of FC in the identified networks), steady decreases in FC strength from age 14 to age 23 were also observed for both neural factors (externalizing slope $\beta_{mean} = -9.44$, 95% CI = [−10.49, −8.39], $t = -17.64$, Cohen's $d = -0.68$, $P = 1.95 \times 10^{-57}$; internalizing slope $\beta_{mean} = -2.33$, 95% CI = [−2.57, −2.09], $t = -18.89$, Cohen's $d = -0.73$, $P = 4.83 \times 10^{-64}$). During this critical developmental period, the normative decrease in connectivity strength could be explained by the neural pruning for a more efficient brain information process[26]. Lastly, we investigated the correlations between psychiatric symptoms at age 14 and the rate of decline in the stratified neural factors from age 14 to 23. We observed that individuals with higher baseline externalizing symptoms may have undergone an under-pruning process of the externalizing neural factor from adolescence to early adulthood ($N = 575$, $r = -0.20$, 95% CI = [−0.28, −0.12], $t = -4.92$, $P = 1.12 \times 10^{-6}$); conversely, individuals with higher baseline internalizing symptoms experienced an over-pruning process of the internalizing neural factor from adolescence to early adulthood ($N = 575$, $r = 0.12$, 95% CI = [0.04, 0.20], $t = 2.96$, $P = 0.003$). These results indicated that while both the externalizing and internalizing behavioral domains showed strong within-domain intra-correlations for both observed and neural predicted symptoms, each behavioral domain may be represented by a distinct cross-disorder neural substrate.

Neuroanatomical characterization of stratified neural factors

We characterized the above two stratified neural factors at multiple neuroanatomical levels. In terms of the regional network degree, the externalizing neural factor was mainly located in brain regions such as the middle cingulate cortex (MCC), precentral gyrus (PreCG), precuneus (PreCun), supramarginal gyrus (SMG) and putamen (Fig. 2a and Supplementary Table 6a), which were commonly implicated in the habitual control process[27]. By contrast, the internalizing neural factor

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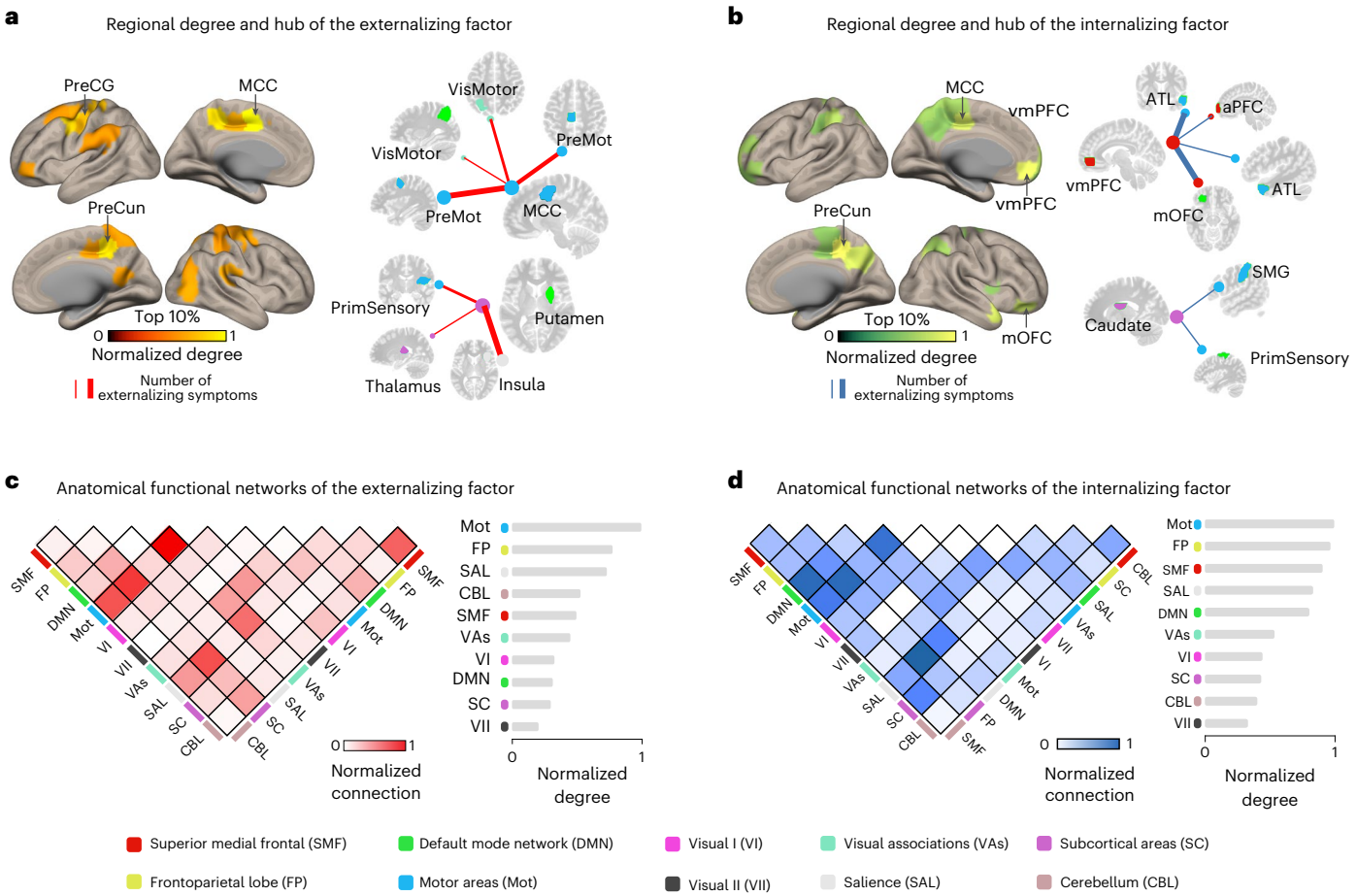

Fig. 2 | Multilevel neuroanatomical characterization of the two stratified neural factors. a,**b**, The top 10% nodes and hub node connections (with high regional connections) in the externalizing (**a**) and internalizing (**b**) factors. The color bar indicates the normalized node degree (that is, the number of connections with other nodes). **c**,**d**, The functional connections of the externalizing (**c**) and internalizing (**d**) factors shared similar large-scale network configurations that both were mainly localized between the motor, frontoparietal and salience networks. The color bar indicates the strength of normalized inter- or intra-network connections, where the number of connections between or within networks was divided by the largest connection number observed. Abbreviations: PreMot, premotor cortex; ATL, anterior temporal lobe; aPFC, anterior prefrontal cortex; VisMotor, visual motor; PrimSensory, primary sensory cortex.

was primarily enriched in regions such as the PreCun, ventromedial prefrontal cortex (vmPFC), medial orbitofrontal cortex (mOFC) and caudate (Fig. 2b and Supplementary Table 6b), all known to play crucial roles in goal-directed processing[28].

Next, while the two stratified neural factors did not share overlapping edges, they did share similar network configurations at a higher neuroanatomical level. For instance, the externalizing and internalizing neural factors exhibited similar network-level configurations, primarily in the motor, frontoparietal and salience networks (Fig. 2c,d and Supplementary Table 7). Notably, the salience network plays a pivotal role in attending to motivational stimuli and recruiting appropriate functional brain-behavior networks to modulate behavior[29]. Therefore, the hyperconnectivity of the externalizing neural factor (for example, in high-risk individuals) might be associated with excessive perception of external stimuli and a lack of inhibitory control over automatic responses[30,31]. Conversely, the hypoconnectivity of the internalizing neural factor might be related to limited salience processing, resulting in difficulties in engaging goal-directed behaviors in individuals with internalizing disorders[32].

Functional and genetic bases of stratified neural factors

We then investigated the correlations between task performance measures with the two stratified neural factors. Both the externalizing and internalizing neural factors showed significant negative correlations with accuracies in the MID task (externalizing, $N = 1{,}620$, $r = -0.14$, 95% CI = [−0.19, −0.09], $t = -5.73$, $P < 0.001$; internalizing, $N = 1{,}620$, $r = -0.08$, 95% CI = [−0.13, −0.03], $t = -3.22$, $P = 0.001$) and the go-trials in the SST (externalizing, $N = 1{,}567$, $r = -0.26$, 95% CI = [−0.31, −0.21], $t = -10.62$, $P < 0.001$; internalizing, $N = 1{,}567$, $r = -0.20$, 95% CI = [−0.25, −0.15], $t = -8.01$, $P < 0.001$), but no significant correlations with the reaction time in the MID task (externalizing, $N = 1{,}620$, $r = -0.05$, 95% CI = [−0.10, 0.001], $t = -1.97$, $P = 0.05$; internalizing, $N = 1{,}620$, $r = -0.02$, 95% CI = [−0.07, 0.03], $t = -0.84$, $P = 0.40$) nor stop-signal delay in the SST (externalizing, $N = 1{,}567$, $r = -0.04$, 95% CI = [−0.09, 0.01], $t = -1.51$, $P = 0.13$; internalizing, $N = 1{,}567$, $r = -0.04$, 95% CI = [−0.09, 0.01], $t = -1.77$, $P = 0.08$). These results were similar to the general neural factor (that is, the NP factor) findings in our previous study[7].

Next, we examined the functional specificity of the two stratified neural factors across a wide range of cognitive-behavioral phenotypes. Here we applied the Benjamini–Hochberg procedure to control the false discovery rate (FDR). The externalizing neural factor exhibited specific correlations with impulsive and substance use behaviors (Fig. 3a and Supplementary Table 8a), where impulsivity is a characteristic feature of externalizing disorders and a known risk factor for future substance abuse[33]. By contrast, the internalizing neural factor was primarily correlated with

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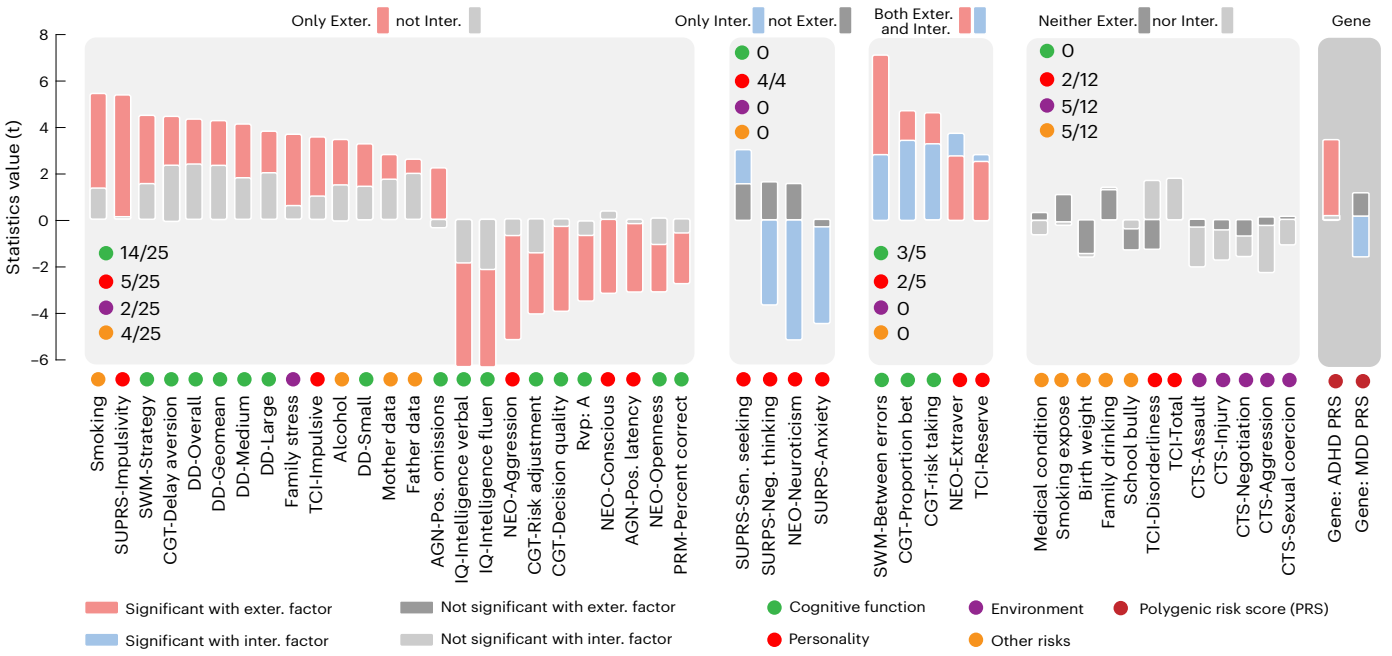

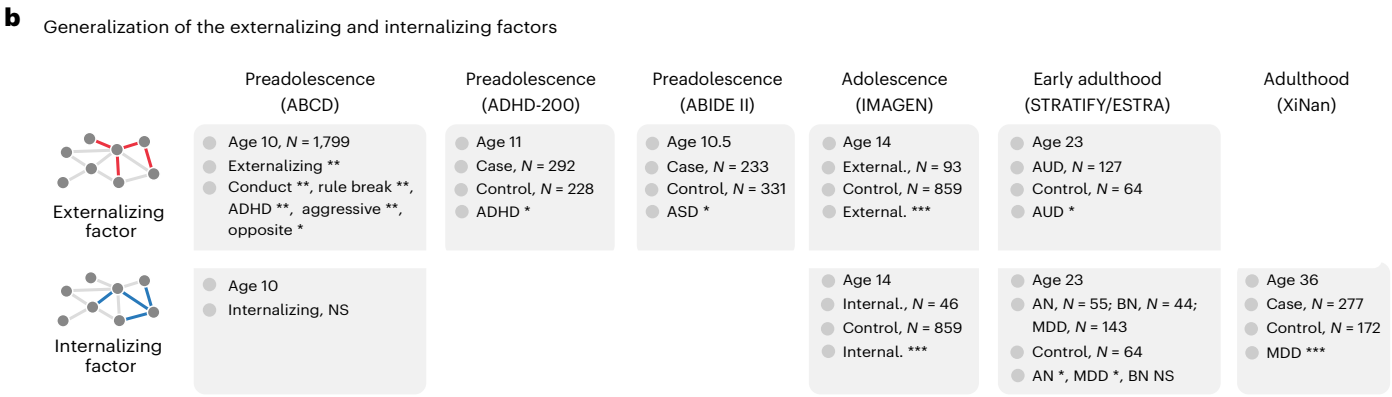

Fig. 3 | Functional specificity and generalization of the stratified neural factors. a, The externalizing factor was specifically associated with most cognitive functions (14 of 25). The internalizing factor was specifically correlated with personality traits (4/4), especially neuroticism and anxiety. Two executive function measurements (between errors in SWM and proportion bet in Cambridge Gambling Task (CGT)) and two personality traits (extroversion of NEO and reserve of TCI) showed distinct correlations with externalizing and internalizing symptoms. The PRS of ADHD and MDD showed a specific correlation with externalizing and internalizing factors, respectively. **b**, Generalization of the NP factor across multiple developmental periods from preadolescence to adulthood in both population and clinical case–control datasets (ABCD, $N = 1{,}799$; ADHD-200, $N = 520$; ABIDE II, $N = 564$; IMAGEN, $N = 998$; STRATIFY and ESTRA, $N = 433$; and XiNan, $N = 449$). The significance level (that is, the gray color) was given as an FDR of 0.05. As these were confirmatory analyses with expected effect directions, one-tailed tests were applied (* < 0.05, ** < 0.01, *** < 0.001). Abbreviations: fluen, fluency; Sen., sensation; Extraver, extraversion; Exter., externalizing; Inter., internalizing; AGN, affective go-no go; BMI, body mass index; DD, delay discounting task, which measured 'waiting' impulsivity[64]; NEO, NEO Personality Inventory; RVP: A, target sensitivity from rapid visual information processing task; PRM, pattern recognition memory task; SURPS, Substance Use Risk Personality Scale; SWM, spatial working memory task; TCI, Temperament and Character Inventory—Revised; AN, anorexia nervosa; BN, bulimia nervosa; AUD, alcohol use disorder.

maladaptive traits, such as neuroticism and negative thinking (Fig. 3a and Supplementary Table 8b), where neuroticism plays a pivotal role in longitudinally predicting various internalizing disorders, such as anxiety and depression[34].

Lastly, we investigated whether the two stratified neural factors had different genetic substrates by examining their correlations with the polygenic risk scores (PRSs) of attention-deficit/hyperactivity disorder (ADHD) and major depressive disorder (MDD) as the representations of externalizing and internalizing disorders, respectively. We observed a significant correlation of the externalizing neural factor with an increased PRS of ADHD ($N = 1{,}594$, $r = 0.082$, 90% CI = [0.03, ∞), $t = 3.27$, $P_{\text{one-tailed}} < 0.001$), but not with the PRS of MDD ($N = 1{,}594$, $r = 0.024$, 90% CI = [−0.03, 0.08], $t = 0.96$, $P = 0.33$) (we used one-tailed tests when examining correlations between neural factors and their hypothesized disorders, and two-tailed tests for all other correlations where no directional hypotheses existed). Conversely, a lower internalizing neural factor was only correlated with the PRS of MDD ($N = 1{,}594$, $r = -0.04$, 90% CI = (-∞, −0.00], $t = -1.74$, $P_{\text{one-tailed}} = 0.041$), but not with that of ADHD ($N = 1{,}594$, $r = 0.008$, 90% CI = [−0.04, 0.06], $t = 0.32$, $P = 0.74$). The above results hence suggested that the externalizing and internalizing neural factors have distinct behavioral and genetic implications for their corresponding psychiatric comorbidity.

Generalization of stratified neural factors

We evaluated the generalization performance of the two stratified neural factors in multiple population and clinical datasets.

First, with the MID task and SST in the Adolescent Brain Cognitive Development cohort (ABCD) dataset[35], we found that the externalizing neural factor was significantly correlated with a wide range of externalizing symptoms at age 10, including externalizing (N = 1,799, r = 0.059, 90% CI = [0.01, ∞), t = 2.51, $P_{\text{one-tailed}}$ = 0.006), rule break (N = 1,799, r = 0.070, 90% CI = [0.02, ∞), t = 2.97, $P_{\text{one-tailed}}$ = 0.002), conduct (N = 1,799, r = 0.063, 90% CI = [0.02, ∞), t = 2.69, $P_{\text{one-tailed}}$ = 0.006), aggressive (N = 1,799, r = 0.057, 90% CI = [0.01, ∞), t = 2.41, $P_{\text{one-tailed}}$ = 0.008), oppositional defiant (N = 1,799, r = 0.054, 90% CI = [0.01, ∞), t = 2.30, $P_{\text{one-tailed}}$ = 0.011) and attention symptoms (N = 1,799, r = 0.050, 90% CI = [0.01, ∞), t = 2.10, $P_{\text{one-tailed}}$ = 0.018) (one-tailed tests were used here as we were validating previously established directional relationships between stratified factors and behaviors). In addition, the externalizing neural factor estimated at age 10 could also predict the summary score of all externalizing symptoms at age 11 (N = 1,042, r = 0.052, 90% CI = [0.00, ∞), t = 1.67, $P_{\text{one-tailed}}$ = 0.047), as well as the subscores (N = 1,042, attention, r = 0.078, 90% CI = [0.02, ∞), t = 2.49, $P_{\text{one-tailed}}$ = 0.007; oppositional defiant, r = 0.062, 90% CI = [0.00, ∞), t = 2.03, $P_{\text{one-tailed}}$ = 0.021; rule break, r = 0.062, 90% CI = [0.01, ∞), t = 2.00, $P_{\text{one-tailed}}$ = 0.022). By contrast, the internalizing neural factor showed no significant correlation with the internalizing-related symptom at age 10 or 11.

We also compared high-severity individuals (marked as severe or high risk for at least one externalizing or internalizing disorder) with healthy controls for the two stratified neural factors in the IMAGEN and ABCD datasets (owing to the unbalanced design, we report effective sample size and Cohen's d with 95% CIs; Methods). For the externalizing neural factor, we found that externalizing participants had significantly higher factor scores than control groups in both IMAGEN (externalizing participants N = 93, the effective sample size $N_{\text{effective}}$ = 336, t = 7.10, Cohen's d = 0.77, 90% CI = [0.73, 0.82], P < 0.001) and ABCD datasets (externalizing participants N = 206, the effective sample size $N_{\text{effective}}$ = 728, t = 2.63, Cohen's d = 0.20, 90% CI = [0.17, 0.22], P = 0.009). However, the comparison of the internalizing neural factor between diagnosed patients and healthy controls was only significant in IMAGEN (internalizing participants, N = 46, the effective sample size $N_{\text{effective}}$ = 174, t = −3.42, Cohen's d = −0.52, 90% CI = [−0.55, −0.48], P < 0.001), but not in ABCD dataset (internalizing participants N = 32, the effective sample size $N_{\text{effective}}$ = 126, t = 1.85, Cohen's d = 0.33, 90% CI = [0.30, 0.36], P = 0.067).

Next, we investigated whether the two stratified neural factors had clinical relevance in the case–control STRATIFY and ESTRA cohort (age = 23) with the SST[36]. We found that the externalizing and internalizing neural factors were differentially associated with psychiatric disorders. To elaborate, the externalizing neural factor of patients with alcohol use disorder (N = 127) was significantly higher than in the healthy controls (N = 64) (t = 1.82, Cohen's d = 0.28, 90% CI = [0.03, ∞), $P_{\text{one-tailed}}$ = 0.035), but no significant group differences were found for this neural factor between healthy controls (N = 64) and patients with internalizing disorders (anorexia nervosa, N = 55, t = −0.54, Cohen's d = 0.10, 95% CI = [−0.26, 0.46], P = 0.059; bulimia nervosa, N = 44, t = 1.47, Cohen's d = 0.29, 95% CI = [−0.11, 0.69], P = 0.15; major depression, N = 143, t = 1.44, Cohen's d = 0.22, 95% CI = [−0.08, 0.52], P = 0.15). However, the internalizing neural factor was significantly lower in patients with internalizing disorders than in healthy controls (N = 64) (internalizing patients, N = 242, t = −2.31, Cohen's d = 0.32, 90% CI = (−∞, −0.06], $P_{\text{one-tailed}}$ = 0.011; anorexia nervosa, N = 55, t = −3.04, Cohen's d = 0.56, 90% CI = (−∞, −0.06], $P_{\text{one-tailed}}$ = 0.002; bulimia nervosa, N = 44, t = −0.83, Cohen's d = 0.16, 90% CI = [−0.56, 0.24], $P_{\text{one-tailed}}$ = 0.20; major depression, N = 143, t = −2.04, Cohen's d = 0.31, 90% CI = (−∞, −0.02], $P_{\text{one-tailed}}$ = 0.021), but no significant group difference was found for the alcohol use disorder (N = 127, t = −0.92, Cohen's d = 0.14, 95% CI = [−0.44, 0.16], P = 0.36).

Finally, we found that the externalizing factor generated using resting-state functional magnetic resonance imaging (with the same set of FC as defined in the IMAGEN cohort) was significantly higher in patients with autism spectrum disorder (ASD) (N = 233) than in healthy controls (N = 331) (ABIDE II, mean age = 10.5, t = 1.90, Cohen's d = 0.08, 90% CI = [−0.03, ∞), $P_{\text{one-tailed}}$ = 0.029). A significant difference was also observed in the group comparison between patients with ADHD (N = 292) and healthy controls (N = 228) (ADHD-200, mean age = 11, t = 2.06, Cohen's d = 0.18, 90% CI = [0.067, ∞), $P_{\text{one-tailed}}$ = 0.020). Furthermore, the internalizing factor generated using resting-state functional magnetic resonance imaging (with the same set of FC as defined in the IMAGEN cohort) of depressive patients (N = 277) was significantly lower than the control group (N = 172) (XiNan dataset, mean age = 36.1, t = −3.11, Cohen's d = −0.30, 90% CI = (−∞, −0.18], $P_{\text{one-tailed}}$ < 0.001). These results further supported the distinct contribution of externalizing and internalizing neural factors to externalizing and internalizing comorbidity, respectively.

Neural specificities of the three cross-disorder networks

Our previous study identified a general neural factor (NP factor) across the externalizing and internalizing symptoms. Here we would like to closely examine the specific configurations of the three cross-disorder neural factors (one general and two stratified neural factors) based on the specificity score, that is, the contribution of a factor after controlling for the other two factors (Fig. 4a, with further details available in Methods).

We first estimated the specificity score of each brain region for the three cross-disorder neural factors, respectively (Fig. 4b, total 268 regions). We found that 79 regions exhibited predominant correlations (that is, with the highest specificity score) with the general NP factor, with the most prominent regions including the ventral precuneus, middle occipital cortex and inferior frontal cortex (Supplementary Table 9a). In addition, 97 regions were associated predominantly with the externalizing neural factor, most notably the primary sensorimotor cortex areas such as the precentral and middle cingulate cortex (Supplementary Table 9b). Finally, 92 regions showed predominant correlations with the internalizing neural factor, with notable regions including the medial prefrontal cortex and orbitofrontal cortex (Supplementary Table 9c). The specificity scores of the three cross-disorder neural factors were significantly different ($F_{(2,265)}$ = 15.80, partial η^2 = 0.11, 95% CI = [0.05, 0.16], P < 0.001), with the general NP factor demonstrating significantly higher scores compared with either the externalizing or internalizing counterparts (NP versus externalizing, $t_{(174)}$ = 4.70, Cohen's d = 0.71, 95% CI = [0.41, 1.01], P < 0.001; NP versus internalizing, $t_{(169)}$ = 3.85, Cohen's d = 0.59, 95% CI = [0.29, 0.89], P < 0.001).

As previous findings have suggested that heterogeneous regions of the same psychiatric disorder might be linked in a common brain network[16], we next investigated whether the three cross-disorder factors may also share common network configurations (Fig. 4b, 55 networks in total). We found that 20 networks were predominantly associated with the general neural factor, primarily consisting of connections with the superior medial frontal (SMF) network (Supplementary Table 10a). In addition, 18 networks were predominantly associated with the externalizing neural factor, mainly encompassing connections with the motor areas networks (Mot) (Supplementary Table 10b). Moreover, 17 networks were predominantly associated with the internalizing neural factor, primarily connected to the default mode network (DMN) (Supplementary Table 10c). However, at the network level, we observed indifferentiable specificity scores among the three cross-disorder networks ($F_{(254)}$ = 0.18, partial η^2 = 0.007, 95% CI = [0.000, 0.024], P = 0.83). In summary, our findings indicated that the general and stratified factors exhibited increased neural specificity along the neuroanatomical coarse–fine gradient from regional to network level.

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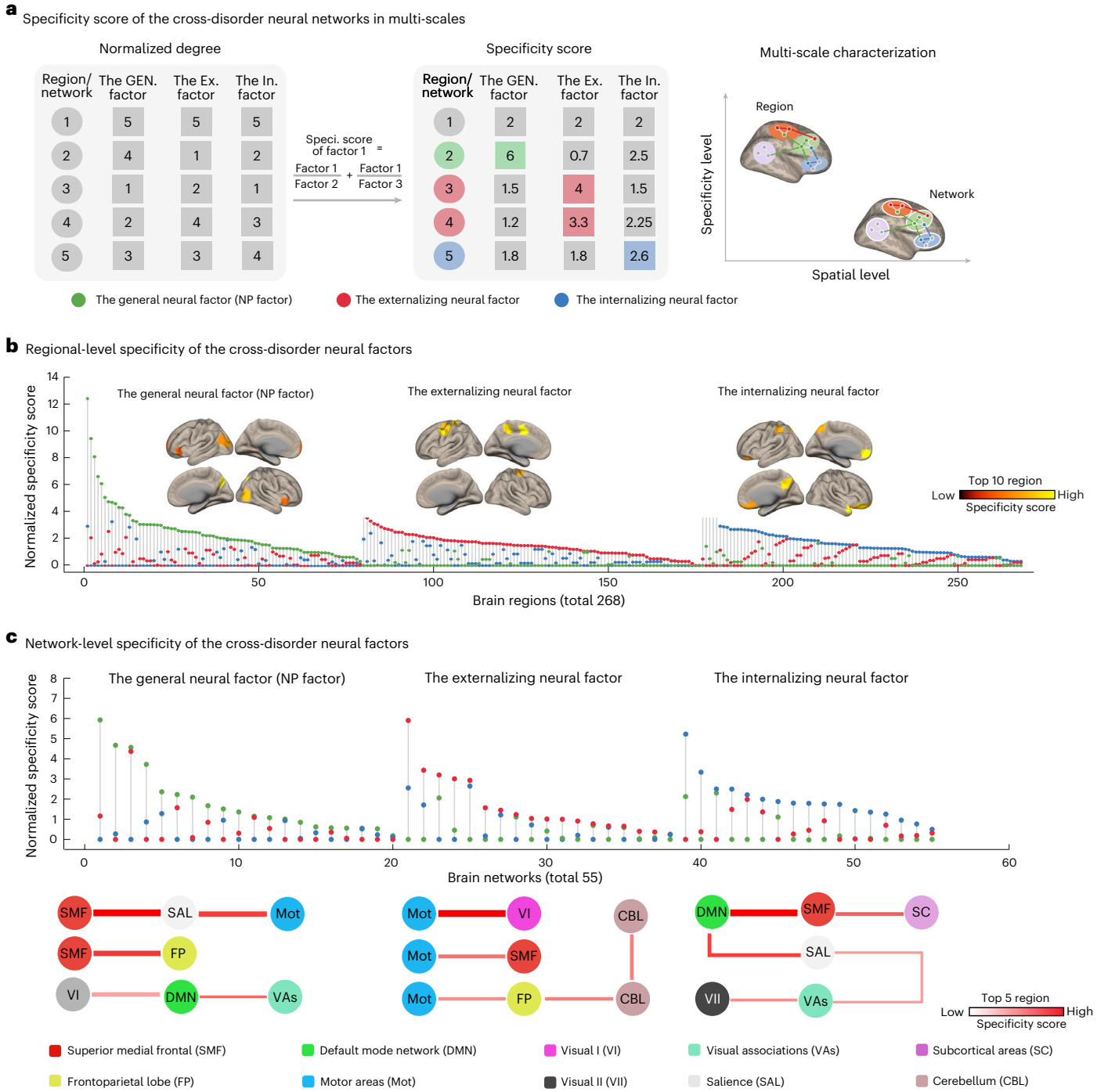

Fig. 4 | Characterizing the specificity of the cross-disorder neural factors at the levels of brain regions and extended networks. a, Specificity score comparison of the three cross-disorder networks using regional-level node degree as an example. We first normalized the node degree to facilitate subsequent cross-factor comparisons. Then, we used a weighted method for calculating the regional specificity score with the following formula: specificity score of factor 1 = factor 1/factor 2 + factor 1/factor 3. By weighting the contribution of the brain region in the other two cross-disorder factors (factor 2 and factor 3), the estimated specificity score provides a more robust measure of the unique contribution of each brain region within this cross-disorder factor (factor 1). Building upon previous findings[16], we hypothesize that as the brain scale increases from region to network, the specificity between cross-disorder factors will decrease. **b**, Specificity scores were first computed for each of the 268 brain regions across the three cross-disorder factors (general/NP, externalizing, internalizing). For each region, the factor with the highest specificity score was considered to represent its dominant cross-disorder specificity. Regions are ranked by specificity score, and the top regions for each factor are visualized on the cortical surface. **c**, The same procedure was then applied at the network level (55 brain networks). Specificity scores were estimated for each network across the three cross-disorder factors. For each network, the highest specificity score was used to indicate its dominant factor-level specificity. Networks are ranked accordingly, and the top networks for each factor are highlighted. Abbreviations: GEN., general; Ex.,externalizing; In., internalizing; Speci., specificity.

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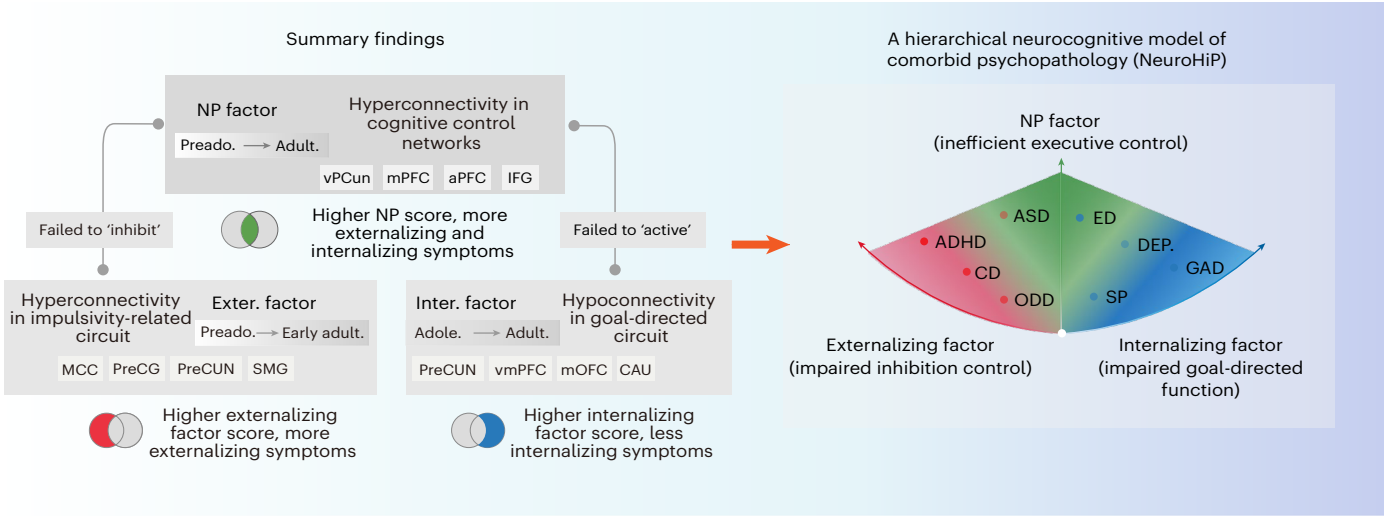

Fig. 5 | A hierarchical neurocognitive model of comorbid psychopathology (NeuroHiP). Abbreviations: preado., preadolescence; adole., adolescence; adult., adulthood; vPCun, ventral precuneus; mPFC, medial prefrontal cortex; IFG, inferior frontal gyrus; CAU, caudate; Exter., externalizing; Inter., internalizing.

Discussion

In the present study, based on a large longitudinal cohort from adolescence to early young adulthood, we identified two stratified neural factors, respectively, underlying the externalizing and internalizing symptoms, each characterized by unique neurobiological configurations, genetic underpinnings and clinical relevance. These two stratified neural factors, along with the previously identified general NP factor, collectively constitute a hierarchical neurocognitive model that characterizes neural mechanisms underlying psychiatric comorbidity (NeuroHiP), with implications for early prevention and therapeutics in psychiatry (Fig. 5).

The externalizing neural factor is characterized by hyperconnectivity of primary sensory and motor regions, which has specific correlations with higher impulsivity and inhibitory deficits compared with other behavioral phenotypes. This neural factor may serve as a neural mechanism underlying poor impulse control, a core dimension of externalizing psychopathology[37,38]. In addition, the externalizing neural factor was longitudinally predictive of externalizing symptoms across developmental stages, from preadolescence to adulthood, elucidating neural mechanisms behind the enduring impact of impulsivity on the externalizing spectrum[39]. By contrast, the internalizing factor is characterized by hypoconnectivity of the vmPFC and mOFC, and both are crucial components of the goal-directed circuitry[40,41]. Notably, the internalizing neural factor was specifically linked to neuroticism/negative affect traits, which predisposed individuals to experience negative emotional states and life events and was proposed as a common vulnerability factor for internalizing psychopathology[42]. Hypoconnectivity of the internalizing neural factor might lead to challenges in responding adaptively to negative events, which perpetuate negative emotional states and result in the development of mood disorders[43–45].

Interestingly, the PreCun emerged as a hub region in both externalizing and internalizing neural factors, but with opposite connectivity patterns—hyperconnectivity in the externalizing network and hypoconnectivity in the internalizing network. The PreCun is a critical node of the DMN involved in self-referential processing, social cognition and attentional control[46]. In the context of externalizing disorders, the hyperconnectivity of the PreCun may reflect excessive self-focus and heightened salience of immediate environmental stimuli, potentially contributing to impulsive responses to external triggers without adequate self-reflection or consideration of consequences[47]. This pattern aligns with the impaired inhibitory control characteristic of externalizing disorders. Conversely, in internalizing disorders, the hypoconnectivity of the PreCun may indicate deficits in adaptive self-referential processing and difficulty in disengaging from negative self-focus, which are central to rumination and worry[48]. This reduced connectivity might impair the integration of self-relevant information with goal-directed behavior, contributing to the avoidance behavior and difficulty in overcoming negative emotional states typical of internalizing symptoms. The bidirectional alterations in PreCun connectivity across these two transdiagnostic domains suggest that this region may serve as a flexible neural substrate that can be differentially recruited depending on the specific psychopathological context, potentially representing a shared vulnerability factor that manifests differently based on other neurobiological and environmental influences[49,50].

Notably, we previously identified a general cross-disorder neural factor (NP factor), characterized by hyperconnectivity of executive control networks, which inefficiently regulate/support other neural networks[51]. Our studies help to clarify how the three cross-disorder networks interact in the manifestation of comorbid neuropsychopathology (summarized as a hierarchical neurocognitive model in Fig. 5): externalizing comorbid symptoms may result from the combination of hyperconnectivity in the impulsivity circuit and the executive control network's failure to inhibit impulsive behaviors, whereas internalizing comorbid symptoms may stem from the combination of the hypoconnectivity of the goal-directed circuit and the executive control network's failure to initiate adaptive behavior.

Furthermore, our findings indicated that the general and stratified factors exhibited increased neural specificity along the neuroanatomical coarse–fine gradient from the network level to the region level. This observation aligns with recent transdiagnostic findings by Segal et al.[16], who used normative modeling and network mapping approaches to show that phenotypic differences between cases assigned the same diagnosis may arise from heterogeneous localization of specific regional deviations, whereas phenotypic similarities may be attributable to the dysfunction of common functional circuits and networks. This cross-disorder phenomenon likely relates to the functional degeneracy in the brain[52], where multiple structurally distinct neural systems can support similar cognitive functions or behavioral outputs. In our study, rather than assuming isolated basic units or one-to-one mappings between brain regions and disorders, we characterized each psychiatric disorder's connectome across different neuroanatomical scales. The functional degeneracy framework explains how psychiatric comorbidity can exist across different scales of brain organization,

with broader network-level dysfunction potentially accounting for transdiagnostic symptoms, while more specific regional patterns may contribute to distinct clinical presentations. Future research could leverage multilevel network approaches and advanced brain-behavior mapping techniques[53,54] to further characterize pathophysiological mechanisms of psychiatric comorbidity and develop more targeted and effective treatments.

Nevertheless, several limitations necessitate further investigation in future research endeavors. First, this study mainly focused on delineating the cross-disorder neural foundations associated with internalizing and externalizing symptoms from preadolescence to adulthood, overlooking the dimension of psychotic experiences, which typically manifest in late developmental stages[55]. Future research could investigate whether early internalizing and externalizing neural factors (the shared and stratified ones) are risk factors for subsequent thought disorders, which, such as bipolar disorder, also demonstrate impaired behavior that falls into externalizing and internalizing domains. Second, we failed to identify a stable cross-disorder neural basis in the EFT, in which the standard emotional face was used to induce basic emotion. Future investigations could also capitalize on more ecologically naturalistic paradigms, such as movie-watching, to illuminate the shared emotion-related neural substrates across psychiatric disorders[56]. Third, we observed a differential detectability of the internalizing neural factor across developmental stages. While this factor was robustly identified in the IMAGEN cohort (age 14), it was not significantly detected in the ABCD cohort (age 10). This discrepancy likely reflects the developmental trajectory of internalizing disorders, which typically emerge later in adolescence compared with externalizing disorders[57]. The neural substrates of internalizing symptoms may not be fully established in preadolescence, becoming more pronounced during mid-to-late adolescence as the prevalence of these symptoms increases. This developmental difference underscores the importance of considering age-specific effects when investigating transdiagnostic neural markers and suggests that certain neurobiological risk factors may have age-dependent manifestations. Future longitudinal research spanning from childhood through adolescence is needed to better characterize the developmental emergence of distinct neural factors associated with psychiatric symptoms. Fourth, the Research Domain Criteria framework suggests that psychiatric disorders lie along a continuum of neurobehavioral dimensions. Our findings partially support this hypothesis in that the stratified factors identified at the population level were not validated in high-risk groups (IMAGEN and ABCD), while they were validated in clinical groups (STRATIFY/ESTRA, ADHD, ABIDE II and XiNan). This discrepancy challenges the straightforward application of dimensional approaches across various points along the health-to-illness continuum. Future studies should track high-risk populations longitudinally to better capture neural signature emergence during the critical transition from at-risk status to clinical manifestation. Fifth, this study focused on identifying comorbidity networks at age 14 (wherein functional connections are linked to at least two psychiatric disorders at the same time). Nonetheless, previous longitudinal clinical studies had reported prevalent temporal comorbidity between psychiatric disorders[58], for example, individuals initially diagnosed with externalizing disorders at baseline subsequently transition to internalizing disorders during follow-up assessments. This diagnostic shift over time implies the presence of a transition neural network, of which connections are initially associated with externalizing symptoms that later become associated with internalizing symptoms. Integrating persistent and transition comorbidity networks in future research will offer a more comprehensive understanding of the evolution and interaction mechanisms underlying psychiatric comorbidity. Lastly, recent research has identified a nonlinear relationship between mental health symptoms and general cognition in adolescents[59]. Future studies were needed to investigate whether and how nonlinear relationships between FC and psychopathology might provide additional insights. Although we controlled for basic demographic variables in our models, residual confounding from unmeasured variables such as socioeconomic status, medication exposure and environmental factors may still influence the findings. Future research using propensity score matching or instrumental variable approaches could provide more robust insights into the relationships between neural factors and psychiatric symptoms.

In conclusion, we identified two cross-disorder neural factors for internalizing and externalizing symptoms that persist longitudinally from adolescence to early adulthood. The two stratified neural factors demonstrated neuroanatomical specificity and are further delineated by cognitive, behavioral and genetic risk factors. Combining with the previously identified general NP factor, we present a hierarchical neurocognitive model for psychiatric comorbidity (NeuroHiP). These findings might help provide a unified neurobehavioral-based psychiatric nosology that could improve diagnostic precision and treatment efficacy[60].

Methods

Study overview

In the present study, we aimed to identify a stratified cross-disorder neural factor for externalizing and internalizing symptoms with multivariate associations between psychiatric symptoms and task-based FC, which were estimated at age 14. These multivariate associations have also been used in the identification of a general neural factor in the previous study[7]. Following a pre-established analytic plan, we first preprocessed both behavioral and connectivity data to control for potential confounding variables, including age, sex, handedness, acquisition site and framewise displacement. In brief, we then used a mutually exclusive approach to identify specific externalizing and internalizing edges. For example, externalizing edges, composed of FC, were predictive only of externalizing symptoms and not internalizing symptoms, and vice versa for internalizing edges. Only those stratified edges surviving permutation-based reliability analysis were identified as the externalizing or internalizing neural factor. Following identification of these neural factors, we examined their longitudinal persistence of the externalizing and internalizing neural factors across age 19 and age 23. Lastly, we conducted multilevel specificity characterizations of the externalizing and internalizing neural factors, such as anatomical, cognitive-behavioral, genetic and generalization analyses. Throughout these analyses, appropriate multiple comparison corrections were applied using the Benjamini–Hochberg procedure to control the FDR at 0.05. Detailed information about the psychiatric questionnaire (Development and Well-Being Assessment (DAWBA) and the Strengths and Difficulties Questionnaire (SDQ)) and task design (MID task, SST and EFT) was provided in Supplementary Methods.

Connectome-behavior mapping

We used connectome-based predictive modeling to identify functional brain connections associated with behavioral symptoms and predict these symptoms in novel participants. Before conducting our main analyses, we implemented rigorous procedures to control for potential confounding variables. For all datasets, both connectivity matrices and behavioral measures were residualized with respect to age, sex, handedness, acquisition site and mean framewise displacement to minimize the influence of these confounding factors. Our connectome-based predictive modeling implementation followed a 50-fold cross-validation approach. For each fold, we correlated each edge in the connectivity matrix with behavioral measures in the training dataset. Edges significantly associated with behavior ($P < 0.01$) were selected and their strengths were summed to create a single predictor value for each participant. This value was used in a linear regression model to predict behavior in the testing dataset. This process was repeated 1,000 times, and only edges selected in over 95% of models were retained for further analysis to ensure robustness. The final model

performance was evaluated using Spearman's correlation between predicted and actual behavioral scores.

Externalizing and internalizing factors

The stratified neural factor was constructed to represent specific brain signatures of externalizing or internalizing symptoms. Specifically, we first removed the general cross-disorder edges that were associated with both externalizing and internalizing symptoms simultaneously[7]. Next, we identified two types of stratified cross-disorder edge: (1) the externalizing edges that predict at least two externalizing symptoms and (2) the internalizing edges that predict at least two internalizing symptoms. Then, for each task condition, we investigated whether the number of stratified edges identified was significantly higher than a random observation using a permutation test (see Supplementary Methods for more details). Only the significant task conditions and their stratified edges were kept in the following analyses. Next, to improve the interpretability of results, the stratified edges were split into four different groups according to the predictive effect directions: positive–positive (or negative–negative) edges that have the same predictive effect on externalizing/internalizing symptoms positively (or negatively); positive–negative (or negative–positive) edges that have different predictive directions to externalizing/internalizing symptoms. We found that only the positive–positive externalizing edges (that is, positively associated with externalizing symptoms) and the negative–negative internalizing edges (that is, negatively associated with internalizing symptoms) were significantly higher than a random observation. Therefore, the two groups of stratified edges were termed the externalizing factor (positive–positive externalizing edges) and internalizing factor (negative–negative internalizing edges), respectively, and used in the following analyses.

Longitudinal analysis of stratified neural factors

To examine the temporal stability and developmental trajectories of the externalizing and internalizing neural factors, we conducted comprehensive longitudinal analyses across ages 14, 19 and 23 using the IMAGEN cohort. First, we assessed the predictive validity of each neural factor across time points by computing Pearson correlations between the neural factor at an earlier age (for example, age 14) and corresponding psychiatric symptoms at later ages (19 and 23). Statistical significance was determined using one-tailed *t*-tests, as we hypothesized positive correlations for the externalizing factor and negative correlations for the internalizing factor based on their identified directionality in the initial analyses. Second, we investigated developmental changes in the connectivity strength of both neural factors by calculating the mean FC strength at each age point. Linear mixed-effects models with subject-specific random intercepts were used to quantify the rate of change (slope) in FC strength from age 14 to 23. In addition, we examined correlations between baseline psychiatric symptoms at age 14 and longitudinal changes in the neural factors by correlating symptom severity with individualized slopes of FC strength from age 14 to 23. This allowed us to determine whether individuals with higher baseline symptoms showed different developmental trajectories (potentially reflecting atypical neural pruning processes) compared with those with lower symptom levels. All longitudinal analyses were conducted using individuals with complete neuroimaging data across all three time points ($N = 575$) to ensure consistent within-subject comparisons.

Multilevel neuroanatomical characterization

We characterized the stratified neural factors at multiple neuroanatomical levels to provide comprehensive mechanism insights into their neurobiological substrates. At the regional level, we calculated the node degree (number of predictive edges) for each brain region within each neural factor network. The regional degrees were normalized by dividing by the total number of edges in the respective network to facilitate cross-network comparisons. This allowed identification of hub regions with particularly high edges within each neural factor. At the network level, we mapped the functional connections of each neural factor onto established large-scale brain networks using the Shen 268-node atlas, which assigns each brain region to one of ten major functional networks. For each pair of networks, we calculated the normalized connection strength by dividing the number of between-network connections by the maximum number of possible connections between those networks. This produced a network-to-network connectivity matrix representing the macro-scale organization of each neural factor. To quantify the specificity of brain regions and networks to each cross-disorder neural factor (the general NP factor, externalizing factor and internalizing factor), we developed a specificity score (detailed in below). This approach allowed us to identify brain regions and networks that were uniquely associated with one neural factor while controlling for their involvement in the others, thereby mapping the distinct neuroanatomical fingerprints of the general and stratified neural factors.

Specificity score of cross-disorder neural factors

In delineating the specific underpinnings of each cross-disorder neural factor, we devised a specificity score for the brain measurements, assessing their relative contribution. At the brain region level, we initially normalized the region degree by dividing the total sum of degrees for each cross-disorder factor, respectively, and then adding 1 to prevent potential singularities in subsequent calculations. This normalized region degree ranged from 1 to 2, indicating the relative importance of each brain region to the cross-disorder neural factor. Lastly, for each brain region, the normalized brain degree was divided by that of the other two cross-disorder neural factors, and the sum of these two ratios is then calculated as the specificity score. This score reflects the importance of this brain region to the cross-disorder factor and controls for its influence on the other two cross-disorder factors. The same computational steps were applied at the network level.

Multilevel neurocognitive characterization

To comprehensively characterize the functional and genetic specificity of the externalizing and internalizing neural factors, we conducted a multilevel neurocognitive analysis (cognitive function, environmental risks, personality and genetic risks). First, we examined the correlations between each neural factor and a wide range of cognitive-behavioral phenotypes measured in the IMAGEN cohort at age 14. These phenotypes included multiple cognitive domains (executive functions, working memory, impulsivity and cognitive flexibility), personality traits (neuroticism, extraversion, reward sensitivity and anxiety) and substance use behaviors. For each phenotype, we calculated Pearson correlations with both the externalizing and internalizing neural factors and with FDR correction for multiple comparisons. To determine the specificity of correlations, we conducted comparative analyses for each cognitive-behavioral measure. A measure was considered specifically associated with the externalizing (or internalizing) neural factor if it showed a significant correlation with that factor but not with the other, or if the difference between correlation coefficients was statistically significant (tested using Steiger's *Z*-test for dependent correlations). This approach allowed us to create a comprehensive neurocognitive profile for each neural factor, identifying which behavioral domains were uniquely linked to externalizing versus internalizing neural substrates. For the genetic characterization, we calculated PRSs for ADHD and MDD using summary statistics from the latest available genome-wide association studies. To examine genetic specificity, we tested correlations between each neural factor and both PRSs using Pearson correlations. On the basis of previous literature suggesting specific genetic influences on externalizing and internalizing dimensions, we used one-tailed tests for the hypothesized relationships (ADHD PRS with externalizing factor, MDD PRS with internalizing factor) and two-tailed tests for the cross-domain relationships.

Generalization datasets

To investigate whether the two cross-disorder factors identified with the adolescent population-based IMAGEN dataset could be generalized into other developmental periods and clinical conditions, we utilized multiple large-scale population-based datasets (the Adolescent Brain Cognitive Development cohort[35], ABCD) and clinical case–control datasets (the STRATIFY and ESTRA[36], ADHD-200[61], ABIDE II and XiNan). For each clinical dataset, we reconstructed the externalizing and internalizing neural factors using the same edge configurations identified in the IMAGEN discovery sample and tested their correlations with diagnostic status using *t*-tests comparing patients with matched controls. This cross-dataset validation approach allowed us to assess whether the identified neural factors represented stable biomarkers across development and across different manifestations of externalizing and internalizing psychopathology. The details of these datasets are provided in Supplementary Methods.

Unbalanced group comparison in IMAGEN and ABCD

We conducted group comparisons between high-severity participants and healthy controls using data from the IMAGEN and ABCD datasets. In the IMAGEN dataset, the externalizing group consisted of 93 participants, while the control group included 859 participants; the internalizing group comprised 46 participants, with the same control group of 859. In the ABCD dataset, the externalizing group included 206 participants and the control group 1,596 participants, while the internalizing group had 32 participants against the same control group of 1,596. Given the highly unbalanced design of these case–control comparisons, we calculated the effective sample size ($N_{\text{effective}}$) for each group comparison to estimate the equivalent sample size required for a balanced design while maintaining identical statistical power. The effective sample size was computed using the harmonic mean formula:

$$N_{\text{effective}} = 2 \times \frac{2}{\frac{1}{n_1} + \frac{1}{n_2}}$$

where n_1 represents the sample size of the case group (externalizing or internalizing participants) and n_2 represents the sample size of the control group. This approach accounts for the disparity in group sizes and provides a standardized metric for interpreting statistical power in unbalanced designs[62]. Group differences were assessed using independent samples *t*-tests, with Cohen's *d* calculated as the effect size and one-tailed *P* values reported to test directional hypotheses. To further ensure the robustness of our findings and address potential inflation of results owing to the unbalanced design, we used a random under-sampling approach[63]. Specifically, we randomly selected 80% of control participants while maintaining a matched gender ratio from the full control sample and repeated the comparison 1,000 times. We then reported the mean effect size and 95% CIs for Cohen's *d* across all iterations to demonstrate the stability and reliability of our findings, regardless of which specific subset of controls was selected for comparison.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

IMAGEN data are available from a dedicated database, https://imagen2.cea.fr; STRATIFY data are also available from the IMAGEN database, https://imagen2.cea.fr; ABCD data are available from a dedicated database, https://abcdstudy.org/; HCP data are available from a dedicated database, https://www.humanconnectome.org/; ADHD-200 data are available from a dedicated database, http://fcon_1000.projects.nitrc.org/indi/adhd200. ABIDE II data are available from a dedicated database, http://fcon_1000.projects.nitrc.org/indi/abide/abide_II.html. XiNan and STRATIFY/ESTRA datasets are available from the principal investigator of the study and are subject to local ethics committee requirements. Shen 268 parcellation is available at https://www.nitrc.org/frs/?group_id=51.

Code availability

All data needed to evaluate the conclusions in the paper are present in the paper and/or Supplementary Information. All data analyses were performed using MATLAB (The MathWorks Inc., version R2022a). The code has been uploaded to https://github.com/xiec199/Stratified-factors.

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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 paper reflects the views of the authors and may not reflect the opinions or views of the NIHR Biomedical Research Centre, NIH or ABCD consortium investigators.

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T.J., G.S., T.W.R. and J.F. conceptualized the study. C.X. and T.J. designed the analytic approach. C.X. analyzed the data. C.X. and T.J. wrote the paper. S.X. preprocessed the neuroimaging data. C.S., Y. Zheng, Y.L. and S.X. helped with visualization. T.W.R., G.S., B.J.S. and J.F. revised the first draft. T.B., G.J.B., A.L.B., C.B., S.D., J.F., H.F., A.G., H.G., P.G., A.H., J.-L.M., M.-L.P.M., F.N., L.P., J.H.F., M.N.S., H.W., R.W. and G.S. were the principal investigators of IMAGEN. E.A., G.J.B., M.B., M.J.B., T.B., A.B., C.B., P.C., T.F., H.F., A.G., Y.G., H.G., P.G., A.H., C.I., V.K., H.L., J.-L.M., M.-L.P.M., B.M.v.N., F.N., D.P.O., J.P., L.P., J.H.F., U.S., J.S., M.N.S., A.S., M.S., H.W., R.W., S.D. and G.S. contributed to data acquisition and management for the IMAGEN dataset. N.V., Z.Z., L.R., J.W., Y. Zhang, S.K., G.J.B., A.L.B., R.B., H.K., H.L., F.N., D.P.O., U.S., J.S., R.W., H.W., S.D. and G.S. contributed to data acquisition and management for the STRATIFY dataset. Z.Z., M.B., L.R., A.L.B., H.L., D.P.O., U.S., G.S. and S.D. contributed to data acquisition and management for the ESTRA dataset. C.X., S.X., W.C., G.S., J.F. and T.J. acquired and managed the ZIB dataset. D.W., P.X. and J.Q. acquired and managed the XiNan dataset. All authors critically revised the paper. We thank the additional raters for the Development and Well-Being Assessment Strengths and Difficulties Questionnaire: P.C., King's College London, Institute of Psychiatry, London, UK; M.S., King's College London, Institute of Psychiatry, London, UK; J.P., Department of Social and Health Care, Psychosocial Services Adolescent Outpatient Clinic Kauppakatu 14, Lahti, Finland; V.K., Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Charité University Hospital Berlin, Berlin, Germany; Y.G., Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; T.F., Systems Neuroscience, University Medical Centre Hamburg–Eppendorf, Hamburg, Germany; C.I., Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Centre Göttingen, Göttingen, Germany; and A.B., Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Centre Göttingen, Göttingen, Germany. These individuals received no compensation for their contributions outside of regular wages or salary.

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Software and code

Policy information about availability of computer code

Data collection	Psytool platform was used to collect data for both SDQ and DAWBA assessment
Data analysis	All statistical analyses were conducted in the Matlab. Preprocessing and first level analyses of task-based fMRI data were conducted in SPM8 and CONN.16.h

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XiNan depression data is from Prof. Jiang Qiu

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Reporting on sex and gender	In this study, sex and gender were carefully considered in both the design and analysis phases. Participants were categorized based on self-reported sex (male or female) to ensure appropriate representation in the sample. However, given the prevalence rates of internalizing and externalizing behaviors in adolescents, detailed analysis of sex differences in the neural mechanisms was not conducted. As such, the results presented focus on overall neural mechanisms without delving into sex-specific neural effects. Furthermore, gender identity was not explicitly assessed, so our analyses are limited to biological sex distinctions.
Reporting on race, ethnicity, or other socially relevant groupings	Healthy Caucasian adolescents at age 14 were recruited from middle-class school from multiple sites across Europe
Population characteristics	Healthy Caucasian adolescents at age 14 were recruited from middle-class school across Europe. Over 1700 participants investigated in this study, clinical DAWBA ratings are available.
Recruitment	Healthy Caucasian adolescents at age 14 were recruited from middle-class school from multiple sites across Europe (London, Nottingham, Dublin, Paris, Manhannm, Berlin, Dresden, Humberg).
Ethics oversight	The IMAGEN Study was approved by local ethics research committees at each research site: King's College London, University of Nottingham, Trinity College Dublin, University of Heidelberg, Technische Universität Dresden, Commissariat à l'Energie Atomique et aux Energies Alternatives, and University Medical Center. Informed consent was sought from all participants and a parent/guardian of each participant.

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Life sciences study design

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Sample size	Over 1700 individuals with complete data of fMRI or behaviours were involved in the present study. This sample size is sufficiently to detect an effect size as little as R^2 = 2% with a statistical power over 95% at the significance level 0.0001.
Data exclusions	Individuals with incomplete data across fMRI and behaviours were excluded in the cross-disorder network analysis.
Replication	The resting-state fMRI of the IMAGEN study was used for internal replication/generalisation; data from the ABCD, HCP, ABIDE II, XiNan, STRATIFY/ESTRA and ADHD-200 studies were used for external replication/generalisation
Randomization	As a population study, no randomization was conducted. Nevertheless, covariates (e.g. research sites, handedness and sex) were included wherever suitable to control for potential confounding effects.
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Seed stocks: N/A

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Magnetic resonance imaging

Experimental design

Design type: two even-related tasks: Monetary Incentive Delay Task (MID), Stop Signal Task (SST); one block design task: Emotional Face Task (EFT)

Design specifications: MID: The task consisted of 66 10-second trials. In each trial, participants were presented with one of three cue shapes (cue, 250 ms) denoting whether a target (white square) would subsequently appear on the left or right side of the screen and whether 0, 2 or 10 points could be won in that trial. After a variable delay (4,000-4,500 ms) of fixation on a white crosshair, participants were instructed to respond with left/right button-press as soon as the target appeared. Feedback on whether and how many points were won during the trial was presented for 1,450 ms after the response.

SST:The task was composed of Go trials and Stop trials. During Go trials (83%; 480 trials) participants were presented with arrows pointing either to the left or to the right. During these trials, subjects were instructed to make a button response with their left or right index finger corresponding to the direction of the arrow. In the unpredictable Stop trials (17%; 80 trials), the arrows pointing left or right were followed (on average 300 ms later) by arrows pointing upwards; participants were instructed to inhibit their motor responses during these trials.

EFT: Participants watched 18-second blocks of either a face movie (depicting anger or neutrality) or a control stimulus. Each face movie showed black and white video clips (200-500ms) of male or female faces. Five blocks each of angry and neutral expressions were interleaved with nine blocks of the control stimulus. Each block contained eight trials of 6 face identities (3 female). The same identities were used for the angry and neutral blocks. The control stimuli were black and white concentric circles expanding and contracting at various speeds that roughly matched the contrast and motion characteristics of the face clips.

Behavioral performance measures: For both event related tasks MID and SST, performance tracking systems were implemented to adjust difficulty of the tasks to ensure the overall performance of each participant (i.e. successfully responded on ~66% of trials in the MID and 50% successful rate in inhibition trials in the SST). As a passive viewing task, there is no performance measure for the EFT.

Acquisition

Imaging type(s): BOLD functional signal

Field strength: 3 Tesla

Sequence & imaging parameters: Structural and functional MRI data were acquired at eight IMAGEN assessment sites with 3T MRI scanners of different manufacturers (Siemens, Philips, General Electric, Bruker). The scanning variables were specifically chosen to be compatible with all scanners. The same scanning protocol was used in all sites. In brief, high-resolution T1-weighted 3D structural images were acquired for anatomical localization and co-registration with the functional time-series. Blood-oxygen-level-dependent (BOLD) functional images were acquired with gradient-echo, echo-planar imaging (EPI) sequence. For all fMRI tasks, 300 volumes were acquired for each participant, and each volume consisted of 40 slices

aligned to the anterior commission/posterior commission line (2.4 mm slice thickness, 1 mm gap). The echo-time (TE) was optimized (TE=30 ms, repetition time (TR)=2,200 ms) to provide reliable imaging of subcortical areas.

Area of acquisition: Whole brain scan

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software: Functional MRI data were analysed with SPM8 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm). Spatial preprocessing included: slice time correction to adjust for time differences due to multi-slice imaging acquisition, realignment to the first volume in line, non-linearly warping to the MNI space (based on a custom EPI template (53x63x46 voxels) created out of an average of the mean images of 400 adolescents), resampling at a resolution of 3x3x3 mm3 and smoothing with an isotropic Gaussian kernel of 5 mm full-width at half-maximum.

Normalization: see above

Normalization template: see above

Noise and artifact removal: At the first level of analysis, changes in the BOLD response for each subject were assessed by linear combinations at the individual subject level, for each experimental condition (e.g. reward anticipation high gain of Monetary Incentive Delay (MID) task), each trial was convolved with the hemodynamic response function to form regressors that account for potential noise variance, e.g. head movement, associated with the processing of reward anticipation. Estimated movement parameters were added to the design matrix in the form of 18 additional columns (three translations, three rotations, three quadratic and three cubic translations, and every three translations with a shift of ±1 TR).

Volume censoring: N/A

Statistical modeling & inference

Model type and settings: At the first level of analysis, we estimated the condition-specific functional connectivity with weighted GLM (wGLM) method. We get these condition-specific functional connectivity matrices, including reward positive feedback, reward negative feedback and reward anticipation of monetary incentive delay (MID) task; stop failure, stop success and go wrong of stop-signal task (SST); angry and neutral of emotional face task (EFT). At the second level of analysis, we used the Pearson correlation test to estimate the association between task-based functional connectivity and behavioural measurements.

Effect(s) tested: The T-Test was used to measure the strength of functional connectivity.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☒ Both

Anatomical location(s): A 268-node functional brain atlas was used (doi: 10.1016/j.neuroimage.2013.05.081.)

Statistic type for inference (See Eklund et al. 2016): The connectome-based predictive model was used to estimate the associations of whole-brain functional connectivity with externalising and internalising symptoms.

Correction: Either permutation or Multiple correction was applied wherever applicable.

Models & analysis

n/a	Involved in the study
☐	☒ Functional and/or effective connectivity
☒	☐ Graph analysis
☐	☒ Multivariate modeling or predictive analysis

Functional and/or effective connectivity: Pearson correlation

Multivariate modeling and predictive analysis: First, functional connectivity (FC) was calculated for each task condition per individual using the CONN toolbox. Second, at each task condition, the FC was used to predict different psychiatric disorder scores (i.e. the sum of corresponding symptoms) with the connectome-based predictive model. Finally, the brain signatures (i.e. the contributing FC) of each externalising and internalising disorder were identified and utilized to construct the specific neuropsychopathological factors (i.e. the externalising and internalising factor)