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# Common functional brain networks between attention deficit and disruptive behaviors in youth

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ABSTRACT

Attention deficits (AD) and disruptive behavior (DB) are highly comorbid youth externalizing behaviors. This study aimed to study reliable functional brain networks shared by AD and DB in youth aged from 8 to 21 years from the Philadelphia Neurodevelopmental Cohort (PNC). The PNC study assessed AD and DB behaviors via Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS). This study employed sparse canonical correlation analysis (SCCA) to examine the correlation of AD and DB behaviors with resting-state functional connectivity maps of the brain regions identified via activation likelihood estimation (ALE) meta-analyses on attention deficit/hyperactivity disorder (ADHD) and DB disorder (DBD). Our meta-analyses identified that the middle cingulate cortex, pre-supplementary motor area (pre-SMA), and striatum had a great consensus in existing ADHD studies and the amygdala and inferior parietal lobule were consistently found in existing DBD studies. Our SCCA analysis revealed that the AD and DB behavioral items relevant to inattention and delinquency were correlated with the functional connectivity of the pre-SMA with the ventral attentional and frontoparietal networks (FPN), and the striatum with the default mode (DMN) and dorsal attentional networks. The AD and DB behavioral items relevant to inattention and irritability were associated with the functional connectivity between the amygdala and the DMN and FPN. Our findings suggest that the functional organization of the ADHD- and DBD-related brain regions provides insights on the shared neural basis in AD and DB.

## 1. Introduction

Attention deficit/hyperactivity disorder (ADHD) and disruptive behavior disorders (DBD; i.e., conduct disorder and oppositional defiant disorder, CD/ODD), are externalizing behavior disorders in youth that share a high degree of comorbidity (Reed et al., 2019). A comorbidity rate of ADHD and DBD is between 25 and 35% based on national mental health surveys of population-based youth samples (Ford et al., 2003; Nock et al., 2007) and between 16 and 64% in clinical samples (August et al., 1996; Reale et al., 2017; Singh, 2008; Willcutt et al., 1999). While ADHD and DBD are considered distinct disorders, they do share clinical and cognitive characteristics, such as impulsivity (Beauchaine et al., 2017) and poor executive functioning (Hummer et al., 2011; Schoemaker et al., 2013, 2012). Particularly, executive dysfunctions are increasingly found to be related to both ADHD and DBD (Atherton et al., 2019; Glenn et al., 2017; Hobson et al., 2011; Hwang et al., 2016; Petrovic and Castellanos, 2016). An overlap of putative genetic variants associated with ADHD and DBD further supports shared neurobiological bases between the two disorders (Thapar et al., 2001; Tuvblad et al., 2009). These shared clinical and cognitive phenotypes, and genetic factors suggest that ADHD and DBD may have a common neural basis. Such a neural basis may also provide insight on understanding neurobiological markers associated with the continuous dimension of AD and DB externalizing behaviors across general populations.

Nevertheless, previous reviews suggest that ADHD is categorized by abnormalities in “cool” executive functions that constitute non-affective top-down control, including inhibition and attention (Zelazo and Carlson, 2012). In contrast, DBD is associated with abnormalities of “hot” executive functions that signify regulatory processes related to affect

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and motivation that is usually examined by emotion processing and reward tasks (Hummer et al., 2011; Rubia, 2011). Aligning with these, whole-brain meta-analyses using activation likelihood estimation (ALE; Eickhoff et al., 2012, 2009) quantitatively integrate existing task-based functional findings and have shown that youth with ADHD have abnormal functional activations related to cognitive control in the supplementary motor cortex, cingulate, putamen and prefrontal cortex (Cortese et al., 2012; Hart et al., 2013). In contrast, task-based fMRI studies in youth with DBD reveal aberrant activations related to emotion and reward processing in the amygdala, insula, striatum, and medial prefrontal cortex (Alegria et al., 2016; Noordermeer et al., 2016). However, the aforementioned findings may be biased since a majority of existing neuroimaging studies in ADHD examine cool EF tasks whereas DBD research focuses primarily on hot EF tasks (Castellanos et al., 2006; Noordermeer et al., 2016; Rubia, 2018), which may 'stack the deck' in favor of specific findings.

This study integrated ALE meta-analyses and a data-driven approach to examine common brain functional networks that contribute to both AD and DB behaviors in a population youth sample aged from 8 to 21 years. For this, we first employed ALE meta-analyses on existing task-based fMRI studies of ADHD or DBD and identified brain regions (meta-analytic brain loci) whose functional activation was associated with ADHD or DBD. We then used resting-state fMRI (rs-fMRI) and sparse canonical correlation analysis (SCCA) to examine the functional networks of these meta-analytic brain loci and their relation to the AD and DB externalizing behavioral profiles. Previous studies suggest that the functional connections of brain activation regions derived from meta-analysis can shed light on the brain functional organization of psychiatric disorders (Bressler, 1995; Darby et al., 2019; Genon et al., 2018; Price and Friston, 2005; Tononi et al., 1998). Moreover, the standard diagnostic categorization system of psychiatric disorders considering disorders as discrete disease-entities has been challenged, resulting in the introduction of Research Domain Criteria (RDoC; Insel et al., 2010) framework. This framework augments discrete characterization by infusing categorical approaches that better capture the overlapping clinical features across disorders. Furthermore, resting-state fMRI (rs-fMRI) can characterize the intrinsic functional organization of the brain, and has been widely used to understand the brain functional organization in neurodevelopment and psychiatric disorders (Horien et al., 2019; Shehzad et al., 2009). We expected that ALE meta-analyses can identify reliable brain regions in relation with ADHD or DBD. Their functional connectivity maps can facilitate the discovery of the brain functional organization shared by the AD and DB behaviors. In particular, the functional networks that are to some extent involved in the cool and hot EF, such as the limbic network consisting of the cingulate, the attentional network, and the frontoparietal network comprising the prefrontal and parietal cortex, may be the common neural basis in the AD and DB externalizing behaviors.

## 2. Methods

### 2.1. Activation likelihood estimation (ALE) meta-analysis

Our study aimed to identify functional loci that are consistently involved in externalizing disorders via ALE meta-analysis on existing fMRI studies in youth with ADHD and/or DBD. Fig. 1 for the steps of systematic search based on PRISMA criteria (Moher et al., 2015). We first reviewed two up-to-date meta-analyses on ADHD (Cortese et al., 2012; literature till December 2011) and DBD (Alegria et al., 2016; literature till August 2015) and updated recent studies published prior to 31 August 2019 via PubMed (http://www.pubmed.org). For ADHD studies, we used keywords "ADHD", "attention deficit disorder", "hyperactivity disorder", or "attention-deficit hyperactivity disorder" paired with "fMRI" or "neuroimaging". For DBD studies, we used keywords "conduct disorder", "oppositional defiant disorder", "conduct problems", "callous-unemotional", "psychopathic traits", "psychopathy", "disruptive behavior", "aggression", or "antisocial behavior" paired with "fMRI" or "neuroimaging". Exclusion criteria included: (1) no whole-brain analysis; (2) small volume correction was applied; participants older than 18 years old; (4) sample size less than 10; (5) no healthy control comparison; (6) no information on MNI or Talairach atlas space.

In ALE, "study" represents any scientific publication while "an experiment" stands for a contrast analysis within a study (Fox et al., 2005). Our ALE meta-analyses included 91 independent fMRI studies (ADHD: 71; DBD: 27) and 215 experiments with 1035 foci reported (Table S1 in the Supplementary Material). The ADHD studies included 1582 youths with ADHD and 1642 healthy controls, while the DBD studies included 647 youths with DBD and 584 healthy controls. The foci were grouped according to diagnosis (ADHD or DBD versus controls), activation direction (*hyperactivation*: cases > controls; *hypoactivation*: controls > cases; *combined*: hyperactivation, hypoactivation, and "NA" if the contrast direction of activation cannot be identified), cognitive domains (hot or cool EF), and task domains (emotion, reward or cognitive control (McTeague et al., 2017)). Hence, there were 36 possible combinations for meta-analyses (2 diagnostic groups x 3 activation directions x 2 cognitive domains x 3 task domains). We conducted 17 meta-analyses in which each had at least 16 experiments to ensure sufficient statistical power based on the revised version of ALE algorithm implemented in MATLAB (Eickhoff et al., 2012, 2009; Turkeltaub et al., 2002) to investigate topographic convergence in systematic meta-analyses. Each meta-analysis identified brain regions with cluster-level $p$-value < 0.05 by familywise error (cFWE) and voxel-level $p < 0.005$ (Müller et al., 2018). Henceforth, the convergent brain abnormalities were termed as meta-analytic loci.

To further characterize functions that each meta-analytic locus is involved in, we calculated the probability of functional activation to the "Behavioral Domain" in the BrainMap database (Laird et al., 2011). "Behavioral Domain" refers to mental processes including action, cognition, emotion, interoception, and perception; each category is further subdivided into sub-categories. Details about the taxonomy can be retrieved from the BrainMap website (http://www.brainmap.org/taxonomy).

### 2.2. Philadelphia neurodevelopmental cohort (PNC)

The Philadelphia Neurodevelopmental Cohort (PNC) includes a population-based sample of over 9500 individuals from the greater Philadelphia area, ages 8–21 years who received medical care at the Children's Hospital of Philadelphia network (Calkins et al., 2015; Satterthwaite et al., 2016, 2014). The participants were initially enrolled in the genetic study at CHOP's Center for Applied Genomics (CAG). Upon assent/consent, participants were genotyped during the time of their clinical visit and provided written permission to be recontacted for studies of complex pediatric disorders (Calkins et al., 2015; Satterthwaite et al., 2016, 2014). In the PNC, 1601 participants completed the MRI acquisition. We included 936 participants without excessive head motion of the rs-fMRI sequence (i.e., mean framewise displacement, FD, less than 0.2 mm) and any neurological problems.

### 2.3. AD and DB behavioral scores in the PNC study

Abbreviated and modified Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) for school-age children was used in the PNC to assess psychiatric disorders (Calkins et al., 2015). The PNC study adopted GOASSESS, a computerized structured interview, to assess K-SADS for rapid training and standardization across a large number of subjects. The PNC assessed lifetime occurrence of major domains of psychopathology including psychosis spectrum symptoms, mood (major depressive episode, mania), anxiety (agoraphobia, generalized anxiety, panic, specific phobia, social phobia, separation anxiety), behavioral disorders (oppositional defiant, attention deficit/hyperactivity, conduct), eating disorders (anorexia, bulimia), and suicidal thinking and behavior. For the sake of our research question, this study only used 22

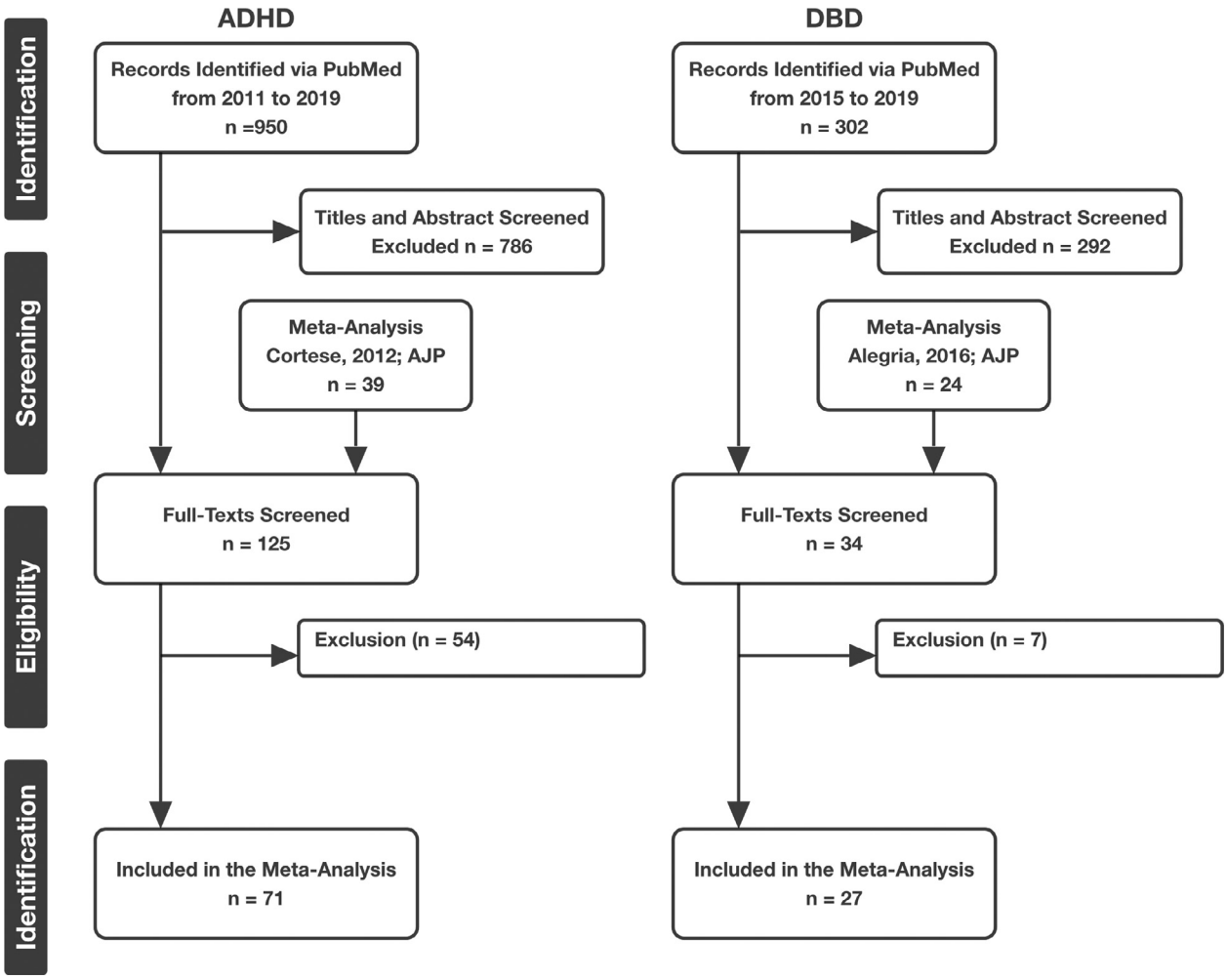



**Fig. 1.** The PRISMA flowchart for ALE meta-analyses.

items related to AD and DB externalizing behaviors. Table S2 in the Supplement Material describes each of these 22 behavioral items. Each item was coded binarily by its presence.

### 2.4. MRI acquisition in the PNC study

As previously described (Satterthwaite et al., 2014), structural and functional data were acquired on a 3T Siemens Tim Trio scanner with a 32-channel head coil (Erlangen, Germany). Structural images were acquired using a magnetization-prepared, rapid-acquisition gradient-echo (MPRAGE) T1-weighted sequence (TR= 1810 ms; TE = 3.51 ms; FoV= 180 × 240 mm; resolution 0.9375 × 0.9375 × 1 mm). Approximately 6 min of rs-fMRI data were acquired for each subject using a blood oxygen level-dependent (BOLD-weighted) sequence (TR= 3000 ms; TE = 32 ms; FoV= 192 × 192 mm; resolution 3 mm isotropic; 124 vol). Further details can be found in the PNC neuroimaging protocol (Satterthwaite et al., 2014).

### 2.5. Functional connectivity maps of meta-analytic loci

We preprocessed the PNC rs-fMRI data using FSL (version 5.0.10; Jenkinson et al., 2012) for slice timing correction, motion correction, skull stripping, and intensity normalization. We excluded rs-fMRI data if mean FD exceeded 0.2 mm (Power et al., 2012). Linear regression analysis was performed to partial out six motion parameters (three translations and three rotation parameters), global signal, white matter, and cerebrospinal fluid signals from the rs-fMRI signals. Global signal regression was carried out to eliminate artifactual variance due to head motion, known to be a problem in pediatric populations (Power et al., 2014). Band-pass filtering (0.01–0.08 Hz) was then applied. For each subject, the mean functional volume was aligned to the corresponding anatomical image via rigid-body alignment (Greve and Fischl, 2009). The functional data were then transformed to the atlas space via large deformation diffeomorphic metric mapping (LDDMM; Tan and Qiu, 2016) obtained based on the T1-weighted MRI.

Individual functional connectivity (FC) maps of each meta-analytic locus were computed via Pearson's correlation between the time course in each locus with that of the rest of the brain voxels. Next, the correlation coefficients were converted into $z$-values using Fisher's $r$-to-$z$ transformation. The FC map (excluding the meta-analytic locus) of each meta-analytic locus was summarized according to 268 cortical and subcortical nodes of Shen's atlas (Shen et al., 2013). Shen's atlas was chosen because it is constructed based on whole-brain rs-fMRI compared to other functional atlases that focus on cortical regions only (Schaefer et al., 2018; Thomas Yeo et al., 2011). Shen's atlas has been widely used in exploring brain functional networks associated with psychopathology and the prediction of cognitive abilities (Beaty et al., 2018; Bertolero et al., 2015; Rosenberg et al., 2015). Only for the interpretation of our findings, cortical nodes were then grouped into Yeo's 7 networks (Thomas Yeo et al., 2011), including the visual network (VIS), somatomotor network (SMN), dorsal attention network (DAN), ventral attention network (VAN), limbic network (LIM), frontoparietal network (FPN) and default mode network (DMN). Subcortical nodes were grouped into the subcortical network (SBN), including the amyg-

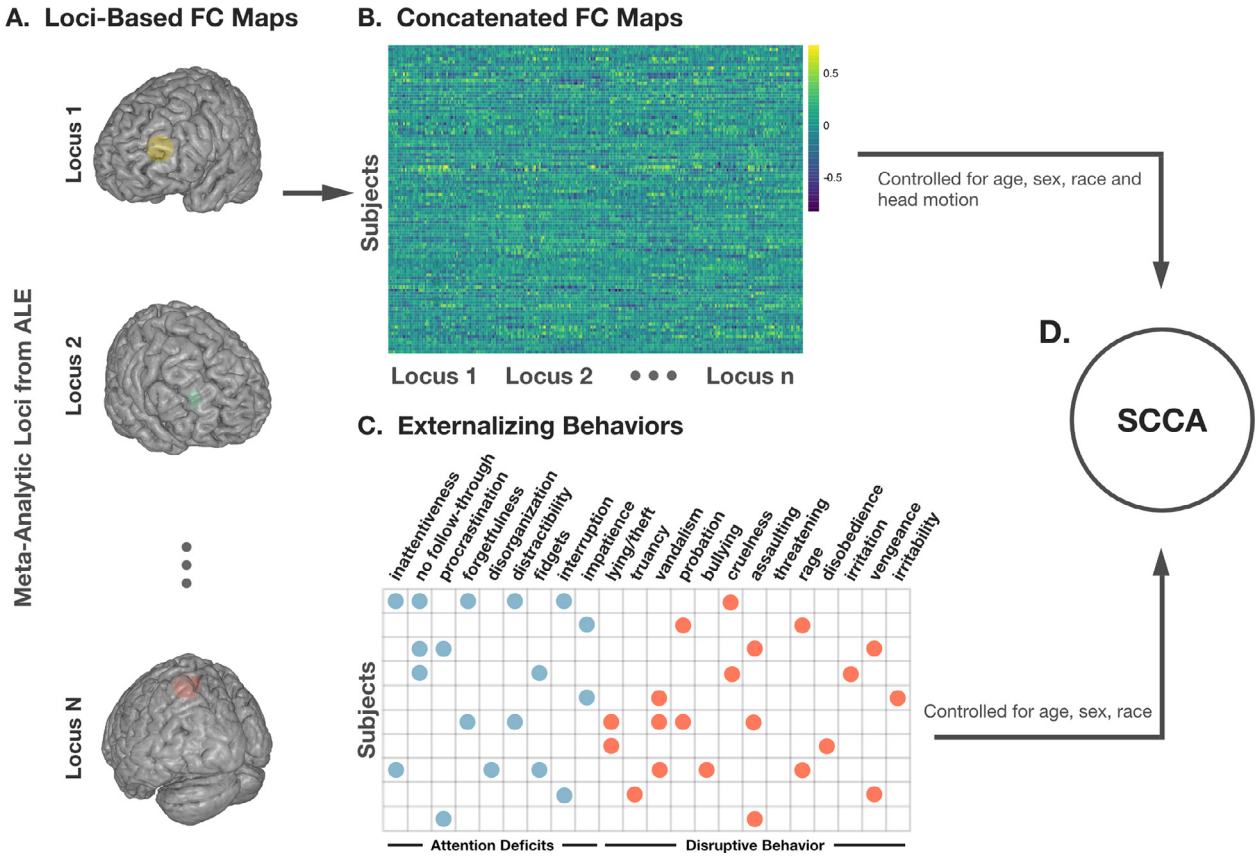



**Fig. 2.** SCCA flowchart. A. Based on the meta-analyses, functional connectivity (FC) maps based on the meta-analytic loci were calculated. B. FC maps were summarized based on Shen atlas and that of the loci related to ADHD or DBD were concatenated together, creating an input matrix. C. An externalizing behavior input matrix includes ADHD and DBD assessed using K-SADS. D. Input matrices of FC maps and externalizing behaviors after controlled for confounding variables, were fused by sparse canonical correlation analysis (SCCA) to identify distinct components across brain and behavior.

dala, hippocampus, thalamus, and striatum, and the cerebellum network (CBN), including the cerebellum and brainstem.

### 2.6. Sparse canonical correlation analysis between the FC maps and externalizing behaviors

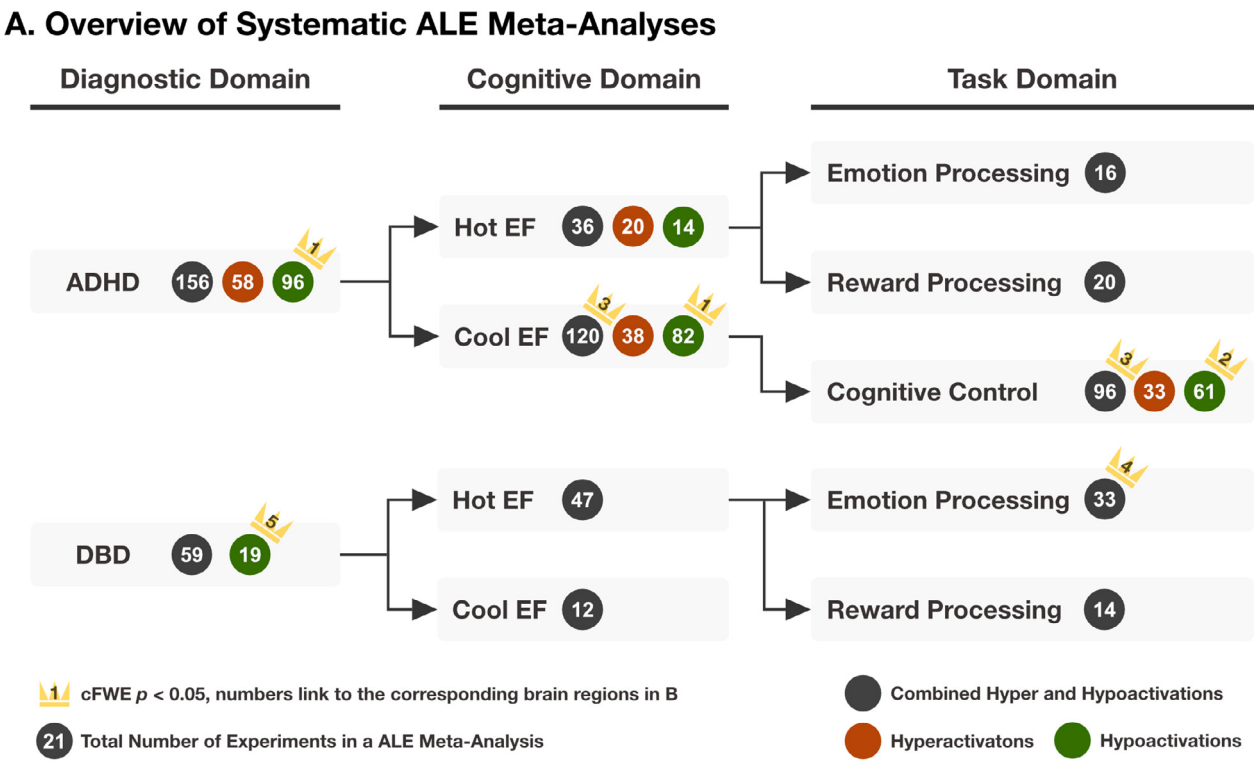
To quantify the maximal relationships of the FC maps from the meta-analytic loci from the ADHD or DBD studies with externalizing behaviors, we performed sparse canonical correlation analysis (SCCA) using the R-package "PMA" (version 1.2.1). SCCA is a multivariate technique that finds the correlation between two sets of multidimensional variables with sparse constraints (Wang et al., 2020). Fig. 2 shows the SCCA analysis workflow for this study. In detail, we used SCCA to identify the distinct canonical modes between the FC maps and externalizing behaviors. For this, we performed two SCCA analyses. In the first SCCA analysis, the 22 externalizing behavioral measures of all the participants in the discovery sample were considered as one set of variables, the functional connectivity of the ADHD-related loci (e.g., MCC, pre-SMA, Striatum) with the 268 brain regions were considered as the other set of variables. The SCCA was used to examine the relationship between these two sets of variables. In the second SCCA, the functional connectivity of the DBD-related loci (e.g., amygdala and IPL) were used. Before SCCA, effects of sex, age, and race were regressed out from the brain and behavioral data. Additionally, head motion effect was regressed out from the FC maps.

To determine the statistical significance of each canonical mode, a permutation testing procedure was performed to create a null distribution of correlations. We permuted the original data 5000 times by shuffling the externalizing behaviors of the participants and keeping the order of the FC maps. This procedure aimed at breaking the linkage between the FC maps and the behaviors of the participants. SCCA was then performed on the permutated data using the same procedure described above. To adjust arbitrary axis rotation or reflection in SCCA due to permutation, we reordered the canonical modes resulting from permutated data to the ones obtained from the original data by comparing their clinical loadings (Mišić et al., 2016; Xia et al., 2018). P-values were estimated as the number of null correlations from the permutated dataset that exceeded the SCCA correlations estimated on the original dataset over a total number of null correlations (i.e., $N = 5000$) with Bonferroni correction across the selected modes.

To assess the stability of features within each significant mode, we created 5000 bootstrapped datasets by randomly resampling the data with replacement. The corresponding modes were matched to the original one. The behavioral features whose 95% confidence interval or the FC features whose 99% confidence interval did not cross zero were considered stable features across bootstrapped samples. Only these modes were presented in the result section.

### 2.7. Code availability and data source

All analysis codes are available at https://github.com/kamione/pnc_externalizing_scca. The data reported in this paper have been deposited in the database of Genotypes and Phenotypes (dbGaP): accession no. [phs000607.v3.p2].



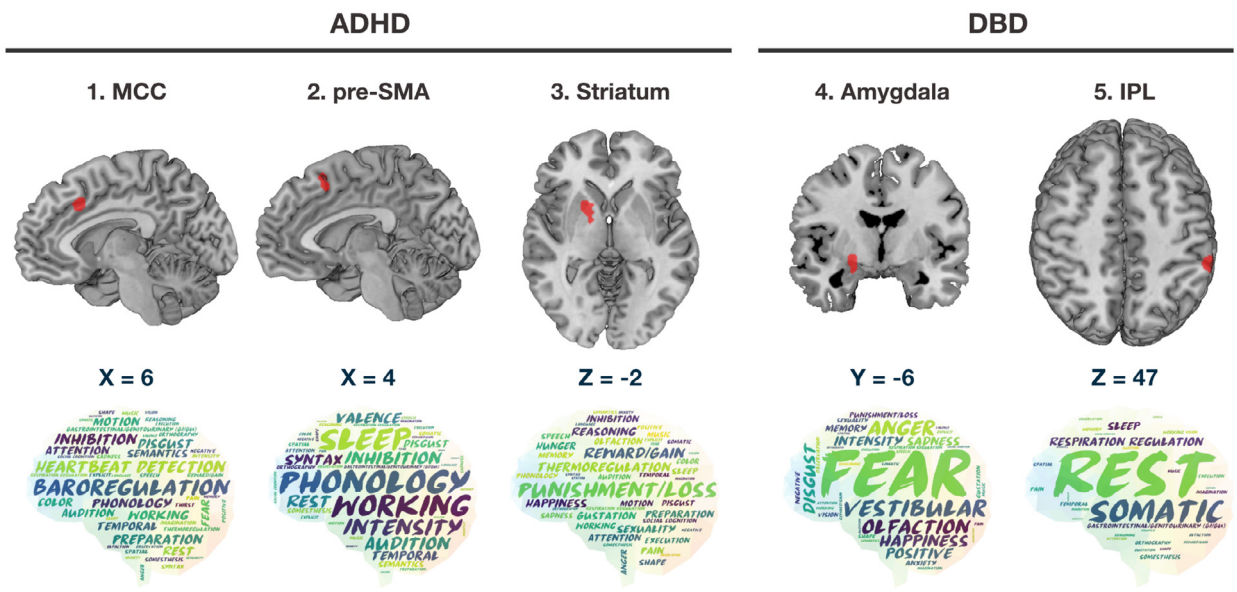




**Fig. 3.** The ALE meta-analysis results. A. An overview of the 17 ALE meta-analyses. A meta-analysis was conducted if there were 16 experiments under this condition. The number on the crown corresponds to the panel in part B of this figure. B. The meta-analyses revealed 5 distinct brain regions associated with different behavioral domains. The upper row displays the results of ALE meta-analyses. The bottom row displays the cognitive decoding of the brain regions shown above. The larger the font size, the higher probability of performing a particular behavioral domain when activations are observed within the brain region given above.

## 3. Results

### 3.1. Meta-Analytic loci for ADHD and DBD

The ALE meta-analysis was performed only if more than 16 experiments were identified. Fig. 3A displays 17 meta-analyses under different diagnostic groups, activation directions, cognitive domains, and task domains. Table S3 in the Supplementary Material lists the results and anatomical coordinates of each meta-analysis. Consistently, youths with ADHD relative to healthy controls showed aberrant functional abnormalities in the right midcingulate cortex (MCC), pre-supplementary motor cortex (pre-SMA), and left striatum (Fig. 3B). For simplicity, we labeled these three regions as “ADHD-related loci.”. Compared to healthy controls, youths with DBD showed abnormalities in the left amygdala and right inferior parietal lobule (IPL) (Fig. 3B), which a label “DBD-related loci” was given. The bottom row of Fig. 3B illustrates the likely

**Table 1**
Demographics of the discovery and replication samples.

| | Discovery ($N$ = 626) | Replication ($N$ = 310) | p-value[c] |
|---|---|---|---|
| Age | 15.37±3.35 | 15.28±3.41 | 0.709 |
| Sex | 363 Males | 159 Males | 0.06 |
| Race | White: 259 | White: 138 | 0.647 |
| | Black: 299 | Black: 139 | |
| | Other: 68 | Other: 33 | |
| Attention Deficits[a] | 0.31±0.31 | 0.32±0.31 | 0.582 |
| Disruptive Behaviors[a] | 0.17±0.19 | 0.15±0.17 | 0.082 |
| Externalizing Behaviors[b] | 14.09±12.27 | 14.01±11.11 | 0.576 |

a. Attention deficits and disruptive behaviors were a proportion to the total of available items. See Table S2 in the Supplementary Material for details of items in each domain.
b. Externalizing behaviors were the total sum of 22 externalizing behavior assessed by K-SADS.
c. The sample differences of continuous variables were assessed by student's *t*-test and that of categorical variables were assessed by chi-square test.

functions of each meta-analytic locus. The MCC and pre-SMA were predominantly associated with attention, inhibition, working memory, semantics, language, as well as interoception. The striatum was associated with reward processing as well as processing related to cognitive control. Furthermore, the amygdala was primarily associated with emotion processing and the IPL was mainly associated with rest and somatic processes. Previous studies also demonstrated that the IPL decoded facial emotional information, suggesting that it is involved in an emotion processing network (Adolphs et al., 1996; Sarkheil et al., 2013).

### 3.2. PNC sample characteristics

We randomly split the PNC sample into discovery ($n$ = 626; 263 males; age = 15.37 ± 3.35 years) and replication ($n$ = 310; 151 males; age = 15.28 ± 3.41 years) datasets. The characteristics of these two datasets had similar distributions in terms of age, sex, race, attention deficits (AD), and disruptive behavior (DB) as well as overall psychopathology (Table 1 and Figure S1 in the Supplementary Material).

### 3.3. Canonical modes between the FC maps of the ADHD-related loci and externalizing behaviors

In the discovery dataset, the top three modes were selected based on the scree plot. These modes explained 40.7% of variances linking the FC maps of the ADHD-related loci (i.e., the MCC, pre-SMA, and striatum) and externalizing behaviors (Fig. 4A). Only the first two modes were statistically significant (Mode 1: $r = 0.339$, $p_{bonf} = 0.033$; Mode 2: $r = 0.331$, $p_{bonf} = 0.04$). We repeated the analysis using the replication dataset ($n$ = 310). The top three modes explained 41.0% of variance linking the FC maps of the ADHD-related loci (i.e., the MCC, pre-SMA and striatum) and externalizing behaviors (Fig. 4A). The first two modes showed the same patterns as those derived from the discovery dataset (Fig. 4B, C). However, only the first mode was statistically significant ($r = 0.476$; $p_{bonf} = 0.024$) and the second mode showed a trend of significance ($r = 0.452$, $p_{bonf} = 0.076$) in the replication dataset (see Figure S2A in the Supplementary Material).

Mode 1 was characterized by symptoms of inattentiveness, no follow-through, forgetfulness, and disobedience and hence we termed this mode as "inattention" (Fig. 4B). The left panel in Fig. 4B shows the canonical loading of the functional maps of the MCC, pre-SMA, and striatum and the middle panel in Fig. 4B summarizes them in individual functional networks for easy interpretation. Our findings showed that inattention was mainly associated with the functional connections of the MCC and pre-SMA with the VAN and FPN and connections of the striatum with the DMN, DAN, SMN, and SBN.

Mode 2 comprised of truancy, probation, threatening, and rage and hence we termed this mode as "delinquency" (Fig. 4C). Delinquency was found to be associated with the functional connections of the pre-SMA with the VAN, DAN, and FPN and the striatum connections with the DMN and DAN.

Across these two modes, we observed that both inattention and delinquency were highly associated with the functional connections of the pre-SMA with the VAN and FPN, and the striatum with the DMN and DAN.

### 3.4. Canonical modes between the FC maps of the DBD-related loci and externalizing behaviors

In the discovery dataset, the top three modes were selected based on the scree plot and they explained 40.2% of variances linking the FC maps of the DB-related loci (i.e., the amygdala and IPL) and externalizing behaviors (Fig. 5A). All three modes were statistically significant (Mode 1: $r = 0.354$, $p_{bonf} = 0.006$; Mode 2: $r = 0.351$, $p_{bonf} = 0.017$; Mode 3: $r = 0.335$, $p_{bonf} = 0.048$). In the replication sample ($n$ = 310), the top three modes explained 37.7% of variances. Figure S2B illustrates these modes. The first two modes (Mode 1: $r = 0.50$, $p < 0.001$; Mode 2: $r = 0.47$, $p = 0.01$) were largely overlapped with those derived from the discovery dataset. The third mode only showed a trend of significance ($r = 0.44$, $p = 0.087$).

Fig. 5B shows Mode 1 related to threatening, rage, disobedience, and irritability and hence we termed this mode as "irritability". In this mode, the amygdala showed relatively strong connections with the DMN, FPN, LIM, DAN, and VIS while the IPL had stronger connections with the DAN and SMN.

Fig. 5C shows Mode 2 related to "inattention". The behavioral profile incorporated inattentiveness, no follow-through, forgetfulness, and distractibility. This mode showed the strong coupling between the amygdala and DMN, followed by the FPN and VAN. Compared with the amygdala, the IPL had weaker connectivity with all the networks.

Fig. 5D illustrates Mode 3 related to "antisocial" characterized by items of lying/theft, probation, and bullying. This mode had the strong connections between the amygdala and the LIM and between the IPL and the SBN, CBN, and VIS.

Across these modes, we observed that irritability and inattention were associated with the strong functional coupling of the amygdala with the DMN and FPN.

## 4. Discussion

There has been a significant increase in the number of data-driven and meta-analytic studies that have identified neural, behavioral and/or psychological impairments present across different psychiatric disorders (McTeague et al., 2017, 2016). This study integrated both meta- and data-driven analyses to provide new evidence on functional brain networks that are shared in both AD and DB in youth. Our meta-analysis on existing task-based fMRI studies reached to a consensus and suggested

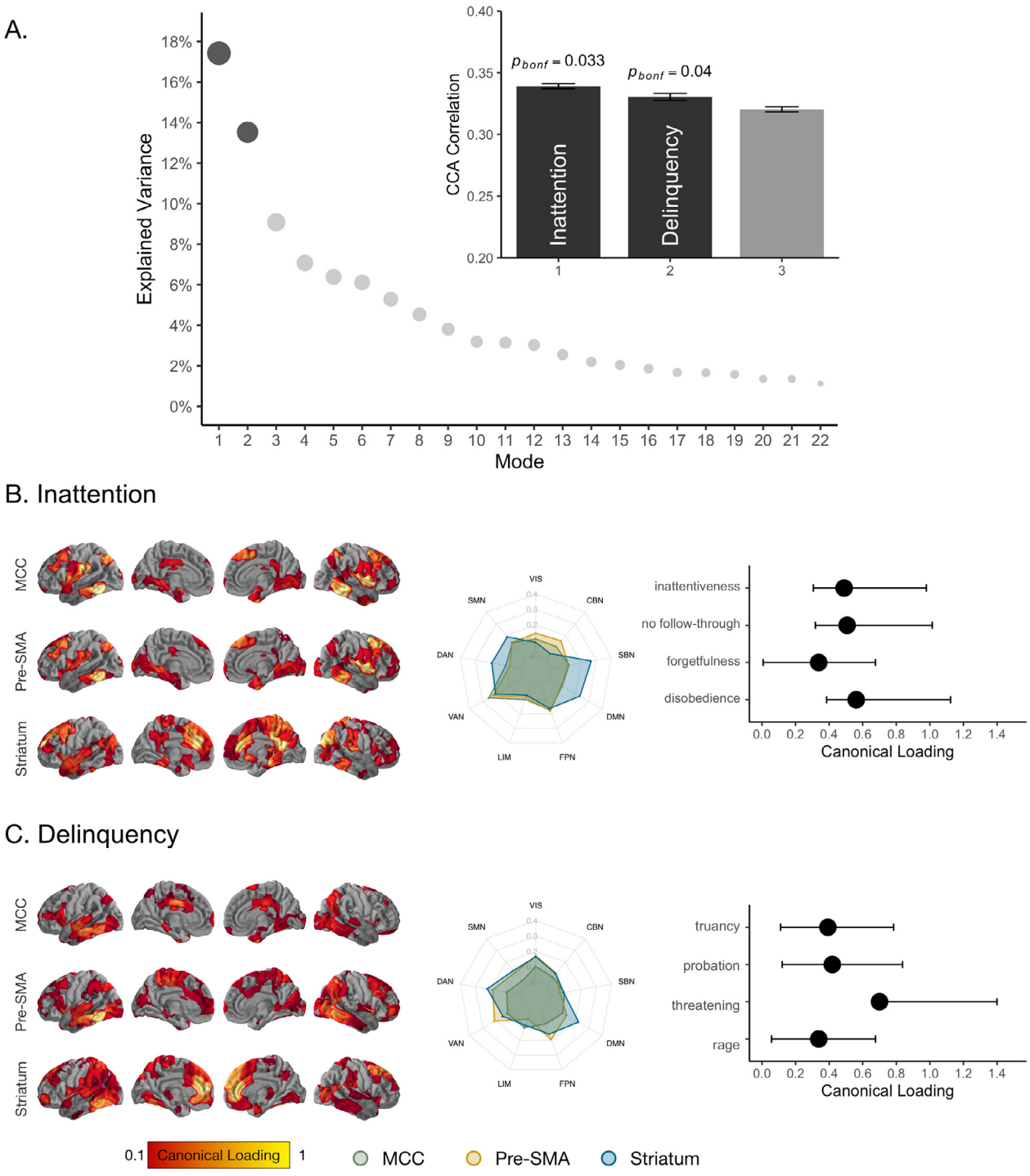



**Fig. 4.** Correlation patterns between FC Maps of ADHD meta-analytic loci and externalizing behaviors in the discovery samples. A. The first three components were examined and found that only the first two modes survived the permutation test. B and C. Functional connectivity and behavioral loadings within the first mode related to AD: Inattention and the second mode related to DB: Delinquency. The left panel of B and C shows FC loadings (ranging from 0.1 to 1). The middle panel summarizes the FC loadings in 9 macroscale networks. The right panel shows the behavioral loadings.
Abbreviations: VIS: visual network; SMN: somatomotor network; DAN: dorsal attention network; VAN: ventral attention network; LIM: limbic network; FPN: frontoparietal network; DMN: default mode network; SBN: subcortical network; CBN: cerebellum network.

that the MCC, pre-SMA, and striatum were the ADHD-related loci, while the amygdala and IPL were the DBD-related loci. The functional organization of these loci provided insight on the functional brain networks present in youth with AD and DB behaviors. Our data exploratory SCCA analysis identified the AD and DB behaviors related to inattention and delinquency (see Fig. 4B and C) in the association with the functional connectivity of the pre-SMA with the VAN and FPN, and the striatum with the DMN and DAN. Moreover, inattention and irritability were associated with the functional coupling of the amygdala with the DMN and FPN. These findings suggested that the DMN, FPN, and attentional networks are the key functional brain networks shared in both the AD and DB behaviors in a general youth population.

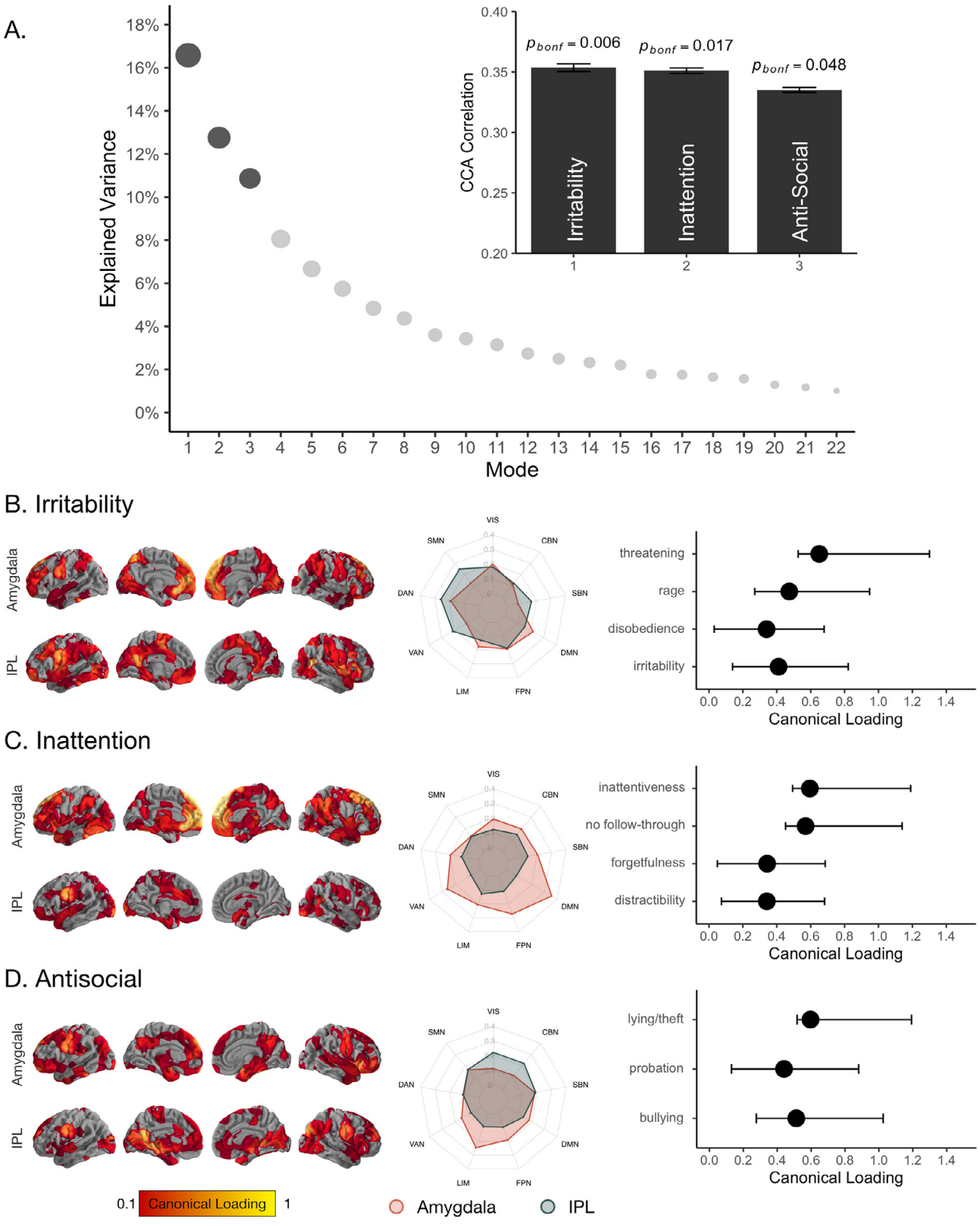



**Fig. 5.** Correlation patterns between FC Maps of DBD meta-analytic loci and externalizing behaviors in the discovery samples. A. The first three components were examined and found that all three modes survived the permutation test. B to D. Functional connectivity and behavioral loadings within the first mode related to DB: Irritability, the second mode related to AD: Inattention, and the third mode related to DB: Antisocial. The left panel shows FC loadings (ranging from 0.1 to 1). The middle panel summarizes the FC loadings in 9 macroscale networks. The right panel shows the behavioral loadings.
Abbreviations: VIS: visual network; SMN: somatomotor network; DAN: dorsal attention network; VAN: ventral attention network; LIM: limbic network; FPN: frontoparietal network; DMN: default mode network; SBN; subcortical network; CBN: cerebellum network.

The functional organization of the ADHD-related loci (i.e., the striatum and pre-SMA) and DBD-related loci (i.e., the amygdala) with the DMN, FPN, and attentional networks was associated with inattention as well as irritability and delinquency. These results are consistent with recent meta-analytic evidence that dynamic interactions between multiple large-scale networks such as DMN, FPN, attentional networks, and affective networks may play a role in the psychopathology of ADHD and DBD (Dugré and Potvin, 2021; Gao et al., 2019; Sutcubasi et al., 2020). Table S4 in the Supplementary lists the key findings from the existing meta-analysis on ADHD while the meta-analysis on DBD is scarce. It is noteworthy that Cortese et al. (2021) did not find spatially convergent evidence across rs-fMRI studies in ADHD in their meta-analysis. The DMN comprises the posterior cingulate (PCC), medial prefrontal cortex (mPFC), precuneus, and other limbic regions that are thought to be activated during internal mental-state processes and deactivated when the brain attends to an external stimulus (Raichle, 2015). Likewise, the FPN and attentional networks consist of the dorsolateral prefrontal cortex (dlPFC), pre-SMA, and parietal cortex and play a crucial role in attention and cognitive control (Marek and Dosenbach, 2018) as well as regulating functions of other networks (Menon, 2018). Well-synchronized neural activity among the DMN, FPN, and attentional networks helps regulate thoughts to focus attention. Weaker interaction among these networks is associated with more severe attentional symptoms in children (Castellanos and Aoki, 2016). The functional connectivity of the striatum-related and amygdala-related circuits with FPN are also identified as neural substrates for dimensional aspects of ADHD (Castellanos and Aoki, 2016; Grimm et al., 2021). Moreover, irritability has recently been formulated as a transdiagnostic marker for both internalizing and externalizing disorders (Dennis et al., 2019). More irritable individuals show larger mPFC and cingulate (major regions of DMN), as well as a smaller striatum volume (Dennis et al., 2019). Congruent with our findings, a recent meta-analysis on rs-fMRI in individuals with antisocial problems revealed convergent dysconnectivity in brain regions of DMN, FPN as well as the amygdala, MCC, and premotor cortex, which are the meta-analytic loci in the current study (Dugré and Potvin, 2021). Similarly, adolescents with conduct disorder manifest decreased functional connectivity between the DMN and pre-SMA (Lu et al., 2015). Delinquent youth often show abnormal selective and sustained attention (Frías-Armenta et al., 2011) and inability to respond adequately in socio-emotional context (Northam and Dadds, 2020) and reduced reward sensitivity (Murray et al., 2017). Convergent evidence from fMRI studies suggests decreased activation in the cingulate, mPFC, pre-SMA, and ventral striatum in subjects with disruptive problems (Alegria et al., 2016). Youths with disruptive behavior disorder show not only reduced mPFC activation but also hyperactivation in cognitive control mediating the FPN and striatum (Alegria et al., 2016). Failure in suppressing the DMN activity can increase error rates in inhibitory control (Eichele et al., 2008). These neural findings support the concept that the AD and DB behaviors are related to both cool and hot EF.

Our findings additionally revealed that inattention was related to the functional connectivity of the striatum with the SBN and SMN, while irritability and antisocial behavior were related to the functional connectivity of the amygdala with the VIS and the IPL with SMN, SBN, and CBN. These may suggest that the ADHD- and DBD-related loci could play a crucial role in both bottom-up and top-down regulatory processes. The amygdala and striatum may receive input from the sensory, subcortical, and cerebellar networks, engage the DMN, FPN, and attentional networks to switch internal state to external state, and to execute. These two brain regions together with the MCC, pre-SMA, and IPL may monitor and exert control of decisions or actions. We speculate that distinct sensory inputs received by the ADHD- and DBD-related loci play a role in differentiating AD and DB while the decoding of sensory inputs and cognitive control engaging these regions and high-level networks may be shared between AD and DB.

There were several limitations in this study. Our findings in this study derived from a general population may not be generalized to clinical samples. Further investigation is needed to understand whether the functional brain networks identified in this study can be considered transdiagnostic for ADHD and DBD based on clinical samples. Second, our study cannot infer any sequential relation between AD and DB even though ADHD in preschool-age may increase the risk of developing CD in later childhood and adolescence (Beauchaine et al., 2010). Third, the population-based component of our study lacked measures of cool and hot EF, which could strengthen the interpretation of their relationship to the shared functional brain networks between the AD and DB behaviors. Also, externalizing behaviors in this study were assessed via K-SADS. Attention problems can also be examined via neuropsychological testing (Danckaerts et al., 1999), which can be incorporated in future research. Furthermore, the current approach adopts a macroscale network perspective for the interpretation of our findings. Although this approach could provide boarder insight into common neuroimaging features across ADHD and DBD related behaviors, it might overlook those functional networks with a specific cognitive function such as affective regulation. Finally, the common functional brain networks identified in this study may also be associated with other psychiatric symptoms beyond externalizing behaviors since the DMN, FPN, and the attention networks have also been highlighted in autism, schizophrenia, depression, etc. (Menon, 2018; Sha et al., 2019; Xia et al., 2018; Yan et al., 2019). Nevertheless, their connections with disease-related brain regions may play a role in distinguishing AD and DB from others.

## Conclusion

Our study highlighted the importance of meta-analysis and data-driven multivariate analysis in helping advance and shape our understanding of the neural basis associated with a broader dimensional aspect of behavioral problems. The functional organization of the ADHD- and DBD-related loci provides insights on understanding the shared neural basis in AD and DB, supporting the idea that the biological factors aligning with the AD and DB behavioral dimensions also likely cut across traditional diagnostic boundaries of ADHD and DBD. Our findings may suggest reframing clinical questions and to engender novel and important new avenues for intervention and prevention that are much more widely applicable than more traditional disorder-specific approaches to treatment.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118732.

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