

# Dimensional Brain-Behavior Relationships in Children with Attention-Deficit/Hyperactivity Disorder

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**Background:** Emerging neuroscientific and genetic findings emphasize the dimensional rather than the categorical aspects of psychiatric disorders. However, the integration of dimensional approaches within the current categorical diagnostic framework remains unclear. Here, we used resting state functional magnetic resonance imaging to examine whether dimensional measures of psychiatric symptomatology capture brain-behavior relationships unaccounted for by categorical diagnoses. Additionally, we examined whether dimensional brain-behavior relationships are modified by the presence of a categorically defined illness, attention-deficit/hyperactivity disorder (ADHD).

**Methods:** Resting state functional magnetic resonance imaging scans were collected from 37 typically developing children (aged  $10.2 \pm 2$ ; 21 female subjects) and 37 children meeting DSM-IV Text Revision criteria for ADHD ( $9.7 \pm 2$ ; 11 female subjects). Parent-rated Child Behavior Checklist Externalizing and Internalizing scores served as dimensional measures in our analyses of default network (DN) resting state functional connectivity (RSFC).

**Results:** Regardless of diagnosis, we observed several significant relationships between DN RSFC and both internalizing and externalizing scores. Increased internalizing scores were associated with stronger positive intra-DN RSFC, while increased externalizing scores were associated with reduced negative RSFC between DN and task-positive regions such as dorsal anterior cingulate cortex. Several of these brain-behavior relationships differed depending on the categorical presence of ADHD.

**Conclusions:** Our findings suggest that while categorical diagnostic boundaries provide an inadequate basis for understanding the pathophysiology of psychiatric disorders, psychiatric illness cannot be viewed simply as an extreme of typical neural or behavioral function. Efforts to understand the neural underpinnings of psychiatric illness should incorporate both categorical and dimensional clinical assessments.

**Key Words:** ADHD, children, default network, dimensional scale, functional connectivity, functional magnetic resonance imaging (fMRI)

Category-based diagnostic classification systems for psychiatric illness (e.g., bipolar disorder vs. schizophrenia vs. obsessive-compulsive disorder) are central to modern-day clinical practice. Despite providing a standardized nomenclature and common clinical framework, high degrees of symptom overlap among disorders and extensive patterns of comorbidity have raised questions about the adequacy of a purely categorical psychiatric nosology (1,2). The recent identification of common neural and genetic substrates crossing current diagnostic categories has further intensified concerns about the biological validity of categorical boundaries of psychiatric disorders. In response, researchers and clinicians are increasingly shifting toward dimensional conceptualizations of psychiatric illness (3,4).

This reconceptualization has implications for our understanding of both diagnostic assessment and pathophysiology of psychiatric illnesses. Over the past three decades, the psychiatric neuroimaging community has primarily compared diagnostic groups (i.e., clinical probands vs. control subjects) to identify the neural correlates of psychiatric disorder. Dimensional measures of illness are rarely examined or have been limited to measures of disease severity

among patients. In contrast, a dimensional approach implies that the behavioral characteristics of a given disorder can be examined across both healthy and clinical populations, with the assumption that psychiatric disorders represent extreme variants of typical behavior. From this perspective, neural dysfunction associated with psychopathology likely represents variation along a spectrum that includes healthy brain function (5).

Resting state functional magnetic resonance imaging is emerging as an effective means of mapping dimensional brain-behavior relationships because of its moderate to high test-retest reliability and the relative simplicity of data acquisition. Initial studies have explored brain-behavior relationships using a variety of cognitive and behavioral measures (e.g., response time variability, working memory accuracy, reading competence) (6–8). Studies examining psychiatric phenotypes are also beginning to emerge. For example, Di Martino *et al.* (9) related a measure of autistic traits in healthy adults to the strength of resting state functional connectivity (RSFC) between the anterior cingulate cortex (ACC) and insula. Similarly, Assaf *et al.* (10) observed that more severe social and communication Autism Diagnostic Observation Schedule scores were correlated with weaker positive RSFC between precuneus and ACC in patients with autism.

Although potentially fruitful, dimensional brain-behavior relationships must be interpreted with caution. Specifically, the relationship between dimensional measures and brain functional measures may vary as a function of whether or not pathological processes are present (i.e., the relationship between connection X and dimension Y may vary as a function of whether or not disease Z is present). Accordingly, certain relationships between dimensional measures of psychopathology and brain function demonstrated in healthy individuals may not be observed in clinical populations (i.e., they may not simply represent the extreme end of the measured dimension).

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Here, to account for both dimensional and categorical effects, we investigated brain-behavior relationships in typically developing children (TDC) and children with attention-deficit/hyperactivity disorder (ADHD). Beyond the classic triad of hyperactivity, inattention, and impulsivity, the high rates of externalizing (i.e., conduct or oppositional defiant disorders in 42% to 93% of cases) (11) and internalizing disorders (i.e., anxiety or depression in 13% to 51% of cases) in children with ADHD suggest the utility of dimensional approaches. Moreover, inclusion of TDC, who exhibit a lower prevalence of such disorders (e.g., major depressive disorder between 4% and 8% [12]), permits an examination of the full distribution of dimensional symptoms, as well as the exploration of their neural correlates according to the presence/absence of inferred psychopathological processes.

We focused our exploration of RSFC on the default network (DN) (13,14), as abnormalities in this network are increasingly appreciated in ADHD (15–17) and in populations characterized by either increased externalizing (18,19) or internalizing symptoms (20,21). Accordingly, we predicted that internalizing and externalizing scores derived from the Child Behavior Checklist (CBCL) (19) would be associated with differential RSFC within the DN. Moreover, we predicted that DN modulations would be observed across the full range of scores (i.e., across both ADHD and TDC participants). Finally, we hypothesized that the presence of a pathological process (i.e., ADHD) would further mediate dimensional brain-behavior relationships.

## Methods and Materials

### Participants

Thirty-seven children with ADHD (aged  $9.7 \pm 1.6$  years; 11 female subjects) and 37 TDC (aged  $10.2 \pm 2.0$  years; 21 female subjects) group-matched on age and estimates of Full-scale Intelligence Quotient (FSIQ) were included in this analysis. The DSM-IV Text Revision diagnosis of ADHD (22) was based on responses from parents and children to the Schedule of Affective Disorders and Schizophrenia for Children-Present and Lifetime Version; additionally, a T score  $> 60$  on at least one ADHD-related index of the Conners' Parent Rating Scale-Revised: Long Version was required. Thirty-one children with ADHD were naïve to psychoactive medications. Of the remaining six children, four (11%) were currently treated with psychostimulants (three with immediate release methylphenidate and one with extended release methylphenidate—withheld 24 hours before scanning), two children had been treated with extended release methylphenidate, and another had been treated with selective serotonin reuptake inhibitors in the past. Inclusion criteria for TDC required absence of any Axis I psychiatric diagnoses per parent and child Schedule of Affective Disorders and Schizophrenia for Children-Present and Lifetime Version interview, as well as T scores below 60 for all the Conners' Parent Rating Scale-Revised: Long Version ADHD summary scales. Estimates of FSIQ above 80, right-handedness, and absence of other chronic medical conditions were required for all children. All parents provided demographic information and socioeconomic status was estimated with the Hollingshead Index of social position (23) (Table 1). The study was approved by the Institutional Review Boards of New York University and New York University School of Medicine. Before participation, written assent and consent were obtained from children and their parents/legal guardians, respectively.

### Behavioral Measures

All parents completed the CBCL (24), one of the most validated and commonly used screening tools for caregiver reporting of child

behavioral and emotional problems. We used externalizing and internalizing problems scores in our analyses. The internalizing problems score combines social withdrawal, somatic complaints, and anxiety/depression scales, while the externalizing problems score combines delinquent behavior and aggressive behavior scales.

### Data Acquisition

Imaging data were acquired using a Siemens (Iselin, New Jersey) Allegra 3.0T scanner (New York University Center for Brain Imaging). For each participant, a 6-minute resting state scan comprising 180 contiguous whole-brain functional volumes was acquired using a multi-echo echo-planar imaging sequence (repetition time = 2000 milliseconds; flip angle =  $90^\circ$ ; 33 slices; voxel size =  $3 \times 3 \times 4$  mm; effective echo time = 30 milliseconds, field of view =  $240 \times 192$  mm). Forty-six participants were instructed to rest with eyes open and 28 were instructed to rest with eyes closed (due to requirement for counterbalancing in our grant-funded protocols). The diagnostic groups did not differ significantly in acquisition during eyes open or closed (Table 1). Regardless, eyes open/closed status was included as a covariate in group-level analyses to account for variation related to scan condition (25,26). Diagnostic groups did not differ significantly in terms of head movement (mean maximum displacement over time; Table 1). A T1-weighted anatomical image was also acquired using a magnetization-prepared gradient-echo sequence (repetition time = 2530 milliseconds; echo time = 3.25 milliseconds; inversion time = 1100 milliseconds; flip angle =  $7^\circ$ ; 128 slices; field of view = 256 mm; voxel size =  $1.3 \times 1.3 \times 1$  mm).

### Image Preprocessing

We made use of a combination of AFNI (<http://afni.nimh.nih.gov/afni/>) and FSL (<http://www.fmrib.ox.ac.uk/fsl>) utilities. Image preprocessing comprised slice time correction (interleaved acquisition), motion correction, despiking, spatial smoothing (full width at half maximum = 6 mm), mean-based intensity normalization of all volumes by the same factor, temporal bandpass filtering (.009–.1 Hz), and linear and quadratic detrending. Linear registration of high-resolution structural images to the Montreal Neurological Institute 152 (MNI152) template with  $2 \times 2 \times 2$  mm resolution was carried out using the FSL tool FLIRT and was then refined using FNIRT nonlinear registration (27). Linear registration of each participant's functional data to their high-resolution structural image was also carried out using FLIRT. This functional-to-anatomical co-registration was improved by intermediate registration to a low-resolution image and b0 unwarping (using FSL Fugue).

### Nuisance Signal Regression

To control for motion and physiological nuisance signals, we regressed the preprocessed data on nine nuisance covariates, removing variance associated with signals derived from white matter, cerebrospinal fluid, the global signal, and six motion parameters (28). The resultant four-dimensional residual time series were transformed into MNI152 space and used for subsequent analyses.

### Selection of Regions of Interest

We used 10 of the 11 DN regions of interest (ROIs) (seeds) defined by Andrews-Hanna *et al.* (14). These comprised the anterior medial prefrontal cortex (amPFC) and posterior cingulate cortex (PCC), representing the midline core subsystem; temporo-parietal junction, lateral temporal cortex (LTC), temporal pole, and dorsal medial prefrontal cortex (dMPFC), constituting the dMPFC subsystem; and posterior inferior parietal lobule (piPL), retrosplenial cortex (Rsp), parahippocampal cortex, and hippocampal formation (HF), constituting the medial temporal lobe (MTL) subsystem. For

**Table 1.** Demographic and Clinical Characteristics of TDC and Children with ADHD

			Chi-Square					
	TDC (n = 37)	ADHD (n = 37)	$\chi^2_{(1)}$	p				
Males, n (%)	16 (43)	26 (70)	5.50	.02				
SES (Class 4 or 5), n (%)	22 (59)	27 (73)	1.34	.25				
Eyes (Open/Closed) (%)	23/14 (62/38)	22/15 (60/40)	.057	.81				
			$\chi^2_{(3)}$	p				
Ethnicity (%)			2.99	.39				
Caucasian	41	51						
African American	24	14						
Hispanic/Latino	22	13						
Other <sup>a</sup>	13	22						
	ANOVA							
	Mean (SD)	Min	Max	Mean (SD)	Min	Max	F(1,73)	p
Age	10.2 (2.0)	7.2	13.3	9.7 (1.6)	7.2	13.5	1.06	.31
Full Scale IQ	111 (13.8)	80	138	111 (12.9)	84	134	.08	.78
Mean of Maximum Displacement (mm) <sup>b</sup>	.73 (.45)	.22	2.4	.70 (.43)	.19	2.38	.13	.72
CPRS-R:LV <sup>c</sup>								
ADHD index	46 (5.6)	41	67	68 (12.7)	43	90	92.64	<.0001
DSM-IV total	45 (4.7)	40	58	72 (8.9)	55	90	263.39	<.0001
CBCL Parent								
Total problems	41 (9.8)	24	61	63 (8.1)	43	75	119.79	<.0001
Externalizing problems	42 (9.2)	14	58	60 (10.1)	33	78	67.80	<.0001
Internalizing problems	45 (9.6)	33	68	58 (10.6)	34	74	31.31	<.001

ADHD, attention-deficit/hyperactivity disorder; ANOVA, analysis of variance; CBCL, Child Behavior Checklist; CPRS-R:LV, Conners' Parent Rating Scale-Revised: Long Version; IQ, intelligence quotient; Max, maximum; Min, minimum; SD, standard deviation; SES, socioeconomic status; TDC, typically developing children.

<sup>a</sup>"Other" includes Asian, Native American, and mixed ethnic group.

<sup>b</sup>Maximum displacement is an output of the Analysis of Functional Neuroimages motion correction program 3dvolreg. It quantifies the maximal voxel displacement due to motion at each time point.

<sup>c</sup>The CPRS-R:LV questionnaire was not available for one TDC.

each region, we created a spherical seed ROI (4 mm radius), centered on the published coordinates (14). We did not include the ventral medial prefrontal cortex (a part of the MTL subsystem) in our analyses because of inconsistent coverage of this region across participants.

### Subject-Level RSFC Analyses

For each participant, the representative time series for each seed ROI was extracted from their four-dimensional residuals standard-space volume by averaging the time series across all voxels within the ROI. We then calculated the correlation between each seed ROI time series and that of every other brain voxel in native space. The resultant participant-level correlation maps were Fisher z-transformed to Z-value maps and transformed into MNI152 2-mm standard space for group-level analyses.

### Group-Level RSFC Analyses

For each seed, group-level analyses were carried out using a random-effects ordinary least squares model that included the following predictors: 1) constant (overall mean), 2) diagnostic group (TDC, ADHD, i.e., 1 or -1 depending on the categorical diagnosis), 3) CBCL score, and 4) CBCL score  $\times$  diagnostic group (i.e., interaction, obtained by multiplying the CBCL score by the group score). Additional covariates included age, sex, and eyes status (open vs. closed). Separate analyses were run for internalizing and externalizing scores. Cluster-level Gaussian random field theory was employed for multiple comparison correction ( $Z > 2.3$ ;  $p < .05$ , corrected).

In addition to the two primary internalizing and externalizing scales, the CBCL contains an attention problems scale that is generally elevated in probands with ADHD. This scale was not suitable for examining brain/behavior relationships in our sample of typically developing children because of floor effects as shown in Figure S1 in Supplement 1.

### Statistical Correction

In studies of RSFC, the common approach to multiple comparison correction is the same as that employed for task-based functional magnetic resonance imaging: to account for the number of voxels in a statistical map but not the number of seeds (or contrasts) explored (i.e., the number of maps generated). As recently noted (29), there is value in using an omnibus correction that accounts for the number of seeds to minimize false-positives. Here, the 10 seeds employed engender a relatively high degree of correlation with one another, particularly those within the same subsystem (i.e., MTL, dMPFC, and midline core subsystems [14]). This lack of independence reduces the requirement for correction for each individual seed, which would otherwise be overly conservative. Bonferroni-corrected results accounting for the number of seeds (i.e., the most conservative correction, which treats seeds as independent) exceeding an omnibus cluster-level correction of  $p < .005$  and Bonferroni-corrected results accounting for the number of subsystems exceeding an omnibus cluster-level correction of  $p < .017$  are presented in Table 2. Results that were significant after cluster-level Gaussian random field theory for multiple comparison correction

**Table 2.** Clusters of Connectivity that Showed a Significant Relationship with Behavior for Each of the Default Network Seeds

	Cluster Size	Center of Mass			<i>p</i>
		x	y	z	
Externalizing Behaviors					
pIPL					
Positive	1052	8	34	26	.00744 <sup>a</sup>
Interaction	1510	−28	62	14	.00196 <sup>b</sup>
Rsp					
Negative	1133	54	−76	28	.00736 <sup>a</sup>
TempP					
Interaction	1930	16	−52	8	.000318 <sup>b</sup>
Interaction	1670	12	40	32	.000929 <sup>b</sup>
Interaction	1149	−32	30	50	.00955 <sup>a</sup>
Internalizing Behaviors					
aMPFC					
Positive	1761	−8	−40	36	.00109 <sup>b</sup>
Negative	1778	52	−2	42	.00102 <sup>b</sup>
HF					
Positive	913	56	6	−22	.00851 <sup>a</sup>
PCC					
Positive	1015	−6	2	20	.00799 <sup>a</sup>
Positive	901	−6	52	14	.0154 <sup>a</sup>
pIPL					
Positive	1112	−10	−38	22	.00172 <sup>b</sup>
Rsp					
Negative	1846	−46	4	0	.000623 <sup>b</sup>
Negative	1612	−6	4	48	.0016 <sup>b</sup>
Negative	1262	56	14	10	.00718 <sup>a</sup>

aMPFC, anterior medial prefrontal cortex; HF, hippocampal formation; Interaction, group difference in nature of relationship between externalizing behaviors and resting state functional connectivity; Negative, negative relationship between externalizing behaviors and resting state functional connectivity; PCC, posterior cingulate cortex; pIPL, posterior inferior parietal lobule; Positive, positive relationship between externalizing behaviors and resting state functional connectivity; Rsp, retrosplenial cortex; TempP, temporal pole.

<sup>a</sup>Bonferroni-corrected results accounting for the number of default network subnetworks (i.e., dorsal medial prefrontal cortex subsystem, medial temporal lobe subsystem, default network cores; Andrews-Hanna *et al.* [14]) examined (i.e.,  $p = .05/3 = .017$ ).

<sup>b</sup>Bonferroni-corrected results accounting for the number of default network seeds examined (i.e.,  $p = .05/10 = .005$ ).

( $Z > 2.3$ ;  $p < .05$ ) but that did not exceed these Bonferroni-corrected thresholds are presented in Figure S2 (for positive brain/behavior relationships), Figure S3 (for negative brain/behavior relationships), and Figure S4 (for dimensions-by-group interactions) in Supplement 1.

## Results

### Behavioral Findings

As expected, individuals with ADHD exhibited significantly greater scores on both internalizing and externalizing symptoms, with the greatest group differences on externalizing symptoms. The groups did not differ on age, FSIQ, socioeconomic status, or parent-identified ethnicity (Table 1). The two groups differed in sex ratio but there were no sex differences for internalizing or externalizing scores in ADHD [ $F(1,36) = .001$ ,  $p = .974$  and  $F(1,36) = 2.3$ ,  $p = .138$ , respectively] nor in TDC [ $F(1,36) = 1.772$ ,  $p = .192$  and  $F(1,36) = .235$ ,  $p = .631$ , respectively].

### Dimensional Analyses: Externalizing symptoms

**Positive Brain-Behavior Relationships.** Regression analyses revealed significant positive relationships between RSFC and externalizing symptoms, observed across all participants regardless of group membership, for the MTL subsystem (Figure 1). The brain-behavior relationships observed were consistent with a previous report demonstrating reduced segregation (weaker negative RSFC) between DN regions and task-positive network regions (such as dorsal ACC [dACC]) and supplementary motor area (SMA) in adults with ADHD (19,20). Higher externalizing scores were associated with weaker negative RSFC between the pIPL (MTL subsystem) and dACC and SMA.

**Negative Brain-Behavior Relationships.** A negative relationship was also observed between RSFC and externalizing symptoms (Figure 2). Again, the MTL subsystem was involved. Specifically, higher externalizing behaviors were associated with reduced positive RSFC between the Rsp and posterior parietal/dorsal occipital cortex. As above, this relationship was observed across all participants.

### Dimensional Analyses: Internalizing Symptoms

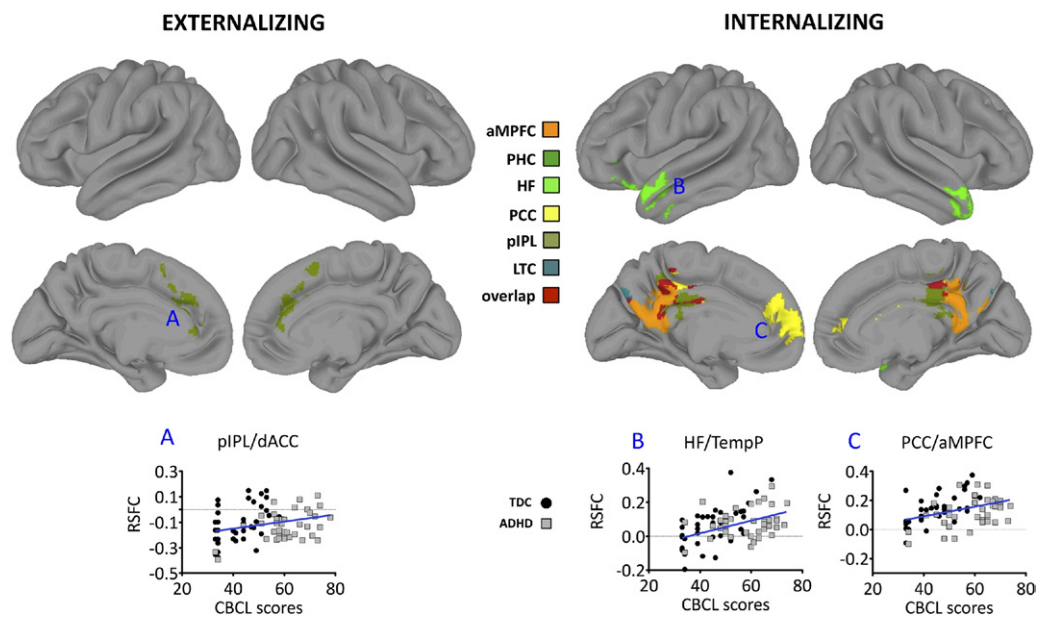
**Positive Brain-Behavior Relationships.** The core DN regions, PCC and aMPFC, as well as regions across the MTL and the dMPFC networks, exhibited increased positive RSFC in association with increasing internalizing scores across all participants (Figure 1). These observations are consistent with the notion that DN RSFC is related to self-referential internal thoughts (14,20). They are also consistent with a previously reported association between increased positive RSFC and rumination scores across depressive and healthy young adults (30). Specifically, we found reciprocally increased positive RSFC between the core regions of the DN (i.e., aMPFC and PCC) in relation to higher internalizing scores. Stronger RSFC between pIPL and the LTC and PCC was also related to higher internalizing scores. Finally, higher internalizing scores were related to increased RSFC between HF and the temporal poles.

**Negative Brain-Behavior Relationships.** Higher internalizing scores were associated with stronger negative RSFC between DN and task positive regions, such as dACC, SMA, and anterior insula (Figure 2). Specifically, aMPFC exhibited stronger negative RSFC with ventrolateral prefrontal and premotor cortex as a function of increasing internalizing scores. Similarly, Rsp exhibited stronger negative RSFC with the insula, dACC, and SMA in association with increasing internalizing scores.

### Dimension-by-Group Interactions

We tested for connections whose brain-behavior relationships were modulated by diagnostic status (i.e., dimension-by-diagnosis interactions). Both internalizing and externalizing scores exhibited differential patterns of RSFC as a function of the presence or absence of ADHD, but only brain/behavior relationships related to externalizing scores remained significant after correction (Figure 3 and Figure S4 in Supplement 1).

Interactions between diagnosis and externalizing scores revealed several dissociations. Specifically, children with ADHD showed decreased positive RSFC between temporal pole and several DN regions, including precuneus, PCC, and superior frontal cortex, as externalizing scores increased. In contrast, TDC showed the opposite relationship (Figure 3). A similar pattern was observed for RSFC between pIPL and the frontal pole: while children with ADHD showed decreasing positive RSFC between pIPL and the frontal pole in association with higher externalizing scores, TDC showed the opposite relationship (Figure 3).



**Figure 1.** Positive relationships between resting state functional connectivity (RSFC) and dimensional measures (internalizing and externalizing scores per Child Behavior Checklist [CBCL]). For externalizing (left panel) and internalizing CBCL scores (right panel), surface inflated maps display the clusters with significant positive relationships between scores and RSFC for each of the default network seeds examined. Red colored areas represent regions for which a significant brain-behavior relationship was observed for multiple seeds. The scatter plots at the bottom illustrate each participant's relationship between RSFC and CBCL scores. Left: Higher externalizing scores were associated with weaker negative RSFC between A, the posterior inferior parietal lobule (piPL) and dorsal anterior cingulate cortex (displayed in khaki). Right: Higher internalizing scores were associated with increased positive RSFC between B, the hippocampal formation and left and right temporal poles, and C, the core nodes of the default network (i.e., anterior medial prefrontal cortex and posterior cingulate cortex [PCC], displayed in yellow and orange, respectively). Similar relationships were found for the RSFC between the piPL and the PCC (displayed in khaki) and between the lateral temporal cortex and the precuneus (displayed in blue). Bonferroni correction accounting for the number of subsystems exceeding an omnibus cluster-level correction of  $p < .017$  was employed for multiple comparison correction. ADHD, attention-deficit/hyperactivity disorder; aMPFC, anterior medial prefrontal cortex; dACC, dorsal anterior cingulate cortex; HF, hippocampal formation; LTC, lateral temporal cortex; PHC, parahippocampal cortex; TDC, typically developing children; TempP, temporal pole.

### Group Comparisons: ADHD Versus TDC

Along with our primary examination of brain-behavior relationships, we compared RSFC between ADHD and TDC, independent of CBCL scores. Direct voxel-wise comparisons of the two groups, controlling for age, sex, and eyes status, revealed significant group differences (Figure S5 in Supplement 1). Specifically, the piPL (MTL subsystem) and LTC (dMPFC subsystem) exhibited greater negative RSFC with the lingual gyrus and cuneus in individuals with ADHD, relative to TDC. In contrast, the negative RSFC between HF and a region of temporoparietal cortex was decreased in children with ADHD relative to TDC. Finally, we noted decreased negative long-range RSFC between aMPFC and a temporoparietal region in ADHD relative to TDC.

### Follow-Up Analyses

Since previous studies have shown that psychostimulants may affect RSFC (31–34), supplemental analysis (Figure S6 in Supplement 1) excluded children with past or present stimulant therapy. Results were fundamentally similar, suggesting history of psychostimulant treatment did not confound our dimensional brain-behavior examinations.

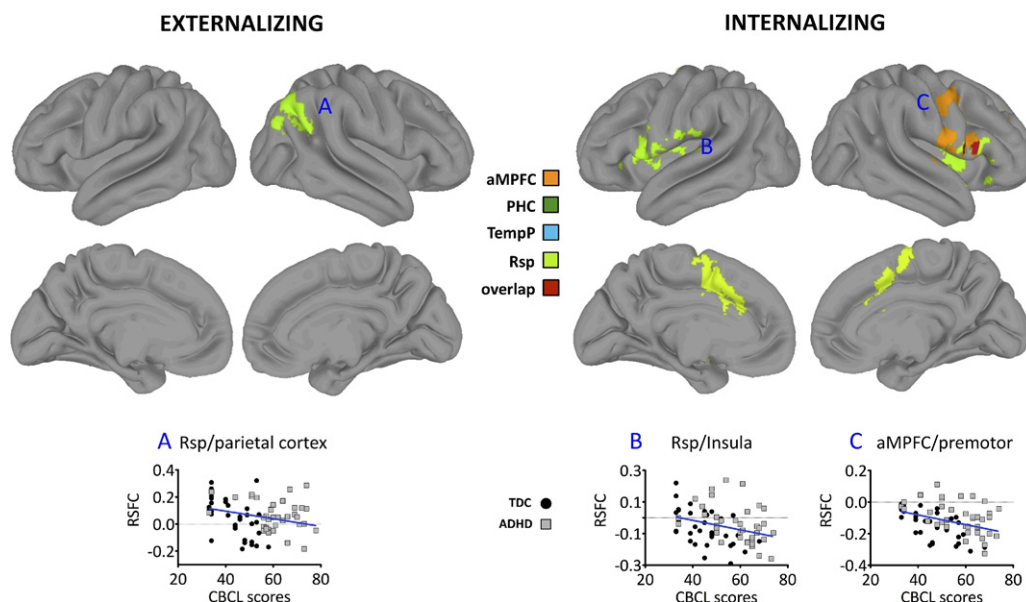
### Discussion

By adopting a hybrid approach in which we investigated brain-behavior relationships both dimensionally and categorically, we identified novel neural correlates of internalizing and externalizing scores in children aged 7 to 13 years. We identified dimensional brain-behavior relationships that were common to the two groups

(TDC, ADHD), as well as relationships that were specific to one of the diagnostic groups or distinct across diagnoses.

We observed several significant relationships between CBCL scores and RSFC within the DN across all children, independent of diagnosis. That both internalizing and externalizing symptoms were related to DN RSFC is not altogether surprising. The putative functions of the DN have been suggested by empirical studies demonstrating a common pattern of brain activation across tasks involving “internal mentation” (14), including moral decision making (35), autobiographical memory (36), making predictions about the future (36), or inferring mental states to others (37). These functions have been reported to be altered in psychopathologies associated with higher internalizing (e.g., depression [38]) as well as higher externalizing symptoms (e.g., ADHD [39]). For example, a recent report demonstrated that higher levels of externalizing symptoms were associated with impaired affective decision making in children (40). Studies have also shown that psychopathologies associated with increased internalizing symptoms such as depression were associated with impairments in theory of mind (41,42). In addition, the complexity of the DN is being increasingly appreciated. For example, Andrews-Hanna *et al.* (43) demonstrated that the MTL subsystem, implicated in remembering and formulating thoughts prospectively, can be dissociated from the dMPFC subsystem, which is implicated in the representation of mental states (self- or externally oriented). Taken together, these findings support the relevance of DN dysfunction to both internalizing (e.g., depression) and externalizing (e.g., impulsivity) symptoms.

Distinct brain-behavior relationships between DN RSFC and CBCL scores were observed, depending on whether externalizing



**Figure 2.** Negative relationships between resting state functional connectivity (RSFC) and dimensional measures (internalizing and externalizing symptoms per Child Behavioral Checklist [CBCL]). For externalizing (left panel) and internalizing CBCL scores (right panel), surface inflated maps display the clusters with significant negative relationships between scores and RSFC for each of the default network seeds examined. Red colored areas represent regions for which a significant brain-behavior relationship was observed for multiple seeds. The scatter plots at the bottom illustrate each participant's relationship between RSFC and CBCL scores. Left: Higher externalizing symptoms were associated with reduced positive RSFC between A, the retrosplenial cortex (Rsp) and posterior parietal/dorsal occipital cortex (represented in bright green) Right: Higher internalizing scores were associated with stronger negative RSFC between B, the Rsp and anterior insula (displayed in bright green), and C, the anterior medial prefrontal cortex and ventrolateral prefrontal and premotor cortex. Bonferroni correction accounting for the number of subsystems exceeding an omnibus cluster-level correction of  $p < .017$  was employed for multiple comparison correction. ADHD, attention-deficit/hyperactivity disorder; aMPFC, anterior medial prefrontal cortex; PHC, parahippocampal cortex; TDC, typically developing children; TempP, temporal pole.

or internalizing scores were examined. Regardless of diagnostic group, higher externalizing scores were associated with decreased negative RSFC between the MTL subsystem (part of the DN) and dorsal midline regions (part of the task-positive network) commonly implicated in cognitive control. Decreased negative RSFC between DN areas and so-called task-positive regions (6,7) has been reported in 1) typical control subjects who exhibit increased response time variability (7) and 2) individuals with an ADHD diagnosis (19), of which response time variability is the single strongest behavioral predictor (44–46). Interestingly, a recent report demonstrated a relationship between response time variability and task-related brain activity in ACC in TDC but in temporal pole in children with ADHD, thus suggesting differential involvement of these regions in response time variability, depending on diagnosis (47). Our findings suggest that further investigation into the links between functional connectivity, externalizing behaviors, ADHD, and increased response time variability is warranted.

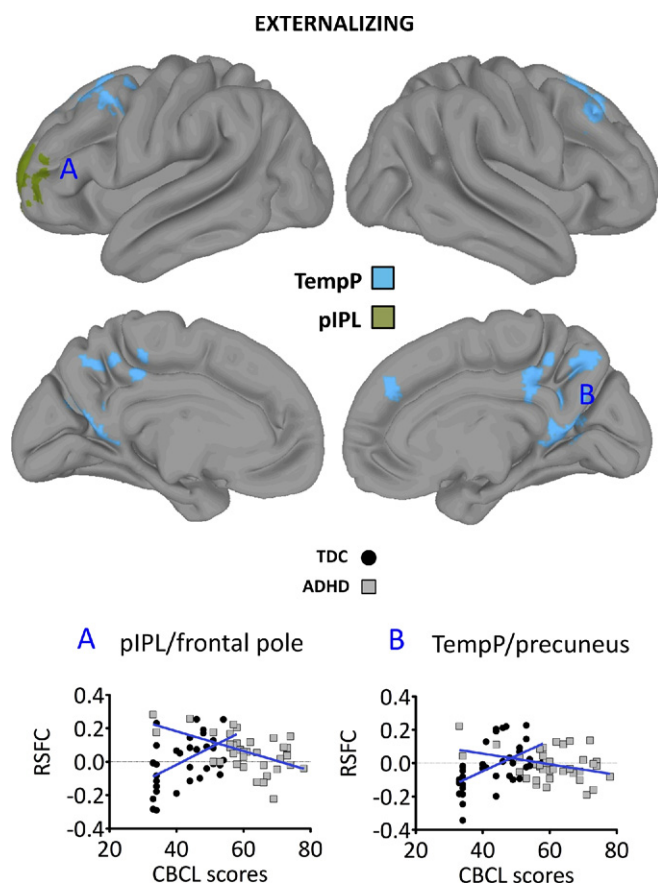
In considering why the brain-behavior relationships for externalizing scores appeared to be specific to the MTL subsystem, we note recent work implicating this subsystem in simulation of the future, or prospection, using episodic processes (14). Because prospection involves using and recombining stored information to plan and predict future events, it is not surprising that dysfunction in prospection has been discerned in participants exhibiting elevated externalizing behaviors such as impulsivity and/or hyperactivity (39,48,49).

Our findings draw attention to a recurring question—namely, what is the functional significance of patterns of negative functional connectivity? Negative RSFC is thought to reflect functional segregation or differentiation between brain systems (50). Accordingly, we speculate that decreased negative RSFC between the MTL

subsystem and dorsal midline regions (such as dACC) in individuals with higher externalizing scores reflects reduced functional differentiation between these systems and increased tendency toward cross-talk or interference—factors that likely contribute to suboptimal behavioral self-regulation. Similar observations have been noted in task-based studies. For example, Weissman *et al.* (51) suggested that suppression of activity within DN component regions is crucial to efficient task performance during attentionally demanding conditions. Consistent with this proposal, several studies have demonstrated that a failure to effectively suppress DN activity is associated with decreased activation within task-relevant processing systems and compromised behavioral performance (17,51,52).

The brain-behavior relationships observed for internalizing scores differed markedly from those observed for externalizing scores. Higher internalizing scores were associated with stronger positive RSFC between the midline core DN regions (i.e., PCC, aMPFC), as well as between PCC and pIPL (part of the MTL subsystem). Internalizing scores comprise anxious, inhibited, and depressed symptoms related to self-referential thoughts that affect the self-psychological environment. As such, our findings can be understood in the context of recent work implicating DN regions in spontaneous self-relevant cognition (14,43). The direction of the relationships we observed (i.e., stronger positive RSFC within the DN associated with higher internalizing scores) is consistent with a recent report implicating DN hyperconnectivity in depression and rumination. Specifically, Berman *et al.* (30) reported that excessive RSFC between the PCC and the subgenual cingulate cortex in depressed participants compared with healthy individuals was related to higher rumination traits.

Finally, we found that children exhibiting higher internalizing scores show increased RSFC between HF and the bilateral temporal



**Figure 3.** Relationships between resting state functional connectivity (RSFC) and categorical  $\times$  dimensional interactions. For externalizing scores measured with the Child Behavior Checklist (CBCL), surface maps display regions showing significant differences between typically developing children (TDC) and children with attention-deficit/hyperactivity disorder (ADHD) in the relationship between CBCL scores and RSFC for each of the default network seeds. The scatter plots at the bottom illustrate each participant's relationship between RSFC and symptom scores according to diagnostic status. Higher externalizing scores were associated with decreased positive RSFC between A, posterior inferior parietal lobule and frontal pole (displayed in khaki), and B, temporal pole and precuneus (displayed in blue) in children with ADHD, while in TDC, such relationships were absent. Bonferroni correction accounting for the number of subsystems exceeding an omnibus cluster-level correction of  $p < .017$  was employed for multiple comparison correction. pIPL, posterior inferior parietal lobule; TempP, temporal pole.

poles. Consistent with this pattern, Gorno-Tempini *et al.* (53) reported behavioral changes in a patient following temporal pole degeneration and described a clear shift from an extravert to an introvert personality. Other authors have also associated temporal pole dysfunction with both depression and anxiety (54). Together with these observations, our findings suggest that, although not yet well understood, temporal pole dysfunction could play a role in the pathophysiology of internalizing symptoms.

As expected, multiple DN components exhibited differences in RSFC related to internalizing and externalizing dimensions, regardless of diagnosis. Such findings support emerging dimensional perspectives of psychiatric illness (5). However, our results also suggest that neither categorical nor dimensional measures alone provide a complete characterization of the relationships between behavior/symptoms and brain function. For several functional connections, we found that the specific nature of the

dimensional brain-behavior relationships varied depending on whether or not psychopathology was present. For these functional connections, dimensional relationships were nested within diagnostic classification. These findings suggest that psychiatric illnesses (e.g., ADHD) should not be oversimplified as extremes of brain function (i.e., too much or too little functional connectivity). Instead, the presence of a psychopathological process may signify a more profound disturbance in aspects of brain function, with some, but not all, systems exhibiting qualitative differences. At the same time, the relevance of dimensional brain-behavior relationships to symptom severity also highlights the importance of not oversimplifying psychiatric diagnoses (i.e., by taking purely categorical approaches).

Our results should be considered in light of limitations. We selected the two broad scales of the CBCL as measures of symptom severity, reflecting a wide variety of behaviors and symptoms. Although each scale may be subdivided further into psychopathological syndromes (e.g., depression, anxiety disorders), our sample size did not provide sufficient power to investigate each syndrome scale in detail. Another limitation was our use of a priori seed regions limited to the DN, which constrained the brain regions and networks we investigated. Therefore, although we observed several significant brain-behavior relationships, our analyses were necessarily incomplete, with type II errors likely. One conceptual limitation may relate to evidence that children with ADHD exhibit a delayed developmental trajectory, relative to TDC (55). As such, the distinct dimensional brain/behavior findings observed in ADHD could, in part, reflect brain immaturity, which has been suggested to characterize various developmental disorders (e.g., [56]). Further developmental studies, ideally longitudinal, are required to determine the extent to which ADHD brain differences reflect differences in developmental status (i.e., brain maturity) versus age-independent aberrations. Although externalizing and internalizing scores did not differ between the sexes within either group and while no diagnosis by sex interaction was found, we cannot exclude the possibility that the higher proportion of male subjects in the ADHD group may have exerted a confounding effect, as sex effects have been previously reported (57,58). Finally, although we followed current recommendations to minimize introducing biases in ROI analyses (59), the exploratory nature of our work necessitates future replication in independent samples.

In summary, our findings highlight that RSFC provides a powerful tool for examining dimensional brain-behavior relationships and demonstrate the utility of considering both categorical and dimensional approaches when conceptualizing psychopathology. As such, they support the incorporation of dimensional scales in addition to the classical categorical approach in future diagnostic classifications (i.e., DSM-V).

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