Archival Report

Associations Between Resting-State Functional Connectivity and a Hierarchical Dimensional Structure of Psychopathology in Middle Childhood

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ABSTRACT

BACKGROUND: Previous research from the Adolescent Brain Cognitive Development (ABCD) Study delineated and validated a hierarchical 5-factor structure with a general psychopathology (p) factor at the apex and 5 specific factors (internalizing, somatoform, detachment, neurodevelopmental, externalizing) using parent-reported child symptoms. The present study is the first to examine associations between dimensions from a hierarchical structure and resting-state functional connectivity (RSFC) networks.

METHODS: Using 9- to 11-year-old children from the ABCD Study baseline sample, we examined the variance explained by each hierarchical structure level (p-factor, 2-factor, 3-factor, 4-factor, and 5-factor models) in associations with RSFC. Analyses were first conducted in a discovery dataset (n = 3790), and significant associations were examined in a replication dataset (n = 3791).

RESULTS: There were robust associations between the p-factor and lower connectivity within the default mode network, although stronger effects emerged for the neurodevelopmental factor. Neurodevelopmental impairments were also related to variation in RSFC networks associated with attention to internal states and external stimuli. Analyses revealed robust associations between the neurodevelopmental dimension and several RSFC metrics, including within the default mode network, between the default mode network with cingulo-opercular and "Other" (unassigned) networks, and between the dorsal attention network with the Other network.

CONCLUSIONS: The hierarchical structure of psychopathology showed replicable links to RSFC associations in middle childhood. The specific neurodevelopmental dimension showed robust associations with multiple RSFC metrics. These results show the utility of examining associations between intrinsic brain architecture and specific dimensions of psychopathology, revealing associations especially with neurodevelopmental impairments.

The Research Domain Criteria (1,2) and Hierarchical Taxonomy of Psychopathology (HiTOP) (3,4) are transdiagnostic initiatives that have pushed psychiatric research to move beyond traditional diagnostic categories toward examining psychiatric problems as a multidimensional structure. One advantage of this approach is that dimensional constructs may align more closely with underlying neural mechanisms than diagnoses (2,5). The HiTOP model proposes that dimensions of psychopathology are organized hierarchically, from narrowest to broadest, with each dimension potentially providing important information in terms of functional and biological correlates (6,7).

Several dimensions of psychopathology have been identified in children and adolescents (8–11). In particular, a study of the Child Behavioral Checklist (CBCL) (8) in Adolescent Brain Cognitive Development (ABCD) Study data found a hierarchical structure of psychopathology with a broad general psychopathology (p) factor at the apex, which progressively differentiates into narrower factors, with the most fine-grained structure representing 5 lower-order major dimensions (internalizing, externalizing, neurodevelopmental, somatoform, and detachment) (Figure S1) (12–16). The p-factor has been hypothesized as critical to understanding mental disorders (13). Alternatively, others have suggested that the p-factor may be too general and heterogeneous to reveal etiology (17,18). Thus, it remains unclear what level of specificity in phenotypes is most informative for understanding neural mechanisms.

At other levels of the hierarchy (12), the 2-factor solution was composed of broad internalizing and broad externalizing factors consistent with prior research (19–21). In the 3-factor structure, a neurodevelopmental factor (e.g., inattention, hyperactivity, impulsivity, clumsiness, repetitive behaviors) emerged from broad externalizing and internalizing dimensions. For the 4-factor solution, a somatoform factor separated from the broad internalizing factor. In the 5-factor structure, the broad internalizing factor split into

internalizing problems (e.g., anxiety, some mood symptoms) and detachment (e.g., social withdrawal). In this model, internalizing, externalizing, detachment, and somatoform problems clearly map on the corresponding HiTOP spectra. Although a neurodevelopmental spectrum is not yet represented in HiTOP, the ABCD Study and other evidence (22) supports its validity and potential inclusion of a neurodevelopmental spectrum in dimensional models of psychopathology.

This hierarchical structure was also validated using a number of clinically relevant measures. While the child p-factor alone was sufficient to account for some clinical variables (e.g., medical and mental health service utilization), more fine-grained dimensions, including some from the 5-factor structure, were necessary to more fully account for variance in other clinically relevant features, such as developmental delays and cognitive, social, and educational functioning. Overall, this previous study (12) delineated a hierarchical dimensional structure of psychopathology in one of the largest samples of children available to date, but also provided evidence for the incremental clinical utility of levels in this hierarchy. The present study sought to expand upon this previous investigation to examine the associations between the previously identified hierarchical structure of psychopathology and resting-state functional connectivity (RSFC) in the ABCD Study.

Previous studies in children and adolescents have examined the neural correlates of psychopathology, including RSFC. RSFC is based on using the temporal correlations of spontaneous fluctuations in blood oxygen level–dependent functional magnetic resonance imaging to parse the brain into functionally organized networks of brain regions (23). RSFC can be particularly useful for understanding brain-behavior relationships, as it can be used to examine the entire functional architecture of the brain, it has low participant burden, and there is evidence that the findings can be reproducible (24). Furthermore, alterations in brain network organization during development are implicated in the emergence of psychopathology (25).

Previous RSFC studies have focused either on a limited set of psychopathology dimensions (e.g., internalizing and externalizing) or on diagnostic categories (26–29) and did not examine hierarchy of psychopathology dimensions consistent with the HiTOP model. Among children and adolescents, greater p-factor scores derived from the CBCL were associated with reduced maturation of the default mode network (DMN), although this was driven primarily by neurodevelopmental symptoms (30). The DMN is a group of functionally correlated brain regions showing lower activation during goal-oriented tasks (31) and is involved in attention to internal states (23). Externalizing problems, including aggression and risky behaviors, and neurodevelopmental symptoms, including attention-deficit/hyperactivity disorder (ADHD) symptoms, have also been associated with a number of connectivity associations (28,32). These include lower anticorrelation (negative RSFC) between the DMN and both the cingulo-opercular network (CON) [a network associated with information integration, including salience attribution (33)] (34) and sensorimotor regions (28). The externalizing dimension also

has been linked to associations with connectivity with the salience network (a network involved in detection of relevant stimuli), such as lower connectivity with the DMN (28,32). Other studies found that child and adolescent internalizing symptoms (i.e., encompassing symptoms of anxiety and depression) were associated with alterations in connectivity in DMN regions (28,32,35), as well as disruptions in the ventral attention network (VAN) [a network associated with orienting and responding to novel stimuli (36)] (32,37).

Despite these promising findings, several questions remain unanswered regarding the associations between psychopathology and RSFC in middle childhood. First, most previous studies delineated only a general factor and/or internalizing and externalizing dimensions, despite evidence that more specific dimensions, such as a neurodevelopmental spectrum, may be important for investigating associations with clinically relevant risk indicators and outcomes (12). No previous research has investigated the associations between RSFC and hierarchically organized psychopathology dimensions consistent with the HiTOP model. Second, it is unclear whether associations with connectivity are associated with specific psychopathology dimensions over and above a p-factor.

The present study addressed these gaps by examining the relationship between middle childhood parent-reported hierarchical dimensions of psychopathology and RSFC throughout the brain (13 networks from the Gordon parcellation) in a large sample of 9- to 11-year-olds from the ABCD Study. Based on previous research, we hypothesized that the p-factor, internalizing symptoms, and neurodevelopmental symptoms would be associated with DMN connectivity and that internalizing symptoms would be associated with VAN connectivity. We tested these specific hypotheses in the context of an unbiased whole-brain network parcellation approach. Importantly, this study also incorporated best analytic practices, including examining results in a discovery dataset and then testing findings in a replication dataset. We used cumulative nested hierarchical models to test whether finer-grained factors that share variance with the p-factor account for variance over and above the p-factor when examining within- and between-network RSFC (38–40).

METHODS AND MATERIALS

Participants

A sample of 11,873 individuals was obtained from the ABCD Study, a large-scale study tracking 9- to 10-years-olds recruited from 21 research sites across the United States (see the Supplemental Methods for exclusion criteria) (41). These data were accessed from the National Institutes of Mental Health Data Archive (https://doi.org/10.15154/1460410) (see Acknowledgments). The present study is based on 9987 unrelated children, randomly selecting 1 child per family when more than 1 participated, from the baseline ABCD 2.0.1 data release (12).

Participants were removed from analyses in the present study for not having at least 1 resting-state scan that passed quality assurance criteria (n = 550), for imaging run on a Philips scanner (n = 1208) owing to a processing error in the ABCD 2.0.1 data release, and for missing data (n = 631) (Table S1).

Functional Connectivity and Psychopathology Dimensions

Table 1. Demographic Characteristics for the Discovery and Replication Datasets

	Discovery Dataset (n = 3790)	Replication Dataset (n = 3791)	Test Statistic[a]	p Value
Sex, Female, %	48.9%	47.5%	1.349	.25
Race/Ethnicity, White, %	50.8%	51.3%	0.941	.92
Age, Years	9.920 (0.620)	9.899 (0.618)	−1.495	.14
Financial Adversity[b]	0.476 (1.111)	0.485 (1.122)	0.386	.67
Average Head Motion[c]	0.250 (0.229)	0.257 (0.238)	1.322	.19
Scanner Type, Siemens, %	70.3%	72.0%	2.739	.10
Hierarchical Dimensions of Psychopathology				
p-factor	0.020 (0.944)	0.026 (0.915)	0.323	.75
2-factor				
Internalizing	0.041 (0.900)	0.035 (0.896)	−0.310	.76
Externalizing	0.033 (0.891)	0.043 (0.864)	0.495	.62
3-factor				
Internalizing	0.060 (0.893)	0.049 (0.886)	−0.495	.62
Externalizing	0.049 (0.850)	0.054 (0.829)	0.243	.81
Neurodevelopmental	0.020 (0.830)	0.034 (0.833)	0.733	.46
4-factor				
Internalizing	0.055 (0.855)	0.058 (0.831)	0.15	.88
Externalizing	0.061 (0.860)	0.049 (0.861)	−0.604	.55
Neurodevelopmental	0.028 (0.831)	0.044 (0.830)	0.842	.40
Somatoform	0.069 (0.779)	0.065 (0.774)	−0.24	.81
5-factor				
Internalizing	0.065 (0.867)	0.067 (0.838)	0.079	.94
Externalizing	0.041 (0.841)	0.051 (0.828)	−0.713	.48
Neurodevelopmental	0.041 (0.841)	0.057 (0.832)	0.815	.42
Somatoform	0.093 (0.790)	0.085 (0.781)	−0.443	.66
Detachment	0.049 (0.749)	0.039 (0.761)	−0.595	.55

Results are presented as mean (SD) except where noted.

[a]Independent-sample t tests were used to compare means for the discovery and replication dataset samples. χ^2 tests were used to compare ordinal/binary variables across samples.

[b]Summation of endorsement from 7 questions of parent-rated financial difficulties.

[c]Average framewise displacement in mm.

Next, the remaining dataset was divided into discovery (n = 3790) and replication (n = 3791) datasets (Table 1).

Measures

We used psychopathology dimensions factor-analytically derived in the ABCD sample (12) (see Figure S1) using the parent-rated CBCL from the Achenbach System of Empirically Based Assessment (21) (see Table S2 for factor and dimension reliabilities). Parents (mean age = 39.94 years, SD = 6.93, 89.03% female) rated their children's psychopathology occurring in the past 6 months on a 3-point scale (0 = never, 1 = sometimes, 2 = often). The hierarchical structure of psychopathology used in this study was delineated in the previous investigation through exploratory factor analysis with oblique (geomin) rotation, whereby the maximal number of factors was determined using parallel analyses and interpretability of factor solutions (42). For more details of the creation of factor scores used in analyses, see Michelini et al. (12).

Imaging Procedure

ABCD imaging procedures have been detailed in previous studies (43,44). All children were scanned in a 3T scanner (either Siemens or General Electric) with a 32-channel head coil and completed T1-weighted and T2-weighted structural scans (1 mm isotropic). Participants also completed four 5-minute resting-state blood oxygen level–dependent functional magnetic resonance imaging scans, with their eyes open and fixated on a crosshair. Resting-state images were acquired in the axial plane using an echo-planar imaging sequence. A data analysis pipeline was created in which resting-state data were normalized and time course detrended. Signals of noninterest, including motion, white matter, ventricles, and whole brain, were removed by generalized linear model regression (43). Then, frames with excessive motion were removed (i.e., >0.3-mm framewise displacement, ≥5 contiguous frames, motion filtered for respiratory signals). Data were band-pass filtered between 0.009 Hz and 0.08 Hz. Other resting-state image parameters varied by 3T scanner and have been previously detailed (https://abcdstudy.org/images/Protocol_Imaging_Sequences.pdf). Fisher Z-transformed averages of all pairwise correlations within each of the 13 Gordon networks (e.g., within the DMN or frontoparietal network [FPN]) and between each of the 13 networks with the other 12 networks (e.g., between the DMN and the FPN) were examined (38).

Statistical Analysis

We first randomly split the data into discovery (n = 3790) and replication (n = 3791) datasets. All analyses were first conducted

in the discovery dataset. Every model was conducted as a hierarchical linear model (HLM) using the R *lme4* package (45). The research sites were modeled as random intercepts to account for nonindependence of observations, and every model included age, sex, financial adversity [a proxy for socioeconomic status, because previous research links socioeconomic status with altered RSFC (46)], race/ethnicity, average motion, and scanner type as covariates, following ABCD Study recommendations for best practice (47) (see Table S3 for associations between covariates with replicated RSFC and psychopathology metrics). Analyses proceeded in 2 steps.

Step 1. Following the general approach of the previous study in delineating and validating the investigated hierarchical structure (12), we conducted a series of hierarchical cumulative nested HLMs for each RSFC metric. For these models, we entered factor structures with progressively greater number of factors (baseline model [only covariates]; p-factor; 2-factor: internalizing and externalizing; 3-factor: internalizing, externalizing, neurodevelopmental; 4-factor: internalizing, externalizing, neurodevelopmental, somatoform; 5-factor: internalizing, externalizing, neurodevelopmental, somatoform, detachment) as blocks with each RSFC metric as the dependent variable. Models were progressively hierarchically nested, so that the final model contained the 5-factor structure in addition to each of the more parsimonious structures (i.e., baseline, p-factor, 2-factor, 3-factor, and 4-factor). Thus, using HLMs, for every

RSFC outcome metric, we tested whether each hierarchy level as a block accounted for an increase in variance compared with a model not accounting for this hierarchy level (e.g., whether the 5-factor structure accounted for greater variance than a model not including this structure). Changes in fit were assessed using change in R^2 [ΔR^2] and the *lmer* package *anova* function (45) [follow-up analyses obtained F statistics using the *pbkrtest* package (48); see Table S4 for Akaike information criterion]. Any factor structures that passed adjusted false discovery rate (aFDR) [which uses an adaptive procedure to keep the FDR close to the specified target proportion of true null hypotheses and has been found to be useful when coping with data dependencies (49)] in the discovery dataset were examined in the replication dataset.

Step 2. When adding a factor structure produced an aFDR-corrected significant increase in variance explained—that is, aFDR $p < .05$ with 455 aFDR-corrected comparisons (i.e., 91 tests [13 within-network, 78 between-network] $\times$ 5 models)—we ran an additional HLM to examine the association with each of the individual dimensions included in that factor structure in both the discovery and the replication datasets. For example, if the 5-factor structure accounted for a significant increase in variance over simpler structures, we examined an additional model including only the significant structure (e.g., 5-factor structure) to examine which of the dimensions in the 5-factor structure was responsible for the increment in variance accounted for.

Table 2. Statistics for Models in the Discovery and Replication Sets for All Models Surviving aFDR Correction in the Discovery Set[a]

RSFC Metric	Model	Discovery Set			Replication Set		
		F Statistic[b]	aFDR p Value	ΔR^2	F Statistic[b]	p Value	ΔR^2
p-Factor							
DMN–DMN	p-factor	11.790	.037	.25%	7.948	.005	.17%
DMN–VAN	p-factor	12.254	.027	.30%	2.407	.112	.06%
2-Factor[c]							
3-Factor							
CON–CON	3 factor	7.955	.006	.59%	1.435	.224	.13%
CON–DMN	3 factor	9.142	.002	.66%	5.616	.001	.44%
DMN–AUD	3 factor	6.502	.027	.47%	0.738	.525	.05%
DMN–DMN	3 factor	6.998	.027	.50%	7.924	< .001	.51%
DMN–Other	3 factor	6.099	.027	.43%	3.095	.025	.23%
DAN–Other	3 factor	4.486	.027	.32%	3.259	.025	.19%
4-Factor							
FPN–FPN	4 factor	4.559	.041	.45%	1.224	.300	.12%
FPN–Other	4 factor	4.580	.041	.47%	1.931	.100	.20%
5-Factor							
Other–RSP	5 factor	4.456	.027	.58%	1.704	.129	.22%
SA–SA	5 factor	4.308	.032	.55%	1.485	.189	.19%

ΔR^2, change in marginal proportion of variance explained by the entire model from the more parsimonious cumulative nested model (e.g., from the cumulative nested 3-factor model to the 2-factor model); aFDR, adjusted false discovery rate; AUD, auditory network; CON, cingulo-opercular network; DAN, dorsal attention network; DMN, default mode network; FPN, frontoparietal network; RSFC, resting-state functional connectivity; RSP, retrosplenial network; SA, salience network; VAN, ventral attention network.

[a]aFDR correction was applied only to the discovery dataset, not to the replication dataset. To obtain these results, cumulative nested hierarchical linear models were run. For example, the 2-factor structure model included covariates in addition to the p-factor, and 2-factor solutions as predictors and the fit of this model were compared with a model with covariates and p-factor solutions as predictors.

[b]F statistics were examined in follow-up analyses using the Krmodcomp function.

[c]No models survived aFDR correction.

We used the HLM procedure described above to analyze the associations between factor scores [i.e., p-factor, 2-factor, 3-factor, 4-factor, and 5-factor extracted factor scores as in previous research (12)] and functional connectivity within and between each of the 13 Gordon networks (38) (auditory, CON, cinguloparietal, DMN, dorsal attention [DAN], FPN, Other [also referred to as the unassigned network], retrosplenial-temporal, salience, sensorimotor-hand, sensorimotor-mouth, VAN, and visual). Results were defined as replicating if both the significant factor solution ($p < .05$ in the replication dataset) and the significant dimension within that factor solution ($p < .05$ in the replication dataset) replicated (see the Supplement for results when using broader definitions of replication). See Table S5 for overall means for each of the within- and between-network metrics. Follow-up analyses examined models when including pubertal status and total cognition (Supplemental Methods; Table S3), as well as without the inclusion of financial adversity, given the possibility that these variables may be contributing to the association between psychopathology and

RSFC, with results generally remaining consistent when accounting for these variables (Table S6). Results are expressed as standardized estimates (βs).

RESULTS

Associations Between RSFC and the Hierarchical Dimensions of Psychopathology

p-Factor Model. As predicted, lower within-network connectivity in the DMN was associated with higher child p-factor scores (Table 2; Figure 1). Specifically, the p-factor model accounted for a significant increment in variance over the baseline model, with the p-factor associated with lower within-network DMN connectivity (Table 3; Figure 2; Figure S2 for scatterplots). This finding replicated in the independent data set (Tables 2 and 3). Without the inclusion of financial adversity, the p-factor was associated with lower within-network DAN RSFC ($\beta = -.06$, $p = .001$). There were no other RSFC associations with p-factor scores that passed aFDR correction
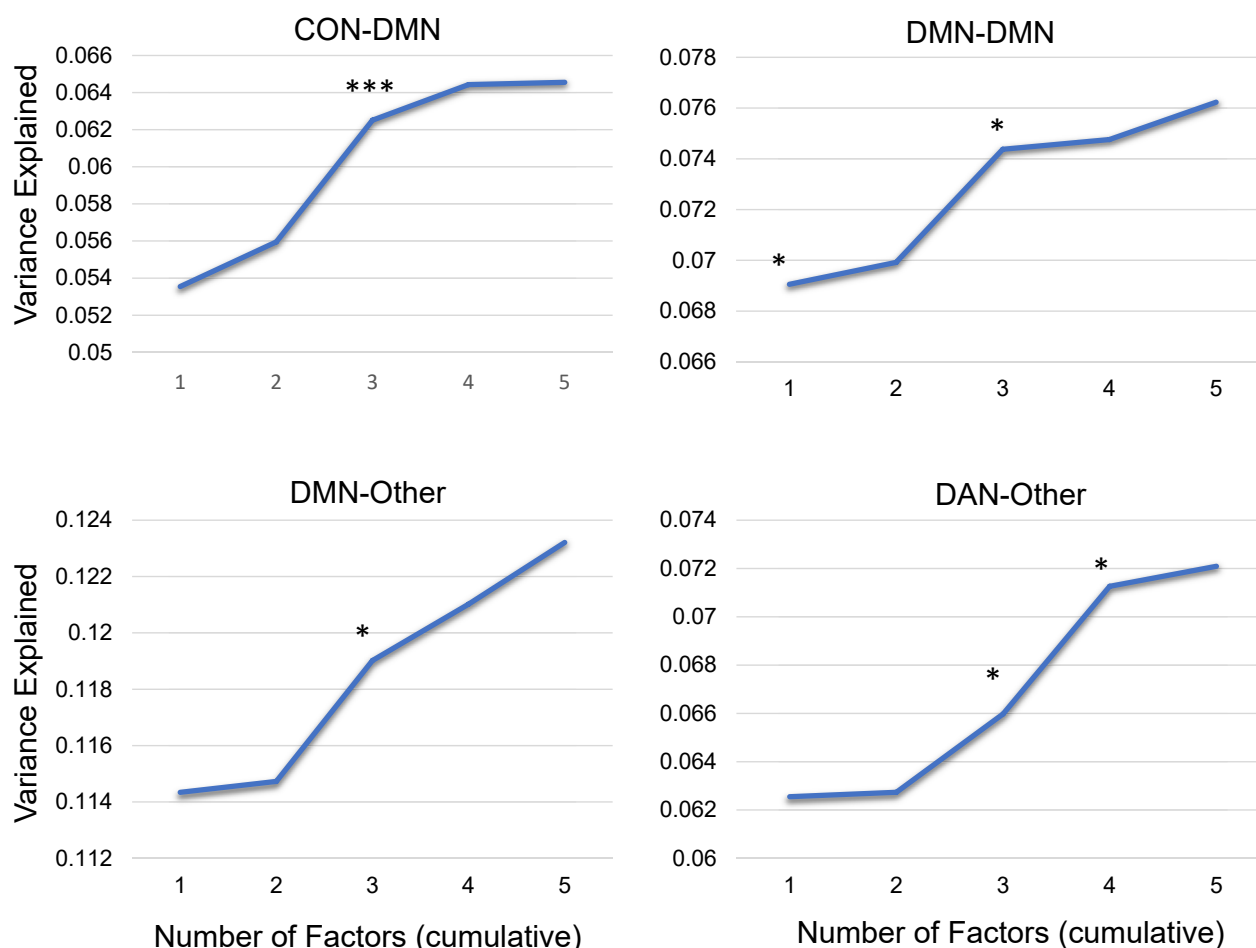

Figure 1. Proportion of variance explained (R^2) for each cumulative nested factor model (1- to 5-factor solutions) for resting-state functional connectivity metrics in the discovery dataset. Asterisks indicate significant change in R^2 for that factor model vs. the more parsimonious model: *$p < .05$, **$p < .01$, ***$p < .001$. To obtain these results, cumulative nested hierarchical linear models were run. For example, the 2-factor structure model included covariates in addition to the 1-factor (i.e., p-factor) and 2-factor solutions. The fit of this model was compared with a model with covariates and 1-factor solutions as predictors. CON, cingulo-opercular network; DAN, dorsal attention network; DMN, default mode network.

Table 3. Model Estimates for All Dimensions for Significant Models Examining Associations Between Resting-State Functional Connectivity and Hierarchical Dimensions of Psychopathology[a]

Model	Discovery Set			Replication Set		
	β	t	p	β	t	p
p-Factor						
DMN–DMN	−.055	−3.350	.001	−.045	−2.823	.005
3-Factor						
CON–DMN						
Internalizing	−.104	−4.531	<.001[b]	−.050	−2.333	.02
Externalizing	.012	0.593	.55	.012	0.638	.52
Neurodevelopmental	.125	5.637	<.001	.099	4.752	<.001
DMN–DMN						
Internalizing	.052	2.290	.02	.019	0.857	.39
Externalizing	−.012	−0.589	.56	.023	1.223	.22
Neurodevelopmental	−.114	−5.150	<.001	−.104	−4.894	<.001
DMN–Other						
Internalizing	.049	2.174	.03	.005	0.242	.81
Externalizing	.003	0.173	.86	.028	1.536	.13
Neurodevelopmental	−.088	−4.101	<.001	−.064	−3.095	.002
DAN–Other						
Internalizing	−.059	−2.553	.01	−.008	−0.362	.72
Externalizing	−.022	−1.067	.29	−.023	−1.202	.23
Neurodevelopmental	.083	3.743	<.001	.057	2.654	.008

CON, cingulo-opercular network; DAN, dorsal attention network; DMN, default mode network.

[a]Models with connectivity as the outcomes and dimensions entering simultaneously as predictors, and controlling for age, sex, race/ethnicity, financial adversity, average head motion, and scanner type as covariates.

[b]Although these models are significant in discovery and replication samples, when examining a model with just internalizing symptoms with resting-state functional connectivity, internalizing symptoms are not significant, indicating multicollinearity (see Table S21).

in the discovery dataset and replicated in the replication dataset. See Table 2 for results for all models that were significant in the discovery dataset but failed to replicate in the replication dataset; for the p-factor, DMN-to-VAN connectivity did not replicate.

2-Factor Model. The 2-factor model (internalizing and externalizing) did not account for a significant increment in variance over the model with baseline + p-factor in the discovery dataset following aFDR correction for any of the RSFC metrics (see Tables S7–S19 for all step 1 models run in the discovery dataset).

3-Factor Model. As can be seen in Table 2 and Figure 1, focusing on results that replicated, the 3-factor model (internalizing, externalizing, and neurodevelopmental) accounted for additional variance over the baseline + p-factor + 2-factor model for several RSFC metrics, including within-network DMN, DMN–CON and DMN–Other, and DAN–Other. For within-network DMN connectivity, the follow-up analyses examining each individual factor of the 3-factor model indicated that lower within-network DMN connectivity was associated with higher 3-factor neurodevelopmental dimension scores (Table 3). See Table S20 for models results when including both neurodevelopmental dimension and p-factor scores, with results generally remaining consistent, although the association between p-factor scores with within-network DMN was reduced: p = .14 (of note, p-factor

and 3-factor neurodevelopmental factor showed a very strong association [β = .80] and the models in Table S20 show evidence of multicollinearity). See Table S21 for results with each of the individual 3-factor dimensions. Furthermore, follow-up analyses indicated that lower connectivity between the DMN and Other network was also associated with higher 3-factor neurodevelopmental dimension scores (Table 3). Additional analyses further indicated that lower anticorrelation (i.e., less negative connectivity) between the CON and DMN and between the DAN and Other network were associated with higher neurodevelopmental dimension scores (Table 3). See Figure 2 for a summary of these results.

4- and 5-Factor Models. The 4-factor (internalizing, externalizing, neurodevelopmental, and somatoform) and 5-factor (internalizing, externalizing, neurodevelopmental, somatoform, and detachment) models did not add a significant increment in variance over the simpler structures for any RSFC measure in both the discovery and replication datasets (Table 2).

DISCUSSION

This study contributes significantly to our understanding of the neural correlates of hierarchically organized psychopathology dimensions consistent with the HiTOP model in middle childhood. The results provide novel information about the

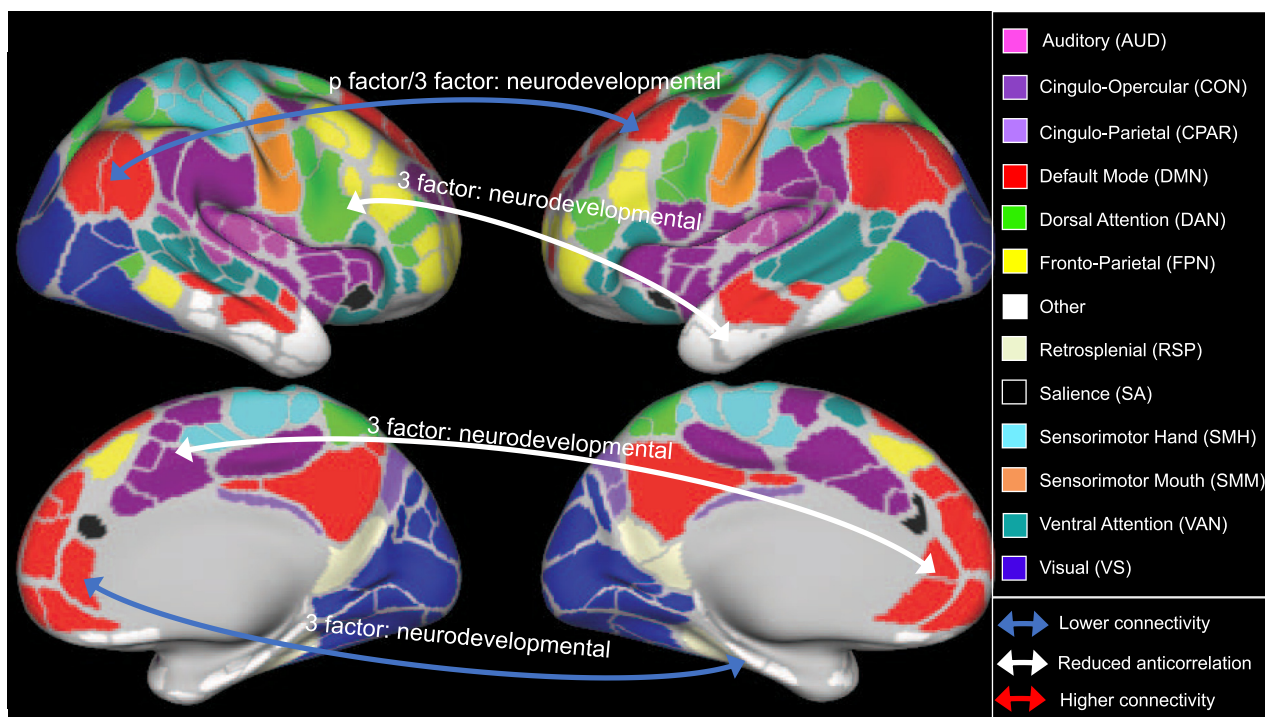Functional Connectivity and Psychopathology Dimensions

Figure 2. An illustration of all significant resting-state functional connectivity associations with hierarchical dimensions of psychopathology for the Gordon network parcellation.

relationship of functional networks across the entire brain architecture with specific dimensions of psychopathology. Using a robust and rigorous 2-sample strategy, this study tested hypotheses about associations between RSFC and psychopathology dimensions in the ABCD baseline sample using an unbiased whole-brain networks approach. In terms of robust associations, we found evidence for associations between p-factor and within-network DMN underconnectivity. There was also evidence that greater neurodevelopmental problems were associated with within-network DMN underconnectivity, but also associations with RSFC among other networks, including the CON, DAN, and Other network. The present study indicates that p-factor and neurodevelopmental problems are associated with RSFC networks associated with attention to internal states and external stimuli (e.g., DMN, CON), which may have important implications for the etiology of these problems.

This study found that higher p-factor scores were robustly associated with lower within-network DMN connectivity. This is consistent with previous findings of an association between DMN connectivity and general psychopathology (27,30). However, lower within-network DMN connectivity was also associated with neurodevelopmental symptoms. When using a broader definition of replication (see Supplemental Results), there was also limited evidence of reduced DMN–VAN connectivity. Potentially consistent with these findings, a consensus is beginning to form that dysfunctional DMN connectivity may be a general marker of psychopathology (50), although it is perhaps most strongly related to neurodevelopmental features. Interestingly,

without the inclusion of financial adversity, the p-factor was also associated with lower within-network RSFC in the DAN, a network associated with top-down attentional processes (36), which is consistent with previous research finding DAN RSFC alterations with a range of psychopathology (51–53). This suggests that the inclusion of financial adversity attenuated the association between p-factor and DAN RSFC.

In addition, the present study indicates that several RSFC metrics are associated with greater severity of neurodevelopmental symptoms in middle childhood. This neurodevelopmental dimension includes questions tapping into inattention, hyperactivity, clumsiness, repetitive behavior, and impulsivity. These neurodevelopmental symptoms are associated with deficits in cognitive abilities, including attentional processes (12,54). Previous work using the dimensions examined here found that the neurodevelopmental spectrum showed the strongest associations with cognitive factors (i.e., fluid and crystalized intelligence) (r values from $-.13$ to $-.20$) compared with other hierarchical dimensions (12). Notably, in the present study, associations with RSFC remained consistent when including cognition in the models, indicating that these associations are independent of general cognitive impairments. The identified connectivity metric associations indicate that greater neurodevelopmental symptoms are associated with several specific networks: DMN (3 findings), CON (2 findings), and Other (2 findings). Furthermore, when using a somewhat broader definition of replication (see Supplemental Results), there was also some evidence for reduced within-network CON and within-network FPN connectivity being associated with increased neurodevelopmental

dimension scores. Several of these networks are implicated in attention to both internal and external stimuli (e.g., DMN and CON) (55), as well as in the ability to reorient attention between internal thoughts and external attention (26). Research indicates that specifically diminished anticorrelation between DMN and task positive networks (e.g., CON) may contribute to attention difficulties (28), with impairments in connectivity between these networks associated with worse developmental trajectories for attention (26).

Considering associations that replicated across 2 samples, neurodevelopmental symptoms were linked to several associations with DMN connectivity. Elevated neurodevelopmental dimension symptoms were associated with lower within-network DMN connectivity—a relationship that showed some evidence of being stronger than the associations found for the p-factor—and other associations involving the DMN, including smaller anticorrelation with the CON and lower connectivity with the Other network. These observations are consistent with previous research linking DMN associations with attention-deficit/hyperactivity disorder symptoms (28,34,56–59). Although speculative, these findings indicate an important role for the DMN and point to disruptions in DMN-regulated functions, such as mental simulations and attention to internal thoughts (23,60), as potentially important correlates of neurodevelopmental symptoms.

The present study also found robust associations between higher neurodevelopmental symptoms and connectivity impairments in the CON and DAN. The CON is a network associated with information integration and salience attribution (33). These findings are consistent with previous research that found evidence for altered CON connectivity associated with neurodevelopmental symptoms (61–63). In addition, impaired anticorrelations between the DAN and the Other network may be reflective of impairments in neural functional integration that may contribute to neurodevelopmental symptoms (36). However, these hypotheses about the potential functional significance of RSFC associations are speculative and in need of direct testing.

A number of significant RSFC results were found specifically with the neurodevelopmental factor. Previous research has found evidence indicating developmental consistency of factors over the course of childhood and adolescence (64). However, connectivity associations are implicated in the etiopathogenesis of neurodevelopmental disorders (65,66). We therefore cannot rule out that the neurodevelopmental factor may be more strongly associated with RSFC than other factors in middle childhood because of factors associated with ongoing maturation and the development of neurodevelopmental psychopathology. The possibility exists that the neurodevelopmental factor may be indexing symptoms that are more prevalent during childhood (e.g., hyperactivity symptoms) (67), and that associations with other factors may become more robust at different points in development. For example, associations with internalizing and externalizing symptoms may strengthen over development. Theories regarding the development of internalizing and externalizing symptoms implicate associations with networks involved in rumination and attention to internal states (DMN) and attention responding to novel stimuli (VAN). However, the present study raises questions about whether associations with the networks, especially the DMN, may be more attributable to greater neurodevelopmental than internalizing or externalizing symptoms, at least in middle childhood. Future research using ABCD data should examine associations between RSFC and clinical levels of internalizing and externalizing symptoms.

Several limitations of the present study should be noted. The ABCD data used in this study are cross-sectional. Future studies in this sample could examine the association between the RSFC metrics and changes in neurodevelopmental problems over time to shed light on these associations. The psychopathology measure is limited to parent report and a single, albeit comprehensive, assessment system (the CBCL). Future research should examine whether reports from other raters (e.g., teachers, other caregivers, the youth) show similar associations with RSFC. Furthermore, results were conducted using the Gordon parcellation, and future research should examine the results using another parcellation definition [e.g., the Schaefer parcellation (68)]. The findings in this study were smaller than reported estimates in other, smaller samples (26,28). This may be expected with a large, nonclinical, heterogeneous sample. In addition, owing to computational challenges in analysis and data sharing in datasets of this size, we examined parcel-based results. There were a number of other potential statistical approaches to this study, including working with voxelwise data or combining task and rest data to increase the amount of functional connectivity data. Furthermore, data-driven analyses of RSFC may enable the identification of more fine-grained associations between variation within RSFC networks and symptoms. These more fine-grained analyses may reveal robust associations with other psychopathology dimensions. Such alternative approaches are important future directions. In addition, a number of metrics of connectivity at the network level do not reach intraclass correlation coefficients of 0.60 at 20 minutes (69) and may require greater amounts of data to achieve higher intraclass correlation coefficients, although some research indicates that intrasession network intraclass correlation coefficients approximate 0.60 starting around 12 minutes (70). Thus, the present results, although replicated, should be interpreted with caution as some of the nonsignificant findings could reflect lower reliability due to the relatively short length of the resting-state session.

In summary, this study constitutes first steps in examining associations between RSFC and the hierarchical dimensional structure of psychopathology in middle childhood. We found evidence that RSFC connectivity associations were specific to the p-factor and the neurodevelopmental dimension, and that the other dimensions of psychopathology (e.g., internalizing, externalizing) were not associated with RSFC associations. This study shows that both p-factor and neurodevelopmental factors may be important in understanding functional neural associations with psychopathology in middle childhood. That the neurodevelopmental dimension emerged in several robustly related RSFC associations across 2 large samples highlights the importance of delineating this factor in neuroimaging studies of psychopathology dimensions to better understand neural underpinnings. This suggests that further research on connectivity associations should target specific dimensions of psychopathology, although comprehensive assessment of psychopathology is essential for confirming specificity.

ARTICLE INFORMATION

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REFERENCES

1. Cuthbert BN (2014): The RDoC framework: Facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry 13:28–35.
2. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. (2010): Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. Am J Psychiatry 167:748–751.
3. Kotov R, Krueger RF, Watson D (2018): A paradigm shift in psychiatric classification: The Hierarchical Taxonomy Of Psychopathology (HiTOP). World Psychiatry 17:24–25.
4. Kotov R, Krueger RF, Watson D, Achenbach TM, Althoff RR, Bagby RM, et al. (2017): The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. J Abnorm Psychol 126:454–477.
5. Braun U, Schaefer A, Betzel RF, Tost H, Meyer-Lindenberg A, Bassett DS (2018): From maps to multi-dimensional network mechanisms of mental disorders. Neuron 97:14–31.
6. Krueger RF, Kotov R, Watson D, Forbes MK, Eaton NR, Ruggero CJ, et al. (2018): Progress in achieving quantitative classification of psychopathology. World Psychiatry 17:282–293.
7. Latzman RD, DeYoung CG, Workgroup HNF (2020): Using empirically-derived dimensional phenotypes to accelerate clinical neuroscience: The Hierarchical Taxonomy of Psychopathology (HiTOP) framework. Neuropsychopharmacology 45:1083–1085.
8. Achenbach TM (1966): The classification of children's psychiatric symptoms: A factor-analytic study. Psychol Monogr 80:1–37.
9. Martel MM, Pan PM, Hoffmann MS, Gadelha A, do Rosario MC, Mari JJ, et al. (2017): A general psychopathology factor (p factor) in children: Structural model analysis and external validation through familial risk and child global executive function. J Abnorm Psychol 126:137–148.
10. Patalay P, Fonagy P, Deighton J, Belsky J, Vostanis P, Wolpert M (2015): A general psychopathology factor in early adolescence. Br J Psychiatry 207:15–22.
11. Tackett JL, Lahey BB, van Hulle C, Waldman I, Krueger RF, Rathouz PJ (2013): Common genetic influences on negative emotionality and a general psychopathology factor in childhood and adolescence. J Abnorm Psychol 122:1142–1153.
12. Michelini G, Barch DM, Tian Y, Watson D, Klein DN, Kotov R (2019): Delineating and validating higher-order dimensions of psychopathology in the Adolescent Brain Cognitive Development (ABCD) Study. Transl Psychiatry 9:261.
13. Caspi A, Houts RM, Belsky DW, Goldman-Mellor SJ, Harrington H, Israel S, et al. (2014): The p factor: One general psychopathology factor in the structure of psychiatric disorders? Clin Psychol Sci 2:119–137.
14. Lahey BB, Applegate B, Hakes JK, Zald DH, Hariri AR, Rathouz PJ (2012): Is there a general factor of prevalent psychopathology during adulthood? J Abnorm Psychol 121:971–977.
15. Lahey BB, Krueger RF, Rathouz PJ, Waldman ID, Zald DH (2017): A hierarchical causal taxonomy of psychopathology across the life span. Psychol Bull 143:142–186.
16. Murray AL, Eisner M, Ribeaud D (2016): The development of the general factor of psychopathology "p factor" through childhood and adolescence. J Abnorm Child Psychol 44:1573–1586.
17. Bonifay W, Lane SP, Reise SP (2017): Three concerns with applying a bifactor model as a structure of psychopathology. Clin Psychol Sci 5:184–186.
18. Bornovalova MA, Choate AM, Fatimah H, Petersen KJ, Wiernik BM (2020): Appropriate use of bifactor analysis in psychopathology research: appreciating benefits and limitations. Biol Psychiatry 88:18–27.
19. Olino TM, Dougherty LR, Bufferd SJ, Carlson GA, Klein DN (2014): Testing models of psychopathology in preschool-aged children using a structured interview-based assessment. J Abnorm Child Psychol 42:1201–1211.
20. Waldman ID, Poore HE, van Hulle C, Rathouz PJ, Lahey BB (2016): External validity of a hierarchical dimensional model of child and adolescent psychopathology: Tests using confirmatory factor analyses and multivariate behavior genetic analyses. J Abnorm Psychol 125:1053–1066.
21. Achenbach TM, Rescorla LA (2001): Manual for the ASEBA School-Age Forms and Profiles. Burlington, VT: Research Center for Children, Youth, and Families, University of Vermont.
22. Andrews G, Pine DS, Hobbs MJ, Anderson TM, Sunderland M (2009): Neurodevelopmental disorders: Cluster 2 of the proposed meta-structure for DSM-V and ICD-11. Psychol Med 39:2013–2023.
23. Raichle ME (2015): The brain's default mode network. Annu Rev Neurosci 38:433–447.
24. Woodward ND, Cascio CJ (2015): Resting-state functional connectivity in psychiatric disorders. JAMA Psychiatry 72:743–744.
25. Ernst M, Torrisi S, Balderston N, Grillon C, Hale EA (2015): fMRI functional connectivity applied to adolescent neurodevelopment. Annu Rev Clin Psychol 11:361–377.
26. Whitfield-Gabrieli S, Wendelken C, Nieto-Castañón A, Bailey SK, Anteraper SA, Lee YJ, et al. (2020): Association of intrinsic brain architecture with changes in attentional and mood symptoms during development. JAMA Psychiatry 77:378–386.
27. Elliott ML, Romer A, Knodt AR, Hariri AR (2018): A connectome-wide functional signature of transdiagnostic risk for mental illness. Biol Psychiatry 84:452–459.
28. Chabernaud C, Mennes M, Kelly C, Nooner K, di Martino A, Castellanos FX, et al. (2012): Dimensional brain-behavior relationships in children with attention-deficit/hyperactivity disorder. Biol Psychiatry 71:434–442.

29. Wee CY, Poh JS, Wang Q, Broekman BF, Chong YS, Kwek K, et al. (2018): Behavioral heterogeneity in relation with brain functional networks in young children. Cereb Cortex 28:3322–3331.

30. Sato JR, Biazoli CE Jr, Salum GA, Gadelha A, Crossley N, Satterthwaite TD, et al. (2015): Temporal stability of network centrality in control and default mode networks: Specific associations with externalizing psychopathology in children and adolescents. Hum Brain Mapp 36:4926–4937.

31. Whitfield-Gabrieli S, Ford JM (2012): Default mode network activity and connectivity in psychopathology. Annu Rev Clin Psychol 8:49–76.

32. Xia CH, Ma Z, Ciric R, Gu S, Betzel RF, Kaczkurkin AN, et al. (2018): Linked dimensions of psychopathology and connectivity in functional brain networks. Nat Commun 9:3003.

33. Palaniyappan L, Liddle PF (2012): Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. J Psychiatry Neurosci 37:17–27.

34. Choi J, Jeong B, Lee SW, Go HJ (2013): Aberrant development of functional connectivity among resting state–related functional networks in medication-naive ADHD children. PLoS One 8:e83516.

35. Ernst M, Benson B, Artiges E, Gorka AX, Lemaitre H, Lago T, et al. (2019): Pubertal maturation and sex effects on the default-mode network connectivity implicated in mood dysregulation. Transl Psychiatry 9:103.

36. Corbetta M, Patel G, Shulman GL (2008): The reorienting system of the human brain: From environment to theory of mind. Neuron 58:306–324.

37. Sylvester CM, Barch DM, Corbetta M, Power JD, Schlaggar BL, Luby JL (2013): Resting state functional connectivity of the ventral attention network in children with a history of depression or anxiety. J Am Acad Child Adolesc Psychiatry 52:1326–1336.e1325.

38. Gordon EM, Laumann TO, Adeyemo B, Huckins JF, Kelley WM, Petersen SE (2016): Generation and evaluation of a cortical area parcellation from resting-state correlations. Cereb Cortex 26:288–303.

39. Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, et al. (2011): Functional network organization of the human brain. Neuron 72:665–678.

40. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. (2011): The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 106:1125–1165.

41. Barch DM, Albaugh MD, Avenevoli S, Chang L, Clark DB, Glantz MD, et al. (2018): Demographic, physical and mental health assessments in the Adolescent Brain and Cognitive Development Study: Rationale and description. Dev Cogn Neurosci 32:55–66.

42. Fabrigar LR, Wegener DT, MacCallum RC, Strahan EJ (1999): Evaluating the use of exploratory factor analysis in psychological research. Psychol Methods 4:272–299.

43. Casey BJ, Cannonier T, Conley MI, Cohen AO, Barch DM, Heitzeg MM, et al. (2018): The Adolescent Brain Cognitive Development (ABCD) Study: Imaging acquisition across 21 sites. Dev Cogn Neurosci 32:43–54.

44. Hagler DJ Jr, Hatton S, Cornejo MD, Makowski C, Fair DA, Dick AS, et al. (2019): Image processing and analysis methods for the Adolescent Brain Cognitive Development Study. NeuroImage 202:116091.

45. Bates D, Mächler M, Bolker B, Walker S (2015): Fitting linear mixed-effects models using lme4. J Stat Softw 67:1–48.

46. Farah MJ (2017): The neuroscience of socioeconomic status: correlates, causes, and consequences. Neuron 96:56–71.

47. Heeringa SG, Berglund PA (2020): A guide for population-based analysis of the Adolescent Brain Cognitive Development (ABCD) Study baseline data. bioRxiv. https://doi.org/10.1101/2020.02.10.942011.

48. Halekoh U, Højsgaard S (2014): A Kenward-Roger approximation and parametric bootstrap methods for tests in linear mixed models—the R package pbkrtest. J Stat Softw 59:1–30.

49. Benjamini Y, Hochberg Y (2000): On the adaptive control of the false discovery rate in multiple testing with independent statistics. J Educ Behav Stat 25:60–83.

50. Menon V (2011): Large-scale brain networks and psychopathology: A unifying triple network model. Trends Cogn Sci 15:483–506.

51. Brennan BP, Wang D, Li M, Perriello C, Ren J, Elias JA, et al. (2018): Use of an individual-level approach to identify cortical connectivity biomarkers in obsessive-compulsive disorder. Biol Psychiatry Cogn Neurosci Neuroimaging 4:27–38.

52. Elton A, Alcauter S, Gao W (2014): Network connectivity abnormality profile supports a categorical-dimensional hybrid model of ADHD. Hum Brain Mapp 35:4531–4543.

53. Guo W, Zhang F, Liu F, Chen J, Wu R, Chen DQ, et al. (2018): Cerebellar abnormalities in first-episode, drug-naive schizophrenia at rest. Psychiatry Res Neuroimaging 276:73–79.

54. Sanefuji M, Craig M, Parlatini V, Mehta MA, Murphy DG, Catani M, et al. (2017): Double-dissociation between the mechanism leading to impulsivity and inattention in attention deficit hyperactivity disorder: A resting-state functional connectivity study. Cortex 86:290–302.

55. Seli P, Risko EF, Purdon C, Smilek D (2017): Intrusive thoughts: Linking spontaneous mind wandering and OCD symptomatology. Psychol Res 81:392–398.

56. di Martino A, Yan CG, Li Q, Denio E, Castellanos FX, Alaerts K, et al. (2014): The autism brain imaging data exchange: Toward a large-scale evaluation of the intrinsic brain architecture in autism. Mol Psychiatry 19:659–667.

57. Fair DA, Posner J, Nagel BJ, Bathula D, Dias TG, Mills KL, et al. (2010): Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. Biol Psychiatry 68:1084–1091.

58. Norman LJ, Carlisi CO, Christakou A, Cubillo A, Murphy CM, Chantiluke K, et al. (2017): Shared and disorder-specific task-positive and default mode network dysfunctions during sustained attention in paediatric attention-deficit/hyperactivity disorder and obsessive/compulsive disorder. Neuroimage Clin 15:181–193.

59. Uddin LQ, Kelly AM, Biswal BB, Margulies DS, Shehzad Z, Shaw D, et al. (2008): Network homogeneity reveals decreased integrity of default-mode network in ADHD. J Neurosci Methods 169:249–254.

60. Fair DA, Nigg JT, Iyer S, Bathula D, Mills KL, Dosenbach NU, et al. (2012): Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. Front Syst Neurosci 6:80.

61. de Lacy N, Doherty D, King BH, Rachakonda S, Calhoun VD (2017): Disruption to control network function correlates with altered dynamic connectivity in the wider autism spectrum. Neuroimage Clin 15:513–524.

62. Sripada C, Kessler D, Fang Y, Welsh RC, Prem Kumar K, Angstadt M (2014): Disrupted network architecture of the resting brain in attention-deficit/hyperactivity disorder. Hum Brain Mapp 35:4693–4705.

63. Tao J, Jiang X, Wang X, Liu H, Qian A, Yang C, et al. (2017): Disrupted control-related functional brain networks in drug-naive children with attention-deficit/hyperactivity disorder. Front Psychiatry 8:246.

64. McElroy E, Belsky J, Carragher N, Fearon P, Patalay P (2018): Developmental stability of general and specific factors of psychopathology from early childhood to adolescence: Dynamic mutualism or p-differentiation? J Child Psychol Psychiatry 59:667–675.

65. Coben R, Mohammad-Rezazadeh I, Frohlich J, Jurgiel J, Michelini G (2017): Imaging brain connectivity in autism spectrum disorder. In: Casanova MF, El-Baz A, Suri JS, editors. Autism Imaging and Devices. Boca Raton, FL: CRC Press, 261–302.

66. Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, et al. (2012): Toward systems neuroscience of ADHD: A meta-analysis of 55 fMRI studies. Am J Psychiatry 169:1038–1055.

67. Lahey BB, Lee SS, Sibley MH, Applegate B, Molina BSG, Pelham WE (2016): Predictors of adolescent outcomes among 4–6-year-old children with attention-deficit/hyperactivity disorder. J Abnorm Psychol 125:168–181.

68. Schaefer A, Kong R, Gordon EM, Laumann TO, Zuo XN, Holmes AJ, et al. (2018): Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. Cereb Cortex 28:3095–3114.

69. Elliott ML, Knodt AR, Cooke M, Kim MJ, Melzer TR, Keenan R, et al. (2019): General functional connectivity: Shared features of resting-state and task fMRI drive reliable and heritable individual differences in functional brain networks. Neuroimage 189:516–532.

70. Birn RM, Molloy EK, Patriat R, Parker T, Meier TB, Kirk GR, et al. (2013): The effect of scan length on the reliability of resting-state fMRI connectivity estimates. Neuroimage 83:550–558.