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An Integrated Analysis of Neural Network Correlates of Categorical and Dimensional Models of Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous neurodevelopmental disorder, putatively induced by dissociable dysfunctional biobehavioral pathways. Here, we present a proof-of-concept study to parse ADHD-related heterogeneity in its underlying neurobiology by investigating functional connectivity across multiple brain networks to 1) disentangle categorical diagnosis-related effects from dimensional behavior-related effects and 2) functionally map these neural correlates to neurocognitive measures.

METHODS: We identified functional connectivity abnormalities related to ADHD across 14 networks within a large resting-state functional magnetic resonance imaging dataset (n = 409; age = 17.5 $\pm$ 3.3 years). We tested these abnormalities for their association with the categorical ADHD diagnosis and with dimensional inattention and hyperactivity/impulsivity scores using a novel modeling framework, creating orthogonalized models. Next, we evaluated the relationship of these findings with neurocognitive measures (working memory, response inhibition, reaction time variability, reward sensitivity).

RESULTS: Within the default mode network, we mainly observed categorical ADHD-related functional connectivity abnormalities, unrelated to neurocognitive measures. Clusters within the visual networks primarily related to dimensional scores of inattention and reaction time variability, while findings within the sensorimotor networks were mainly linked to hyperactivity/impulsivity and both reward sensitivity and working memory. Findings within the cerebellum network and salience network related to both categorical and dimensional ADHD measures and were linked to response inhibition and reaction time variability.

CONCLUSIONS: This proof-of-concept study identified ADHD-related neural correlates across multiple functional networks, showing distinct categorical and dimensional mechanisms and their links to neurocognitive functioning.

Keywords: Attention-deficit/hyperactivity disorder, Categorical-dimensional analysis, Connectivity, Neural networks, Neuropsychology, Resting-state functional magnetic resonance imaging, rfMRI

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Interindividual differences are a hallmark of neurodevelopmental disorders such as attention-deficit/hyperactivity disorder (ADHD) (1). In ADHD, heterogeneity between diagnosed individuals is believed to originate partly from dissociable cognitive deficits and neural mechanisms (1,2). As an example, several large-scale brain networks have been associated with ADHD, comprising localized networks including the visual and motor cortices as well as networks distributed across the association cortex (e.g., the default mode network [DMN] and the salience network) (3,4).

Most studies investigating pathophysiological mechanisms of ADHD rely on case-control study designs, testing for systematic (i.e., categorical) differences between cases and controls. However, there is increasing evidence that ADHD can also be understood as an "extreme" on a continuum of typical functioning (i.e., dimensional attentive and hyperactive/impulsive traits) (5–10). Accordingly, new initiatives, such as the Research Domain Criteria (11,12), seek to employ dimensional approaches to study the behavioral, neural, and genetic features of mental disorders. Of note, recent results endorse that the pathophysiology of ADHD can be conceptualized by a complex interplay between categorical and dimensional mechanisms (13–16). However, this prior work on categorical/dimensional mechanisms focused on a limited set of one to four neural networks (with a central place for the DMN) and separate analyses for dimensional and categorical measures and their interaction (13,14).

Here, we aim to advance our understanding of ADHD by extending this prior work in several ways. In particular, we use

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a novel modeling framework to investigate categorical and dimensional effects of ADHD on functional brain architecture in an integrated way while focusing on multiple brain networks derived from resting-state functional magnetic resonance imaging (rfMRI) data. We further examined the association between categorical and dimensional effects on functional connectivity (FC) and measures of neurocognitive functioning.

Improving our understanding of the interplay of categorical and dimensional aspects of ADHD necessitates the integration of these aspects into one analysis. However, this poses methodological challenges owing to the close relationship between categorical and dimensional measures, leading to highly collinear statistical models that suffer from decreased sensitivity (i.e., increased false negative results) (17,18) (R.H.R. Pruim, Ph.D., *et al.*, unpublished data, August 2018). To address these challenges, we employed an analytical framework including orthogonalized models that allows the identification of a set of biomarkers related to ADHD and subsequently characterizing these effects in terms of the distinct contribution of categorical and dimensional mechanisms (R.H.R. Pruim, Ph.D., *et al.*, unpublished data, August 2018).

Dissociable biobehavioral pathways underpinning ADHD will not be restricted to the neural and behavioral domains and can be expected to also relate to neurocognitive dysfunction. To further explore such biobehavioral pathways, we related our brain network findings to neurocognitive measures. We investigated core neurocognitive features in line with proposed dissociable neurocognitive pathways implicated in ADHD (19), including reward processing, reaction time variability (RTV), response inhibition, and working memory.

We hypothesized that ADHD symptoms would be related to aberrant FC of the DMN (posterior cingulate and precuneus) and frontal-striatal-cerebellar regions (prefrontal cortex, anterior cingulate, striatum, and cerebellum) in networks related to cognitive control (3,19–21). We expect such findings to associate with neurocognitive measures extracted from executive tasks (e.g., response inhibition and RTV) (22,23). Primary sensory networks have not been prominently implicated in ADHD, yet, in line with Castellanos and Proal (3) and an extensive review by Cortese *et al.* (24), who suggest that the visual network might be involved in regulating attentional processes, we hypothesize that FC within the visual network might be related to ADHD symptomatology. Given that the latent structure of ADHD at the behavioral level is believed to be dimensional (9,10,25), we predominantly expect dimensional findings at the neurobiological level. However, in light of previous work by Elton *et al.* (14), we expected categorical relationships, but mainly within the DMN and cognitive network.

METHODS AND MATERIALS

Participants

We included participants from the NeuroIMAGE study cohort (26), which is a Dutch follow-up study of the IMAGE (International Multicenter ADHD Genetics) study (27–30). In the NeuroIMAGE study (on average 6 years after IMAGE), diagnostic, cognitive, MRI, and genetic data were acquired from ADHD and control participants as well as their siblings. Informed consent was signed by all participants (parents signed informed consent for participants under 12 years of age), and the study was approved by the ethical committee (Centrale Commissie Mensgebonden Onderzoek). Diagnosis of ADHD and comorbid disorders was assessed by a semistructured diagnostic interview and Conners' questionnaires (31,32). For the interview, we used the Dutch version of the Parental Account of Children's Symptoms (33,34) in the IMAGE study and the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version in the NeuroIMAGE study (35). We used the phenotypic information available across the IMAGE and NeuroIMAGE studies to categorize all participants into four diagnostic groups: typically developing control (TDC) subjects, ADHD (meeting criteria for ADHD at the two time points), unaffected siblings (sibling), or remitted ADHD (rem-ADHD) (i.e., an ADHD diagnosis at the time of the IMAGE study, but not in the NeuroIMAGE study). Moreover, Conners' parent ADHD questionnaires provided dimensional DSM-IV scores of both inattention and hyperactivity/impulsivity symptoms (36). Importantly, we only included siblings and rem-ADHD participants to increase power and reduce dichotomy for dimensional analyses and defined them as separate groups (i.e., did not assign them to the TDC or ADHD groups) to avoid pollution of any categorical TDC versus ADHD effects in upcoming analyses (see below). See Table 1 for participant characteristics and the Supplement for a more detailed description of the participants and study procedures.

Resting-State fMRI Data

We selected participants from the NeuroIMAGE study who completed both an rfMRI and a structural MRI scan. After applying exclusion criteria (see Supplement), 455 participants were left, of which 46 TDC subjects were randomly selected to define template resting-state networks (see below); the remaining 409 participants were included in our main analyses. The rfMRI data were preprocessed using a typical preprocessing pipeline, complemented with Independent Component Analysis—Automatic Removal of Motion Artifacts (ICA-AROMA), an advanced strategy for identifying and removing residual motion artifacts from fMRI data (37,38). All individual-level rfMRI images were normalized to a study-specific anatomical template in Montreal Neurological Institute (MNI) 152 standard space (3-mm isotropic). See the Supplement for a detailed description of the MRI acquisition, participant exclusion, and rfMRI preprocessing.

Deriving Functional Brain Networks

We used the preprocessed rfMRI data to investigate FC measures related to a set of functional brain networks (i.e., resting-state networks). In a first step, we derived these networks through ICA with MELODIC as implemented in FSL (version v5.0.6) (39–43). To this end, we applied group ICA with automatic dimensionality estimation to temporally concatenated rfMRI data of 46 randomly selected TDC participants. The participants used to derive these networks were excluded from all further analyses. The subsequent FC analyses, on the remaining 409 participants, used participant-level spatial representations of the networks identified by the group ICA, using

Table 1. Participant Characteristics and Association of These Characteristics With Diagnostic Group and Symptom Scores

	Group ICA			Diagnostic Group											Statistical Test		
	TDC Group (n = 46)			TDC Group (n = 90)			ADHD Group (n = 179)			Sibling Group (n = 109)			rem-ADHD Group (n = 31)			Between Diagnostic Groups	Inattentive Symptoms[a]	Hyperactive/ Impulsive Symptoms[a]
	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD			
General																		
Male	48			48			73			44			52			$\chi^2_3 = 28.8^c$	$F_{1,407} = 1.5$	$F_{1,407} = 1.9$
Site (Nijmegen)	37			37			54			50			65			$\chi^2_3 = 10.3^b$	$F_{1,407} = 9.7^c$	$F_{1,407} = 11.1^c$
ODD-CD	0			0			28			4			19			$\chi^2_3 = 51.4^c$	$F_{1,406} = 88.5^c$	$F_{1,406} = 93.0^c$
Age, years		17.2	2.9		16.8	3.1		17.7	3.2		17.7	3.9		17.7	2.3	$F_{3,405} = 1.7$	$r_{407} = -.02$	$r_{407} = .04$
IQ		106	15		106	13		96	15		101	13		99	14	$F_{3,401} = 11.2^c$	$r_{403} = -.22^c$	$r_{403} = -.23^c$
Medication, years[d]		0.0	0.0		0.0	0.0		4.0	3.2		0.2	0.8		3.3	3.7	$F_{3,363} = 78.0^c$	$r_{365} = .50^c$	$r_{365} = .51^c$
SES		13.2	2.2		13.2	2.8		11.4	2.2		11.4	2.3		12.0	2.5	$F_{3,399} = 12.4^c$	$r_{401} = -.12^b$	$r_{401} = -.19^c$
RMS-FD		0.14	0.14		0.14	0.11		0.17	0.16		0.13	0.12		0.14	0.13	$F_{3,405} = 2.8^b$	$r_{407} = -.11^b$	$r_{407} = .09$
ICs removed		24.4	8.2		24.7	7.0		27.0	7.8		23.7	7.9		25.5	7.9	$F_{3,405} = 4.6^c$	$r_{407} = .15^c$	$r_{407} = .14^c$
ICs preserved		11.4	2.8		11.7	3.4		11.9	3.6		11.7	4.1		11.4	4.6	$F_{3,405} = 0.2$	$r_{407} = .02$	$r_{407} = .01$
Symptom Scores																		
Inattentive symptoms[a]		47	6		46	6		66	11		48	8		56	9	$F_{3,405} = 134.6^c$	–	$r_{407} = .76^c$
Hyperactive/impulsive symptoms[a]		46	5		47	6		69	15		49	8		58	13	$F_{3,405} = 110.8^c$	$r_{407} = .76^c$	–
Neurocognitive Measures																		
Response inhibition, ms		261	59		260	53		267	150		260	55		250	53	$F_{3,215} = 1.2$	$r_{217} = .14^b$	$r_{217} = .05$
Working memory, %		0.80	0.12		0.75	0.11		0.72	0.13		0.72	0.13		0.73	0.12	$F_{3,240} = 1.3$	$r_{242} = -.14^b$	$r_{242} = -.22^c$
Reward sensitivity, ms		22	22		31	35		30	36		31	27		23	23	$F_{3,204} = 0.2$	$r_{206} = .08$	$r_{206} = .04$
Reaction timing variability		170	27		179	56		217	96		192	60		193	60	$F_{3,369} = 3.9^c$	$r_{371} = .19^c$	$r_{371} = .20^c$

Significant between-group differences and association with symptom scores were assessed using analysis of variance (F test), χ^2 statistical test, or Pearson correlation (r). The 46 TDC participants used for group ICA were not included in these statistical tests because they were excluded from all categorical/dimensional analyses presented in this manuscript (i.e., they are not part of the TDC diagnostic group).

ADHD, attention-deficit/hyperactivity disorder; ICA, independent component analysis; ICs removed/preserved, number of independent components removed/preserved by Independent Component Analysis—Automatic Removal of Motion Artifacts (ICA-AROMA); ODD-CD, oppositional defiant disorder–conduct disorder; rem-ADHD, remitted ADHD; RMS-FD, root mean square framewise displacement (head motion summary score) (77); SES, socioeconomic status (see Supplement); TDC, typically developing control.

[a]Obtained using the Conners Parent ADHD questionnaire (36), standardized t score (range, 40–90).

[b]$p < .05$.

[c]$p < .01$.

[d]Number of days (converted to years) on which any type of stimulants were prescribed.

a multivariate regression strategy called dual regression (42,44). The participant-level spatial maps represent the connectivity strength of every voxel within a specific network (i.e., association of the time series of each single voxel with the overall temporal dynamics of a specific network).

Categorical and Dimensional FC Analysis

To evaluate categorical and dimensional effects of ADHD on network connectivity, we used the obtained participant-specific spatial maps for each network as dependent variables and defined a standard general linear regression model (see Figure 1) including the following predictors: a main effect for the four diagnostic subgroups (TDC, ADHD, sibling, rem-ADHD) and two additional regressors for the symptom scores. The model was completed with covariates for age, sex, and scan site. The categorical effect of an ADHD diagnosis was assessed by evaluating the contrast between the main effects of the TDC and ADHD participants (i.e., ignoring sibling and rem-ADHD participants). We tested dimensional effects by respectively evaluating scores of inattention and hyperactivity/impulsivity across all 409 participants.

Importantly, the high association (i.e., high statistical collinearity) between the categorical and dimensional predictors (see Table 1) raises methodological challenges. Simply evaluating the three predictors within the single regression model as defined above [for instance, as done by Chabernaud *et al.* (13) and Elton *et al.* (14)] would reduce sensitivity to any effect of interest, as the large portion of shared variance between the predictors would have been disregarded within the regression procedure (17). In contrast, evaluating the three effects within separate models could have yielded findings that are in reality driven by shared variance with a nonmodeled variable (i.e., by the overlapping areas, as illustrated in the variance visualization of the regression model in Figure 1), thus reducing the interpretability of the findings. To accommodate these concerns, we used a two-stage framework, in which different variations of the defined regression model were tested (R.H.R. Pruim, Ph.D., *et al.*, unpublished data, August 2018). In short, in step 1, we identified effects of interest by testing for the full variance of every single predictor separately, i.e., we tested the effect of a predictor, unadjusted for the other two predictors. Subsequently, in step 2, we characterized these obtained effects of interest by testing for the unique contribution of every single predictor, i.e., test for the effect of every single predictor, adjusted for the other two predictors.

Step 1: Identifying Findings of Interest (Full Variance Modeling). First, we evaluated three regression models that respectively modeled the full variance of each of our three predictors (i.e., ADHD diagnosis, inattention score, and hyperactivity/impulsivity score). For each evaluated predictor, we obtained a full variance model by regressing the tested predictor from the other two predictors and subsequently replacing these other predictors in the model with their respective residuals. As a result, the tested predictor was assigned all the variance in the model that was originally shared with the other two predictors. See Figure 1 for a visualization of the specific variance tested by the three different models. Every model was evaluated using nonparametric permutation testing (n = 5000 permutations) as implemented in FSL Randomise (which utilizes general linear model–style design matrices), applying threshold-free cluster enhancement, correcting for familywise error ($p < .05$), and only considering spatial clusters with a minimum cluster size of eight voxels (45,46). Of note, although we here utilize multiple regression models, no additional multiple comparison correction compared with traditional analyses using a single non-orthogonalized model is required. All models explain the same

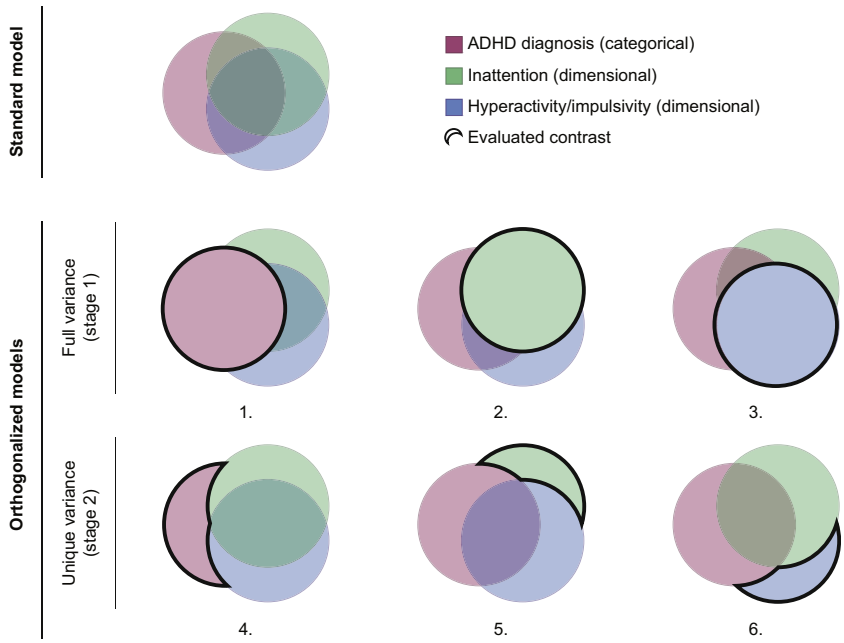

Figure 1. Visualization of the modeled variance for the standard model and orthogonalized model variants as utilized to investigate categorical and dimensional effects in the context of attention-deficit/hyperactivity disorder (ADHD). Note that shared variance (i.e., overlapping areas) is by definition disregarded in a general linear model regression procedure (17). The black outline represents the variance we tested within that respective model.

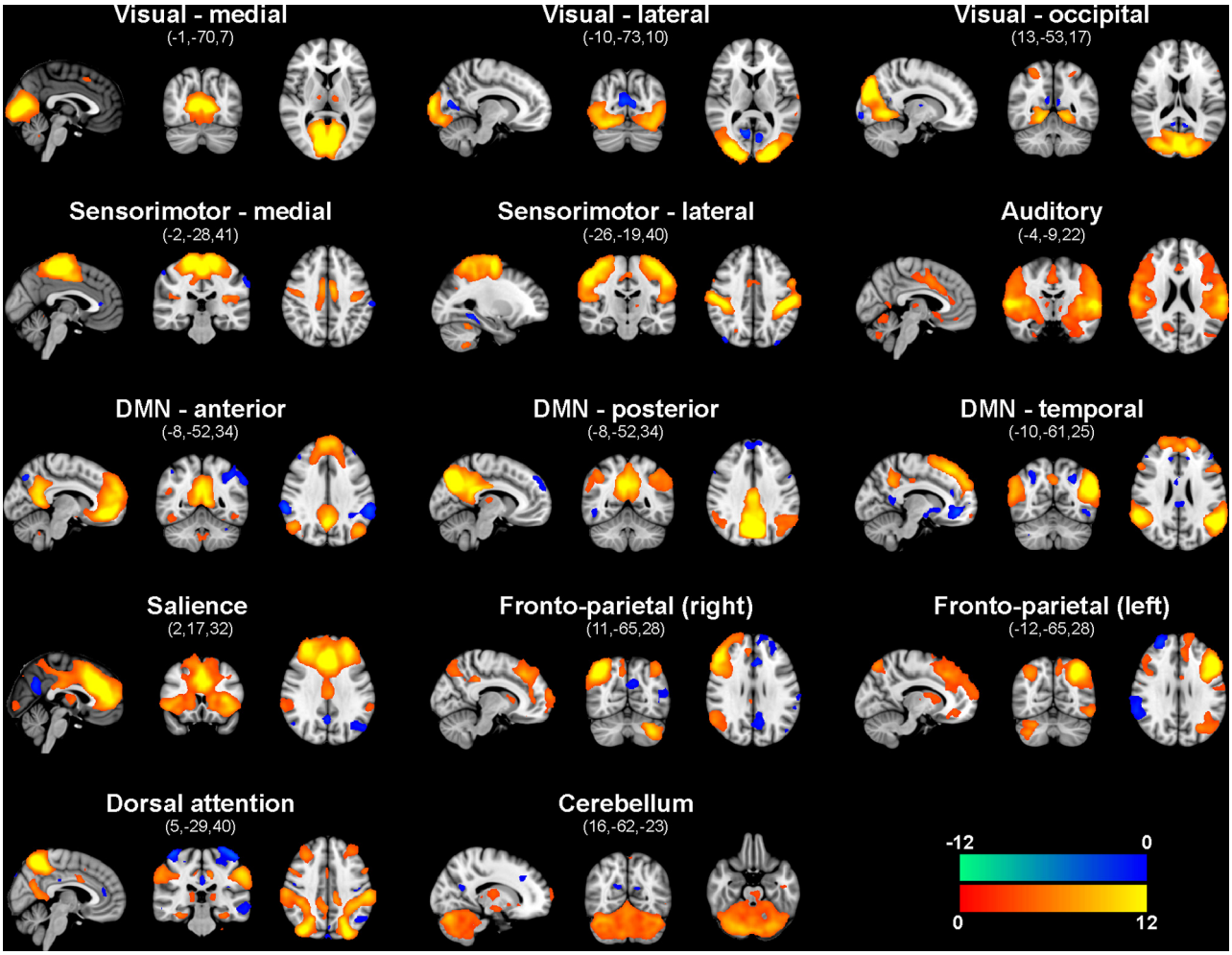

Figure 2. The 14 functional brain networks obtained by group independent component analysis on resting-state functional magnetic resonance imaging data of 46 typically developing control participants (thresholded using mixture modeling at $p > .5$; x, y, z coordinates presented between brackets). DMN, default mode network.

total variance and are therefore equivalent with respect to signal versus noise considerations. This yielded a set of spatial clusters ($n = 27$), which we refer to as FC markers. See Results for further details.

Step 2: Characterizing the Findings of Interest (Unique Variance Modeling). The precise association of the FC markers for categorical or dimensional mechanisms of ADHD as obtained in step 1 is not evident, as we did not account for the shared variance among the three predictors. In step 2, we addressed this issue by disentangling the specific association of the FC markers with the categorical ADHD diagnosis and the dimensional inattention and hyperactivity/impulsivity scores. To that end, we obtained participant-level scores for every FC marker. This score was defined as the mean beta value across the voxels in the FC marker's spatial cluster within each participant's network map that was obtained via dual regression. For every FC marker, these scores were used as the dependent variable to evaluate three models that respectively evaluated the unique variance of the three effects of interest. We obtained a unique variance model for every evaluated predictor by replacing the tested predictor with its residual after regressing out the other two predictors (i.e., the opposite procedure compared with step 1). This effectively resulted in the evaluated predictor only representing its unique variance, while all shared variance was modeled by the other predictors (see Figure 1). Note that evaluating the three measures jointly within a single (nonorthogonalized) model will also only evaluate their unique variance, as any shared variance would be separated by the model. The only difference in testing for the unique variance using multiple orthogonalized models versus a single nonorthogonalized model is that the variance associated with the parameter estimates (i.e., reliability) will differ owing to differences in collinearity of the model. These models were evaluated using nonparametric permutation testing ($n = 5000$ permutations; $p < .05$). To maximize sensitivity of our analysis, we decided not to implement additional correction for multiple comparison

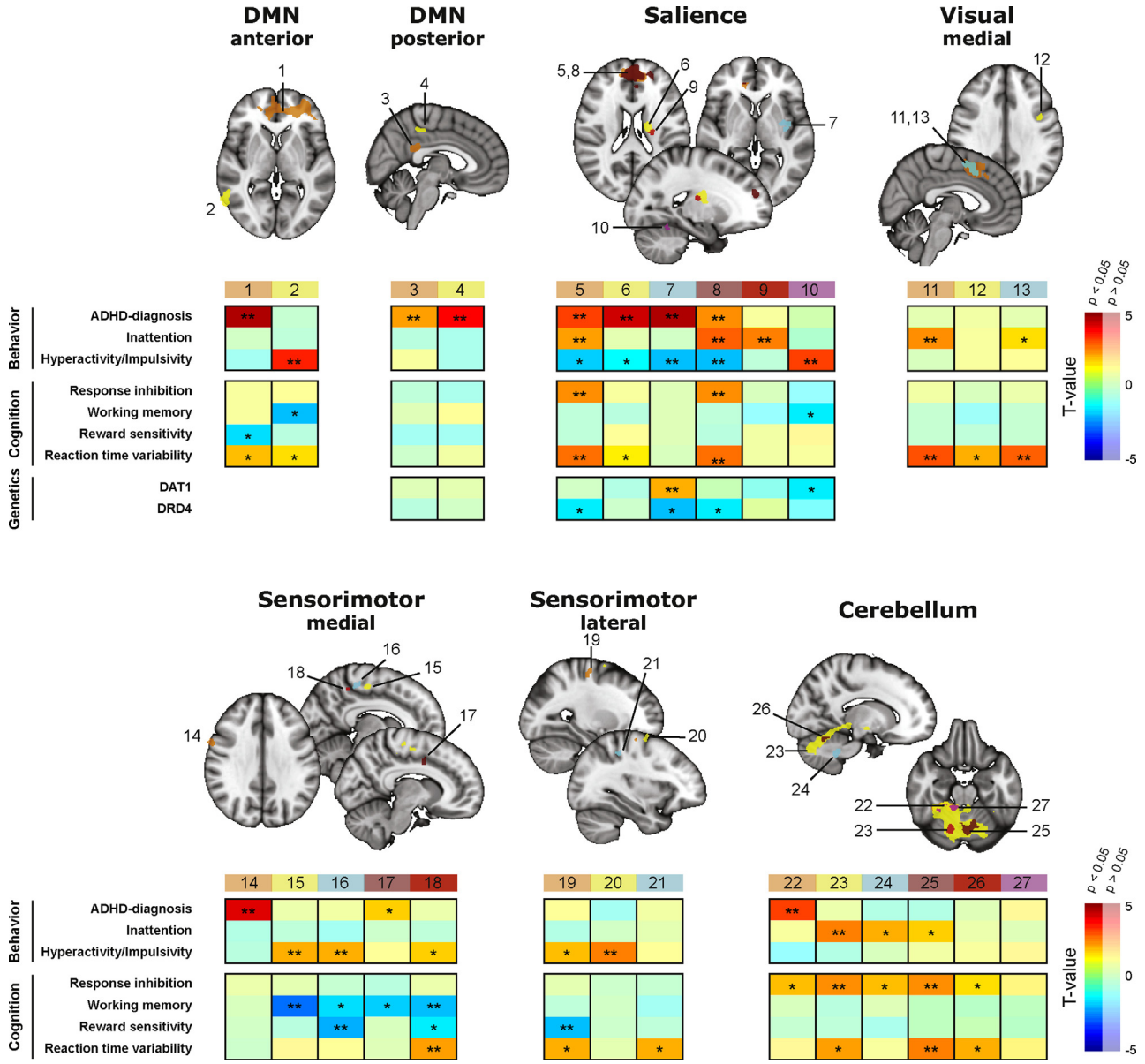

Figure 3. The 27 significant spatial clusters (as also presented in Table 2) related to attention-deficit/hyperactivity disorder (ADHD) across functional networks and their association with behavioral and neurocognitive measures. The clusters were obtained by evaluating the full variance models presented in Figure 1 on all 14 functional networks (see Figure 2), whereas the unique categorical and dimensional behavioral effects as illustrated in the colored table below the brain slices were obtained by evaluating unique variance models for each of the 27 significant clusters. $^{*}p < .05$, $^{**}p < .01$. *DAT1*, dopamine transporter gene; DMN, default mode network; *DRD4*, dopamine receptor D4 gene.

for conducting statistical tests for each of the 14 networks. Finally, we conducted a post hoc sensitivity analysis to verify that the observed effects were not related to socioeconomic status, oppositional defiant disorder diagnosis, conduct disorder diagnosis, stimulant medication use, or amount of head motion during the scanning session (see Supplement).

Neurocognitive Pathway Associations

We investigated our network findings in relation to neurocognitive measures. Specifically, we tested for an association across participants of the FC marker scores, as obtained in step 2 of our framework, with neurocognitive measures known to be associated with ADHD. We used nonparametric permutation testing (n = 5000 permutations; $p < .05$), including covariates for age, sex, and scan site.

We mapped all significant FC markers to four neurocognitive domains/measures: response inhibition (stop-signal reaction time), visuospatial working memory (percentage correct responses), reward sensitivity (reaction time difference between a reward vs. nonreward cue), and RTV on a motor timing task (47–50). Stop-signal reaction time, visuospatial

Table 2. Significant Spatial Clusters Related to ADHD Across Functional Networks and Their Association With Behavioral and Neurocognitive Measures

					Behavior			Neurocognitive Functioning			
Cl	Network and Brain Area	Full Variance Model	Size (Voxels)	Center of Gravity (x, y, z) (mm)	ADHD Diagnosis (*df* = 269)	Inattentive Symptoms (*df* = 409)	Hyperactive/ Impulsive Symptoms (*df* = 409)	Response Inhibition (*df* = 219)	Visuospatial Working Memory (*df* = 244)	Reward Sensitivity (*df* = 208)	Reaction Time Variability (*df* = 373)
	Anterior DMN										
1	dACC, PAC, vPFC	Cat	491	−6, 51, 3	5.3 (0.0002)[b]	0.1 (0.44)	−1.2 (0.11)	1.2 (0.12)	1.2 (0.12)	−2.0 (0.02)[a]	2.2 (0.01)[a]
2	MTG (R)	Dim-I	68	59, −56, 4	−0.3 (0.38)	−0.4 (0.36)	4.0 (0.0002)[b]	1.4 (0.09)	−2.4 (0.01)[a]	−0.6 (0.30)	1.8 (0.03)[a]
	Posterior DMN										
3	PCC (R)	Cat	29	4, −41, 25	2.5 (0.01)[b]	−0.6 (0.27)	1.2 (0.10)	−0.5 (0.30)	0.4 (0.35)	−1.3 (0.11)	−0.0 (0.48)
4	PCC (R)	Cat	20	5, −35, 46	4.4 (0.0002)[b]	−1.0 (0.15)	−0.9 (0.17)	−1.0 (0.15)	1.5 (0.07)	−1.2 (0.10)	1.0 (0.16)
	Salience Network										
5	dmPFC (PAC, dACC)	Cat	236	−2, 49, 16	3.7 (0.0006)[b]	2.5 (0.007)[a]	−2.1 (0.02)[a]	2.7 (0.006)[b]	−0.5 (0.30)	−0.5 (0.31)	3.0 (0.002)[b]
6	Caud. N./putamen (L, Post)	Cat	49	−21, −12, 17	4.9 (0.0002)[b]	0.7 (0.25)	−1.7 (0.05)[a]	1.2 (0.11)	−0.6 (0.28)	1.3 (0.09)	1.7 (0.05)[a]
7	Putamen/insula (L, Post)	Cat	42	−36, −8, −1	5.3 (0.0002)[b]	0.2 (0.43)	−2.4 (0.01)[a]	0.5 (0.33)	0.4 (0.34)	0.6 (0.28)	0.2 (0.40)
8	dmPFC, (PAC, dACC), dlPFC	Dim-I	314	−7, 47, 17	2.7 (0.0005)[b]	3.3 (0.0006)[b]	−2.3 (0.009)[b]	2.8 (0.0003)[b]	−0.5 (0.31)	−0.7 (0.24)	3.1 (0.002)[b]
9	WM (L)	Dim-I	15	−22, −18, 18	1.2 (0.12)	2.8 (0.0003)[b]	−0.4 (0.35)	0.4 (0.35)	−1.5 (0.07)	0.9 (0.17)	1.1 (0.14)
10	Left VI (part cerebellum)	Dim-H	12	−20, −54, −18	0.3 (0.38)	−0.4 (0.33)	3.6 (0.0004)[b]	−1.5 (0.06)	−1.8 (0.04)[a]	1.6 (0.06)	1.3 (0.10)
	Medial Visual Network										
11	PAC	Dim-I	294	−1, 14, 49	0.7 (0.22)	2.8 (0.0004)[b]	0.2 (0.41)	1.0 (0.15)	−0.3 (0.39)	−0.3 (0.40)	3.4 (0.0008)[b]
12	Precentral gyrus (L)	Dim-I	11	−41, 2, 32	1.0 (0.17)	1.2 (0.13)	1.2 (0.11)	0.3 (0.40)	−1.4 (0.08)	−0.4 (0.36)	2.3 (0.01)[a]
13	PAC	Dim-H	83	0, 11, 49	0.7 (0.25)	1.8 (0.05)[a]	1.5 (0.07)	0.9 (0.19)	−0.3 (0.39)	−0.3 (0.38)	3.4 (0.001)[b]
	Medial Sensorimotor Network										
14	Precentral gyrus (R)	Cat	15	61, 6, 33	4.7 (0.0002)[b]	−0.9 (0.19)	−0.7 (0.25)	0.8 (0.22)	0.2 (0.40)	0.0 (0.49)	−0.1 (0.47)
15	Precentral gyrus	Dim-H	78	6, −20, 56	0.8 (0.22)	−0.6 (0.29)	2.3 (0.009)[b]	0.6 (0.26)	−3.4 (0.0006)[b]	−0.7 (0.24)	1.5 (0.06)
16	Precentral gyrus (L)	Dim-H	28	−11, −33, 51	1.1 (0.13)	−1.1 (0.13)	2.4 (0.01)[b]	−0.3 (0.37)	−2.0 (0.02)[a]	−2.6 (0.004)[b]	1.4 (0.08)
17	ACC (R)	Dim-H	12	8, 2, 41	1.9 (0.03)[a]	−0.1 (0.45)	1.4 (0.07)	−0.6 (0.28)	−2.1 (0.02)[a]	0.4 (0.36)	0.4 (0.35)
18	Precuneus (L)	Dim-H	10	−11, −44, 50	0.8 (0.21)	−0.4 (0.33)	1.9 (0.03)[a]	0.9 (0.18)	−2.3 (0.009)[b]	−1.9 (0.03)[a]	2.6 (0.007)[b]
	Lateral Sensorimotor Network										
19	Precentral gyrus (L)	Dim-H	17	−28, −20, 60	1.3 (0.09)	−0.8 (0.20)	2.2 (0.02)[a]	0.6 (0.28)	−0.5 (0.29)	−2.3 (0.009)[b]	2.4 (0.01)[a]
20	Precentral gyrus (L)	Dim-H	14	−29, −4, 48	−1.2 (0.13)	0.1 (0.47)	2.8 (0.001)[b]	−0.1 (0.49)	0.1 (0.48)	−0.0 (0.51)	0.6 (0.28)
21	Postcentral gyrus (L)	Dim-H	11	−33, −38, 48	1.0 (0.15)	0.6 (0.28)	1.5 (0.07)	−0.2 (0.43)	−1.2 (0.11)	−0.5 (0.30)	2.3 (0.01)[a]
	Cerebellum										
22	Right V + VI	Cat	115	27, −41, −27	3.7 (0.0002)[b]	1.3 (0.10)	−1.6 (0.05)	2.1 (0.02)[a]	0.4 (0.36)	−0.3 (0.40)	1.6 (0.07)
23	Cerebellum, OFG (L)	Dim-I	2222	1, −59, −26	0.8 (0.21)	2.8 (0.002)[b]	−0.9 (0.19)	2.8 (0.0003)[b]	−0.6 (0.26)	−0.5 (0.31)	2.4 (0.01)[a]
24	WM (L)	Dim-I	27	−15, 45, 37	−0.9 (0.19)	2.3 (0.01)[a]	0.3 (0.36)	2.2 (0.01)[a]	0.4 (0.37)	−1.0 (0.16)	1.2 (0.13)
25	Vermis VI, left V, right V	Dim-H	120	−4, −62, −19	−0.9 (0.19)	1.9 (0.03)[a]	1.1 (0.14)	2.8 (0.0004)[b]	−0.1 (0.44)	−0.1 (0.48)	2.9 (0.0004)[b]

working memory, reward sensitivity, and RTV were available for 219, 244, 208, and 373 participants, respectively, after excluding outliers (see Supplement). Importantly, the direction of the association of the four measures with ADHD differs: stop-signal reaction time and RTV are expected to be positively associated, whereas visuospatial working memory and reward sensitivity are expected to be negatively associated to ADHD symptom severity or ADHD diagnosis (47–50).

To further explore biobehavioral pathways, we performed a supplemental analysis in which we related our network findings to ADHD-related genetic variants. For the procedures and results related to these analyses, refer to the Supplement.

RESULTS

Functional Brain Networks

The group ICA aimed at identifying the resting-state networks to use in our further analyses yielded 14 independent components. These 14 components did not yield any noise components and therefore exclusively reflected functional networks, which closely corresponded to functional networks identified in previous research (see Figure 2) (51–56). The absence of noise components is consistent with previous research applying ICA to data that were denoised for motion-related artifacts using ICA-AROMA (37,38). Given the inconsistent nomenclature of neural networks (predominantly regarding networks related to cognitive functioning), refer to the Supplement and Supplemental Figures S1–S6 for an extensive comparison of the spatial maps and nomenclature of our networks compared with networks previously reported by other studies. In the current work, we chose to follow the nomenclature used in the first key papers that (in line with our work) used ICA to identify functional networks (51,57).

Categorical and Dimensional FC Analysis

We tested all 14 functional networks for association between FC scores and ADHD-diagnosis, inattention, and hyperactivity/impulsivity scores by exploiting three separate full-variance models. This analysis yielded 27 significant spatial clusters located throughout the DMN (anterior and posterior), salience, visual-medial, sensorimotor (medial and lateral), and cerebellum networks (see Figure 3 and Table 2).

Characterization of the 27 FC markers by relating participant-level scores of these markers to the unique variance of ADHD diagnosis and the two-dimensional scores yielded distinct associations across networks, as shown in Figure 3 and summarized in Table 2. For the DMN, three FC markers located within the posterior cingulate cortex (PCC) and prefrontal cortex of the posterior and anterior DMN subnetworks were specifically related to the categorical ADHD diagnosis. In contrast, the FC marker located in the middle temporal gyrus of the anterior DMN was positively related to hyperactivity/impulsivity scores. Similarly, markers located within the sensorimotor subnetworks were mainly positively related to hyperactivity/impulsivity, while increased scores of markers within the cerebellum and visual-medial networks were predominantly positively related to inattention symptoms. Finally, FC markers located within the salience network, mainly covering the dorsomedial prefrontal cortex (including parts of

Table 2. Continued

					Behavior			Neurocognitive Functioning			
CI	Network and Brain Area	Full Variance Model	Size (Voxels)	Center of Gravity (x, y, z) (mm)	ADHD Diagnosis (*df* = 269)	Inattentive Symptoms (*df* = 409)	Hyperactive/ Impulsive Symptoms (*df* = 409)	Response Inhibition (*df* = 219)	Visuospatial Working Memory (*df* = 244)	Reward Sensitivity (*df* = 208)	Reaction Time Variability (*df* = 373)
26	Right VI	Dim-H	32	15, −67, 23	0.4 (0.34)	0.8 (0.20)	1.3 (0.10)	1.8 (0.03)[a]	−0.2 (0.40)	0.0 (0.47)	2.3 (0.01)[a]
27	Right I–IV	Dim-H	26	19, −40, −23	1.5 (0.07)	0.4 (0.33)	1.5 (0.07)	1.6 (0.06)	−0.1 (0.45)	−0.2 (0.41)	1.7 (0.06)

Values are *t* (*p*), unless otherwise indicated. The clusters were obtained by evaluating the Fullvar models (step 1 of the framework) presented in Figure 1 (models 1–3) on all 14 functional networks (see Figure 2 and Fullvar model column), whereas the unique categorical and dimensional behavioral effects as presented in the current table were obtained by evaluating unique variance models obtained in step 2. Cluster size is reported in number of 3-mm isotropic voxels.

ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; Cat, categorical model; Caud. N., caudate nucleus; CI, cluster index; dACC, dorsal anterior cingulate cortex; Dim-H, hyperactivity/impulsivity model; Dim-I, inattention model; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; dmPFC, dorsomedial prefrontal cortex; L, left hemisphere; MTG, middle temporal gyrus; OFG, occipital fusiform gyrus; PAC, paracingulate cortex; PCC, posterior cingulate cortex; Post, posterior; R, right hemisphere; vPFC, ventral prefrontal cortex; WM, white matter.

[a] $p < .05$.

[b] $p < .01$.

the dorsal anterior cingulate and paracingulate cortex) and posterior parts of the left striatum, were related to both categorical and (both positive and negative) dimensional effects. Post hoc sensitivity analysis showed that none of the findings described above were related to oppositional defiant disorder, conduct disorder, socioeconomic status, stimulant medication use, or head motion (see Supplemental Table S2).

Neurocognitive Pathway Associations

Mapping the FC markers to neurocognitive measures yielded no results for markers within the DMN-posterior network. Within the salience network, high connectivity with the dorsomedial prefrontal cortex was associated with poorer response inhibition and higher RTV. Markers located within the cerebellum showed a similar association with both of these neurocognitive measures, whereas markers located within the visual-medial network were only positively associated with RTV. In contrast, FC markers within the anterior DMN and sensorimotor network showed a broad association across all cognitive metrics except for response inhibition (see Figure 3 and Table 2).

DISCUSSION

We aimed to parse ADHD-related heterogeneity by investigating FC across multiple brain networks, disentangling categorical and dimensional effects, and mapping these neural correlates to neurocognitive measures. We disentangled such categorical and dimensional neurobiological underpinnings through application of specific regression models in a large sample of adolescents and young adults. Effects observed in the DMN were mainly related to the categorical definition of ADHD, while effects located within the visual-medial and sensorimotor networks mainly related to inattentive and hyperactive/impulsive behavior, respectively. Effects within the salience network and cerebellum showed both categorical and dimensional mechanisms.

Corroborating and extending previous studies, we found aberrant FC of the PCC and frontal areas within the DMN (14,20,58–60). These findings mainly comprised categorical relationships between FC and an ADHD diagnosis. We found that the frontal FC marker within the DMN was associated with multiple neurocognitive measures, whereas two PCC markers were unrelated to the neurocognitive measures, suggesting that subdivisions within the DMN play a dissociable role in the etiology of ADHD. Specifically, regarding PCC, its absent association with neurocognitive measures and the myriad of findings described in literature on PCC abnormalities across psychiatric disorders (61) support the idea that abnormalities of this region 1) are directly related to ADHD, 2) are not influenced by cognitive risk factors for ADHD, or 3) are unspecific to ADHD and a consequence of accumulating remote pathological effects (62).

In contrast to the categorical effects within the DMN, we identified a profound dimensional effect related to inattention within the visual network. The relevance of this network in the pathophysiology of ADHD is being increasingly acknowledged (3,24). Especially, the regulation of visual function by attentional processes is considered an important remaining research area (3). More specifically, our significant finding is located within the posterior part of the paracingulate cortex and extends to superior frontal gyrus and presupplementary motor area, regions related to visual attention shifting (63–65). A large meta-analysis by Cortese *et al.* across 55 fMRI studies confirmed hypoactivation of the paracingulate cortex within ADHD patients as one of the main findings in the literature (24). Cortese *et al.* related this finding to the salience network, which in their work is referred to as the ventral attention network. In line with the framework proposed by Nigg and Casey (66), Cortese *et al.* hypothesized that salience network hypoactivation underpins deficits in detecting environmental (ir) regularities. This, in turn, would lead to behavioral problems when patients with ADHD are unable to modulate their behavior in accordance to these environmental changes. Interestingly, visual areas are involved in maintaining or suppressing spatial attention to irrelevant stimuli (63,67), and it has been proposed that hyperactivation within the visual network might act as a neural compensatory mechanism for impaired function of prefrontal cortex and anterior cingulate cortex, areas associated with the salience network (68). Given that our analysis specifically links aberrant paracingulate connectivity to the visual network instead of the salience network, we can now integrate these hypotheses by proposing that ADHD-related deficits in detecting environmental irregularities might be related to visual attention processing as regulated by the paracingulate cortex, possibly as a compensatory mechanism for dysfunction of the salience network. This hypothesis is supported by our observation that the paracingulate FC marker strongly and specifically related to RTV, which is in agreement with the known relation between RTV and inattentive behavior (69–72). In line with these within-network findings, Barber *et al.* (73) found a relationship between attention control and connectivity between the DMN and visual network. The strength of this association differed between the TDC and ADHD groups, suggesting an interaction effect. Although evaluating such interactions is outside the scope of the current work, these related observations offer a promising lead for further research.

Increased FC within the two sensorimotor networks was predominantly related to increased hyperactivity/impulsivity symptoms and poorer outcome on a broad range of neurocognitive measures, most strongly on working memory. These findings relate to the notion that motor control impairments are associated with higher-order cognitive difficulties (74) and support the idea that hyperactivity might be a compensatory mechanism to cope with environmental demands related to cognitive/executive functioning (75,76). We furthermore observed that FC markers located within the cerebellum were predominantly related to 1) both categorical ADHD diagnosis and dimensional scores of inattentive behavior and 2) poorer outcomes on response inhibition and RTV. Given that both of these neurocognitive functions involve (motor) timing processing, our findings support the hypothesized neurobiological pathway, in which dysfunction of the cerebellum is associated with impaired (motor) timing processing (19).

Various clusters identified within the salience network were associated with both categorical and dimensional effects of ADHD. The associations of these markers with neurocognitive measures suggested two differential neurobiological pathways: 1) a pathway in which frontostriatal connections within the salience network affect motor timing and inhibitory control and 2) a pathway connectivity within the putamen/insula,

unrelated to neurocognitive functioning. Notably, we found opposite directionality of the relationship between the FC marker and scores of inattention and hyperactivity/impulsivity respectively.

Our work could be compared to recent work by Elton *et al.* (14), who implemented a categorical-dimensional hybrid model to investigate functional neural correlates related to ADHD across four networks. Whereas the current study replicates some of their findings, including decreased FC within the medial prefrontal cortex and its relationship to increased scores of hyperactivity/impulsivity, other findings spatially correspond but are found in different networks or yield an alternative categorical-dimensional interpretation (e.g., altered anterior cingulate cortex connectivity in the cognitive network vs. visual network, respectively). Next to inherent differences in the study samples, observed differences in results are likely attributable to methodological differences. It is quite possible that some differences in results are related to the delineation of the investigated networks. Elton *et al.* (14) employed univariate seed-based regression to model neural networks, which differs from our multivariate approach that aimed at preventing mixing of neural signals of overlapping networks (see dual regression above). Likewise, Elton *et al.* (14) evaluated inattention and impulsivity/hyperactivity scores using separate categorical-dimensional models, leading to a suboptimal correction of all dimensional effects when evaluating categorical effects, and not fully disentangling dimensional effects related to inattention versus hyperactivity/impulsivity.

Detecting distinct neural mechanisms that underlie similar behaviors (i.e., the concept of multifinality) and symptom patterns is methodologically challenging. To be able to detect these mechanisms, we adopted a more explorative approach and performed a proof-of-concept study in which we evaluated 14 networks without correcting for multiple comparison across these networks. Although most findings fit well within current literature, caution is required, as it is possible that some significant relationships with the data extracted from the spatial clusters are false positive. To that end, replication of our results is required. Moreover, note that we ignored sibling and rem-ADHD participants when investigating categorical effects, while dimensional effects were assessed across all 409 participants, yielding relatively increased power toward detecting dimensional effects compared with the analyses assessing the categorical effects.

We presented an analysis strategy for disentangling categorical and dimensional disease mechanisms in ADHD and mapped our results to neurocognitive measures, thereby characterizing dissociable neurobiological underpinnings of ADHD-related behavior. Using this approach, we provided new insights supporting a categorical-dimensional model of ADHD and refined current hypotheses on the etiology of this disorder. Our results emphasize that ADHD should be investigated throughout multiple neural systems and by combining both categorical and dimensional models, rather than focusing on one or the other.

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REFERENCES

1. Faraone SV, Asherson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiroga JA, *et al.* (2015): Attention-deficit/hyperactivity disorder. Nat Rev Dis Primers 1:15020.

2. Coghill DR, Seth S, Matthews K (2014): A comprehensive assessment of memory, delay aversion, timing, inhibition, decision making and variability in attention deficit hyperactivity disorder: Advancing beyond the three-pathway models. Psychol Med 44:1989–2001.
3. Castellanos FX, Proal E (2012): Large-scale brain systems in ADHD: Beyond the prefrontal-striatal model. Trends Cogn Sci 16:17–26.
4. Mostert JC, Shumskaya E, Mennes M, Onnink AMH, Hoogman M, Kan CC, *et al.* (2016): Characterising resting-state functional connectivity in a large sample of adults with ADHD. Prog Neuropsychopharmacol Biol Psychiatry 67:82–91.
5. Asherson P, Trzaskowski M (2015): Attention-deficit/hyperactivity disorder is the extreme and impairing tail of a continuum. J Am Acad Child Adolesc Psychiatry 54:249–250.
6. Levy F, Hay DA, McStephen M, Wood C, Waldman I (1997): Attention-deficit hyperactivity disorder: A category or a continuum? Genetic analysis of a large-scale twin study. J Am Acad Child Adolesc Psychiatry 36:737–744.
7. Marcus DK, Norris AL, Coccaro EF (2012): The latent structure of attention deficit/hyperactivity disorder in an adult sample. J Psychiatr Res 46:782–789.
8. Marcus DK, Barry TD (2011): Does attention-deficit/hyperactivity disorder have a dimensional latent structure? A taxometric analysis. J Abnorm Psychol 120:427–442.
9. Haslam N, Holland E, Kuppens P (2012): Categories versus dimensions in personality and psychopathology: A quantitative review of taxometric research. Psychol Med 42:903–920.
10. Haslam N, Williams B, Prior M, Haslam R, Graetz B, Sawyer M (2006): The latent structure of attention-deficit/hyperactivity disorder: A taxometric analysis. Aust N Z J Psychiatry 40:639–647.
11. 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.
12. Morris SE, Cuthbert BN (2012): Research domain criteria: Cognitive systems, neural circuits, and dimensions of behavior. Dialogues Clin Neurosci 14:29–37.
13. Chabernaud C, Mennes M, Kelly C, Nooner K, Di Martino A, Castellanos FX, Milham MP (2011): Dimensional brain-behavior relationships in children with attention-deficit/hyperactivity disorder. Biol Psychiatry 71:434–442.
14. 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.
15. van Ewijk H, Heslenfeld DJ, Zwiers MP, Faraone SV, Luman M, Hartman CA, *et al.* (2014): Different mechanisms of white matter abnormalities in attention-deficit/hyperactivity disorder: A diffusion tensor imaging study. J Am Acad Child Adolesc Psychiatry 53:790–799.e3.
16. Wu Z-M, Bralten J, Cao Q-J, Hoogman M, Zwiers MP, An L, *et al.* (2017): White matter microstructural alterations in children with ADHD: Categorical and dimensional perspectives. Neuropsychopharmacology 42:572–580.
17. Mumford JA, Poline J-B, Poldrack RA (2015): Orthogonalization of regressors in fMRI models. PLoS One 10:e0126255.
18. York R (2012): Residualization is not the answer: Rethinking how to address multicollinearity. Soc Sci Res 41:1379–1386.
19. Durston S, van Belle J, de Zeeuw P (2011): Differentiating frontostriatal and fronto-cerebellar circuits in attention-deficit/hyperactivity disorder. Biol Psychiatry 69:1178–1184.
20. Posner J, Park C, Wang Z (2014): Connecting the dots: A review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. Neuropsychol Rev 24:3–15.
21. Cubillo A, Halari R, Smith A, Taylor E, Rubia K (2012): A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with attention deficit hyperactivity disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex 48:194–215.
22. Cubillo A, Halari R, Ecker C, Giampietro V, Taylor E, Rubia K (2010): Reduced activation and inter-regional functional connectivity of fronto-striatal networks in adults with childhood attention-deficit hyperactivity disorder (ADHD) and persisting symptoms during tasks of motor inhibition and cognitive switching. J Psychiatr Res 44:629–639.
23. Liddle EB, Hollis C, Batty MJ, Groom MJ, Totman JJ, Liotti M, *et al.* (2011): Task-related default mode network modulation and inhibitory control in ADHD: Effects of motivation and methylphenidate. J Child Psychol Psychiatry 52:761–771.
24. Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, Castellanos FX (2012): Toward systems neuroscience of ADHD: A meta-analysis of 55 fMRI studies. Am J Psychiatry 169:1038–1055.
25. Coghill D, Sonuga-Barke EJS (2012): Annual research review: Categories versus dimensions in the classification and conceptualisation of child and adolescent mental disorders–implications of recent empirical study. J Child Psychol Psychiatry 53:469–489.
26. von Rhein D, Mennes M, van Ewijk H, Groenman AP, Zwiers MP, Oosterlaan J, *et al.* (2015): The NeuroIMAGE study: A prospective phenotypic, cognitive, genetic and MRI study in children with attention-deficit/hyperactivity disorder. Design and descriptives. Eur Child Adolesc Psychiatry 24:265–281.
27. Müller UC, Asherson P, Banaschewski T, Buitelaar JK, Ebstein RP, Eisenberg J, *et al.* (2011): The impact of study design and diagnostic approach in a large multi-centre ADHD study. Part 1: ADHD symptom patterns. BMC Psychiatry 11:54.
28. Müller UC, Asherson P, Banaschewski T, Buitelaar JK, Ebstein RP, Eisenberg J, *et al.* (2011): The impact of study design and diagnostic approach in a large multi-centre ADHD study: Part 2: Dimensional measures of psychopathology and intelligence. BMC Psychiatry 11:55.
29. Nijmeijer JS, Hoekstra PJ, Minderaa RB, Buitelaar JK, Altink ME, Buschgens CJM, *et al.* (2009): PDD symptoms in ADHD, an independent familial trait? J Abnorm Child Psychol 37:443–453.
30. Rommelse NNJ, Altink ME, Martin NC, Buschgens CJM, Buitelaar JK, Sergeant JA, Oosterlaan J (2008): Neuropsychological measures probably facilitate heritability research of ADHD. Arch Clin Neuropsychol 23:579–591.
31. Conners CK, Erhardt D, Sparrow EL (1999): Conners' Adult ADHD Rating Scales: Technical Manual. New York: Multi-Health Systems.
32. Conners CK, Sitarenios G, Parker JD, Epstein JN (1998): Revision and restandardization of the Conners Teacher Rating Scale (CTRS-R): Factor structure, reliability, and criterion validity. J Abnorm Child Psychol 26:279–291.
33. Taylor E, Schachar R, Thorley G, Wieselberg M (1986): Conduct disorder and hyperactivity: I. Separation of hyperactivity and antisocial conduct in British child psychiatric patients. Br J Psychiatry 149: 760–767.
34. Taylor E (1991): Developmental neuropsychiatry. J Child Psychol Psychiatry 32:3–47.
35. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, *et al.* (1997): Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36:980–988.
36. Conners CK, Sitarenios G, Parker JD, Epstein JN (1998): The revised Conners' Parent Rating Scale (CPRS-R): Factor structure, reliability, and criterion validity. J Abnorm Child Psychol 26:257–268.
37. Pruim RHR, Mennes M, Buitelaar JK, Beckmann CF (2015): Evaluation of ICA-AROMA and alternative strategies for motion artifact removal in resting state fMRI. Neuroimage 112:278–287.
38. Pruim RHR, Mennes M, van Rooij D, Llera A, Buitelaar JK, Beckmann CF (2015): ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. Neuroimage 112:267–277.
39. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, *et al.* (2004): Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23(suppl 1):S208–S219.
40. Woolrich MW, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T, *et al.* (2009): Bayesian analysis of neuroimaging data in FSL. Neuroimage 45(1 suppl):S173–S186.
41. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM (2012). FSL. Neuroimage 62:782–790.

42. Beckmann C, Mackay C, Filippini N, Smith S (2009): Group comparison of resting-state FMRI data using multi-subject ICA and dual regression. Neuroimage 47:S148.
43. Beckmann CF, Smith SM (2004): Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE Trans Med Imaging 23:137–152.
44. Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, *et al.* (2009): Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. Proc Natl Acad Sci U S A 106:7209–7214.
45. Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE (2014): Permutation inference for the general linear model. Neuroimage 92:381–397.
46. Smith SM, Nichols TE (2009): Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44:83–98.
47. von Rhein D, Cools R, Zwiers MP, van der Schaaf M, Franke B, Luman M, *et al.* (2015): Increased neural responses to reward in adolescents and young adults with attention-deficit/hyperactivity disorder and their unaffected siblings. J Am Acad Child Adolesc Psychiatry 54:394–402.
48. van Rooij D, Hoekstra PJ, Mennes M, von Rhein D, Thissen AJAM, Heslenfeld D, *et al.* (2015): Distinguishing adolescents with ADHD from their unaffected siblings and healthy comparison subjects by neural activation patterns during response inhibition. Am J Psychiatry 172:674–683.
49. Thissen AJAM, Luman M, Hartman C, Hoekstra P, van Lieshout M, Franke B, *et al.* (2014): Attention-deficit/hyperactivity disorder (ADHD) and motor timing in adolescents and their parents: Familial characteristics of reaction time variability vary with age. J Am Acad Child Adolesc Psychiatry 53:1010–1019.e4.
50. van Ewijk H, Heslenfeld DJ, Luman M, Rommelse NN, Hartman CA, Hoekstra P, *et al.* (2013): Visuospatial working memory in ADHD patients, unaffected siblings, and healthy controls. J Atten Disord 18:369–378.
51. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, *et al.* (2009): Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A 106:13040–13045.
52. Damoiseaux JS, Rombouts SARB, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF (2006): Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 103:13848–13853.
53. 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.
54. Zuo X, Kelly C, Adelstein JS, Klein DF, Castellanos FX, Milham MP (2010): Reliable intrinsic connectivity networks: Test-retest evaluation using ICA and dual regression approach. Neuroimage 49:2163–2177.
55. 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.
56. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, *et al.* (2007): Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27:2349–2356.
57. Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005): Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 360:1001–1013.
58. Qiu M, Ye Z, Li Q, Liu G, Xie B, Wang J (2011): Changes of brain structure and function in ADHD children. Brain Topogr 24:243–252.
59. Castellanos FX, Margulies DS, Kelly C, Uddin LQ, Ghaffari M, Kirsch A, *et al.* (2008): Cingulate-precuneus interactions: A new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol Psychiatry 63:332–337.
60. Fair DA, Posner J, Nagel BJ, Bathula D, Dias TGC, Mills KL, *et al.* (2010): Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. Biol Psychiatry 68:1084–1091.
61. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJS (2009): Default-mode brain dysfunction in mental disorders: A systematic review. Neurosci Biobehav Rev 33:279–296.
62. Leech R, Sharp DJ (2014): The role of the posterior cingulate cortex in cognition and disease. Brain 137:12–32.
63. Shulman GL, Astafiev SV, Franke D, Pope DLW, Snyder AZ, McAvoy MP, Corbetta M (2009): Interaction of stimulus-driven reorienting and expectation in ventral and dorsal frontoparietal and basal ganglia-cortical networks. J Neurosci 29:4392–4407.
64. Nelissen N, Stokes M, Nobre AC, Rushworth MFS (2013): Frontal and parietal cortical interactions with distributed visual representations during selective attention and action selection. J Neurosci 33:16443–16458.
65. Arrington CM, Carr TH, Mayer AR, Rao SM (2000): Neural mechanisms of visual attention: object-based selection of a region in space. J Cogn Neurosci 12(suppl 2):106–117.
66. Nigg JT, Casey BJ (2005): An integrative theory of attention-deficit/hyperactivity disorder based on the cognitive and affective neurosciences. Dev Psychopathol 17:785–806.
67. Capotosto P, Babiloni C, Romani GL, Corbetta M (2009): Frontoparietal cortex controls spatial attention through modulation of anticipatory alpha rhythms. J Neurosci 29:5863–5872.
68. Fassbender C, Schweitzer JB (2006): Is there evidence for neural compensation in attention deficit hyperactivity disorder? A review of the functional neuroimaging literature. Clin Psychol Rev 26:445–465.
69. Kofler MJ, Rapport MD, Sarver DE, Raiker JS, Orban SA, Friedman LM, Kolomeyer EG (2013): Reaction time variability in ADHD: A meta-analytic review of 319 studies. Clin Psychol Rev 33:795–811.
70. Tamm L, Narad ME, Antonini TN, O'Brien KM, Hawk LW, Epstein JN (2012): Reaction time variability in ADHD: A review. Neurotherapeutics 9:500–508.
71. Antonini TN, Narad ME, Langberg JM, Epstein JN (2013): Behavioral correlates of reaction time variability in children with and without ADHD. Neuropsychology 27:201–209.
72. Leth-Steensen C, Elbaz ZK, Douglas VI (2000): Mean response times, variability, and skew in the responding of ADHD children: A response time distributional approach. Acta Psychol (Amst) 104:167–190.
73. Barber AD, Jacobson LA, Wexler JL, Nebel MB, Caffo BS, Pekar JJ, Mostofsky SH (2015): Connectivity supporting attention in children with attention deficit hyperactivity disorder. Neuroimage Clin 7:68–81.
74. Georgopoulos AP (2000): Neural aspects of cognitive motor control. Curr Opin Neurobiol 10:238–241.
75. Kofler MJ, Raiker JS, Sarver DE, Wells EL, Soto EF (2016): Is hyperactivity ubiquitous in ADHD or dependent on environmental demands? Evidence from meta-analysis. Clin Psychol Rev 46:12–24.
76. Sarver DE, Rapport MD, Kofler MJ, Raiker JS, Friedman LM (2015): Hyperactivity in attention-deficit/hyperactivity disorder (ADHD): Impairing deficit or compensatory behavior? J Abnorm Child Psychol 43:1219–1232.
77. Jenkinson M, Bannister P, Brady M, Smith S (2002): Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17:825–841.