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Network Connectivity Abnormality Profile Supports a Categorical-Dimensional Hybrid Model of ADHD

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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity, and impulsivity, but there is no consensus regarding whether ADHD exists on the extreme end of a continuum of normal behavior or represents a discrete disorder. In this study, we sought to characterize both the categorical and dimensional variations in network functional connectivity in order to identify neural connectivity mechanisms of ADHD. Functional connectivity analyses of resting-state fMRI data from 155 children with ADHD and 145 typically developing children (TDC) defined the dorsal attention network (DA), default mode network (DM), salience processing network (SAL) and executive control network (CON). Regional alterations in connectivity associated with categorical diagnoses and dimensional symptom measures (inattention and hyperactivity/impulsivity) as well as their interaction were systematically characterized. Dimensional relationships between symptom severity measures and functional connectivity that did not differ between TDC and children with ADHD were observed for each network, supporting a dimensional characterization of ADHD. However, categorical differences in functional connectivity magnitude between TDC and children with ADHD were detected after accounting for dimensional relationships, indicating the existence of categorical mechanisms independent of dimensional effects. Additionally, differential dimensional relationships for TDC versus ADHD children demonstrated categorical differences in brain–behavior relationships. The patterns of network functional organization associated with categorical versus dimensional measures of ADHD accentuate the complexity of this disorder and support a dual characterization of ADHD etiology featuring both dimensional and categorical mechanisms. *Hum Brain Mapp 35:4531–4543, 2014.*

Key words: attention-deficit/hyperactivity disorder; resting state functional magnetic resonance imaging; dimensional disorders, attention; impulsivity; functional neural networks

Additional Supporting Information may be found in the online version of this article.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is characterized by developmentally inappropriate levels of inattention, impulsivity, and hyperactivity [Kuntsi et al., 2006]. A clinical diagnosis of ADHD is assigned when symptoms surpass a particular threshold of severity, implying an underlying categorical mechanism [Sonuga-Barke, 1998]. However, an alternative perspective considers symptoms as lying at the extreme end of normal behavior [Chabernaud et al., 2012], a conceptualization supported by genetic association studies [Bidwell et al., 2011; Larsson et al., 2012; Thapar et al., 2006], the graded relationship of subthreshold symptoms of ADHD and psychiatric comorbidities [Fergusson and Horwood, 1995; Malmberg et al., 2011], and taxometric analyses of ADHD-related behavioral measures [Haslam, 2007; Marcus and Barry, 2011]. The integration of dimensional measures of psychopathology into standard diagnostic criteria has thus gained support in recent years [Helzer, 2006; Hudziak et al., 2007; Marcus and Barry, 2011; Swanson et al., 2011]. In fact, the latest edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-V) adopts an approach that employs both categorical diagnosis and symptom severity assessments. Whether ADHD represents a discrete disorder or lies on an extreme of a continuum of normal behaviors has implications for how this disorder is diagnosed, treated, and studied. However, the precise nature of the neural mechanisms that underlie ADHD has not been systematically characterized.

The brain mediates the impact of genetic and environmental etiological factors on the outward expression of symptoms, making it a prime target for investigating the mechanisms of ADHD. Particularly, the identification of large-scale functional neural networks enabled by the recently emerged resting state functional fMRI (rsfMRI) technique [Biswal et al., 1995; Lowe et al., 1998; Paloyelis et al., 2007] provides a compelling means of exploring the neural mechanisms underlying different brain disorders [Chabernaud et al., 2012; Greicius, 2008]. Regarding ADHD, several candidate functional neural networks may be of particular importance. Specifically, the default mode network (DM) [Raichle et al., 2001] of posterior cingulate cortex, medial prefrontal cortex, bilateral angular gyrus, and temporal cortex demonstrates hypo-connectivity among children with ADHD [Fair et al., 2010], and a failure to down-regulate the DM during external goal-directed tasks is thought to contribute to attentional lapses [Gao et al., 2013; Mason et al., 2007; Sonuga-Barke and Castellanos, 2007; Weissman et al., 2006]. Additionally, the dorsal attention network (DA)[Corbetta and Shulman, 2002], covering bilateral intraparietal sulcus (IPS), frontal eye fields (FEF), and middle temporal visual regions (MT), is engaged during tasks requiring attention to external goals and has similarly been implicated in the etiology of ADHD [Castellanos and Proal, 2012; Cortese et al., 2012; Vance et al., 2007]. A frontal-parietal control system [Dosenbach et al., 2008; Seeley et al., 2007] consisting of a cingulo-opercular "salience network" (SAL) and a frontal-parietal "executive control network" (CON) may likewise contribute to ADHD: the CON network of dorsolateral, ventrolateral, and dorsomedial prefrontal and bilateral parietal connectivity is implicated in control of attention [de Fockert et al., 2001; Gao and Lin, 2012; Rossi et al., 2009; Turatto et al., 2004] and exhibits decreased activity in children with ADHD during attention tasks [Cortese et al., 2012; Hart et al., 2012). The SAL network of anterior insula and anterior cingulate connectivity is involved in salience detection [Menon and Uddin, 2010], including behavioral monitoring and error detection [Ullsperger et al., 2010], processes impaired in individuals with ADHD [Liotti et al., 2005; O'Connell et al., 2009]. Therefore, a closer examination of these large-scale neural networks associated with ADHD and its behavioral symptoms may expose the underlying categorical and dimensional characteristics of ADHD.

Adopting a network functional connectivity perspective, we aimed to unveil the neural mechanisms of ADHD characterized by a large sample of both typically developing children (TDC, $n = 145$) and children with ADHD ($n = 155$). Given evidence supporting both categorical and dimensional properties of ADHD [Chabernaud et al., 2012; Lubar, 2001; Thapar et al., 2006], we tested a hybrid model based on a systematic rsfMRI investigation of four networks implicated in cognitive processes impaired in ADHD (i.e., DA, DM, SAL, and CON). To characterize the mechanisms underpinning ADHD-related brain abnormalities, we investigated the contributions of dimensional symptom measures, categorical diagnosis, and their interaction to functional connectivity of these networks. Three types of effects were explored: (1) Functional connectivity-behavior relationships that do not differ between TDC and ADHD children and are independent of categorical diagnosis, which we term "congruent dimensional relationships," would suggest that ADHD lies on a continuum; (2) On the other hand, categorical differences in functional connectivity after controlling for dimensional relationships would suggest the existence of categorical mechanisms of ADHD; (3) Furthermore, categorical differences between TDC and ADHD children in the relationship of functional connectivity to behavior would suggest that symptoms of ADHD qualitatively differ from the spectrum of normal behavior, providing further evidence for categorical mechanisms of ADHD. We present results supporting each of these characterizations and subsequently discuss the implications.

METHODS

Subjects

Data from 145 TDC and 155 ADHD children were obtained from the ADHD-200 Sample database [Milham

et al., 2012] (http://fcon_1000.projects.nitrc.org/indi/adhd200/). The ADHD sample included 88 children diagnosed with the combined type, 64 with the predominantly inattentive type and 3 with the predominantly hyperactive-impulsive type. Given known sex differences in brain structure and function [Cahill, 2006], we focused this study on males, as this sex constitutes the majority of childhood ADHD cases [Cuffe et al., 2005]. Only data from research sites contributing resting-state fMRI scans from both TDC and ADHD children in addition to dimensional measures of ADHD were included [i.e., Kennedy Krieger Institute, Johns Hopkins University (KKI), New York University Child Study Center (NYU), and Peking University (PU)]. Study procedures were approved by the Johns Hopkins Medical and New York University Institutional Review Boards and Research Ethics Review Board of the Institute of Mental Health at Peking University. Parental written informed consent and child assent were obtained following explanation of study procedures.

Inclusion/Exclusion Criteria by Site

KKI

ADHD children met criteria for ADHD based on the Diagnostic Interview for Children and Adolescents, Fourth Edition (DICA-IV [Reich et al., 1997]) and had a T-score of at least 65 on the Conners Parent Rating Scale-Revised, Long Form (CPRS [Conners et al., 1998]) for either DSM-IV Inattentive and/or DSM-IV Hyperactive/Impulsive subscales or met ADHD criteria on the ADHD Rating Scale IV [DuPaul, 1998]. TDC children had *T*-scores lower than 60 or lower on both the DSM-IV Inattentive and DSM-IV Hyperactive/Impulsive subscales. Subjects were excluded for an estimated IQ below 80, language disorder or reading disability, visual or hearing impairment, psychoactive medication use other than stimulants for ADHD children, neurological disorders, or psychiatric disorders other than specific phobias or oppositional defiant disorder (ADHD subjects only).

NYU

ADHD diagnosis required a diagnosis based on parent and child responses to the Schedule of Affective Disorders and Schizophrenia for Children-Present and Lifetime Version (K-SADS [Kaufman et al., 1997]) and a *T*-score of at least 65 on either the DSM-IV Inattentive and/or DSM-IV Hyperactive/Impulsive subscales of the CPRS. TDC children had a *T*-score below 60 on any CPRS ADHD subscale. Exclusion criteria were an IQ below 80, left-handedness, and chronic medical conditions. TDC children had no Axis-I psychiatric disorders.

PU

ADHD was assessed with the Computerized Diagnostic Interview Schedule IV [Bacon, 1997] and verified with parent responses on the K-SADS. Subjects were excluded for an IQ below 80, left-handedness, loss of consciousness due to head trauma, neurological illness, schizophrenia, affective disorder, pervasive development disorder, or substance abuse.

Parent ratings from the CPRS (KKI, NYU) or ADHD Rating Scale IV (PU) provided dimensional measures of symptoms of inattention and hyperactivity/impulsivity related to DSM-IV diagnostic criteria. Corresponding subscale scores for these two instruments demonstrate good convergent validity [Zhang et al., 2005]. To control for differences in ranges of potential scores obtained from different instruments and to enable comparison across sites, symptom subscales were rescaled to have a range of 0.0–1.0 for each site by normalizing all scores to their corresponding maximum. Intelligence (IQ) was assessed with the Wechsler Intelligence Scale for Children, Fourth Edition [Kaufman et al., 2006] (KKI), Wechsler Abbreviated Scale of Intelligence [Wechsler, 1999] (NYU), or the Wechsler Intelligence Scale for Chinese Children-Revised [Dan et al., 1990] (PU). For the 116 children with ADHD for which medication status was available, 69 (59%) were medication naïve. The inattention and impulsivity scores used in the current analysis were obtained as part of the study procedures and therefore reflect symptoms exhibited after medication use for treated subjects. Subjects from all imaging sites were free of stimulant medication for at least 24 h prior to the scan.

Image Acquisition

Magnetic resonance imaging time series were collected in resting conditions using Siemens Magnetom Allegra and Trio (Siemens Medical Solutions, Erlangen, Germany) for NYU and PU and Philips Gyroscan (Philips Medical Systems, Amsterdam, Netherlands) 3 Tesla MRI scanners for KKI. Detailed imaging parameters are presented in Supporting Information Table S1.

Preprocessing

Functional images were preprocessed using Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm/) and Analysis of Functional NeuroImages (AFNI [Cox, 1996]) software. The first five volumes were removed to allow magnetization to reach equilibrium. Images were corrected for slice timing and realigned to the second available scan in each functional series. Next, the subject's T1 image was registered to an MNI template in SPM8 and the functional images were warped using the same transformation field and then re-sliced to 3 mm cubic voxels. Functional images were spatially smoothed with an 8 mm FWHM Gaussian kernel and band-pass filtered between 0.008 and 0.08 Hz in AFNI. Regression analysis was performed to remove nuisance signals from white matter, cerebral spinal fluid, global signal, and six motion parameters.

To further remove motion artifacts, a new data scrubbing method was implemented [Power et al., 2012]. Specifically, thresholds for global signal change at each volume and displacement between acquired volumes were set at less than 0.5% BOLD signal and 0.5 mm, respectively. Briefly, if both measures of any volume reached their respective thresholds, that volume, the one previous and the two after were removed. Total displacement between consecutive volumes was measured by taking the sum of the distance moved across six directions [Power et al., 2012], including three translations (x, y, z) and three rotations (roll, pitch, yaw, converted into distance). An analysis of the mean volume-to-volume displacement across all volumes indicated no significant difference in motion between ADHD children (0.19 ± 0.20 mm) and TDC (0.14 ± 0.22 mm). An average of 7.3 ± 14.3 ($4.2 \pm 8.1\%$) and 6.8 ± 14.3 ($4.4 \pm 9.2\%$) volumes were removed for ADHD children and TDC, respectively, indicating no significant difference between groups in the total number ($t = 0.30$, $P > 0.05$) or percent ($t = -0.12$, $P > 0.05$) of volumes removed.

Network Functional Connectivity

Network-level functional connectivity was defined as the voxel-wise Pearson correlation with a reference time series using AFNI's 3dfim+. Reference time series were extracted as the simple average time series of all voxels within a 6 mm spherical seed. In accordance with Seeley et al. [2007], the CON was defined by connectivity with a right dorsolateral prefrontal cortex seed (Montreal Neurologic Institute coordinates (MNI): 44, 36, 20) and the SAL by a seed in the right anterior insula (MNI: 38, 26, −10). Similarly, DM and DA were defined by seeds in the posterior cingulate cortex (MNI: 1, −55, 17) and bilateral intraparietal sulcus (MNI: −27, −52, 57; 24, −56, 55), respectively, as in [Gao and Lin, 2012] and [Vincent et al., 2008]. Pearson correlation maps were subsequently normalized using a Fisher-z transform.

Statistical Analyses

Linear regression models included categorical diagnosis and either inattention or hyperactivity/impulsivity as predictors of functional connectivity, covarying for age, and imaging sites. Inattention and hyperactivity/impulsivity were tested in separate models to avoid multicollinearity as these variables share a large portion of variance ($R^2 = 0.56$). These models enabled the detection of dimensional effects that demonstrate consistent linear relationships across both groups (i.e., not explained by categorical differences). We describe these effects as "congruent dimensional relationships" in subsequent sections. Furthermore, these analyses also identified those regions for which categorical differences in functional connectivity magnitude were evident after controlling for effects of dimensional variables. Such effects are referred to as "categorical effects on functional connectivity" in subsequent sections. To account for the full effects of both inattention and hyperactivity/impulsivity, categorical effects were defined using a conjunction analysis of significant effects of ADHD diagnosis that were present in both models. Significant categorical and dimensional effects ($P < 0.05$) were cluster-level-corrected to $\alpha < 0.05$ with a minimum cluster size of 154 voxels based on 10,000 Monte Carlo simulations conducted with 3dClustSim in AFNI.

Furthermore, to determine if ADHD is associated with categorical effects on dimensional relationships, we tested the interaction of diagnosis and dimensional variables as predictors of voxel-wise functional connectivity in linear regression models, with age and imaging sites included as covariates. Again, inattention and hyperactivity/impulsivity symptoms were modeled separately. These models identified those regions for which the linear relationship between symptom measures and functional connectivity was categorically different between TDC and ADHD. Subsequent sections refer to these effects as "categorical effects on brain–behavior relationships." The threshold for a significant interaction effect was set at $P < 0.05$ with a minimum cluster size of 154 voxels based on 3dClustSim in AFNI providing a corrected false positive rate of 0.05.

Finally, the intersection of the maps of significant (cluster-level corrected) regions showing categorical effects (in functional connectivity magnitude or in brain–behavior relationships) with a map of significant regions showing congruent dimensional relationships was calculated in order to identify regions that demonstrate effects of both mechanisms.

RESULTS

Demographic and clinical variables for TDC and ADHD subjects are summarized in Table I. Figure 1 presents the spatial maps of all four networks for the TDC group. Consistent with previous reports [Fox et al., 2005], the DA consisted of positive correlations between the superior parietal lobules/IPS, FEF, inferior and middle frontal gyri, MT, and cerebellum. DM connectivity was present in posterior cingulate cortex, inferior parietal lobules, medial prefrontal cortex, middle temporal cortex, and parahippocampal gyrus [Buckner et al., 2008; Greicius et al., 2003]. Consistent with the network topology of healthy adults [Seeley et al., 2007], the SAL included bilateral inferior frontal cortex/insula, anterior cingulate cortex/medial prefrontal cortex, and inferior parietal lobules and the CON included bilateral middle and inferior frontal gyri, dorsomedial prefrontal cortex and bilateral parietal cortex. The spatial topologies of all four functional connectivity maps for children with ADHD were qualitatively similar to those for TDC (Supporting Information Fig. S1).

Congruent Dimensional Relationships Across TDC and ADHD

Significant dimensional effects on functional connectivity across both children with ADHD and TDC were observed

TABLE I. Demographic and clinical variables for typically developing children, ADHD patients, and the pooled sample

	All sites		KKI		NYU		PU	
N	300		46		132		122	
TDC	145		34		45		66	
ADHD	155		12		87		56	
Age	11.7	*2.4*	10.4	*1.4*	11.7	*2.9*	12.3	*1.8*
TDC	11.8	*2.3*	10.3	*1.4*	12.3	*3.2*	12.1	*1.7*
ADHD	11.7	*2.5*	10.4	*1.5*	11.4	*2.7*	12.4	*2.0*
IQ	112.7	*15.2*	113.0	*13.8*	109.3	*14.6*	116.1	*15.6*
TDC	117.4	*13.6*	115.3	*13.0*	113.5	*13.6*	121.1	*13.2*
ADHD	108.4	*15.2*	106.5	*14.5*	107.3	*14.6*	110.4	*16.3*
Inattention score	43.9	*21.4*	51.2	*11.0*	60.8	*13.6*	21.7	*7.4*
TDC	33.5	*15.7*	45.4	*5.3*	45.0	*7.2*	15.4	*3.6*
ADHD	57.3	*21.5*	66.7	*6.0*	68.7	*8.0*	28.3	*3.6*
Impulsivity score	42.2	*23.0*	52.8	*11.4*	60.1	*14.2*	17.7	*7.0*
TDC	31.7	*16.9*	47.0	*4.6*	45.3	*4.6*	13.1	*3.5*
ADHD	51.2	*23.8*	68.2	*9.9*	67.4	*11.3*	22.4	*6.6*

Mean and standard deviation (*italics*) are provided for each continuous measure. N, number; IQ, intelligence quotient; ADHD, attention-deficit/hyperactivity disorder; TDC, typically developing children; KKI, Kennedy Krieger Institute; NYU, New York University; and PU, Peking University.

for all networks tested (Fig. 2, Supporting Information Tables S2 and S3). Higher inattention scores were associated with connectivity of bilateral fusiform gyrus for DM (decreased) and SAL (increased), as well as increased connectivity of the precuneus for DM and CON. There was also a notable association of greater inattention with lesser connectivity of anterior cingulate cortex and bilateral middle frontal gyrus regions within CON. Greater severity of

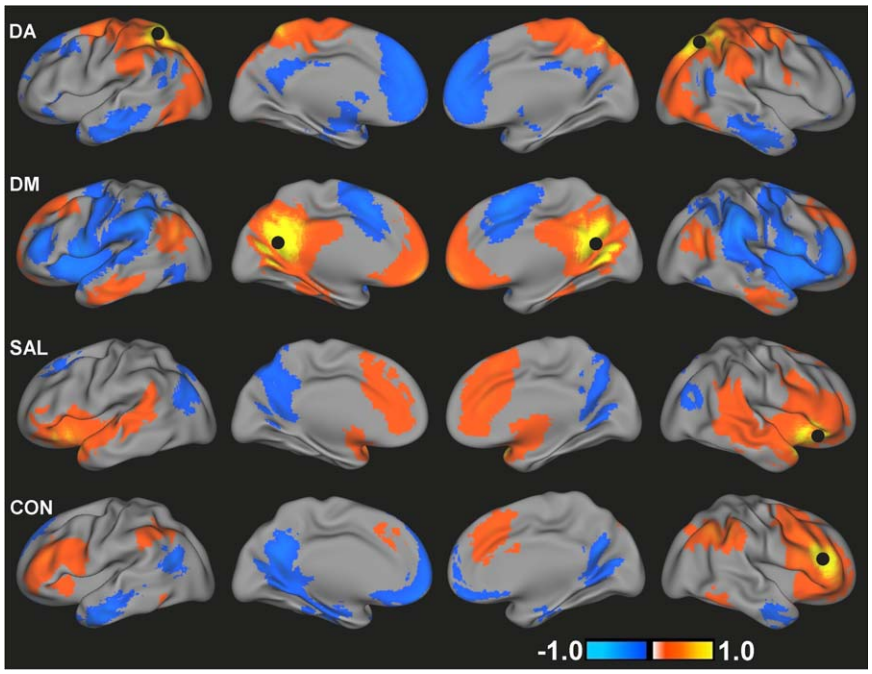

Figure 1.
Group mean functional connectivity maps for DA, DM, SAL, and CON for TDC. Black circles indicate the location of seed regions used to generate each map. Images are displayed using a threshold of an absolute value of $r > 0.1$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

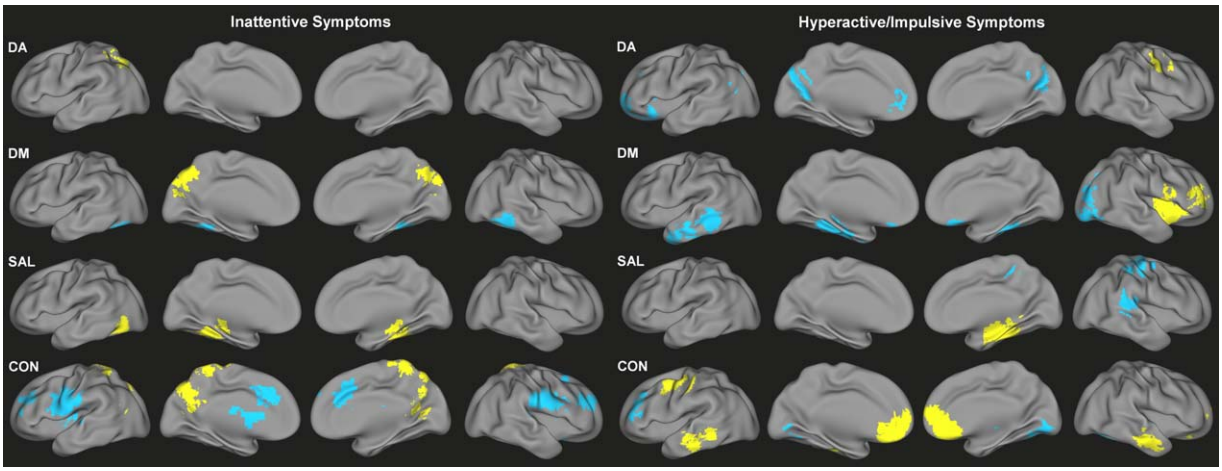

Figure 2.

Congruent functional connectivity-behavior relationships across TDC and ADHD for inattention scores (left) and hyperactivity/impulsivity scores (right) for DA, DM, SAL, and CON. Yellow indicates positive associations with symptoms; blue indicates negative associations with symptoms. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

hyperactive/impulsive symptoms was associated with connectivity of the fusiform and parahippocampal gyri for DM (decreased) and SAL (right-lateralized, increased), medial prefrontal cortex for DA (decreased) and CON (increased), left inferior/middle temporal gyrus and right lateral occipital cortex for DM (decreased), and bilateral inferior/middle temporal gyrus for CON (increased).

Categorical Effects of ADHD on Functional Connectivity

After accounting for congruent dimensional relationships, there were regions that demonstrated categorical effects of ADHD diagnosis on functional connectivity of DM, SAL and CON (Fig. 3, Supporting Information Table S4). Hyper-connectivity in children with ADHD—after adjusting for dimensional relationships with symptom severity—was observed for DM connectivity with sensorimotor and visual association regions and CON connectivity with anterior cingulate cortex, superior frontal gyrus, insula, and cerebellum. Hypo-connectivity associated with categorical effects of ADHD was observed for DM connectivity with the medial prefrontal cortex and superior frontal gyrus, SAL connectivity with the left fusiform gyrus and left frontal eye field, and CON connectivity with the precuneus and sensorimotor cortex.

Categorical Effects of ADHD on Brain–Behavior Relationships

Categorical differences in the slope of the relationship of ADHD-related behaviors to functional connectivity were also identified across all four networks (Fig. 4, Supporting Information Tables S5 and S6). Significant interaction effects between ADHD diagnosis and inattentive symptoms on functional connectivity were identified for DA primarily along the precentral and postcentral gyri, supplementary motor area and cerebellum, showing a greater positive relationship in children with ADHD. Similar effects were observed in the precuneus and anterior cingulate cortex for DM, in the right amygdala and parahippocampal gyrus for SAL, and in the middle temporal gyrus for CON. Conversely, the relationship between inattention and functional connectivity of the bilateral caudate with SAL was weaker in ADHD children than TDC.

For the interaction of ADHD diagnosis and hyperactive/impulsive symptoms, children with ADHD demonstrated a greater relationship of symptoms to DA connectivity with the right middle and inferior temporal gyrus, DM connectivity with bilateral inferior frontal gyrus and inferior parietal lobule, SAL connectivity with bilateral paracentral lobule and left angular gyrus, and CON connectivity with the posterior cingulate cortex, precuneus, right superior frontal gyrus, and right angular gyrus. There was also a decreased relationship among children with ADHD of hyperactive/impulsive symptoms to functional connectivity of the cuneus/precuneus and right superior temporal gyrus with DM, cerebellum and visual associations regions with SAL, and bilateral superior temporal gyrus and left inferior frontal gyrus with CON.

Overlap of Categorical and Dimensional Mechanisms

Overall, the patterns of dimensional effects and categorical effects on the functional connectivity of DA, DM, SAL and CON suggest these mechanisms largely impact

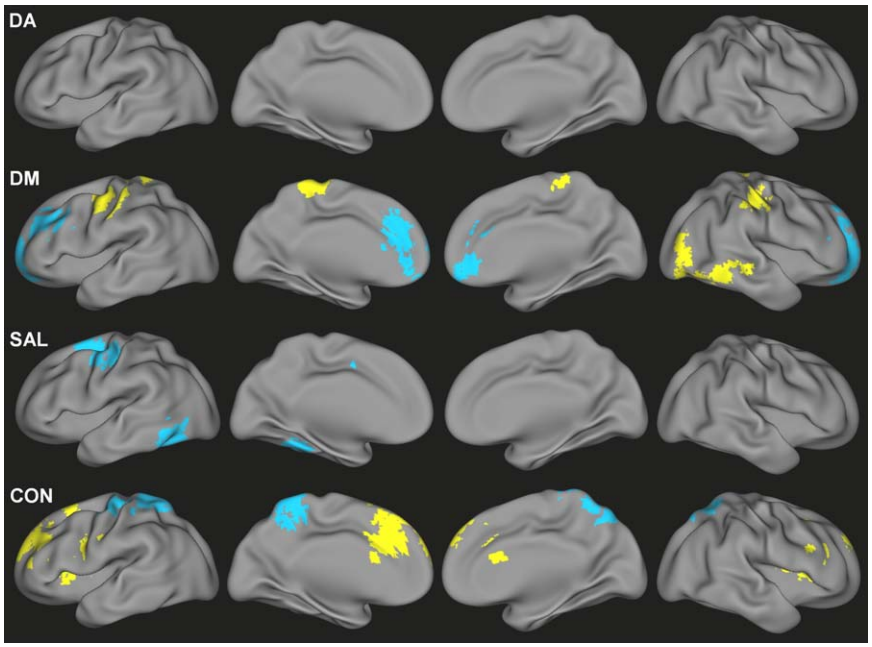

Figure 3.

Categorical differences in functional connectivity values associated with an ADHD diagnosis and unaccounted for by either inattentive or hyperactive/impulsive scores for DA, DM, SAL, and CON. Yellow indicates ADHD > TDC; blue indicates TDC > ADHD. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

separate regions. However, there were also several regions affected by both mechanisms, showing consistent brain–behavior relationships across TDC and ADHD children in addition to categorical effects on functional connectivity that exist independent of dimensional relationships (blue regions, Fig. 5). Such regions included the precuneus, anterior cingulate cortex, and bilateral middle frontal gyrus for CON, the fusiform gyrus for DM and SAL, as well as

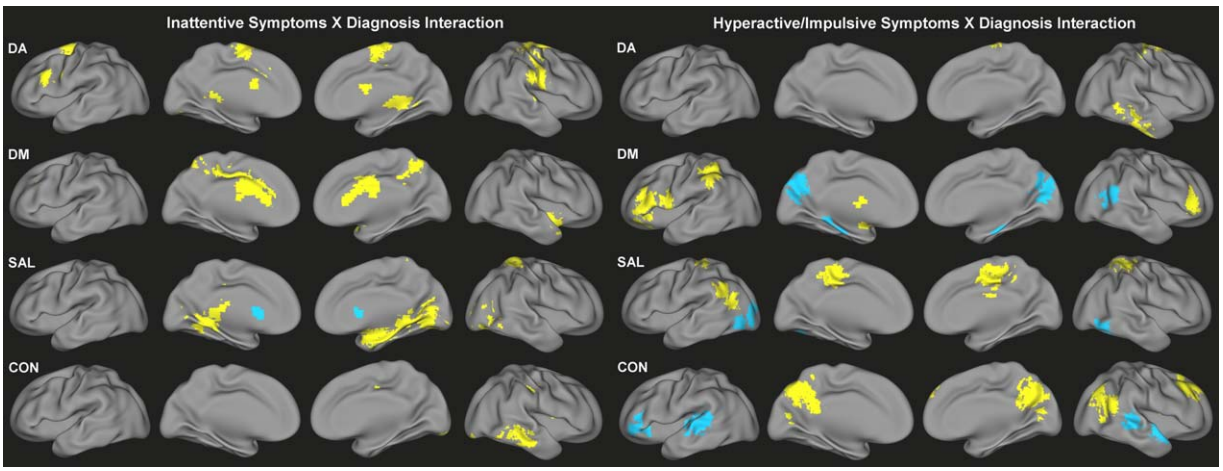

Figure 4.

Significant interaction effects of ADHD diagnosis and symptoms of inattention (left) and significant interaction effects of ADHD diagnosis and symptoms of hyperactivity/impulsivity (right) on functional connectivity of DA, DM, SAL, and CON. Yellow indicates more positive association with symptoms for children with ADHD; blue indicates more positive association with symptoms for TDC. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

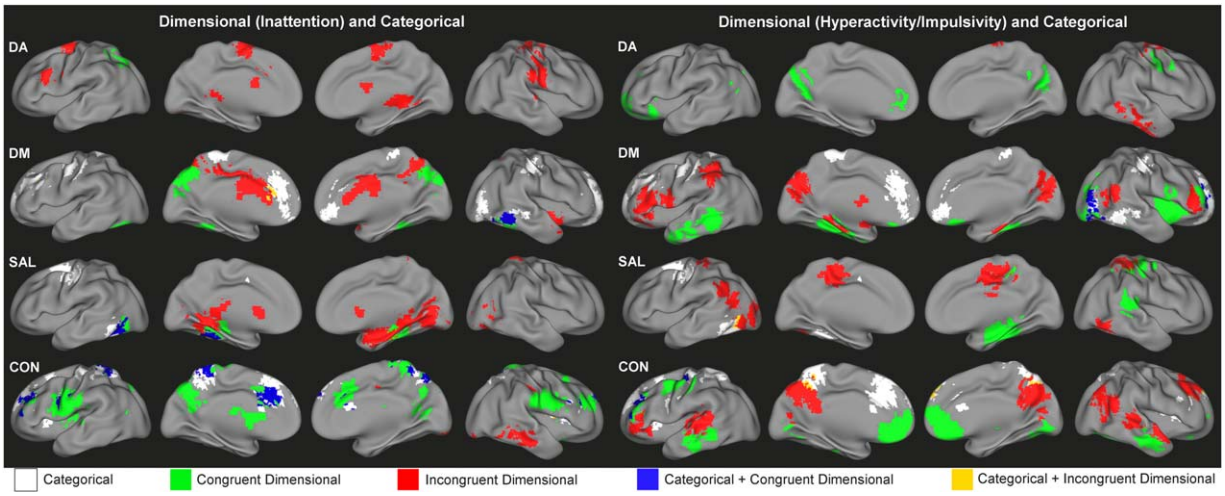

Figure 5.

Composite maps showing the regional connectivity alterations associated with categorical effects of ADHD diagnosis (categorical, white), dimensional effects of inattention (left) or hyperactivity/impulsivity (right) (congruent dimensional, green), the interaction of categorical and dimensional effects (incongruent dimensional, red), the overlap of categorical and congruent dimensional effects (blue) and the overlap of categorical and incongruent dimensional effects (yellow) for DA, DM, SAL, and CON. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

lateral visual areas for DM. Minimal overlap was observed between brain regions showing categorical effects on functional connectivity and those associated with categorical effects on brain–behavior relationships (yellow regions, Fig. 5).

Exemplar network connectivity effects showing various dimensional and/or categorical relationships are provided in Figure 6. An example of only congruent dimensional effects on SAL connectivity is presented in Figure 6A; two examples of DM connectivity showing only categorical effects on functional connectivity are presented in Figure 6B,C; two examples of DA and CON connectivity depicting an interaction between categorical diagnosis and dimensional brain–behavior relationships are shown in Figure 6D,E; finally, an example of CON connectivity demonstrating both congruent dimensional and categorical effects is presented in Figure 6F.

DISCUSSION

In this study, both categorical differences associated with ADHD diagnosis and significant dimensional effects of two symptom measures were observed for functional connectivity across four theoretically derived neural networks (i.e., DA, DM, SAL, and CON). The detection of a number of regions associated with consistent brain–behavior relationships across both TDC and ADHD endorses the dimensional characteristics of this disorder. Additionally, categorical differences in functional connectivity magnitude that were not driven by dimensional effects, as well as the presence of brain–behavior relationships that were moderated by ADHD diagnosis, indicate the existence of categorical mechanisms of ADHD. Therefore, our results support a dual characterization of ADHD etiology and highlight the importance of considering influences from both categorical and dimensional factors.

The consistent, linear relationship of dimensional variables to functional connectivity across both ADHD children and TDC (congruent dimensional relationships) provides strong evidence for a dimensional characterization of the functional connectivity etiology of ADHD (Chabernaud et al., 2012). The subscales for the CPRS and ADHD Rating Scale, which provided the dimensional variables for this study, measure symptoms that correspond with the DSM-IV inattention and hyperactive/impulsive symptom criteria for a diagnosis of ADHD. However, these scales are modeled on the recognition that the behaviors they assess are present to a varying degree in all children. The correspondence of these dimensional subscales to functional connectivity indicates that the degree of expression of ADHD-related behaviors is driven by greater or lesser connectivity in particular brain regions, exemplifying the dimensional aspect of ADHD etiology. One example of such a dimensional mechanism is shown in Figure 6A; regardless of the presence of an ADHD diagnosis, greater expression of hyperactive/impulsive behaviors was related to greater connectivity of the SAL seed with the right hippocampus/parahippocampal gyrus. Intuitively, aberrant connectivity in such regions would promote the increased expression of ADHD symptomology, resulting in a positive diagnosis of ADHD. This relationship is thus

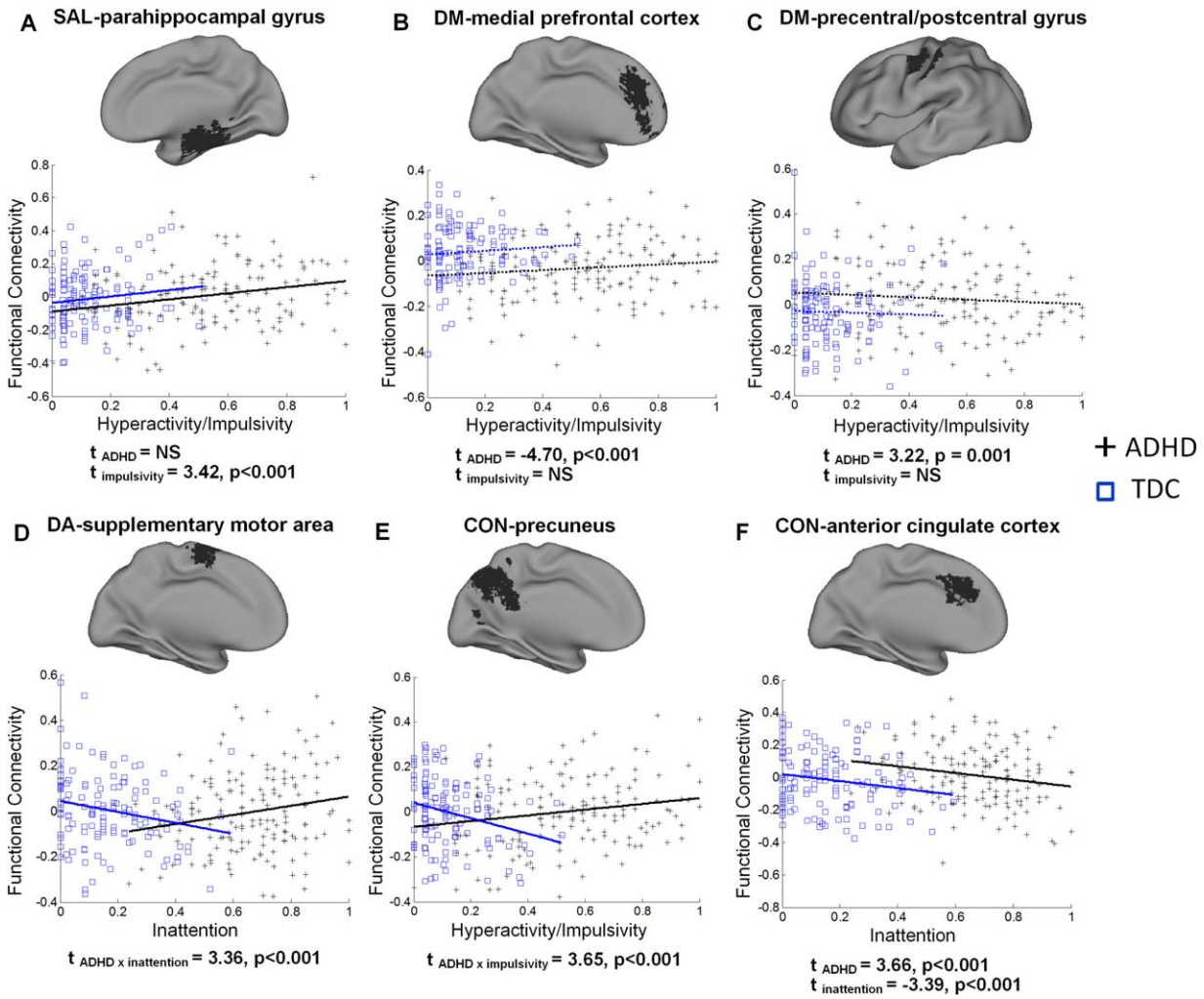

Figure 6.

Scatter plots of the relationship between behavior scores and functional connectivity for TDC and children with ADHD for selected regions. Least-squares regression lines demonstrate statistically significant relationships (solid lines) or nonsignificant relationships (dashed lines). *T*-statistics for the effects of categorical and dimensional variables on regional connectivity are reported below each plot demonstrating dimensional effects only (**A**), categorical effects only (**B, C**), an interaction of categorical and dimensional effects (**D, E**), and both dimensional and categorical effects (**F**). Functional connectivity values (*y*-axis) represent residuals after removing effects of age and site. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

consistent with the perspective of ADHD as existing along a continuum that includes typical brain function.

In addition, categorical differences in functional connectivity magnitude that were independent of symptom measures (Figs. 3 and 6B,C) as well as categorically different functional connectivity-behavior relationships for TDC versus ADHD (Figs. 4 and 6D,E), were also observed across multiple networks and regions. A series of factors could contribute to the existence of such categorical effects. First, clinically defined ADHD may encompass impairments in constructs not fully accounted for by the two studied behavioral domains. For example, functional alterations in sensorimotor cortical regions [Mostofsky et al., 2006; Tian et al., 2008] may contribute to sensory processing impairments in ADHD [Cheung and Siu, 2009; Yochman et al., 2004]. Other processes associated with a categorical diagnosis of ADHD, including temporal discounting behavior [Paloyelis et al., 2010], error processing [O'Connell et al., 2009; Senderecka et al., 2012] and reward processing [Paloyelis et al., 2012] could also have differential underlying neurobiology and contribute to the observed categorical effects. However, it is unlikely that these secondary behavioral

deficits could fully account for the presence of wide-spread categorical effects on both functional connectivity values (Fig. 3) and brain–behavior relationships (Fig. 4) that are independent of the examined dimensional relationships as shown in this study. Second, part of the observed categorical effects may represent effects of comorbidities, as childhood ADHD frequently presents alongside anxiety disorders, conduct disorder and oppositional-defiant disorder [Costello et al., 2003]. However, many comorbid psychiatric and neurological disorders were considered exclusion criteria across the three imaging sites. Therefore, it is again unlikely that secondary or subthreshold disorders would be sufficient to account for the observed wide-spread categorical effects.

A remaining possibility, which we tentatively support, is that ADHD etiology comprises categorical mechanisms in addition to dimensional characteristics. This explanation largely corroborates factor analytic studies indicating that a separate "general" ADHD mechanism together with "specific" inattention and hyperactive/impulsive factors best account for variation in ADHD symptoms [Martel et al., 2010; Toplak et al., 2009]. Such mechanisms are supported by the finding that a number of regions showed categorical differences in their functional connectivity after controlling for dimensional effects. For example, sensorimotor regions exhibited categorical hypo-connectivity with CON but hyper-connectivity with DM. The CON plays a role in initiating task sets for adaptive control of behavior by preparing secondary sensory and motor processes [Dosenbach et al., 2008; Pochon et al., 2001]. The observed disruption of connectivity between CON and sensorimotor regions may represent a deficit in coordination between these regions that contributes, in a qualitative manner, to heightened symptoms of ADHD. On the other hand, the DM and sensorimotor network are negatively correlated during rest and finger tapping in healthy adults [Gao and Lin, 2012], a relationship which may reduce interference from internally directed processes of the DM during externally directed motor behaviors. Thus an increased association between DM and sensorimotor regions could again contribute, in a qualitative manner, to impaired motor control [Tseng et al., 2004] and heightened responsiveness to sensory stimuli [Dunn and Bennett, 2002] in children with ADHD. The diminished medial prefrontal cortical connectivity within the DM, which is a replicated deficit in ADHD [Castellanos et al., 2008; Fair et al., 2010; Qiu et al., 2010], persisted after controlling for behavioral measures (Figs. 3 and 6B). It could be speculated that hypo-connectivity of the medial prefrontal cortex within the DM hinders uniform DM suppression during externally directed attention, contributing, in a categorical manner, to difficulties with maintaining attention [Sonuga-Barke and Castellanos, 2007]. Finally, children with ADHD also exhibited hyper-connectivity of CON in medial and inferior frontal/insula cortical regions consistent with core SAL regions. The CON and SAL undergo functional segregation throughout typical development [Fair et al., 2007], becoming functionally distinct in adulthood [Dosenbach et al., 2008; Elton and Gao, in press; Seeley et al., 2007]. These networks appear to be less functionally segregated in children with ADHD, potentially contributing to cognitive deficits in this disorder [Fair et al., 2007].

Evidence that the presence of psychopathology alters the relationship of behaviors to functional connectivity in particular regions across all four networks also supports the postulation of categorical mechanisms. The implications for such a discrepancy in brain–behavior relationships between TDC and ADHD children is that the expression of ADHD symptomology does not lie exclusively on the continuum of normal behavioral expression. For example, greater CON connectivity with a cluster extending from the precuneus to posterior cingulate cortex was associated with greater severity of hyperactive/impulsive symptoms in children with ADHD; however, this same region showed a negative brain–behavior relationship in TDC (Fig. 6E). In healthy individuals, the posterior cingulate and precuneus, core regions of the DM, functionally interact with the CON to support goal-directed planning [Gerlach et al., 2011; Spreng et al., 2010]. However, in children with ADHD, this same functional interaction is apparently associated with increased impulsive behavior, suggesting poorer planning ability [Marzocchi et al., 2008]. Thus, at least for certain regions, ADHD symptoms exhibit a qualitatively different profile of functional connectivity from those behaviors that fall in the nonclinical range. Such findings not only provide evidence for a categorical nature of ADHD but also highlight the importance of considering both categorical and dimensional measures when characterizing this disorder [Chabernaud et al., 2012]. Thus, overall, our results indicate that both dimensional factors and categorical mechanisms likely contribute to ADHD.

Finally, there were several regions including the fusiform gyrus in DM and SAL and the anterior cingulate cortex in CON that showed effects of both dimensional and categorical variables. As shown in Figure 6F, for the connectivity of the anterior cingulate cortex to the CON seed, there were remaining categorical differences after controlling for the consistent negative relationship between functional connectivity and inattention symptoms across both TDC and ADHD. The existence of such regions highlights the fact that dimensional and categorical mechanisms of ADHD not only express separately in different brain areas but could also function independently in the same brain region. Such convergence of categorical and dimensional effects on common neural targets may indicate a functionally relevant etiological mechanism and deserves further investigation.

Limitations

Several methodological limitations should be considered. First, we only considered males in this study, but future work should investigate potential sex differences in the neural network alterations underlying ADHD. Second, although imaging site was a covariate in all statistical analyses, we

further tested the interaction of site and ADHD diagnosis on regions of each network showing a significant effect of ADHD in the pooled sample to confirm our results were not driven by a single site. There were no significant effects of site on ADHD-related connectivity alterations for any network. Third, due to the extent of missing data regarding psychostimulant medication use, our analyses did not control for this variable. However, we explored the potential contribution of medications [Konrad et al., 2007] in the subsample of ADHD children for which medication status was available by conducting a two-sample *t*-test on the mean functional connectivity within regions showing an effect of ADHD in primary analyses. We found no significant differences between medication naïve and nonmedication naïve children in ADHD-affected regional connectivity. Furthermore, we opted not to adjust for intelligence (IQ) since cognitive-behavior deficits in ADHD tend to produce lower IQ scores and controlling for this variable can provide counterintuitive estimates of effects of interest [Dennis et al., 2009]. Nonetheless, post-hoc tests of the effects of IQ on regional connectivity related to categorical and dimensional measures of ADHD confirmed that intelligence did not account for our findings. We also investigated potential differences between ADHD subtypes in regions identified in primary analyses and detected no significant effects of the combined type ($n = 88$) versus inattentive type ($n = 64$) on either categorically defined regions or dimensional brain–behavior relationships. Because hyperactivity/impulsivity and inattention are correlated, including hyperactivity/impulsivity and inattention variables in separate models reduced the interpretability of observed effects as being specific to the symptom being tested. However, since these variables share a substantial portion of variance (56%), on top of the multicollinearity concern in linear regression, including both of these variables in the same model would have minimized the effects of either. Also, the contention that observed correlations between brain regions are revealed rather than "introduced" by removal of the global signal time series is debated [Fox et al., 2009; Murphy et al., 2009], and thus it is possible that such processing contributed to our results. Additionally, although the study sample consisted of children, the data was registered to an adult template (MNI), potentially resulting in a larger degree of registration error than would be observed for adult studies. Finally, the use of full Pearson correlation for estimating network connectivity limits inferences regarding "direct" versus "indirect" connections between regions and may be less sensitive to detecting true connections than other methods [Smith et al., 2011]. Future work utilizing partial correlation or other connectivity measures may provide a more informed picture of ADHD-related functional connectivity abnormalities.

CONCLUSIONS

In this study, we characterized the effects of dimensional behavioral measures of ADHD on functional connectivity of four large-scale neural networks. We also documented categorical differences, in both brain–behavior relationships and functional connectivity magnitude, that were distinct from effects of dimensional relationships, potentially reflecting certain categorical mechanisms underlying the etiology of ADHD. This study contributes novel insight to the ongoing debate regarding diagnostic and investigative models of ADHD and provides support for a characterization that includes both categorical diagnosis and symptom severity indices.

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