Archival Report

Biological Psychiatry: CNNI

Aberrant Time-Varying Cross-Network Interactions in Children With Attention-Deficit/Hyperactivity Disorder and The Relation to Attention Deficits

Weidong Cai, Tianwen Chen, Luca Szegletes, Kaustubh Supekar, and Vinod Menon

ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is thought to stem from aberrancies in large-scale cognitive control networks. However, the exact nature of aberrant brain circuit dynamics involving these control networks is poorly understood. Using a saliency-based triple-network model of cognitive control, we tested the hypothesis that dynamic cross-network interactions among the salience, central executive, and default mode networks are dysregulated in children with ADHD, and we investigated how these dysregulations contribute to inattention.

METHODS: Using functional magnetic resonance imaging data from 140 children with ADHD and typically developing children from two cohorts (primary cohort = 80 children, replication cohort = 60 children) in a case-control design, we examined both time-averaged and dynamic time-varying cross-network interactions in each cohort separately.

RESULTS: Time-averaged measures of salience network–centered cross-network interactions were significantly lower in children with ADHD compared with typically developing children and were correlated with severity of inattention symptoms. Children with ADHD displayed more variable dynamic cross-network interaction patterns, including less persistent brain states, significantly shorter mean lifetimes of brain states, and intermittently weaker cross-network interactions. Importantly, dynamic time-varying measures of cross-network interactions were more strongly correlated with inattention symptoms than with time-averaged measures of functional connectivity. Crucially, we replicated these findings in the two independent cohorts of children with ADHD and typically developing children.

CONCLUSIONS: Aberrancies in time-varying engagement of the salience network with the central executive network and default mode network are a robust and clinically relevant neurobiological signature of childhood ADHD symptoms. The triple-network neurocognitive model provides a novel, replicable, and parsimonious dynamical systems neuroscience framework for characterizing childhood ADHD and inattention.

Keywords: Cognitive control, Dynamic brain state, Functional connectivity, Human, Inattention, Salience network

https://doi.org/10.1016/j.bpsc.2017.10.005

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with global prevalence rates of over 5% in children and adolescents (1–3). The primary behavioral features of ADHD are inattention, hyperactivity, and impulsivity, which have profound effects on children's cognitive, affective, and social development (4–9). Neurobiologically, ADHD is now increasingly viewed as a disorder stemming from disturbances in large-scale brain networks (10–17). However, the precise nature of these disturbances is not well understood, as extant studies of functional brain connectivity in ADHD have produced conflicting findings, with some studies reporting hyper- and hypoconnectivity relative to neurotypical controls and others reporting null findings, often between the same brain regions (10,16,18–23), likely owing to weak theoretical models, inadequate quantitative approaches, and variation in protocols and measures across data collection sites. Crucially, little is known about brain network dynamics in ADHD, as previous studies have assumed functional interactions between brain networks to be stationary. Here, we overcome limitations of previous work by using a principled systems neuroscience approach (24) to characterize aberrancies in dynamic time-varying interactions among key cognitive control networks and investigate how such altered dynamic functional circuits contribute to core cognitive deficits associated with childhood ADHD, in two independent cohorts.

Our analysis of the neurobiological basis of childhood ADHD is based on a triple-network model involving three large-scale brain networks that play important and distinct roles in higher-order cognition (25–29): the salience network (SN), the central executive network (CEN), and the default mode

ISSN: 2451-9022

network (DMN). The SN, which is anchored in the anterior insula and the anterior cingulate cortex, plays a crucial role in identifying biologically and cognitively salient events necessary for guiding attention and goal-directed behaviors (28). The CEN, which is anchored in the dorsolateral prefrontal cortex and the posterior parietal cortex, is important for the active maintenance and manipulation of information in working memory (30–32). The DMN, which is anchored in the posterior cingulate cortex and the medial prefrontal cortex, plays an important role in self-referential mental processes (33). Notably, the SN, CEN, and DMN are often coactivated or deactivated during attentionally demanding tasks (34–37), suggesting that these networks function in concert to support attention and cognition. In particular, the triple-network model posits a central role for the SN in initiating switching between the CEN and DMN, a process essential for attention and flexible cognitive control (38–41).

A systematic investigation using theoretically informed neurocognitive models has the potential to significantly advance a principled understanding of the neurobiology of childhood ADHD. Meta-analyses of task-based functional magnetic resonance imaging studies have consistently pointed to aberrant activation of SN, CEN, and DMN regions in individuals with ADHD compared with neurotypical individuals (42,43). Previous studies have pointed to abnormal time-averaged functional connectivity within the DMN, and between the DMN and cingulo-opercular and occipital regions in children and adolescents with ADHD (10,16,19,20) and their associations with cognitive control deficits and clinical symptoms. However, no studies to date have investigated dynamic time-varying interactions among large-scale brain networks in children with ADHD, and a comprehensive understanding of dysfunctional interactions among the SN, CEN, and DMN and their relation to clinical symptoms is still missing. Based on growing evidence that attention and cognitive control in adults relies on dynamic cross-network interactions (44–47), we investigated both time-averaged and dynamic time-varying cross-network interactions among the SN, CEN, and DMN. The specific goals of our study were therefore to investigate whether 1) time-averaged cross-network interactions between the SN-CEN and SN-DMN would be weaker in children with ADHD compared with typically developing (TD) children, 2) weak time-averaged cross-network interactions would predict inattention, 3) children with ADHD would show considerably more temporal variability in dynamic cross-network interactions, and 4) variability of dynamic cross-network interactions would predict inattention symptoms.

We used data from two independent cohorts of 140 children with ADHD and age-, gender-, handedness-, IQ-, and motion-matched TD children. An SN-centered network interaction index (NII) (48) was used to assess the integrity of cross-network interactions and the extent to which the SN is temporally integrated with the CEN while simultaneously dissociated from the DMN (28,49). SN-centered cross-network interaction was defined as the difference between the strength of SN interactions with the CEN and DMN (48). Time-averaged cross-network interactions were measured across the entire time series, and time-varying interaction measured using 40-second-long moving windows centered were computed at each time point (45,50,51). Time-averaged NII measures were first compared between the two groups, and their relation to inattention was examined. Next, we examined time-varying cross-network interactions among the three networks. To identify distinct brain states associated with time-varying cross-network interactions, we applied a groupwise temporal clustering on the time-dependent functional correlation matrices. The optimal number of clusters was determined based on maximal silhouette value, which measures validity (specifically, how well the resulting clusters are separated), across multiple iterations of the clustering procedures (52). Each temporal cluster characterizes a dynamic brain state. Dynamic features associated with these brain states, including mean lifetime (how long a state lasts before switching to another state) and dynamic NII measures, were then compared between the two groups. We predicted that the number of brain states would be greater and their mean lifetime would be shorter in children with ADHD compared with TD children, which is indicative of more volatile and variable cross-network interactions across time in affected children. We further predicted that greater variability of dynamic NII would predict inattention.

METHODS AND MATERIALS

Dataset Access and Participant Selection

Behavioral and brain imaging data acquired by researchers at New York University (primary cohort) and Peking University (replication cohort), and made available through the ADHD-200 Consortium (53) were used in this study (Table 1; Supplemental Methods and Materials).

Medication Status

We conducted an additional analysis comparing medication naïve and nonnaïve individuals with ADHD and demonstrated that our findings were not confounded by medication status (Supplemental Methods and Materials).

Functional Magnetic Resonance Imaging Preprocessing and Analysis

A standard preprocessing procedure was implemented using SPM8, including slice-timing correction, realignment, normalization, spatial smoothing (6-mm smoothing kernel), regression of nuisance variables (24 motion parameters, white matter, and cerebrospinal fluid signals), and bandpass filtering ($0.008\ \text{Hz} < f < 0.1\ \text{Hz}$).

Preprocessed data from the ADHD and TD samples were concatenated and entered into a group independent component analysis (ICA) to identify large-scale networks in the combined population for each cohort separately (MELODIC; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC). The number of components was set to 30. Determining the number of components using an unsupervised learning algorithm such as ICA remains an unresolved challenge. Our choice was therefore based on common practices in the field (48,54). Four components (SN, left and right CEN, and DMN) corresponding to the previously described triple-network model (28) were determined based on a widely used visual inspection procedure (54,55).

Table 1. Descriptive Statistics for the ADHD and TD Groups Across the Two Cohorts

	Primary Cohort			Replication Cohort		
	TD (*n* = 40)	ADHD (*n* = 40)	*p*	TD (*n* = 30)	ADHD (*n* = 30)	*p*
Age, Years	11.9 (3.2)	11.7 (2.9)	.66	12.3 (1.5)	12.6 (2.1)	.47
Gender (Female/Male), *n*	17/23	13/27	.36	0/30	0/30	1.00
Handedness Score[a]	0.6 (0.3)	0.6 (0.3)	.84	0.9 (0.2)	1 (0)	.33
IQ	111 (15)	107 (14)	.26	113 (10)	113 (9)	1.00
Inattention	45 (5)	71 (9)	.00	15 (3)	28 (4)	.00
Hyperactivity/Impulsivity	46 (5)	66 (12)	.00	12 (4)	23 (7)	.00
Head Motion						
Range						
X, mm	0.307 (0.194)	0.324 (0.203)	.71	0.271 (0.161)	0.241 (0.135)	.44
Y, mm	0.545 (0.392)	0.676 (0.5)	.19	0.596 (0.301)	0.563 (0.333)	.69
Z, mm	0.555 (0.309)	0.667 (0.346)	.13	0.884 (0.498)	0.922 (0.458)	.76
Pitch, °	0.012 (0.007)	0.014 (0.009)	.27	0.013 (0.007)	0.015 (0.008)	.56
Roll, °	0.006 (0.003)	0.006 (0.004)	.43	0.007 (0.004)	0.008 (0.005)	.74
Yaw, °	0.007 (0.003)	0.007 (0.002)	.65	0.006 (0.005)	0.006 (0.003)	.72
RMS						
X, mm	0.093 (0.064)	0.091 (0.092)	.92	0.097 (0.082)	0.093 (0.079)	.86
Y, mm	0.217 (0.178)	0.235 (0.192)	.66	0.257 (0.149)	0.198 (0.124)	.10
Z, mm	0.196 (0.137)	0.247 (0.198)	.19	0.341 (0.222)	0.324 (0.225)	.77
Pitch, °	0.005 (0.003)	0.005 (0.003)	.64	0.005 (0.004)	0.005 (0.004)	.56
Roll, °	0.002 (0.001)	0.002 (0.002)	.65	0.002 (0.002)	0.003 (0.002)	.34
Yaw, °	0.003 (0.002)	0.003 (0.002)	.46	0.003 (0.003)	0.002 (0.002)	.57
Scan-to-scan motion, mm	0.08 (0.036)	0.092 (0.04)	.16	0.082 (0.033)	0.093 (0.039)	.25

Values are mean (SD) unless otherwise indicated. Within each cohort, the two groups were matched on age, gender, handedness, IQ, and head motion during functional magnetic resonance imaging. The Conners' Parent Rating Scale–Revised: Long Version and the ADHD Rating Scale were used as dimensional measures of ADHD symptoms in the primary and replication cohorts, respectively. Inattention and hyperactivity/impulsivity scores are raw scores provided by the ADHD-200 Consortium.

ADHD, attention-deficit/hyperactivity disorder; RMS, root mean square; TD, typically developing.

[a]Handedness scores: 1 = right handed, 0 = left handed.

Time-Averaged Cross-Network Interaction

We computed an NII (48) to assess cross-network interactions among the three networks based on the hypothesized role of the SN in switching interactions with the CEN and DMN (28,49). An NII has the advantage of capturing interactions simultaneously among all three networks. Specifically, the NII was computed as the difference in correlation between the SN and CEN time series and correlation between the SN and DMN. The rationale here is that the SN and CEN are typically coactivated during cognitively demanding tasks, while the SN and DMN are typically anticorrelated (49,56). The NII thus captures the extent to which SN can temporally integrate itself with the CEN and dissociate itself from the DMN. We computed the NII for each participant and compared the NII values between the ADHD and TD groups in each cohort (see the Supplemental Methods and Materials for details).

Relation of Time-Averaged NII Measures to Clinical Symptoms

The relation between the time-averaged NII and individual clinical scores was investigated using Pearson's correlation and its significance was examined using a permutation testing procedure because of nonnormal distribution of clinical scores in our samples (Supplemental Methods and Materials).

Dynamic Time-Varying Cross-Network Interactions

Time-varying cross-network interaction was measured using a dynamic functional connectivity approach (50). We estimated dynamic functional interactions between brain regions using a temporal sliding window approach with a rectangle shape and a window length of 40 seconds (20 repetition times) and a sliding step of 2 seconds (1 repetition time) (45,50). A sliding window with an exponentially decaying shape and a window length of 40 seconds was also used to test the robustness of our findings and results are reported in the Supplemental Methods and Materials. Within each time window, we computed the *z*-transformed Pearson correlation between the ICA time series taken pairwise. This resulted in a time-series of correlation matrices (T × C); here T is the number of time windows and C is number of pairwise interactions among the SN, CEN, and DMN at each time point. To identify distinct group-specific states associated with dynamic functional connectivity, we applied groupwise k-means clustering on the time-series of correlation matrices in each group separately with the number of clusters (k) ranging from 2 to 20. Twenty-five different initializations were used to reduce the chance of local minima. Clustering performance was estimated using the silhouette method, and the optimal number of clusters was determined based on the maximal silhouette across all the iterations (Supplemental Figure 2)

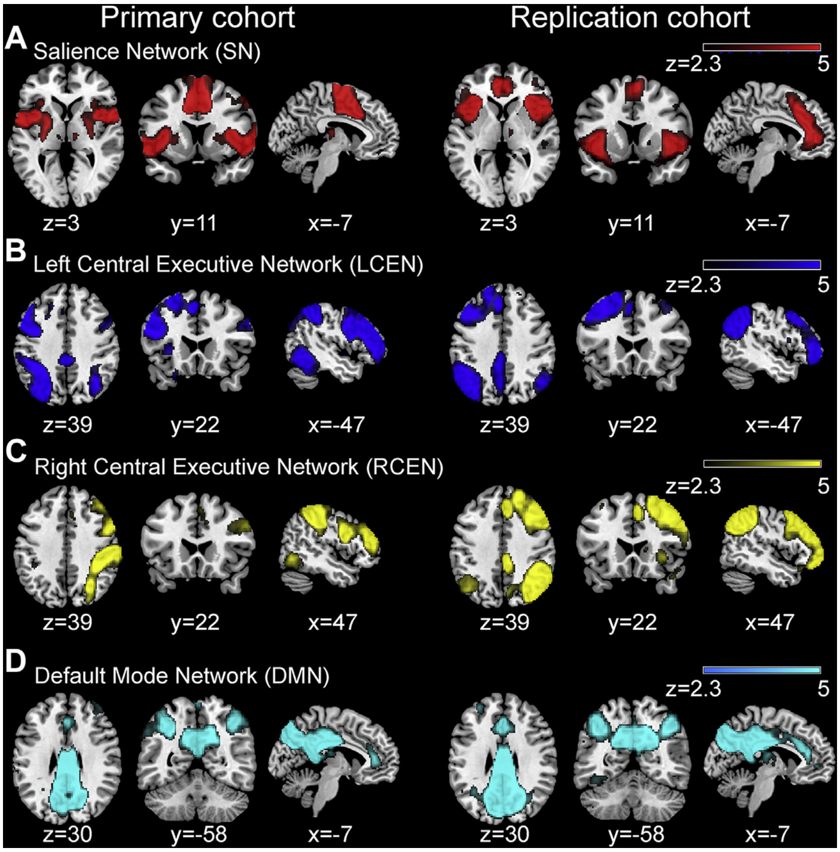

Figure 1. The salience network (SN), central executive network (CEN), and default mode network (DMN) in the primary and replication cohorts: **(A)** SN, **(B)** left CEN (LCEN), **(C)** right CEN (RCEN), and **(D)** DMN. Group-level independent component analysis was used to identify these networks in data from each cohort. Maps are displayed at $z > 2.3$ ($p < .01$, corrected).

(52). Because our goal was to investigate whether dynamic temporal properties, including the number of states and their mean lifetimes, differed between the two groups, we allowed the number of clusters to differ between the ADHD and control groups, instead of keeping them exactly the same (50). Statistical significance of differences in the number of clusters between the two groups was evaluated using a permutation testing procedure. In each permutation, group labels were randomly shuffled, groupwise k-means clustering was conducted, and a group difference in the optimal number of clusters was computed. Group differences in the optimal number of clusters from 500 permutations were used to construct the empirical null distribution, from which a p value was obtained. Robustness of our findings was tested using different window lengths. To quantify dwelling time of dynamic brain states, we computed the mean lifetime of each brain state for each participant, based on the average time spent continuously in that state. Two-sample t tests were conducted to evaluate the difference in mean lifetime between brain states in TD children and in children with ADHD. A brain state–specific NII was used to characterize cross-network interaction in each dynamic brain state. We computed the NII for each sliding window and averaged NIIs for the windows corresponding to the same dynamic brain state. Two-sample t tests were used to test the difference in NIIs of brain states in TD children and in children with ADHD.

Relation of Dynamic Time-Varying NII Measures to Clinical Symptoms

We first computed the variability (measured by standard deviations) of time-varying NIIs across all the dynamic brain states for each participant and examined the difference between the variability of time-varying NIIs between the two groups using two-sample t tests. We then examined the relation between variability of time-varying NIIs and clinical symptoms using the same procedures as described above.

RESULTS

Time-Averaged Cross-Network Interaction

The NII, a cross-network coupling measure, was used to investigate interactions among the four ICA-identified brain networks (Figure 1). NII values were normally distributed in each dataset (Supplemental Methods and Materials). Notably, the SN-centered NII was significantly lower in the ADHD group than in the TD group in the primary cohort ($p < .005$, Cohen's $d = 0.64$) and replication cohort ($p < .05$, Cohen's $d = 0.55$; Figure 2A). Additional analyses further confirmed significantly lower NII values in the ADHD group than in the TD group after controlling for movement and other parameters including age, gender, handedness, and IQ in the primary cohort ($p = .005$) and replication cohort ($p = .03$; Supplemental Table 1).

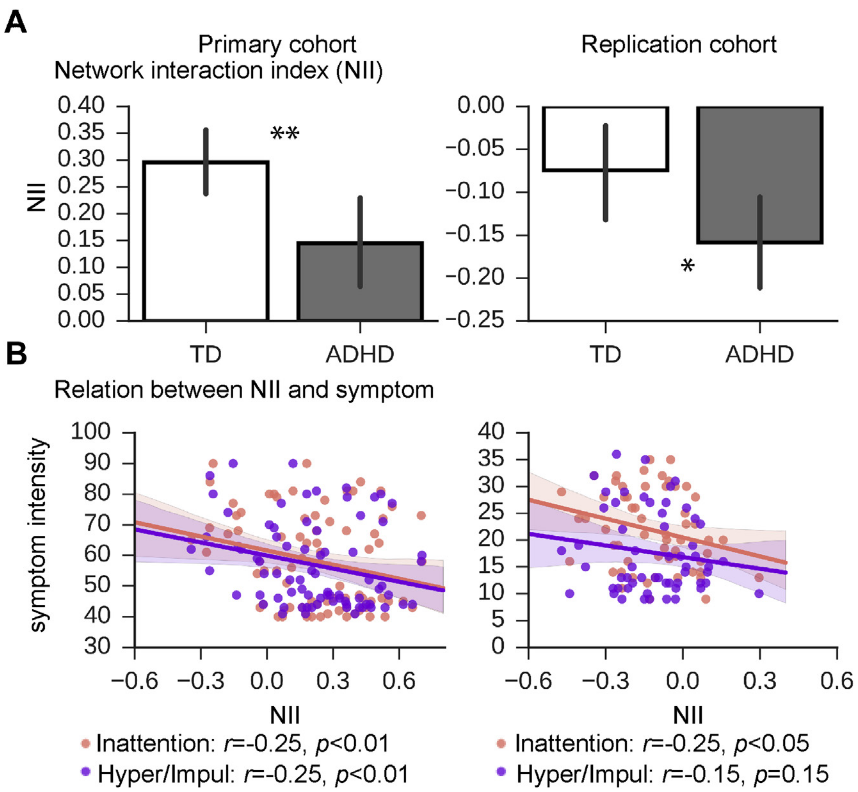

Figure 2. Time-averaged cross-network interactions among the salience network (SN), central executive network, and default mode network in children with attention-deficit/hyperactivity disorder (ADHD) and typically developing (TD) children, and relation to ADHD symptoms. **(A)** Cross-network interaction, assessed using an SN-centered network interaction index (NII) (see Methods and Materials), was significantly lower in children with ADHD than in TD children for each cohort. $^{*}p < .05$; $^{**}p < .01$. **(B)** The SN-centered NII was strongly negatively correlated with the inattention symptoms of ADHD in both cohorts. The SN-centered NII was correlated with hyperactivity/impulsivity (Hyper/Impul) in data from the primary cohort. The Conners' Parent Rating Scale–Revised: Long Version and the ADHD Rating Scale were used as dimensional measures of ADHD symptoms in the primary and replication cohorts, respectively.

We then examined the specificity of the above effects by testing two alternative models involving parallel constructs with a CEN-centered network and a DMN-centered network. Neither index was consistently different between groups across the two cohorts (Supplemental Methods and Materials).

Next, we investigated whether functional connectivity between any two of the SN, CEN, and DMN was different between the ADHD and TD groups. Pairwise correlations did not differ between the groups in the two cohorts (all $ps > .05$; Supplemental Figure 3).

Time-Averaged Cross-Network Interactions in Relation to Inattention

We found that individual inattention scores were negatively correlated with the SN-centered NII in the primary cohort ($r = -.25$, $p < .01$) and in the replication cohort ($r = -.25$, $p < .05$), despite the use of different questionnaires at each cohort (Figure 2B). Multiple linear regression further demonstrated that the SN-centered NII outperformed other measures, including scan-to-scan head motion, age, and IQ, in predicting inattention scores in both cohorts (Table 2). The relation between the SN-centered NII and hyperactivity/impulsivity scores was significant in the primary cohort ($r = -.25$, $p < .01$) but not in the replication cohort ($p = .15$), suggesting that the relation to inattention is a more replicable finding.

Dynamic Time-Averaged Cross-Network Interactions

Analysis of dynamic functional interactions among the SN, CEN, and DMN revealed two states (temporal clusters) in the TD group and five states in the ADHD group in both cohorts (Figure 3A), reflecting variation in cross-network interactions across time in both groups. Permutation analysis revealed significantly more states in the ADHD groups than in the TD groups in the primary cohort ($p < .05$) and replication cohort ($p = .002$).

Next, we compared the mean lifetime of dynamic brain states between the two groups. In the primary cohort, the

Table 2. Multiple Linear Regression Revealed That SN-Centered Interactions With CEN and DMN, as Assessed Using the NII, Were the Most Robust Predictor of Inattention Symptoms in Children With ADHD

	Inattention		Hyperactivity/Impulsivity	
	B	p	B	p
Primary Cohort				
NII	−14.54	.04[a]	−14.81	.03[a]
Motion	34.38	.45	34.98	.39
Age	−0.19	.75	−0.16	.76
IQ	0	.86	0.01	.15
Replication Cohort				
NII	−12.72	.04[a]	−8.55	.2
Motion	26.15	.35	31.29	.3
Age	−0.34	.56	−0.58	.35
IQ	−0.02	.86	−0.01	.94

ADHD, attention-deficit/hyperactivity disorder; CEN, central executive network; DMN, default mode network; NII, network interaction index; SN, salience network.

[a]$p < .05$.

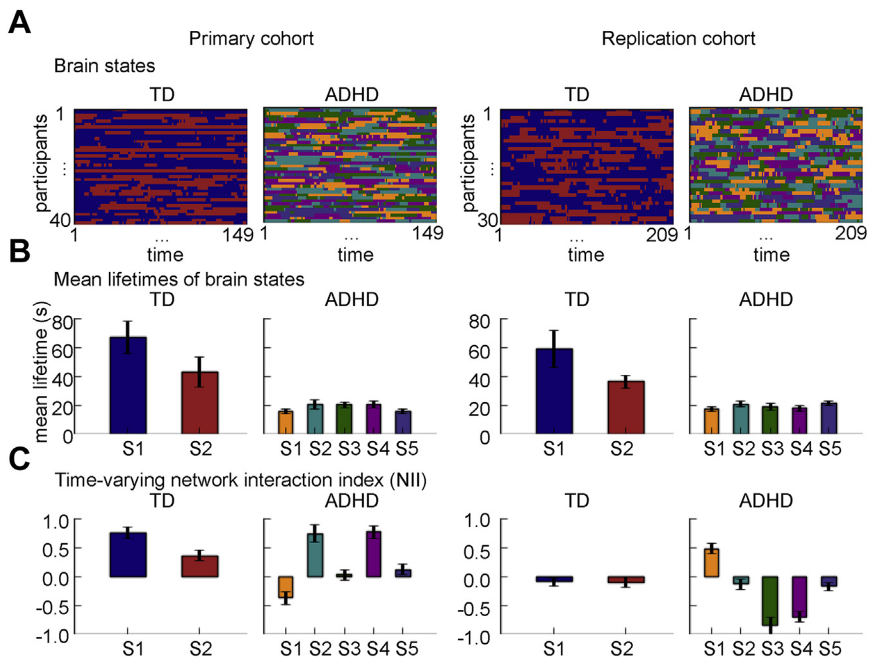

Figure 3. Dynamic time-varying cross-network interactions among the salience network, central executive network, and default mode network in children with attention-deficit/hyperactivity disorder (ADHD) and typically developing (TD) children. **(A)** In both the primary and replication cohorts, children with ADHD showed five states (S), significantly higher than the two states in TD children. Color codes distinct states in each participant. **(B)** Mean lifetimes of dynamic brain states were shorter in children with ADHD compared with TD children in both cohorts. **(C)** The network interaction index (NII) of dynamic brain states shows intermittently weaker, and more variable, salience network–centered cross-network interactions in children with ADHD compared with TD children in both cohorts.

mean lifetime of state 1 in the TD group was significantly longer than the mean lifetime of any of the five states in the ADHD group ($ps < .001$). The mean lifetime of state 2 in the TD group was significantly longer than the mean lifetime of states 1 and 5 in the ADHD group ($ps < .05$). In the replication cohort, the mean lifetime of states 1 and 2 in the TD group was significantly longer than the mean lifetime of any of the five states in the ADHD group ($ps < .05$; Figure 3B). Bonferroni correction was used for multiple comparisons. These results demonstrate that compared with TD, children with ADHD show less persistent and more volatile brain states. Note that states are defined independently in the primary and replication cohorts.

We then compared the NII of dynamic brain states between the two groups. In the primary cohort, the NII of states 1 and 3 in the ADHD group was significantly lower than the NII of any of the states in the TD group ($ps < .05$). In the replication cohort, the NII of states 3 and 4 in the ADHD group was significantly lower than the NII of all states in the TD group ($ps < .05$), and the NII of state 1 in the ADHD group was significantly higher than the NII of the states in the TD group ($ps < .05$; Figure 3C). Bonferroni correction was used for multiple comparisons. These results demonstrate an intermittent lack of integration of the SN with the CEN and decoupling of the SN from the DMN in children with ADHD, and that cross-network interactions are more variable in children with ADHD than in TD children.

Variability of Dynamic Time-Averaged Cross-Network Interactions and Its Relation to Inattention

Compared with TD children, children with ADHD showed greater variability in dynamic NII strength across states in both cohorts ($ps < .001$; Figure 4A). Additional analyses further confirmed lower NII values in children with ADHD than in TD children after controlling for confounds (Supplemental Table 2). Notably, we found that individual inattention scores were positively correlated with variability of time-varying NII measures in the primary ($r = .39$, $p = .002$) and replication ($r = .65$, $p = .002$) cohorts, despite the use of different clinical questionnaires at each cohort (Figure 4B). Effect sizes (R^2) were much higher for time-varying interactions (primary = .15; replication = .42) as compared with time-averaged interactions (primary = .06; replication = .06). Individual hyperactivity/impulsivity scores were also positively correlated with variability of time-varying NII measures in the primary and replication cohorts ($p = .002$; Figure 4B). Multiple linear regression further demonstrated that variability of dynamic time-varying NII outperformed other variables in predicting clinical symptom scores (Table 3).

Robustness of Findings With Respect to Temporal Windows

The aforementioned findings were replicated using window lengths of 60 and 80 seconds ($ps < .05$) as well as exponentially decaying sliding window, in both cohorts (Supplemental Methods and Materials).

DISCUSSION

Our findings support the triple-network model, which posits that the integrity and mutual interactions of the SN, CEN, and DMN play a crucial role in cognition (28) and that dysregulation in cross-network interactions can lead to deficits in attention, cognitive control, and other goal-directed and adaptive behaviors (24,28). In agreement with this hypothesis, we found that children with ADHD had weaker time-averaged cross-network interactions among the SN, CEN, and DMN, and that the degree of these brain aberrations was related to severity of inattention symptoms. Analysis of dynamic functional connectivity further revealed that cross-network interactions vary

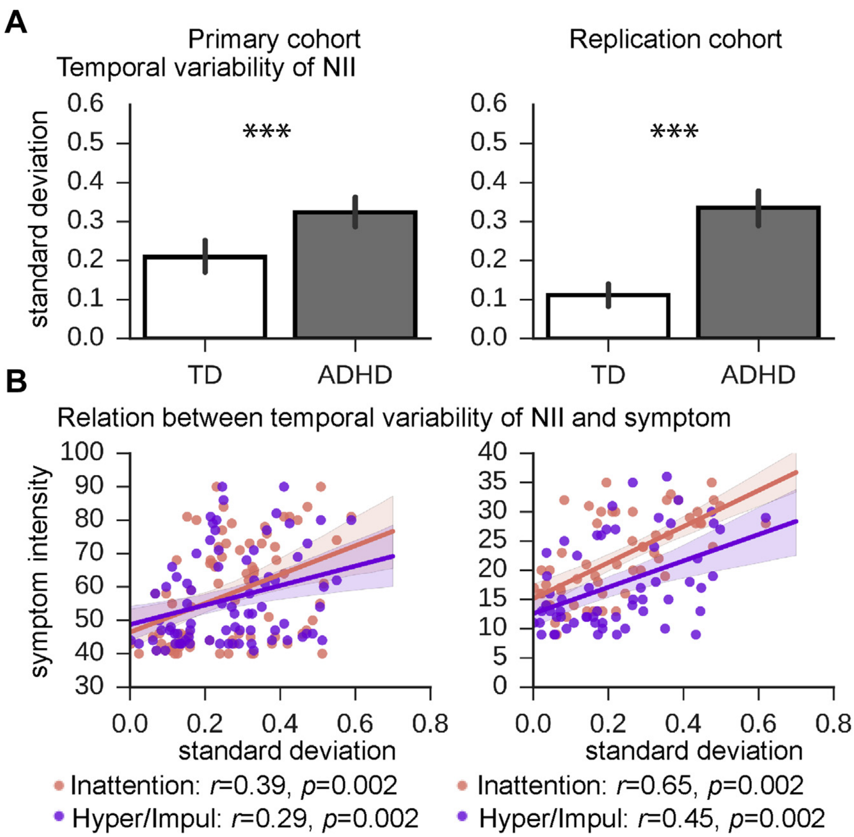

Figure 4. Variability of dynamic cross-network interactions among the salience network, central executive network, and default mode network in children with attention-deficit/hyperactivity disorder (ADHD) and typically developing (TD) children, and relation to ADHD symptoms. **(A)** Temporal variability of dynamic cross-network interaction, assessed using the standard deviation of dynamic network interaction indices (NIIs) across states, was significantly higher in children with ADHD, compared with TD children, in both cohorts. ***$p <$ .001. **(B)** Temporal variability of dynamic NIIs was strongly positively correlated with inattention and hyperactivity/impulsivity (Hyper/Impul) symptoms of ADHD in both cohorts. The Conners' Parent Rating Scale-Revised: Long Version and the ADHD Rating Scale were used as dimensional measures of ADHD symptoms in the primary and replication cohorts, respectively.

considerably across time and that these networks exhibit variable, and weaker, dynamic cross-network interactions in ADHD, compared with TD children. Furthermore, variability of dynamic time-varying cross-network interaction was strongly related to severity of inattention symptoms. Crucially, we replicated our findings in two independent cohorts consisting of 140 children from distinct geographical sites, demonstrating the robustness of our findings.

Table 3. Multiple Linear Regression Revealed That Variability of Dynamic Time-Varying NIIs Was the Most Robust Predictor of Inattention Symptoms in Children With ADHD

	Inattention		Hyperactivity/Impulsivity	
	B	*p*	*B*	*p*
Primary Cohort				
NII	45.4	.001	29.82	.007
Motion	69.26	.1	65.41	.1
Age	0.05	.93	−0.02	.96
IQ	−0.01	.49	0.007	.34
Replication Cohort				
NII	30.86	.001	22.64	.001
Motion	7.26	.74	17.01	.52
Age	−0.34	.43	−0.86	.1
IQ	−0.02	.78	−0.01	.94

ADHD, attention-deficit/hyperactivity disorder; NII, network interaction index.

Aberrant SN-Centered Time-Averaged Cross-Network Interactions in Children With ADHD

The first key finding of our study is that the SN-centered cross-network interactions were weaker in children with ADHD relative to their TD peers. Previous studies using seed-based functional connectivity have reported abnormal functional connectivity between the DMN and cingulo-opercular and occipital regions in children with ADHD (10,16), suggesting atypical interaction between the DMN and other brain networks underlying dysfunction in ADHD. However, temporal interactions among the SN, CEN, and DMN have not been examined, thereby limiting our understanding of impairments in neurocognitive control systems involved in attention. The current study was designed to specifically test a triple-network model of cognitive control and test the hypothesis that SN interactions with the CEN and DMN are impaired in children with ADHD (24,28). We found evidence that SN-centered interactions with the CEN and DMN were impaired in ADHD, and this finding was observed in both the primary and replication cohorts. Further, control analyses using CEN- and DMN-centered cross-network interactions did not show such differences. Moreover, single pairwise correlations between the networks were not different between the ADHD groups and the

TD groups in either cohort. Thus, our findings demonstrate that the NII has the advantage of capturing aberrant interactions simultaneously among all three networks, and quantifies the extent to which the SN is temporally integrated with the CEN and dissociated from the DMN.

The SN has been shown to play a crucial role in switching between the CEN and the DMN to facilitate access to task-relevant attentional resources (28,40). Specifically, the anterior insula node of the SN is thought to be involved in detecting salient events and signaling the frontoparietal CEN to recruit cognitive resources essential for attentionally demanding cognitive tasks (28,29,34,57). This is in line with previous evidence of aberrant attention-related responses in the anterior insula and the anterior cingulate cortex in ADHD (58,59). Our findings suggest that aberrant interactions of the SN with the CEN and DMN may contribute to the atypical activations on a wide range of cognitive tasks in ADHD (9,60–67).

Aberrant and More Variable Time-Averaged Cross-Network Interactions in Children With ADHD

The second key finding of our study relates to the temporal characteristics of cross-network interactions in children with ADHD. In the two independent cohorts, we revealed more than one dynamic brain state in each group and a greater number of dynamic brain states in the ADHD groups, compared with the TD groups. Notably, the mean lifetime of dynamic brain states was shorter in the ADHD group compared with the TD group, suggesting that cross-network interactions are not only highly variable, but also highly volatile in children with ADHD. Additionally, dynamic cross-network interactions in the ADHD groups were characterized by intermittent lack of integration of the SN with the CEN and decoupling of the SN from the DMN, and the strength of these dynamic interactions was more variable in children with ADHD. These results provide further insights into the temporally variable nature of aberrant network interactions underlying ADHD. These findings are particularly noteworthy in the context of intraindividual response variability and transient fluctuations in task performance that are a hallmark of ADHD (68–70). Moreover, a prominent neurocognitive model of ADHD suggests that abnormal fluctuation of brain states may underlie attentional lapses and atypical goal-directed behaviors in affected individuals (71). Our demonstration that children with ADHD have more variable and short-lived brain states than TD children and greater temporal variability in state-specific cross-network interactions provides experimental evidence in support of this model.

Aberrant SN-Centered Cross-Network Interactions Are Related to Attention Deficits

The third important finding our study is that SN-centered cross-network interactions were significantly correlated with inattention symptoms. Importantly, this finding was observed with both time-averaged and time-varying measures of cross-network interactions, and replicated across two independent cohorts. Notably, we did not find differences in brain-inattention symptom relations between the ADHD and TD groups, and the strongest relations emerged with the combined group of participants. It should also be noted that inattention scores were continuous across groups. Importantly, our methodology is consistent with the research domain criteria framework, which emphasizes the use of measures that capture the entire range of clinically relevant behavioral measures, from typical to atypical (72). Consistent with our hypothesis that abnormal fluctuations in brain states may underlie attention difficulties, we found that greater temporal variability in state-specific cross-network interactions was associated with increased inattention symptoms in children. Crucially, dynamic measures of temporal variability in cross-network interactions were more strongly correlated with inattention symptoms than time-averaged measures of cross-network interactions. We postulate that inattention symptoms in children with ADHD are related to their difficulty in engaging task-relevant brain states while disengaging from task-irrelevant brain states, arising from weak dynamic modulation of cross-network interactions among the SN, CEN, and DMN.

Reproducibility

Reproducibility is particularly important for clinical neuroimaging studies (73). Leveraging datasets shared by the ADHD-200 Consortium (53), we demonstrate replicable neurobiological signatures of childhood ADHD. Despite differences in geographical location, scanner, acquisition protocols, and sample size, we replicated five key findings across the two cohorts: 1) weaker SN-centered cross-network interactions in children with ADHD compared with TD children, 2) correlation between the strength of SN-centered network interactions and the severity of inattention symptoms, 3) more variable and volatile time-varying network interactions in children with ADHD compared with TD children, 4) correlation between the variability of network interactions across time and the severity of inattention symptoms, and 5) measures of network dynamics outperformed measures of static network interactions in predicting a core clinical symptom of ADHD.

Limitations

While the case-control design using here is optimal for minimizing the impact of confounds such as extensive head motion and low IQ, the extent to which findings can be generalized to low-functioning individuals remains unknown. Puberty is another potential confound whose effects could not be examined in our study, as these measures were not available in the ADHD-200 Consortium cohorts. Because the primary goal of the present work was to test a theory-based model of circuit deficits in children with ADHD, the present study has focused on network interactions among cognitive control systems involving the SN, CEN, and DMN. Their interconnectivity with other brain systems, such as the basal ganglia and reward pathways implicated in ADHD, remains to be investigated (74–76). Further work is also needed to investigate how the circuit deficits identified in this study influence stimulus processing during attention and cognitive control tasks in children with ADHD, and how their developmental maturation is altered with respect to their TD peers (77).

Conclusions

Our study demonstrates a robust neurobiological signature of ADHD using a theoretically informed systems neuroscience model and suggests that dysregulation of cross-network interactions is a key feature of the disorder. Crucially, the replication of the study findings across two independent cohorts further suggests that the triple-network model of SN-centered deficits in dynamic functional interactions encompassing CEN and DMN provides a novel and parsimonious framework for investigating attention and cognitive deficits in ADHD.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by a National Institutes of Health (NIH) Career Development award (Grant No. MH105625 to WC); a NARSAD Young Investigator award (to KS); NIH BRAINS initiative Grant Nos. NS086085 and EB022907; and the Stanford Child Health Research Institute (to VM).The Primary data cohort was acquired at New York University with grant support from the NIH (Grant No. MH083246), Autism Speaks, The Stavros Niarchos Foundation, The Leon Levy Foundation, and an endowment provided by Phyllis Green and Randolph Cōwen. The Replication data cohort was acquired at Peking University with grant support from The Commonwealth Sciences Foundation, Ministry of Health, China (Grant No. 200802073), The National Foundation, Ministry of Science and Technology, China (Grant No. 2007BAI17B03), The National Natural Sciences Foundation, China (Grant No. 30970802), The Funds for International Cooperation of the National Natural Science Foundation of China (Grant No. 81020108022), The National Natural Science Foundation of China (Grant No. 8100059), and Open Research Fund of the State Key Laboratory of Cognitive Neuroscience and Learning.

We thank Dr. Aarthi Padmanabhan for useful suggestions. Last, but not the least, we would like to thank the ADHD-200 Consortium for openly sharing the data, without which this work would not have been possible.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry & Behavioral Sciences (WC, TC, LS, KS, VM), Department of Neurology & Neurological Sciences (VM), and Stanford Neurosciences Institute (VM), Stanford University School of Medicine, Stanford, California; and the Department of Automation and Applied Informatics (LS), Budapest University of Technology and Economics, Budapest, Hungary.

Address correspondence to Weidong Cai, Ph.D., 401 Quarry Rd, Stanford, CA 94305; E-mail: wdcai@stanford.edu.

Received Aug 23, 2017; revised Oct 16, 2017; accepted Oct 17, 2017.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2017.10.005.

REFERENCES

1. Faraone SV, Biederman J (2005): What is the prevalence of adult ADHD? Results of a population screen of 966 adults. J Atten Disord 9:384–391.
2. Faraone SV, Sergeant J, Gillberg C, Biederman J (2003): The worldwide prevalence of ADHD: Is it an American condition? World Psychiatry 2:104–113.
3. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (2007): The worldwide prevalence of ADHD: A systematic review and meta-regression analysis. Am J Psychiatry 164:942–948.
4. Alessandri SM (1992): Attention, play, and social behavior in ADHD preschoolers. J Abnorm Child Psychol 20:289–302.
5. Barkley RA (1997): Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. Psychol Bull 121:65–94.
6. Biederman J (2004): Impact of comorbidity in adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry 65(suppl 3):3–7.
7. Nigg JT, Stavro G, Ettenhofer M, Hambrick DZ, Miller T, Henderson JM (2005): Executive functions and ADHD in adults: Evidence for selective effects on ADHD symptom domains. J Abnorm Psychol 114:706–717.
8. Pennington BF, Ozonoff S (1996): Executive functions and developmental psychopathology. J Child Psychol Psychiatry 37:51–87.
9. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF (2005): Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. Biol Psychiatry 57:1336–1346.
10. Barber AD, Jacobson LA, Wexler JL, Nebel MB, Caffo BS, Pekar JJ, *et al.* (2015): Connectivity supporting attention in children with attention deficit hyperactivity disorder. Neuroimage Clin 7:68–81.
11. Castellanos FX, Proal E (2012): Large-scale brain systems in ADHD: Beyond the prefrontal-striatal model. Trends Cogn Sci 16:17–26.
12. Elton A, Alcauter S, Gao W (2014): Network connectivity abnormality profile supports a categorical-dimensional hybrid model of ADHD. Human Brain Mapp 35:4531–4543.
13. Konrad K, Eickhoff SB (2010): Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. Human Brain Mapp 31:904–916.
14. Makris N, Biederman J, Monuteaux MC, Seidman LJ (2009): Towards conceptualizing a neural systems-based anatomy of attention-deficit/hyperactivity disorder. Dev Neurosci 31:36–49.
15. 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.
16. Sripada C, Kessler D, Fang Y, Welsh RC, Prem Kumar K, Angstadt M (2014): Disrupted network architecture of the resting brain in attention-deficit/hyperactivity disorder. Human Brain Mapp 35:4693–4705.
17. Sripada CS, Kessler D, Angstadt M (2014): Lag in maturation of the brain's intrinsic functional architecture in attention-deficit/hyperactivity disorder. Proc Natl Acad Sci U S A 111:14259–14264.
18. Cao X, Cao Q, Long X, Sun L, Sui M, Zhu C, *et al.* (2009): Abnormal resting-state functional connectivity patterns of the putamen in medication-naive children with attention deficit hyperactivity disorder. Brain Res 1303:195–206.
19. 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.
20. Fair DA, Posner J, Nagel BJ, Bathula D, Dias TG, Mills KL, *et al.* (2010): Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. Biol Psychiatry 68:1084–1091.
21. Hoekzema E, Carmona S, Ramos-Quiroga JA, Richarte Fernandez V, Bosch R, Soliva JC, *et al.* (2013): An independent components and functional connectivity analysis of resting state fMRI data points to neural network dysregulation in adult ADHD. Human Brain Mapp 35:1261–1272.
22. McCarthy H, Skokauskas N, Mulligan A, Donohoe G, Mullins D, Kelly J, *et al.* (2013): Attention network hypoconnectivity with default and affective network hyperconnectivity in adults diagnosed with attention-deficit/hyperactivity disorder in childhood. JAMA Psychiatry 70:1329–1337.
23. Tian L, Jiang T, Wang Y, Zang Y, He Y, Liang M, *et al.* (2006): Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neurosci Lett 400:39–43.
24. Menon V (2011): Large-scale brain networks and psychopathology: A unifying triple network model. Trends Cogn Sci 15:483–506.
25. Corbetta M, Shulman GL (2002): Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201–215.
26. Dosenbach NU, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, *et al.* (2006): A core system for the implementation of task sets. Neuron 50:799–812.
27. Leech R, Kamourieh S, Beckmann CF, Sharp DJ (2011): Fractionating the default mode network: Distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. J Neurosci 31:3217–3224.
28. Menon V, Uddin LQ (2010): Saliency, switching, attention and control: A network model of insula function. Brain Struct Funct 214:655–667.

29. 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.
30. Owen AM, McMillan KM, Laird AR, Bullmore E (2005): N-back working memory paradigm: A meta-analysis of normative functional neuro-imaging studies. Human Brain Mapp 25:46–59.
31. Smith EE, Jonides J (1998): Neuroimaging analyses of human working memory. Proc Natl Acad Sci U S A 95:12061–12068.
32. Wager TD, Smith EE (2003): Neuroimaging studies of working memory: A meta-analysis. Cogn Affect Behav Neurosci 3:255–274.
33. Gusnard DA, Akbudak E, Shulman GL, Raichle ME (2001): Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. Proc Natl Acad Sci U S A 98: 4259–4264.
34. Cai W, Ryali S, Chen T, Li CS, Menon V (2014): Dissociable roles of right inferior frontal cortex and anterior insula in inhibitory control: Evidence from intrinsic and task-related functional parcellation, connectivity, and response profile analyses across multiple datasets. J Neurosci 34:14652–14667.
35. Cole MW, Bassett DS, Power JD, Braver TS, Petersen SE (2014): Intrinsic and task-evoked network architectures of the human brain. Neuron 83:238–251.
36. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005): The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 102:9673–9678.
37. 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.
38. Cai W, Chen T, Ryali S, Kochalka J, Li CS, Menon V (2016): Causal interactions within a frontal-cingulate-parietal network during cognitive control: Convergent evidence from a multisite-multitask investigation. Cereb Cortex 26:2140–2153.
39. Chen T, Michels L, Supekar K, Kochalka J, Ryali S, Menon V (2015): Role of the anterior insular cortex in integrative causal signaling during multisensory auditory-visual attention. Eur J Neurosci 41:264–274.
40. Sridharan D, Levitin DJ, Menon V (2008): A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci U S A 105:12569–12574.
41. Supekar K, Menon V (2012): Developmental maturation of dynamic causal control signals in higher-order cognition: A neurocognitive network model. PLoS Comput Biol 8:e1002374.
42. Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, *et al.* (2012): Toward systems neuroscience of ADHD: A meta-analysis of 55 fMRI studies. Am J Psychiatry 169:1038–1055.
43. Dickstein SG, Bannon K, Castellanos FX, Milham MP (2006): The neural correlates of attention deficit hyperactivity disorder: An ALE meta-analysis. J Child Psychol Psychiatry 47:1051–1062.
44. Braun U, Schafer A, Walter H, Erk S, Romanczuk-Seiferth N, Haddad L, *et al.* (2015): Dynamic reconfiguration of frontal brain networks during executive cognition in humans. Proc Natl Acad Sci U S A 112:11678–11683.
45. Chen T, Cai W, Ryali S, Supekar K, Menon V (2016): Distinct global brain dynamics and spatiotemporal organization of the salience network. PLoS Biol 14:e1002469.
46. Spadone S, Della Penna S, Sestieri C, Betti V, Tosoni A, Perrucci MG, *et al.* (2015): Dynamic reorganization of human resting-state networks during visuospatial attention. Proc Natl Acad Sci U S A 112: 8112–8117.
47. Vatansever D, Menon DK, Manktelow AE, Sahakian BJ, Stamatakis EA (2015): Default mode dynamics for global functional integration. J Neurosci 35:15254–15262.
48. Lerman C, Gu H, Loughead J, Ruparel K, Yang Y, Stein EA (2014): Large-scale brain network coupling predicts acute nicotine abstinence effects on craving and cognitive function. JAMA Psychiatry 71: 523–530.
49. Menon V (2015): Large-scale functional brain organization. In: Toga AW, editor. Brain Mapping: An Encyclopedic Reference. New York: Elsevier, 449–459.
50. Rashid B, Arbabshirani MR, Damaraju E, Cetin MS, Miller R, Pearlson GD, *et al.* (2016): Classification of schizophrenia and bipolar patients using static and dynamic resting-state fMRI brain connectivity. Neuroimage 134:645–657.
51. Zalesky A, Fornito A, Cocchi L, Gollo LL, Breakspear M (2014): Time-resolved resting-state brain networks. Proc Natl Acad Sci U S A 111:10341–10346.
52. Bellec P, Rosa-Neto P, Lyttelton OC, Benali H, Evans AC (2010): Multi-level bootstrap analysis of stable clusters in resting-state fMRI. Neuroimage 51:1126–1139.
53. Consortium HD (2012): The ADHD-200 Consortium: A model to advance the translational potential of neuroimaging in clinical neuroscience. Front Syst Neurosci 6:62.
54. Uddin LQ, Supekar K, Lynch CJ, Khouzam A, Phillips J, Feinstein C, *et al.* (2013): Salience network-based classification and prediction of symptom severity in children with autism. JAMA Psychiatry 70: 869–879.
55. Calhoun VD, Adali T, McGinty VB, Pekar JJ, Watson TD, Pearlson GD (2001): fMRI activation in a visual-perception task: Network of areas detected using the general linear model and independent components analysis. Neuroimage 14:1080–1088.
56. Greicius MD, Krasnow B, Reiss AL, Menon V (2003): Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A 100:253–258.
57. Cai W, Chen T, Ide JS, Li CR, Menon V (2017): Dissociable fronto-operculum-insula control signals for anticipation and detection of inhibitory sensory cue. Cereb Cortex 27:4073–4082.
58. Orinstein AJ, Stevens MC (2014): Brain activity in predominantly inattentive subtype attention-deficit/hyperactivity disorder during an auditory oddball attention task. Psychiatry Res 223:121–128.
59. Tamm L, Menon V, Ringel J, Reiss AL (2004): Event-related FMRI evidence of frontotemporal involvement in aberrant response inhibition and task switching in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 43:1430–1440.
60. Alderson RM, Kasper LJ, Hudec KL, Patros CH (2013): Attention-deficit/hyperactivity disorder (ADHD) and working memory in adults: A meta-analytic review. Neuropsychology 27:287–302.
61. Alderson RM, Rapport MD, Kofler MJ (2007): Attention-deficit/hyperactivity disorder and behavioral inhibition: A meta-analytic review of the stop-signal paradigm. J Abnorm Child Psychol 35:745–758.
62. Boonstra AM, Oosterlaan J, Sergeant JA, Buitelaar JK (2005): Executive functioning in adult ADHD: A meta-analytic review. Psychol Med 35:1097–1108.
63. Homack S, Riccio CA (2004): A meta-analysis of the sensitivity and specificity of the Stroop Color and Word Test with children. Arch Clin Neuropsychol 19:725–743.
64. Kasper LJ, Alderson RM, Hudec KL (2012): Moderators of working memory deficits in children with attention-deficit/hyperactivity disorder (ADHD): A meta-analytic review. Clin Psychol Rev 32:605–617.
65. Lansbergen MM, Kenemans JL, van Engeland H (2007): Stroop interference and attention-deficit/hyperactivity disorder: A review and meta-analysis. Neuropsychology 21:251–262.
66. Lijffijt M, Kenemans JL, Verbaten MN, van Engeland H (2005): A meta-analytic review of stopping performance in attention-deficit/hyperactivity disorder: Deficient inhibitory motor control? J Abnorm Psychol 114:216–222.
67. Metin B, Roeyers H, Wiersema JR, van der Meere J, Sonuga-Barke E (2012): A meta-analytic study of event rate effects on Go/No-Go performance in attention-deficit/hyperactivity disorder. Biol Psychiatry 72:990–996.
68. Castellanos FX, Tannock R (2002): Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 3:617–628.
69. Klein C, Wendling K, Huettner P, Ruder H, Peper M (2006): Intra-subject variability in attention-deficit hyperactivity disorder. Biol Psychiatry 60:1088–1097.
70. Kuntsi J, Klein C (2012): Intraindividual variability in ADHD and its implications for research of causal links. Curr Topics Behav Neurosci 9:67–91.

71. Sonuga-Barke EJ, Castellanos FX (2007): Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis. Neurosci Biobehav Rev 31:977–986.
72. 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.
73. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, *et al.* (2013): Power failure: Why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci 14:365–376.
74. Cha J, Fekete T, Siciliano F, Biezonski D, Greenhill L, Pliszka SR, *et al.* (2015): Neural correlates of aggression in medication-naive children with ADHD: Multivariate analysis of morphometry and tractography. Neuropsychopharmacology 40:1717–1725.
75. Costa Dias TG, Iyer SP, Carpenter SD, Cary RP, Wilson VB, Mitchell SH, *et al.* (2015): Characterizing heterogeneity in children with and without ADHD based on reward system connectivity. Dev Cogn Neurosci 11:155–174.
76. Oldehinkel M, Beckmann CF, Pruim RH, van Oort ES, Franke B, Hartman CA, *et al.* (2016): Attention-deficit/hyperactivity disorder symptoms coincide with altered striatal connectivity. Biol Psychiatry Cogn Neurosci Neuroimaging 1:353–363.
77. Kessler D, Angstadt M, Sripada C (2016): Growth charting of brain connectivity networks and the identification of attention impairment in youth. JAMA Psychiatry 73:481–489.