Archival Report

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

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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 naive and nonnaive 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 Hz < f < 0.1 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

<table>
<thead>
<tr>
<th></th>
<th>Primary Cohort</th>
<th>Replication Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TD (n = 40)</td>
<td>ADHD (n = 40)</td>
</tr>
<tr>
<td>Age, Years</td>
<td>11.9 (3.2)</td>
<td>11.7 (2.9)</td>
</tr>
<tr>
<td>Gender (Female/Male)</td>
<td>17/23</td>
<td>13/27</td>
</tr>
<tr>
<td>Handedness Scorea</td>
<td>0.6 (0.3)</td>
<td>0.6 (0.3)</td>
</tr>
<tr>
<td>IQ</td>
<td>111 (15)</td>
<td>107 (14)</td>
</tr>
<tr>
<td>Inattention</td>
<td>45 (5)</td>
<td>71 (9)</td>
</tr>
<tr>
<td>Hyperactivity/Impulsivity</td>
<td>46 (5)</td>
<td>66 (12)</td>
</tr>
<tr>
<td>Head Motion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X, mm</td>
<td>0.307 (0.194)</td>
<td>0.324 (0.203)</td>
</tr>
<tr>
<td>Y, mm</td>
<td>0.545 (0.392)</td>
<td>0.676 (0.5)</td>
</tr>
<tr>
<td>Z, mm</td>
<td>0.555 (0.309)</td>
<td>0.687 (0.348)</td>
</tr>
<tr>
<td>Pitch, °</td>
<td>0.012 (0.007)</td>
<td>0.014 (0.009)</td>
</tr>
<tr>
<td>Roll, °</td>
<td>0.006 (0.003)</td>
<td>0.006 (0.004)</td>
</tr>
<tr>
<td>Yaw, °</td>
<td>0.007 (0.003)</td>
<td>0.007 (0.002)</td>
</tr>
<tr>
<td>RMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X, mm</td>
<td>0.093 (0.064)</td>
<td>0.091 (0.092)</td>
</tr>
<tr>
<td>Y, mm</td>
<td>0.217 (0.178)</td>
<td>0.235 (0.192)</td>
</tr>
<tr>
<td>Z, mm</td>
<td>0.196 (0.137)</td>
<td>0.247 (0.198)</td>
</tr>
<tr>
<td>Pitch, °</td>
<td>0.005 (0.003)</td>
<td>0.005 (0.003)</td>
</tr>
<tr>
<td>Roll, °</td>
<td>0.002 (0.001)</td>
<td>0.002 (0.002)</td>
</tr>
<tr>
<td>Yaw, °</td>
<td>0.003 (0.002)</td>
<td>0.003 (0.002)</td>
</tr>
<tr>
<td>Scan-to-scan motion, mm</td>
<td>0.08 (0.036)</td>
<td>0.092 (0.04)</td>
</tr>
</tbody>
</table>

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.

aHandedness 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).
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. 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 NIIIs for the windows corresponding to the same dynamic brain state. Two-sample t tests were used to test the difference in NIIIs 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 NIIIs across all the dynamic brain states for each participant and examined the difference between the variability of time-varying NIIIs between the two groups using two-sample t tests. We then examined the relation between variability of time-varying NIIIs 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).
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

![Figure 2](image-url) **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.

![Table 2](image-url) **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

<table>
<thead>
<tr>
<th></th>
<th>Inattention</th>
<th>Hyperactivity/Impulsivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>p</td>
</tr>
<tr>
<td>Primary Cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NII</td>
<td>−14.54</td>
<td>.04*</td>
</tr>
<tr>
<td>Motion</td>
<td>34.38</td>
<td>.45</td>
</tr>
<tr>
<td>Age</td>
<td>−0.19</td>
<td>.75</td>
</tr>
<tr>
<td>IQ</td>
<td>0</td>
<td>.86</td>
</tr>
<tr>
<td>Replication Cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NII</td>
<td>−12.72</td>
<td>.04*</td>
</tr>
<tr>
<td>Motion</td>
<td>26.15</td>
<td>.35</td>
</tr>
<tr>
<td>Age</td>
<td>−0.34</td>
<td>.56</td>
</tr>
<tr>
<td>IQ</td>
<td>−0.02</td>
<td>.86</td>
</tr>
</tbody>
</table>

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

*p < .05.
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 (p < .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 (p < .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 (p < .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 (p < .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 (p < .05), and the NII of state 1 in the ADHD group was significantly higher than the NII of the states in the TD group (p < .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, and that cross-network interactions among 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 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 (R²) 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 (p < .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...
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.

**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

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

<table>
<thead>
<tr>
<th></th>
<th>Inattention</th>
<th>Hyperactivity/Impulsivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>p</td>
</tr>
<tr>
<td><strong>Primary Cohort</strong></td>
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<td></td>
</tr>
<tr>
<td>NII</td>
<td>45.4</td>
<td>.001</td>
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<tr>
<td>Motion</td>
<td>69.26</td>
<td>.1</td>
</tr>
<tr>
<td>Age</td>
<td>0.05</td>
<td>.93</td>
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<tr>
<td>IQ</td>
<td>-.01</td>
<td>.49</td>
</tr>
<tr>
<td><strong>Replication Cohort</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NII</td>
<td>30.86</td>
<td>.001</td>
</tr>
<tr>
<td>Motion</td>
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<td>.74</td>
</tr>
<tr>
<td>Age</td>
<td>-.34</td>
<td>.43</td>
</tr>
<tr>
<td>IQ</td>
<td>-.02</td>
<td>.78</td>
</tr>
</tbody>
</table>

ADHD, attention-deficit/hyperactivity disorder; NII, network interaction index.
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 approach to examine the neural basis of inattention symptoms in children.
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.

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