Lag in maturation of the brain's intrinsic functional architecture in attention-deficit/hyperactivity disorder

Chandra S. Sripada[1], Daniel Kessler, and Mike Angstadt

Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109

Edited by Marcus E. Raichle, Washington University in St. Louis, St. Louis, MO, and approved August 15, 2014 (received for review April 28, 2014)

Attention-deficit/hyperactivity disorder (ADHD) is among the most common psychiatric disorders of childhood, and there is great interest in understanding its neurobiological basis. A prominent neurodevelopmental hypothesis proposes that ADHD involves a lag in brain maturation. Previous work has found support for this hypothesis, but examinations have been limited to structural features of the brain (e.g., gray matter volume or cortical thickness). More recently, a growing body of work demonstrates that the brain is functionally organized into a number of large-scale networks, and the connections within and between these networks exhibit characteristic patterns of maturation. In this study, we investigated whether individuals with ADHD (age 7.2–21.8 y) exhibit a lag in maturation of the brain's developing functional architecture. Using connectomic methods applied to a large, multisite dataset of resting state scans, we quantified the effect of maturation and the effect of ADHD at more than 400,000 connections throughout the cortex. We found significant and specific maturational lag in connections within default mode network (DMN) and in DMN interconnections with two task positive networks (TPNs): frontoparietal network and ventral attention network. In particular, lag was observed within the midline core of the DMN, as well as in DMN connections with right lateralized prefrontal regions (in frontoparietal network) and anterior insula (in ventral attention network). Current models of the pathophysiology of attention dysfunction in ADHD emphasize altered DMN–TPN interactions. Our finding of maturational lag specifically in connections within and between these networks suggests a developmental etiology for the deficits proposed in these models.

resting state | connectomics | default network

Attention-deficit/hyperactivity disorder (ADHD) is a serious neuropsychiatric disorder characterized by inattention, hyperactivity, and impulsivity. One influential neurodevelopmental model of the disorder posits a lag in the maturational trajectories of key features of the brain (1–4). This model has mostly been investigated by examining developmental pathways of structural features of the brain (3, 5–8). In recent years, however, theorists have increasingly used resting state functional MRI (fMRI)—scanning participants in a task-free resting state—to explore the brain's functional architecture. This work has led to the recognition that the human brain is organized into several large-scale intrinsic connectivity networks (ICNs), each associated with specific neurocognitive functions (9, 10). ICNs have been shown to undergo significant maturation from childhood to early adulthood, with individual ICNs exhibiting spatially specific reliable patterns of integration (increased connectivity with age) and segregation (decreased connectivity with age) with other ICNs (11–17). These advances raise possibilities for investigating maturational lag in ADHD in the developing ICN architecture of the brain (18).

Independent lines of research suggest that attention dysfunction in ADHD is linked to altered ICN interrelationships. According to current theoretical models (19, 20), inattention in ADHD involves altered competitive balance between (*i*) default network, an ICN implicated in internally directed mentation (21, 22); and (*ii*) several task-positive ICNs (TPNs), including dorsal attention network (DAN), ventral attention network (VAN), and frontoparietal network (FPN), which are involved in cognitively demanding externally focused processing. Consistent with these models, previous resting state fMRI studies in ADHD have reliably found abnormalities in functional connections within DMN (23, 24) and in its interconnections with TPNs (25–27). Importantly, however, it is not currently known whether these abnormalities reliably observed in ADHD are linked to maturational lag. The current study sought to investigate this question. Based on current network models of ADHD, we hypothesized that maturational lag in ADHD in the brain's intrinsic functional architecture would be focused within DMN and in its interconnections with three TPNs: DAN, VAN, and FPN.

To test this hypothesis, we used recently developed whole-brain connectomic methods (28–30). Traditional seed-based strategies examine connectivity using a single or a handful of regions of interest (ROIs) or average connectivity values across entire ICNs. However, recent work demonstrates that ICN interrelationships are not unitary; rather, connectivity alterations during maturation in DMN and TPNs are highly variable across individual connections within ICNs (13, 14, 31, 32). Thus, conventional seed-based strategies are likely to produce summary measures that do not capture underlying fine-grained patterns of variation or can miss trends that are detectable only when looking across large populations of connections. Connectomic methods remedy this problem by examining connectivity patterns among hundreds of seeds. To produce comprehensive connectomic maps, we placed 907 ROIs at regular intervals throughout the cortex and calculated connectivity between each pair of ROIs (410,871 unique connections). Using a multiple regression approach, we then calculated the effect of age and the effect of ADHD at each connection of the connectome, controlling for nuisance effects (sex,

Significance

It was proposed that individuals with attention-deficit/hyperactivity disorder (ADHD) exhibit delays in brain maturation. In the last decade, resting state functional imaging has enabled detailed investigation of neural connectivity patterns and has revealed that the human brain is functionally organized into large-scale connectivity networks. In this study, we demonstrate that the developing relationships between default mode network (DMN) and task positive networks (TPNs) exhibit significant and specific maturational lag in ADHD. Previous research has found that individuals with ADHD exhibit abnormalities in DMN–TPN relationships. Our results provide strong initial evidence that these alterations arise from delays in typical maturational patterns. Our results invite further investigation into the neurobiological mechanisms in ADHD that produce delays in development of large-scale networks.

Author contributions: C.S.S. and D.K. designed research; C.S.S., D.K., and M.A. performed research; C.S.S., D.K., and M.A. analyzed data; and C.S.S. and D.K. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

[1]To whom correspondence should be addressed. Email: sripada@umich.edu.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1407787111/-/DCSupplemental.

IQ, handedness, motion, and scanner site). This regression modeling yielded two comprehensive maps of effect of age and effect of ADHD, respectively. Examining patterns of spatial correspondence across populations of connections in these whole-cortex connectomic maps provides a powerful way to investigate the maturational lag hypothesis.

In our connectomic framework, we operationalized maturational lag as spatial co-occurrence of effects of age and effects of ADHD at the same connections. In particular, lag exists at an individual connection when the effect of ADHD at that connection opposes the effect of maturation. The presence of lag in a population of connections can be tested statistically by using a count-based framework that compares the number of observed lagged connections to a suitable chance distribution. Alternatively, a correlation-based framework can be used to investigate whether the strength of the effect of maturation is proportionately opposed by the effect of ADHD. That is, to the extent that a connection tends to more strongly integrate with age (i.e., effect of age is more positive), then its connectivity should be correspondingly reduced in ADHD relative to typically developing controls (TDCs). Conversely, to the extent that a connection tends to more strongly segregate with age (i.e., effect of age is more negative), then its connectivity should be correspondingly increased in ADHD relative to TDCs.

We used both correlation- and count-based tests to investigate the spatial co-occurrence of effects of age and opposed effects of ADHD that is predicted by the maturational lag hypothesis. ICNs exhibit substantial intra- and internetwork dependency across connections. Thus, we assessed the significance of all statistical tests with nonparametric permutation tests, which are robust to deviations from independence and normality assumptions of conventional tests (33). We calculated estimates of effect of age and effect of ADHD used in these tests from participants in the ADHD-200 sample (34). This sample consisted of 481 TDCs and 275 children with ADHD and, after demographic and quality control exclusions, encompassed 421 participants (288 TDC and 135 ADHD). In addition, we also performed a partially independent second analysis. In particular, the preceding connectomic analyses were done a second time using effect of age estimates derived from a different sample, 155 TDC participants from the multisite Autism Brain Image Date Exchange (ABIDE) sample (35). The effect of ADHD estimates were derived from the ADHD-200 sample, and thus it bears emphasis that this second analysis is not completely independent from the first. Results were remarkably similar in this second analysis, and (with the exception of a single statistical test) all significant statistical tests reported below from the first analysis were also statistically significant in the second analysis (*SI Results*). Although not a fully independent replication, this second analysis nonetheless provides additional support for the reliability of our findings.

Results

Maturational Lag in ADHD Is Relatively Specific to DMN and Its Interconnections with Two TPNs. Fig. 1 shows the Pearson's correlation coefficients across connections of the connectome between effect of age and effect of ADHD. These correlations were calculated separately for each of seven major ICNs and their interconnections, with ICN boundaries determined by a widely used seven network parcellation (36). Three network pairs showed highly statistically significant negative correlations (assessed with permutation tests) evidencing maturational lag: DMN-DMN, DMN-FPN, and DMN-VAN. Moreover, these negative correlations were relatively specific to these three network interconnections (only two other cells were significant at $P < 0.05$). This result is consistent with our a priori prediction that maturational lag in ADHD would be focused in DMN and its interconnections with TPNs.

We next examined scatter plots of the relationship between effect of age and effect of ADHD among connections linking

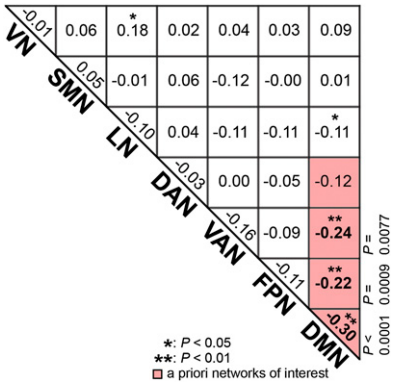

Fig. 1. Correlations across connections between effect of age and effect of ADHD. Correlations are shown separately for interconnections between seven major intrinsic connectivity networks. We had a priori hypotheses that we would observe maturational lag in the cells shaded red. Consistent with our hypotheses, highly statistically significant negative correlations indicating maturational lag were observed in DMN-DMN, DMN-FPN, and DMN-VAN. LN, limbic network; SMN, somatomotor network; VN, visual network.

DMN-DMN, DMN-FPN, and DMN-VAN. We were specifically interested in the question of whether maturational lag due to ADHD could be detected in the subpopulation of connections that exhibit relatively strong maturation with age (based on a $P < 0.01$ threshold). If ADHD does produce a lag in the maturation of these connections, then these strongly maturing connections should be more likely to lie in the upper left and lower right quadrants; in these lagged quadrants, the directional effect of maturation, i.e., either integration or segregation, is opposed by the effect of ADHD. We used permutation tests to assess whether the odds of lying in a lagged quadrant were significantly different from chance.

There Is Lag in Integration of the Medial Prefrontal Cortex-Posterior Cingulate Cortex Core of the DMN in ADHD. Results for connections within DMN-DMN are shown in Fig. 2. As illustrated in the scatter plot (Fig. 2*A*), the odds that a strongly maturing connection was lagged (vs. being unlagged) were 6.68 to 1, which is highly statistically significant ($P < 0.0001$; permutation test). Visualization of the pattern of altered connections with circle graphs (Fig. 2*B*) revealed that there was a concentration of lagged connections between the dorsomedial prefrontal cortex (dmPFC) and posterior cingulate cortex (PCC), two regions widely regarded as the core of the DMN (37).

FPN Exhibits Lag in Integration with Diffuse Regions of DMN in ADHD. Fig. 3 shows results for interconnections between DMN and FPN. The odds that a strongly maturing connection was lagged (vs. being unlagged) were 3.26 to 1, which is highly statistically significant ($P < 0.0001$; permutation test). Visualization of this pattern of lagged connections revealed that the vast majority of FPN termini of these connections involved the right dorsal lateral prefrontal cortex (dlPFC) and right superior frontal gyrus (SFG). The DMN termini of these connections were diffusely spread across the network including midline regions (dmPFC and PCC) as well as lateral regions in temporal and parietal lobes.

The Anterior Insula in VAN Exhibits Prominent Lagged Segregation with DMN in ADHD. Fig. 4 shows results for DMN-VAN interconnections. The odds that a strongly maturing connection was lagged (vs. being unlagged) were 2.21 to 1, which is statistically significant ($P < 0.03$; permutation test). Visualization of the pattern of altered connections revealed prominent lag in segregation between anterior insula in VAN and PCC in DMN.

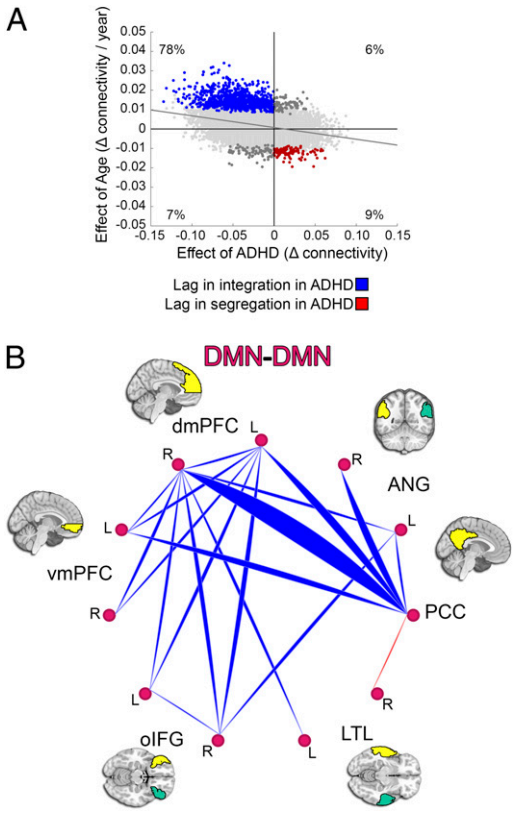

Fig. 2. Maturational lag in DMN. (*A*) Scatter plot of the relationship between effect of age and effect of ADHD in DMN. Weakly maturing connections are shown in light gray. Strongly maturing connections that are lagged in ADHD are shown in blue and red, respectively. Strongly maturing, unlagged connections are shown in dark gray. Percentages refer to the percent of strongly maturing connections that lie within the respective quadrant. (*B*) Circle graph displays the interregion distribution of the lagged connections shown in the scatter plot; the width of an arc linking two subregions represents the proportion of lagged connections linking those two regions. This circle graph shows a concentration of lagged connections between the dmPFC and PCC.

Individuals with More Severe Inattention Show Greater Maturational Lag in DMN–TPN Interconnections. We next examined how continuous scale measures of inattention impacted maturational lag in DMN-DMN, DMN-FPN, and DMN-VAN interconnections. The Inattention Subscale of either the Conners' Parent Rating Scale-Revised, Long Version (CPRS-LV) (38) or Conners' Rating Scale, 3rd Edition (39) was available for 180 (ADHD = 77) of the 421 participants in the present analysis (other participants had either different measures of ADHD symptom severity or none at all). Using a multiple regression framework, we calculated βs representing the effect of inattention severity scores (this regression was similar to the one described earlier except that the inattention severity measure was used in place of dichotomous ADHD diagnosis). Next we calculated Pearson's correlation coefficients across connections of the connectome between effect of age and effect of inattention severity. This analysis revealed statistically significant negative correlations for all three networks [DMN-DMN (r=-0.18; P = 0.05), DMN-FPN (r=-0.14; P = 0.02), and DMN-VAN (r=-0.21; P = 0.01); all P values from permutation tests]. This result supports the hypothesis that with greater severity of inattention, there is correspondingly greater lag in maturation of DMN and its interconnections with TPNs.

Discussion

It has been hypothesized that the brains of individuals with ADHD exhibit maturational lag relative to typically developing children. In this study, we extend investigation of this hypothesis to the brain's developing network architecture. We combined large samples (leveraging fMRI resting state scans from two independent multisite datasets) with connectomic methods to provide a comprehensive picture of effects of age and ADHD across major brain networks. We demonstrate that functional connectivity both within DMN and in DMN interconnections with two task-positive networks (FPN and VAN) is significantly lagged in ADHD. Previous longitudinal investigations of a large cohort of children found maturational lag of structural features of the brain in ADHD (3, 6–8). Our results demonstrate that there is also maturational lag in the brain's developing functional architecture, and it is relatively specific to connections within DMN and between DMN and TPNs.

According to current network models of ADHD, DMN and TPNs are, respectively, specialized for introspective vs. extrospective orientations of attention (19, 20). Individuals with ADHD are proposed to exhibit insufficient regulatory control over DMN (40). Diminished control leads to inappropriate intrusion of DMN during externally demanding tasks, producing lapses in attention (19, 41), distractibility (42), and increased variability in task performance (43). Many of the networks and specific regions postulated to be abnormal in this model—including regions involved in network regulation such as anterior insula and cognitive control such as dlPFC—were found to exhibit maturational lag in the present study. Our results thus add to

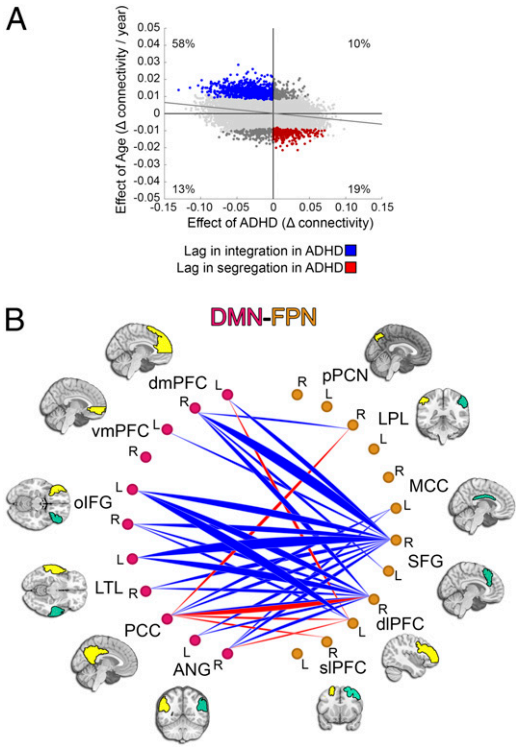

Fig. 3. Maturational lag in connections between DMN and FPN. (*A*) Scatter plot of the relationship between effect of age and effect of ADHD in DMN-FPN. Weakly maturing connections are shown in light gray. Strongly maturing connections that are lagged in ADHD are shown in blue and red, respectively. Strongly maturing, unlagged connections are shown in dark gray. Percentages refer to the percent of strongly maturing connections that lie within the respective quadrant. (*B*) Circle graph displays the interregion distribution of the lagged connections shown in the scatter plot; the width of an arc linking two subregions represents the proportion of lagged connections linking those two regions. This circle graph shows lag in integration between (*i*) right dlPFC and right SFG in FPN and (*ii*) diffuse regions of DMN.

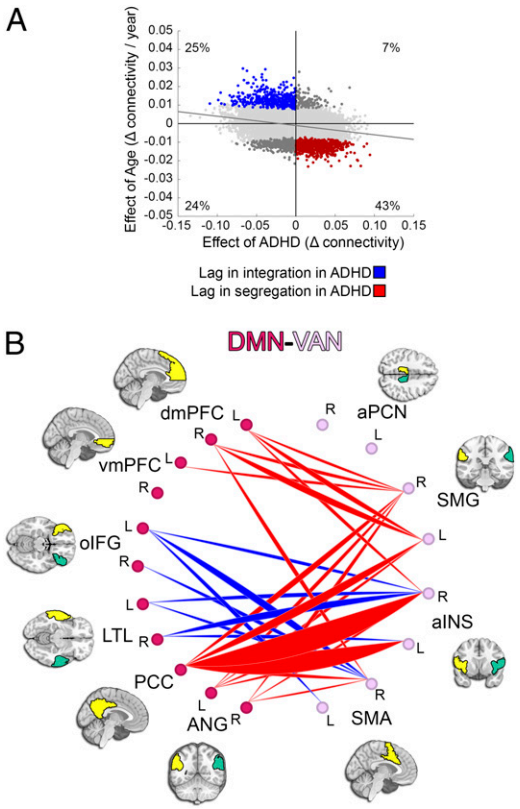

Fig. 4. Maturational lag in connections between DMN and VAN. (*A*) Scatter plot of the relationship between effect of age and effect of ADHD in DMN-VAN. Weakly maturing connections are shown in light gray. Strongly maturing connections that are lagged in ADHD are shown in blue and red, respectively. Strongly maturing, unlagged connections are shown in dark gray. Percentages refer to the percent of strongly maturing connections that lie within the respective quadrant. (*B*) Circle graph displays the interregion distribution of the lagged connections shown in the scatter plot; the width of an arc linking two subregions represents the proportion of lagged connections linking those two regions. This circle graph shows prominent lagged segregation between anterior insula in VAN and PCC in DMN.

this network regulation model of ADHD by suggesting a developmental explanation for the observed pattern of network and regional abnormalities.

We found prominent maturational lag in DMN interconnections with VAN, with a concentration of lagged connections involving anterior insula, a key hub in VAN. Anterior insula has been implicated in salience processing (i.e., detecting salient stimuli in the external environment) (44, 45) and in regulating shifts between introspective and extrospective modes of attention (44, 46). Evidence for this proposal comes from structural imaging (44), fMRI studies using activation paradigms (e.g., oddball tasks) (47), functional and effective connectivity studies (46), and investigations using pharmacological manipulations (48). In addition, imaging studies in ADHD routinely find abnormalities in anterior insula and adjacent regions of inferior frontal gyrus (i.e., fronto-opercular cortex) during inhibition of irrelevant stimuli (49–51). These observations suggest that lagged maturation in anterior insula could contribute to several forms of inattention in ADHD. For example, aberrant salience attribution by anterior insula could produce excessive distractibility by situational stimuli, and diminished anterior insula regulation of DMN might contribute to intrusion of DMN during externally focused tasks (resulting in lapses of attention).

There was also a lag in ADHD in integration of interconnections linking DMN and FPN (Fig. 3). FPN is a core network underlying adaptive cognitive control (52). This network flexibly binds to other ICNs in accordance with task demands and rapidly modulates widespread ICN interconnectivity patterns (52–54). Key nodes in FPN, such as the dlPFC, generate critical task control signals, especially in novel, nonpracticed situations (52, 55, 56). In addition, FPN has been proposed to specifically modulate DMN activity in task contexts where introspective modes of attention are relevant (e.g., planning for one's personal future) (53, 57). Relative immaturity of DMN-FPN connections in ADHD might thus manifest as reduced flexibility in control over DMN across diverse task contexts, especially in tasks where introspective attention is involved. More broadly, our finding of lagged maturation of regulatory control networks in ADHD fits well with a previous study in juvenile offenders that found that relative immaturity of connectivity of motor planning regions with other brain regions, including DMN regions, predicted greater impulsivity (58). These results suggest maturational lag of regulatory control networks contributes to inattention and/or impulsivity across different clinical populations, and they invite new research aimed at direct comparative investigation (59).

We also observed maturational lag in integration of the dmPFC and PCC (Fig. 2*A*)—the two regions that are widely thought to make up the functional core of the DMN (37). Functional abnormalities in DMN are among the most reliably seen in ADHD (18, 24, 26). Interestingly, a growing body of evidence links these functional abnormalities with disturbances in structural development (31). The cingulum fiber bundle connects dmPFC and PCC, and maturation of this structural connection has been shown to predict maturation of functional connectivity between these two regions (16). In a seminal investigation (3), Shaw et al. found diffuse maturational delay in cortical thickness in ADHD, with peak delays in medial prefrontal regions in DMN. These findings across imaging modalities underscore a broader point: the functional abnormalities we observed within and between DMN and TPNs are likely to be part of a larger picture of developmental delays of structural characteristics such as cortical thickness and white matter tracts (see ref. 31 for a review). Joint, multimodal investigation of this ensemble of structural and functional characteristics in ADHD could provide insights into the mechanisms that produce and sustain the disorder.

In summary, this study extends investigation of the maturational lag hypothesis in ADHD to the brain's developing functional architecture. We demonstrate maturational lag specifically in connections within and between DMN and TPNs. Our results add a developmental perspective to current network models of ADHD and provide strong initial evidence that altered DMN-TPN relationships that are reliably seen in ADHD are related to delays in typical maturational patterns.

Methods

Sample. Participants and scans for this study derive from two large, multisite datasets that are available at http://fcon_1000.projects.nitrc.org/indi/.

ADHD-200 sample. A total of 756 participants underwent resting state scanning and had complete phenotypic information (diagnosis, age, gender, and handedness) at seven contributing sites. The dataset comprised 481 typically developing control participants and 275 participants with a DSM-IV-TR diagnosis of ADHD.

ABIDE. This sample comprised 573 TDC from 20 contributing sites. Although participants with autism were also available from this dataset, only healthy controls were used from this sample.

The samples were restricted to participants who met criteria for high-quality scans and motion correction (*SI Methods*). After applying these criteria, we analyzed resting state scans from 421 individuals (TDC = 288; ADHD = 133) from seven sites in the ADHD-200 sample. The age of the ADHD-200 sample participants ranged from 7.2 to 21.8 y. The TDC participants from the ABIDE dataset had a wider age range, and because we were primarily interested in age effects, the age range from the ABIDE sample was trimmed to fall within that of the ADHD-200 sample. In addition, 30 TDC participants in the ABIDE sample were excluded due to their also being present in our post-exclusion ADHD-200 sample, leaving 155 TDC participants from nine sites

from the ABIDE sample (see *SI Methods* for detailed demographics of the preexclusion and postexclusion samples). In previous reports using the ADHD-200 dataset (60) and the ABIDE dataset (35), comprehensive descriptions of data provenance, additional demographic/phenotypic information, and scanner protocols are available.

Preprocessing and Connectome Generation. Preprocessing for resting state functional connectivity analyses was carried out as described in our previous work (27, 61–63) (*SI Methods*). In brief, after linear detrending, nuisance effects in each voxel's time series were removed by regression and band-pass filtering was performed, followed by motion scrubbing (censoring of individual frames from the time series). Spatially averaged time series were extracted from each of 907 ROIs placed in a regular 12-mm grid throughout the neocortex (see ref. 63 for an extensive discussion of the advantages of this grid-based method for placing ROIs). Next, Pearson's correlation coefficients were calculated pairwise between time courses for each of the ROIs, producing a cross-correlation map with 410,871 nonredundant entries. Based on Yeo et al.'s network map (36), each connection was then assigned to a network pair based on the large-scale ICN in which it originated and terminated.

Calculating Effect of ADHD and Effect of Age. Calculation of the effect of ADHD and effect of age was done for each connection of the connectome using multiple regression. Regression models were controlled for the effects of sex, full-scale IQ, handedness, motion, and scanner site. ICNs exhibit substantial intra- and internetwork dependency across connections, so nonparametric permutation tests (33) were used to assess significance of all statistical tests to account for this dependency. Details of regression models and the permutation tests are provided in *SI Methods*.

ACKNOWLEDGMENTS. C.S.S.'s research was supported by National Institutes of Health Grant K23-AA-020297, a University of Michigan Center for Computational Medicine pilot grant, and the John Templeton Foundation.

1. Gogtay N, Giedd J, Rapoport JL (2002) Brain development in healthy, hyperactive, and psychotic children. *Arch Neurol* 59(8):1244–1248.
2. El-Sayed E, Larsson JO, Persson HE, Santosh PJ, Rydelius PA (2003) "Maturational lag" hypothesis of attention deficit hyperactivity disorder: An update. *Acta Paediatr* 92(7):776–784.
3. Shaw P, et al. (2007) Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci USA* 104(49):19649–19654.
4. Rubia K (2007) Neuro-anatomic evidence for the maturational delay hypothesis of ADHD. *Proc Natl Acad Sci USA* 104(50):19663–19664.
5. Castellanos FX, et al. (2002) Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA* 288(14): 1740–1748.
6. Shaw P, et al. (2006) Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 63(5):540–549.
7. Shaw P, et al. (2012) Development of cortical surface area and gyrification in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 72(3):191–197.
8. Shaw P, et al. (2013) Trajectories of cerebral cortical development in childhood and adolescence and adult attention-deficit/hyperactivity disorder. *Biol Psychiatry* 74(8):599–606.
9. Fox MD, et al. (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci USA* 102(27):9673–9678.
10. Power JD, et al. (2011) Functional network organization of the human brain. *Neuron* 72(4):665–678.
11. Fair DA, et al. (2007) Development of distinct control networks through segregation and integration. *Proc Natl Acad Sci USA* 104(33):13507–13512.
12. Fair DA, et al. (2008) The maturing architecture of the brain's default network. *Proc Natl Acad Sci USA* 105(10):4028–4032.
13. Fair DA, et al. (2009) Functional brain networks develop from a "local to distributed" organization. *PLOS Comput Biol* 5(5):e1000381.
14. Anderson JS, Ferguson MA, Lopez-Larson M, Yurgelun-Todd D (2011) Connectivity gradients between the default mode and attention control networks. *Brain Connect* 1(2):147–157.
15. Supekar K, Musen M, Menon V (2009) Development of large-scale functional brain networks in children. *PLoS Biol* 7(7):e1000157.
16. Supekar K, et al. (2010) Development of functional and structural connectivity within the default mode network in young children. *Neuroimage* 52(1):290–301.
17. Menon V (2013) Developmental pathways to functional brain networks: Emerging principles. *Trends Cogn Sci* 17(12):627–640.
18. Fair DA, et al. (2010) Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 68(12):1084–1091.
19. Sonuga-Barke EJS, Castellanos FX (2007) Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis. *Neurosci Biobehav Rev* 31(7):977–986.
20. Castellanos FX, Proal E (2012) Large-scale brain systems in ADHD: Beyond the prefrontal-striatal model. *Trends Cogn Sci* 16(1):17–26.
21. Raichle ME, et al. (2001) A default mode of brain function. *Proc Natl Acad Sci USA* 98(2):676–682.
22. Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 1124:1–38.
23. Tomasi D, Volkow ND (2012) Abnormal functional connectivity in children with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 71(5):443–450.
24. Uddin LQ, et al. (2008) Network homogeneity reveals decreased integrity of default-mode network in ADHD. *J Neurosci Methods* 169(1):249–254.
25. Tian L, et al. (2006) Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. *Neurosci Lett* 400(1-2):39–43.
26. Castellanos FX, et al. (2008) Cingulate-precuneus interactions: A new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biol Psychiatry* 63(3): 332–337.
27. Sripada C, et al. (2014) Disrupted network architecture of the resting brain in attention-deficit/hyperactivity disorder. *Hum Brain Mapp* 35(9):4693–4705.
28. Bressler SL, Menon V (2010) Large-scale brain networks in cognition: Emerging methods and principles. *Trends Cogn Sci* 14(6):277–290.
29. Sporns O, Chialvo DR, Kaiser M, Hilgetag CC (2004) Organization, development and function of complex brain networks. *Trends Cogn Sci* 8(9):418–425.
30. Castellanos FX, Di Martino A, Craddock RC, Mehta AD, Milham MP (2013) Clinical applications of the functional connectome. *Neuroimage* 80:527–540.
31. Konrad K, Eickhoff SB (2010) Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. *Hum Brain Mapp* 31(6):904–916.
32. Fair DA, et al. (2007) Development of distinct control networks through segregation and integration. *Proc Natl Acad Sci USA* 104(33):13507–13512.
33. Good P (2000) *Permutation Tests: A Practical Guide to Resampling Methods for Testing Hypotheses* (Springer, New York), 2nd Ed.
34. HD-200 Consortium (2012) The ADHD-200 Consortium: A model to advance the translational potential of neuroimaging in clinical neuroscience. *Front Syst Neurosci* 6:62.
35. Di Martino A, et al. (2014) The autism brain imaging data exchange: Towards a large-scale evaluation of the intrinsic brain architecture in autism. *Mol Psychiatry* 19(6):659–667.
36. Yeo BTT, et al. (2011) The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol* 106(3):1125–1165.
37. Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL (2010) Functional-anatomic fractionation of the brain's default network. *Neuron* 65(4): 550–562.
38. Conners CK, Sitarenios G, Parker JDA, Epstein JN (1998) The revised Conners' Parent Rating Scale (CPRS-R): Factor structure, reliability, and criterion validity. *J Abnorm Child Psychol* 26(4):257–268.
39. Kao GS, Thomas HM (2010) Test Review: C. Keith Conners "Conners 3rd Edition" Toronto, Ontario, Canada: Multi-Health Systems, 2008. *J Psychoeduc Assess* 28:598–602.
40. Anticevic A, et al. (2012) The role of default network deactivation in cognition and disease. *Trends Cogn Sci* 16(12):584–592.
41. Weissman DH, Roberts KC, Visscher KM, Woldorff MG (2006) The neural bases of momentary lapses in attention. *Nat Neurosci* 9(7):971–978.
42. Fassbender C, et al. (2009) A lack of default network suppression is linked to increased distractibility in ADHD. *Brain Res* 1273:114–128.
43. Castellanos FX, et al. (2005) Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. *Biol Psychiatry* 57(11):1416–1423.
44. Menon V, Uddin LQ (2010) Saliency, switching, attention and control: A network model of insula function. *Brain Struct Funct* 214(5-6):655–667.
45. Eckert MA, et al. (2009) At the heart of the ventral attention system: The right anterior insula. *Hum Brain Mapp* 30(8):2530–2541.
46. 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 USA* 105(34):12569–12574.
47. Downar J, Crawley AP, Mikulis DJ, Davis KD (2000) A multimodal cortical network for the detection of changes in the sensory environment. *Nat Neurosci* 3(3): 277–283.
48. Dang LC, O'Neil JP, Jagust WJ (2012) Dopamine supports coupling of attention-related networks. *J Neurosci* 32(28):9582–9587.
49. Rubia K, et al. (2009) Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naïve children with ADHD during a rewarded continuous performance task. *Neuropharmacology* 57(7-8):640–652.
50. Rubia K (2011) "Cool" inferior frontostriatal dysfunction in attention-deficit/hyperactivity disorder versus "hot" ventromedial orbitofrontal-limbic dysfunction in conduct disorder: A review. *Biol Psychiatry* 69(12):e69–e87.
51. Hart H, Radua J, Nakao T, Mataix-Cols D, Rubia K (2013) Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: Exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry* 70(2):185–198.
52. Cole MW, et al. (2013) Multi-task connectivity reveals flexible hubs for adaptive task control. *Nat Neurosci* 16(9):1348–1355.
53. Spreng RN, Sepulcre J, Turner GR, Stevens WD, Schacter DL (2013) Intrinsic architecture underlying the relations among the default, dorsal attention, and frontoparietal control networks of the human brain. *J Cogn Neurosci* 25(1):74–86.
54. Gao W, Lin W (2012) Frontal parietal control network regulates the anti-correlated default and dorsal attention networks. *Hum Brain Mapp* 33(1):192–202.

55. Dosenbach NUF, et al. (2007) Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci USA* 104(26):11073–11078.
56. Dosenbach NUF, Fair DA, Cohen AL, Schlaggar BL, Petersen SE (2008) A dual-networks architecture of top-down control. *Trends Cogn Sci* 12(3):99–105.
57. Spreng RN, Stevens WD, Chamberlain JP, Gilmore AW, Schacter DL (2010) Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *Neuroimage* 53(1):303–317.
58. Shannon BJ, et al. (2011) Premotor functional connectivity predicts impulsivity in juvenile offenders. *Proc Natl Acad Sci USA* 108(27):11241–11245.
59. Dennis EL, Thompson PM (2013) Mapping connectivity in the developing brain. *Int J Dev Neurosci* 31(7):525–542.
60. Fair DA, et al. (2012) Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. *Front Syst Neurosci* 6:80.
61. Sripada CS, et al. (2013) Distributed effects of methylphenidate on the network structure of the resting brain: A connectomic pattern classification analysis. *Neuroimage* 81:213–221.
62. Sripada C, et al. (2014) Volitional regulation of emotions produces distributed alterations in connectivity between visual, attention control, and default networks. *Neuroimage* 89:110–121.
63. Watanabe T, Kessler D, Scott C, Angstadt M, Sripada C (2014) Disease prediction based on functional connectomes using a scalable and spatially-informed support vector machine. *Neuroimage* 96:183–202.