Lifespan development of resting-state brain functional networks and its associations with ADHD symptoms

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is increasingly being diagnosed in both children and adults, but the neural mechanisms underlying its distinct symptoms and whether children and adults share the same mechanism remain poorly understood. Here, we used a nested-spectral partition (NSP) approach to study resting-state brain functional networks for ADHD patients (n=97) and healthy controls (HCs, n=97) across the lifespan (7-50 years). Compared to the linear developmental trajectory in HCs, ADHD patients have a quadratic trajectory in the whole brain and in most functional systems, whereas the limbic system dominantly affected by ADHD has a faster development. Furthermore, the limbic system better predicts hyperactivity, and the salient attention system better predicts inattention. These predictions are shared in children and adults with ADHD but not in HCs. Our findings reveal a lifespan developmental trajectory of brain networks in ADHD patients and provide shared neural bases of distinct ADHD symptoms in children and adults.
Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurological disorder in childhood \(^1\) and is clinically diagnosed with age-inappropriate hyperactivity/impulsivity and inattention. Approximately 40–60\% of children with ADHD have persistent symptoms in adulthood, and a recent finding also reported a significant percentage of ADHD in adults \(^2\). Although adults with ADHD show brain structures and functions different from children with ADHD \(^3\), \(^4\), their core clinical descriptions are essentially the same \(^1\). Meanwhile, due to clinical heterogeneity and subjective psychiatric diagnoses \(^5\), \(^6\), it is still challenging to accurately diagnose ADHD \(^7\). Lifespan exploration of the neural mechanisms of ADHD and tying neural signatures to clinical symptoms are promising approaches for developing more objective and individual-specific diagnoses.

In a worldwide meta-analysis on brain anatomies across the lifespan (4-63 years) \(^8\), ADHD patients were found to have smaller volumes in several regions than healthy controls (HCs), such as the accumbens, amygdala and hippocampus \(^8\). And these anatomical alterations were only apparent in children and disappeared in adults, suggesting a maturation delay during childhood \(^8\), \(^9\), \(^10\), \(^11\), \(^12\), \(^13\), \(^14\). However, whether a delay of maturation in brain functional organization in children parallels anatomical immaturity is still controversial. For example, functional integration (i.e., global cooperation between different systems) in normal brain networks increases with age \(^15\), \(^16\), \(^17\), but both decreased and increased integration were reported in children with ADHD relative to HCs \(^18\), \(^19\), \(^20\), \(^21\). Meanwhile, it also remains unclear how brain functional organizations develops with age in ADHD adults. The above questions require a lifespan exploration of functional brains in ADHD patients. In a frontocentral event-related potential (ERP) study, ADHD patients (18-59 years) had a quadratic correlation between NoGo P3 amplitude and age, different from the linear correlation in HCs \(^22\). It is thus suspected that brain functional organizations of ADHD patients may also have a quadratic developmental trajectory across the lifespan.

Hyperactivity and inattention are the major clinical symptoms of ADHD, and these symptoms are thought to have different neural bases \(^20\). Sudre et al observed that persistent inattentional symptoms are tied to anomalous connectivity in the default mode network (DMN) \(^23\). Sanefuji et
al found that the symptoms of the hyperactive subtype of ADHD are related to the corticostriatal network, whereas the symptoms of the inattentive subtype of ADHD are associated with the right ventral attention network. However, as age and ADHD symptoms jointly affect brains across the lifespan, the developmental trajectory of brain functional organization is supposed to be modulated by ADHD. Brain developmental trajectories dominantly affected by ADHD are thus expected to signify the underlying neural bases for hyperactivity or inattention. Meanwhile, children and adults with ADHD show different brain functions relative to HCs, but whether they share the same mechanisms of hyperactivity and inattention is still unknown.

To address the above questions, neural signatures linking brain development to ADHD symptoms need to be extracted. Normal brain functions depend on not only sufficiently segregated processing in specialized systems but also effective global integration among them. Functional segregation and integration in brain functional connectivity (FC) networks have been shown to be reliable biomarkers for cognitive functions, and their abnormalities have been linked to brain disorders, including ADHD. However, graph measures of segregation and integration (e.g., modularity and participant coefficient) are based on the modular partition at a single level in brain networks that does not allow the detection of segregated and integrated processing across multiple scales. Recently, we developed a nested-spectral partition (NSP) method to detect hierarchical modules in brain networks according to the eigenmodes and described segregation and integration across multiple levels. Hierarchical segregation and integration have been demonstrated to be better neural signatures of cognitive functions than classical ones. We thus expected that NSP-based analysis could better reveal neural biomarkers underlying distinct ADHD symptoms across the lifespan.

Therefore, in this work, we studied the development of hierarchical segregation and integration in brain FC networks and explored associations with distinct ADHD symptoms. Hierarchical modules in FC networks were analyzed using resting-state fMRI datasets of children and adults with ADHD and HCs with a wide range of ages (7-50 years). We first extracted the developmental trajectories of brain FC networks in the ADHD and HC groups and studied the alterations of network segregation and integration related to ADHD and age. Second, we identified the dominant effects of age and ADHD on different functional systems and investigated their heterogeneous...
developmental trajectories. Finally, we tested whether brain systems differentially affected by ADHD or age could selectively predict distinct ADHD symptoms and whether these predictions are specific in ADHD patients relative to HCs.

**Results**

Ninety-seven ADHD patients and 97 age/sex-matched HCs were included, and clinical scores of hyperactivity, inattention and total symptoms were collected to describe the severity of ADHD symptoms. Resting-state FC networks (N=100 regions) were constructed for each participant using the Pearson correlation coefficient, and negative FC was excluded. Functional segregation and integration components (i.e., $H_{sc}$ and $H_{in}$, see Materials and methods) were computed using the NSP method. At the whole-brain level, $H_{sc}$ and $H_{in}$ were negatively correlated across subjects in both groups (Fig. S1), and a higher $H_{sc}$ or smaller $H_{in}$ reflected stronger network segregation. Since the shorter length of fMRI series biased the network to more segregation, group-averaged segregation and integration components were calibrated to the corresponding values of the stable FC network that was constructed by concatenating all fMRI time series of all participants in each group. This calibration generated the fMRI length-independent network measures for all participants. Pertinently, calibrated segregation and integration components for each region (i.e., $H_{sc}^i$ and $H_{in}^i$, $i=1\cdots N$) were also extracted to reflect the regional contribution to overall network segregation and integration.

**Abnormal developmental trajectories of whole-brain networks in ADHD patients**

The likelihood ratio test (LRT) was used to determine whether brain network segregation/integration was linearly or quadratically related to age (see Table S1). In HCs, we found a linear developmental trajectory of brain functional organization with age (Fig. 1a). Across the lifespan (7-50 years), the global integration component $H_{in}$ is positively correlated with age ($P<0.001$), and the segregation component $H_{sc}$ is negatively related to age ($P<0.001$, see Fig. 1a), indicating that development increases the network integration of the normal brain on the global scale, consistent with the previous result using single-level module detection. However, ADHD patients have a typically quadratic developmental trajectory in brain FC networks (Fig. 1b). The integration component first increases with age and then decreases after approximately 30
years of age. This trajectory was significantly predicted by the quadratic fitting model with respect to age ($P=0.005$, see Fig. 1b). Meanwhile, the segregation component first decreased with age and then increased, and this quadratic fitting trajectory was also significant ($P=0.009$, see Fig. 1b). Furthermore, we divided each group into three age-binned subgroups, roughly termed childhood (CH, 7-19 years), adulthood (AH, 20-35 years) and old adults (OA, 36-50 years). In HCs, the OA subgroup had the highest connectivity density in FC networks, and CH had the smallest density (Fig. 1c and S2), consistent with the increase in network integration with age. In ADHD patients, the AH subgroup had the highest connectivity density compared with the CH and OA subgroups, further proving the first rising and then declining trajectory of network integration. Therefore, on the global scale, ADHD results in an abnormal developmental trajectory of the resting-state brain functional network, wherein network integration first increases and then decreases with age.

Figure 1. ADHD induces abnormal developmental trajectories of brain networks. Developmental trajectories of network segregation and integration components with age in (a) HC participants and (b)
ADHD patients. These fitting models were determined by the LRT (see Table S1 for a detailed process).

(e) Averaged FC networks for different subgroups with different age ranges, visualized using BrainNet Viewer with a binarizing threshold of 0.7. The connectivity densities were provided (see Fig. S2 for more comparisons with other binarizing thresholds).

(d) Comparisons of the network integration component $H_{in}$ and segregation component $H_{sc}$ between the ADHD and HC groups in all participants (ALL), children (7-19 years) and adults (20-50 years). * MANOVA $P<0.05$.

(f) Visualizations of subnetworks in different comparisons. These regions have significant alterations in the integration component or segregation component ($P<0.05$), and they form subnetworks. A larger size of nodes represents a higher increase in degree (total FC to the node) in the weighted subnetwork, and a thicker edge indicates a higher increase in FC. Regions were colored according to their belongings to different systems, and those marked with regional names had significantly increased degrees within the subnetworks ($P<0.05$).

**Heterogeneous network alterations induced by ADHD in children and adults**

Previous works have reported inconsistent effects of ADHD on brain network segregation and integration in children or adults. When taking all participants into consideration, ADHD patients had a higher integration component on the global scale (Fig. 1d, MANONA, $P=0.038$) but an insignificant alteration in the segregation component ($P=0.493$). But notably, the inverted U-like trajectory of functional organization in ADHD patients implies that ADHD has different effects on the brains of children and adults. In children, ADHD patients had a higher integration component and smaller segregation component (Fig. 1d), but these alterations on the global scale were insignificant ($P=0.111$ and 0.487). Similarly, adults with ADHD had a higher integration component and smaller segregation component than HCs, and these alterations were also insignificant ($P=0.161$ and 0.797). There was also no significant difference between ADHD children and ADHD adults in the integration component ($P=0.413$) and segregation component ($P=0.375$).
Thus, the alterations induced by ADHD may be located in local regions. In all participants, regions with significant alterations of $H'_{in}$ and $H'_{se}$ induced by ADHD were mainly located in the control and DMN systems (all $P<0.05$, uncorrected, Fig. 1e). More importantly, most of these regions did not show a significant ADHD-induced alteration if we considered connectivity degrees in the whole-brain FC network (Fig. S3). However, while a subnetwork was formed by these regions with significantly altered integration or segregation components, we found that regions with a significantly increased degree of connectivity within the subnetwork induced by ADHD were distributed in the control and DMN systems (Fig. 1e, $P<0.05$). With the same procedure, we defined the subnetworks for children and adults wherein regions had significantly altered integration components or segregation components (Fig. 1e, $P<0.05$). In children and adults, the significant regions have increased degree, but for children they are distributed in the control, dorsal attention and visual systems, and for adults they are concentrated on the DMN. Furthermore, we also identified the subnetwork in the comparison between ADHD adults and ADHD children (Fig. 1f). Those significant regions in ADHD adults had a higher contribution to functional integration than ADHD children ($P<0.05$), as well as a higher degree in the subnetwork. Nearly all significantly different regions between ADHD adults and ADHD children are located in the motor and control systems.

Overall, ADHD mainly induces abnormal hyperconnectivity in the DMN and control systems across the lifespan, but children and adults have more specific alterations. Abnormalities in children are mainly located in the control, dorsal attention and visual systems, but they are located in the DMN in adults. Crucially, children with ADHD and adults with ADHD have significant differences in motor and control systems.

**Heterogeneous effects of ADHD and age on brain functional organization**

As both ADHD and age affect the brain development, we next investigated their dominant effects on functional systems. Using a multiple-regression approach (see Materials and methods), we evaluated the effect of age and the effect of ADHD on segregation/integration components ($H_{in}$ or $H_{se}$) in each functional system. In all patients, age and ADHD had heterogeneous effects on different functional systems (Fig. 2a). For the network integration component, age has the largest
negative effect on the salient attention system, and ADHD has the largest effect on the limbic system (Fig. 2a). In terms of the network segregation component, age has the largest positive effect on the salient attention system, and ADHD has the largest effect on the limbic system (Fig. 2a). While performing principal component analysis (PCA) on the effects of age and ADHD on network integration and segregation components, we obtained an overall coeffect defined as the difference between the first component for $H_{In}$ (explaining 83.2% of the variance) and the first component for $H_{Se}$ (explaining 84.5% of the variance). A larger positive coeffect indicates a higher effect of ADHD on brain network integration, and a larger negative coeffect represents a higher effect of age. It is clear to see a higher effect of ADHD on the limbic system and a higher effect of age on the salient attention and motor systems (Fig. 2b). However, if we performed the analysis separately for the children and adult subgroups, this coeffect exhibits great heterogeneity between children with ADHD and adults with ADHD. In ADHD children, age has the largest effect on the dorsal attention system, but it is in the salient attention system for ADHD adults. While ADHD has a large effect on the motor, salient attention and limbic systems in children, it greatly affects the limbic system in adults.

We found that heterogeneous effects of ADHD and age on functional systems in children and adults relate to different developmental trajectories. All systems have similar quadratic developmental trajectories in integration and segregation components (Figs. 2c, S4 and Table S1), except for the limbic system. The trajectory of the $H_{In}$ of the limbic system in ADHD patients was always above that for HCs (Fig. 2c), and this difference in fitted trajectories between the ADHD and HC groups was significant ($P=0.001$), indicating faster development in the limbic system.

More importantly, this faster development was mainly distributed in the functional pattern within the limbic system and involved the connectivity between limbic and DMN systems (Fig. S5). Thus, compared to HCs, ADHD patients have a faster development of the limbic system across the lifespan, but other systems show a faster development during childhood and the opposite aging trend during adulthood.

Therefore, while age and ADHD jointly affect the brain’s resting state of patients, limbic and salient attention systems have different preferences across the lifespan. ADHD children and ADHD adults share a preference in the limbic system that is greatly affected by ADHD and has a
faster development across the life span; however, they also have specific preferences for the age effect wherein age prefers to affect the salient attention system in adults but prefers to affect the dorsal attention system in children.

Figure 2. Heterogeneous developmental trajectories of functional systems in ADHD patients. (a) Effect of age and effect of ADHD on network integration (upper panel) and segregation components (lower panel) in different functional systems. (b) PCA-based overall coeffect between age and ADHD on brain network integration for all ADHD patients, ADHD children and ADHD adults. (c) Developmental trajectories of $H_{in}$ in each system across the lifespan (see Fig. S4 for the trajectories of $H_{Se}$). These curves were obtained by fitting the $H_{in}$ of HC and ADHD participants with age, and the fitting models were determined by the LRT. The shadow indicates the confidence interval. The predicted values by linear fitting models in the limbic system were first obtained, and then the Kolmogorov-Smirnov test was applied to the predicted values between the ADHD and HC groups ($P=0.001$). The test result indicates that the trajectory in ADHD patients is significantly above that for HCs in the limbic system.

The limbic system better predicts hyperactive symptoms in ADHD patients

While functional systems are heterogeneously affected by ADHD and age and have different
developmental trajectories in ADHD patients, we expected that these heterogeneous trajectories signify distinct mechanisms of hyperactivity or inattention. To test this possibility, linking resting-state brain network properties to ADHD symptoms is urgently required. In addition to the network integration and segregation components $H_{in}$ and $H_{se}$, we further measured the heterogeneity of regional segregation/integration components (i.e., $CV_{in}$ and $CV_{se}$, see Materials and methods) since the brain requires heterogeneous activation of certain regions to achieve task switching. The heterogeneities were respectively calculated for the whole-brain and all functional systems. The highly negative correlation between $CV_{in}$ (or $CV_{se}$) and $H_{in}$ (or $H_{se}$) indicates that brain networks with higher integration/segregation correspond to a more homogeneous distribution of the regional integration/segregation component (Fig. 3a).

In all ADHD patients, the $H_{in}$ of the limbic system had the highest correlation with the hyperactive score (see Fig. 3b, $R=-0.268$, $P=0.030$). The negative correlation implies higher hyperactivity for less network integration. Meanwhile, the $CV_{in}$ of the visual system was positively correlated with the hyperactive score ($R=0.252$, $P=0.041$), indicating higher hyperactivity for a more heterogeneous distribution of the regional integration component, matching less network integration. Thus, it seems consistent that limbic and visual systems dominantly affected by ADHD can better predict the hyperactivity of ADHD patients.

However, there is another possibility that this better prediction on hyperactivity is the intrinsic property of the systems. If this assumption is true, we would expect that the limbic system can also better predict the hyperactive score no matter in ADHD children/adults and HCs. In children and adults with ADHD, we also found that a higher hyperactive score was related to less network integration (Fig. 3c, d). The limbic system had the highest correlations between $CV_{in}$ and hyperactive score in children with ADHD ($R=0.368$, $P=0.064$, see Fig. 3d) and between $H_{in}$ and the score in adults with ADHD ($R=-0.448$, $P=0.004$). While controlling for sex and age, the linear regression model also supports that the limbic system significantly and better predicts the hyperactive score in both ADHD children and ADHD adults (see Fig. S6). Thus, in ADHD patients, the limbic system dominantly affected by ADHD better predicts hyperactivity, independent of age.

In addition, we further collected the hyperactive score of healthy children ($n=26$, 8-16 years, data
not available for healthy adults) and used different brain measures to predict it. Contrary to the ADHD children, healthy children have a positive correlation between the hyperactive score and network integration. This prediction was significant in the motor and salient attention systems ($P<0.05$, see Fig. 3e), wherein the salient attention system better predicted the hyperactive score. These results are also robust in the linear regression models (see Fig. S7). Therefore, the limbic system better predicts hyperactivity in ADHD patients, which is an intrinsic property closely related to its faster development dominantly affected by ADHD.

![Figure 3. The limbic system better predicts hyperactivity in ADHD patients. (a) Definitions of CV$_{in}$ and CV$_{sc}$ measuring the spreading of the regional $H_{in}$ and $H_{sc}$ (left panel) and their correspondences to the integration and segregation components in the whole brain. (b) Correlations between hyperactive score and brain measures in ADHD patients, (c) ADHD children, (d) ADHD adults and (e) healthy children for the whole-brain (ALL) networks and seven functional systems. The best predictions were provided in the right panel by the corresponding scatter plots. Here, yellow “x” indicates significant correlations ($P<0.05$).]
The salient attention system better predicts inattention in ADHD patients

Similar to hyperactivity, we next tested whether there is a special system that can better predict inattentive scores and whether this system is specific in ADHD patients. In ADHD patients, none of the brain measures was significantly related to the inattentive score ($P>0.05$, see Fig. S8). In children with ADHD, the $CV_{sa}$ of the salient attention system has the highest correlation with the inattentive score ($R=0.317$, $P=0.114$, see Fig. 4a), and this prediction is also the best and significant in the linear regression model ($P=0.049$, see Fig. S6), indicating that higher inattention is associated with a more heterogeneous distribution of the regional segregation component. Meanwhile, the salient attention system also better predicts inattentive scores in adults with ADHD ($R=-0.413$, $P=0.008$, see Figs. 4b and S6), and the negative correlation between $CV_{ln}$ and inattentive scores indicates higher inattention for a more homogeneous distribution of the regional integration component. Since the salient attention system is dominantly affected by age in ADHD adults but not in ADHD children, this result indicates that the salient attention system better predicting inattentive severity in ADHD patients is intrinsic and independent of the effects of age and ADHD.

Figure 4. The salient attention system better predicts inattentive scores in ADHD patients.

Correlations between hyperactive score and brain measures in (a) ADHD children, (b) ADHD adults and (c) healthy children for the while-brain (ALL) networks and seven functional systems. The best predictions are provided in the right panel. Here, yellow “x” indicates significant correlations ($P<0.05$).
However, in healthy children, the control system could better predict the inattentive score \((R=0.471, P=0.015, \text{see Figs. 4c and S7})\). The \(\text{CV}_{\text{in}}\) of this system is positively related to the inattentive score, indicating a higher inattentive score for a more heterogeneous distribution of the regional integration component, contrary to that in ADHD patients. Therefore, the salient attention system better predicting inattention in ADHD patients is a specific property relative to HCs.

**Discussion**

To link the brain development with ADHD clinical symptoms across the lifespan, we measured functional segregation and integration based on hierarchical modules in brain FC networks. We first found the quadratic developmental trajectory of brain FC networks in ADHD patients. Second, ADHD mainly induces abnormal hyperconnectivity in the DMN and control systems across the lifespan, wherein the abnormal regions are mainly located in the control system for children and in the DMN for adults. Compared to ADHD children, ADHD adults have higher integration in several regions that are mainly located in the motor and control systems. Third, the limbic system is dominantly affected by ADHD in both children and adults, and this system has a faster development. However, age dominantly affects the dorsal attention system in children with ADHD and the salient attention system in adults with ADHD. Finally, the limbic system better predicted hyperactivity, and the salient attention system better predicted inattention. These predictions were consistent and shared between ADHD children and adults but not in HCs. Our results support several basic hypotheses on ADHD across the lifespan and reveal the distinct neural bases of hyperactive and inattentive symptoms.

Development has complex effects on the segregation and integration of resting brain functional organizations, such as increased network integration with enhanced average FC (4-7 years) or decreased FC (6-10 years) with age \(^{16,39}\). Several studies have reported that elderly individuals exhibit higher integration than younger individuals \(^{15,17}\), but decreased integration was also reported \(^{40}\). Another study found that network segregation increases during childhood development and peaks in young adulthood \(^{41}\). Here, we found a significantly positive linear correlation between age (7-50 years) and network integration in HCs, providing further evidence that development increases brain network integration across the lifespan \(^{15,17}\). In children with ADHD
(7-16 years), previous studies found a decrease in local FCs within the DMN with age \(^{42, 43}\), but FCs in HCs contrarily showed inconsistent relations with age \(^{42, 43}\). Meanwhile, using independent component analysis (ICA), a component loading appeared to decrease with age in children with ADHD (8-15 years), while it appeared to become greater in HCs \(^{44}\). In ADHD adults (21-60 years), FC within the executive control network decreased with age \(^{45}\). These cross-sectional and local FC explorations are not sufficient to identify the manner in which development affects the network segregation and integration of resting-state brains on a global scale in ADHD patients. Here, we found that brain FC networks have a quadratic correlation with age in ADHD patients across the lifespan relative to the linear trajectory in HCs. Thus, our work provides the first lifespan evidence that ADHD first increases network integration and then decreases it during development. On the one hand, this result may be consistent with the ERP result, where ADHD patients (18-59 years) have a quadratic developmental trajectory of NoGo P3 amplitude, different from the linear trajectory in HCs \(^{22}\). On the other hand, a worldwide lifespan meta-analysis reported delayed maturation of brain volumes in children with ADHD but insignificant structural alterations in adults with ADHD \(^{8}\). Thus, our results further indicate that the functional alterations may not parallel the structural abnormalities in ADHD patients.

Across the lifespan, ADHD has different effects on brain FC networks in children and adults. Generally, ADHD has been hypothesized to be a DMN-dysconnectivity disorder \(^{23, 46, 47, 48, 49, 50}\), embracing the abnormalities of the DMN in ADHD and its return to normal functioning after treatment with methylphenidate \(^{51}\). Indeed, aberrant FC within the DMN was present in children and adults with ADHD \(^{4, 48}\), but the alterations were inconsistent in children with ADHD \(^{20, 42, 52, 53}\) or adults \(^{3, 53, 54, 55}\). An insignificant connectivity change within the DMN was also observed in children with ADHD \(^{47}\). Recently, a lifespan meta-analysis combining children and adults with ADHD reported significantly altered FCs distributed in the DMN and control systems \(^{48}\). This is matched with our result that ADHD patients have functionally abnormal regions within the DMN and control systems, and these regions have increased integration contribution (or degree) compared to HCs. Since the DMN is highly active during rest but becomes deactivated during task performance \(^{56, 57}\), the DMN hypothesis proposed that due to poor deactivation during tasks \(^{52}\), the DMN is less able to effectively transition from a baseline to an active state \(^{58}\). Our results may
imply that the hyperconnected DMN at rest in ADHD patients lost its segregation ability to flexibly transit to task states. Meanwhile, the control system plays a key role in regulating the functions of other networks and associates with ADHD-related mind wandering and symptom remission. A longitudinal follow-up study reported that persistent ADHD induces higher FC within the control system than HCs, and remitting ADHD further increases FC. Here, we found that in all ADHD patients, the control system has regions with significantly increased integration contribution (or degree) but is not related to ADHD symptoms. This higher integration may compensate for the ADHD deficit and may be an efficient mechanism to suppress ADHD symptoms.

Even though a previous study reported that children with ADHD and adults with ADHD shared altered FCs within the DMN and between the DMN and ventral attention network, we did not find any shared abnormal regions. According to neurodevelopmental theory, ADHD remission is driven by improved prefrontal top-down control. A longitudinal follow-up study reported that increased FC within the control system corresponds to smaller ADHD symptoms. Here, higher integration in the control system predicts smaller hyperactivity in ADHD adults (Fig. 3), wherein the abnormal regions are located in the DMN system. However, this prediction is not observed in children with ADHD, wherein the abnormal regions are distributed in the control, dorsal attention and visual systems. Part of our results matches the neurodevelopmental theory, but our results further suggest the neural mechanism transition of ADHD from widespread abnormalities in children to more concentrated abnormalities in adults. These results also indicate the intrinsic difference between ADHD adults and ADHD children. A meta-analysis showed that hypoactivation in the motor system during tasks was less prominent in ADHD adults than in ADHD children, in line with the decrease in hyperactivity with age. Compared to ADHD children, we found a smaller inattentive score in ADHD adults and a higher integration contribution of regions in motor and control systems during resting. Thus, enhanced executive control functions may contribute to the remission of ADHD symptoms.

Children/adolescents (7.2–21.8 years) with ADHD have been found to have a functional maturation lag in the DMN, and young ADHD rats (4-6 weeks) have a lag in limbic regions. However, in ADHD patients across the lifespan, we found that the limbic system was dominantly
affected by ADHD and showed a faster developmental pattern mainly located in the intrasystem FC. From the perspective of cognitive function, the limbic system involves a set of regions in the paleocortex, which supports a variety of functions related to emotion regulation and motivation and has been known to be associated with ADHD. The normal development of limbic circuitry underlies the reduction in impulsive choices from early adolescence to mid-adulthood, and the immature limbic system confidently predicts hyperactivity. Sanefuji et al also found that the hyperactive subtype is related to the corticostriatal network that is involved to some extent in limbic cortices. However, during lifespan development, whether the functional pattern of the limbic system is still closely correlated with hyperactivity is unclear. Here, we demonstrated that the limbic system dominantly affected by ADHD can better predict hyperactivity in both children and adults with ADHD. This result provides further knowledge that the abnormal faster development of the limbic system in functional organization also underlies the increase in hyperactive choice. Therefore, abnormal development in the limbic system across the lifespan seems to be related to hyperactive symptoms in ADHD patients.

The salient attention system (also called the ventral attention system) is dominantly affected by age in ADHD adults, not in ADHD children. However, this system can better predict inattention in both children and adults with ADHD and is not related to inattentive scores in healthy children. This result indicates the intrinsic property of the salient attention system relating to inattention, uniquely in ADHD patients rather than in HCs. Meanwhile, the predictions reveal that brains with more homogeneous integration components or more heterogeneous segregation component distributions in the salient attention system correspond to higher inattention. Indeed, to achieve task switching, the brain needs to activate certain regions of the salient attention system and suppress others, which may generate higher heterogeneity in the integration component. Thus, our results indicate that a more homogeneous integration component or a more heterogeneous segregation component in the salient attention system at rest may contribute to inefficient task switching requiring manipulation of attention. From the perspective of cognitive function, the salient attention system was thought to enable brains to direct attention toward salient stimuli by excluding irrelevant noise, supporting automatic “bottom-up” forms of attention. Dysfunction of the salient attention system was thus believed to cause attention deficits related to ADHD.
For example, compared to the combined and hyperactive subtypes of ADHD, the predominantly inattentive subtype is more specifically related to an abnormal salient attention system, such as increased FC in the right salient attention system. Meanwhile, the salient attention system is a typical task-positive network that modulates the dynamic switching between the DMN and control system. Abnormal communications among salient attention, DMN and control systems may induce inattention. Thus, even though we did not observe significant changes in the salient attention system related to ADHD, the significantly abnormal DMN and control systems may contribute to the close mapping between the salient attention system and inattention in ADHD patients. In particular, children with ADHD have abnormalities in the control system, but adults with ADHD have abnormal DMN. Our results may suggest discriminative neural mechanisms of inattention in children and adults with ADHD, wherein inattentive symptoms are indirectly driven by abnormalities in the control system in children but indirectly driven by the DMN in adults.

In conclusion, hierarchical module analysis enabled the discovery of hypothesis-driven functional systems that revealed heterogeneous developmental trajectories and robustly predicted hyperactive and inattentive symptoms of ADHD patients. The identified functional circuits provide insight into the neurobiological mechanisms supporting important clinical components of ADHD shared in children and adults, which may in turn have implications for the development of more objective and accurate diagnostic standards and contribute to the ability to distinguish hyperactive and inattentive ADHD subtypes.

**Materials and methods**

**Dataset.** Data for 57 children with ADHD and 57 healthy children were extracted from the Peking University Center and New York University (NYU) Child Study Center in the ADHD-200 project (Table 1). The data for 40 ADHD adults and 40 healthy adults were collected from the University of California, Los Angeles (UCLA) project. In the Peking and UCLA datasets, the ADHD Rating Scale IV (ADHD-RS) was used to evaluate the clinical scores of hyperactivity/impulsivity, inattention and total symptoms, and in the NYU data, the Conners’ Parent Rating Scale-Revised, Long version (CPRS-LV) was used to obtain the ADHD scores. Here, the ADHD-RS scores were
used to study the relationship between brain networks and ADHD symptoms. Adults with ADHD had smaller total symptom scores and inattentive scores than children with ADHD (ANOVA, $P=0.044$ and $0.013$), and there was an insignificant difference in hyperactivity ($P=0.614$).

Table 1. Demographic, clinical and neuropsychological features of ADHD patients and healthy controls.

|                | ADHD-200 (age 7-19) | UCLA (age 20-50) |
|----------------|---------------------|------------------|
| N/female      | 57/18               | 57/30            |
| Age           | 10.78±2.37          | 10.72±2.25       |
| Hyperactivity | 21.81±6.33          | 15.40±3.84       |
| Inattention   | 26.75±5.19          | 18.54±3.85       |
| Total         | 48.17±6.18          | 33.94±6.04       |
| FD            | 0.14±0.05           | 0.14±0.11        |

MRI data processing. MRI data of these participants had the same repetition time [TR] = 2 s, and more detailed scanning parameters are provided in the Supplementary Information. Analysis of Functional NeuroImages (AFNI) (http://afni.nimh.nih.gov/afni/) and the FMRIB Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl/) were used to preprocess the resting-state fMRI data. The mean framewise displacement (FD) was significantly smaller than the standard value (0.5 mm), and there was no significant difference in FD between the ADHD and HC groups (two-sample t-test, $P=0.605$). Echoplanar imaging (EPI) images were motion- and slice-time corrected and spatially smoothed using a Gaussian kernel of 6 mm full-width at half-maximum (FWHM). The fMRI signal was further filtered with a bandpass of $0.01 \text{ Hz} < f < 0.1 \text{ Hz}$. Additionally, several sources of nuisance covariates were eliminated using linear regression: 1) 6 rigid body motion correction parameters and 2) the signal from the white matter and the signal from a ventricular region of interest. The global whole-brain signal was not removed.

Brain functional connectivity. The Schaefer atlas was used to parcellate the brain into $N=100$ regions of interest (ROIs). This atlas is based on the transitions of FC patterns and has been widely used in recent works. The blood oxygen level-dependent (BOLD) signals of voxels belonging to one region were averaged to obtain the regional fMRI data. To overcome the effect of different lengths on the results, the length of the BOLD signal was controlled to be the same, lasting for 304 s (152 frames). The Pearson correlation coefficient was used to compute the FC between any two regions. Here, stable FCs within groups and individual static FCs were separately constructed.
First, fMRI time series were concatenated among all participants in each group, and then stable FCs were obtained. Second, in each participant, the total fMRI series was used to construct the individual static FC. Finally, negative correlations in FC matrices were set to zero, and diagonal elements were kept to one.

**Hierarchical modules of FC networks.** The nested-spectral partition (NSP) method was applied to identify the segregation and integration of brain FC networks based on eigenmodes \(^{33,34}\). Using the eigendecomposition, eigenvectors \(U\) and eigenvalues \(\Lambda\) of FC matrix \(C\) were sorted in descending order of \(\Lambda\). NSP first detected the hierarchical modules of FC networks with the following procedures \(^{34}\):

1. The 1\(^{st}\) mode had the same sign of eigenvector values for all regions and was regarded as the first level with one module (i.e., whole-brain network).
2. In the 2\(^{nd}\) mode, regions with positive eigenvector signs were assigned to a module, and the remaining regions with negative signs formed the second module. This mode was regarded as the second level with two modules.
3. According to the positive or negative eigenvector sign of regions in the 3\(^{rd}\) mode, each module in the second level could be further partitioned into two submodules, forming the third level. Successively, the FC network could be partitioned into modules of multiple levels as the order of functional modes increased. When each module contained only a single region at a given level, the partitioning process was stopped. Additionally, regions within a module at a specific level may have the same sign of eigenvector values in the next level; then, the module was indivisible, which had no effect on the subsequent iterative process. During the partitioning process, the module number \(M_i(i = 1,\ldots,N)\) and modular size \(m_j(j = 1,\ldots,M)\) at each level were recorded.

**Hierarchical segregation and integration in brain FC networks.** Different from the classical segregation and integration based on modules at a single level \(^{31}\), hierarchical segregation and integration components of brain FC networks were defined across multiple levels \(^{34}\). The first level in the FC network had a single large module, corresponding to the global network integration with the largest eigenvalue \(\Lambda\). The second level with two modules supported the local integration within each module and the segregation between them, requiring a decreased eigenvalue. With increasing mode order, more modules reflected deeper levels of the segregated process, accompanied by smaller eigenvalues \(\Lambda\). The segregation and integration components at
each level can be defined as \(^{34}\):

\[
H_i = \lambda_i^2 M_i (1 - p_i) / N
\]  

(1)

with

\[
p_i = \frac{\sum_j |m_j - N/M_i|}{N}.
\]  

(2)

Here, \(N\) is the number of regions, \(p_i\) is a correction factor for heterogeneous modular size and reflects the deviation from the optimized modular size \(m_j = N/M_i\) in the \(i\)-th level. The global integration component is thus taken from the first level:

\[
H_{io} = H_1 / N,
\]  

(3)

and the segregation component is summed from the 2nd - \(N\)th levels:

\[
H_{so} = \sum_{i=2}^{N} H_i / N.
\]  

(4)

At the whole-brain level, \(H_{so}\) and \(H_{io}\) were negatively correlated across subjects in both groups (Fig. S1). Based on the orthogonal and standard eigenvectors, the network integration and segregation components in each level could be mapped to each region \(j\):

\[
H_{io}^j = H_1 U_{i,j}^2 \quad \text{and} \quad H_{so}^j = \sum_{i=2}^{N} H_i U_{i,j}^2,
\]  

(5)

where \(U_j\) is the eigenvector value for the \(j\)-th region at the \(i\)-th level. The segregation and integration of a functional system could be obtained by averaging the corresponding components of regions in this system. Then, the distributions of regional segregation/integration components were measured with the coefficient of variance:

\[
CV_{io} = \frac{\sigma_{H_{io}}}{\overline{H_{io}}} \quad \text{and} \quad CV_{so} = \frac{\sigma_{H_{so}}}{\overline{H_{so}}}.
\]  

(6)

Here, \(\sigma_{H_{io}}\) and \(\sigma_{H_{so}}\) are the standard variances among regions across the whole brain or any functional system, and \(\overline{H_{io}}\) and \(\overline{H_{so}}\) represent the corresponding averages. These measures based on NSP are more powerful in linking brain networks to distinct ADHD symptoms than classical FC analysis (Fig. S9)

**fMRI length calibration.** A proportional calibration strategy was used to overcome the bias of brain FC networks to higher segregation in shorter fMRI series \(^{34,37}\). The group-stable segregation and integration components, i.e., \(H_{io}^s\) and \(H_{so}^s\), could be calculated from each stable FC matrix
built from concatenated fMRI time series. The vectors of segregation (or integration) components from individual static FC networks for all participants in each group are

\[ H_{in} = \left[ H_{in}(1), H_{in}(2), \ldots, H_{in}(97) \right] \quad \text{and} \quad H_{se} = \left[ H_{se}(1), H_{se}(2), \ldots, H_{se}(97) \right] , \]

which were calibrated to

\[ H_{in}^{'}(n) = H_{in}(n) \times H_{in}^{'}/\langle H_{in} \rangle \quad \text{and} \quad H_{se}^{'}(n) = H_{se}(n) \times H_{se}^{'}/\langle H_{se} \rangle \]

for the \( n \)-th participant. Here, \( \langle \rangle \) represents the average across all participants. This calibration was separately performed in each group. Then, the calibration of regional segregation and integration was also performed. For region \( j \) of the \( n \)-th participant, the calibrated segregation and integration components are

\[ H_{se}^{'} = H_{se}^{'}/H_{se}(n) \times H_{in}^{'}/H_{in}(n) \quad \text{and} \quad H_{in}^{'} = H_{in}^{'}/H_{in}(n) \times H_{se}^{'}/H_{se}(n) , \]

where the relative contribution of each region to network segregation/integration remained consistent. This calibration greatly highlighted the relationship between the brain and cognitive abilities.

**Effects of age and ADHD.** We built different multiple-regression models to obtain the effect of age and the effect of ADHD on the brain. In all patients, the regression model was

\[ H = \beta_1 \times age^2 + \beta_2 \times ADHD + \beta_3 \times age + \beta_4 \times sex + \beta_5 \times FD + \varepsilon . \] (7)

Here, \( H \) is the brain measure and \( \varepsilon \) is the residual. In this model, the brain measures were affected by age, ADHD symptoms, sex and head motion (FD). The parameter \( \beta_1 \) measures the effect of age, and \( \beta_2 \) stands for the effect of ADHD. To maintain consistency, this model was also applied to the limbic system even though it had a linear developmental trajectory (see Table S1).

In children with ADHD or adults with ADHD, the regression model was

\[ H = \beta_1 \times age + \beta_2 \times ADHD + \beta_3 \times sex + \beta_4 \times FD + \varepsilon \] (8)

This model does not consider the nonlinear effect of age on brain functional organization. The above models were separately fitted for \( H_{in} \) and \( H_{se} \) in each functional system. Thus, each model has the \( \beta_1 \) and \( \beta_2 \) series for each measure. Then, principal component analysis (PCA) was performed, and the subtraction difference between the first components for integration and segregation components was obtained to measure the coeffect of age and ADHD on participants’
brains.

**Statistical tests**

The linear regression model $y \sim x$ and quadratic regression model $y \sim x^2 + x$ were applied to fit the developmental trajectory, and the likelihood ratio test (LSR) was used to identify which model was chosen. If the $p$-value of LSR was smaller than 0.05, we chose the quadratic regression model; otherwise, the linear regression model was used. Multivariate analysis of covariance (MANOVA) was used to assess alterations induced by ADHD in Fig. 1c-e, controlling for sex, age and FD. MANOVA was also used to identify differences in networks between ADHD children and ADHD adults in Fig. 1d, f, controlling for sex, age, FD and total ADHD symptom score. A linear regression model was conducted to examine the relationships between distinct ADHD symptoms and brain measures in Figs. 3 and 4. These statistical tests were performed in $R$.

**Code and data availability**

The original datasets are available at [https://openneuro.org/datasets/ds000030](https://openneuro.org/datasets/ds000030) and [http://fcon_1000.projects.nitrc.org/indi/adhd200/index.html](http://fcon_1000.projects.nitrc.org/indi/adhd200/index.html). The brain atlas and the partition of seven functional systems are available at [https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation](https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation). The codes used in this study are available at [https://github.com/TobousRong/ADHD](https://github.com/TobousRong/ADHD).

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**Competing interests**

The authors declare no competing interests.