Association between Adolescent Brain Morphometry and Cognitive Function: Insights from a Cross-Sectional Analysis of ABCD Data from 9 to 15 Years Old

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Abstract

During the adolescent developmental stage, significant changes occur in both brain structure and cognitive function. Brain structure serves as the foundation for cognitive function and can be accurately assessed using a comprehensive set of brain cortical and subcortical morphometry measures. Exploring the association between whole-brain morphometry and cognitive function during adolescence can help elucidate the underlying relationship between brain structural development and cognitive development. Despite extensive research in this area, previous studies have two main limitations. Firstly, they often use a limited number of brain morphometry measures, which do not provide a comprehensive representation of brain structure. Secondly, most previous studies rely on relatively small sample sizes, increasing the risk of sampling error, low statistical power, and even overestimation of effects. To address these limitations, we analyzed the Adolescent Brain Cognitive Development (ABCD) dataset, which includes 8543 subjects (13,992 scans) aged 9-15 years. These scans were categorized into six groups with one-year intervals based on their ages for independent age-specific analysis. We computed 16 brain regional morphometry measures derived from Structural Magnetic Resonance Imaging (SMRI), Diffusion Tensor Imaging (DTI), and Restriction Spectrum Imaging (RSI), and integrated them with morphometric similarity networks (MSNs). This approach enabled us to compute 16,563 morphometry measures encompassing brain region, connection, and hub aspects. Subsequently, these measures were input into a robust large-scale computational model to investigate their relationship with cognitive performances. We found that brain regions making the most significant contributions to cognitive function during adolescence, and those exhibiting the greatest variability in their contributions over time, were primarily situated in the frontal and temporal lobes. Subcortex were the least involved. We also observed strong correlations between key brain morphometry measures related to different cognitive performances within same domain. Furthermore, SMRI measures demonstrated stronger associations with cognitive performances compared to DTI and RSI measures. Overall, our study aims to facilitate a comprehensive and reliable understanding of the association between adolescent brain morphometry and cognitive function.

Keywords: whole-brain morphometry, adolescent cognitive function, ABCD, large-scale

computational model

Introduction:

Mounting evidence highlights the intricate relationship between brain morphometry and cognitive function (Genon et al., 2022; Assaf and Pasternak, 2008; Bullmore and Sporns, 2012). Since brain morphometry and cognitive function change significantly during adolescence, a comprehensive study of the association between adolescent brain morphometry and cognitive function holds the promise of improving our understanding of brain structural development and its potential corollary effects on cognitive development. Many studies have shown that region-wise brain morphometry measures are significantly correlated with cognitive performances (Genon et al., 2022; Kanai and Rees, 2011). Local brain cortical thickness, area, and volume are three fundamental region-wise brain morphometry measures. Their significant correlations related to cognitive performances have been demonstrated by various researchers (Burgaleta et al., 2014; De Chastelaine et al., 2023; Karama et al., 2011; Sowell et al., 2004; Zhao et al., 2022). Moreover, variations in regional gyrification have been found to be related to cognitive performances (Gregory et al., 2016; Tadayon et al., 2020). Researchers have also explored the relationship between region-wise microstructure based on DTI and cognitive performances, revealing promising correlations (Tamnes et al., 2011).

In the pursuit of cognitive functions, it's not solely about individual brain regions but also entails understanding how these regions are interconnected (Assaf and Pasternak, 2008; He et al., 2007; Seidlitz et al., 2018). Patterns of fiber connections identified through DTI show promising impacts on cognitive function (Stammen et al., 2023; Tamnes et al., 2011). Further, structural connections identified through advanced MSNs methods have been found to be associated with cognitive performances (Seidlitz et al., 2018; Wu et al., 2023). Researchers have shown that cortex-subcortex dissimilarity based on MSNs is highly correlated with cognitive performances (Wu et al., 2023).

In addition to brain regions and connections, the organization of brain structural networks also plays a crucial role in cognitive function (Bullmore and Sporns, 2012, 2009; Colom et al., 2010). In keeping with this, the Parieto-Frontal Integration Theory (P-FIT) emphasizes that communication between specific brain hubs is pivotal for cognitive functioning (Jung and Haier, 2007). Numerous studies have demonstrated that the organization of the structural brain networks as characterized by DTI, including measures like modular segregation, is linked to cognitive performances (Baum et al., 2017; Fischer et al., 2014; Kocevar et al., 2019). Moreover, studies focusing on structural covariance networks (SCNs) have yielded similar results (Khundrakpam et al., 2017) and the degree of MSN hubs has been found to be highly correlated with both verbal and non-verbal cognitive performances.

Overall, previous research has explored the association between brain morphometry and cognitive function from region, connection, and hub aspects. However, no study has simultaneously combined all of these brain morphometry measures to offer a potentially more exhaustive representation of brain structure and its relationship to cognitive function differences.

Additionally, sample size represents another limitation of previous studies. While some studies utilizing the ABCD old release dataset have incorporated thousands of subjects (Chen et al., 2022; Wu et al., 2023; Zhao et al., 2022), many others have sample sizes of fewer than 500 datapoints. Although in these studies based on the ABCD old release, the age range typically spans from 9 to 11 years old, which does not adequately capture the full scope of the adolescent stage. Analyzing a larger sample can help mitigate sampling error, low statistical power, and even overestimation of effects that may arise in small samples. Moreover, a large sample size can establish the foundation

for independent age-specific analysis. Given the considerable changes in brain morphometry and cognitive function during adolescence, there can be significant variation between each year (Bethlehem et al., 2022; Larsen and Luna, 2018; Paus, 2005).

To address the above limitations, we conducted a comprehensive analysis utilizing data from the ABCD dataset to explore the association between adolescent brain morphometry and cognitive function. The ABCD dataset encompasses multimodal brain imaging data, including SMRI, DTI, and RSI (Casey et al., 2018). Leveraging these modalities, we computed 16 region-wise brain morphometry measures aiming to represent a comprehensive map of brain structure (Hagler et al., 2019). These measures comprised 6 SMRI measures, 4 DTI measures, and 6 RSI measures. Notably, RSI, as an advanced technique, offers enhanced accuracy in depicting tissue microstructure compared to DTI (White et al., 2014, 2013). Using the 16 regional brain morphometry measures, we calculated the structural connections between each pair of regions across the whole brain based on MSNs (Seidlitz et al., 2018). MSNs reflect similarities in cytoarchitecture, gene expression between brain regions, and white matter connections (Seidlitz et al., 2020, 2018). Variations in MSNs topology have been shown to correlate with age, cognitive function (Fenchel et al., 2020), and mental health disorders (Morgan et al., 2019). Compared to DTI, which may suffer from under-recovered long-distance projections and false-positive connections, and SCNs, which rely solely on a single measure, MSNs are considered to be a more comprehensive and accurate method for assessing brain structural connections (Seidlitz et al., 2018). Additionally, we computed 6 common local and overall graphical measures to capture the hub-wise features based on the structural networks constructed by MSNs (Rubinov and Sporns, 2010). This approach enabled us to establish a comprehensive whole-brain morphometry set, encompassing region-wise, connection-wise, and hub-wise measures, thereby better representing brain structure and facilitating a more comprehensive exploration of the association between adolescent brain morphometry and cognitive function.

Furthermore, to address the limitations associated with small sample sizes, we utilized the ABCD 5.1 release dataset. Following stringent subject exclusion criteria, we included 8543 subjects (13,992 scans, some longitudinal) aged from 9 to 15 years old for analysis. These scans were categorized into six groups with one-year intervals based on their corresponding ages. For each group, we have a large sample to explore the age-specific association between brain morphometry and cognitive function. Moreover, we employed a robust large-scale computational model based on previous work (Spreng et al., 2020) to obtain stable and reliable results. Our study was guided by three primary objectives. Firstly, we aimed to identify key brain regions, connections, and hubs associated with adolescent cognitive performances and development. Secondly, we investigated the correlation between these key regions, connections, and hubs across various cognitive abilities during adolescence. Lastly, we analyzed the key fundamental brain morphometry measures relevant to adolescent cognitive performances. We believe our research effectively addresses the two main limitations of previous studies. Our overarching goal is to facilitate a comprehensive and dependable understanding of the association between adolescent brain morphometry and cognitive function.

Methods:

Participants

The full ABCD 5.1 release cohort includes 27595 scans of 11868 subjects across 22 sites (Casey et al., 2018). We first selected brain images that passed quality control. Further details can be found in

Hagler et al. (2019). Subsequently, data defined as clinically abnormal was excluded. Then, only subjects with both cognitive scores and adequate brain morphometry measures were included. Following this, subjects with outliers in whole-brain morphometry measures and cognitive scores (> 3 SD above/below the mean) were excluded (Cohen and D'Esposito, 2016). As shown in Fig. 1A, this process yielded a final cohort comprising 8543 subjects (13,992 scans) aged 9 to 15 years. Scans were subsequently partitioned into six groups with one-year intervals based on their ages for further cross-sectional analysis. Note that some subjects were included in multiple groups because they have longitudinal data. The group aged 120 – 131 months had the highest number of subjects (N=3,734), while the group aged 168 – 179 months had the fewest (N=940).

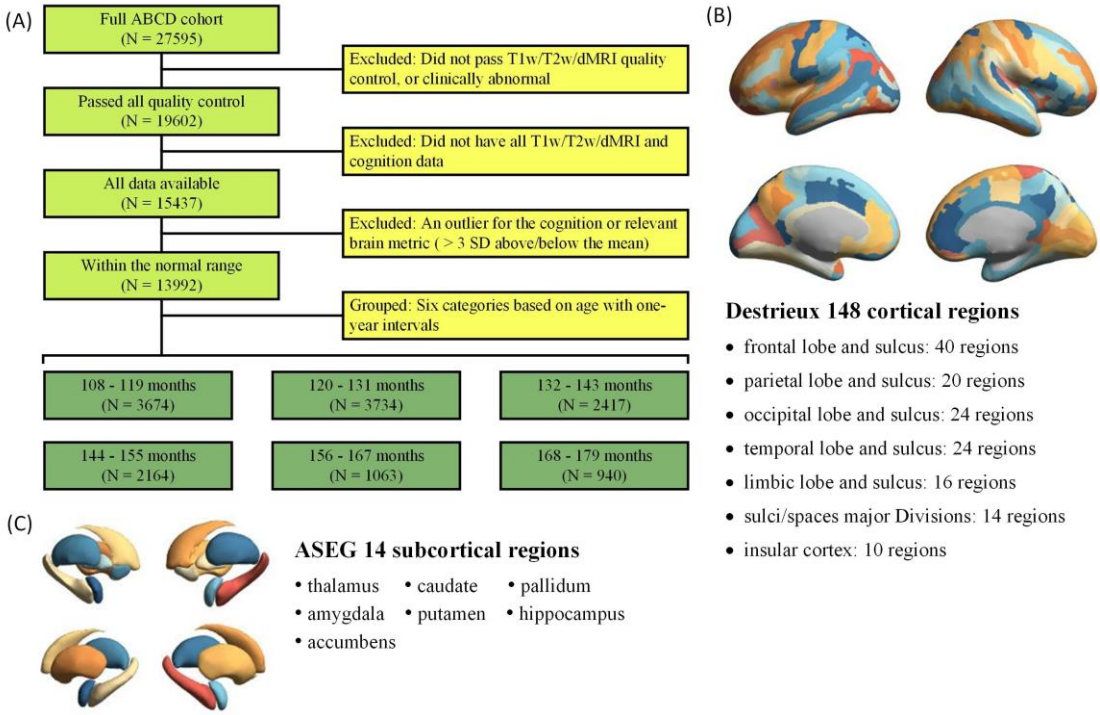

Fig. 1. Overview of data preprocessing. (A) Subject selection and exclusion. (B) 148 cortical regions based on Destrieux atlas. (C) 14 subcortical regions based on ASEG atlas.

Imaging acquisition and processing

We employed three types of structural imaging data, comprising T1w, T2w, and dMRI data, preprocessed using the ABCD pipeline. SMRI data (T1w and T2w) were preprocessed by grad warp correction, bias field correction, and resampling to isotropic. DMRI data were preprocessed by eddy current distortion, motion correction, B0 distortion correction, grad warp correction, and resampling to isotropic (Hagler et al., 2019). Then 16 region-wise brain morphometry measures were derived from these modalities using FreeSurfer 7.1.1 and FSL 5.0.2.2 (Hagler et al., 2019). These measures include 6 SMRI measures: cortical area, cortical thickness, sulci depth, volume, T1w density, and T2w density. Additionally, there are 4 DTI measures: Fractional Anisotropy (FA), Mean Diffusivity (MD), Longitudinal Diffusivity (LD), and Transverse Diffusivity (TD). Further, there are 6 RSI measures: Hindered Normalized Directional (HND), Hindered Normalized Isotropic (HNI), Hindered Normalized Total (HNT), Restricted Normalized Directional (RND), Restricted Normalized Isotropic (RNI), and Restricted Normalized Total (RNT). Note that subcortical regions

lack three measures: cortical area, cortical thickness, and sulci depth. In the preprocessing stage, brain cortex parcellation (Fig. 1B) was performed using the Destrieux atlas with 148 regions of interest (ROIs), and delineation of subcortical regions (Fig. 1C) was achieved using the ASEG atlas with 14 ROIs (Destrieux et al., 2010; Fischl et al., 2002).

Whole-brain morphometry measures

We constructed whole-brain morphometry measures from three perspectives: region, connection, and hub. As previously mentioned, each of the 148 cortical regions possesses 16 regional brain morphometry measures, while each of the 14 subcortical regions has 13 regional brain morphometry measures. This leads to a total of 2550 region-wise features, encompassing SMRI, DTI, and RSI measures. We then used MSNs to compute structural connections between every pair of brain regions. Specifically, after normalizing the individual data as described in Seidlitz et al. (2018), we calculated the connections between cortical regions using Pearson correlation based on the 16 regional brain morphometry measures. As subcortical regions possess only 13 regional brain morphometry measures, connections related to these regions used only these existing measures. This yielded a total of 13041 connection-wise features. We further calculated 6 most common graphical measures for each brain hubs within individual MSNs (Rubinov and Sporns, 2010). These 6 measures include strength, clustering coefficient, local efficiency, betweenness centrality, within-module degree, participation coefficient. All graphical measures were calculated at a 10% connection density, consistent with the previous study (Seidlitz et al., 2018). And we also calculated graphical measures at 15%, 20%, and 25% connection densities. It was found that the measures calculated at 10% demonstrated the highest correlation with cognitive performances. Consequently, there are 972 features calculated based on MSNs that capture hub-wise characteristics. In total, we extracted 16563 whole-brain morphometry measures from the region, connection, and hub aspects, respectively. All these measures were adjusted for sex, age, scanner (using combat), and a proxy measure of brain volume (PBV), as outlined in Table 1 (Karama et al., 2011). Note that the PBV here refers to the whole brain volume excluding the cortex and subcortex. We used PBV instead of the whole brain volume because our constructed brain morphometry measures include cortical and subcortical information.

Table 1. Participant characteristics.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Age in months	112.90±3.67	126.08±3.63	137.19±3.54	149.23±3.42	160.62±3.59	173.59±3.48
Female / Male	1832 / 1842	1773 / 1961	1176 / 1241	999 / 1165	515 / 548	447 / 493
Sites	22	22	21	21	21	21
Scanners	29	30	29	26	27	26
PBV in mm^3	8.36e5±9.78e4	8.58e5±9.59e4	8.69e5±9.94e4	8.97e5±9.87e4	9.07e5±1.04e5	9.12e5±1.16e5

Cognitive measures

To assess cognitive functions in our study, we utilized all the cognitive assessments available within the ABCD dataset (Luciana et al., 2018). These assessments included vocabulary (PV), attention (Flanker), reading (ORR), processing speed (PCPS), episodic memory (PSM), visuospatial accuracy (LMT Acc), and visuospatial efficiency (LMT EFF). Among these assessments, vocabulary and reading are traditional measures for assessing crystallized cognitive ability (Casaletto et al., 2015).

Attention, processing speed, and episodic memory are conventional measures for evaluating fluid cognitive ability (Casaletto et al., 2015). Visuospatial accuracy and visuospatial efficiency are standard measures for measuring visuospatial abilities (Nixon et al., 2014). Although the ABCD dataset includes a total of 12 cognitive measurements, we utilized only 7 due to missing data. To ensure the representativeness of our cognitive selection, we calculated the correlation between different sets of cognitive measures and found high correlation (r=0.89) in baseline data (details in Supplementary Materials S1). This analysis validates our cognitive selection as reasonable and capable of representing conventional cognitive measurements. All cognitive measures used in our analysis were adjusted for sex, age, site, and PBV, as shown in Table 1.

Large-scale computational model

A randomly optimized LASSO method combined with 10000 bootstraps (Fig. 2) was used to investigate the association between brain morphometry measures and cognitive measures. This computational model built on the method developed by Spreng et al. (2020), with several modifications to better suit our requirements. Specifically, the previous method calculated Pearson correlations between tract microstructure measures and loneliness measures using 100 bootstraps. However, in our study, we believe that brain morphometry measures complement each other and collectively contribute to cognitive function rather than acting independently. Therefore, we employed a regression model instead of independent Pearson correlations, allowing the brain morphometry measures to control for each other and providing a more integrated analysis.

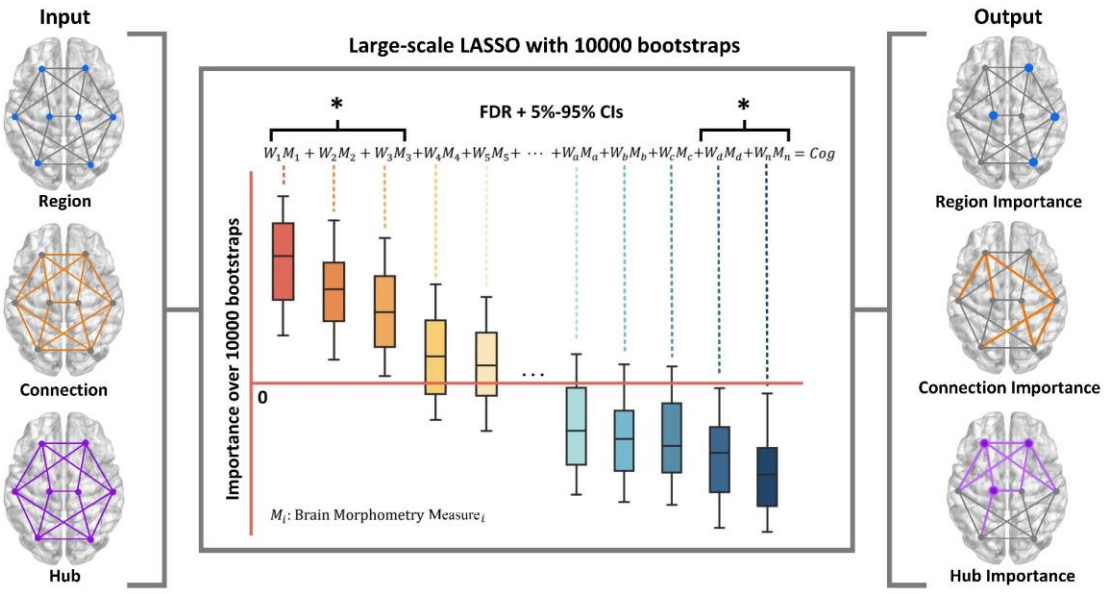

Fig. 2. Overview of the Large-scale computational model.

We constructed three distinct models focusing on region, connection, and hub aspects, respectively. Taking region-wise data as an example, we inputted 2550 regional brain morphometry measures into the model to estimate a specific cognitive ability score. Following 10,000 bootstraps, we generated 10,000 parameters for each region-wise morphometry measure to assess its significance in relation to a cognitive score. Only measures that passed Bonferroni false discovery rate (FDR) correction (mean value compared to 0 across all region-wise features) and exhibited statistically

significant 5-95% bootstrap confidence intervals (all values are non-positive or non-negative) were considered significant. Then the average value of the 10,000 parameters of a significant measure was regarded as the importance of that measure contributing to cognitive performance. The importance of other measures was set to 0. Subsequently, these 2550 importance values were normalized to ensure their sum equaled 1. We adopted this computational model for several reasons. Firstly, given the abundance of brain morphometry measures, a LASSO method effectively sifts out truly useful features from a large pool, mitigating the negative effects of feature collinearity. Secondly, by employing a feature random optimization strategy, we introduced variability in the order of feature parameter computation across 10,000 bootstraps, further mitigating collinearity effects. Thirdly, building 10,000 models based on 10,000 bootstraps and then performing strict significant feature selection helped ensure reliable results based on a large-scale sample. Moreover, we also split testing dataset within each bootstrap. Although these test results cannot be technically considered accurate estimations of cognitive ability, the calculated coefficient of determination can still be used to validate the efficacy of our model.

Results:

Utilizing a large ABCD sample, we employed a comprehensive computational model to investigate the association between adolescent brain morphometry and cognitive function across 6 years and 7 cognitive performances, examining region, connection, and hub aspects. Firstly, we averaged the results across the 7 cognitive performances to explore the key brain regions, connections, and hubs for adolescent cognitive function over the 6-year period, as well as the changes in brain regions, connections, and hubs importance during development. Secondly, we averaged the results across the 6-year period to investigate the relationships between the key brain regions, connections, and hubs related to 7 different cognitive performances, aiming to assess consistency with previous research findings. Thirdly, we focused on 16 fundamental region-wise brain morphometry measures and 6 fundamental hub-wise measures based on MSNs to study their importance related to adolescent cognitive function across 6 years and 7 cognitive performances. Finally, we employed two validation methods to test the effectiveness and stability of our large-scale computational model, ensuring robustness and reliability in our findings.

Key brain regions, connections, and hubs related to cognitive function over 6 years during adolescence

After identifying significant brain morphometry measures associated with cognitive function across 6 years and 7 cognitive performances, we initially computed the average results across the 7 cognitive performances (Fig. 3A) and then proceeded to calculate the correlations between importance values of key brain regions, connections, and hubs across different years (Fig. 3B). Given the considerable number of brain morphometry measures (in total 16563) and limited space, we opted to compute the sum importance values of all measures for each brain ROI to derive ROI-wise results in Fig. 3. Then the ROIs are categorized into 8 lobes on both the left and right hemispheres (Zhao et al., 2022). The results with whole measures are shown in Supplementary Fig. 1. The corresponding correlation values of both ROI-wise results and whole measure results are presented in Table 2. As we can see from both qualitative and quantitative results, region-wise results (mean r=0.41, 0.36) and connection-wise results on ROI-wise (mean r=0.55) are similar across 6 years, which indicates that key brain regions and connection-end regions crucial for

cognitive function remain relatively constant during this developmental phase. However, the connection-wise results on whole measures (mean r=0.03) and hub-wise results (mean r=0.03, 0.01) exhibit considerable variability over the same period, which indicates that the key brain connections and hubs undergo fluctuations during adolescence. Only the correlation between hub results on ROI-wise of year 5 and year 6 is higher than 0.1 (r=0.11).

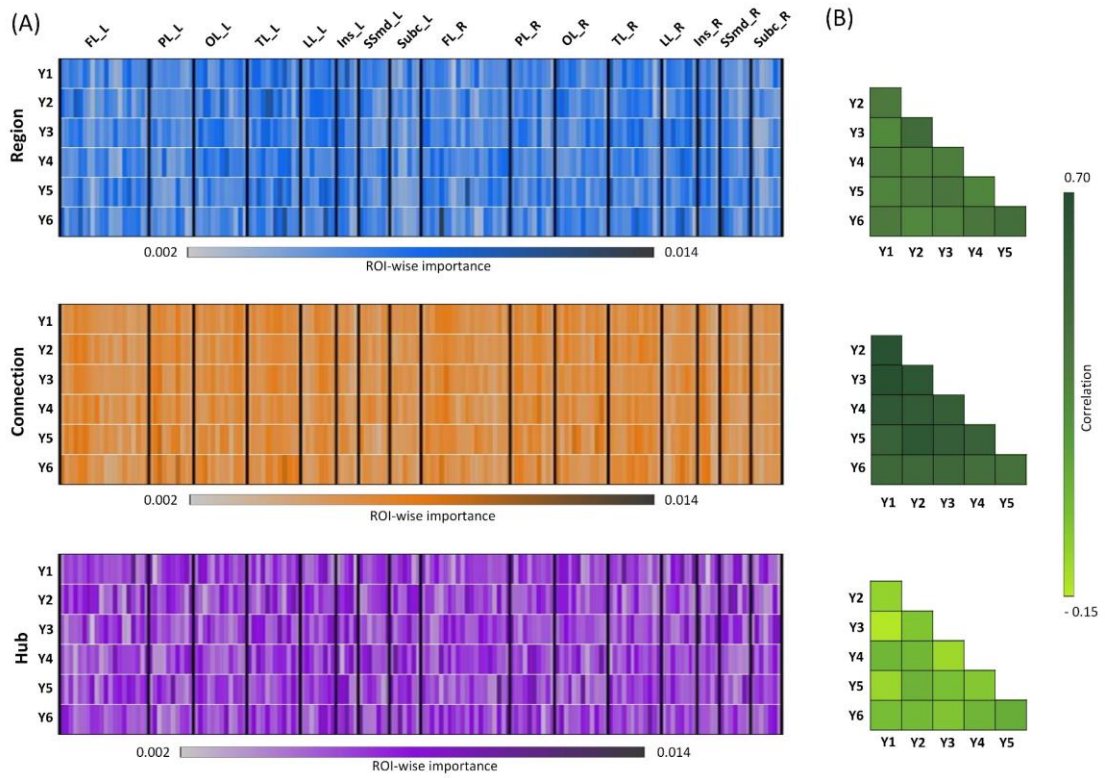

Fig. 3. Results of key brain morphometry measures for adolescent cognitive function over 6 years. (A) ROI-wise importance values over 6 years. The brain ROIs are categorized into 8 lobes on both the left and right hemispheres: limbic lobe (LL), frontal lobe (FL), temporal lobe (TL), parietal lobe (PL), occipital lobe (OL), insular cortex (Ins), and sulci/spaces major divisions (SSmd). The list is in Supplementary Table 1. (B) Correlation values of ROI-wise results between years.

Table 2. Correlations between key brain morphometry measures for cognitive function of 6 years.

Correlation	Region-wise	Connection-wise	Hub-wise
Years (whole)	0.41±0.03	0.03±0.01	0.03±0.04
[Min, Max]	[0.36, 0.47]	[0.02, 0.04]	[-0.03, 0.09]
Years (ROI)	0.36±0.05	0.55±0.08	0.01±0.07
[Min, Max]	[0.30, 0.47]	[0.42, 0.67]	[-0.14, 0.11]

Subsequently, we identified common findings regarding key brain regions, connections, and hubs over the 6-year period and calculated their average importance values across 6 years in Fig. 4. Here we calculated the sum importance values of all measures on each brain ROI to obtain ROI-wise results, the whole measure results are in Supplementary Fig. 2. Key brain regions and hubs are represented on a brain map with corresponding importance values, while key connections are depicted in a connection map based on a top 1% selection (other top p% results are in Supplementary

Fig. 3). To ensure fair comparisons among different lobes, considering variations in the number of ROIs across lobes, we exclusively selected the top 20% of key brain regions, connection-end regions, and hubs. Subsequently, we calculated the numbers within each lobe in Fig. 4B (other top p% results are in Supplementary Fig. 4). The results highlight the frontal and temporal lobes as the most pivotal brain lobes for cognitive function across all three measurement aspects. Conversely, subcortex demonstrate relatively lower influence, with the exception of the right amygdala, as indicated by the hub-wise results (Fig. 4A).

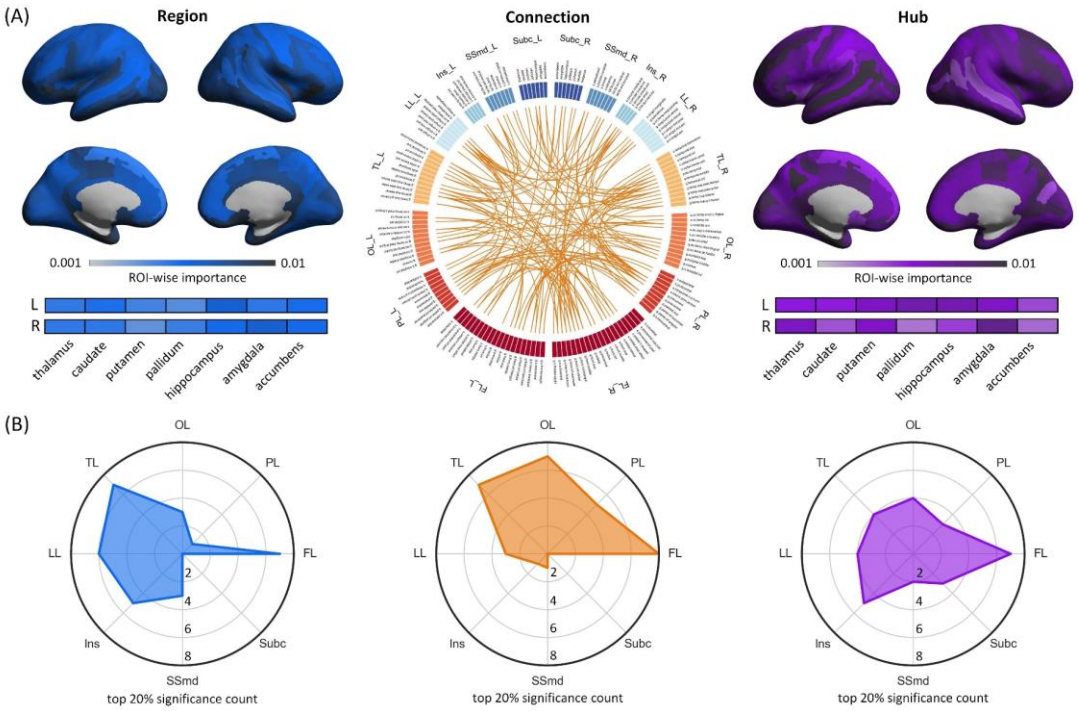

Fig. 4. Common key brain regions, connections, and hubs for adolescent cognitive function over 6 years. (A) Common key brain regions, connections, and hubs for cognitive function over 6 years. (B) Numbers of top 20% most important brain regions, connection-end regions, and hubs within each lobe.

Furthermore, we delved into the dynamics of brain regions, connections, and hubs importance values for cognitive function over the 6-year period. We computed correlations between the year indices and their corresponding importance values to measure these changes. Similar to the common results, the change outcomes are depicted in Fig. 5A and Supplementary Fig. 5. Subsequently, we identified the top 20% most positively and negatively age-correlated results and conducted a lobe-wise count (other top p% results are in Supplementary Fig. 6). Note that we initially converted all correlations into absolute values and then selected the top 20%. Due to the noticeable asymmetry in the change results (Fig. 5A), we also visualized the count results for the left and right hemispheres in Fig. 5B. We observed significant differences in the changes of brain regions, connection-end regions, and hubs between the left and right hemispheres. We observed a roughly similar number of brain regions and hubs becoming more important and less important with age. However, the number of connections becoming less important outweighed those becoming more important. Moreover, we found that the changed brain ROIs mainly concentrate in the frontal and temporal lobes, while the

changes in subcortex and insular are relatively minimal. This finding is consistent with previous common results.

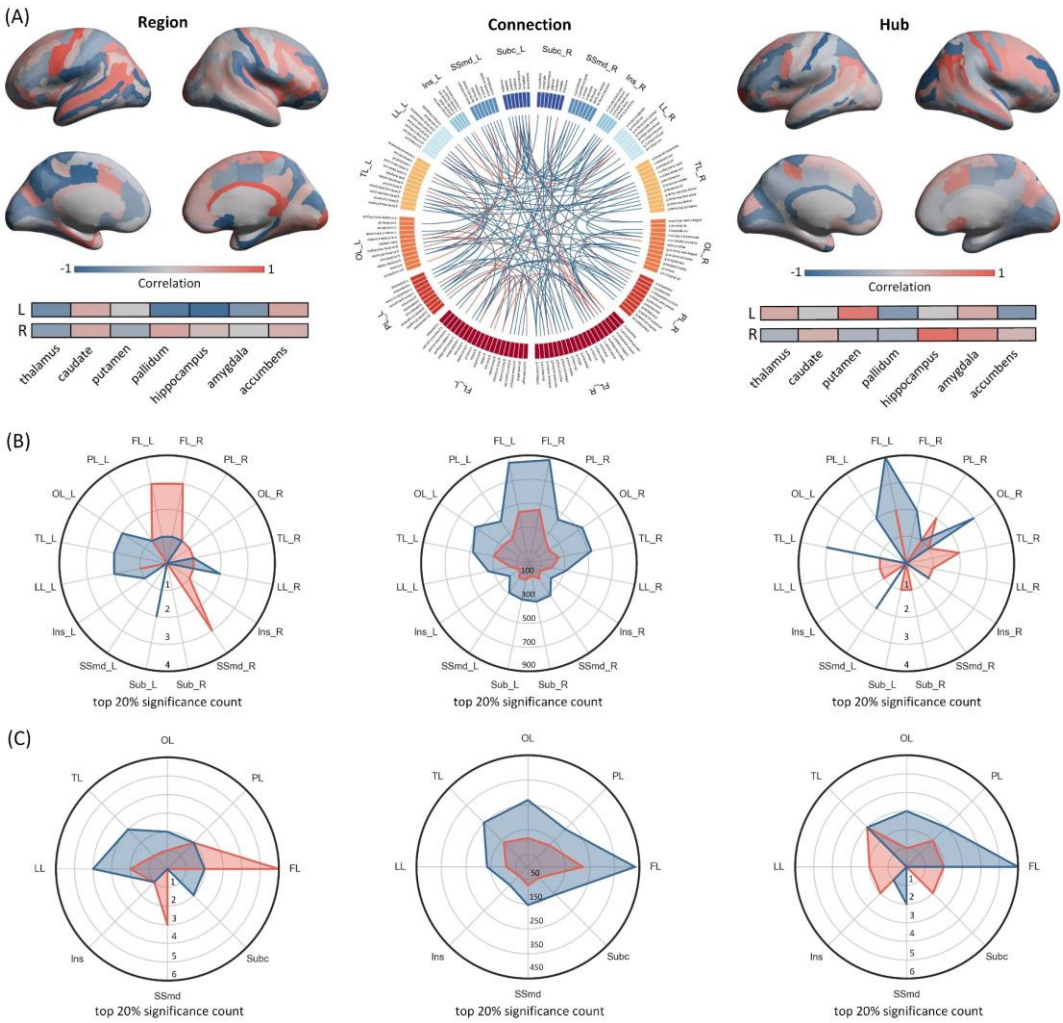

Fig. 5. Changes of importance values of brain regions, connections, and hubs for adolescent cognitive function over 6 years. (A) Changes of importance values of brain regions, connections, and hubs. Red and blue are used to represent increasing and decreasing importance values, respectively. (B) Numbers of top 20% most changed brain regions, connection-end regions, and hubs within 16 lobes (left and right). (C) Numbers of top 20% most changed brain regions, connection-end regions, and hubs within 8 lobes.

Correlation between key brain regions, connections, and hubs for 7 different cognitive performances during adolescence

After identifying key brain regions, connections, and hubs for adolescent cognitive function over 6 years, we aimed to investigate the relationships between the key brain regions, connections, and hubs related to 7 different cognitive performances. Initially, we computed the average results across the 6 years (Fig. 6A) and subsequently calculated correlations between importance values of key brain regions, connections, and hubs across 7 different cognitive performances (Fig. 6B). Consistent with the findings over the 6 years, we present ROI-wise results here, while providing all measure results in the Supplementary Fig. 7. The corresponding correlation values of both ROI-wise results

and whole measure results are presented in Table 3. Our qualitative and quantitative analyses reveal that region-wise results (mean r=0.46, 0.44) and connection-wise results on ROI-wise (mean r=0.61) exhibit similarity across the 7 cognitive performances. This suggests that key brain regions and connection-end regions crucial for different cognitive performances are similar during adolescence. However, the connection-wise results on whole measures (mean r=0.09) and hub-wise results (mean r=0.09, 0.07) demonstrate less similarity between different cognitive performances. Notably, correlations of key brain morphometry results between vocabulary and reading, as well as between visuospatial accuracy and visuospatial efficiency, exceed 0.25 across all measurement aspects. These findings suggest that key brain connections and hubs only exhibit dissimilarity between certain cognitive performances. Furthermore, hierarchical clustering analysis was conducted on the key brain morphometry results of different cognitive performances, incorporating all region-wise, connection-wise, and hub-wise results, as depicted in Fig. 6A. The clustering revealed that vocabulary and reading fall within the same class. Similarly, visuospatial accuracy and visuospatial efficiency episodic are grouped together, although there's a deviation noted in the connection-wise result. Attention, episodic memory, and processing speed also form a cluster, despite an exception observed in the region-wise result. While there are variations in clustering results across different measurement aspects, our findings generally align with previous research.

Table 3. Correlations between key brain morphometry measures for cognitive function of 7 cognitive performances.

Correlation	Region-wise	Connection-wise	Hub-wise
Cognitions (whole)	0.46±0.05	0.09±0.07	0.09±0.09
[Min, Max]	[0.42, 0.59]	[0.04, 0.27]	[0.02, 0.38]
Cognitions (ROI)	0.44±0.05	0.61±0.05	0.07±0.14
[Min, Max]	[0.34, 0.57]	[0.51, 0.70]	[-0.19, 0.40]

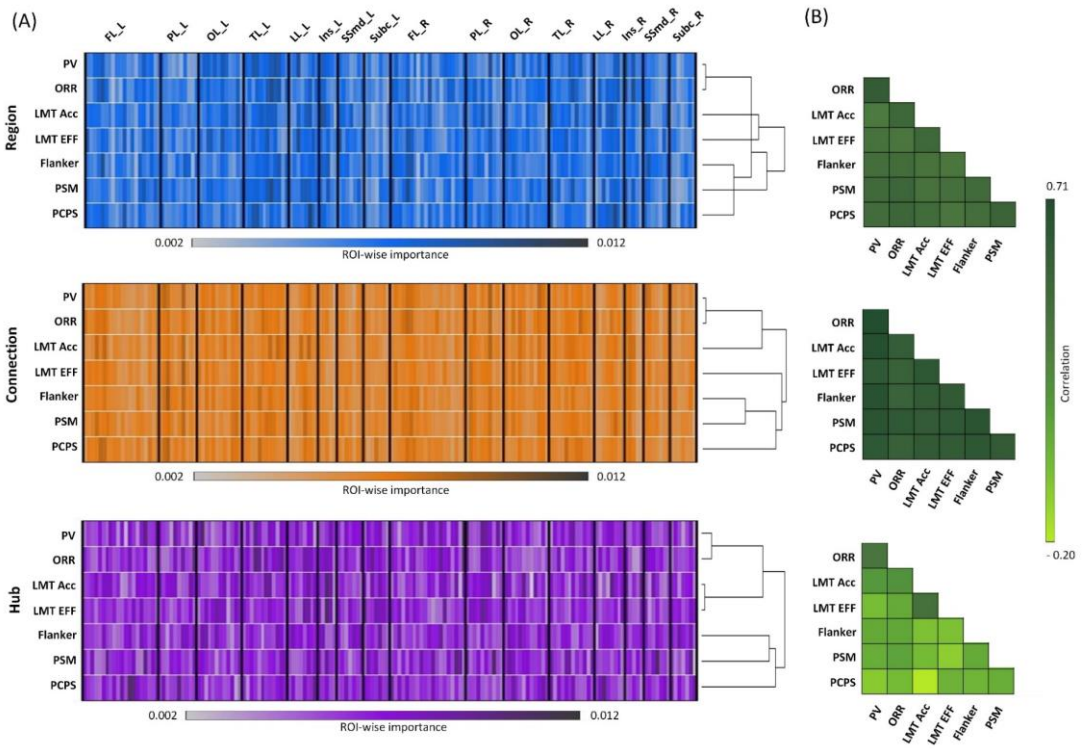

Fig. 6. Results of key brain morphometry measures for adolescent cognitive function over 7 cognitive performances. (A) ROI-wise importance values over 7 cognitive performances. (B) Correlation values of ROI-wise results between cognitive performances.

Key fundamental brain morphometry measures related to 7 cognitive performances over 6 years during adolescence

In the previous sections, we delved into the significance of key brain regions, connections, and hubs across different years and cognitive performances. Now, we shift our focus to examining the importance of 16 fundamental region-wise brain morphometry measures and 6 hub-wise measures related to adolescent cognitive function over 6 years and 7 cognitive performances. As illustrated in Fig. 7A, the results show that SMRI measures exhibit greater importance for cognitive function compared to DTI and RSI measures, although measures such as FA and LD in DTI, and HND in RSI, also display significance. Notably, the mean correlation of these importance values of region-wise brain morphometry measures reaches 0.94 across the 6-year period and 7 cognitive performances, indicating remarkable stability in our findings. Additionally, the importance values of 6 hub-wise measures based on MSNs across 6 years and 7 cognitive performances are shown in Fig. 7B. The results show that measures related to the local attribute of the structural network (clustering coefficient and local efficiency) are less important. And the measures associated with the global attribute (strength, betweenness centrality, within-module degree, participation coefficient) are more important. The mean correlation of these importance values reaches 0.46 across the 6-year period and 7 cognitive performances.

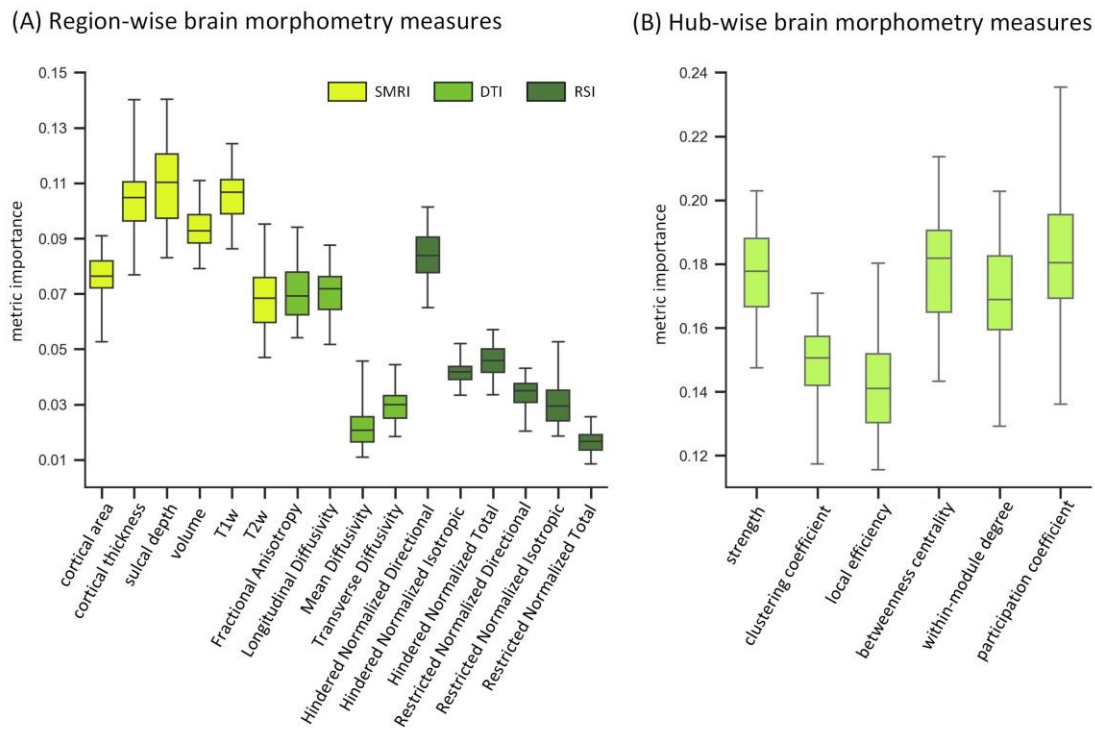

Fig. 7. Key fundamental brain morphometry measures for adolescent cognitive function. (A) Key fundamental region-wise brain morphometry measures. (B) Key fundamental hub-wise brain morphometry measures.

Effectiveness and stability of utilized large-scale computational model

In order to test the effectiveness of our large-scale computational model, we calculated the coefficient of determination (R^2) between cognitive scores and estimated scores based on testing dataset during 10000 bootstraps, as described in Method section. Subsequently, we calculated the average value of these 10000 R^2 values to represent how well our model can capture the association between adolescent brain morphometry and cognitive function. For each of the 6 years and each of the 7 cognitive measures, we obtained a mean R^2 value, as illustrated in Fig. 8A. These values ranged from 0.06 to 0.46, indicating satisfactory performance of our model. Furthermore, we assessed the stability of our large-scale computational model by varying the number of bootstraps used. We focused on the data (processing speed in year 2) where our model exhibited the lowest R^2 values, as estimation models with lower accuracy tend to be more unstable. We conducted iterations with 50, 100, 250, 500, 750, 1000, 2500, and 5000 bootstraps, each repeated 100 times. Subsequently, we calculated the correlations between the association results obtained from these 100 repetitions to represent the stability of our mode (Fig. 8B). The findings show that once the number of bootstraps surpasses 250, the correlations consistently exceed 0.99, indicating strong stability in our model across 10,000 bootstraps.

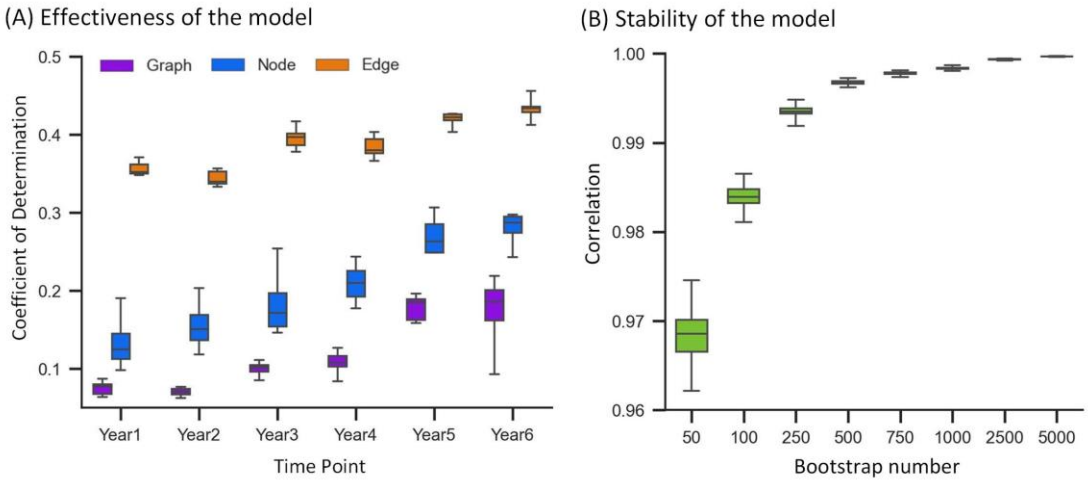

Fig. 8. Validations of the utilized large-scale computational model. (A) The effectiveness of the model. (B) The stability of the model.

Discussion

Based on the large-sample ABCD 5.1 release, we conducted a comprehensive and robust analysis to investigate the association between adolescent brain morphometry and cognitive function. When examining the key brain regions, connections, and hubs linked to cognitive function over a span of six years, we observed promising correlations between brain regions and between connection-end regions across different years. However, the correlations between brain connections and between hubs were found to be low. Notably, brain ROIs that made significant contributions to cognitive function, as well as those exhibiting the most variability in their contributions over time, were primarily located in the frontal and temporal lobes. In our examination of the key brain regions, connections, and hubs relevant to seven distinct cognitive performances, we discovered that the correlation results are similar to those observed over the years across various measurement aspects. Additionally, we found that key brain morphometry measures associated with cognitive

performances within the same domain tended to display higher correlations. Furthermore, we noted that SMRI measures played a much more crucial role in cognitive function compared to DTI and RSI measures. Moreover, hub-wise measures assessing overall structural network attributes were deemed more significant than those measuring local network attributes.

Correlation between key brain regions, connections, and hubs for cognitive function of 6 different years during adolescence

When exploring the key brain nodes, connections, and hubs relevant to adolescent cognitive function from 9 to 15 years old, we derived the importance of brain morphometry measures from three measurement aspects: region, connection, and hub. Subsequently, we computed the correlations between key brain regions, connections, and hubs of 6 years. Two intriguing findings emerged from our analysis. Firstly, we observed significant differences among the results derived from the three measurement aspects. While the correlations between brain region importance remained consistently stable over 6 years ($r > 0.35$), the results for connections exhibited notable variability ($r < 0.05$). Given the considerable changes in structural connections during adolescence, it is unsurprising that the outcomes of graph hubs exhibit substantial variability. Then we computed the cumulative values of connection importance for each connection-end region as their significance related to cognitive function. The intriguing finding is the remarkable stability of connection-end region importances ($r > 0.4$). These findings highlight the remarkable stability of key brain regions and connection-end regions. Enhanced cognitive function may indeed be facilitated by improved communications between specific brain regions (Jung and Haier, 2007). Furthermore, the results suggest that the key connections and hubs undergo continual changes during adolescence, potentially reflecting ongoing optimization of brain organization for heightened effectiveness (Dennis et al., 2013; Koenis et al., 2015; Richmond et al., 2016). Secondly, several intriguing trends emerge from the correlation analysis of three measurement aspects over a six-year period. Regarding region-wise results based on ROI-wise measurements, correlations between ages 9-12 and 13-15 are higher than those between ages 11-14. For whole measure results, correlations between ages 9-11 and 12-15 are higher than those between ages 10-13. These results suggest more significant brain regional changes related to cognitive function between ages 11-13. In terms of connection-wise results, the correlations between adjacent years show a consistent annual decrease during adolescence, as observed from ROI-wise analyses. This trend suggests that connection-end regions of key brain structural connections undergo increasing changes from ages 9 to 15. In the hub-wise results based on ROI-wise measurements, correlations between ages 9-14 are notably low. However, a notable increase in correlation is observed between year 5 (13-14 years old) and year 6 (14-15 years old), reaching 0.11. This suggests significant changes in key hubs from ages 9 to 14, with stabilization beginning from ages 13 to 15. Connection-wise results and hub-wise results on whole measures were not discussed, as no correlation value exceeded 0.1. Generally, key brain regions undergo more pronounced changes during ages 11-13, while key hubs exhibit substantial variability from ages 9 to 13. Both tend to become more stable during ages 13-15. These results may be attributed to puberty, such as the influence of testosterone (Nguyen et al., 2013a, 2013b). Additionally, the connection-end regions of key brain connections show increasing changes throughout ages 9-15 (Dennis et al., 2013; Koenis et al., 2015; Richmond et al., 2016).

Key common brain regions, connections, and hubs for cognitive function over 6 years during

adolescence

We computed the common key brain regions, connections, and hubs for adolescent cognitive function over 6 years. In the region-wise analysis, we observed that the frontal lobe, temporal lobe, limbic lobe, and insular cortex contain the most critical brain regions associated with adolescent cognitive function. The frontal lobe is linked with advanced cognitive abilities (Larsen and Luna, 2018), the temporal lobe with language comprehension (Ralph et al., 2016), and the limbic lobe and insular cortex with emotion processing and regulation (Catani et al., 2013; Gu et al., 2013). These cognitive functions undergo rapid development during adolescence (Larsen and Luna, 2018; Paus, 2005). Our connection-wise analysis revealed that the structural connections between the frontal lobe, parietal lobe, occipital lobe, and temporal lobe are of utmost importance. This finding aligns with the P-FIT theory, suggesting that enhanced communication between these brain lobes leads to improved cognitive function (Jung and Haier, 2007). In the hub-wise results, the frontal lobe and insular cortex emerge as the most important hubs in MSNs. This suggests that during adolescence, the frontal lobe and insular cortex act as graph hubs, contributing to the development of cognitive control and emotional regulation separately (Friedman and Robbins, 2022; Gu et al., 2013). Although the subcortex did not show significant results across the three measurement aspects, the right amygdala emerged as an important graph hub in the hub-wise analysis (Šimić et al., 2021). This finding may also be related to the rapid improvement of individuals in handling emotions and adapting to social environments during adolescence (Larsen and Luna, 2018; Paus, 2005; Šimić et al., 2021). Furthermore, we observed that the mean correlation between key common regions, connection-end regions, and hubs reached 0.28, indicating that certain brain lobes such as the frontal and temporal lobes play an important role in adolescent cognitive function across all three measurement aspects (Jung and Haier, 2007; Paus, 2005). Overall, while there are differences between the results of the three measurement aspects, brain ROIs associated with cognitive control, emotional regulation, and those playing significant roles in the P-FIT theory demonstrate the greatest importance in relation to adolescent cognitive function.

Changes of importance of brain regions, connections, and hubs for adolescent cognitive function over 6 years

We studied the changes of importance values of brain morphometry measures related to adolescent cognitive function over 6 years and counted the numbers of most changed brain regions, connections, and hubs across different lobes. In our region-wise analysis, we observed that the count of regions with significantly increased importance in the frontal lobe far exceeded those with decreased importance. Conversely, the limbic lobe exhibited a greater number of regions with decreased importance compared to those with increased importance. However, in our hub-wise analysis, the results for both lobes exhibited an intriguing inversion. This suggests a potential specialization within the frontal regions towards the development of local information processing capabilities (Dennis et al., 2013; Romine and Reynolds, 2005), while the limbic lobe assumes a pivotal role as graph hubs, emphasizing communication within the brain network (Khundrakpam et al., 2013). The connection-wise findings are particularly intriguing. Across all lobes, we observed a consistent trend where the number of connection-end regions experiencing decreased importance exceeded those with increased importance. This suggests a potential pruning process in brain structural connections, leading to enhanced efficiency (Dennis et al., 2013; Koenis et al., 2015; Richmond et al., 2016; Wenger et al., 2017). Furthermore, our analysis indicates that the frontal and temporal lobes undergo

the most significant changes during the ages of 9 to 15, consisting with previous studies (Dumontheil et al., 2010; Hu et al., 2013; Whitford et al., 2007). The parietal lobe did not emerge as particularly significant in our study. This may be attributed to the observation that the plasticity of primary sensory areas is highest during childhood rather than adolescence (Keshavan and Eack, 2019). Hence, it is conceivable that the parietal lobe, which is most closely related to primary sensory processing, does not play as pivotal a role during adolescence. Furthermore, we observed asymmetrical changes in the importance of brain regions, connections, connection-end regions, and hubs related to adolescent cognitive function between the brain's left and right hemispheres. This contrasts with previous findings indicating symmetry in key common brain regions (r=0.75) and connection-end regions (r=0.78) during adolescence. It suggests that while important brain regions and connection-end regions may exhibit symmetry, the connections and hubs, along with changes in all brain morphometry measures, display asymmetry. This underscores the nuanced differences in the roles played by the left and right hemispheres in adolescent cognitive function, particularly in the realm of structural connections and structural network attributes (Duboc et al., 2015; Yamazaki et al., 2018; Zhong et al., 2017).

Correlation between key brain regions, connections, and hubs for 7 different cognitive performances during adolescence

In addition to examining the correlations between key brain morphometry measures related to cognitive function over a six-year period, we also investigated the correlations between key brain morphometry measures for seven different cognitive performances during adolescence. Our region-wise analysis revealed striking similarities among the key brain regions associated with these seven cognitive performances. Similarly, in our connection-wise analysis on ROI-wise, we found a high correlation among all key connection-end regions across different cognitive performances. These findings suggest that the shared variance among different cognitive performances is closely linked to specific key brain regions and connection-end regions (Chen et al., 2022; Yan et al., 2022). However, in the connection-wise analysis of whole measures, only four correlation values exceed 0.1. These correlations are observed between vocabulary and reading, reading and visuospatial accuracy, visuospatial accuracy and visuospatial efficiency, as well as attention and processing speed. This suggests that only these four pairs of cognitive functions share variance in structural connections based on MSNs. Regarding hub-wise results, six pairs of cognitive functions exhibit correlations higher than 0.1 in both ROI-wise and whole measures analyses. Among these, three pairs are common to the connection-wise results (vocabulary and reading, reading and visuospatial accuracy, and visuospatial accuracy and visuospatial efficiency). The remaining six pairs include correlations between reading and episodic memory, reading and attention, vocabulary and visuospatial accuracy, vocabulary and episodic memory, processing speed and visuospatial efficiency, as well as processing speed and attention. Within these pairs, it is intriguing to note that three pairs (reading and attention, reading and episodic memory, as well as vocabulary and episodic memory) exhibit promising correlations across different cognitive domains (Casaletto et al., 2015; Harvey, 2019; Luciana et al., 2018). This suggests that even cognitive functions from disparate domains can share variance in hubs (Yan et al., 2021; Zhang et al., 2021). Another noteworthy finding is the negative correlation (-0.19) between processing speed and visuospatial accuracy in hub-wise results on ROI-wise. This suggests that hubs associated with higher processing speed could potentially lead individuals to make mistakes when dealing with visuospatial tasks (Luciana

et al., 2018). In summary, despite variations in the shared variance of different cognitive performances across brain regions, connections, connection-end regions, and hubs, cognitive performances within the same domain exhibit similar results across all three measurement aspects. This consistency aligns with findings from previous studies and serves to validate the robustness and reliability of our analysis.

Key fundamental brain morphometry measures related to cognitive function during adolescence

We investigated key fundamental brain morphometry measures associated with 7 cognitive performances over 6 years. Among the 16 region-wise brain morphometry measures examined, our results indicate that cortical thickness, sulcal depth, and T1w density emerge as the most influential measures linked to cognitive function. While the significance of cortical thickness and sulcal depth is expected (Burgaleta et al., 2014; De Chastelaine et al., 2023; Genon et al., 2022; Gregory et al., 2016; Karama et al., 2011; Tadayon et al., 2020), the significance of T1w density may stem from its indirect provision of information regarding the structural aspects of neurons, glial cells, and synaptic connections in the brain gray matter, which are crucial for cognitive processes (Franke et al., 2012; Laule et al., 2006; Lewis et al., 2018; Rooney et al., 2007). We also observed that the significance of SMRI measures is notably higher than that of DTI measures and RSI measures. This could be attributed to the notion that the shapes of brain regional gray matter contain more information relevant to computational abilities compared to some regional microstructure features during adolescence (Tadayon et al., 2020; Wang et al., 2009). Nonetheless, two important DTI measures (FA, LD) and one important RSI measure (HND) remain noteworthy. Higher FA values typically indicate more organized and intact neural fiber structures, while reduced LD values may suggest damage or degeneration within neural fiber bundles, potentially affecting cognitive function (Colom et al., 2010). Regarding HND, it primarily reflects the restricted diffusion of water molecules along the direction of neural fiber bundles, providing insights into their directional orientation and microstructural integrity (White et al., 2014, 2013). Thus, for microstructural measures like DTI and RSI, measures measuring fiber bundle directionality and microstructural integrity are deemed more important for cognitive function. We also assessed the significance of 6 hub-wise measures. Measures related to graphical local attributes, such as clustering coefficient and local efficiency, were found to be less influential (Rubinov and Sporns, 2010). Conversely, measures tied to overall brain attributes, like overall connection strength (strength) and shortest paths (betweenness centrality), held greater importance. Moreover, measures related to modularity (Cohen and D'Esposito, 2016; Hilger et al., 2017), such as within-module degree and participation coefficient, were also deemed more significant than local measures. Hence, this finding supports the notion that cognitive function arises from complex network interactions and communication, rather than being solely reliant on local brain regions (Bullmore and Sporns, 2012, 2009).

Assessing adolescent cognitive estimation with a large-scale computational model over 6 years

We computed the R^2 between cognitive scores and estimated values derived from the testing dataset across 10,000 bootstraps over 7 cognitive performances and 6 years. Our findings reveal a strengthening association between brain morphometry and cognitive function throughout adolescent development. This trend persists when considering cognitive estimation with brain regions, connections, and hubs individually. This may be attributed to brain optimization during adolescent

development for effective cognitive processes, such as synaptic pruning, leading to a more efficient and organized brain structure and higher cognitive function (Dennis et al., 2013; Koenis et al., 2015; Richmond et al., 2016; Wenger et al., 2017). Compared to the more complex and chaotic brain structure observed during childhood, the developed brain exhibits more clearly delineated brain regions, connections, and hubs. These refined brain morphometry features are more strongly associated with cognitive function. Another finding is that the association based on connections is stronger than that based on regions, while the association based on the hubs is the weakest. This could be attributed to technical reasons, as our accuracy results based on bootstrap may be influenced by the number of measures used.

Limitations

Although we included adolescent subjects aged 6 to 15 years based on ABCD release 5.1, we did not cover the entire adolescent stage. We observed significant changes in the association between brain morphometry and cognitive function between the ages of 11 and 13. Whether these associations remain stable or become unstable after 15 years old is still unknown. Therefore, with the release of new ABCD data updates, we plan to investigate these associations further to uncover new findings. Furthermore, our current results are solely based on the Destrieux atlas. In our future work, we aim to enhance the robustness and reliability of our findings by incorporating additional atlases, such as the 68-region DK atlas and the 318-region DK atlas (Desikan et al., 2006).

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