Association between Brain Morphometry and Cognitive Function during Adolescence: Insights from a Comprehensive Large-Scale Analysis 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 and did not consider the complementarity among different measures. 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 6 groups with one-year intervals based on their ages for independent age-specific analysis. Moreover, we calculated 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 calculate 16,563 morphometry measures encompassing brain region, connection, and hub aspects. Subsequently, these measures were input into a robust large-scale computational model to control for each other and investigate their relationship with 8 cognitive performances. We found that the brain areas most significantly associated with cognitive function during adolescence, as well as those showing the greatest variability in their associations between ages 9 and 15, were primarily situated in the frontal and temporal lobes. In contrast, the subcortex was the least involved. Additionally, we observed strong correlations between key brain morphometry measures related to cognitive performances within same domain. Furthermore, we found that SMRI measures demonstrated stronger associations with cognitive performances compared to DTI and RSI measures. And overall structural network measures were more important than local ones. Overall, our study aims to facilitate a comprehensive and reliable understanding of the association between

brain morphometry and cognitive function during adolescence.

Keywords: adolescence, brain cortical and subcortical morphometry, 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 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 associates with 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 associations with cognitive function (Stammen et al., 2023; Tamnes et al., 2011). Moreover, 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 found 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 brain hubs containing information about 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). And 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). The degree of MSN hubs has also been found to be highly correlated with both verbal and non-verbal cognitive performances (Seidlitz et al., 2018).

Overall, previous research has explored the association between various brain morphometry and cognitive function. However, no study has simultaneously combined all these brain morphometry measures to offer a potentially more exhaustive representation of brain structure and studied its relationship to cognitive function differences during adolescence. Since different brain morphometry measures complement each other to achieve the structural foundation of the cognitive function and previous studies utilized inconsistent data samples as well as analysis methods leading to varying scales of statistical effects, adopting comprehensive brain morphometry measures in one

study to study their relationships to cognitive function differences during adolescence can help obtain more accurate results and enhance comparability between different measures.

Additionally, sample size represents another limitation of previous studies. Many studies have sample sizes of fewer than 500 subjects. Although 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), 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 obtained through strict quality control can help mitigate sampling error, low statistical power, and even overestimation of effects that may arise in small samples. Furthermore, 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). And a large sample size can establish the foundation for independent age-specific analysis to obtain more detailed results.

To address the above limitations, we conducted a comprehensive analysis utilizing data from the ABCD 5.1 release dataset to explore the association between adolescent brain morphometry and cognitive function during adolescence. The ABCD dataset encompasses multimodal brain imaging data, including SMRI, DTI, and RSI (Casey et al., 2018). Leveraging these modalities, we calculated 16 region-wise brain morphometry measures aiming to represent a comprehensive map of region-wise 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 calculated 6 common graphical measures to capture the hub-wise characteristics 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 brain morphometry and cognitive function during adolescence. Moreover, we developed a robust large-scale computational model based on previous work (Spreng et al., 2020) to make inputted brain morphometry measures control for each other and obtain comparable results among different measures.

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 6 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. And we performed the robust large-scale computational model combined with 1000 bootstraps on these large sample and obtained 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 study how the associations change during development. Secondly, we investigated the correlations between these key regions, between connections, and between hubs related to various cognitive performances during adolescence. Lastly, we analyzed the key fundamental brain morphometry measures relevant to adolescent cognitive performances. Our overarching goal is to facilitate a comprehensive and reliable understanding of the association between brain morphometry and cognitive function during adolescence.

Methods:

Participants

The full ABCD 5.1 release cohort includes 27595 scans of 11868 subjects across 22 sites (Casey et al., 2018). The subject selection and exclusion process is shown in Fig. 1A. We first selected brain images that passed quality control. Corresponding details can be found in Hagler et al. (2019). Subsequently, subjects defined as clinically abnormal were excluded. Then, only subjects with both adequate cognitive scores and 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 6 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).

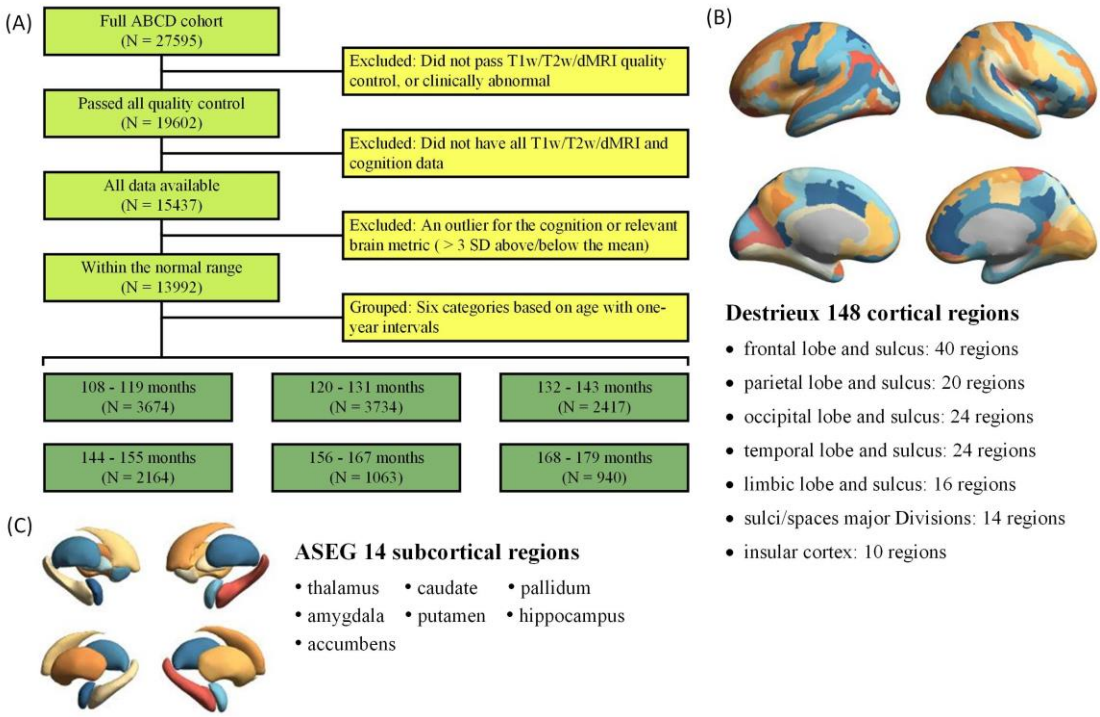

Fig. 1. Overview of data preprocessing. (A) Subject selection and exclusion. (B) 148 cortical regions based on Destrieux atlas. (C) 14 subcortical regions based on ASEG atlas.

Imaging acquisition and processing

We employed three types of structural imaging data, comprising T1w, T2w, and dMRI data, preprocessed by the ABCD group (Hagler et al., 2019). 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. 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 (CA), cortical thickness (CT), sulci depth (SD), volume (VOL), T1w density (T1w), and T2w density (T2w). 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 aspects: region, connection, and hub (Fig. 2). 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 measures, encompassing SMRI, DTI, and RSI measures.

We then used MSNs to calculate 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 and we also didn't utilize the volume because of its inconsistency in cortical and subcortical regions, connections related to subcortical regions used only 12 measures. Calculating such individual MSNs yielded a total of 13041 connection-wise measures. More details can be found in Supplementary Materials S1.

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, and participation coefficient. All graphical measures were calculated at multiple connection densities (10% - 40% in 5% increments) of MSNs, like the previous study (Seidlitz et al., 2018). Since results obtained at different connection densities had promising correlations and 35% shown the best performance on the simple correlation analysis (Supplementary Materials S2), we only shown the results at 35% connection densities in the main text. More details were described in Supplementary Materials S2. In a word, we calculated 972 measures based on MSNs that capture hub-wise characteristics.

In total, we extracted 16,563 whole-brain morphometry measures encompassing three distinct aspects: region, connection, and hub. Although the terms region, connection, and hub can be confused in certain definitions, our study defines them specifically: "region" refers to regional

morphometry, "connection" refers to structural connection strength of individual MSNs, and "hub" refers to graphical properties of ROIs based on MSNs. All these measures were adjusted for sex, age, site, 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. We also eliminated family-related confounding effects, as detailed in the section titled "Large-Scale Computational Model".

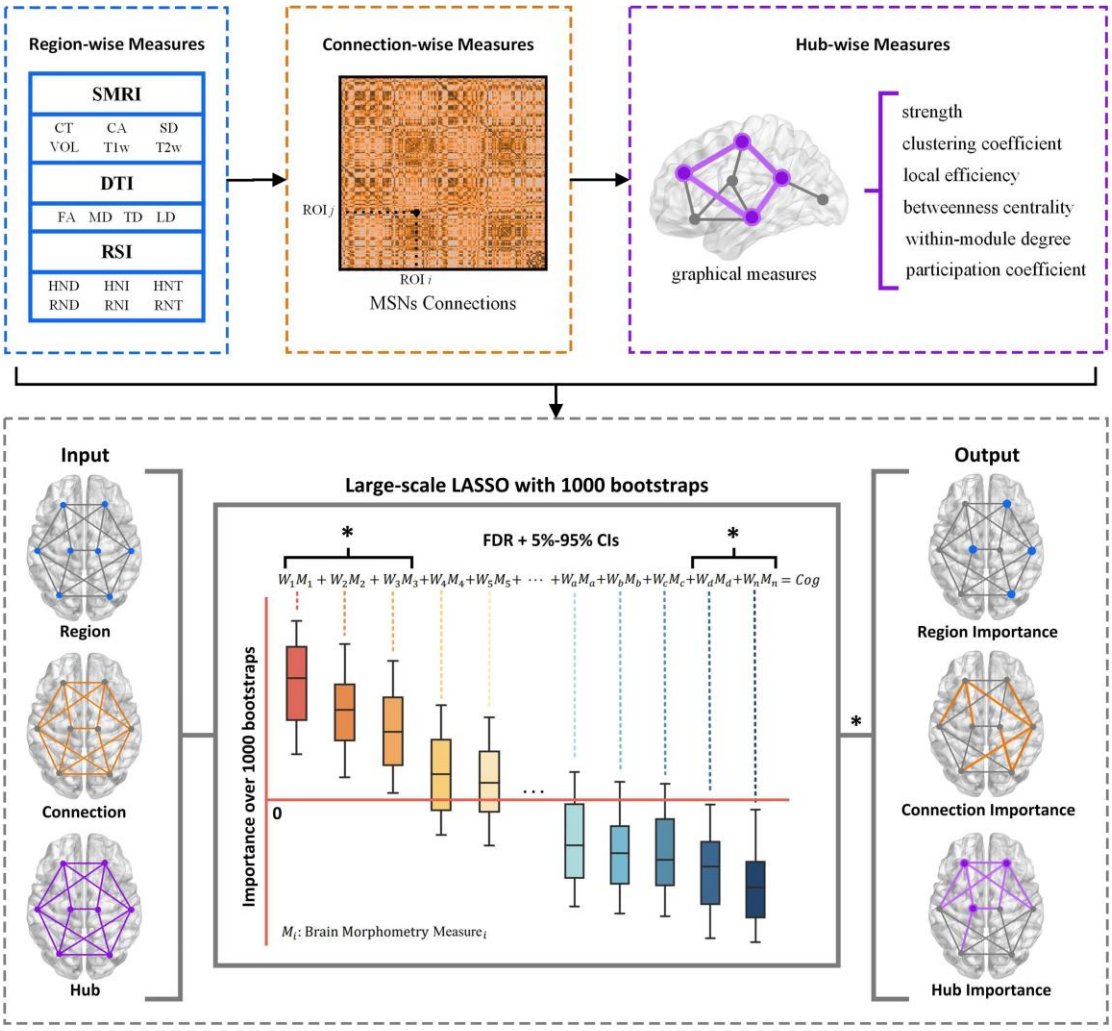

Fig. 2. Overall flowchart of the association analysis. Region-wise, connection-wise, and hub-wise brain morphometry measures are inputted into a large-scale computational model to obtain the association results, respectively.

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
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 performances available within the ABCD dataset (Luciana et al., 2018). These performances included vocabulary (PV), attention (Flanker), reading (ORR), processing speed (PCPS), episodic memory (PSM), visuospatial accuracy (LMT Acc), and visuospatial efficiency (LMT EFF). Among these performances, vocabulary and reading are traditional measures for assessing crystallized cognitive performances (Casaletto et al., 2015). Attention, processing speed, and episodic memory are conventional measures for evaluating fluid cognitive performances (Casaletto et al., 2015). Visuospatial accuracy and visuospatial efficiency are standard measures for measuring visuospatial performances (Nixon et al., 2014). Based on these 7 individual cognitive performances, we calculated the general cognitive score (g), also known as g-factor, to measure the individual general cognitive performance (Barbey, 2018; Colom et al., 2010). Specifically, we utilized Principal Component Analysis (PCA) on these 7 cognitive performances, and then derived the first component as the general cognitive performance. In total, we utilized 8 cognitive performances to measure individual cognitive function. Note that although the ABCD dataset includes a total of 12 cognitive performances, we utilized only 7 due to missing data. To ensure the representativeness of our cognitive performance selection, we calculated the correlation between different sets of cognitive performances and found high correlation ($r > 0.88$) in baseline data (details in Supplementary Materials S3). This analysis validates our cognitive performance selection as reasonable and capable of representing conventional cognitive performances. All cognitive performances used in our analysis were adjusted for sex, age, site, and PBV.

Large-scale computational model

A large-scale computational model (large-scale randomly optimized LASSO method) combined with 1000 family-specific bootstraps (Fig. 2) was used to investigate the association between 16,563 brain morphometry measures and 8 cognitive performances during adolescence. This computational model was 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 large-scale regression model instead of independent Pearson correlations, allowing the brain morphometry measures to control for each other and providing a more integrated analysis. And we also introduced randomly optimized mechanism and 1000 family-specific bootstraps. These techniques are described in the further part in this section.

Since there are 3 different brain morphometry aspects (region, connection, and hub), 6 years, and 8 different cognitive performances, we constructed 144 distinct models to investigate the association between brain morphometry and cognitive function. Taking region-wise brain morphometry and general cognitive performance as an example, we inputted 2550 regional brain morphometry measures into the model to estimate the general cognitive performance. Following 1000 bootstraps, we generated 1000 parameters for each region-wise morphometry measure to assess its significance in relation to the general cognitive performance. Only measures that passed Bonferroni false discovery rate (FDR) correction (mean value compared to 0 across all region-wise measures) and exhibited statistically significant 5-95% bootstrap confidence intervals (values are non-positive or

non-negative) were considered significant. Then the average value of the 1000 parameters of a significant measure was regarded as the importance of that measure contributing to the general cognitive performance. The importance of other measures was set to 0. Subsequently, these 2550 importance values were normalized to ensure their sum equaled 1. Therefore, by utilizing this large-scale model, we were able to obtain the importance values of all 16,563 brain morphometry measures related to all 8 cognitive performances during adolescence.

As mentioned before, we developed this large-scale computational model by combining some techniques to better suit our situation. Firstly, given the large number of the inputted brain morphometry measures, we used a LASSO method. It can effectively sift out truly useful measures 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 parameter computation of morphometry measures across 1000 bootstraps, further mitigating collinearity effects and increasing the robustness of the model. Thirdly, we also introduced family-specific bootstrap to eliminate family-related confounding effects, ensuring that no different subjects from the same family were included in any single bootstrap. Fourthly, we expanded the number of bootstraps to 1000. Calculating 1000 sets of parameters based on 1000 bootstraps and then performing strict significant feature selection can help ensure reliable results based on a large-scale sample. Moreover, we also calculated the coefficient of determination (R^2) between the estimated cognitive scores and the real scores. Although these R^2 results cannot be technically considered as the validation of estimation performance, they can still be used to validate the effectiveness of our large-scale computational model.

Results:

Utilizing a large ABCD sample with comprehensive brain morphometry measures, we employed a robust large-scale computational model to investigate the association between adolescent brain morphometry and cognitive function across 6 years and 8 cognitive performances, examining region, connection, and hub aspects. Firstly, we averaged the association results across the 8 cognitive performances to explore the key brain regions, connections, and hubs related to adolescent cognitive function over the 6-year period, as well as the changes in brain regions, connections, and hubs importance during this period. Secondly, we averaged the association results across the 6-year period and then investigate the relationships between key brain regions, between connections, and between hubs related to 8 different cognitive performances. 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 8 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 8 cognitive performances, we initially calculated the average results across the 8 cognitive performances and then calculated the correlations between importance values of key brain regions, connections, and hubs respectively across different years (Fig. 3). Given the considerable number of brain morphometry measures (in total 16563) and limited space, we calculated the sum

importance values of all measures for each brain ROI to derive ROI-wise results in Fig. 3A (details in Supplementary Materials S4). The results with whole measures are shown in Supplementary Fig. 3. And the ROIs are categorized into 8 lobes on both the left and right hemispheres (Zhao et al., 2022). We also calculated the correlation values of ROI-wise results (Fig. 3A) and whole measure results (Fig. 3B) between adjacent years. And the average correlation results between different years are presented in Table 2.

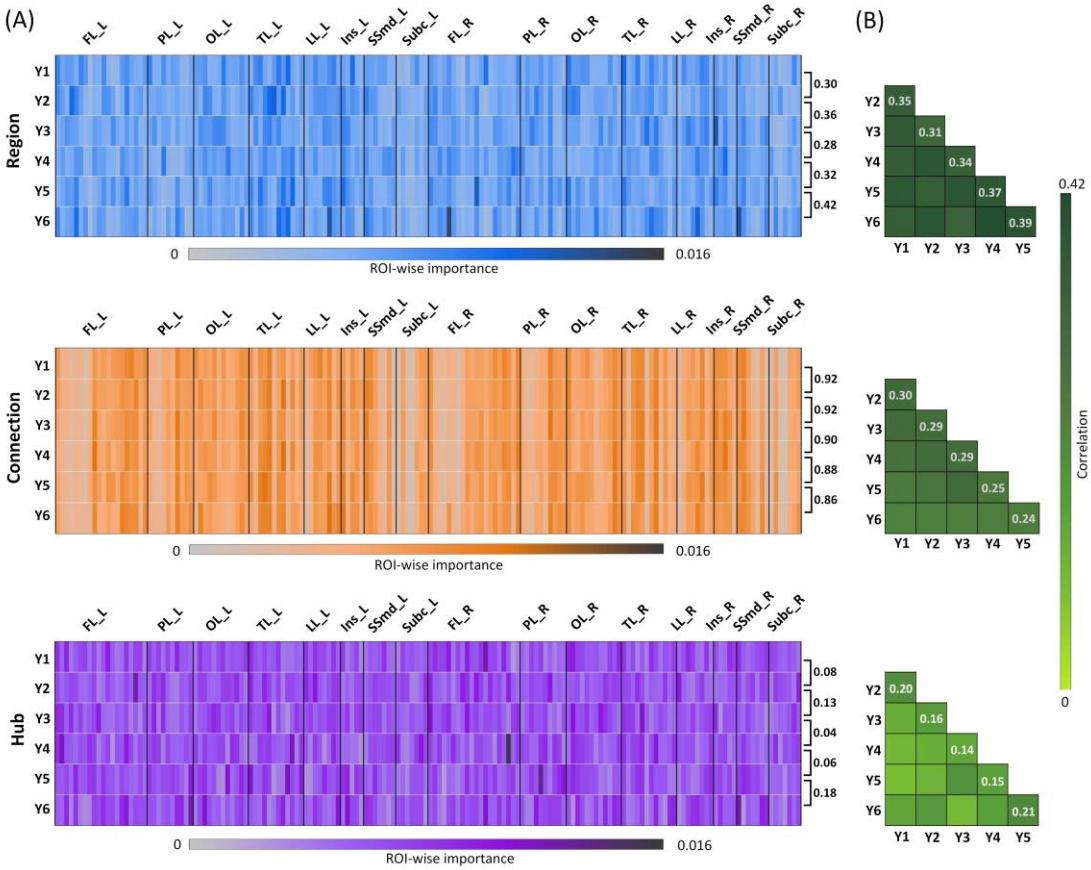

Fig. 3. Results of key brain morphometry measures for adolescent cognitive function over 6 years. (A) ROI-wise importance values of brain morphometry measures to adolescent cognitive function over 6 years and correlation values of ROI-wise results between adjacent years. The brain ROIs are categorized 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 corresponding list is in Supplementary Table 3. (B) Correlation values of whole measure results between adjacent years.

Table 2. Correlations between importance values of key brain morphometry measures related to adolescent cognitive function of 6 years.

Correlation	Region-wise	Connection-wise	Hub-wise
Years (whole)	0.36±0.03	0.27±0.03	0.14±0.04
[Min, Max]	[0.31, 0.41]	[0.23, 0.30]	[0.09, 0.21]
Years (ROI)	0.32±0.06	0.88±0.03	0.06±0.07
[Min, Max]	[0.24, 0.42]	[0.80, 0.92]	[-0.13, 0.18]

As we can see from the results in Fig. 3 and Table 2, region-wise results (mean r = 0.36) and connection-wise results (mean r = 0.27) both achieve relative similarities across 6 years, which indicates that key brain regions and connections crucial for cognitive function remain relatively constant during this developmental phase. And the ROI-wise results show that the connection-end ROIs of the key connections are very stable (mean r = 0.88) while overall importance of each brain hubs are not (mean r = 0.06, inconsistent with whole measure results where mean r = 0.14). Moreover, the results of correlations of brain morphometry measure importance between adjacent years show that the correlations reduce first and then increase in brain regions and hubs, while the correlations keep decreasing in brain connections.

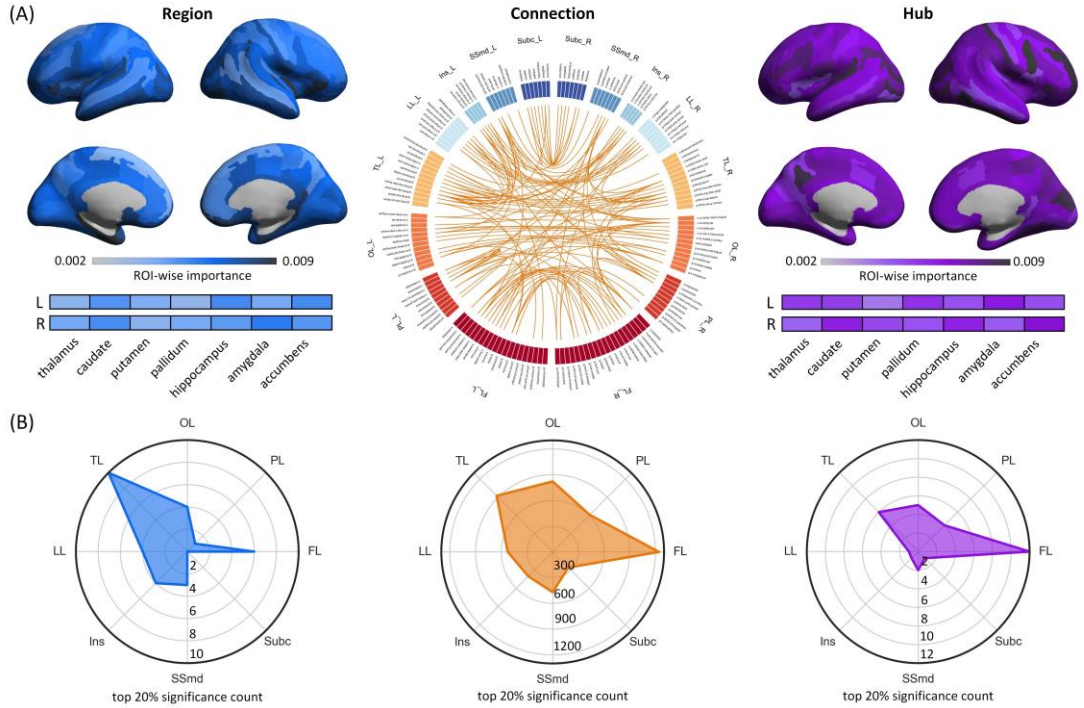

Fig. 4. Common key brain regions, connections, and hubs for adolescent cognitive function over 6 years. (A) Common key brain regions, connections, and hubs over 6 years (connections on a top 1% selection). The list of 162 ROIs is in Supplementary Table 3. (B) Numbers of top 20% most important common key brain regions, connections, and hubs within each lobe.

Subsequently, we identified common findings regarding key brain region-wise, connection-wise, and hub-wise morphometry measures over the 6-year period and calculated their average importance values across 6 years in Fig. 4. For region-wise and hub-wise results, we calculated the sum importance values of all measures on each brain ROI to obtain the ROI-wise importance of key brain regions and hubs to adolescent cognitive function. The whole measure results are in Supplementary Fig. 4. And 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. 5). To ensure fair comparisons among different lobes, considering variations in the number of ROIs across lobes, we need to select top p% of key brain regions, connections, and hubs. We tried p% from 1% to 30% in Supplementary

Materials S5 and chose 20% due to its representativeness. Subsequently, we calculated the numbers within each lobe at top 20% in Fig. 4B (other top p% results are in Supplementary Fig. 6). The results highlight the frontal and temporal lobes as the most pivotal brain lobes for cognitive function across region, connection, and hub aspects. Conversely, subcortex demonstrate relatively lower importance. Note that while calculating the importance values of key brain regions, cortical regions have 16 region-wise morphometry measures and subcortical regions have 13. Therefore, as shown in Supplementary Materials S6, we calculated the average importance values of morphometry measures available in cortical and subcortical regions respectively and recalculated the results. And the above conclusions remain consistent.

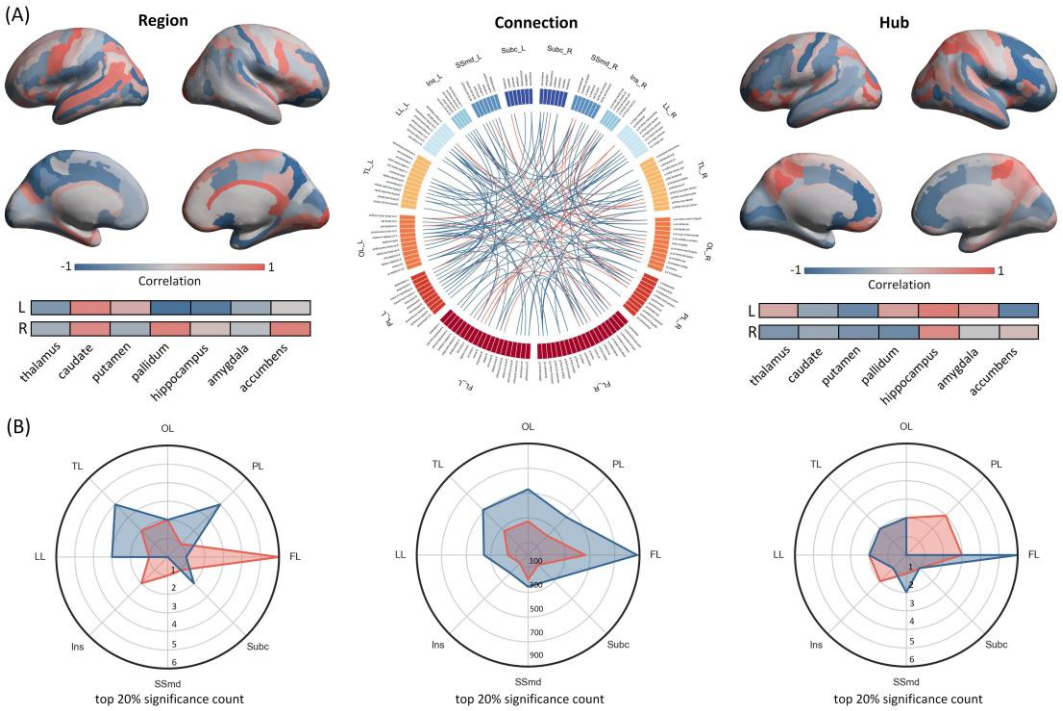

Fig. 5. Changes of importance values of brain regions, connections, and hubs for adolescent cognitive function over 6 years. (A) Changes of importance values of brain regions, connections, and hubs over 6 years. Red and blue are used to represent increasing and decreasing importance, respectively. The list of 162 ROIs is in Supplementary Table 3. (B) Numbers of top 20% most changed brain regions, connections, and hubs within 8 lobes over 6 years.

Furthermore, we delved into the dynamics of brain regions, connections, and hubs importance values for cognitive function over the 6-year period. In order to calculate the change results, we first calculated the sum importance values of region-wise measures and hub-wise measures for each region and hub, respectively. Then we calculated correlations between the year indices and their corresponding importance values of regions, connections, and hubs to measure the changes. The change results are shown in Fig. 5A, and more detailed results of brain connections are shown in Supplementary Fig. 7. Subsequently, we identified the top 20% most positively and negatively age-correlated brain regions, connections, and hubs, and then conducted a lobe-wise count (other top p% results are in Supplementary Fig. 8). Note that we initially converted all correlations into absolute values and then selected the top 20%. Top 20% is chosen due to its representativeness

(Supplementary Materials S5). We observed an equal 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, temporal, and occipital lobes, while the changes in subcortex and insular are relatively minimal. This finding is mostly consistent with previous common results.

Correlation between key brain regions, between connections, and between hubs related to 8 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, between connections, and between hubs related to 8 different cognitive performances. Initially, we calculated the average results across the 6 years (Fig. 6A) and subsequently calculated correlations between importance values of key brain regions, connections, and hubs respectively across 8 different cognitive performances (Fig. 6B). Consistent with the findings over the 6 years, we present ROI-wise results in Fig. 6A, while providing whole measure results in the Supplementary Fig. 9. The corresponding correlation values of both ROI-wise results and whole measure results are presented in Table 3.

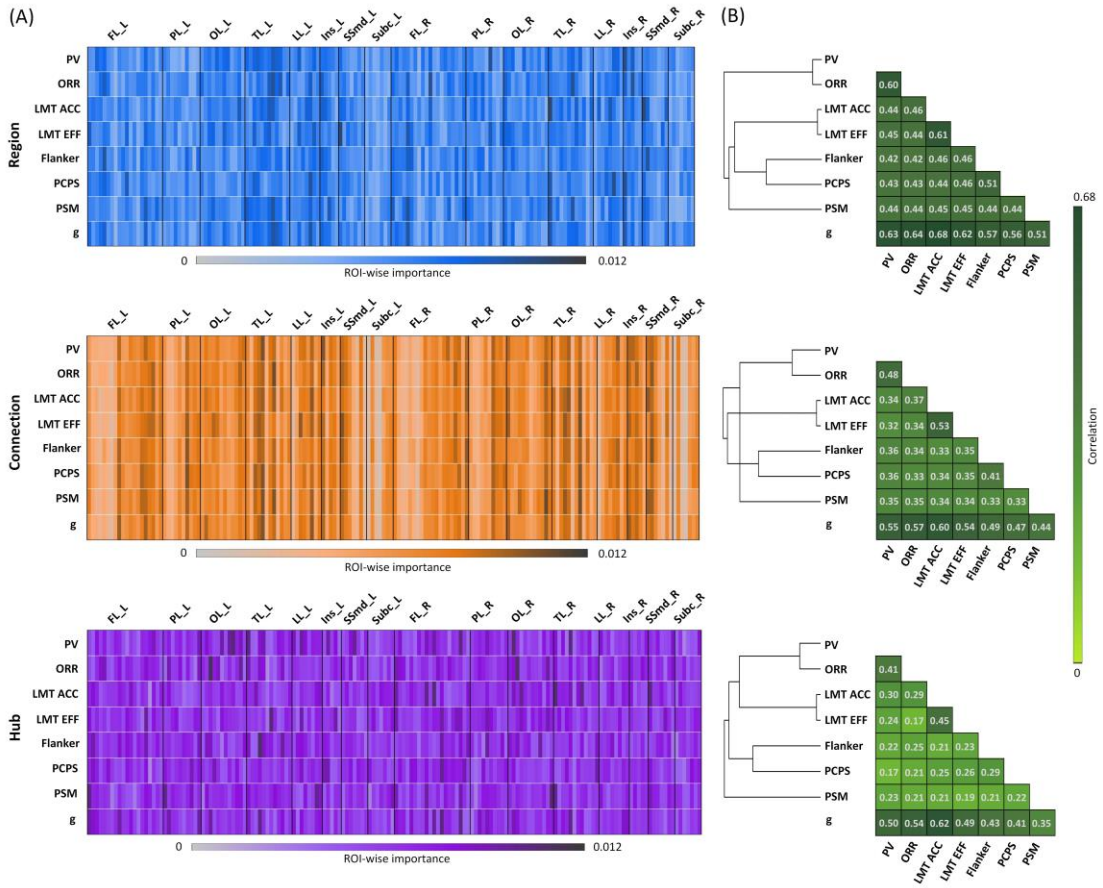

Fig. 6. Results of key brain morphometry measures for adolescent cognitive function over 8 cognitive performances. (A) ROI-wise importance values of brain morphometry measures to adolescent cognitive function over 8 cognitive performances. (B) Correlation values of whole measure results between cognitive performances and the corresponding clustering results.

Table 3. Correlations between importance values of key brain morphometry measures related to adolescent cognitive function of 8 cognitive performances.

Correlation	Region-wise	Connection-wise	Hub-wise
Cognitions (whole)	0.50±0.08	0.40±0.09	0.31±0.13
[Min, Max]	[0.42, 0.68]	[0.32, 0.60]	[0.17, 0.62]
Cognitions (ROI)	0.48±0.08	0.92±0.01	0.19±0.14
[Min, Max]	[0.35, 0.65]	[0.90, 0.95]	[-0.02, 0.49]

Our qualitative and quantitative analyses reveal that region-wise results (mean r = 0.50), connection-wise results (mean r = 0.4), and hub-wise results (mean r = 0.31) exhibit similarity across the 8 cognitive performances. This suggests that key brain regions, connections, and hubs crucial for different cognitive performances are similar during adolescence. Moreover, the connection-wise results on ROI-wise demonstrate remarkable similarity between different cognitive performances (mean r = 0.92). Notably, the key brain morphometry measures associated with the general cognitive performance are highly correlated with those associated with every other sub cognitive performance across all measurement aspects.

Furthermore, hierarchical clustering analysis was conducted on the key brain morphometry results of 7 different cognitive performances (except for the general cognitive performance), incorporating all region-wise, connection-wise, and hub-wise results, as depicted in Fig. 6B. The clustering revealed that vocabulary and reading, visuospatial accuracy and visuospatial efficiency, as well as attention and processing speed fall within the same class. However, the clustering results of episodic memory are not stable across all three measurement aspects.

Importance of fundamental brain morphometry measures related to 8 cognitive performances over 6 years during adolescence

In the previous sections, we delved into the importance of key brain regions, connections, and hubs across different years and different cognitive performances. Now, we shift our focus to examining the importance of 16 fundamental region-wise brain morphometry measures and 6 fundamental hub-wise measures related to adolescent cognitive function over 6 years and 8 cognitive performances. Specifically, for each of the 22 fundamental brain morphometry measures of a specific year and a specific cognitive performance, we calculated the sum importance values across all ROIs to represent the importance of the corresponding fundamental brain morphometry measure. 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 fundamental region-wise measures reaches 0.93 across the 6 years and 8 cognitive performances, indicating remarkable stability. Since subcortical ROIs don't have some of the region-wise measures (cortical area, cortical thickness, and sulcal depth), we also normalized the results by the corresponding ROI numbers in Supplementary Fig. 10. The conclusions remain the same.

Additionally, the importance values of 6 fundamental hub-wise measures based on MSNs across 6 years and 8 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 than those associated with the global attribute (strength, betweenness centrality, within-module degree, participation coefficient). The mean correlation of these importance values of

fundamental hub-wise measures reaches 0.87 across the 6-year period and 8 cognitive performances.

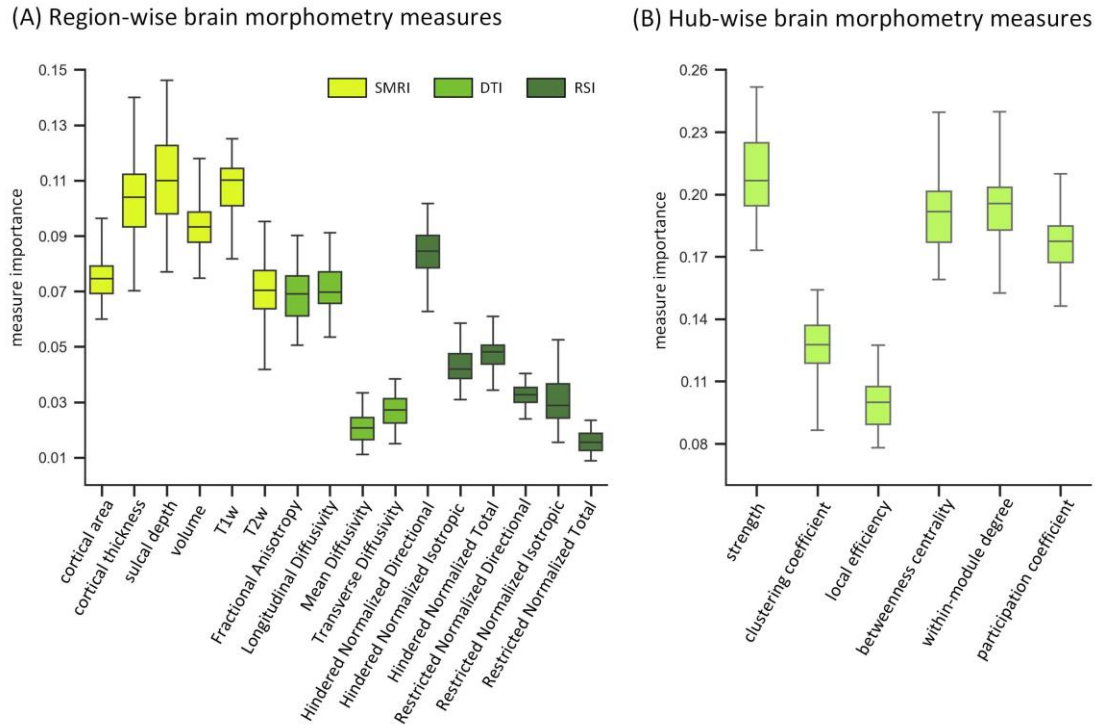

Fig. 7. Importance of fundamental brain morphometry measures for adolescent cognitive function. (A) Key fundamental region-wise brain morphometry measures. (B) Key fundamental hub-wise brain morphometry measures.

Effectiveness and stability of the 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 during 1000 bootstraps, as described in Method section. Subsequently, we calculated the average value of these 1000 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 8 cognitive measures, we obtained three mean R^2 values based on brain regions, connections, and hubs, as illustrated in Fig. 8A. These values ranged from 0.26 to 0.96, indicating satisfactory performance of our model. Furthermore, we assessed the stability of our large-scale computational model by varying the number of bootstraps used. For all 144 computational models (3 measurement aspects, 6 years, and 8 cognitive performances), we conducted iterations with 50, 100, 200, 300, 400, 500 bootstraps, and repeated for 100 times. Subsequently, we calculated the correlations between the association results of the specific computational model and the specific bootstrap number obtained from these 100 repetitions to represent the stability of the mode (Fig. 8B). The findings show that once the number of bootstraps surpasses 400, the correlations consistently exceed 0.98. And when the bootstrap number reaches 500, all the correlation values are over 0.985 and achieve an average of 0.994. Therefore, these results indicate the strong stability in our model across 1000 bootstraps.

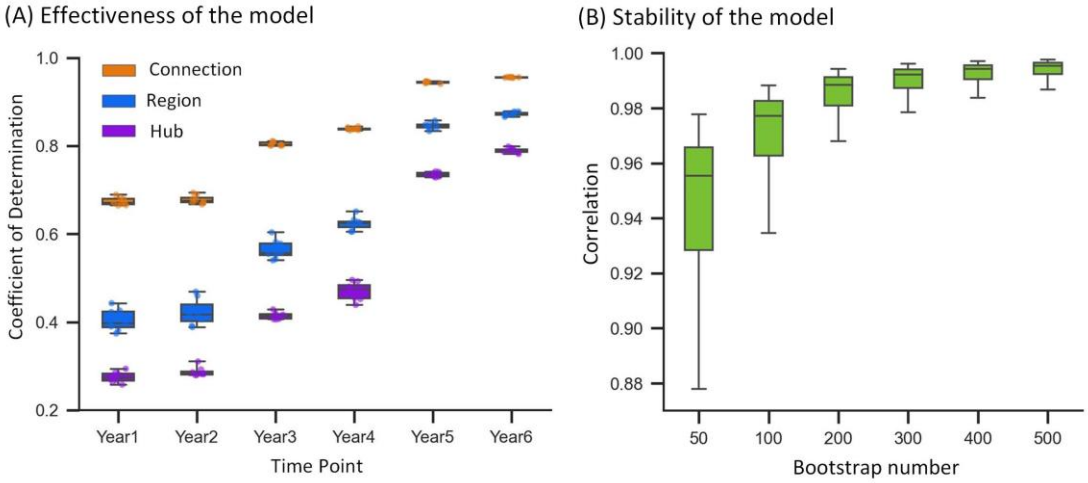

Fig. 8. Validations of the utilized large-scale computational model. (A) The effectiveness of the model. (B) The stability of the model.

Discussion

Based on the large-sample ABCD 5.1 release, we conducted a comprehensive and robust analysis to investigate the association between brain morphometry and cognitive function during adolescence. When examining the key brain regions, connections, and hubs related to cognitive function over 6 years, we observed promising correlations between brain regions and between connections across different years. However, the correlations between ROI-wise importance of hubs were found to be low. Notably, brain ROIs significantly associated with cognitive function, as well as those exhibiting the most variability in the associations over time, were primarily located in the frontal and temporal lobes. The subcortex was the least involved. When examining the key brain regions, connections, and hubs relevant to 8 different cognitive performances, we found that key brain morphometry measures associated with different cognitive performances show relative similarities, and those associated with cognitive performances within the same domain tended to display higher correlations. Furthermore, we found that SMRI measures shown higher associations with cognitive function compared to DTI and RSI measures. Moreover, hub-wise measures assessing overall structural network attributes were deemed more important to cognitive function than those measuring local network attributes. And our large-scale computational model shown promising effectiveness and stability in the validation experiment.

Correlation between key brain regions, between connections, and between 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 calculated the correlations between key brain regions, between connections, and between hubs of 6 years. Two intriguing findings emerged from our analysis. Firstly, we observed relative similarities between different years in key brain regions (mean r = 0.36) and connections (mean r = 0.27). We also calculated the sum values of connection importance for each connection-end ROI as their importance related to cognitive function. The intriguing finding is the remarkable stability of

connection-end ROI importances (mean r = 0.88). These findings highlight the promising stability of key brain regions, connections, and connection-end ROIs. Enhanced cognitive function may indeed be facilitated by improved communications between specific brain regions (Jung and Haier, 2007). However, compared to region-wise and connection-wise results, the correlations in brain hubs are the lowest (mean r = 0.14). And the ROI-wise mean correlation in brain hubs is only 0.06. These results might suggest that the key hubs undergo changes during adolescence, potentially reflecting ongoing optimization of the specific roles of brain hubs and 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 6-year period. Regarding region-wise 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 10-13. In terms of connection-wise results, the correlations between adjacent years show a consistent annual decrease during adolescence. This trend suggests that key brain connections undergo increasing changes from ages 9 to 15. In the hub-wise results, correlations between ages 9-11 and 13-15 are higher than those between ages 10-14. These results suggest more significant brain hub-wise changes related to cognitive function between ages 10-14. Generally, key brain regions undergo more pronounced changes during ages 10-13, while key hubs exhibit more variability from ages 10 to 14. Both tend to become more stable during ages 13-15. One of the reasons may be puberty, such as the influence of testosterone (Nguyen et al., 2013a, 2013b). Additionally, the key connections show increasing changes throughout ages 9-15, which might indicate the continued optimization of brain structural connections during adolescence (Dennis et al., 2013; Koenis et al., 2015; Richmond et al., 2016).

Common key brain regions, connections, and hubs for cognitive function over 6 years during adolescence

We calculated 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 and temporal lobe 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). Moreover, limbic lobe, insular cortex, and occipital lobe shown relative importance. The limbic lobe and insular cortex are linked with emotion processing and regulation (Catani et al., 2013; Gu et al., 2013), and occipital lobe with visual-spatial processing (Renier et al., 2010). 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 the most important. This finding aligns with the P-FIT theory, suggesting that enhanced communication between these brain lobes leads to improved cognitive function during adolescence (Jung and Haier, 2007). In the hub-wise results, the frontal lobe emerges as the most important hub in MSNs. This suggests that during adolescence, the frontal lobe acts as graph hubs and has strong commutations with other brain regions, contributing to cognitive control ability (Friedman and Robbins, 2022). Overall, while there are differences between the results of the three measurement aspects, brain ROIs associated with cognitive control, language comprehension, emotional regulation, and those playing significant roles in the P-FIT theory demonstrate the greatest importance in relation to cognitive function during adolescence.

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

We studied the changes in the 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 parietal 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 these two 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 parietal lobe focus more on emphasizing communication within the brain network during adolescence (Keshavan and Eack, 2019; 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 ROIs 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). From a more holistic perspective, our analysis indicates that the frontal, temporal, and occipital 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).

Correlation between key brain regions, between connections, and between hubs for 8 different cognitive performances during adolescence

In addition to examining the correlations between key brain morphometry measures related to cognitive function over 6 years, we also investigated the correlations between key brain morphometry measures for 8 different cognitive performances during adolescence. Our analysis revealed striking similarities between key brain regions, between connections, and between hubs associated with these 8 cognitive performances. These findings suggest that the shared variance among different cognitive performances is closely linked to specific key brain regions, connections, and hubs (Chen et al., 2022; Yan et al., 2022). Since the lowest correlation of key brain morphometry measures related to cognitive performances of different domains reaches 0.17, it suggests that even cognitive functions from disparate domains can share variance in brain regions, connections, and hubs (Yan et al., 2021; Zhang et al., 2021). Moreover, based on the clustering results, vocabulary and reading, visuospatial accuracy and visuospatial efficiency, as well as attention and processing speed are all categorized into the same class in all measurement aspects. This suggests that the key brain morphometry measures related to the cognitive performances within the same domain are highly correlated (Casaletto et al., 2015; Harvey, 2019; Luciana et al., 2018). It is also interesting to note that the clustering results for episodic memory are quite unstable across the three different measurement aspects. This instability may suggest that achieving episodic memory requires a more complex brain structural foundation than other cognitive abilities. In summary, despite there is promising shared variance of different cognitive performances across brain regions, connections, and hubs, those cognitive performances within the same domain exhibit higher correlations across

all three measurement aspects. This consistency aligns with findings from previous studies and serves to validate the robustness and reliability of our analysis.

Importance of fundamental brain morphometry measures related to cognitive function during adolescence

We investigated fundamental brain morphometry measures associated with 8 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 three most important measures related 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 measures during adolescence (Tadayon et al., 2020; Wang et al., 2009). Another possible reason is that DTI and RSI may introduce more noise during data acquisition and metric calculation compared to SMRI, thereby weakening the strength of the association with cognitive function. Nonetheless, two DTI measures (FA, LD) and one RSI measure (HND) also show relative importance. 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 fundamental hub-wise measures. Measures related to graphical local attributes, such as clustering coefficient and local efficiency, were found to be less important (Rubinov and Sporns, 2010). Conversely, measures related to overall brain attributes, like overall connection strength (strength) and shortest paths (betweenness centrality), held greater importance. Moreover, measures related to modularity (also overall brain attributes, 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 more 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

We calculated the R^2 between cognitive scores and estimated scores across 1000 bootstraps over 8 cognitive performances and 6 years. Our findings reveal a strengthening association between brain morphometry and cognitive function throughout 6-year period. This trend persists when considering cognitive estimation with brain regions, connections, and hubs, respectively. 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. And these refined brain morphometry measures 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 (region: 2550, connection: 13041, hub: 972).

Limitations and future directions

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 10 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. And although our study reveals the comprehensive association between adolescent brain morphometry and cognitive function, we did not utilize brain functional data. Therefore, some associations between brain functional signals and cognitive function were not revealed. We plan to address this part in our future research. 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).

In current study, we try to find the reliable associations between comprehensive whole-brain morphometry and adolescent cognitive function based on the large sample and robust large-scale computational model. It will help construct a foundation and provide guidance for other studies related to adolescent brain structure and cognitive function, like some popular studies about normative modeling (Bethlehem et al., 2022). And building upon this pilot study, we intend to develop a promising computational model for estimating cognitive performances based on brain morphometry. This model will not only aid in identifying atypical adolescent cognitive development but also offer crucial technical support for other studies exploring brain structural and cognitive development during adolescence.

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