Profiling intra- and inter-individual differences in child and adolescent brain development

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Abstract

As we move toward population-level developmental neuroscience, understanding intra- and interindividual variability in brain maturation and sources of neurodevelopmental heterogeneity becomes paramount. Large-scale, longitudinal neuroimaging studies have uncovered group-level neurodevelopmental trajectories, and while recent work has begun to untangle intra- and interindividual differences, they remain largely unclear. Here, we aim to quantify both intra- and inter-individual variability across facets of neurodevelopment from late childhood to early adolescence in the Adolescent Brain Cognitive Development (ABCD) Study, and examine the contributions of age, sex, and puberty to inter-individual variability. Our results provide novel insight into differences in microstructure development between cortical and subcortical gray matter. We found that an individual's starting point is related to how their brain changes, across all brain outcomes. Although both sex and pubertal status contributed to inter-individual variability, we found limited support for hypotheses regarding greater male-than-female variability and increases in inter-individual variability throughout puberty. This work highlights pockets of individual variability across facets of development and across the brain for future investigation, while describing a promising approach for quantifying deviations from normative development.

Keywords: MRI; brain development; cognitive development; individual differences; puberty

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Introduction

Recent years have seen great progress in charting child brain development, with much of the focus on developing normative models of structural change from a macroscale perspective (Aubert-Broche et al., 2013; Bethlehem et al., 2022; Mills et al., 2016; Tamnes et al., 2017; Wierenga et al., 2014a). Convergent research has identified differential, curvilinear trajectories for morphometric aspects of macrostructural development, including cortical volume, thickness, and area, as well as subcortical and white matter volume from mid-childhood to early adulthood (Bethlehem et al., 2022; Herting and Sowell, 2017; Mills et al., 2016). On a more granular level, studies of brain microstructure reveal protracted white matter development into adolescence and through the mid- to late-twenties (Lebel and Deoni, 2018). Functional neuroimaging shows coherent large-scale brain networks in infants with topography similar to those of adults (Grayson and Fair, 2017), that are fine tuned throughout childhood and adolescence (Cui et al., 2020). In this fine-tuning, functional topology of these networks changes, too, following trajectories of segregation and integration in the development of these large-scale brain networks (Fair et al., 2007; Marek et al., 2015). Therefore, there has been substantial progress in our understanding of neurodevelopment, although relatively less emphasis has been placed on understanding and modeling variability in these developmental processes (Becht and Mills, 2020), which is substantially different both within and between individuals (Ferschmann et al., 2022; Foulkes and Blakemore, 2018; Graham et al., 2017; Herting et al., 2018b; Mills et al., 2021; Østby et al., 2009; Wierenga et al., 2014a).

Dimensions of variability inherent to characterizing neurodevelopment include within-individual changes over time and between-individual differences in changes in brain maturation. Within-individual changes over time can vary across age and pubertal status, across regions of the brain, and across different facets of development (e.g., macroscale and microscale structural development, functional development) (Goddings et al., 2014; Herting et al., 2018b; Tamnes et al., 2017). As such, our use of the term *intra-individual variability* is based on repeated assessments of brain MRIs that can be used to measure an individual's developmental change. Such assessments have revealed normative within-individual variability underlying curvilinear development across wide-age ranges, such that rates of change within an individual differ as a function of increasing age and pubertal status (Aubert-Broche et al., 2013; Herting et al., 2017, 2018b). This includes an inverted-U trajectory for gray matter volume with respect to age that peaks during childhood, a general increase in white matter volume across childhood and adolescence (Bethlehem et al., 2022; Paus et al., 2001), puberty-related nonlinearities in trajectories of both structural and functional development (Dai and Scherf, 2019; Goddings et al., 2014; Gracia-Tabuenca et al., 2021; Herting et al., 2015; Herting and Sowell, 2017). Regional variability in development includes differences in gray matter and white matter maturation (Aubert-Broche et al., 2013; Bethlehem et al., 2022; Mills et al., 2016), different developmental trajectories of cortical and subcortical gray matter (Bethlehem et al., 2022; Sowell et al., 2002), and differential timing of development in sensorimotor vs. association areas of the cortex, proceeding from phylogenetically older to newer regions (Gogtay et al., 2004). This intra-individual variability is foundational to studies of inter-individual variability and has implications for cognitive development (Battista et al., 2018; Blakemore and Choudhury, 2006), neurodevelopmental disorders (Grayson and Fair, 2017), and the emergence of psychopathology (Ferschmann et al., 2022; Paus et al., 2008).

Beyond changes within an individual, neurodevelopmental trajectories throughout late childhood and early adolescence vary between-individuals, as well. For example, interindividual differences in brain outcomes are associated with physical and hormonal changes related to puberty (Dai and Scherf, 2019; Goddings et al., 2014; Herting and Sowell, 2017; Marceau et al., 2011; Vijayakumar et al., 2018), which also interact with sex- and age-related differences in neurodevelopment (Herting and Sowell, 2017; Vijayakumar et al., 2018). Moreover, pubertal-, age-, and sex-related differences in development have implications for the neurobiology and emergence of psychopathology (Gogtay and Thompson, 2010; Graham et al., 2021; Paus et al., 2008; Shaw et al., 2010), which is more common during childhood and adolescence than other stages of life (Kessler et al., 2005; Solmi et al., 2022). Understanding associations between interindividual differences in puberty and the brain is crucial to

understanding development. However, much of the research into neurodevelopmental trajectories, and variability therein, focuses on brain macrostructure (e.g., cortical thickness, global and regional volume, white matter tract volume), while development of microstructure (e.g., cortical myelination, neurite density) and function (e.g., regional function and functional connectivity) has received comparatively little attention and is, thus, poorly characterized. Robust studies of individual differences in neuroimaging require substantially increased sample sizes (Button et al., 2013; Dick et al., 2021; Grady et al., 2021; Marek et al., 2022; Yarkoni, 2009), and are made possible by increasingly larger and more diverse samples with increased statistical power, capturing a broader range of individual variability. While developmental cognitive neuroimaging has made recent progress in profiling individual variability in brain development (Mills et al., 2021; Zhu and Qiu, 2022), there is still a long way to go in characterizing individual developmental trajectories and interindividual differences in brain maturation over time.

The Adolescent Brain Cognitive Development℠ Study (ABCD Study®) provides an unprecedented opportunity to study these important questions regarding child and adolescent brain development, as it includes tens of thousands of variables including multimodal neuroimaging measures and pubertal information over multiple years (Jernigan and Brown, 2018). Such a large dataset has the potential to study intra- and interindividual variability in developmental trajectories of brain macrostructure, microstructure, and function, and to elucidate interindividual differences in change in brain development associated with various biological and sociodemographic factors (Feldstein Ewing et al., 2018; Volkow et al., 2018). However, variability in these measures is likely not equally distributed. For example, there is greater variance in brain structure in boys than girls throughout childhood and adolescence (Wierenga et al., 2022, 2018) and greater variability across changes in brain structure during transitions into adolescence and adulthood than during childhood or mid-adolescence (Mills et al., 2021). For a more robust study of individual differences in brain development, researchers should consider not only the variability in developmental trajectories, but the homogeneity of this variability, i.e., heteroscedasticity, across variables of interest and covariates. Assessing heteroscedasticity can reveal differences in brain change variability between levels of variables often included when studying brain development. Further, such insights can help identify pockets of variability for future study and inform sampling and experimental design for future research.

As such, the aims of this study are twofold: to expand the current understanding of sources of intra- and inter-individual variability in child and adolescent brain development and to describe the distribution of this variability across pubertal variables. First, we examine within-person variability in developmental trajectories in brain macrostructure, microstructure, and function by calculating annual percent change across the brain in each individual. Then, we investigate between-individual variability in developmental trajectories by computing the variance in brain changes across the whole sample. Finally, we assess the distribution of between-individual variability in development by assessing heteroscedasticity in brain changes across age, sex, and pubertal stages. In characterizing within-individual, or intra-individual, developmental change we have chosen to calculate annualized percent change (APΔ) for any given measure of brain structure or function. This approach has several advantages. First, computing change within each individual participant estimates the slope of an individual's developmental trajectory between two time points, mitigating the effect of differences in average values between individuals (Mills et al., 2021). Second, annualized percent change removes the effect of measurement scale or brain region size, allowing comparisons across neuroimaging measures (e.g., microstructure, functional connectivity). Third, normative studies of child brain development indicate that multiple, overlapping neurobiological processes occur between ages 9-12 years, including myelination, synaptic pruning, synaptogenesis, and apoptosis (Tau and Peterson, 2010) and associated changes that follow different trajectories across the brain. By modeling annualized percent change in a variety of neuroimaging measures, we can capture intra-individual differences in these trajectories across brain regions, tissue types, and facets of development and provide broadly applicable information about the inherent variability in this dataset, to inform future research. Finally, annualized percent change mitigates the extent to which differences in elapsed time between assessments across individuals confound estimates during this period of such rapid and varied neurodevelopment. Using

these annualized percent changes, we also focus on investigating heterogeneity in intra-individual differences in macrostructural, microstructural, and functional brain changes from ages 9 to 12 years, and to complement the well-developed literature on normative macrostructural development with a preliminary look at variability with respect to age, sex, and puberty. We chose to include a broad swath of neuroimaging measures for a comprehensive look at inter-individual differences in neurodevelopment, to focus on puberty for its ubiquitous impact on ABCD Study participants and its interest to the broad research community using ABCD Study data. In doing so, we hope to identify factors that contribute to diversity in developmental trajectories, and to inform future study of individual differences in child and adolescent brain development.

Methods

Participants

Longitudinal data were collected as a part of the ongoing Adolescent Brain and Cognitive Development (ABCD) Study, and included in the annual 4.0 data release (http://dx.doi.org/10.15154/1523041). The ABCD Study enrolled 11,880 children 9 to 10 years of age (mean age = 9.49; 48% female) in a 10-year longitudinal study. Participants were recruited at 21 study sites across the United States from elementary schools (private, public, and charter schools) in a sampling design that aimed to represent the nationwide sociodemographic diversity (Garavan et al., 2018a)**.** All experimental and consent procedures were approved by the institutional review board and human research protections programs at the University of California San Diego. ABCD Study inclusion criteria included age at enrollment (9.0 to 10.99 years); English fluency; lack of MRI contraindications; no history of traumatic brain injury or major neurological disorder; absence of any non-correctable sensory and/or motor impairments that would preclude the youth's participation in study procedures; current intoxication at appointment; diagnosis of any DSM-I psychotic, autism spectrum, or substance use disorder; an intellectual disability reported by their caregiver; premature birth, very low birth weight, or perinatal complications; and caregiver knowledge at baseline of an impending move to an area beyond reasonable traveling distance to an ABCD Study site. Each participant provided written assent to participate in the study and their legal guardian provided written agreement to participate. For more information, see Garavan et al. (Garavan et al., 2018b) and Volkow et al. (Volkow et al., 2018). Here, we use a subset of data from the ABCD Study, including magnetic resonance imaging (MRI), in addition to measures of participants' sex at birth and pubertal development. Data include assessments from two time points: baseline enrollment and year 2 follow-up. Measures of participants' sex and pubertal stage were all taken from the baseline time point.

Participants were excluded from these analyses if they did not have imaging data collected at the 2-year follow-up visit. From this subset, data were further excluded based on image quality. Structural and diffusion-weighted data were included if a participant's T1- and diffusion-weighted images, respectively, met the ABCD-recommended criteria for inclusion. For T1-weighted images, quality assessments were based on motion, intensity inhomogeneity, white matter and pial surface estimation by Freesurfer, and susceptibility artifacts and exclusion was recommended if an image exhibited severe artifact in any of those categories. For diffusion-weighted images, quality assessments were based on residual B_0 distortion after processing, coregistration to the participant's T1, image quality, and segmentation quality, with exclusion recommended if an image exhibited severe artifact in any of those categories. For resting-state scans, quality assessments were based on the number of frames remaining after high-motion (i.e., framewise displacement > 0.3 mm) frames were censored and periods with fewer than 5 contiguous frames were excluded, coregistration to T1 success, B_0 distortion maps, Freesurfer tissue type segmentation quality, and the number of usable time points per run (after censoring and exclusion, runs with fewer than 100 usable time points were excluded). We further excluded any resting-state fMRI data from participants with fewer than 750 usable (i.e., low-motion) frames, or 10 low-motion minutes, across all runs. This decision was based on estimations of scan lengths necessary for reliable resting-state functional connectivity estimates (Birn et al., 2013; Noble et al., 2017). The final sample characteristics for the

current study are described in Table 1. Because each structural, diffusion-weighted, and resting-state functional data are included based on their image quality, there are different numbers of subjects included for analyses with different imaging modalities. Those values are in Supplementary Table 2.

Table 1: Sample Demographics

	Full ABCD Study Sample		MRI 2-Year Follow-Up	
	N	% of sample	N	% of sample
Total N	11801		7457	
Age at baseline (months)	118.97±7.49		118.74±7.44	
Sex (F)	5636	(48%)	3437	(46%)
Race & Ethnicity				
Other	1493	(13%)	918	(12%)
Hispanic	2402	(20%)	1450	(19%)
Black	1755	(15%)	981	(13%)
White	6149	(52%)	4108	(55%)
Household Income				
< $75,000	3194	(27%)	1922	(26%)
$75,000 to $100,000	3056	(26%)	2082	(28%)
> $100,000	4543	(38%)	2876	(39%)
Caregiver Education				
Up to high school diploma, GED	2022	(17%)	1147	(15%)
Some college, associate's degree	3464	(29%)	2233	(30%)
Bachelor's degree	3317	(28%)	2204	(30%)
Graduate degree	2981	(25%)	1863	(25%)
Caregiver Marital Status				
Married	7951	(67%)	5192	(70%)
Widowed	96	(<1%)	60	(<1%)
Divorced	1077	(9%)	659	(9%)
Separated	461	(4%)	262	(4%)
Never Married	1444	(12%)	850	(11%)

Table 1: Sample Demographics

	Full ABCD Study Sample		MRI 2-Year Follow-Up	
	N	% of sample	N	% of sample
MRI Scanner Manufacturer				
Siemens	7303	62%	4539	61%
GE Medical Systems	2977	25%	2013	27%
Philips Medical Systems	1521	13%	905	12%

Note. Differences in baseline demographic composition of the complete sample and the sample including individuals with high-quality MRI data collected at a 2-year follow-up appointment were assessed using Mann-Whitney U tests. Bold values indicate significant differences at $\alpha < 0.05$; bold and italicized values, at $\alpha < 0.01$. Within-category percentages that add to <100% are due to missing data and participants who declined to answer, i.e., in the case of household income. *MRI 2-Year Follow-Up* indicates the sample used in analyses presented here. The "Other" Race/Ethnicity category includes participants whose caregiver identified them as American Indian/Native American, Alaska Native, Native Hawaiian, Guamanian, Samoan, Other Pacific Islander, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, Other Race, or as belonging to more than one race.

Puberty

Pubertal status was calculated from the Pubertal Development Scale (Petersen et al., 1988), completed by the caregiver about the participant (Barch et al., 2018; Herting et al., 2021). The PDS consists of a total of 5 distinct questions for males and females, based on sex assigned at birth. For males, the five questions are in regard to height growth, body hair, skin changes, vocal changes, and facial hair. For females, the five questions consist of assessing changes in height growth, body hair, skin, breast development, and menarche. For each of the 5 questions, parents/caregivers and youth were asked to separately rate their development on a 4-point scale (1 = has not begun yet, 2 = barely begun, 3 = definitely begun, 4 = seems complete), except for the menarche question for females, which consisted of a yes/no answer choice. Each question also consisted of an "I don't know" answer. A pubertal category score was derived for male participants by summing the body hair growth, voice change, and facial hair items and categorizing them as follows: prepubertal = 3; early pubertal = 4 or 5 (no 3-point responses); mid-pubertal = 6-8 (no 4-point responses); late pubertal = 9-11; postpubertal = 12. The puberty category score was derived for female participants by summing the body hair growth, breast development, and menarche and categorizing them as follows: prepubertal = 3; early pubertal = 3 and no menarche; midpubertal = 4 and no menarche; late pubertal<=7 and menarche; postpubertal= 8 and menarche. These category scores roughly correspond to Tanner stages and fall on a scale from 1 (prepubertal) to 5 (post pubertal) (Cheng et al., 2021; Herting et al., 2021).

Neuroimaging Data

The ABCD Study's imaging protocol includes structural, diffusion, and both task-based and resting-state functional MRI collected every two years, as described by Casey et al. (Casey et al., 2018). The ABCD consortium

has reported image processing and analysis methods in great detail (Hagler et al., 2019). Important for multi-site studies, ABCD MRI methods and assessments have been optimized and harmonized across the 21 sites for 3 Tesla scanners (Siemens Prisma, General Electric 750, Philips) (Casey et al., 2018; Hagler et al., 2019). Here, we incorporated a range of measures across these MRI modalities for a more comprehensive assessment of brain development. Broadly, these measures assess brain morphometry (i.e., macrostructure), microstructure, and function, and are described below in Table 2.

Table 2: Neuroimaging Measures of Interest

	Modality	Measures	Description
Macrostructure	sMRI	Intracranial volume	Estimated volume of the cranial capacity; (Buckner et al., 2004; Sgouros et al., 1999; Durham et al., 2021)
		Cortical area	Surface area of each cortical region of interest (ROI; Fischl et al., 1999)
		Cortical thickness	Thickness of the cortical ribbon (i.e., from the pial surface to gray/white matter boundary) of each cortical ROI (Fischl & Dale, 2000)
		Subcortical volume	Volume of each subcortical ROI (Fischl et al., 2002)
	dMRI	White matter tract volume	Volume of each white matter tract (Hagler et al., 2009)
Microstructure	sMRI	Gray matter/white matter contrast	Contrast of T1-weighted image intensity across gray-white matter boundary in cortical ROIs, indicative of neural tissue properties (Lewis et al., 2018; Salat et al., 2009)
	dMRI - DTI	Fractional anisotropy	Degree to which diffusion follows a single direction within each white matter tract, a proxy for cellular microstructure (Alexander et al., 2007; Clark et al., 2011)
		Mean diffusivity	Magnitude of diffusion within each white matter tract, estimates the restriction of water movement in tissue (Alexander et al., 2007; Clark et al., 2011)
		Transverse diffusivity	Average of the magnitude of diffusion in secondary and tertiary diffusion directions (i.e., second and third eigenvalues; Alexander et al., 2007)
		Longitudinal diffusivity	Magnitude of diffusion in primary diffusion direction (i.e., first eigenvalue; Alexander et al., 2007)
	dMRI - RSI	Isotropic intracellular diffusion*	Magnitude of spherical intracellular diffusion, as if in a cell body; within each white matter tract,

			cortical and subcortical ROI (Loi et al., 2016; White et al., 2012)
		Directional intracellular diffusion*	Magnitude of directional intracellular diffusion, as if in an axon or dendrite; within each white matter tract, cortical and subcortical ROI (Loi et al., 2016; White et al., 2012)
Function	rs-fMRI	BOLD temporal variance	Variance in the average BOLD signal across each cortical and subcortical ROI resting-state fMRI scans, reflecting the magnitude of low-frequency BOLD oscillations.
		Between-network functional connectivity	Pairwise correlations between BOLD signals from each large-scale brain network (Gordon et al., 2016)
		Within-network functional connectivity	Average BOLD signal correlation of regions within each large-scale brain network (Gordon et al., 2016)
		Network-subcortical functional connectivity	Pairwise correlations between BOLD signals from each large-scale brain network (Gordon et al., 2016) and each subcortical ROI

Note. Cortical regions of interest are defined using automated FreeSurfer parcellations (Desikan et al., 2006), including 68 cortical regions. Subcortical regions of interest are defined using automated FreeSurfer parcellations based on the Harvard-Oxford probabilistic atlas (Fischl?), from which 22 subcortical structures are included here. White matter tracts are defined using AtlasTrack (Hagler et al 2009?), from which 35 tracts are included here. Cortical networks are functionally defined (Gordon et al., 2017), comprising 13 canonical networks and a grouping of extra-network regions for a total of 14 parcels. *Isotropic intracellular diffusion corresponds to restricted normalized isotropic diffusion in the ABCD Study data dictionaries; directional intracellular diffusion, to restricted normalized directional diffusion. This is reflected in their abbreviation (RNI, RND) in figures throughout the manuscript.

Analyses

An analysis plan was registered for this project with the Open Science Framework (OSF) and can be found here. Prior to data analysis, missingness was assessed across variables and for the purposes of assessing intra- and inter-individual variability only complete cases were used, per variable.

Intra-individual change

Intra-individual changes in brain and cognition measures were modeled as annualized percent change, calculated by dividing the percent change in each measure by the elapsed time between observations, per the following formula (Mills et al., 2021):

$$annualized\ percent\ change\ (AP\Delta) = [((Measure_{x+1} - Measure_x) \div (Measure_x + Measure_{x+1}))/2) \times 100] \div (Age_{x+1} - Age_x)$$

Given prior findings that an individual's developmental trajectory is related to their starting point, we further computed Pearson correlation coefficients between the baseline values and APΔ for each brain measure, in addition to the partial correlation coefficients between baseline values and APΔ (after removing the effect of baseline age).

Inter-individual differences

First, we assessed multicollinearity (via Variance Inflation Factor) and pairwise correlations (point biserial, Spearman where appropriate) between age, sex, and pubertal status across participants, to address any potential confounding of results.

To assess inter-individual differences in brain changes, distributions of intra-individual differences were, then, compared across levels of the following developmental variables using the Fligner-Killeen test for homogeneity of variances (Fligner and Killeen, 1976): participants' sex assigned at birth; pubertal status (i.e., pubertal category score from the Pubertal Development Scale); and age at baseline (across 4 equal-sized bins: 9.0 - 9.39 years old, 9.4 - 9.99 years old, 10.0 - 10.49 years old, 10.5 - 10.99 years old).

Significance was assessed at $\alpha_{adjusted} < 0.05$, corrected for the number of effective comparisons across APΔ per measure, per region (Li and Ji, 2005; Šidák, 1967). This approach used all 1477 APΔ values (each region's value per measure) and uses the eigenvalues of a matrix of pairwise correlations between APΔ variables to determine the number of effective comparisons to correct for, thus accounting for dependence between variables.

Then, post hoc rank-sum tests were performed for measures of brain change across significantly heteroscedastic variables, to determine which levels of each variable demonstrate relatively more or less variance than others. Intra-individual differences were then plotted across groups to visualize inter-individual differences. Finally, patterns were assessed across measures of brain change according to (a) which biological concepts (i.e., macrostructure, microstructure, and function) exhibited the greatest difference in variance across developmental variables, and (b) which brain regions exhibited the greatest differences in variance.

All code used to perform these analyses and generate the associated figures was written in Python 3.7 and is available at github.com/62442katieb/deltaABCD_variability. A mapping between those scripts and the relevant analyses, figures, and tables is provided in Supplemental Table 0.

Results

The analyses included here reveal differences in distributions of change within individuals, across facets of development (i.e., macrostructure, microstructure, function), across tissue types (i.e., gray and white matter), and across brain regions, white matter tracts, and networks. Further, greater interindividual variability is seen in measures of function and functional connectivity than in macro- and microstructural measures. Finally, assessments of heteroscedasticity indicate that this interindividual variability in developmental change is not homogeneously distributed across age, sex, or puberty, to varying degrees across measures, tissue types, and regions. The Li & Ji adjustment to the Šidák correction to control familywise error rate revealed 689 "effective" comparisons between all 1477 APΔ variables, adjusting $\alpha < 0.05$ to $\alpha < 0.000074$. This threshold was used as the significance threshold for all reported p-values. Measures of developmental change demonstrated different neuroanatomical patterns of heteroscedasticity with respect to age, sex, and puberty, despite collinearity between age and puberty. Below we report greater details regarding these patterns of intra-individual variability and inter-individual differences seen between the ages of 9-12 years.

Intra-individual changes in brain development

Intra-individual differences as measured by APΔ differed between metrics of macrostructure, microstructure, and brain function (Figure 1; Table 3). Consistent with extant literature on this age range, cortical thickness and gray matter volume decreased annually across brain regions, while white matter volume increased. Likewise, measures of white matter organization (i.e., fractional anisotropy) largely increased, while magnitudes of diffusion (i.e., longitudinal, transverse, and mean diffusivity) decreased. However, isotropic intracellular diffusion

increased in both gray and white matter regions, while directional intracellular diffusion increased in white matter tracts but decreased in gray matter regions. Both isotropic and directional intracellular diffusion exhibited greater variability in gray matter than in white matter, which is interesting as such microstructural measures are more commonly assessed in white matter. Finally, measures of brain function exhibited greater variability, including positive and negative APΔ, with standard deviations an order of magnitude larger, on average, than those of macrostructure and microstructure measures.

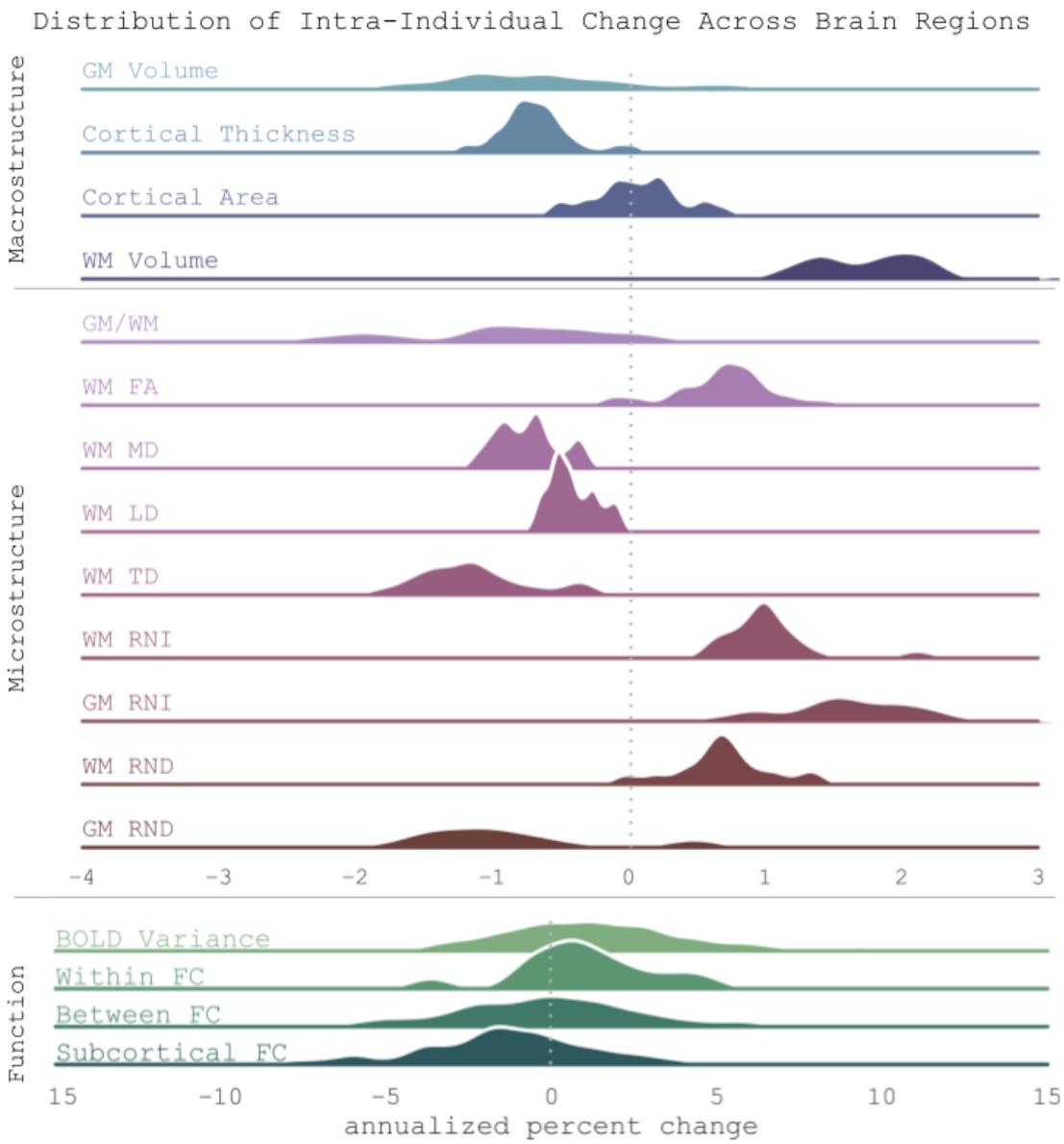

Figure 1. Distributions of annualized percent change in brain measures (across participants and regions), separated by measure and color-coded by biological construct the measure represents. In order, measures of macrostructure include gray matter volume (GM Volume), cortical thickness, cortical area, and white matter volume (WM Volume); measures of microstructure include gray-to-white matter contrast (GM/WM contrast), mean diffusivity (WM MD), fractional anisotropy (WM FA), isotropic intracellular diffusion of white matter and both cortical and subcortical gray matter (WM RNI, GM RNI), directional intracellular diffusion of white matter and both cortical and subcortical gray matter (WM RND, GM

RND); and measures of brain function include BOLD temporal variance (BOLD Variance), cortical within-network functional connectivity (Within FC), cortical between-network functional connectivity (Between FC), subcortical-network connectivity (Subcortical FC). Dotted line marks zero point, indicating no change per year.

Table 3: Annualized percent change across brain regions, per measure

	Measure	$\bar{x}_{AP\Delta}$	$\sigma_{AP\Delta}$	$[Q_1, Q_3]$
Macrostructure	Gray matter volume	-0.50	2.70	[-1.06, 0.07]
	Cortical area	0.07	2.48	[-0.53, 0.67]
	Cortical thickness	-0.67	1.85	[-1.12, -0.22]
	White matter volume	1.80	2.92	[0.79, 2.8]
Microstructure	Gray-to-white matter contrast	-0.93	4.00	[-1.9, 0.04]
	Fractional anisotropy	0.69	2.47	[-0.16, 1.54]
	Mean diffusivity	-0.73	1.95	[-1.4, -0.06]
	Transverse diffusivity	-0.41	1.96	[-1.08, 0.27]
	Longitudinal diffusivity	-1.12	2.17	[-1.87, -0.37]
	Isotropic intracellular diffusion (WM)	1.04	1.76	[0.37, 1.71]
	Isotropic intracellular diffusion (GM)	1.54	3.24	[0.89, 2.2]
	Directional intracellular diffusion (WM)	0.69	2.13	[-0.12, 1.5]
	Directional intracellular diffusion (GM)	-0.93	5.28	[-1.99, 0.14]
Function	BOLD variance	1.42	25.40	[-1.02, 3.85]
	Within-network cortical connectivity	0.94	14.49	[-7.81, 9.7]
	Between-network cortical connectivity	0.00	43.27	[-9.75, 9.76]
	Subcortical-network connectivity	-1.51	48.16	[-7.55, 4.52]

Note. Values represent average mean and average standard deviation of annualized percent change across brain regions.

The heterogeneity of these patterns of intra-individual brain development across the brain, within each metric and between metrics, are illustrated in Figure 2.

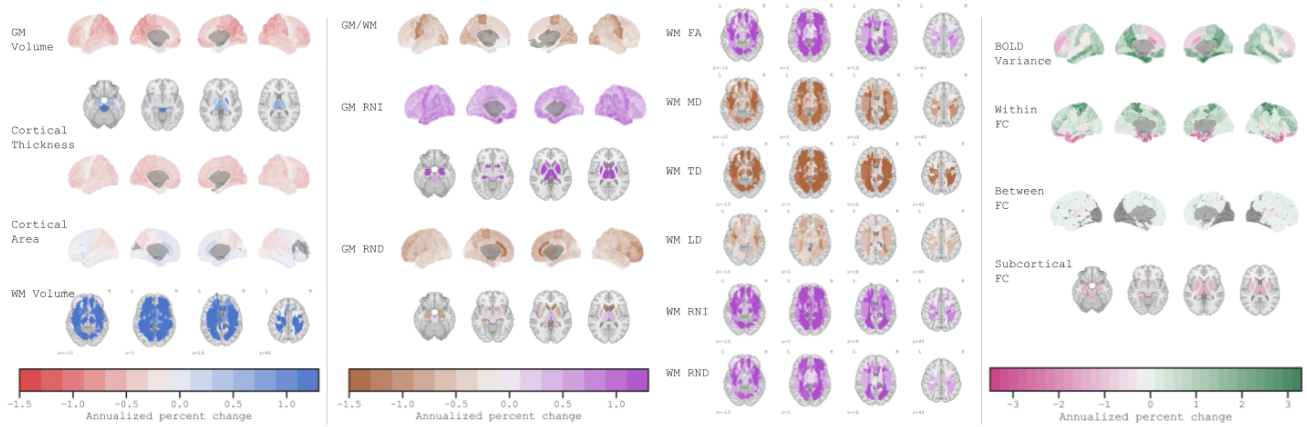

Figure 2. Average annualized percent change in brain measures across participants, separated by measure and color-coded by biological construct the measure represents. In order, measures of macrostructure change range from -1.5 to 1.5 and include gray matter volume (GM Volume), cortical thickness, cortical area, and white matter volume (WM Volume). Measures of microstructure change range from -1.5 to 1.5 include gray-to-white matter contrast (GM/WM), white matter fractional anisotropy (WM FA), white matter mean diffusivity (WM MD), white matter transverse diffusivity (WM TD), white matter longitudinal diffusivity (WM LD), isotropic intracellular diffusion of white matter and both cortical and subcortical gray matter (WM RNI, GM RNI), directional intracellular diffusion of white matter and both cortical and subcortical gray matter (WM RND, GM RND). Measures of brain function change range from -3.5 to 3.5 include BOLD temporal variance (BOLD Variance), cortical within-network functional connectivity (Within FC), cortical between-network functional connectivity (Between FC), subcortical-network connectivity (Subcortical FC).

Macrostructure changes

The largest decreases of *cortical volume* were in posterior regions, both laterally and medially, including the rostral middle frontal gyrus, posterior cingulate gyrus, and right supramarginal gyrus. On the other hand, increases were seen in fewer cortical regions, including bilateral paracentral gyri, lateral orbitofrontal gyri, and lingual gyri. Conversely, *subcortical* structures all showed considerably larder increases in volume. *Cortical thickness* followed a similarly posterior trend, with the largest decreases in cuneus, precuneus, lingual gyri, and pericalcarine cortex, although with notable decreases in more rostral frontal areas such as the orbitofrontal gyrus. Increases in cortical thickness were few, only seen in bilateral entorhinal cortices. *Cortical area* showed lower magnitudes of change overall, including more anterior and medial increases (e.g., in cingulate, parahippocampal, and insular cortex) and posterior decreases (e.g., in parietal cortex, precuneus, and supramarginal gyrus). *White matter volume* increased across tracts, with the largest increases in the cingulum and parietal section of the superior longitudinal fasciculus; smallest, in the fornix and anterior thalamic radiations.

Microstructure changes

Changes in microstructural were of the same magnitude as macrostructural changes and were largely heterogeneous depending on the measure and, to a lesser extent, the region. *Gray-to-white matter contrast* saw marked decreases in pre-, para-, and postcentral gyri, and increases only in more frontal regions (e.g., temporal pole, entorhinal cortex, rostral anterior cingulate cortex, frontal pole). *Fractional anisotropy* increased on the whole, with the greatest changes in the cingulum (both cingulate and parahippocampal portions), right inferior longitudinal fasciculus, and bilateral inferior fronto-occipital fasciculus. *Mean diffusivity* decreased overall, with the largest decreases in posterior portions of the superior longitudinal fasciculus, and the smallest decreases in the

fornix and anterior thalamic radiations. *Longitudinal diffusivity* decreased most in the parietal portion of the superior longitudinal fasciculus, forceps minor, and in white matter between inferior and superior frontal cortex (frontal aslant tract). *Transverse diffusivity* decreased most in the forceps major, cingulum, and superior longitudinal fasciculus, and decreased least in the forceps minor and anterior thalamic radiation. I*sotropic restricted (i.e., intracellular) diffusion in white matter* increased most in the cingulum, decreased in the fornix. *Cortical isotropic intracellular diffusion* increased most in caudal middle frontal, superior frontal, pericalcarine, and transverse temporal gyri, but decreased in the banks of the superior temporal sulcus, pars orbitalis and triangularis of the inferior frontal gyrus, entorhinal cortex, and precentral gyrus. *Subcortical isotropic intracellular diffusion* only increased in the caudate, and decreased most in the nucleus accumbens, amygdala, and hippocampus. *Directional intracellular diffusion in white matter* increased most in the cingulum, internal capsule, and corona radiata, and least in the fornix. *Cortical directional intracellular diffusion* increased most in the right superior frontal and left caudal middle frontal gyri, but decreased most in the left superior frontal gyrus and the banks of the superior temporal sulcus. *Subcortical directional intracellular diffusion* only increased in the caudate and decreased most in bilateral amygdala, hippocampus, and accumbens.

Functional changes

Functional measures demonstrated a wider magnitude of change than did macro- and microstructural measures. *BOLD variance* increased most in left lateral occipital cortex, bilateral postcentral gyri, and bilateral entorhinal cortex, but decreased most in right lateral occipital cortex, pars orbitalis of the inferior frontal gyri, rostral middle frontal gyri, and rostral anterior cingulate cortex. *Within-network connectivity* increased most within the motor-hand and cingulo-parietal networks, but decreased most in the salience and ventral attention networks, as well as extra-network orbitofrontal and anterior temporal regions. *Between-network connectivity* increased most between the somatomotor hand network and somatomotor mouth, frontoparietal, and frontoparietal networks, as well as between the salience network and both frontoparietal and cingulo-parietal networks. Between-network connectivity decreased the most between the ventral attention network and salience, default mode, and extra-network regions, as well as between the salience network and auditory, retrosplenial temporal, and dorsal attention networks. Finally, *connectivity between subcortical regions and cortical networks* (i.e., subcortical FC in Figure 1) increased the most between the nucleus accumbens and auditory, dorsal attention, and salience networks; between the brainstem and retrosplenial temporal and frontoparietal networks; between the right caudate and sensorimotor hand, retrosplenial temporal, and auditory networks; and between the left ventral diencephalon and auditory, retrosplenial, salience, and somatomotor hand networks. Subcortical-to-cortical network connectivity decreased most between the left putamen and cingulo-opercular, retrosplenial temporal, and frontoparietal networks; between the right putamen and visual and auditory networks; between the right thalamus and somatomotor mouth network; and between the left thalamus and both salience and cingulo-parietal networks.

Brain changes with respect to baseline values

Assessment of the correspondence between baseline values and APΔ revealed overwhelmingly significant, largely negative associations across measures and brain regions (Table 4). Thus, individuals with higher baseline values displayed smaller positive changes than those with lower baseline values over the observed age range. Similarly, we observed significant negative associations between baseline brain measures and corresponding APΔ, which became even stronger for many outcomes after accounting for each participant's age as assessed by partial correlation. Across brain regions, measures of brain function demonstrated larger, negative correlations between baseline and APΔ values as compared to other brain metrics, suggesting that greater BOLD variance and functional connectivity at ages 9-10 years was associated with less positive change with development over time and lower BOLD variance, with more positive change over time. On the other hand, measures of brain macrostructure demonstrated smaller negative correlations, suggesting that a brain region's size at ages 9-10 was only slightly, if at all, related to how that individual changed over the two year period. Correlations for measures

of brain microstructure fell between these two relative extrema, with the largest negative correlations between age and directional intracellular diffusion, and the smallest negative correlations, between age and gray-to-white matter contrast.

Table 4: Associations between baseline values and annualized percent change across brain regions, per measure

	Measure	Correlation		Partial correlation*	
		$\bar{r}_{base,\,AP\Delta}$	[Q_1, Q_3]	$\bar{r}_{base,\,AP\Delta}$	[Q_1, Q_3]
Macrostructure	Gray matter volume	-0.13†	(-0.17, -0.07)	-0.16	(-0.19, -0.1)
	Cortical thickness	-0.28	(-0.32, -0.24)	-0.34	(-0.4, -0.28)
	Cortical area	-0.13†	(-0.15, -0.08)	-0.17	(-0.22, -0.12)
	White matter volume	-0.21	(-0.24, -0.18)	-0.25	(-0.28, -0.22)
Microstructure	Gray-to-white matter contrast	-0.27	(-0.32, -0.24)	-0.31	(-0.36, -0.27)
	Fractional anisotropy	-0.35	(-0.38, -0.3)	-0.45	(-0.48, -0.42)
	Mean diffusivity	-0.34	(-0.38, -0.28)	-0.50	(-0.52, -0.47)
	Transverse diffusivity	-0.39	(-0.45, -0.35)	-0.55	(-0.59, -0.52)
	Longitudinal diffusivity	-0.28	(-0.32, -0.23)	-0.35	(-0.4, -0.29)
	Isotropic intracellular diffusion (white matter)	-0.34	(-0.38, -0.29)	-0.40	(-0.44, -0.35)
	Isotropic intracellular diffusion (gray matter)	-0.41	(-0.47, -0.35)	-0.46	(-0.51, -0.41)
	Directional intracellular diffusion (white matter)	-0.33	(-0.35, -0.31)	-0.45	(-0.48, -0.43)
	Directional intracellular diffusion (gray matter)	-0.57	(-0.63, -0.54)	-0.68	(-0.75, -0.64)
Function	BOLD variance	-0.40	(-0.44, -0.37)	-0.33	(-0.39, -0.3)
	Within-network cortical connectivity	-0.57	(-0.61, -0.53)	-0.52	(-0.55, -0.5)
	Between-network cortical connectivity	-0.49	(-0.5, -0.48)	-0.52	(-0.54, -0.5)
	Subcortical-network connectivity	-0.62	(-0.65, -0.6)	-0.56	(-0.57, -0.55)

Note. Correlations were significant for all brain regions across measures, with the exceptions of gray matter volume and cortical area, for which only 94% and 99% exhibited significant correlations between baseline and annualized percent change values across individuals. *Partial correlations between baseline

and annualized percent change control for the effect of baseline age and were significant for all regions across all measures across individuals. †For cortical volume and cortical area, annualized percent change and baseline values were only significantly correlated for 91% and 97% of regions. All other measures' correlations were significant across all brain regions. After accounting for age, all regions's changes were significantly associated with their baseline values across all measures.

Inter-individual changes in brain development

Inter-individual differences of APΔ (i.e., within-individual changes) across all participants showed that brain regions, tracts, and networks demonstrated lower average inter-individual, or between-subject, variance in macro- and microstructural measures (Figure 3A) than in functional measures (Figure 3B), which displayed broader distributions with higher average variance. Age, sex, and puberty do exhibit multicollinearity with variance inflation factors of 4.53, 2.29, and 5.61, respectively. Likewise, pairwise correlations indicate that age and sex are significantly related (Point biserial r = -0.036, $p < 0.01$), age and puberty are significantly related (Spearman r = 0.15, $p < 0.01$), and puberty and sex are significantly related (Spearman r = 0.42, $p < 0.01$). However, neuroanatomical differences in significantly heteroscedastic regions with respect to each variable indicate that these results do uncover unique differences in variance with respect to each.

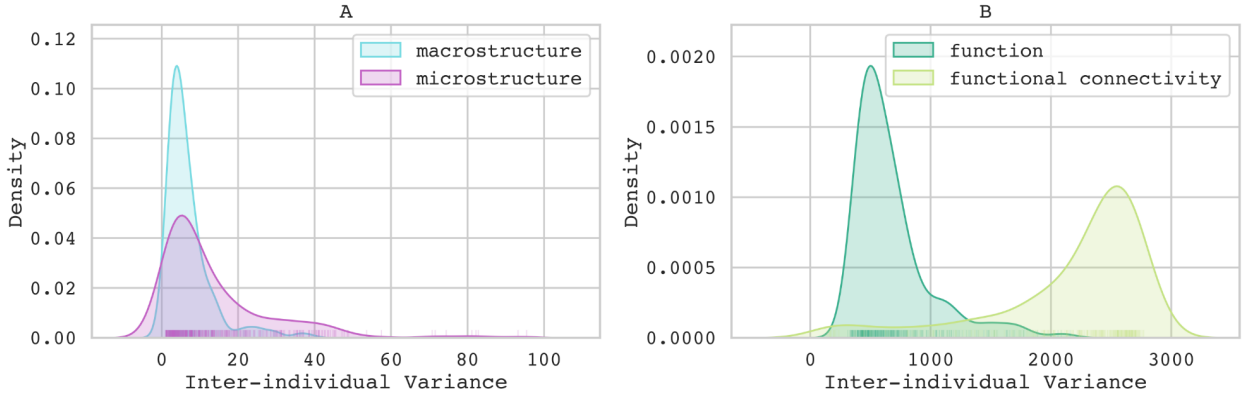

Figure 3. Distributions of inter-individual variance of annualized percent change in brain measures across all participants, separated by modality. For descriptions of the individual brain measures contributing to each broad category, see Table 2.

Comparisons of variance across categorically-assessed developmental variables, revealed significant heteroscedasticity that also varied across neuroimaging modalities (Figure 4, Table 5), suggesting that the variance in the rate of brain development of macrostructure, microstructure, and function is different across age, sex, and the child's pubertal status at study enrollment. Overall, the proportion of brain regions displaying significant variance in brain development over time based on initial age of study enrollment were larger for macrostructure and microstructure measures, as compared to functional patterns. Similarly, a larger proportion of brain development patterns were found to differ across the child's pubertal status for structural development versus functional connectivity outcomes, and pubertal effects are common across the brain compared to age. Larger inter-individual differences in brain development attributed to sex were more apparent for macrostructure, compared to microstructure or functional outcomes. We outline additional details as to significant variability by each developmental factor below. To further interpret heterogeneity in variance of brain development of

macrostructure, microstructure, and function, we display the significance of heteroscedasticity (as quantified by the Fligner-Killeen statistic) for each brain region (Figures 5-7) for each developmental variable.

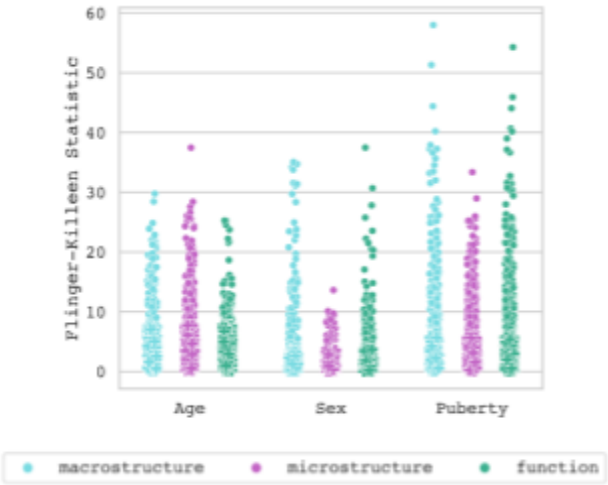

Figure 4. Magnitude and significance of heteroscedasticity in brain changes (per Fligner-Killeen statistic) across developmental, sociodemographic variables, and MRI manufacturer. Significant heteroscedasticity of each brain region is indicated by a circular marker; non-significant, by a "+" marker. Color indicates neuroimaging concept (i.e., macrostructure, microstructure, function), each point represents heteroscedasticity of a single measure (e.g., brain region, global estimate). Note, y-axis scales are different between subplots, representing differences in the order of magnitude of heteroscedasticity associated with each group of variables.

Age

Above within-individual associations between age and APΔ of brain macrostructure, microstructure, and function, assessments of homogeneity of variance across 6-month bins in baseline age uncovered associations between age and between-individual *variability* of APΔ. On average, 4% of regions or tracts across macrostructural measures (Figure 5A), 4% of regions or tracts across microstructural measures (Figure 6A), and <1% of regions or networks across functional measures (Figure 7A) demonstrated significant inter-individual differences in variance in annual brain changes across children based on their age at study enrollment: 9.0-10.99 years binned in 6 month increments. Cortical thickness, gray-to-white matter contrast, and directional intracellular diffusion (in white matter) displayed significant differences in inter-individual variability in brain development for the most regions or tracts (10-15%) with respect to baseline study age, compared to other measures. On the other hand, no other microstructural measures showed significant differences in variability between individuals of different ages, nor did cortical volume or between-network connectivity. Pairwise, *post hoc* rank-sum test between binned ages revealed that there were no significant differences in variance across all measures of APΔ or within the coarse groupings of macrostructure, microstructure, and function, after correcting for multiple comparisons.

Sex

With respect to sex, 8% of regions or tracts across macrostructural measures (Figure 5B), no regions or tracts across microstructural measures (Figure 6B), and 1% of regions or networks across functional measures (Figure 7B) demonstrated significant heteroscedasticity. Cortical area displayed significantly different variability in 13% of regions between sexes; cortical volume, 8%; and white matter volume, 11%. Within-network functional connectivity displayed significant sex-related heteroscedasticity in 15% of networks. Pairwise, *post hoc* rank-sum test between sexes revealed that, after correcting for multiple comparisons, there was no overarching trend

indicating that variability was greater in male than in female participants (or vice versa) across all measures of APΔ or within the coarse groupings of macrostructure, microstructure, and function. However, pairwise, *post hoc* rank-sum tests per measure (i.e., including both significantly and insignificantly heteroscedastic tracts) indicated greater male-than-female variability in changes in mean and longitudinal diffusivity. Most measures of APΔ displayed greater female-than-male variability in some regions, tracts, and networks, but significantly greater male-than-female variability in others. Only cortical volume and area showed greater male-than-female variability across all significantly heteroscedastic regions, while white matter volume and BOLD variance showed greater female-than-male variability across all significantly heteroscedastic regions.

Table 5: Proportion of brain regions that are significantly heteroscedastic with respect to developmental variables

Measure	Age	Sex	Puberty
Macrostructure	0.04	0.08	0.16
Gray matter volume	0.00	0.08	0.28
Cortical thickness	0.13	0.00	0.01
Cortical area	0.01	0.13	0.18
White matter tract volume	0.00	0.11	0.09
Microstructure	0.04	0.00	0.06
Gray matter/white matter contrast	0.15	0.00	0.01
Fractional anisotropy	0.00	0.00	0.00
Mean diffusivity	0.00	0.00	0.00
Longitudinal diffusivity	0.00	0.00	0.06
Transverse diffusivity	0.00	0.00	0.03
Isotropic intracellular diffusion (WM)	0.00	0.00	0.00
Isotropic intracellular diffusion (GM)	0.00	0.00	0.14
Directional intracellular diffusion (WM)	0.10	0.00	0.03
Directional intracellular diffusion (GM)	0.01	0.00	0.06
Function	0.01	0.01	0.06
BOLD temporal variance	0.01	0.00	0.07
Between-network functional connectivity	0.00	0.15	0.08
Within-network functional connectivity	0.03	0.05	0.03
Subcortical-network functional connectivity	0.00	0.02	0.05

Note. Cortical regions of interest are defined using automated FreeSurfer parcellations (Desikan et al., 2006).

Puberty

With respect to puberty, 16% of regions or tracts across macrostructural measures (Figure 5C), 6% of regions or tracts across microstructural measures (Figure 6C), and 6% of regions or networks across functional measures

(Figure 7C) demonstrated significant heteroscedasticity. Gray matter volume, cortical area, white matter tract volume, transverse diffusivity, isotropic intracellular diffusion (in gray and white matter) displayed the most significant heteroscedasticity with respect to pubertal status, in 9 to 28% of regions or tracts across the brain. On the other hand, fractional anisotropy, mean diffusivity, and isotropic intracellular diffusion (in white matter) each displayed no significant heteroscedasticity. Within regions of heteroscedastic cortical area and volume, pre-pubertal individuals demonstrated the greatest variability; mid-pubertal, the least. The opposite was true for regions of heteroscedastic BOLD variance and some subcortical-cortical network connectivity. The pubertal stages demonstrating greatest and least variability varied across regions of heteroscedastic microstructural changes (i.e., intracellular diffusion, longitudinal diffusivity) and white matter volume. Pairwise, *post hoc* rank-sum tests in global trends per measure (i.e., including both significantly heteroscedastic regions and nonsignificant regions) between PDS scores revealed that mid-pubertal individuals display greater variance than early- or pre-pubertal individuals only across functional measures (both $p < 0.01$) but not across measures of macro- or microstructural change, while mean and longitudinal diffusivity demonstrated significantly greater variability in pre-pubertal individuals than early- or mid-pubertal individuals.

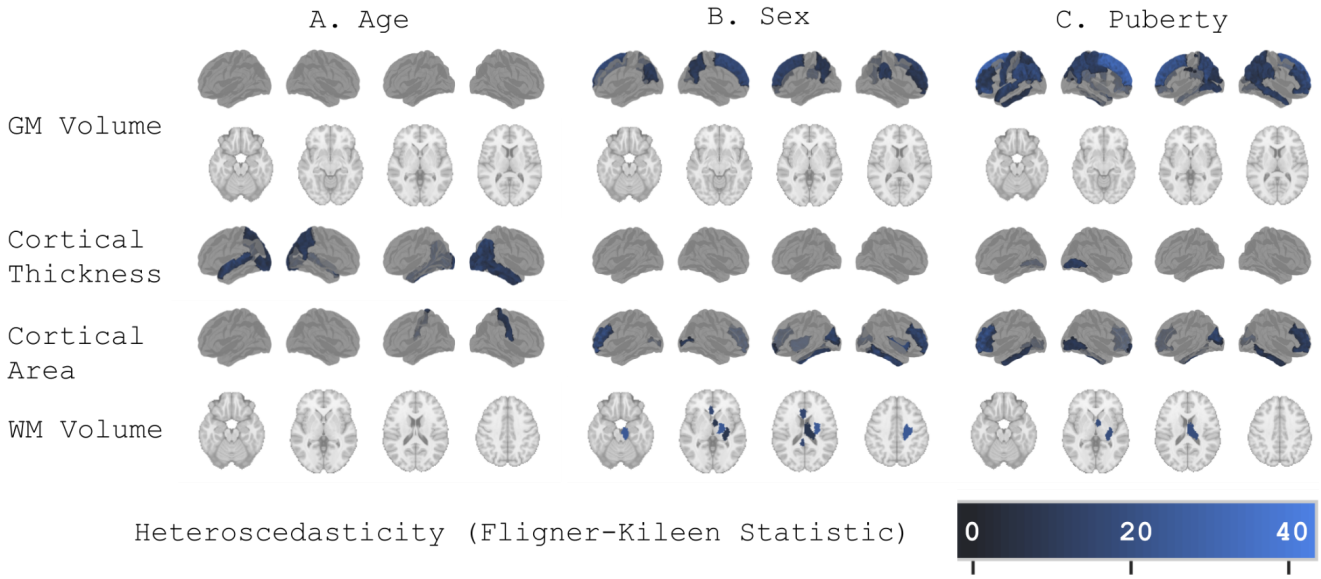

Figure 5. Neuroanatomical distributions of heteroscedasticity across measures of macrostructural brain change and developmental variables. Measures of brain change are represented in rows, while developmental variables (i.e., age, sex, puberty) are represented in columns. Brighter hues indicate greater heteroscedasticity of a brain change with respect to a demographic variable (i.e., larger differences in variance between levels).

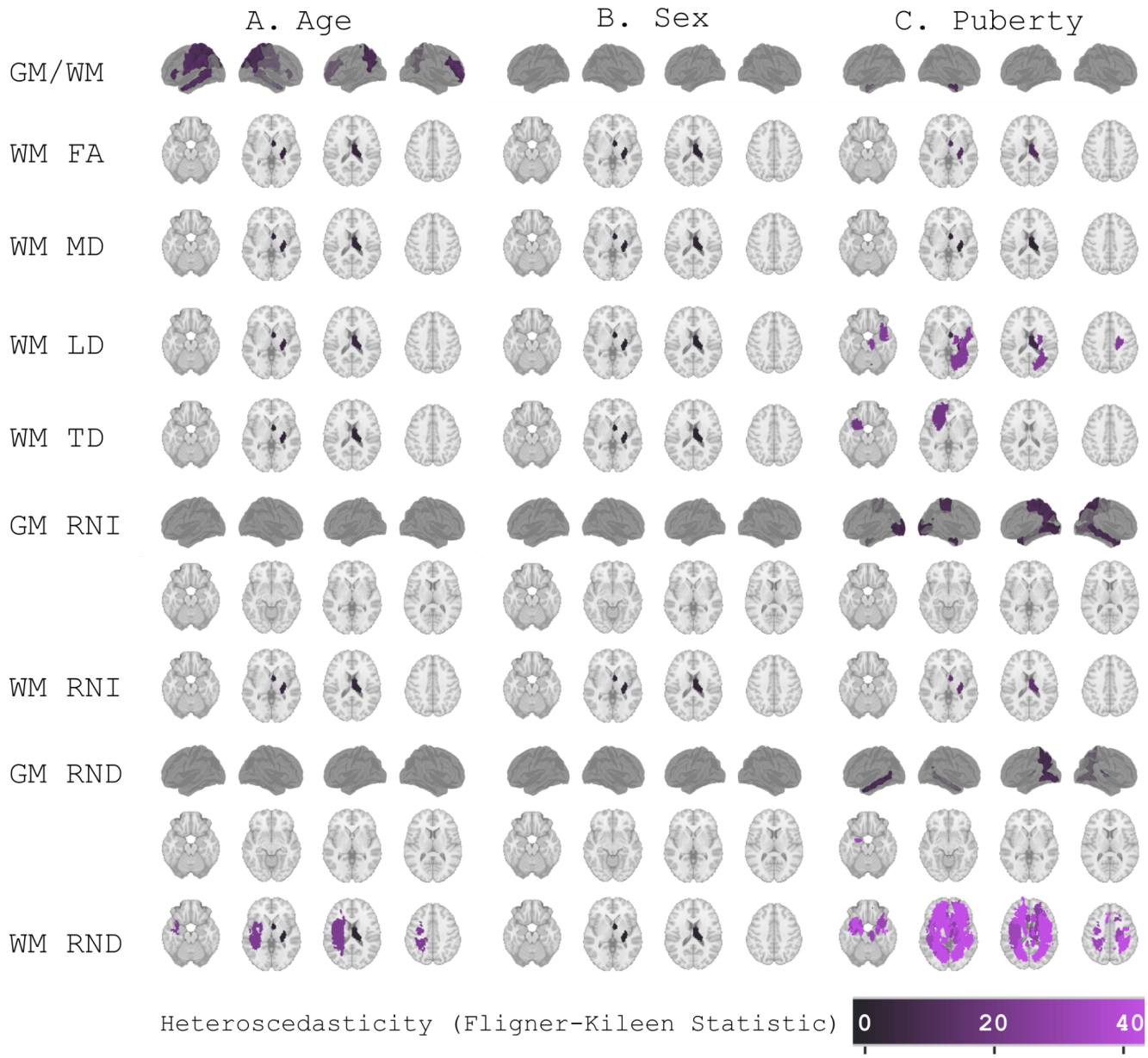

Figure 6. Neuroanatomical distributions of heteroscedasticity across measures of macrostructural brain change and demographic variables. Measures of brain change are represented in rows, while developmental variables (i.e., age, sex, puberty) are represented in columns. Brighter hues indicate greater heteroscedasticity of a brain change with respect to said variable (i.e., larger differences in variance between levels).

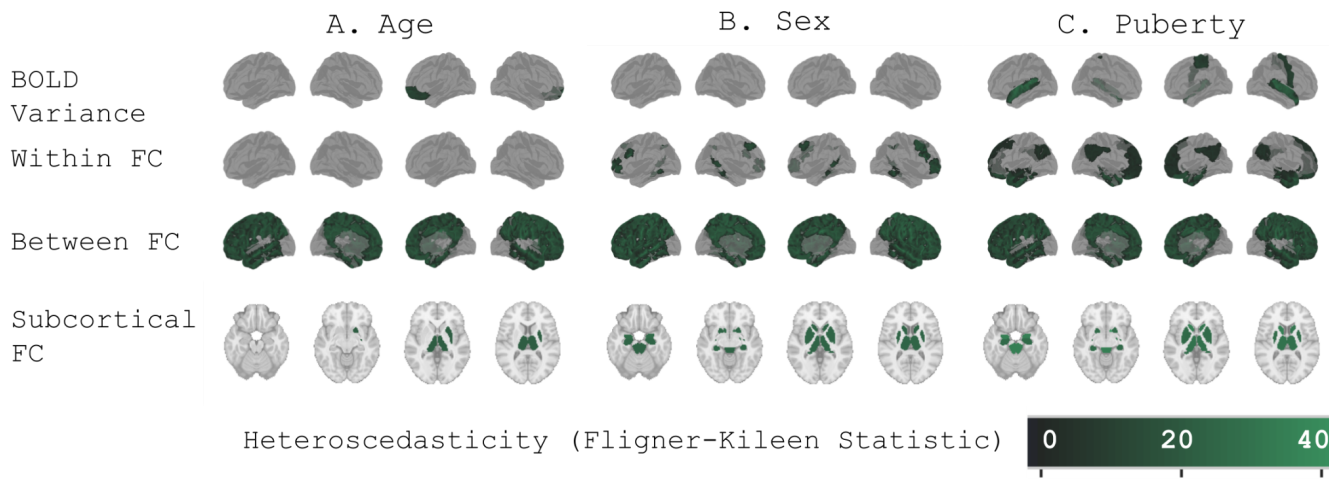

Figure 7. Neuroanatomical distributions of heteroscedasticity across measures of macrostructural brain change and demographic variables. Measures of brain change are represented in rows, while developmental variables (i.e., age, sex, puberty) are represented in columns. Brighter hues indicate greater heteroscedasticity of a brain change with respect to said variable (i.e., larger differences in variance between levels).

Discussion

Here, we assessed within- and between-individual variability in brain development between ages 9-10 and 11-12 years, by characterizing annualized percent change in macrostructural, microstructural, and functional measures in a large sample from the longitudinal ABCD Study. These assessments of intra-individual variability in change revealed differences across brain regions, tissue types, and facets of development along with different magnitudes of variance therein. Furthermore, intra-individual variance in developmental change is not equally distributed across sexes, ages, or pubertal stages; albeit this heterogeneity in inter-individual differences also varies across brain regions and measures of brain macrostructural, microstructural, and functional change.

Intra-individual variability

On a global, whole-brain scale, we identified average annualized percent changes (APΔ) that are broadly consistent with literature on normative brain development across this age range. These include decreases, on average, in gray matter volume (Bethlehem et al., 2022; Lenroot et al., 2007), cortical thickness (Tamnes et al., 2017; Wierenga et al., 2014b), gray-to-white matter contrast (Norbom et al., 2019; Paus et al., 2001), mean diffusivity (Schmithorst and Yuan, 2010), and transverse diffusivity (Asato et al., 2010) In addition, we also replicated increases in white matter volume, fractional anisotropy (Lebel and Deoni, 2018; Schmithorst and Yuan, 2010; Tamnes et al., 2018), white and gray matter isotropic intracellular diffusion (Palmer et al., 2022), white matter directional intracellular diffusion (ibid), and within-network functional connectivity (Fair et al., 2007; Satterthwaite et al., 2012). Also consistent with prior findings, we identified both increases and decreases in gray matter directional intracellular diffusion (Palmer et al., 2022), subcortical-network functional connectivity (Duijvenvoorde et al., 2019; Ji et al., 2019; Langen et al., 2018), and BOLD variance (Nomi et al., 2017; Wang et al., 2021), depending on the brain region or network. Larger decreases in gray matter volume were identified in parietal regions than in frontal, temporal, or occipital regions, consistent with prior findings (Lenroot et al., 2007). Fine-grained comparisons across microstructural measures are more difficult, unfortunately, as many studies of white matter microstructural development capture a much broader age range (e.g., 5 to 30 years), across which trajectories of each fractional anisotropy and mean, longitudinal, and radial diffusivities follow curvilinear

trajectories, and studies of gray matter microstructural development are uncommon. However, there are a few notable similarities, including greater annualized percent change in fractional anisotropy of the cingulum than other tracts, along with virtually no change in the fornix (Lebel et al., 2008). Across functional measures, regional and network-wise comparisons with prior literature are difficult, too, given the narrow age range and overall lack of consensus across functional imaging studies of development (Oldham and Fornito, 2019), and differences in large-scale network definitions across the literature (Uddin et al., 2019).

On the other hand, the current estimates of within-individual variability conflicted with some prior findings, as well. Compared with Sowell et al. (2004), this work only found increased cortical thickness in a much more restricted area, the bilateral entorhinal cortex, instead of extended temporal pole and orbitofrontal regions. However, our age range was a bit older than that of the sample in that study. Findings considering the integration within and segregation between large-scale functional brain networks were mixed, as well. We found that network-wise changes in between-network FC were 0, on average, indicating that changes in functional connectivity strength occur more on a connection level, including weakened connectivity with some networks and strengthened connectivity with others, than as broad network-level segregation. In terms of within-network connectivity, our results are largely in line with prior findings of increased within-network integration (Grayson and Fair, 2017; Satterthwaite et al., 2012). The only exception is that of the "none" network, or regions of typically low signal-to-noise ratio (SNR) in fMRI that were excluded from the parcellation-generating analyses in the original work (Gordon et al., 2016), which demonstrated decreased "within-network" connectivity. As this is not a coherent network, it does not necessarily represent "within-network" connectivity at all. Finally, there is not much literature on the development of intracellular diffusion across this age range. Here, gray matter directional intracellular diffusion showed opposite directions of change between cortical and some subcortical regions, potentially reflecting differential cytoarchitectonic processes underlying the development of cortical and subcortical regions. While this work moves toward a comprehensive understanding of developmental change in late childhood and early adolescence, further time points will be crucial to clarifying these different trajectories.

Moving away from group-level averages, this work also extends recent findings demonstrating that individual rates of change (i.e., APΔ) are significantly associated with their starting point (i.e., baseline values) (Mills et al., 2021). Our current study not only extends these findings for measures of brain macrostructure into a larger and more generalizable sample of children, but also suggests that where an individual starts is related to how they change in terms of all brain measures included here; although to varying degrees across brain regions. That is, after controlling for age effects, all brain regions demonstrated significant negative baseline-change associations, across all measures of brain macrostructure, microstructure, and function. This might indicate that intra-individual developmental trajectories, in general, are curvilinear from 9-12 years such that higher baseline values are associated with less positive change between baseline and follow-up visits. This is consistent with much of the group-level effects reported in the literature on normative trajectories in structural brain development (Bethlehem et al., 2022; Mills et al., 2016; Wierenga et al., 2014b), although there is some evidence of linear developmental trajectories, for example in gray-to-white matter contrast and in white matter area (Norbom et al., 2019; Paus et al., 2001; Wierenga et al., 2014b). Another possible explanation is the idea of *equipotentiality* as presented in developmental psychobiology, which implies that many paths in development can lead to the same outcomes or consequences (Bornstein, 2018). For example, while the rate may differ between individuals, the sequence of development is similar, so that individuals with lower baseline brain metric values had either more increasing or less decreasing to do, depending on the neuroimaging measure and brain region, towards particular brain developmental benchmarks.

Inter-individual variability

Measures of both macrostructure and microstructure change displayed narrower distributions with lower average variance, while measures of functional change (i.e., those from fMRI scans estimating brain function and functional connectivity) displayed broader distributions with higher average variance. Within measures of

macrostructural change, white and gray matter volume showed the greatest inter-individual variability; cortical thickness, the least. In general, measures of microstructural change showed more inter-individual variability than did microstructural measures, with the greatest variability seen in directional intracellular diffusion in gray matter and the least, in isotropic intracellular diffusion in white matter. Inter-individual variability in functional measures was an order of magnitude greater than in structural measures, with subcortical-cortical network connectivity showing the greatest variability and within-network connectivity, the least. With the current MRI data it is difficult to disentangle variability inherent to the MRI scanner and scanning sequence from variability due to underlying neurobiological differences between individuals, though this certainly warrants further study. Differences in variability between macrostructural, microstructural, and functional measures may be due to differences in neurobiological variability or they may be due to differences in image acquisition and processing. Moreover, beyond differences in the magnitude of inter-individual variability across measurement types and given their wide use in describing the ABCD Cohort and as common covariates in ABCD Study related analyses (Dick et al., 2021; Saragosa-Harris et al., 2021; Simmons et al., 2021) we chose to examine inter-individual variability in annualized percent change scores as it pertains to differences in participants' age, sex, and puberty, *a priori*. Below, we highlight key findings regarding differences among participants as to their patterns of within-individual change.

We identified associations between age and changes in development of macrostructural, microstructural, and a few functional imaging measures. Varying degrees of age-related annualized percent change is present across measures, such that some aspects of neurodevelopment show widespread, largely negative associations across the brain (e.g., isotropic intracellular diffusion in white and gray matter, cortical area), while others show little significant association, on average (e.g., functional connectivity, white matter fractional anisotropy). Further, age-related differences in inter-individual variability (i.e., heteroscedasticity) were present in fewer regions than were sex- or puberty-related differences, with the exception of gray-to-white matter contrast, cortical thickness, and directional intracellular diffusion (white matter). No one age group consistently displayed more variability than others within the larger categories of macrostructure, microstructure, and functional changes or within individual, heteroscedastic measures across the brain. Instead, we expect there are nuanced differences in distributions of inter-individual variability, within both measures of brain change *and* specific age ranges, likely reflecting the differential timing and neuroanatomy of aspects of brain development in this age range.

Sex-related heteroscedasticity in brain macrostructure has been previously noted across the lifespan, dominated by greater variability in males as compared to females (Wierenga et al., 2022), which is often referred to as the greater male variability hypothesis. Here, we expand those findings to show heteroscedasticity in cortical area, volume, and, to a lesser extent, thickness exhibit sex differences in variability as it pertains to developmental change. However, our annualized percent change findings only support the greater male variability hypothesis for a few measures of brain change. Male children exhibited greater variability in all regions of significantly heteroscedastic cortical area and volume, in most cortical network connectivity, and in less subcortical-to-cortical network connectivity. However, female children showed greater variability in each region of significantly heteroscedastic white matter tract volume and BOLD variance. Most brain regions across each of these measures displayed no sex differences in variability, nor did most measures of brain change. Mean and longitudinal diffusivity being the exceptions that show greater male-than-female variability across regions regardless of their individual significance. Together, this work extends Wierenga and colleagues' findings to suggest greater male-than-female variability in *changes in* brain macrostructure exist in addition to established cross-sectional differences, along with greater female-than-male variability in other macrostructural and functional measures during early adolescence.Together, these findings provide some neurobiological limitations to the larger, and somewhat controversial, variability hypothesis that posits greater male-than-female variability across a range of psychological and physical attributes (Hyde, 2014; Johnson et al., 2008; Lehre et al., 2009; Winsor, 1927).

Puberty plays a role in neurodevelopmental trajectories (Dai and Scherf, 2019; Goddings et al., 2014; Herting and Sowell, 2017; Vijayakumar et al., 2018), such that individual differences in hormones (Herting et al., 2014;

Vijayakumar et al., 2021a), pubertal tempo (Vijayakumar et al., 2021b, 2021a, 2018), and pubertal staging are associated with brain development (Goddings et al., 2019; Herting and Sowell, 2017). Here, we have identified differences in the variability of annualized percent change across Tanner stages of pubertal development during the narrow age-range of ages 9-10 years. Moreover, we show the patterns of variability in neurodevelopment seen across Tanner Stages are distinct from the differences seen across ages and sexes. Globally, prepubertal individuals exhibit greater variability in white matter tract volume, longitudinal, and mean diffusivity, while mid-pubertal individuals exhibit greater variability in subcortical-network connectivity and BOLD variance. Inter-individual variability across different pubertal stages largely varied across the brain within measures of change (i.e. functional connectivity, intracellular diffusion, etc.). Exceptions include cortical area and volume, which largely displayed greater variability in pre-pubertal individuals, while regions of significant heteroscedasticity in BOLD variance display greater variability in mid-pubertal individuals. Taken together, the diversity of inter-individual variability in brain development does not suggest globally monotonic increasing or decreasing of variability as a function of puberty at ages 9-10 years. Differences in pubertal stages demonstrating the most and least variability between global trends and individual brain regions, tracts, and networks hint at complicated patterns of pubertal maturation. Further research is needed to better understand this diversity in neurodevelopmental trajectories with respect to puberty and whether these patterns reflect differential susceptibility of neurobiological mechanisms to those underlying processes between brain regions.

Variance and heteroscedasticity in developmental cognitive neuroscience

The current study provides novel insight into intra-individual and inter-individual brain development across macrostructure, microstructure, and function, with notable heterogeneity of variance seen in annualized patterns of neurodevelopment across the narrow age range of 9-10 year-olds followed over a two year follow-up period. Understanding variability in brain changes and how this variability may differ across common developmental and sociodemographic categories is essential as large-scale, univariate studies have highlighted the importance of "unmodeled noise", or identifying the various sources of intra- and interindividual variability that are not traditionally accounted for in modeling brain-phenotype associations (Bandettini, 2022; Dubois and Adolphs, 2016). Identifying and profiling variability and sources thereof (e.g., via heteroscedasticity) is crucial for studying deviations from normative development, which may ultimately help facilitate our understanding of neurodevelopmental disorders and the emergence of psychopathology during this crucial period. Well-characterized normative models require robust descriptions of both central tendency *and* spread of the data. While developmental cognitive neuroscience has made substantial, recent advancements in describing average trajectories, the variation in these trajectories as highlighted here has received comparably little attention. Studying deviations from normative development associated with neurodevelopmental disorders, the emergence of psychopathology, and social determinants of health depends on understanding the scope and magnitude of normative variations in development. Furthermore, profiling variation associated with sex, puberty, and sociodemographic characteristics both across various brain regions and MRI measures can provide information about which brain regions, tracts, and networks are susceptible to factors underlying development and sociodemographic (dis-)advantage and the neurobiological processes underlying this susceptibility.

Limitations & Future Directions

Given that developmental trajectories can be better characterized by three or more timepoints, this line of investigation, assessing variability in brain trajectories, will continue to be important to investigate as additional ABCD Study data is released in future years.

Noise introduced by participant head motion is a nontrivial confound in resting state fMRI analyses and there are significant age, clinical, cognitive, and sociodemographic differences between participants exhibiting greater and less head motion in the ABCD cohort (Cosgrove et al., 2022). These differences limit the generalizability of resting state fMRI, confound studies that use these data, and may also contribute to some of the heteroscedasticity in

functional measures identified here. Further, another factor that may confound estimates of variability between MRI modalities (i.e. macrostructure volumes, white matter tracts, and functional networks) is the size of brain regions, tracts, and networks That is, larger regions represent average values for a greater number of data points (voxels) and, thus, may be more robust to random noise, resulting in less variability. On the other hand, within-region, -tract, or -network heterogeneity may increase variability of any given measure. Relatedly, it is impossible to remove the impact of differences test-retest reliability between MRI sequences used to estimate macrostructural (i.e., T1-weighted scans), microstructural (i.e., diffusion-weighted scans), and functional (i.e., BOLD fMRI scans) on between-measure differences in variability (Herting et al., 2018a). For example: although not included here, the task-based fMRI data from the ABCD Study demonstrate notably low reliability even within a session (Kennedy et al., 2022). On the other hand, between-individual differences have been shown to swamp scanner-induced variability across measures of macrostructure, microstructure, and function in an adult sample (Hawco et al., 2018).

Moving to population-level study brings new challenges to neuroimaging research, which has historically depended on small, homogeneous samples, as opposed to the large, diverse samples required for generalizable research. In this transition, researchers should consider the role that various sources of bias play in their work, such as those outlined in bias assessment tools commonly used in environmental epidemiology (Eick et al., 2020), and assess how the structure of variance is associated with sample characteristics and data collection.

Conclusions

Annualized percent change estimates suggest both intra-individual and inter-individual differences in trajectories of macrostructural, microstructural, and functional brain development across gray and white matter throughout the brain from late childhood and into early adolescence. These findings include novel insight as to increases in annualized percent change of isotropic intracellular diffusion in gray and white matter, as well as increases in white matter, but decreases in gray matter, in directional intracellular diffusion. Large-scale brain networks exhibited increased within-network connectivity overall, but both increases and decreases in between-network connectivity, depending on the connection. Across most measures of brain macrostructure, microstructure, and function, individuals with smaller starting values displayed larger increases. Functional measures exhibited much greater inter-individual variability than did structural measures, with changes in functional connectivity exhibiting the greatest variability. Assessments of homogeneity of variance across age, sex, and puberty revealed limited support for the greater male variability hypothesis and for the hypothesis of greater variability between individuals in later stages of puberty. The current study represents an insightful starting point for researchers who are interested in understanding individual differences in childhood and adolescent development.

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Competing Interests

The authors declare no competing interests.

Author Contributions

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Data curation: KLB
Formal Analysis: KLB
Funding acquisition: MMH
Methodology: KLB, MMH
Project administration: KLB, MMH
Resources: MMH
Software: KLB
Supervision: MMH
Visualization: KLB
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