Title: Longitudinal trajectories of brain development from infancy to school age and their relationship to literacy development

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Abstract

Reading is one of the most complex skills that we utilize daily, and it involves the early development and interaction of various lower-level subskills, including phonological processing and oral language. These subskills recruit brain structures, which begin to develop long before the skill manifests and exhibit rapid development during infancy. However, how longitudinal trajectories of early brain development in these structures supports long-term acquisition of literacy subskills and subsequent reading is unclear. Children underwent structural and diffusion MRI scanning at multiple timepoints between infancy and second grade and were tested for literacy subskills in preschool and decoding and word reading in early elementary school. We developed and implemented a reproducible pipeline to generate longitudinal trajectories of early brain development to examine associations between these trajectories and literacy (sub)skills. Furthermore, we examined whether familial risk of reading difficulty and a child's home literacy environment, two common literacy-related covariates, influenced those trajectories. Results showed that individual differences in curve features (e.g., intercepts and slopes) for longitudinal trajectories of volumetric, surface-based, and white matter organization measures in left-hemispheric reading-related regions and tracts were linked directly to phonological processing and indirectly to second-grade decoding and word reading skills via phonological processing. Altogether, these findings suggest that the brain bases of phonological processing, previously identified as the strongest behavioral predictor of reading and decoding skills, may already begin to develop early in infancy but undergo further refinement between birth and preschool. The present study underscores the importance of considering academic skill acquisition from the very beginning of life.

1. Introduction

"…the best way to determine how a child learns is to follow them closely while they are learning." (Siegler et al. 2005; Bonte and Brem, 2024).

Reading acquisition is a multifactorial, developmental process that begins long before the skill manifests. Behaviorally, the acquisition of reading necessitates the acquisition and complex interplay of lower-level literacy subskills. In turn, these subskills represent waypoint products of brain development that began in utero. Therefore, understanding how reading skills emerge requires examining its behavioral subskills and developmental trajectories of the brain areas subserving it starting at the very beginnings of life.

Literacy development represents a model process through which to examine academic skill acquisition, because literacy develops hierarchically, with lower-level "subskills" interacting and driving the emergence of higher-level academic skills (e.g., Kim, 2020). For instance, phonological processing, which refers to the ability to detect, understand, and manipulate speech sounds (Goswami, 2010, 2019; Wagner et al., 1987; Wagner and Torgesen, 1987), is the most consistent predictor of subsequent decoding and word reading (Melby-Lervåg et al., 2012; Moll et al., 2013; Scarborough, 2001; Wagner and Torgesen, 1987). Meanwhile, various studies have shown that both word reading and oral language skills, which encompass abilities supporting listening comprehension (Kendeou et al., 2009; e.g., vocabulary and syntactic knowledge), are important subskills for reading comprehension (Kim, 2017). However, these subskills themselves have protracted development and the brain structures that support them begin developing long before they manifest, with the most rapid development transpiring perinatally (Bethlehem et al., 2022; Gilmore et al., 2018).

Several cross-sectional and prospective studies have been conducted linking performance of these key literacy subskills to brain architecture. For instance, cross-sectional studies in preschoolers and kindergarteners have shown that phonological processing is associated with brain structure and function in left temporoparietal, occipitotemporal, and inferior frontal regions and tracts (Hoeft et al., 2007a; Raschle et al., 2011, 2012a, 2014; Saygin et al., 2013; Vandermosten et al., 2012). This set of regions has also been linked with preschool and kindergarten oral language skills in some studies (Marks et al., 2019; Romeo et al., 2018a, 2018b), but other studies have not shown associations (Davison et al., 2022; Raschle et al., 2014). Looking to early development, infant brain function and white matter organization have been shown to relate prospectively to (pre)school-age literacy outcomes (Guttorm et al., 2005, 2010; Leppänen et al., 2012; Lyytinen et al., 2004; Van Zuijen et al., 2013), including phonological processing and oral language skills (Tang et al., 2024; Yu et al., 2021; Zuk et al., 2021a). Taken

together, these studies suggest that certain brain areas may be important for academic skill *performance* at a particular time during development or as 'neural scaffolding' that supports subsequent language development (Cusack et al., 2024). However, the brain is a dynamic system that undergoes its most rapid development during infancy and early childhood (Bethlehem et al., 2022; Gilmore et al., 2018), making cross-sectional and prospective designs suboptimal to capture individual differences in early skill *acquisition* (Bonte and Brem, 2024). As such, individual longitudinal trajectories, which capture heterogenous rates of brain and skill development between infancy and second grade, are needed to examine the acquisition of (sub)skills important for literacy.

Therefore, the overall goal of the current study is to examine the relationship between longitudinal trajectories of early brain development and acquisition of reading-related subskills, which we undertook in three objectives. The first objective was to generate individual longitudinal trajectories of early brain development spanning infancy to school age. Prior longitudinal studies have examined trajectories of early brain development but only up to the second year of life (e.g., Gilmore et al., 2012), while others have examined developmental trajectories of brain structure spanning infancy to school age but only by harmonizing cross-sectional and longitudinal datasets acquired and processed with varying methods (e.g., Alex et al., 2024). However, to our knowledge, no purely longitudinal studies have mapped the development of brain structure, including white matter organization, from infancy to school age, using a consistent processing pipeline and one that is appropriate for early development. Indeed, methodological challenges associated with infant MRI data have restricted the number and breadth of longitudinal studies in the early developmental period. This is not only because acquiring and processing infant MRI data requires specialized procedures and tools to generate accurate brain estimates (Grotheer et al., 2022; Makropoulos et al., 2018; Pietsch et al., 2019; Prastawa et al., 2005; Raschle et al., 2012b; Zöllei et al., 2020), but also because the use of different procedures and tools for different developmental stages can introduce bias in developmental analyses. However, the alternative—to use identical procedures and tools for all developmental stages—would likely cause estimates to vary in accuracy across ages and could introduce spurious effects and/or obscure true effects in developmental comparisons (Turesky et al., 2021a). Some infant-specific tools offer age-specific adjustments (e.g., different sets of templates) within the first two years of life, and the small number of studies that have examined longitudinal trajectories of brain development in the first two years have opted for a balanced approach, with age-appropriate adjustments to limited processing steps in a way that does not require fundamentally different techniques for different

ages (e.g., additional sequences or different smoothing kernels; Gao et al., 2015; Gilmore et al., 2012). However, methods to accommodate a wider early developmental range are lacking.

In the current study, we extend this work by developing reproducible pipelines for generating longitudinal trajectories of volumetric, surface-based, and white matter organization brain measures from infancy to school age. To do this, we leveraged both infant-specific and standard MRI procedures and tools. In preparation for the second and third objectives, which examine literacy development and literacy-related skill acquisition, estimates were extracted from brain areas and tracts related to reading-related skill development in longitudinal studies in older children (Ben-Shachar et al., 2011; Brem et al., 2010; Dehaene-Lambertz et al., 2018; Di Pietro et al., 2023; Ozernov-Palchik et al., 2023; Reynolds et al., 2019a; Roy et al., 2024; Wang et al., 2017; Yeatman et al., 2012a; Yu et al., 2018a) or prospective studies in infants (Tang et al., 2024; Yu et al., 2021; Zuk et al., 2021a). We then compared among several candidate linear and nonlinear mixed effects models, varying according to function and random parameters (e.g., intercepts alone versus intercepts and slopes), to identify the model with the most parsimonious fit (Vijayakumar et al., 2018). In general, prior longitudinal studies have reported rapid growth at birth that tapers with age (Gilmore et al., 2012; Knickmeyer et al., 2008; Li et al., 2013; Reynolds et al., 2019b), except for cortical thickness, which peaks between ages one and two years (Wang et al., 2019a), suggesting logarithmic functions might provide a better fit compared with other functions for most measures.

Our second objective was to examine the roles of risk factors related to literacy skills in shaping longitudinal trajectories of early brain development. Reading difficulty is heritable, as 40-60% of children with a familial risk (e.g., first-degree relative with a history) of reading difficulty (FHD+) themselves develop reading difficulty (Snowling and Melby-Lervåg, 2016; Vogler et al., 1985). Brain imaging studies of FHD+ preschoolers show reduced gray matter volume, activation, and fractional anisotropy in left occipito-temporal and temporo-parietal regions (Raschle et al., 2011, 2012a, 2014) and tracts (Wang et al., 2017) compared with FHD- preschoolers; these reductions overlap with those observed in children with reading difficulty (Hasan et al., 2012; Hoeft et al., 2007b; Richlan et al., 2009, 2011, 2013; Steinbrink et al., 2008; Temple et al., 2001; Vandermosten et al., 2012), suggesting that the phenotypes characteristic of reading difficulty manifest in some children before the start of formal reading instruction. Concordantly, similar alterations have also been observed earlier in development, where FHD+ infants exhibited lower fractional anisotropy in left arcuate fasciculus compared with FHD- infants (Langer et al., 2017), distinguishable patterns of functional connectivity in left fusiform gyrus as shown by a support vector machine classifier (Yu et al., 2022), and alterations in neural responses to basic speech

sounds as measured by event-related potentials (Guttorm et al., 2001, 2003; van Herten et al., 2008). Relatedly, work in genetics, including recent large-scale genome-wide studies, have shown that reading-related skills (Eising et al., 2022) and reading difficulty (Doust et al., 2022; Price et al., 2022) are associated with variation in genes involved in early developmental processes, including neurogenesis and axon guidance (Watabe-Uchida et al., 2006). Another risk factor repeatedly shown to affect children's literacy skills is the home literacy environment, which includes caregiver–child shared reading and reading-related resources, in preschool literacy skills (Burgess et al., 2002; Bus et al., 1995; Foster et al., 2005; Hamilton et al., 2016; Payne et al., 1994; Schmitt et al., 2011) and in infancy/toddlerhood (Demir-Lira et al., 2019; Hoff, 2003; Karrass and Braungart-Rieker, 2005; Laakso et al., 1999; Malin et al., 2014; Muhinyi and Rowe, 2019; Schmitt et al., 2011). Recent work has identified links between the home literacy environment and brain architecture in preschoolers/kindergarteners (Davison et al., 2022; Hutton et al., 2015, 2017, 2020; Powers et al., 2016; Romeo et al., 2018b) and infants (King et al., 2021; Turesky et al., 2022). Overall, these studies offer strong evidence that genetic and environmental factors related to the development of reading-related skills are likely to affect longitudinal trajectories of brain development starting perinatally. Therefore, we hypothesized that the FHD status and home literacy environment would significantly contribute, as covariates, to longitudinal trajectories of brain development in left hemisphere temporo-parietal, occipito-temporal, and inferior frontal regions and tracts.

Unlike the covariates that influence brain development, it is less well understood how early brain development in turn influences reading acquisition. Accordingly, our third objective was to examine the association of individual differences in early brain development to long-term literacy development. As such, we extracted curve features (e.g., intercepts and slopes) from individual longitudinal trajectories for brain areas and tracts previously shown to relate to reading-related skill development in longitudinal studies in older children (Ben-Shachar et al., 2011; Brem et al., 2010; Dehaene-Lambertz et al., 2018; Di Pietro et al., 2023; Ozernov-Palchik et al., 2023; Reynolds et al., 2019a; Roy et al., 2024; Wang et al., 2017; Yeatman et al., 2012a; Yu et al., 2018a) or prospective studies in infants (Tang et al., 2024; Yu et al., 2021; Zuk et al., 2021a). We then tested these curve features for correlations with two key literacy subskills measured in preschool/early kindergarten: phonological processing and oral language. For the final link between early brain development and reading acquisition, we subsequently examined whether literacy subskills mediated relationships between curve features of early brain development and timed and untimed word reading skill. Based on converging evidence from prior neuroimaging (Tang et al., 2024; Yu et al., 2021; Zuk et al., 2021a) and genetics studies (Carrión-Castillo et al.,

2023; Eising et al., 2022), we hypothesized that literacy subskills would relate to curve intercepts (i.e., brain estimates at birth) and slopes (i.e., rate of brain development) and mediate links between curve features and subsequent decoding and word reading skills. If the foundations of literacy development are largely present at birth, then we expect most of these brain-behavior associations to be with curve intercepts, whereas if the brain development subserving literacy subskills is more protracted, then we expect brain-behavior associations to be with curve slopes. Taken altogether, findings from this study will inform our understanding of how early brain development contributes to later reading-related skill acquisition.

2. Methods

2.1. Participants

Children examined in this study participated in a longitudinal investigation of brain and literacy development from infancy to school age (NIH–NICHD R01 HD065762). Only children with high-quality (i.e., post-QC, please see below) MRI data from infancy (with a maximum age of 24 months) and one or more additional timepoints were included. Due to the multi-modal nature of the study varying numbers of longitudinal datasets were used for structural (n = 57 with 159 observations) versus diffusion analyses (n = 69 with 186 observations). Please see Table 1 for demographic details. Data examined here partially overlap with data used in previous studies examining infant brain development (Alex et al., 2024; Langer et al., 2017; Tang et al., 2024; Turesky et al., 2022; Yu et al., 2021, 2021; Zuk et al., 2021a, 2023).

Families of these children were recruited from the New England Area using the Research Participant Registry provided by the Division of Developmental Medicine at Boston Children's Hospital, and with flyers and ads disseminated in local schools and newspapers, at community events, and on social media. Children were enrolled as infants with the expectation that participation would continue at subsequent developmental stages across the first decade of life. For children ages ≤ 24 months, demographic and behavioral information were provided by caregivers. Race demographics, whose reporting is encouraged to improve equitability in neuroscience (Webb et al., 2022), are as follows: 70% White/ Caucasian, 6% Black/African American, 5% Asian, 16% Multiracial, and 5% Hispanic. Thirty-nine children had a family history (i.e., first-degree relative with a history) of reading difficulty.

Children were excluded from the study if at any timepoint they were diagnosed with neurological, sensory, or motor disorders or had contraindications for MRI evaluation (e.g., metal implants). All children included were from English-speaking families and were born at gestational week 37 or later. Neuroimaging and behavioral testing were conducted at Boston Children's Hospital prior to 2021 and at the Center for Brain Science at Harvard University from 2021 onward. At BCH, children's anatomical MRI scans (please see parameters below) did not show any potentially malignant brain features, as reviewed by a pediatric neuroradiologist. This study was approved by the Institutional Review Boards of Boston Children's Hospital (IRB-P00023182) and Harvard University (IRB21-0916). Informed written consent was provided by each participating infant's parent(s) and children gave verbal assent for participation after 50 months of age.

Table 1. Participant demographics	
General information	
Number of participants	77
Number of observations	220
Number of timepoints	3 ± 1
Age at infant time point (months)	10.0 ± 3.7
Age at literacy-related subskill testing (months)	64 ± 5.8
Age at decoding/word reading testing (months)	82 ± 6.4
Covariates	
Biological sex (F/M)	40/37
Maternal education (years)	18 ± 2.2
Family history of reading difficulty (+/-)	39/38
Home literacy environment (a.u.)	0.033 ± 0.41
Literacy-related subskills	
Phonological processing standard score	103 ± 15
Oral language standard score	113 ± 13
Decoding/word reading	
Word attack standard score	111 ± 14
Word identification standard score	109 ± 17

2.2. Environmental variables

Socioeconomic status was measured with maternal education, consistent with prior brain imaging studies on socioeconomic status (Betancourt et al., 2016; Brito et al., 2016; Lawson et al., 2013; Merz et al., 2018; Noble et al., 2015; Ozernov-Palchik et al., 2018). Maternal education measures were collected during each timepoint, although inter-time-point variability was low, and these were averaged to generate one socioeconomic status measure across the developmental window. Rather than using ordinal coding, we used years of education as a continuous measure, ranging from 12 to 20 years in the current sample.

Parents also completed questionnaires relating to children's home literacy environments home literacy environment, which includes the extent of parent-child shared reading and access to reading-related resources (Denney et al., 2001). Responses, which were indicated using ordinal scales ranging from either 1 to 5 or 1 to 6, were normalized and then averaged, according

to the procedure used previously (please see Yu et al., 2021) for home literacy environment questions and corresponding statistical procedures).

2.3. Literacy measures

Two literacy subskills from the Woodcock-Johnson IV (WJ-IV) were administered to children prior to the beginning of formal reading instruction: phonological processing and oral language. These constructs were selected as representative subskills supporting literacy development (Kim, 2017, 2020, 2023; Melby-Lervåg et al., 2012; Moll et al., 2013; Scarborough, 2001; Wagner and Torgesen, 1987); however, they constitute a small subset of literacy-related measures collected for this cohort. No outliers were detected using the *isoutlier* function in Matlab, which sets an outlier threshold at three scaled median absolute deviations from the median.

First, the composite *phonological processing* was estimated from three subtests from the WJ-IV Tests of Cognitive Abilities: word access, word fluency, and substitution (Schrank et al., 2014a). Word access measures phonetic coding by asking children to identify words containing certain sounds. Word fluency measures speed of lexical access by asking children to name as many words as possible beginning with a certain sound in one minute. Substitution measures children's ability to produce a new word by replacing one sound from a provided word with another sound.

Second, the composite *oral language* was estimated from two subtests from the WJ-IV Tests of Oral Language: picture vocabulary and oral comprehension (Schrank et al., 2014b). Picture vocabulary measures lexical knowledge by asking children to specify a picture corresponding to a given word or naming an object. Oral comprehension measures listening, vocabulary, and reasoning by asking children to identify missing words from short passages. All assessments were administered and double-scored by testers trained by a clinical psychologist and then raw scores were converted to standard scores.

Finally, we measured decoding and word reading with two untimed subtests from the Woodcock Reading Mastery Tests III (Woodcock, 2011): word attack and word identification. For word attack, children were presented with pseudowords that they needed to *decode* using phonological abilities. For word identification, children were presented with individual real words that they needed to *read*. Word attack and word identification subtests were administered at the beginning of formal reading instruction.

2.4. MRI data acquisition

All data were acquired on a 3.0 T Siemens scanner with a 32-channel head coil. Structural T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) scans were acquired with the following parameters: TR = 2270-2520 ms, TE = 1.66-1.73 ms, field of view = 192-224 mm, 1 mm^3 voxels, 144-176 sagittal slices. Diffusion echo planar images were acquired using the following parameters: TR = 3800-8320 ms, TE = 88-89 ms, flip angle = 90°, field of view = 180-256 mm, voxel size = 2 × 2 × 2 mm^3, 62-78 slices, 30 b = 1000 s/mm^2 gradient directions, 10-11 b = 0 s/mm^2 non-diffusion-weighted volumes. Diffusion data were acquired with slice-acceleration (SMS/MB) factor = 2 and one reverse phase encoding (i.e., posterior-to-anterior) volume.

2.5. Image processing

The rapid brain growth transpiring immediately after birth posed serious challenges for structural MRI processing because standard methods that are optimal for older children are suboptimal for infants and vice versa (Turesky et al., 2021a). To circumvent bias associated with choosing a single pipeline for multiple developmental stages, we implemented pipelines that are age-appropriate but not fundamentally different for each developmental stage.

2.5.1. Structural MRI processing and quality control

Raw MPRAGE images were visually inspected for artifacts by a trained rater and scored as “fail,” “check,” or “pass” (Backhausen et al., 2016). Only images scored as “check” or “pass” underwent image processing. The standard, unmodified FreeSurfer v7.3 (https://surfer.nmr.mgh.harvard.edu/) “recon” pipeline was used for brains > 50 months. No brain images were collected when children were between 25 and 50 months. Processing procedures for brains ≤ 24 months were similar in concept to those described in Natu and colleagues (2021). Namely, Infant FreeSurfer was used to extract the brain from the skull, correct for intensity inhomogeneity, and segment MPRAGE images by tissue class (gray matter, white matter, cerebrospinal fluid) and subcortical brain region (Zöllei et al., 2020; https://surfer.nmr.mgh.harvard.edu/fswiki/infantFS). To improve tissue classification accuracy, MPRAGE images were submitted in parallel to iBEATv2.0 Docker 1.0.0 (Li et al., 2019, 2014; Wang et al., 2023); https://github.com/iBEAT-V2/iBEAT-V2.0-Docker). Resulting segmentations from each software package were then hybridized using in-house Matlab code that combined the cortical pial and white matter boundaries labelled by iBEATv2.0 with the subcortical parcellations of Infant FreeSurfer (i.e., effectively relabeling cortical gray and white matter in the Infant FreeSurfer segmentation). Structural processing was finalized by submitting these FreeSurfer-

style hybrid segmentations to a modified version of the standard FreeSurfer v7.3 “recon” pipeline, which incorporated elements from Infant FreeSurfer. For a schematic of the structural processing pipeline, please see Supplementary Figure 1. The code used to process brains ≤ 24 months, including a higher-level function that automatically calls all relevant in-house, Infant FreeSurfer, and modified standard FreeSurfer code using only the participant ID, their age at infancy, and their iBEATv2.0 tissue segmentation, is publicly available (https://github.com/TeddyTuresky/Longitudinal-Trajectories-Early-Brain-Development-Language).

Resulting white and pial surfaces were visually inspected by two (brains > 50 months) or three (brains ≤ 24 months) trained raters on a 3-point scale (0, 1, and 2) and datasets with average ratings > 1.5 were retained for subsequent analyses. Similar to Bethlehem and colleagues 2022, for further quality control, we also extracted Euler numbers (Dale et al., 1999), which quantify topological defects in FreeSurfer’s cortical reconstruction and have been shown to correlate with visual ratings and mark artifactual images (Rosen et al., 2018). Euler numbers from each hemisphere were averaged for each participant and each timepoint (average: Rosen et al. 2018; sum: (Bethlehem et al., 2022) and used in sensitivity analyses (please see below). Finally, all parcellations were visualized to ensure accuracy of anatomical labels. Importantly, for reproducibility purposes, we did not perform manual editing to correct tissue mislabeling in the remaining images; however, structural measures from edited and unedited pediatric brain images processed with FreeSurfer have been shown to be highly correlated (McCarthy et al., 2015), including in children (Pulli et al., 2022). Measures of gray and white matter volume, surface area, cortical thickness, and mean curvature, generated in the final FreeSurfer steps, were extracted from 8 *a priori* left hemisphere regions – banks of the superior temporal sulcus, fusiform gyrus, inferior parietal cortex, middle temporal gyrus, pars opercularis, pars triangularis, superior temporal gyrus, and supramarginal gyrus.

2.5.2. Diffusion MRI processing and quality control

Preprocessed and tractography for all DWI data, regardless of age, were performed with MRtrix3 based on the pipeline established for the Developing Human Connectome Project (Bastiani et al., 2019; Pietsch et al., 2019). DWI data were first denoised using Marchenko–Pastur principal component analysis (Cordero-Grande et al., 2019; Veraart et al., 2016a, b) and then corrected for susceptibility distortions, eddy currents, motion, and intensity inhomogeneity using FSL’s topup and eddy (with slice-to-volume correction) functions (Andersson et al., 2003, 2017; Andersson and Sotiropoulos, 2016; Skare and Bammer, 2010; Smith et al., 2004), and Advanced

Normalization Tools (ANTs) N4 bias correction tool (Tustison et al., 2010). Subsequently, three tissue response functions for spherical deconvolution were estimated using the Dhollander algorithm, a 0.1 fractional anisotropy threshold, and eight maximum harmonic degrees (Dhollander et al., 2019). Fiber orientation densities (FODs) were computed with multi-shell, multi-tissue constrained spherical deconvolution (Jeurissen et al., 2014; Tournier et al., 2004) and then normalized using multi-tissue informed log-domain intensity normalization.

Two million streamlines were tracked from the normalized FOD maps using the Anatomically Constrained Tractography (ACT) technique. Importantly, ACT has been shown to greatly improve tractography, but it relies on accurate tissue segmentations, which are typically challenging to generate with infant brain data. Using the hybrid segmentations generated for brains ≤ 24 months (please see above) circumvented this challenge. Thus, FreeSurfer-style hybrid segmentations for brains ≤ 24 months and standard FreeSurfer segmentations for brains > 50 months were registered to the preprocessed DWI images using ANTs, and then converted to five-tissue-type images for ACT. The remaining whole-brain tractography parameters included seeding at the gray/white matter boundary and tracking with the iFOD1 probabilistic algorithm; step size, minimum and maximum length, and maximum step angle were set to default (Smith et al., 2012; Tournier et al., 2012).

Resulting whole-brain tractography was then submitted to Automated Fiber Quantification (AFQ; Yeatman et al., 2012b) for region-of-interest (ROI)-based fiber tract segmentation and fiber tract cleaning using a statistical outlier rejection algorithm. For brains > 50 months, we used the standard, open-source implementation of AFQ, pyAFQ (Kruper et al., 2021). For brains ≤ 24 months, we used pyBabyAFQ, which relies on infant templates from the University of North Carolina (Shi et al. 2011), smaller ROIs, and shorter distances for outlier rejection (Grotheer et al., 2022). Next, tracts were resampled to 100 equidistant nodes, and diffusion properties (fractional anisotropy; mean diffusivity) were quantified for each node for the left hemisphere tracts of interest – arcuate fasciculus, superior longitudinal fasciculus, and inferior longitudinal fasciculus. Mean fractional anisotropy and mean diffusivity values for each tract were used to examine model fits and contributions of covariates (please see section 2.6.1), whereas a more fine-grained, node-based approach was taken for brain-behavior analyses (please see section 2.6.2). For the latter, to better align tract cores across participants, five nodes on either end were removed, reducing the total number of nodes per tract to 90. Finally, tracts of interest were visually inspected by two trained raters on a 3-point scale (0, 1, and 2) and datasets with average ratings ≥ 1 were retained for subsequent analyses. For a schematic of the diffusion processing pipeline, please see Supplementary Figure 2.

2.6. Statistical analyses

An overview of statistical operations, all of which were performed in RStudio version 4.2.2, can be found in Supplementary Figure 3.

2.6.1. Longitudinal trajectory estimation

Prior to modeling, estimates of brain structure and white matter organization underwent a final quality control procedure to remove neurophysiologically implausible observations by setting inter-timepoint thresholds. For instance, it was unlikely that gray matter volume in any particular brain area changed by more than 10% in children over 50 months. Accordingly, for brains > 50 months, observations for brain areas/tracts of interest (please see above) were flagged if they were preceded or followed by ≥ 10% inter-timepoint change (positive or negative) in any measure. To mitigate data loss, we next identified which timepoint—the earlier timepoint or later timepoint—was more likely to be inaccurate, using an outlier detection procedure. Herein, we generated average (across participants) estimates for each brain area/tract and each brain measure by timepoint (roughly, grade level) to which to compare the observations flagged in the previous step. Out of the pair of flagged observations, the one farther from the average estimate corresponding to its timepoint was discarded and the other flagged observation was preserved. This process was done iteratively to handle cases in which children over 50 months had MRI observations from more than two timepoints. A similar quality control procedure was used for brains ≤ 24 months, but it needed to account for the rapid brain growth already thoroughly reported (Alex et al., 2024; Gilmore et al., 2018). Consequently, observations were only flagged when inter-timepoint changes were negative for gray/white matter volume, surface area, or fractional anisotropy, or positive for mean diffusivity. No inter-timepoint threshold was used for cortical thickness or mean curvature for brains ≤ 24 months. All remaining participants after these additional quality control procedures had multiple observations (i.e., longitudinal datasets), including one from ≤ 24 months.

To generate longitudinal trajectories (i.e., growth curves), we next submitted cleaned, longitudinal structural and white matter organization estimates to linear mixed effects models using linear, logarithmic, and quadratic functions from the R ‘lme4’ package. Intercepts and slopes were modeled as fixed and random effects, and covariates for biological sex, socioeconomic status, home literacy environment, and family history of reading difficulty (binary) were entered as fixed effects. As recommended by Vijayakumar et al. (2018), model fits were compared using Akaike Information Criterion (AIC) and the model (i.e., function and number of random terms) that provided the best fit (i.e., lowest AIC value) was selected for subsequent analyses. Correlations between intercepts and slopes were tested to ensure associations between random terms were

minimized. To determine whether literacy-related covariates (i.e., home literacy environment and FHD status) contributed to the fit of the growth curve after accounting for multiple brain areas and covariates, a significance threshold was set to $p_{FDR} < 0.05$ and applied to measures (e.g., gray matter volume) separately.

2.6.2. Associations between longitudinal trajectories of early brain development and literacy subskills

Next, individual-level curve features (i.e., intercepts and slopes) were extracted and tested for correlations (Pearson) with literacy subskills. The extracted curve features represent individual variation in intercepts or slopes beyond what would be predicted based on the covariates (e.g., biological sex); consequently, we did not include these same covariates in the tests of correlations. Also of note, we did not include literacy subskills in the mixed effects models directly because unlike the covariates, which are thought to affect brain development, we hypothesized that the literacy subskills are the products of such development. To determine whether curve features were associated with literacy subskills after accounting for multiple brain areas/tracts and behavioral measures, a significance threshold was set to $p_{FDR} < 0.05$ and applied to measures (e.g., gray matter volume) separately. As diffusion analyses were performed node-wise, we corrected for multiple comparisons at $p_{FWE} < 0.05$ using a permutation-based, threshold-free cluster enhancement method (Smith and Nichols, 2009), implemented in the permuco package in R (Frossard and Renaud, 2021); these methods are similar to those used previously (Davison et al., 2022; Ozernov-Palchik et al., 2018; Turesky et al., 2022). When significant, individual growth curves were separated into three groups according to scores on their behavioral assessment with low < 85, 85 ≤ average ≤ 115, and high > 115, meaned by group, and then plotted.

2.6.3. Sensitivity analyses

To test the reliability of our results, we performed a replication analysis on gray/white matter volume, and surface area with nonlinear mixed effects models using asymptotic functions from the R 'nlme' package (Pinheiro et al., 2017), similar to that described in Alex and colleagues (2023; https://github.com/knickmeyer-lab/ORIGINs_ICV-and-Subcortical-volume-development-in-early-childhood). Intercepts and asymptotes were modeled as fixed and random effects; rate constants were modeled as fixed effects. The reason that this model was not used in the main analysis is that it does not use a random slopes term and a key aspect of the current study is to examine the relation between brain growth and literacy subskills. However, it should be noted that

the nonlinear model does provide an indirect examination of the relation between growth and literacy subskills; e.g., if there is no association between the intercept and the literacy subskill, but there is an association between the asymptote and the literacy subskill, then it could be inferred that there is an association between brain growth and the literacy subskill.

In addition, we did not control for total intracranial volume (TIV) when modeling longitudinal trajectories of brain structure, consistent with other work examining developmental trajectories of brain structure beginning in infancy (Alex et al., 2024; Bethlehem et al., 2022; Deoni et al., 2012; Groeschel et al., 2010; Matsuzawa et al., 2001; Remer et al., 2017). Further, recent work has shown that TIV correction may be problematic, reducing brain-behavior predictive accuracies for gray matter volume and surface area or potentially generating spurious predictions for cortical thickness (Dhamala et al., 2022). Given these concerns and recommendations to report both raw and TIV-corrected results (Vijayakumar et al., 2018), we thought that an appropriate use of TIV would be to recompute brain-behavior associations for volumetric and surface-based measures using semipartial correlations (Pearson) with the random terms from longitudinal modeling with TIV as covariates of no interest. We report results of the linear mixed model run on brain-behavior relations with TIV.

Lastly, for volumetric and surface-based measures, visual ratings of cortical surfaces were used to identify sub-optimal datasets (visual ratings of tract reconstructions were for measures of white matter organization). However, Euler numbers, which quantify the number the topological defects in FreeSurfer's cortical surface reconstruction (Dale et al., 1999), have been shown to consistently correlate with quality ratings (Rosen et al., 2018) and to serve as reproducible alternatives to manual quality control, including manual editing (Monereo-Sánchez et al., 2021). Comparable to Rosen and colleagues, visual ratings and Euler numbers were highly correlated after controlling for age and biological sex ($r = 0.51$, $p = 5.7 \times 10^{-22}$). Therefore, to account for residual variance due to segmentation quality in a data-driven, reproducible manner, we submitted volumetric and surface-based brain-behavior associations to semipartial correlations (Pearson) with average (across timepoint) Euler numbers.

2.6.4. Indirect Effects between longitudinal trajectories of early brain development and word reading outcomes via literacy subskills

As with previous work (Turesky et al., 2021b), indirect effects were tested when literacy subskills were related to curve features of brain development and decoding and word reading outcomes (after FDR correction). Formal indirect effects modeling was conducted using the Mediation

package in R with 10,000 bootstrapped samples, and effects were determined significant when the 95% confidence interval for the average causal mediation effect did not include 0.

2.7. Data availability

All code used to process and analyze has been made openly available at https://github.com/TeddyTuresky/Longitudinal-Trajectories-Early-Brain-Development-Language. All data used in this study will be made publicly available at upon acceptance of the manuscript.

3. Results

3.1. *Longitudinal trajectories of brain structure and white matter organization in left hemisphere literacy-related brain regions and tracts*

Our first objective was to generate accurate longitudinal trajectories of early brain development. Accordingly, growth curves for regional estimates of gray and white matter volume, surface area, cortical thickness, and mean curvature and for tract estimates of fractional anisotropy and mean diffusivity were generated from 77 children (F/M = 40/37) with 220 observations. Every child had one infant observation and 1-3 observations from later developmental stages (Figure 1). Linear mixed effects models included individual-level intercepts and slopes as well as covariates for biological sex, socioeconomic status, home literacy environment, and familial history of reading difficulty. Nearly all structural and diffusion measures for all regions and tracts were best fit with logarithmic functions according to Akaike Information Criterion (Supplementary Table 1), whereby rates of development were steeper and then slowed across the first ten years following birth (Figure 2; Supplementary Figures 4-9).

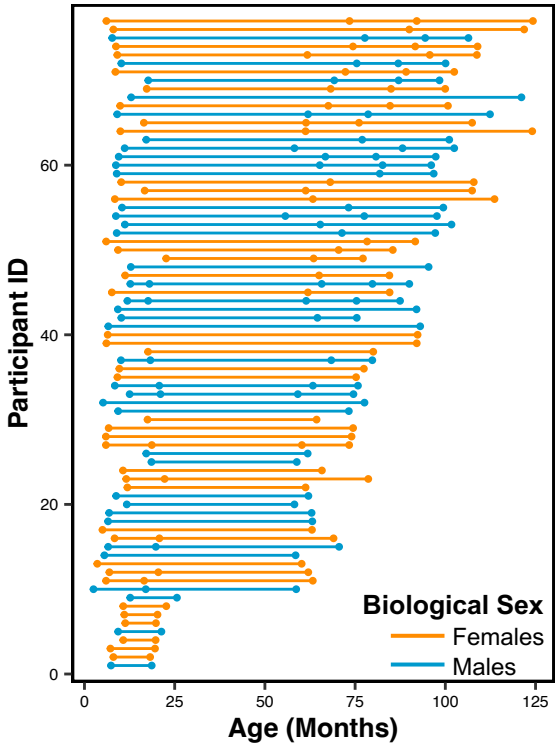

Figure 1. Age distribution of longitudinal dataset from infancy to early adolescence. All children had structural and/or diffusion MRI data obtained from at least two time points (dots), one of which was during infancy.

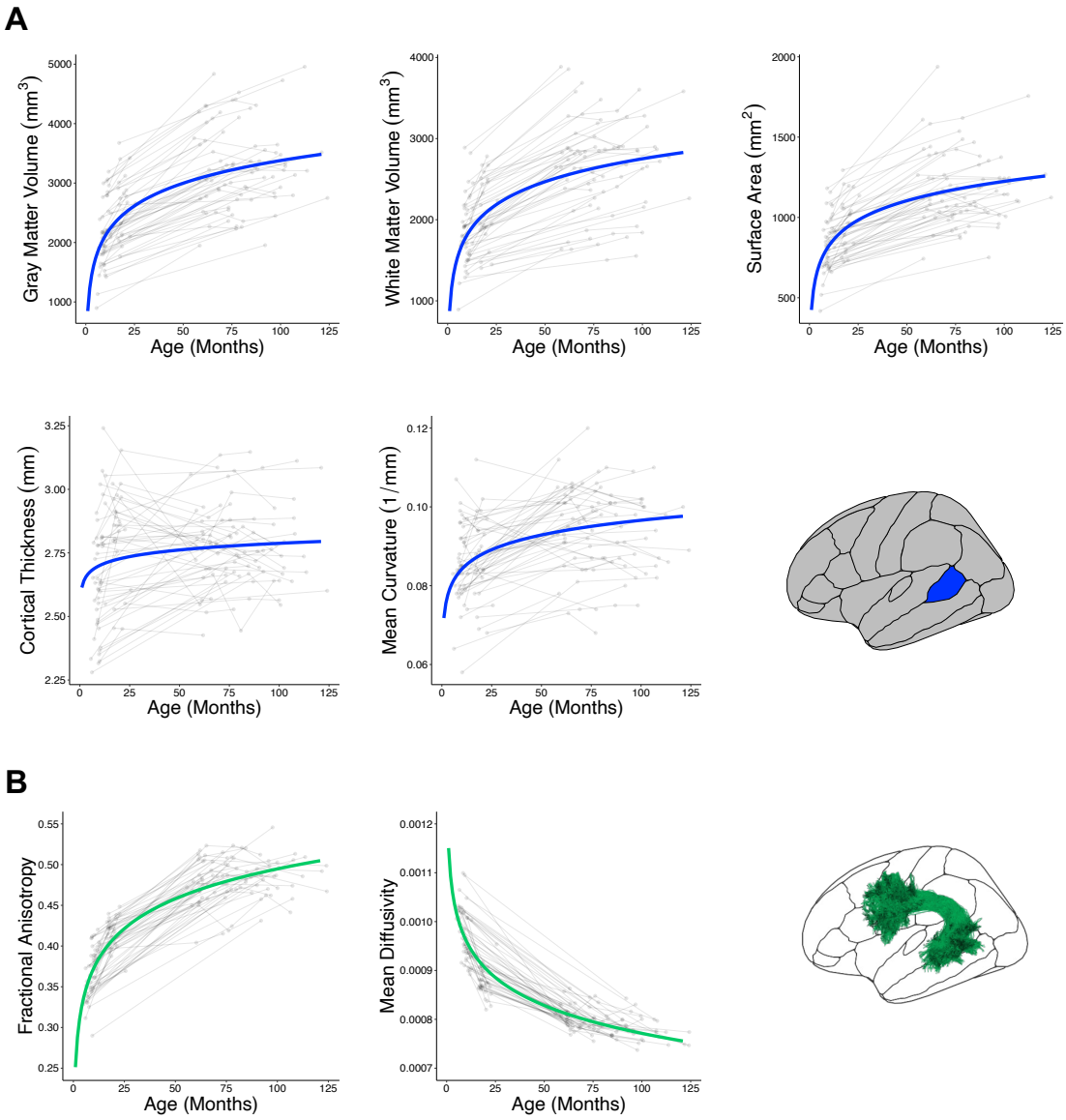

Figure 2. Example longitudinal trajectories from infancy to early adolescence for (A) volumetric and surface-based measures in the left banks of the superior temporal sulcus and for (B) white matter organization in the left arcuate fasciculus. Raw estimates (gray spaghetti plot backdrop) were submitted to linear mixed effects models using a logarithmic function. Individual growth curves predicted by this model were averaged to show the overall longitudinal trajectory of the sample (colored lines). For growth curves for other brain areas and tracts, please see Supplementary Figures 4-9.

3.2. *Contributions of literacy-related factors to longitudinal trajectories of brain structure and white matter organization*

Our second objective was to examine whether family history of reading difficulty and home literacy environment constituted significant contributors to longitudinal trajectories of early brain

development. No consistent patterns, nor significant fixed effects after FDR correction, were observed for either covariate.

3.3. Associations between growth curve features and key literacy subskills

Whereas the covariates included in the mixed effects models were potential candidates for affecting brain development, our third objective was to examine whether brain development, in turn, affects literacy development. Consequently, curve features (i.e., intercepts and slopes) were extracted from individual-level growth curves and tested for correlations (Pearson) with preschool/early kindergarten composites of phonological processing and oral language (as measured with the Woodcock-Johnson IV Tests of Cognitive Abilities (Schrank et al., 2014a) and Oral Language (Schrank et al., 2014b)), two critical subskills whose developmental pathways converge to support literacy (Kim, 2020; Scarborough, 2001).

For volumetric and surface-based measures, curve features of gray/white matter volume and surface area in several left hemisphere regions exhibited associations with phonological processing. Specifically, greater phonological processing was associated with greater intercepts of gray matter volume development in the left banks of the superior temporal sulcus and greater slopes of white matter volume and surface area development in left occipitotemporal, temporoparietal, and inferior frontal regions (Figure 3). Next, individual growth curves corresponding to these measures and regions were separated into three groups according to phonological processing scores with low < 85, 85 ≤ average ≤ 115, and high > 115, meaned by group, and then plotted to visualize variation in longitudinal trajectories by phonological processing score. Children with low phonological processing scores tended to have less gray matter volume in left banks of the superior temporal sulcus at birth but maintained similar rates of development compared with higher scoring children. At the same time, children with lower phonological processing had lower rates of white matter volume and surface area development in occipitotemporal, temporoparietal, and inferior frontal regions (Figure 4). In addition, greater oral language skills correlated with slopes of white matter volume development in left banks of the superior temporal sulcus and inferior parietal cortex. However, no associations were observed between curve features for cortical thickness or mean curvature and literacy subskills.

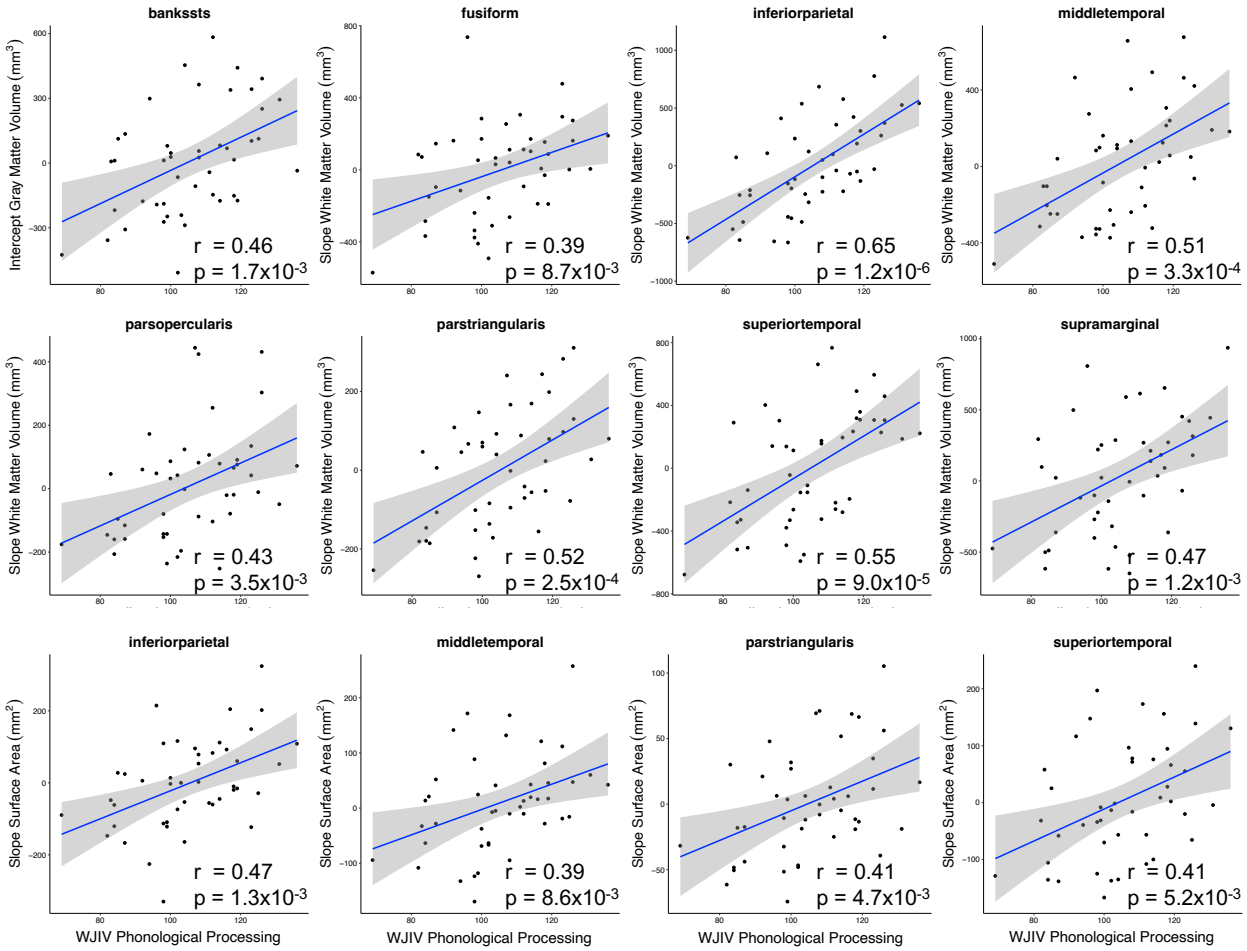

Figure 3. Statically significant associations between growth curve features of brain volume and surface area and preschool phonological processing. Gray matter volume in the left banks of the superior temporal sulcus exhibited an association between growth curve intercepts and phonological processing, whereas all associations with white matter and surface area were between growth curve slopes and phonological processing. All associations pass $p_{FDR} < 0.05$. WJIV, Woodcock-Johnson IV.

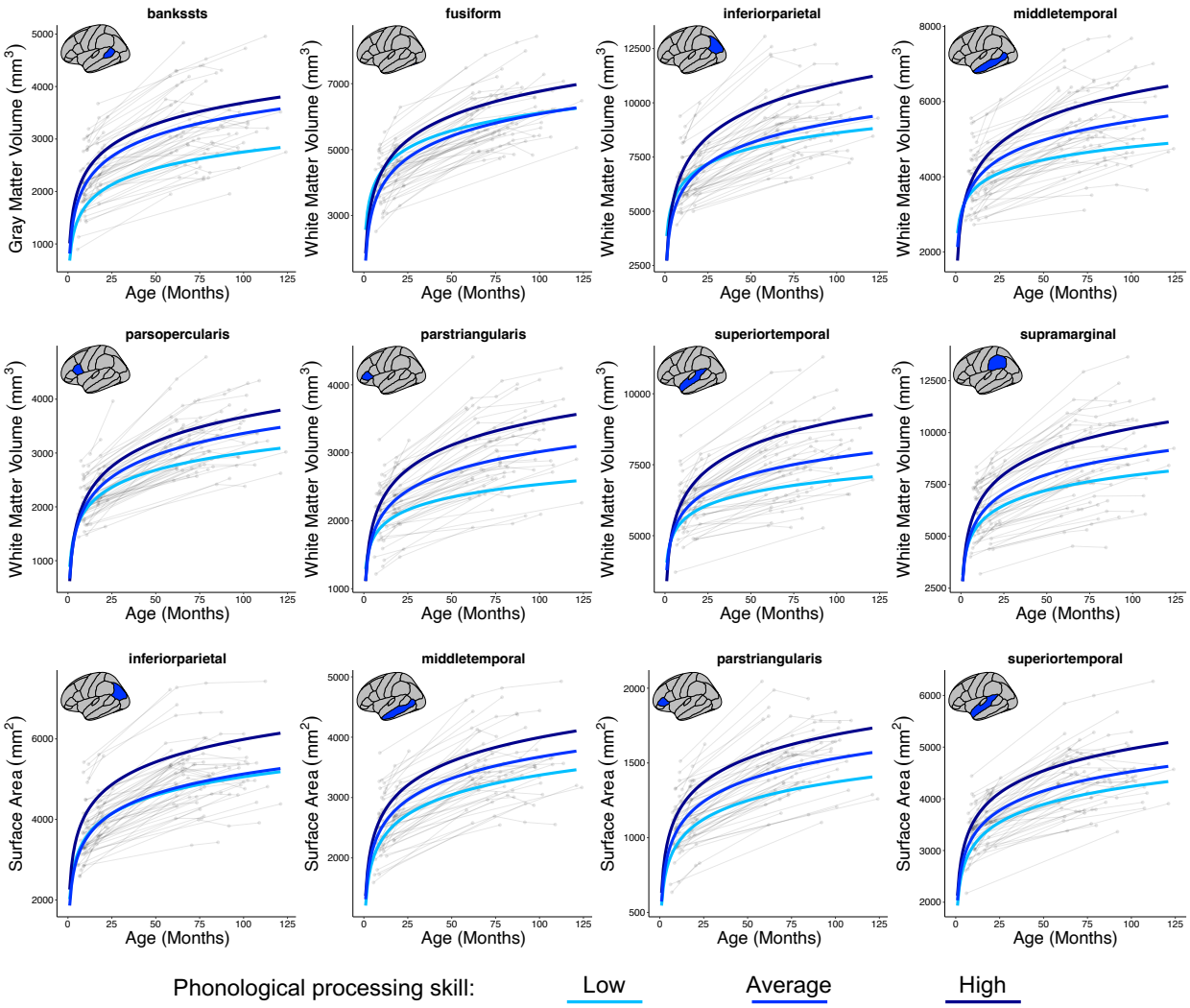

Figure 4. Longitudinal trajectories of brain structure from infancy to early adolescence according to phonological processing skill in preschool. Graphs depict average trajectories for children with low (< 85), average (85 – 115), and high (> 115) standardized phonological processing scores for measures and regions whose intercepts or slopes correlated with phonological processing (p_{FDR} < 0.05). Children with low phonological processing in preschool tended to have attenuated longitudinal trajectories, either because they began lower, as with less gray matter volume in the left banks of the superior temporal gyrus at birth (upper left graph), or because they had slower rates of development, as with white matter volume and surface area trajectories in other left hemisphere brain regions.

Curve features of white matter organization in left hemisphere tracts also correlated with phonological processing outcomes. Greater phonological processing skill was associated with lower intercepts and greater slopes of mean diffusivity along left arcuate fasciculus and superior longitudinal fasciculus (Figure 5). When distinguishing longitudinal trajectories according to literacy subskills (i.e., low < 85, 85 ≤ average ≤ 115, and high > 115), as with volumetric and surface-based measures above, children with low phonological processing scores tended to have

higher mean diffusivity at birth but greater rates of mean diffusivity development (i.e., more negative slopes) compared with higher scoring children (Figure 6). No associations were observed for oral language skill or between fractional anisotropy curve features or mean diffusivity curve features for inferior longitudinal fasciculus and either of the two literacy subskills.

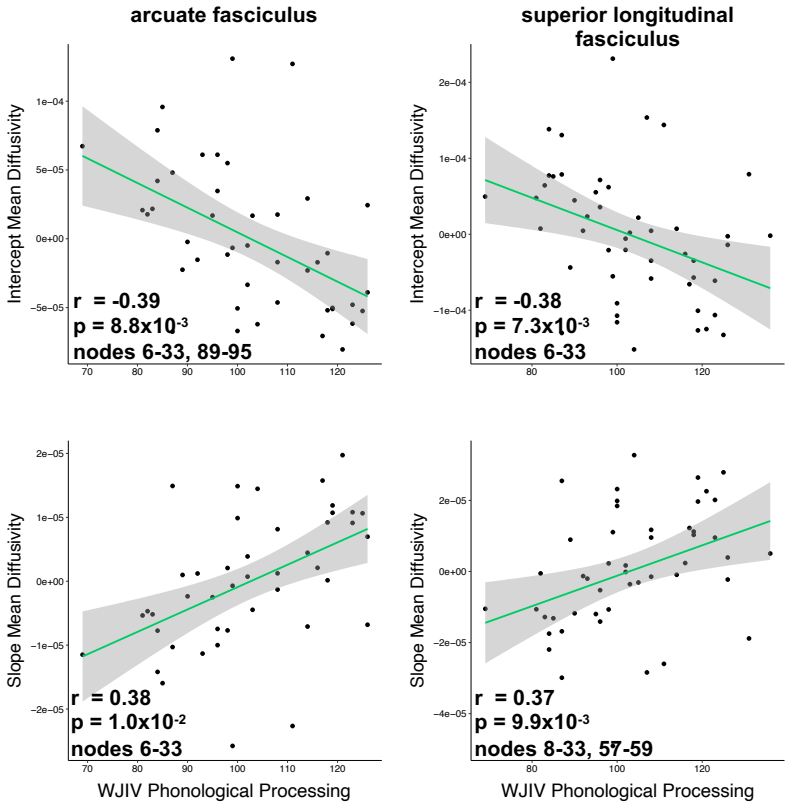

Figure 5. Statistically significant associations between growth curve features of white matter organization and preschool phonological processing. Mean diffusivity in the left arcuate and superior longitudinal fasciculi exhibited associations between growth curve intercepts and slopes and phonological processing. All associations are cluster-level corrected at $p_{FDR} < 0.05$. WJIV, Woodcock-Johnson IV.

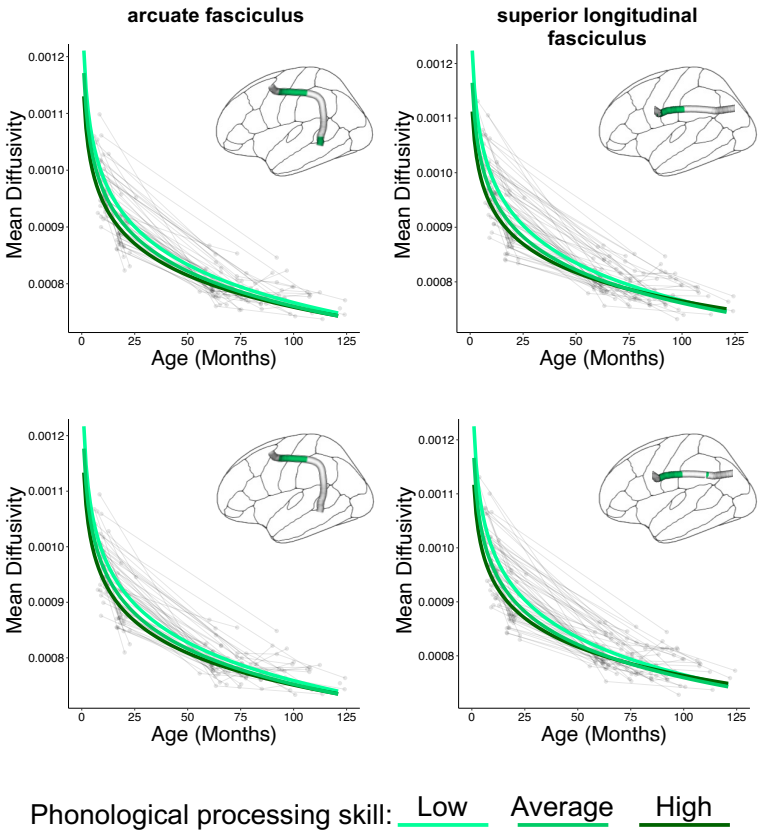

Figure 6. Longitudinal trajectories of mean diffusivity from infancy to early adolescence according to phonological processing skill in preschool. Graphs depict average trajectories for children with low (< 85), average (85 – 115), and high (> 115) standardized phonological processing scores for tracts and nodes whose intercepts (top panel) or slopes (bottom panel) correlated with phonological processing ($p_{FDR} < 0.05$). Children with low phonological processing tended to begin with greater mean diffusivity in anterior arcuate and superior longitudinal fasciculi at birth but exhibit faster development (i.e., more negative slope) in an overlapping region of these tracts.

3.4. *Sensitivity Analyses*

We performed three sensitivity analyses to test the robustness of the observed brain-behavior relationships. For the first sensitivity analysis, we re-fit our volumetric, surface area, and mean diffusivity estimates with nonlinear mixed effects models using asymptotic functions (Supplementary Figures 10-13). This alternative model to characterize longitudinal trajectories was especially important for mean diffusivity findings, where intercepts and slopes from the main analysis were correlated for many nodes in each tract examined.

We observed that greater phonological processing was still associated with greater intercepts of gray matter volume development in the left banks of the superior temporal sulcus. Whereas our main analyses allowed us to examine relationships between brain development and

literacy subskills directly by using a random slopes term, the nonlinear model used in this sensitivity analysis replaces the random slopes term with a random asymptote term (Supplementary Table 2A). As such, relationships between brain development and language outcomes may only be inferred where brain measures and regions exhibit asymptote-behavior correlations without corresponding intercept-behavior correlations. Except for middle temporal cortex white matter volume, for which the model did not converge, all measures of brain structure and regions whose slopes correlated positively with phonological processing in the main analysis also exhibited significant associations between asymptote and phonological processing, although effect sizes were generally smaller (Supplementary Tables 2B, C). Associations with oral language did not replicate. Regarding white matter organization, greater phonological processing was associated with lower mean diffusivity intercepts in left arcuate and superior longitudinal fasciculi and lower mean diffusivity asymptotes in the left arcuate fasciculus in a subset of nodes that overlapped with the nodes identified in the main analysis (Supplementary Tables 2D).

For the second sensitivity analysis, we recomputed brain-behavior associations for volumetric and surface-based measures using semipartial correlations, controlling for curve features of the longitudinal trajectory for total intracranial volume (TIV). Relative to the results of the main analysis, effect sizes were reduced when including curve features of TIV. However, associations with phonological processing remained significant for slopes of white matter volume development in inferior parietal cortex, middle temporal cortex, pars triangularis, and superior temporal cortex and were trending for the intercept for banks of the superior temporal sulcus gray matter volume (Supplementary Table 3).

In the third sensitivity analysis, we again recomputed brain-behavior associations, this time controlling for Euler numbers as a reproducible alternative to manual quality control (Monereo-Sánchez et al., 2021). On average, effect sizes showed little drop relative to the main analysis (r_{avg} = 0.45 compared with r_{avg} = 0.47). All brain-behavior associations significant in the main analysis remained significant with the inclusion of Euler numbers, except for the association between phonological processing and the intercept for banks of the superior temporal sulcus gray matter volume and the association between oral language and inferior parietal cortex white matter volume, both of which were trending (Supplementary Table 4).

3.5. *Indirect effects between longitudinal trajectories of early brain development and word reading outcomes via literacy subskills*

Finally, we examined whether literacy subskills mediated the relationship between brain development curve features (e.g., intercepts and slopes) and timed and untimed word reading

outcomes. As a prerequisite for mediation, the mediator (i.e., phonological processing) must be associated with both the predictor (i.e., brain estimate) and outcome (i.e., word reading). We limited the potential mediator to phonological processing, which related to both untimed decoding ($r = 0.48$; $p < 0.005$) and untimed word reading ($r = 0.52$; $p < 0.001$), as measured by the Woodcock Reading Mastery Tests III word attack and word identification subtests (Woodcock, 2011), because brain-behavior associations with oral language were few and inconsistent in sensitivity analyses, and we limited the potential predictors to brain measures and regions/tracts surviving FDR correction in the main analysis. Indirect effects were reported when the 95% confidence intervals (CI), based on 10,000 bootstrapped samples, for the average causal mediation effect did not include 0 (please see Methods).

Phonological processing mediated the relationship between brain and untimed word identification for the following measures and regions/tracts: intercepts of gray matter volume development in the left banks of the superior temporal sulcus and slopes of white matter volume development in left temporo-parietal and inferior frontal regions, and surface area in inferior parietal cortex. Phonological processing also mediated associations between intercepts and slopes of mean diffusivity development in left arcuate and superior longitudinal fasciculi and untimed decoding and untimed word reading (Figure 7; Supplementary Tables 5, 6).

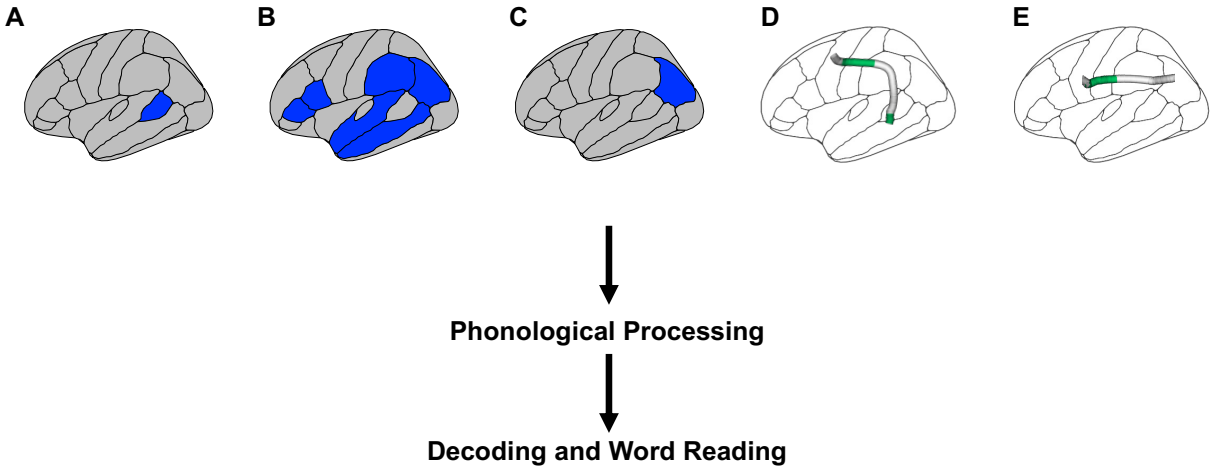

Figure 7. Phonological processing mediates the relationship between early brain development and decoding/word reading. Indirect effects (filled arrows) were found for (A) intercepts of gray matter volume in the left banks of the superior temporal sulcus; (B) slopes of white matter volume in left inferior parietal cortex, pars opercularis, pars triangularis, middle and superior temporal gyri, and supramarginal gyrus; (C) slopes of surface area in left inferior parietal cortex; and intercepts and slopes of mean diffusivity in left (D) arcuate and (E) superior longitudinal fasciculi.

4. Discussion

The brain regions and tracts that eventually support decoding and word reading, including early literacy subskills, begin to develop long before the skill itself emerges. Here, we examined the relationship between longitudinal trajectories of early brain development and acquisition of reading-related (sub)skills in three objectives. First, we generated longitudinal trajectories of early brain structure, including white matter organization, from infancy to school age in regions and tracts previously linked to literacy development (Ben-Shachar et al., 2011; Brem et al., 2010; Dehaene-Lambertz et al., 2018; Di Pietro et al., 2023; Ozernov-Palchik et al., 2023; Reynolds et al., 2019a; Roy et al., 2024; Tang et al., 2024; Wang et al., 2017; Yeatman et al., 2012a; Yu et al., 2018a, 2021; Zuk et al., 2021a), using a novel processing and analysis pipeline appropriate for the early developmental period. Findings showed that longitudinal trajectories were best modeled using logarithmic, compared with linear and quadratic, functions. Second, we examined whether familial risk of reading difficulty and home literacy environment, two common literacy-related covariates, influenced those trajectories and found that they did not. Third, we examined associations between curve features of longitudinal trajectories and long-term literacy development. Results showed that phonological processing measured in preschool/early kindergarten was related to individual differences in curve intercepts for gray matter volume (i.e., gray matter volume at birth) in left banks of the superior temporal sulcus and in curve slopes (i.e., early brain development) for white matter volume, surface area, and mean diffusivity in left temporo-parietal, occipito-temporal, and inferior frontal regions and tracts. Further, phonological processing mediated relations between these brain measures, regions, and tracts and untimed decoding and word reading skills measured between kindergarten and second grade. Overall, these findings suggest that the neural foundations for the subsequent development of phonological processing may be partially present at birth but are still forming in the years between birth and preschool and eventually supports the development of decoding and word reading skills.

Trajectories of early brain development have been generated from longitudinal studies up to the first two years of life (e.g., Gilmore et al., 2012) and from combined cross-sectional and longitudinal datasets spanning infancy to school age (e.g., Alex et al., 2024). However, methodological challenges associated with infant MRI and longitudinal designs in general have created a relative vacuum of longitudinal MRI studies spanning infancy to school age (Turesky et al., 2021a). The current study fills this gap as a purely longitudinal examination of early structural brain development in which longitudinal trajectories are generated with a pipeline designed for the early developmental period. Overall, longitudinal trajectories of gray and white matter volume, surface area, fractional anisotropy, and mean diffusivity exhibited rapid postnatal growth that

slowed with age, which largely comports with previous early developmental studies using cross-sectional 3(Deoni et al., 2012, 2012; Groeschel et al., 2010; Matsuzawa et al., 2001; Remer et al., 2017) and combined longitudinal and cross-sectional designs (Alex et al., 2024; Bethlehem et al., 2022; Geng et al., 2012; Knickmeyer et al., 2008; Reynolds et al., 2019b; Sanchez et al., 2011). As shown previously (Wang et al. 2019a; Remer et al. 2017), the curves for cortical thickness and mean curvature were generally less steep compared with other brain measures, both initially following birth and into childhood. Nonetheless, empirical comparisons with linear and quadratic functions showed that logarithmic models were more parsimonious for all measures examined.

Turning to literacy-related covariates, familial history of reading difficulty (FHD) was hypothesized to influence longitudinal trajectories of early brain development, based on previous findings showing FHD-related alterations in brain architecture in infancy (Langer et al., 2017; Yu et al., 2022) and preschool (Raschle et al., 2012a, 2011; Wang et al., 2017). Consequently, the observation that FHD status did not influence longitudinal trajectories in any regions or tracts examined was initially unexpected. However, it is important to recognize that a child who has an older sibling or parent with a reading difficulty (FHD+) does not necessarily have a genetic susceptibility for reading difficulty (Yu et al., 2018b), nor will they necessarily develop reading challenges given the multifactorial nature of reading difficulties. Rather, FHD status should be considered one of multiple risk factors that can contribute to long-term literacy development (Catts and Petscher, 2018; Ozernov-Palchik et al., 2016), either through intergenerational transmission of genes or environment (Hart et al., 2021). Consistent with this, roughly half of FHD+ children develop typical reading skills (Snowling and Melby-Lervåg, 2016; Vogler et al., 1985), and those who do have, as a group, been shown to exhibit right- and inter-hemispheric compensatory pathways (Yu et al., 2020; Zuk et al., 2021b). Therefore, it may behoove future studies with larger sample sizes to distinguish FHD+ children who develop typical reading skills from FHD+ children who do not.

The home literacy environment also did not significantly influence longitudinal trajectories, despite reported links to brain structure and function in infants (King et al., 2021; Turesky et al., 2022) and preschoolers/kindergarteners (Davison et al., 2022; Hutton et al., 2015, 2017, 2020; Powers et al., 2016; Romeo et al., 2018b). However, with few exceptions (e.g., common FHD-related reductions in left arcuate fasciculus fractional anisotropy in infants (Langer et al., 2017) and preschoolers (Wang et al., 2017), specific brain measures and regions/tracts linked to home literacy environment variables identified at the infant time point were not also identified at the preschool/kindergarten time point, suggesting that brain-home literacy environment relations may

vary across this developmental window. Future longitudinal studies with more frequent sampling of observations will be needed to test whether this explanation is accurate.

After generating longitudinal trajectories with covariates that could influence brain development, we examined how this brain development in turn influenced literacy development by relating curve features of individual trajectories to reading-related subskills measured in preschool/early kindergarten as well as decoding and word reading skills measured between kindergarten and second grade. The finding of direct links to phonological processing and indirect links to word reading and decoding from curve intercepts of gray matter volume (i.e., gray matter volume at birth) specifically in the left banks of the superior temporal sulcus is compelling in the context of a recent large-scale genomics study showing common genetic influences on surface area in this region and reading-related skills (Eising et al., 2022), including from a gene involved in neurogenesis and axon formation (Watabe-Uchida et al., 2006). Combined with prior work showing an association between reading difficulty and left temporo-parietal sulcal patterns determined in utero (Im et al., 2016), these findings offer convergent evidence for a mechanistic pathway through which genetic factors shape the foundations of reading development via prenatal left temporo-parietal brain development. While this intercept-outcome effect was robust when re-analyzing using a nonlinear, as opposed to linear, mixed effects model (i.e., first sensitivity analysis), this interpretation should be viewed with caution, as effects were mitigated in two out of three sensitivity analyses.

The finding in the left banks of the superior temporal sulcus also supports the hypothesis that school-age literacy skill is built on an early-developing foundation (Cusack et al., 2024) or 'neural scaffold' (Tang et al., 2024; Yu et al., 2021; Zuk et al., 2021a). However, the paucity of intercept-outcome associations in contrast to the multitude of slope-outcome associations and brain-behavior associations from cross-sectional studies in older children suggests that this neural scaffold develops substantially over the first several years of life. This is partially exemplified with white matter organization in the left arcuate fasciculus, whereby associations with later phonological processing were observed in prior work in 10-month-old infants (Zuk et al., 2021a) and in the current study for early rates of development but not for estimates at birth. As the arcuate fasciculus undergoes rapid development during the first year, as shown in the current study and elsewhere (Geng et al., 2012), it is possible that it has not yet developed sufficiently by birth to contribute to the neural scaffolding of subsequent literacy development but may have developed sufficiently by 10 months. Overall, the presence of slope-outcome associations offers insights into the early development of a neural scaffold for literacy and in doing so, underscores the importance

of examining individual longitudinal trajectories (Bonte and Brem, 2024), as opposed to cross-sectional and prospective associations.

It was also interesting that most of the slope-outcome findings were with white matter properties, and nearly all of these remained significant in all sensitivity analyses. While no prior study has examined the relationship between long-term literacy subskills and longitudinal trajectories of white matter development beginning in infancy (or early development of surface-based measures) there is a small corpus of literature that has linked reading-related skill performance to short-term, school-age developmental changes in left temporo-parietal white matter volume (Myers et al., 2014) and organization, most consistently in the left arcuate fasciculus (Myers et al., 2014; Roy et al., 2024; Wang et al., 2017; Yeatman et al., 2012a). This is especially compelling when considering that the slope-outcome relationship we observed with white matter organization was specific to the left arcuate fasciculus and to phonological processing, which is highly predictive of subsequent word reading and decoding performance (Melby-Lervåg et al., 2012; Moll et al., 2013; Scarborough, 2001; Wagner and Torgesen, 1987). This finding also comports with a prior mixed longitudinal and cross-sectional study showing that phonological processing was associated with left arcuate fasciculus white matter organization development in children two to seven years of age (Reynolds et al., 2019a). Work from genomics might offer further explanation for the dominance of white matter associations, as genes involved in axon guidance (Hannula-Jouppi et al., 2005), axon formation (Watabe-Uchida et al., 2006), and oligodendrocyte maturation (Reiche et al., 2021) have also been linked to reading-related skills (Eising et al., 2022) and reading disability (Doust et al., 2022; Price et al., 2022). Although white matter volume and organization are not strongly associated and thought to be sensitive to different properties (Fjell et al., 2008), their reliance on myelination, the primary function of oligodendrocytes, and other axonal properties suggests that they may represent another mechanism through which genetic factors may shape early brain development.

Interestingly, nearly all direct brain-behavior associations were with phonological processing and not with oral language skills. Prior brain imaging studies in preschoolers/kindergarteners comport with this finding as phonological processing seems to exhibit more consistent associations with brain architecture (Hoeft et al., 2007a; Raschle et al., 2011, 2012a, 2014; Saygin et al., 2013; Vandermosten et al., 2012), compared with oral language skills (Marks et al., 2019; Romeo et al., 2018a, b; c.f. Davison et al., 2022; Raschle et al., 2014). While both subskills are considered critical for higher-level reading-related skills, they are thought to function on two distinguishable developmental pathways, whereby phonological processing is more involved in recognizing and decoding printed words and oral language skills are more

essential for the development of reading comprehension skills (please see Scarborough's Reading Rope; Scarborough, 2001). It should be noted that this framework also fits with our mediation findings, which show indirect relations between early brain development and untimed decoding and (printed) word reading via phonological processing. Furthermore, whereas phonological processing is limited in its scope, as specifically one's ability to recognize and manipulate sounds in a word (Goswami, 2010, 2019; Wagner et al., 1987; Wagner and Torgesen, 1987), oral language was measured in the current study as a composite of vocabulary and oral comprehension subtests, with the latter requiring children to engage with semantic and syntactic cues. As different brain regions may be more specialized for certain component language skills (e.g., pars opercularis may be more involved in syntactic processing while pars triangularis and middle temporal gyrus may be more involved in semantics; Friederici, 2012; Wang et al., 2019b), aggregating distinct oral language skills may have obscured brain-behavior associations. Conversely, it is also conceivable that oral language acquisition requires additional, moderating factors that were not modeled in the present study (e.g., social interactions (Kuhl, 2004) or conversational turn-taking (Romeo et al., 2018b)). Nevertheless, the necessity of phonological processing for literacy development and its relation to early brain development reported here underscore the importance of examining reading-related subskills at the very beginnings of life.

This study had four main limitations. First, consistent with prior work (e.g., Alex et al., 2024), the models we fit to early brain development generated smooth longitudinal trajectories. In actuality, it is unlikely that early brain development transpires as predictably, especially during sensitive and critical periods (Nelson and Gabard-Durnam, 2020) or specific learning milestones (Bonte and Brem, 2024). Although participants in the current study were sampled nearly three times on average, which is preferred for modeling growth curves (Curran et al., 2010) and more than most longitudinal imaging studies (Telzer et al., 2018), future studies would benefit from increased sampling, particularly around learning milestones germane to literacy development. Second, the sample size in the current study was relatively small when compared with the sample sizes used in multi-site, combined cross-sectional and longitudinal studies (e.g., Alex et al., 2024; Bethlehem et al., 2022). While sensitivity analyses for the most part demonstrated the robustness of the results, future studies with larger sample sizes will be needed to confirm the findings presented here. Third, cortical thickness, mean curvature, fractional anisotropy, and mean diffusivity exhibited high correlations between random parameters (i.e., intercept-slope correlations) when modeled with logarithmic functions, which spurred concerns over the accuracy of the estimated random parameters. For the current findings, inaccurate random parameters could generate false negatives for the former three measures and false positive for mean

diffusivity. Consequently, for the former three parameters, even though they were consistently better fit with logarithmic functions, we re-analyzed intercept-outcome and slope-outcome associations using random parameters from models with quadratic functions, which had considerably lower intercept-slope correlations. Despite this, results remained non-significant. Meanwhile, the first sensitivity analysis addressed concerns for mean diffusivity by showing that nonlinear mixed effects models using asymptotic functions decoupled intercepts and slopes while maintaining the significant results observed in the main analysis. It is also important to note that this limitation does not apply to findings for gray and white matter volume or surface area. Fourth, we took a narrow approach to examining literacy-related factors that could contribute to early brain development by only including FHD status and home literacy environment, and it is likely that factors not included also contribute to the longitudinal trajectories examined (e.g., teaching efficiency or executive functioning skills; Ozernov-Palchik et al., 2016). Overall, interpretations of findings should be considered in the context of these limitations.

In conclusion, this study examined associations between longitudinal trajectories of early brain development beginning in infancy and long-term reading acquisition, specifically literacy subskills. Longitudinal trajectories were generated using a novel, reproducible pipeline we designed specifically for examining early brain development and included familial risk of a reading difficulty and environmental covariates. Findings indicate that preschool/early kindergarten phonological processing, one of the strongest predictors of subsequent word reading development, relates to gray matter volume in the left banks of the superior temporal sulcus at birth and development of white matter volume, surface area, and mean diffusivity in left temporo-parietal, occipito-temporal, and inferior frontal regions and tracts. These findings offer further evidence for a neural scaffold for literacy development, which is present at birth and continues forming across the first several years of life. The present study also provides a roadmap for future longitudinal studies to examine the relationship between early brain development and acquisition of other academic skills. Understanding when the foundations for reading emerge can deliver important insights into the development of instructional approaches and preventative, and intervention strategies.

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Supplementary Tables

Supplementary Table 1. Comparison of Linear Mixed Effects Models

	Random Intercept			Random Intercept and Slope			
Brain Area	Logarithmic	Linear	Quadratic	Logarithmic	Linear	Quadratic	p-value
A. Gray Matter Volume							
bankssts	2180	2231	2191	**2143**	2218	2165	1.68E-12
fusiform	2597	2682	2607	**2571**	2678	2580	9.49E-10
inferiorparietal	2735	2840	2739	**2723**	2841	2732	1.83E-05
middletemporal	2624	2737	2643	**2589**	2730	2620	8.74E-14
parsopercularis	2418	2485	2444	**2392**	2483	2426	2.25E-13
parstriangularis	2368	2469	2375	**2343**	2466	2361	4.15E-09
superiortemporal	2688	2794	2715	**2663**	2792	2697	1.96E-13
supramarginal	2696	2785	2717	**2677**	2785	2696	1.07E-10
B. White Matter Volume							
bankssts	2119	2158	2127	**2059**	2126	2079	8.36E-17
fusiform	2357	2394	2365	**2316**	2381	2344	8.83E-13
inferiorparietal	2473	2523	2468	**2416**	2498	2433	2.17E-13
middletemporal	2362	2383	2356	**2315**	2362	2323	4.35E-11
parsopercularis	2184	2229	2186	**2136**	2202	2152	4.83E-13
parstriangularis	2191	2215	2192	**2109**	2174	2123	2.02E-20
superiortemporal	2349	2365	2352	**2295**	2330	2313	1.33E-14
supramarginal	2537	2565	2544	**2473**	2535	2485	1.44E-17
C. Surface Area							
bankssts	1886	1927	1892	**1843**	1909	1861	9.18E-13
fusiform	2131	2217	2144	**2114**	2217	2139	1.33E-08
inferiorparietal	2319	2397	2320	**2302**	2394	2315	9.96E-06
middletemporal	2123	2188	2135	**2110**	2184	2132	2.27E-07
parsopercularis	1929	1993	1942	**1908**	1984	1934	1.91E-09
parstriangularis	1843	1919	1854	**1806**	1909	1843	1.85E-12
superiortemporal	2205	2276	2219	**2183**	2268	2204	5.46E-10
supramarginal	2348	2406	2361	**2323**	2401	2340	1.74E-10
D. Cortical Thickness							
bankssts	-121	-114	-115	**-133**	-115	-118	6.72E-06
fusiform	-207	-193	-205	**-226**	-200	-214	1.96E-06
inferiorparietal	-223	-215	-221	**-239**	-224	-230	9.05E-06
middletemporal	-127	-96	-119	**-133**	-93	-122	8.28E-05
parsopercularis	-159	-150	-151	**-168**	-150	-155	1.31E-05
parstriangularis	-151	-137	-151	**-163**	-138	-156	2.26E-04
superiortemporal	-161	-127	-151	**-163**	-124	-153	1.88E-04
supramarginal	-184	-169	-181	**-187**	-167	-180	5.55E-03

E. Mean Curvature							
bankssts	-1036	-1024	-1039	**-1057**	-1031	-1057	6.30E-06
fusiform	-1040	-1028	-1039	**-1072**	-1039	-1062	2.76E-09
inferiorparietal	-1029	-1017	-1026	**-1074**	-1035	-1057	1.42E-12
middletemporal	-1006	-996	-1005	**-1029**	-1002	-1021	4.17E-07
parsopercularis	-1029	-1020	-1028	**-1063**	-1036	-1050	1.08E-09
parstriangularis	-1024	-1012	-1022	**-1050**	-1021	-1039	5.06E-08
superiortemporal	-1062	-1052	-1061	**-1088**	-1062	-1080	5.90E-08
supramarginal	-1009	-996	-1010	**-1037**	-1004	-1031	7.77E-08
F. Fractional Anisotropy							
arcuate fasciculus	**-777**	-666	-748	-775	-663	-748	NA
superior longitudinal fasciculus	**-922**	-777	-902	-920	-773	-906	NA
inferior longitudinal fasciculus	-889	-780	-837	**-894**	-778	-843	1.57E-14
G. Mean Diffusivity							
arcuate fasciculus	-2934	-2826	-2880	**-2957**	-2830	-2903	5.71E-19
superior longitudinal fasciculus	-3265	-3115	-3191	**-3294**	-3121	-3218	1.14E-24
inferior longitudinal fasciculus	-3233	-3127	-3175	**-3251**	-3134	-3191	7.35E-19

Bold indicates lowest AIC value

Supplementary Table 2 Brain-behavior associations with nonlinear mixed effects model (phonological processing only)

Brain Area	Intercept		Asymptote	
A. Gray Matter Volume	r	p	r	p
bankssts	0.50	5.2E-04	0.36	1.5E-02
fusiform	0.07	6.7E-01	0.14	3.8E-01
inferiorparietal	0.32	3.4E-02	0.35	1.8E-02
middletemporal	0.24	1.1E-01	0.23	1.4E-01
parsopercularis	0.23	1.3E-01	0.19	2.1E-01
parstriangularis	0.32	3.3E-02	0.34	2.1E-02
superiortemporal	0.27	7.8E-02	0.19	2.2E-01
supramarginal	0.24	1.1E-01	0.12	4.3E-01
	Intercept		Asymptote	
B. White Matter Volume	r	p	r	p
bankssts	0.21	1.6E-01	0.20	1.8E-01
fusiform	0.02	8.7E-01	0.31	3.5E-02
inferiorparietal	0.08	5.8E-01	0.48	7.4E-04
middletemporal	NA	NA	NA	NA
parsopercularis	0.05	7.4E-01	0.35	1.8E-02

parstriangularis	0.25	1.0E-01	0.46	1.5E-03
superiortemporal	0.06	7.0E-01	0.37	1.2E-02
supramarginal	0.13	3.9E-01	0.30	4.2E-02

	Intercept		Asymptote	
C. Surface Area	r	p	r	p
bankssts	0.48	7.8E-04	0.36	1.5E-02
fusiform	0.10	5.0E-01	0.22	1.5E-01
inferiorparietal	0.28	6.7E-02	0.44	2.4E-03
middletemporal	0.19	2.2E-01	0.32	3.2E-02
parsopercularis	0.22	1.4E-01	0.23	1.3E-01
parstriangularis	0.39	7.7E-03	0.39	8.9E-03
superiortemporal	0.26	8.2E-02	0.31	4.0E-02
supramarginal	0.24	1.1E-01	0.14	3.5E-01

	Intercept		Asymptote	
D. Mean Diffusivity	r*	p*	r*	p*
arcuate fasciculus	-0.38	9.3E-03	-0.37	9.9E-03
superior longitudinal fasciculus	-0.36	-3.6E-01	NA	NA

*averaged across $p_{FDR} < 0.05$ significant nodes

Supplementary Table 3. Brain-behavior associations controlling for TIV

Brain Area	Measure-Curve Feature	Behavioral Measure	r	p
bankssts	GMV-intercept	phonological processing	0.42	3.8E-03
fusiform	WMV-slope	phonological processing	0.23	1.3E-01
inferiorparietal	WMV-slope	phonological processing	0.52	2.6E-04
middletemporal	WMV-slope	phonological processing	0.39	9.2E-03
parsopercularis	WMV-slope	phonological processing	0.33	2.8E-02
parstriangularis	WMV-slope	phonological processing	0.38	1.2E-02
superiortemporal	WMV-slope	phonological processing	0.40	7.1E-03
supramarginal	WMV-slope	phonological processing	0.29	5.4E-02
inferiorparietal	SA-slope	phonological processing	0.28	6.9E-02
middletemporal	SA-slope	phonological processing	0.19	2.1E-01
parstriangularis	SA-slope	phonological processing	0.22	1.5E-01
superiortemporal	SA-slope	phonological processing	0.15	3.4E-01
bankssts	WMV-slope	oral language	0.27	6.3E-02
inferiorparietal	WMV-slope	oral language	0.28	5.3E-02

GMV, gray matter volume; WMV, white matter volume; SA, surface area

Supplementary Table 4. Brain-behavior associations controlling for Euler numbers

Brain Area	Measure-Curve Feature	Behavioral Measure	r	p
bankssts	GMV-intercept	phonological processing	0.42	4.3E-03
fusiform	WMV-slope	phonological processing	0.37	1.3E-02
inferiorparietal	WMV-slope	phonological processing	0.62	4.5E-06
middletemporal	WMV-slope	phonological processing	0.50	5.4E-04

parsopercularis	WMV-slope	phonological processing	0.43	3.5E-03
parstriangularis	WMV-slope	phonological processing	0.49	6.7E-04
superiortemporal	WMV-slope	phonological processing	0.54	1.2E-04
supramarginal	WMV-slope	phonological processing	0.45	1.9E-03
inferiorparietal	SA-slope	phonological processing	0.49	6.0E-04
middletemporal	SA-slope	phonological processing	0.46	1.6E-03
parstriangularis	SA-slope	phonological processing	0.39	8.0E-03
superiortemporal	SA-slope	phonological processing	0.48	9.3E-04
bankssts	WMV-slope	oral language	0.33	1.8E-02
inferiorparietal	WMV-slope	oral language	0.30	3.6E-02

GMV, gray matter volume; WMV, white matter volume; SA, surface area

Supplementary Table 5. Indirect effects between brain and decoding via phonological processing

Brain Area	Measure-Curve Feature	Effect size	Lower CI	Upper CI	p-value
bankssts	GMV-intercept	1.3E-02	3.3E-03	2.7E-02	3.8E-03
fusiform	WMV-slope	7.6E-03	-1.7E-04	2.1E-02	5.6E-02
inferiorparietal	WMV-slope	8.7E-03	1.1E-03	2.0E-02	2.2E-02
middletemporal	WMV-slope	1.1E-02	1.5E-03	2.5E-02	1.3E-02
parsopercularis	WMV-slope	2.0E-02	3.9E-03	4.5E-02	5.2E-03
parstriangularis	WMV-slope	2.4E-02	6.1E-03	4.8E-02	2.0E-03
superiortemporal	WMV-slope	9.1E-03	1.9E-03	2.3E-02	8.8E-03
supramarginal	WMV-slope	6.4E-03	2.7E-04	1.6E-02	3.6E-02
inferiorparietal	SA-slope	1.9E-02	2.0E-03	4.6E-02	1.7E-02
middletemporal	SA-slope	2.1E-02	-2.5E-03	6.6E-02	9.2E-02
parstriangularis	SA-slope	6.2E-02	-1.1E-03	1.5E-01	5.8E-02
superiortemporal	SA-slope	1.7E-02	-1.8E-03	4.7E-02	8.6E-02
arcuate fasciculus*	MD-intercept	-5.5E+04	-1.2E+05	-9.8E+03	1.6E-02
arcuate fasciculus*	MD-slope	2.8E+05	5.4E+04	6.1E+05	1.6E-02
superior longitudinal fasciculus*	MD-intercept	-4.9E+04	-1.0E+05	-1.5E+04	4.1E-03
superior longitudinal fasciculus*	MD-slope	1.9E+05	3.9E+04	4.4E+05	3.3E-02

*averaged across $p_{FDR} < 0.05$ significant nodes
GMV, gray matter volume; WMV, white matter volume; SA, surface area; MD, mean diffusivity

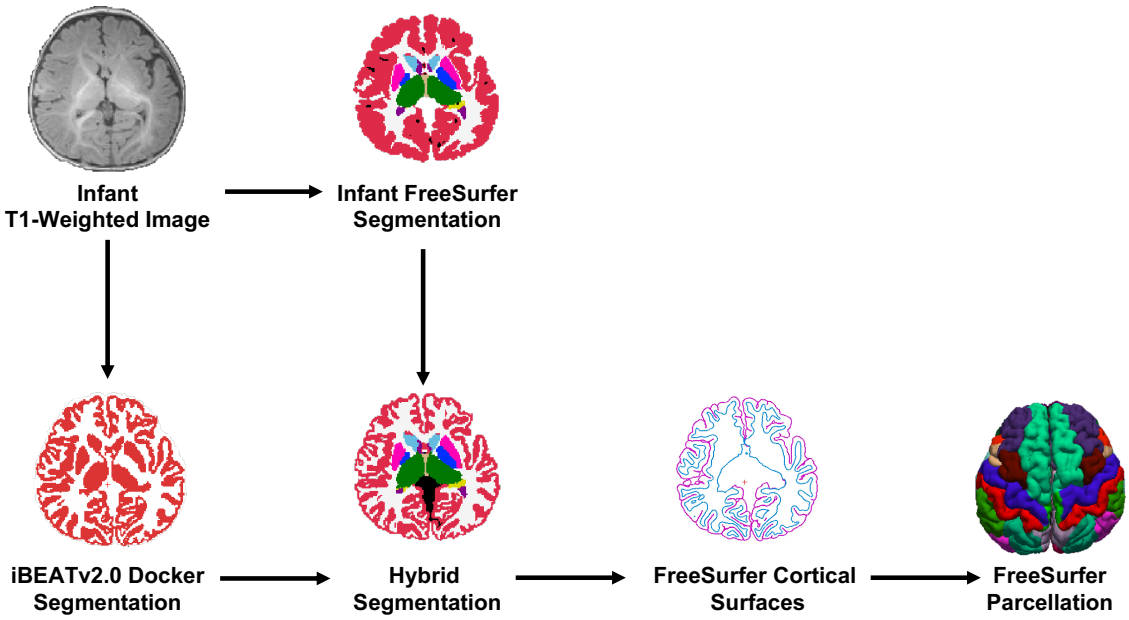
Supplementary Table 6. Indirect effects between brain and word reading via phonological processing

Brain Area	Measure-Curve Feature	Effect size	Lower CI	Upper CI	p-value
bankssts	GMV-intercept	1.7E-02	5.0E-03	3.4E-02	3.2E-03
fusiform	WMV-slope	9.7E-03	-3.5E-04	2.6E-02	5.9E-02

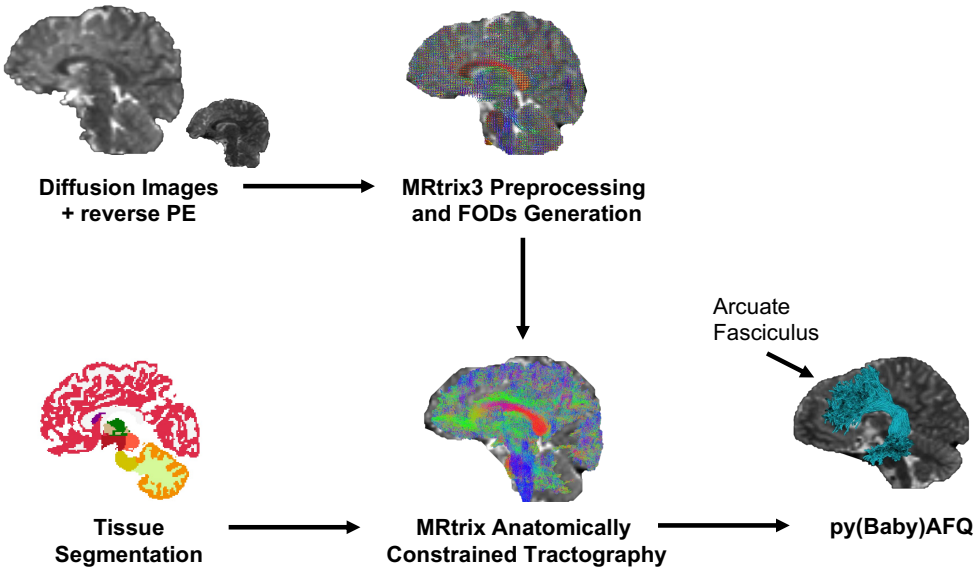
inferiorparietal	WMV-slope	1.1E-02	1.9E-03	2.6E-02	1.4E-02
middletemporal	WMV-slope	1.4E-02	2.6E-03	3.2E-02	1.1E-02
parsopercularis	WMV-slope	2.9E-02	7.1E-03	5.9E-02	5.2E-03
parstriangularis	WMV-slope	3.4E-02	9.5E-03	6.6E-02	1.8E-03
superiortemporal	WMV-slope	1.3E-02	3.2E-03	3.1E-02	2.8E-03
supramarginal	WMV-slope	8.2E-03	5.6E-04	2.0E-02	3.2E-02
inferiorparietal	SA-slope	2.8E-02	4.3E-03	6.5E-02	6.5E-02
middletemporal	SA-slope	3.0E-02	-2.6E-03	9.0E-02	9.0E-02
parstriangularis	SA-slope	8.5E-02	-1.4E-03	2.0E-01	2.0E-01
superiortemporal	SA-slope	2.6E-02	-1.4E-03	6.5E-02	6.5E-02
arcuate fasciculus*	MD-intercept	-6.6E+04	-1.4E+05	-1.4E+04	1.2E-02
arcuate fasciculus*	MD-slope	3.4E+05	7.2E+04	7.4E+05	1.6E-02
superior longitudinal fasciculus*	MD-intercept	-5.8E+04	-1.2E+05	-1.9E+04	3.1E-03
superior longitudinal fasciculus*	MD-slope	2.3E+05	4.8E+04	5.2E+05	3.5E-02

*averaged across $p_{FDR} < 0.05$ significant nodes
GMV, gray matter volume; WMV, white matter volume; SA, surface area; MD, mean diffusivity

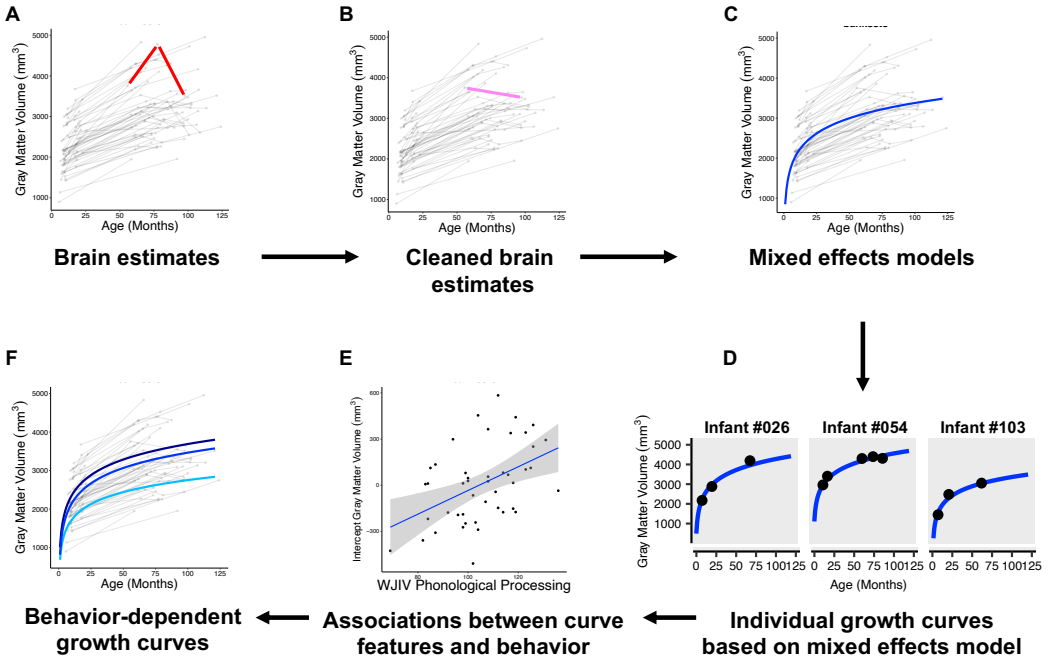
Supplementary Figures



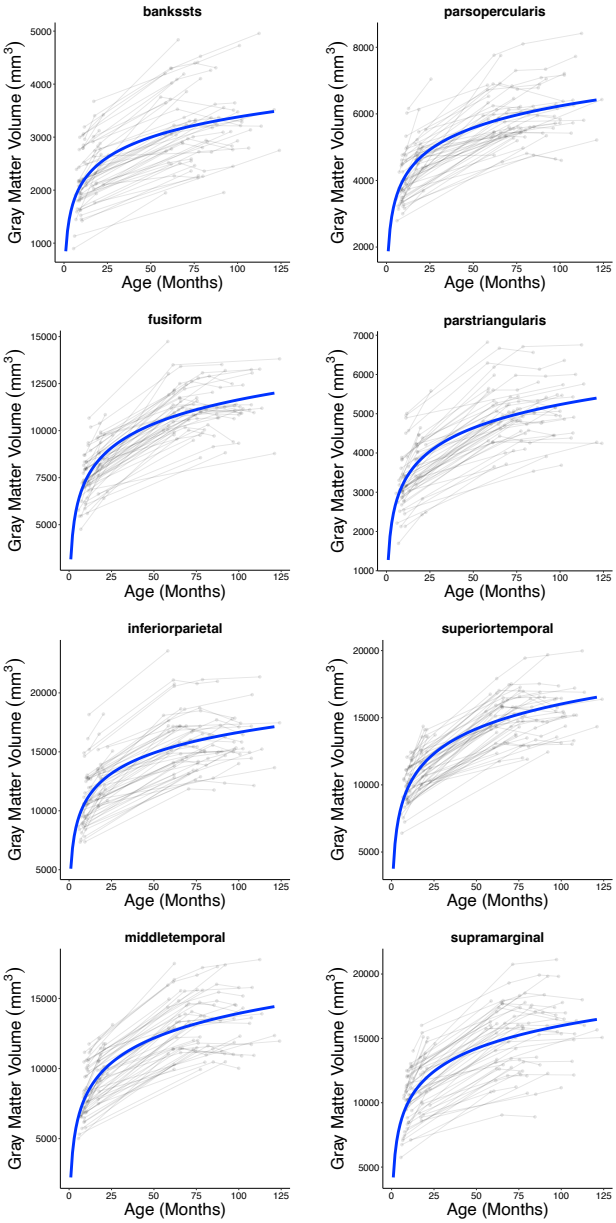
Supplementary Figure 1. Infant Structural Processing Pipeline Overview. Raw images without visual artifacts were processed using a combination of iBEATv2.0 Docker, Infant FreeSurfer, FreeSurfer, and in-house scripts. Cortical surfaces were visually inspected for tissue classification accuracy (please see Methods section for details).



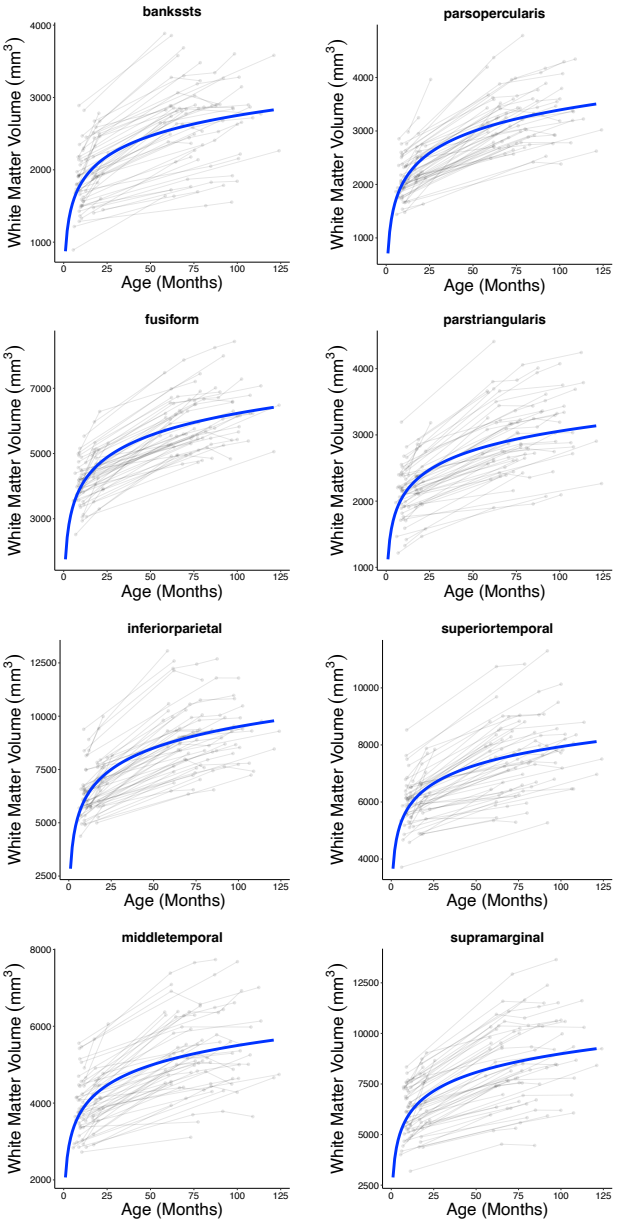
Supplementary Figure 2. Diffusion Processing Pipeline Overview. Diffusion data were denoised and then corrected for susceptibility distortions, eddy currents, head motion, and intensity inhomogeneity using MRtrix with FSL and ANTs implementations. Fiber orientation densities (FODs) were generated using constrained spherical deconvolution. Fibers were tracked with Anatomically Constrained Tractography, which leveraged the tissue segmentations from the structural processing pipeline (Supplementary Figure 1): the hybrid segmentation for brains ≤ 24 months and the standard FreeSurfer segmentation for brains > 50 months. Fibers were segmented into tracts using pyBabyAFQ for brains ≤ 24 months and pyAFQ for brains > 50 months (the left arcuate fasciculus is depicted as an example). PE, phase encoding.



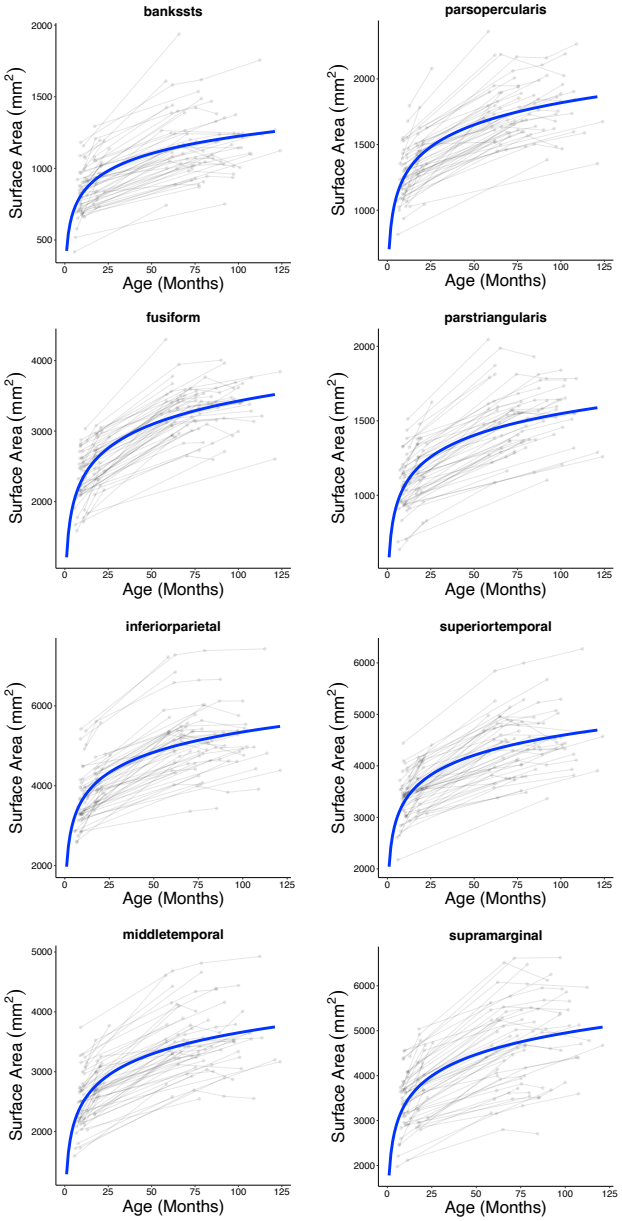
Supplementary Figure 3. Statistical Analysis Overview. (A, B) Structural and diffusion brain estimates for regions and tracts of interest are first cleaned to remove observations with inter-timepoint changes that are not neurophysiologically plausible (example inter-timepoint segments in red); remaining timepoints are then bridged (pink segment). Please see Methods for determining whether to remove the estimate preceding or following the problematic inter-timepoint change. (C) Mixed effects models, here using logarithmic functions and random intercept and slope terms, were used to generate (D) individual growth curves. (E) Brain-behavior associations were tested using curve features (i.e., random intercepts and slopes). (F) Individual growth curves for measures and regions/tracts with significant brain-behavior associations were divided into low (< 85, dotted line), average (85 – 115, solid line), and high (> 115, dashed line) behavioral performance, meaned within groups, and plotted. WJIV, Woodcock-Johnson IV.



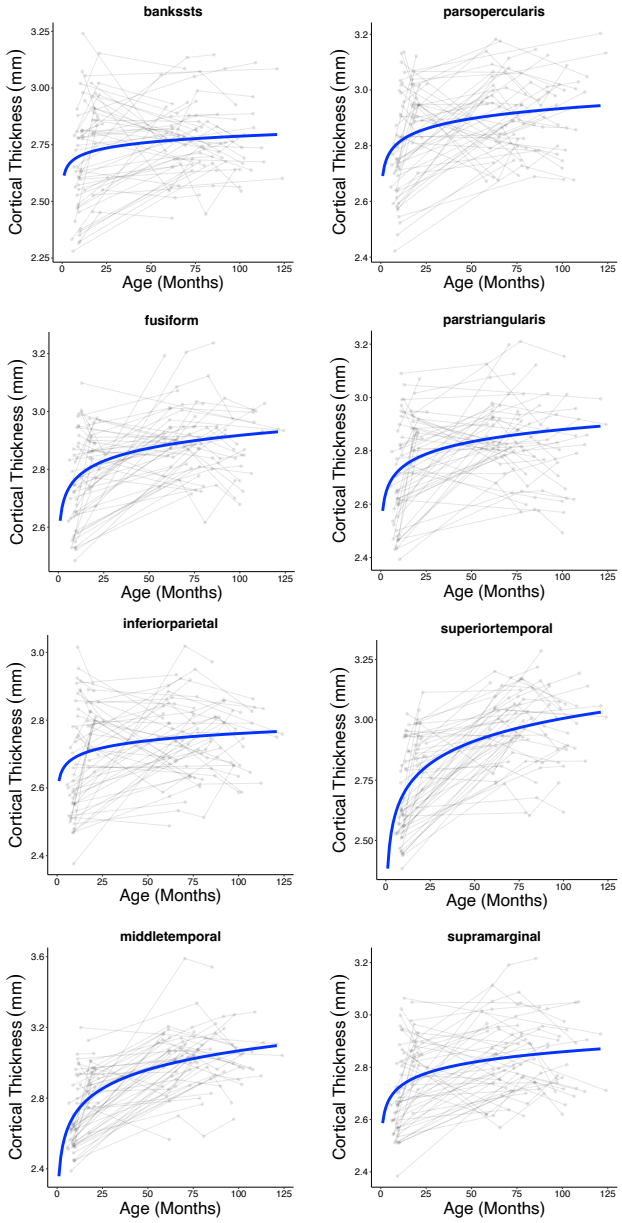
Supplementary Figure 4. Longitudinal trajectories of gray matter volume between infancy and early adolescence. Raw estimates of gray matter volume (gray spaghetti plot backdrop) were submitted to linear mixed effects models using a logarithmic function. Individual growth curves predicted by this model were averaged to show the overall longitudinal trajectory of the sample (blue line).



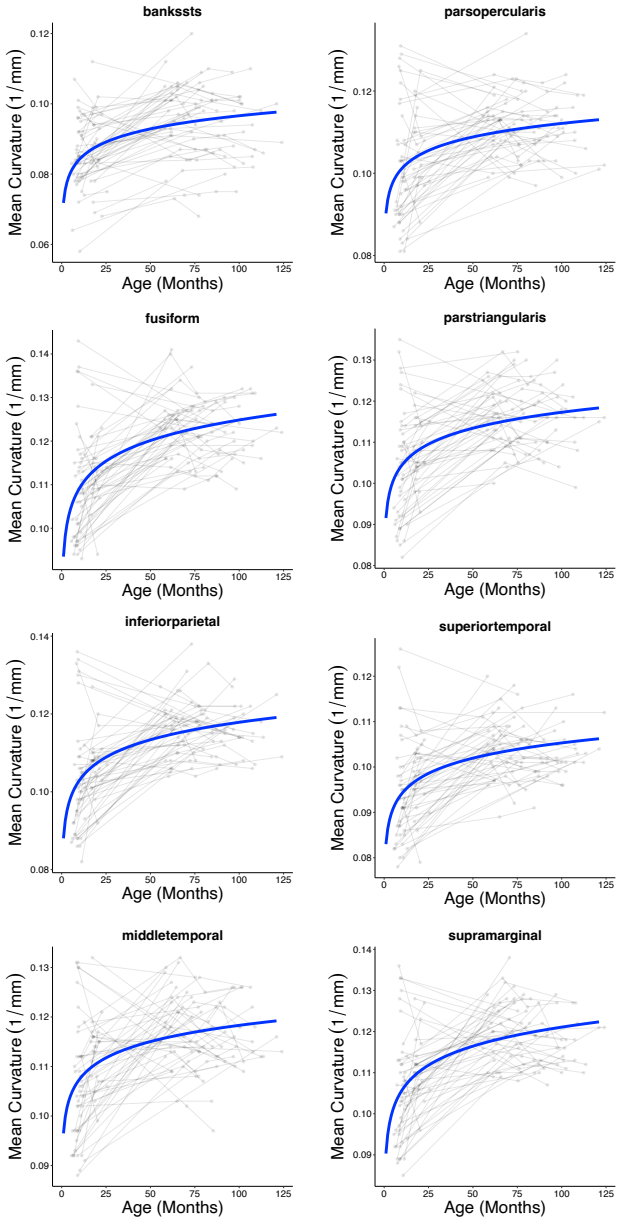
Supplementary Figure 5. Longitudinal trajectories of white matter volume between infancy and early adolescence. Raw estimates of white matter volume (gray spaghetti plot backdrop) were submitted to linear mixed effects models using a logarithmic function. Individual growth curves predicted by this model were averaged to show the overall longitudinal trajectory of the sample (blue line).



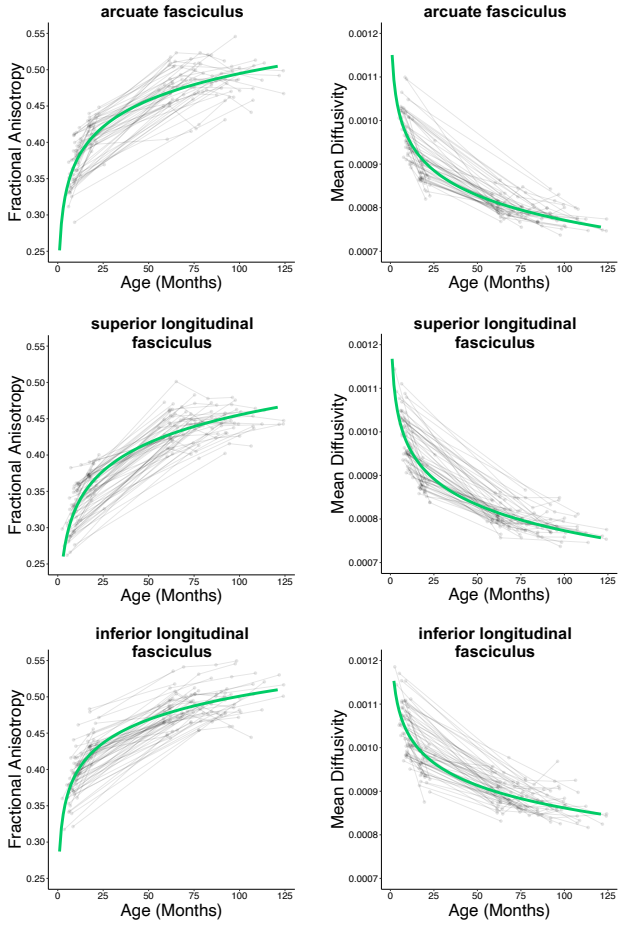
Supplementary Figure 6. Longitudinal trajectories of surface area between infancy and early adolescence. Raw estimates of surface area (gray spaghetti plot backdrop) were submitted to linear mixed effects models using a logarithmic function. Individual growth curves predicted by this model were averaged to show the overall longitudinal trajectory of the sample (blue line).



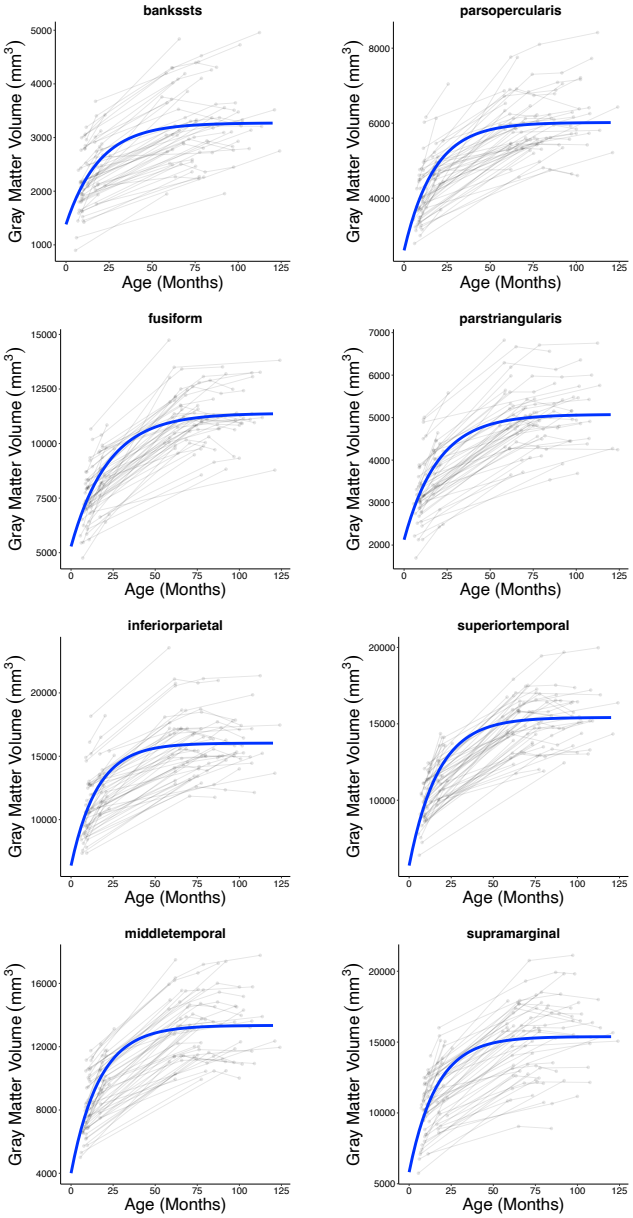
Supplementary Figure 7. Longitudinal trajectories of cortical thickness between infancy and early adolescence. Raw estimates of cortical thickness (gray spaghetti plot backdrop) were submitted to linear mixed effects models using a logarithmic function. Individual growth curves predicted by this model were averaged to show the overall longitudinal trajectory of the sample (blue line).



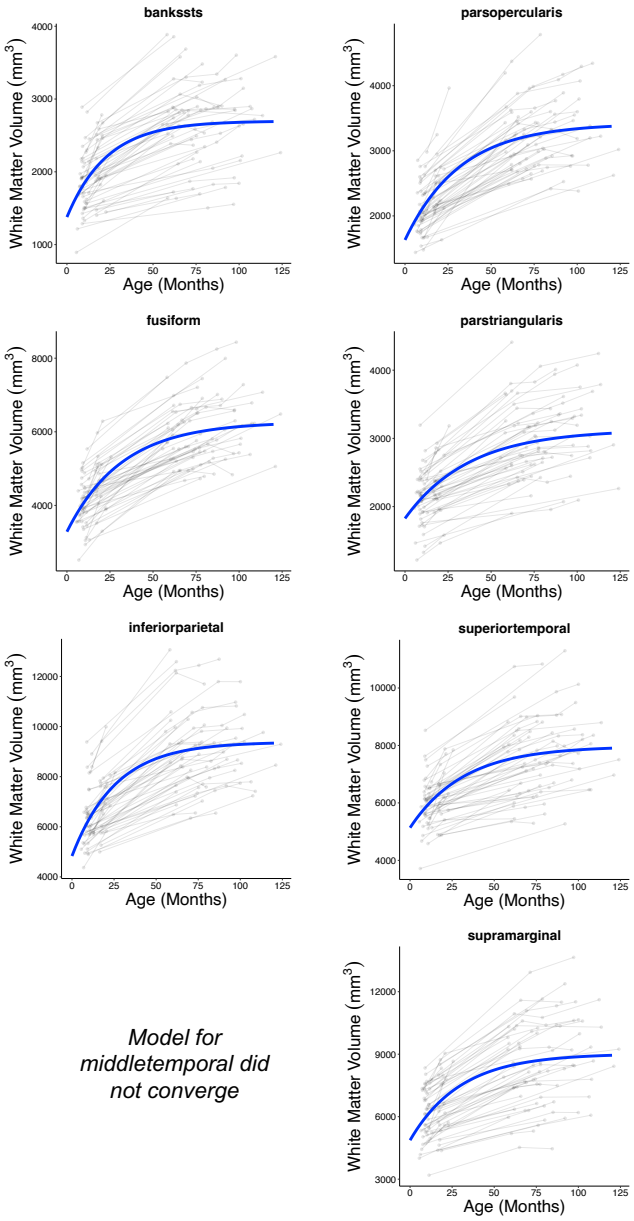
Supplementary Figure 8. Longitudinal trajectories of mean curvature between infancy and early adolescence. Raw estimates of mean curvature (gray spaghetti plot backdrop) were submitted to linear mixed effects models using a logarithmic function. Individual growth curves predicted by this model were averaged to show the overall longitudinal trajectory of the sample (blue line).



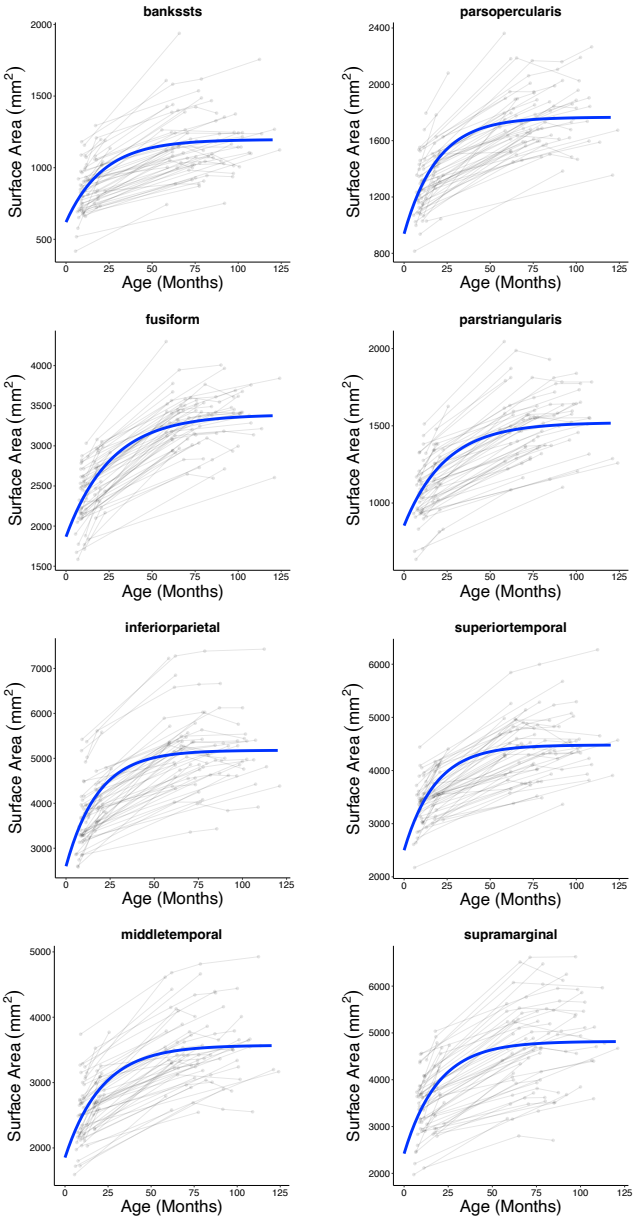
Supplementary Figure 9. Longitudinal trajectories of fractional anisotropy (dark green) and mean diffusivity (light green) between infancy and early adolescence. Raw diffusion estimates (gray spaghetti plot backdrop) were submitted to linear mixed effects models using a logarithmic function. Individual growth curves predicted by this model were averaged to show the overall longitudinal trajectory of the sample (green line).



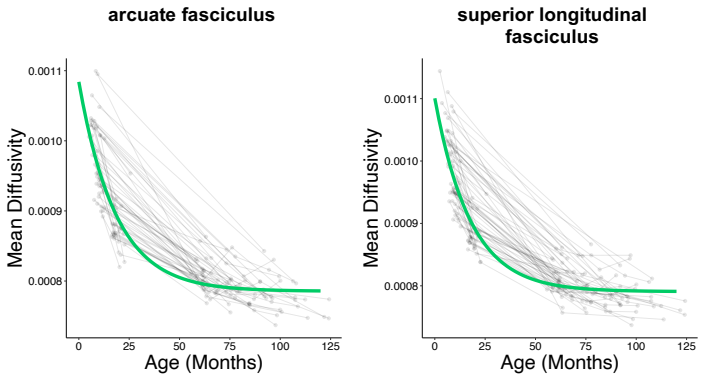
Supplementary Figure 10. Longitudinal trajectories of gray matter volume between infancy and early adolescence generated for sensitivity analyses. Raw estimates of gray matter volume (gray spaghetti plot backdrop) were submitted to nonlinear mixed effects models using an asymptotic function. Individual growth curves predicted by this model were averaged to show the overall longitudinal trajectory of the sample (blue lines).



Supplementary Figure 11. Longitudinal trajectories of white matter volume between infancy and early adolescence generated for sensitivity analyses. Raw estimates of white matter volume (gray spaghetti plot backdrop) were submitted to nonlinear mixed effects models using an asymptotic function. Individual growth curves predicted by this model were averaged to show the overall longitudinal trajectory of the sample (blue lines).



Supplementary Figure 12. Longitudinal trajectories of surface area between infancy and early adolescence generated for sensitivity analyses. Raw estimates of surface area (gray spaghetti plot backdrop) were submitted to nonlinear mixed effects models using an asymptotic function. Individual growth curves predicted by this model were averaged to show the overall longitudinal trajectory of the sample (blue lines).



Supplementary Figure 13. Longitudinal trajectories of mean diffusivity between infancy and early adolescence generated for sensitivity analyses. Raw estimates of mean diffusivity (gray spaghetti plot backdrop) were submitted to nonlinear mixed effects models using an asymptotic function. Individual growth curves predicted by this model were averaged to show the overall longitudinal trajectory of the sample (green lines).