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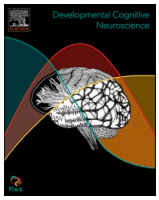

Measuring and interpreting individual differences in fetal, infant, and toddler neurodevelopment

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ABSTRACT

As scientists interested in fetal, infant, and toddler (FIT) neurodevelopment, our research questions often focus on how individual children differ in their neurodevelopment and the predictive value of those individual differences for long-term neural and behavioral outcomes. Measuring and interpreting individual differences in neurodevelopment can present challenges: Is there a "standard" way for the human brain to develop? How do the semantic, practical, or theoretical constraints that we place on studying "development" influence how we measure and interpret individual differences? While it is important to consider these questions across the lifespan, they are particularly relevant for conducting and interpreting research on individual differences in fetal, infant, and toddler neurodevelopment due to the rapid, profound, and heterogeneous changes happening during this period, which may be predictive of long-term outcomes. This article, therefore, has three goals: 1) to provide an overview about how individual differences in neurodevelopment are studied in the field of developmental cognitive neuroscience, 2) to identify challenges and considerations when studying individual differences in neurodevelopment, and 3) to discuss potential implications and solutions moving forward.

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1. Introduction

The human brain undergoes the most dramatic development over the course of the fetal, infant, and toddler (FIT) period. This period of high plasticity presents a critical opportunity for not only characterizing the emergence of foundational cognitive and behavioral processes, but also for identifying neurodevelopmental delays and targeting interventions. A necessary component of this research is the characterization of ***individual differences*** (inter-individual differences, see Table 1 for detailed definitions) in neurodevelopment. Studying individual differences in the brain is complex even in adults (e.g., Finn et al., 2015; Gabrieli et al., 2015; Marek et al., 2022; Sui et al., 2020). Development, however, introduces an additional dimension of complexity because it is a dynamic period when both the brain and behavior are expected to be changing. Thoughtful study design is essential for interpreting concurrent changes and individual differences in brain and behavior. Furthermore, FIT neuroimaging data tend to be lower in quality and quantity than adult data due to the unique challenges of working with a younger population (e.g., higher movement rates and lower attention span). Data collection difficulties with very young children may lead to smaller samples of usable data, which can magnify problems that are already common in developmental cognitive neuroscience work, such as noisy measurements that may interfere with the detection of small effect sizes (Marek et al., 2022; Yarkoni, 2009). Thus, developmental neuroscientists interested in characterizing individual differences in FIT populations need to address many theoretical and methodological challenges in order to draw conclusions about the underlying mechanisms of behavior or for clinical identification or intervention. As a field, we must agree upon an operational definition for individual differences in neurodevelopment and how to determine whether variability in brain and behavioral measurements is valid and meaningful (see Table 1).

In this review, we aim to tackle these challenges by defining individual differences in neurodevelopment and explaining why they are important to study (Section 1), summarizing conceptual and statistical challenges in quantifying individual differences in neurodevelopment (Section 2), surveying the scope of who we are studying to contextualize individual differences (Section 3), identifying challenges and strengths of different neuroimaging methods commonly used with young populations (Section 4), summarizing challenges in interpreting individual differences in neurodevelopment (Section 5), and, finally, looking to the future of the field and how we may overcome these challenges moving forward (Section 6). While this review primarily focuses on the FIT period, it is worth noting that many of these challenges also extend into later developmental periods, such as childhood and adolescence. This review grapples with multidimensional challenges that developmental researchers encounter when studying individual differences. An added layer of complexity is that several different interpretations exist for the topics discussed in this paper, further complicating dialogue amongst researchers. For this review, the authors converged on a set of definitions for key terms used in the paper (Table 1), with the hope that a shared understanding of these terms can be adopted.

1.1. What does it mean to study individual differences in neurodevelopment?

With the rapid advancement of human neuroimaging methods over the past four decades, neuroscientists have significantly advanced our understanding of brain developmental trajectories, particularly at the group level (e.g., grouped by age). Group-based approaches to understanding brain ***development*** have been useful from a statistical lens and have provided tremendous insights into human brain development on average within the populations studied. However, group-based approaches often overlook meaningful individual variability. This limitation has spurred a growing movement in developmental cognitive neuroscience (and in developmental research more broadly; see Pérez-Edgar et al., 2020) to focus on examining ***individual differences.***

Table 1
Terminology relevant to development and individual differences.

Individual Difference	Individual differences refer to the "true" variations or distinctions observed between individuals (inter-individual differences) across various traits, behaviors, abilities, biological characteristics, and other measurable attributes. These variations may result from a combination of genetic, biological, environmental, cultural, social, and experiential factors, collectively shaping each individual's unique profile. Individual differences may be relatively enduring or stable characteristics, but there may also be individual differences in how such characteristics develop or change across the lifespan. Stability factors, such as test-retest or rank-order stability, should also be considered. Therefore, studying individual differences requires diverse methodological approaches, including cross-sectional and, ideally, longitudinal studies across multiple dimensions and timescales, sometimes in reference to a theoretical average.
Development	Development encompasses intra-individual differences and include a broad range of growth and age-related changes across various domains (biological, cognitive, emotional, and social) that an individual undergoes across the lifespan. Development is influenced by both intrinsic (genetic, biological) and extrinsic (environmental, social, cultural) factors, shaping each child's growth trajectory. The nature, rate, and timing of change can vary across biological processes, structures, constructs, and behaviors. For example, brain volume increases rapidly over the course of gestation and infancy, and then slows during childhood, while vocabulary size expands significantly during the toddler and preschool years and then slows in rate during adolescence.
Maturation	Maturation is a subset of development that refers to the dynamic process of reaching full functionality or maturity. It encapsulates the transition towards adult-like biology, cognition, and behavior, focusing on biological age-related changes, such as the development of bodily systems, brain maturation, and attainment of physical or cognitive milestones. It is conceptually tied to a specific goal that may culminate at varying ages on average. For example, total cerebral volume reaches adult size at age 12.5 years on average, while white matter volume peaks at age 28.7 years on average (Bethlehem et al., 2022).
Plasticity	Plasticity refers to the brain's ability to change and adapt in response to, e.g., experience, environmental influences, developmental processes, or injury. It involves changes at multiple levels, including the formation and pruning of synapses, changes in neural pathways, and the adaptation of neural circuits, enabling the brain to incorporate new information, recover from damage, and optimize performance throughout an individual's life. Brain plasticity is most pronounced during critical/sensitive periods of development, such as in early childhood, but it is present throughout the lifespan to varying degrees.
Sensitive Periods	Sensitive periods are specific windows of heightened neuroplasticity when the brain is particularly responsive to certain environmental stimuli or experiences. These periods are crucial for various aspects of neurodevelopment, including those that support sensory processing, language acquisition, socio-emotional development, and higher-order cognitive functions. The timing of sensitive periods varies across different aspects of development and is influenced by genetic predispositions and environmental factors. For instance, the brain typically undergoes sensitive periods for language development during infancy and early childhood, while specific cognitive or social skills may have sensitive periods later in childhood or adolescence (Blakemore and Mills, 2014; Fuhrmann et al., 2015).
Age Periods	In this review, we define the fetal period as before birth; the neonatal/newborn period between birth and one month; infancy between one month and 12 months; and toddlerhood between 12 and 36 months.

Examining individual variations has the potential to yield profound and precise insights into typical and atypical patterns of brain development among fetuses, infants, and toddlers. Identifying unique patterns of brain development may allow for earlier detection of atypical development, which is beneficial for identifying developmental delays and

neurodevelopmental disorders, facilitating early diagnoses, and pinpointing critical or sensitive periods when interventions might be most effective. Indeed, researchers often study individual differences in neurodevelopment as potential predictors of cognitive or behavioral outcomes (Gabrieli et al., 2015; Woodward et al., 2006). Individual differences may result from intrinsic (genetic, biological) and extrinsic (environmental, cultural, social, and experiential) factors, which together shape each individual's unique profile over time. Thus, studying individual differences may elucidate how these factors impact the developing human brain, and may help identify those that influence risk. Such knowledge would ultimately enhance our understanding of developmental processes and inform precision medicine approaches and effective intervention strategies.

Examining individual differences in FIT populations is of particular importance to the field of developmental cognitive neuroscience. The rate of brain growth peaks around the age of 7 months, then gradually slows (Bethlehem et al., 2022). The cortex undergoes apparent thickening during this period, followed by cortical thinning during mid-late childhood and adolescence (Bethlehem et al., 2022). Morphological changes in gray and white matter during the FIT period are consistent with cellular maturational processes, e.g., synaptogenesis, synaptic pruning, and myelination (Jernigan et al., 2011; Ouyang et al., 2019; Pollatou et al., 2022). In work using EEG, there is a broad increase in Alpha power and decrease in Gamma power across the cortex from infancy to preschool age (Marshall et al., 2002; C. L. Wilkinson et al., 2024). Developmental trajectories vary across the brain: different cortical regions and subcortical gray matter structures exhibit distinct maturational trajectories, with the primary sensory cortex maturing earlier than cortical regions involved in higher-order cognitive functions (Lynch et al., 2024; Sydnor et al., 2021). Moreover, white matter fiber tracts also exhibit rapid maturation during the first postnatal year (Dubois et al., 2014).

The "early experience hypothesis" suggests that the neural foundations established within the FIT period are particularly important to subsequent human development (Sheridan and Nelson, 2009). Specifically, ***sensitive periods*** are crucial in shaping various dimensions of human neurodevelopment, including language acquisition, sensory processing, socio-emotional growth, and cognitive functions (Gabard-Durnam and McLaughlin, 2020; Werker and Hensch, 2015). During these periods, brain ***plasticity*** is significantly heightened. This increased plasticity leads to the formation and pruning of synapses as well as adaptations in neural circuitry and pathways, facilitating effective learning and adaptation. Sensitive periods are thought to vary across different developmental domains and result from a complex interplay between genetic predispositions and environmental factors. For instance, genetic factors can set the stage for a sensitive period's onset and duration, while environmental factors, such as exposure to language, social interactions, and sensory experiences, can enhance or hinder the developmental outcomes associated with these critical windows (V. Anderson et al., 2011; Kolb and Gibb, 2011; Kornfeld et al., 2015; Mateos-Aparicio and Rodríguez-Moreno, 2019). Understanding the neural mechanisms underlying sensitive periods at the individual level during the FIT period is essential for elucidating developmental trajectories of cognitive functions, early identification of divergence from ***normative development***, and informing interventions to improve neurodevelopmental outcomes across the lifespan.

In recent years, neuroimaging studies have begun to characterize normative brain developmental trajectories in large populations (Bethlehem et al., 2022; Sydnor et al., 2023). These studies have observed non-linear developmental trajectories across the lifespan in multiple brain metrics, highlighted key periods of rapid growth, and established developmental milestones. Building from this work, developmental neuroscientists are now starting to quantify individual differences in brain maturation. Conceptually, individual differences in brain development can manifest as stable differences over time or variations in the timing and rate of brain growth (see Fig. 1). For example,

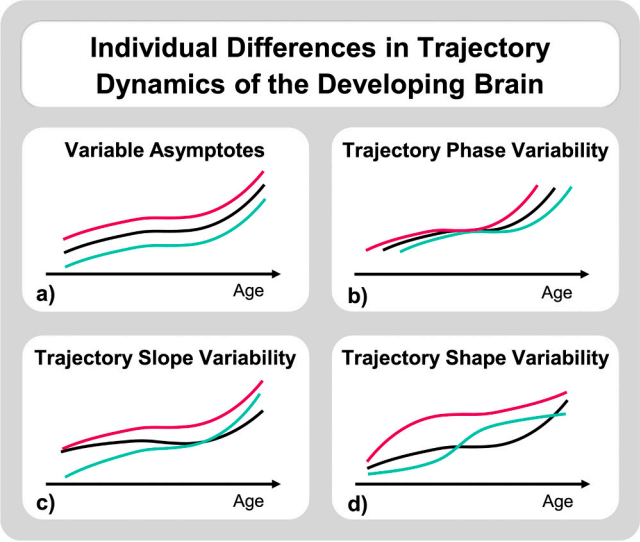

Fig. 1. Individual differences in developmental trajectories illustrated by three hypothetical individuals in pink, black, and mint. Variability can be observed in the a) asymptotes and/or intercepts reflecting stable individual differences in brain structure or function despite superimposed ongoing maturation; b) phase of maturation capturing individual differences in the age at which specific developmental milestones are reached; c) slope, representing individual differences in the rate of change over time, and d) shape depicting individual differences in pattern or curve of the developmental trajectories.

children may vary in ***asymptotes*** (including intercept) due to stable inter-individual differences, regardless of ongoing maturation (Fig. 1**a**); for example, some children display consistently larger structural brain regions (Mills et al., 2021) or oscillatory power (Gabard-Durnam et al., 2019; Rico-Picó et al., 2023) than others. Furthermore, children may differ in their ***phase*** of maturation or developmental timing, indicating variations in the age at which specific brain metrics reach a certain maturity level (Fig. 1**b**). One salient example from older children is inter-individual differences in the maturation phase for the midpoint of cortical thinning, reflecting the age at which the cortex undergoes the most rapid thinning between late childhood and early adulthood. On average, the midpoint of cortical thinning occurs at 14.4 years, yet individual values range from 12.3 to 19.5 years, highlighting considerable variability in developmental timing among individuals (Fuhrmann et al., 2022). In addition, children may differ in their ***slope***, or rate of change, in brain maturation, with some individuals exhibiting a faster or slower pace than others (Fig. 1**c**). Such inter-individual differences are evident in, for example, studies of functional connectivity that find sex-specific individual differences in slopes of connectivity change over time (Gracia-Tabuenca et al., 2021; Sanders et al., 2023; Soman et al., 2023). Finally, children may differ in the ***trajectory shapes*** of brain maturation as they age (Fig. 1**d**). For example, children with single-sided deafness who use a cochlear implant differ in the change in auditory evoked EEG activity over time as compared to children who do not utilize a cochlear implant (Lee et al., 2020).

2. Challenges in studying individual differences in neurodevelopment

2.1. Challenges related to neuroimaging modalities

As noted in Section 1, brain development occurs at various scales, ranging from the cellular and molecular properties of neurons to the structural and functional properties of the brain. We can measure these properties (and their individual differences) using various neuroimaging tools, some of which may be more suited to fetuses, infants, and toddlers than others (see Table 2 for an overview of common neuroimaging

Table 2
Overview of common neuroimaging tools used in FIT studies.

Modality Name	How it works	What you can measure	FIT group can be used in
Structural MRI (sMRI)	MRI uses a magnet to image brain tissue and physiological processes by emitting radiofrequency pulses and measuring the resulting change in signal. Specific to sMRI, tissue is mapped by measuring the longitudinal (T1) or transverse (T2) relaxation time of protons after a radio frequency pulse excites the tissue molecules.	Anatomy: macroscale (volume, cortical thickness, surface area, gyrification)	All ages
Diffusion-weighted MRI (dMRI)	dMRI measures diffusion of water molecules restricted by brain tissues. Magnetic field gradients at different directions and orientations are applied to sensitize the MRI signal to diffusion of water molecules.	Anatomy: macroscale (tract-level morphometry), microscale (voxel-level myelination, neurite orientation dispersion and density)	All ages
Functional MRI (fMRI)	fMRI takes advantage of the fact that hemoglobin becomes paramagnetic when oxygen decouples, making it easier to measure using MRI. This is called blood-oxygen-level-dependent imaging (BOLD).	Physiology: local changes in blood oxygenation	All ages
Functional Near Infrared Spectroscopy (fNIRS)	fNIRS is an optical imaging technique that shines light on the scalp and measures the amount of light absorbed. Light is emitted at wavelengths absorbed by oxygenated (HbO) and deoxygenated (HbR) hemoglobin. Spatial resolution is typically on the order of 1–3 cm^2 and temporal resolution ranges from 5 to 20 Hz.	Physiology: local changes in HbO/HbR concentrations	Infant, Toddler
Diffuse Optical Tomography (DOT)	DOT is also an optical imaging technique. The key difference from fNIRS is that DOT has a higher density of optodes, enabling finer resolution of the cortex. Spatial resolution is on par with MRI (2–4 mm^2) with a temporal resolution of 5–20 Hz.	Physiology: local changes in HbO/HbR concentrations	Infant, Toddler
Electroencephalography (EEG)	EEG records electrical activity from the scalp using electrodes with high temporal resolution but lower spatial sensitivity than fMRI.	Physiology: electrical response pattern, electrical oscillations.	Infant, Toddler
Magnetoencephalography (MEG)	MEG uses superconducting quantum interfering magnometers to measure the magnetic field produced by cortical surface neural population firing.	Physiology: electrical response pattern, electrical oscillations.	All ages
Ultrasound (US)	Sound waves are emitted from a wand, which are transduced through the tissue and reflected to the device (echoes). Can be used to generate 2D or 3D mapping.	Anatomy: macroscale (volume, thickness, area, gyrification) Physiology: blood flow	All ages, though most useful in the fetal period.

methods used with FIT populations).

Structural magnetic resonance imaging (sMRI) provides the best spatial resolution of currently available neuroimaging techniques and has successfully been used across the entire FIT spectrum (e.g., Dubois et al., 2014; Knickmeyer et al., 2008; Pollatou et al., 2022). However, researchers face several challenges when trying to measure and interpret individual differences across age groups using this modality. MRI is extremely sensitive to motion artifacts, which can impede the collection of usable MRI data in FIT populations (Van Dijk et al., 2012; Yendiki et al., 2014). Although infants and toddlers can be scanned during natural sleep to minimize motion (Dean et al., 2014), variation in how much children move during natural sleep can still affect data quality (Kong et al., 2014; Spencer et al., 2018; Yendiki et al., 2014). Some techniques that minimize infant motion (e.g., swaddling) cannot be applied to fetuses, so fetal motion remains a major concern (Rajagopalan et al., 2021). Another challenge is that, due to rapid changes in brain structure (Fig. 2), different sMRI parameters are optimal for different age groups across the FIT period (Korom, Camacho, et al., 2022; Turesky et al., 2021). While T2-weighted images are optimal for identifying gray and white matter boundaries during the first few months of infancy, T1-weighted images are optimal for identifying gray and white matter boundaries from the end of the first year through adulthood (Korom, Camacho, et al., 2022). Thus, researchers studying individual differences across these periods face difficult decisions about whether to use

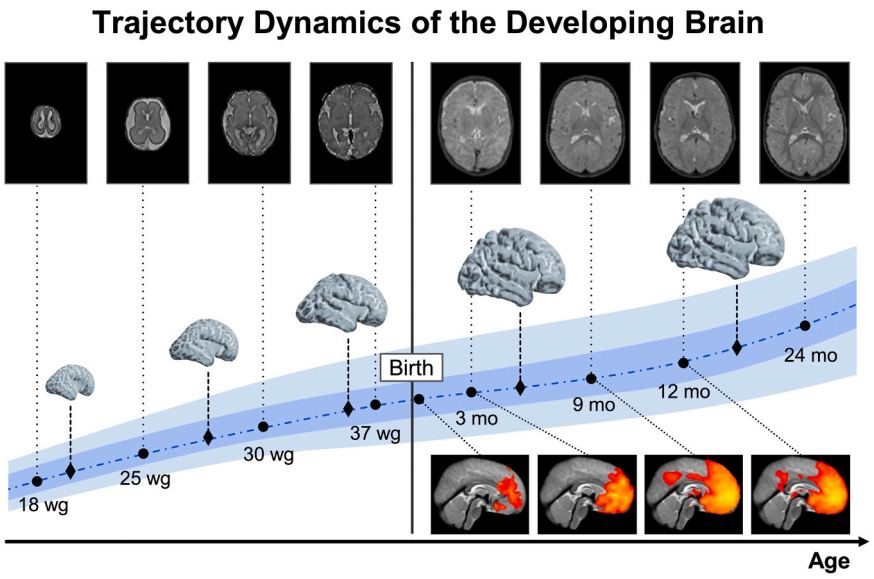

Fig. 2. Trajectory dynamics of the developing brain during the fetal, infant, and toddler (FIT) period. The FIT period is characterized by rapid brain development, including (top/middle) cortical folding, volume expansion, and changing tissue contrast, i.e., due to ongoing myelination, as well as (bottom) expanding functional connectivity patterns, here illustrated with the default mode network (seed placed in the medial prefrontal cortex). Image courtesy: Fetal T2-weighted images, Gregor Kasprian, Medical University of Vienna; infant T2-weighted images from Korom, Camacho, et al., (2022); surface extractions, Roxane Licandro, Medical University of Vienna; functional connectivity maps based on data from Howell et al., 2019.

consistent parameters or optimize the parameters for the age group being scanned. An emerging low-cost alternative for precise measurement of brain structure over time is ultrasound (US). The combination of improved and ubiquitous US imaging technology and new automated segmentation techniques (Yeung et al., 2021) has positioned US as a means of measuring individual differences in development at scale (Namburete et al., 2023). Cost, availability, sensitivity, and other considerations discussed in the sections below are challenges inherent to developmental research and are especially salient in FIT populations.

The methods for measuring individual differences in brain function also present specific challenges pertaining to the FIT period. Limited neuroimaging methods can be applied to fetuses, and depending on the research question, infants and toddlers may need to be scanned while awake. The prevalence of motion in these populations therefore requires thoughtful consideration of how to handle motion artifacts (Ellis et al., 2020; Kosakowski et al., 2022). Additionally, when measuring functional responses during sleep, it is not always possible to tell whether participants are in the same sleep state, and the behavioral and biological characteristics of these sleep states also change over development in FIT populations (Coons and Guilleminault, 1982; Grigg-Damberger, 2017; Korom, Camacho, et al., 2022). In addition to changing biological factors and beyond sleep, different analytic approaches can also yield differing insights into developmental patterns. For instance, estimates of functional connectivity using EEG can vary depending on whether coherence or phase lag indices are used (Fraschini et al., 2019). Across imaging modalities, researchers face many decisions during analysis that can affect interpretations of the results. This challenge becomes especially salient in FIT neuroimaging when comparing across age groups (Cusack et al., 2018).

Functional MRI (fMRI), functional near-infrared spectroscopy (fNIRS), and diffuse optical tomography (DOT) are used to measure brain activation by using changes in local blood flow as a proxy for neuronal population firing. FMRI accomplishes this with a large superconducting magnet and radio frequency coils, while fNIRS and DOT use light sources and detectors embedded in a cap to measure absorption on the surface of the cortex. While fMRI has superior resolution to DOT and fNIRS, even small movements can affect estimates of functional connectivity (Smyser et al., 2011) and task-based responses (Siegel et al., 2014). DOT and fNIRS caps are well tolerated by infants and toddlers (Baek et al., 2023; Gervain et al., 2011; Lloyd-Fox et al., 2010); however, spatial resolution is poorer than fMRI. A challenge common to both fMRI and fNIRS/DOT, though, is that the hemodynamic response function changes over the FIT period (Issard and Gervain, 2018), complicating analyses of individual differences across age. For fNIRS and DOT, anatomical changes (skull thickness, hair growth and color change, brain maturation) can also affect measurements of the signal of interest (Haeussinger et al., 2011; Whiteman et al., 2017), and it is difficult to ensure that brain function is being measured from the same anatomical location both between individuals and within the same individuals over time (Lloyd-Fox et al., 2014). Alternatively, electroencephalography (EEG) and magnetoencephalography (MEG) measure electrical activity directly using electrodes placed on the scalp or sensors designed to measure the magnetic field produced by neurons firing, respectively. EEG and MEG share similar limitations in depth of spatial resolution, sensitivity to motion, and alignment of the underlying brain structures over time; however, the high temporal resolution of neuronal population firing means that more precise questions about cognition (which we know occurs on the order of milliseconds, far faster than what can be gleaned from blood flow) can be studied using these methods. MEG has higher spatial precision than EEG and can be used to measure activity in fetus, infants, and toddlers, while EEG is limited to use in infants and toddlers (Chen et al., 2019). MEG machines are expensive, not commonly found outside of research, and highly sensitive to the recording environment, however.

2.2. *Study designs for capturing developmental change*

In order to capture individual differences in neurodevelopment, an ideal study might collect multi-modal data from a large sample of participants with no attrition over many timepoints that perfectly capture the developmental phenomenon of interest. In reality, researchers must select an experimental design that is not only aligned with their research questions, but is also feasible in the population of interest. Thus, researchers should consider both practical and theoretical implication of different study designs, such as cross-sectional and longitudinal studies. Cross-sectional studies are common and often more feasible than longitudinal studies due to practical constraints (e.g., managing high attrition rates with participants). ***Cross-sectional studies*** can be useful

when an expected developmental change is theoretically and empirically motivated, particularly when "the norm" in development has been thoroughly studied and thus can be well-captured. For instance, a cross-sectional design would be appropriate for comparing brain structure at term-equivalent age among infants who were born at various gestational ages. As another example, using a large, cross-sectional dataset of structural MRI data from healthy children, researchers built a regression machine-learning model that predicted an individual's brain age and assessed the extent to which an individual's neuroanatomy deviated from the norm (Franke et al., 2012). Cross-sectional studies are also preferred in fetal MRI research, where multiple visits are often not feasible, especially in healthy cases.

Unlike cross-sectional studies, ***longitudinal studies*** allow researchers to identify changes in individual developmental trajectories. At a given point in time, there may not be observable individual differences for a particular metric, but the developmental time course may vary greatly between individuals. In general, at least four timepoints are needed to maximize reliability, minimize noise, and estimate individual non-linear trajectories (King et al., 2018), though this recommendation is heavily dependent on other factors, such as participant retention (Elliott et al., 2020; McCormick et al., 2023; McEvoy et al., 2000). One approach to collecting longitudinal data within the real-world constraints that many research programs face is to conduct an accelerated longitudinal design, which involves collecting data from multiple cohorts that are enrolled at different ages (Galbraith et al., 2017). The main advantage of this design is its ability to capture individual trajectories by sampling an age range of interest in a shorter period than would be possible with a single, same-aged cohort. Longitudinal studies within the FIT period are crucial for understanding early neurodevelopmental trajectories, but it is equally important to follow how early differences evolve into childhood and adolescence. Variations in early brain structure or connectivity can shape later cognitive and behavioral outcomes, informing predictions and guiding interventions.

2.3. Analytical considerations

Deciding which variables and timepoints to include in analyses, as well as how to model those variables and timepoints, has important implications for interpreting individual differences. It is typically optimal to select timepoints in which variability is maximized (e.g., studying language-related ERPs during toddlers' "vocabulary spurt" (Borgström et al., 2015)). In studies where key changes occur rapidly, non-linearly, or on a microscopic level, dense sampling (i.e., collecting many data points close together in time) helps to characterize within-subject individual differences across development (Lieven and Behrens, 2011; Poldrack, 2017). Another key analytical decision is how to model the data. Latent profile analysis is a commonly used approach to examine individual differences in longitudinal data by describing groups of children with similar growth trajectories (e.g., Katus et al., 2023). However, since latent profile analysis is a descriptive analysis technique, it cannot be used to test claims about causality or directionality. To predict change over time, rather than describe variations in growth trajectories, cross-lagged autoregressive models can be used to model the developmental sequence of multiple variables at once (e.g., Alonso et al., 2024). Autoregressive models and similar methods are better suited for prediction and examining the sequence of development than latent profile analysis (Scott, 2021). If the goal is to use neuroimaging data to classify children into groups, such as for diagnostic purposes, machine learning algorithms may be most appropriate (e.g., Scheinost et al., 2023). For additional details on different modeling approaches for individual differences in neurodevelopment, see (Becht and Mills, 2020; King et al., 2018; Scheinost et al., 2023).

3. Contextualizing individual differences in the populations being studied

Because inter-individual variability arises from the complex interplay of genetic, environmental, cultural, social, and economic influences, it is crucial to recruit a large and diverse sample when exploring variability in child development. In developmental cognitive neuroscience, the goal is often to make generalizable inferences about human development. However, studying only a subset of the human population can severely limit the generalizability of research findings and, over time, may lead to a biased or even misguided understanding of early human development (L. Singh et al., 2023). Consequently, enrolling families from diverse, representative backgrounds is crucial to enhance the generalizability and reliability of research findings. Nonetheless, it is important to acknowledge that there are practical limitations on the scope of participants that individual labs can feasibly recruit given personnel, time, financial, and geographical constraints. Therefore, we make recommendations for recruitment strategies, open science, and big team science practices that can reduce these limitations and improve generalizability of neurodevelopmental findings in FIT populations.

3.1. Sample size

One crucial factor in any investigation of individual differences is the sample size. Small samples are highly susceptible to sampling variability, leading to potentially contradictory results across studies due to random variations in subsamples of the population. Indeed, small sample sizes are often cited as a major cause of reproducibility issues, especially when the trait of interest has a small effect size, which is characteristic of most brain-behavior relationships (Yarkoni, 2009). Larger samples capture greater population variability, reduce sampling error, and bolster statistical power, thus enabling researchers to chart more generalizable individual neurodevelopmental trajectories. To address the need for generalizability and greater statistical power, the scientific community has invested significantly in creating large-scale, multisite neuroimaging datasets. Notable examples include the Lifespan Human Connectome Project (N = 1500 +), the Adolescent Brain Cognitive Development Study (N = 11,000 +), and the UK Biobank (N = 40,000 +). Indeed, univariate "brain-wide association studies" that link common brain metrics to behavior require thousands of individuals to achieve reproducibility (Marek et al., 2022). Large-scale, consortia FIT neuroimaging studies – such as the HEALthy Brain and Child Development Study, which aims to recruit over 7000 pregnant participants from as early as the second trimester and follow them for up to 10 years at 27 sites across the United States (Nelson et al., 2024; Volkow et al., 2021, 2024) – are similarly poised to significantly advance our understanding of how genetic and environmental factors contribute to brain development. While large-scale studies are critical for advancing our understanding of individual differences, they still have limitations. For instance, the UK Biobank used volunteer-based recruitment, leading to a sample that skewed more female, higher socio-economic status, and, on average, healthier than the general UK population. These biases have been shown to affect genome-phenotype associations, with, for example, 37 % of 49 previously sex-associated single nucleotide polymorphisms showing significantly lower associations following population reweighting (Schoeler et al., 2023). Large-scale data collected across multiple institutions may also face challenges with data harmonization, which may be amplified in FIT populations, requiring teams of researchers to agree on best practices across samples and neuroimaging equipment (e.g., Norton et al., 2021). Furthermore, to date, most large datasets have been acquired in the United Kingdom or the United States and aim to capture diversity by approximating national censuses, thereby limiting global applicability. Efforts to address this disparity are underway, with datasets such as GenomeAsia100k, which aims to sequence the genome of 100,000

individuals from 28 countries across Asia. Consortia – such as Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA), which brings together scientists from more than 40 countries to advance imaging genomics (Thompson et al., 2020) – are also being formed to increase collaboration and harmonize data collection from independent research sites globally. The ENIGMA Organization for Imaging Genomics in Infancy (ENIGMA-ORIGINs) working group has created one of the largest developmental neuroimaging datasets to date, with data from birth through 6 years at eight unique sites across four countries (Alex et al., 2024), demonstrating the promise of the consortium model for FIT neuroimaging.

While large-scale studies are certainly key to studying individual differences, they require significant investments of time and resources and are not well-suited for all research questions. Smaller-scale studies provide important, complementary, and unique insights. For instance, small-scale studies are imperative for pushing experimental boundaries, as paradigms must be well established before being adopted at scale and for studying individual differences in minority populations, such as rare genetic disorders. Large-scale studies typically seek to maximize the number of constructs measured while minimizing participant burden. This often leads to a rich breadth of measures collected, which can come at the expense of depth and detail for each individual construct.

Thus, alternative ways to reduce sampling variability and/or increase reliability in smaller studies include the following:

- Utilizing rigorous, hypothesis-driven research and/or preregistered reports.
- Collecting more data for each construct of interest from each participant (especially for functional brain data).
- Prioritizing neural measures that show good test-retest reliability.
- Collecting multiple measures of the same construct (e.g., both parent report and observation-based measures).
- Using paired and/or causal designs, such as longitudinal designs and intervention studies.
- Collecting additional time points per participant to achieve more densely sampled longitudinal data; this is especially important for detecting age-dependent relationships.

3.2. Sample representativeness

Demographic representation is critical to increasing the generalizability of brain-behavior associations, as demographic factors introduce vital variability – both in confounding factors that must be accounted for, and in the underlying phenotype of interest – which helps to avoid biased interpretations. All studies suffer sampling bias of some sort; that is, no study has perfectly represented the underlying human population because it would be exceedingly difficult to recruit a sample representative of all cultures, ethnicities, social statuses, and so on. Therefore, every study should carefully consider the idiosyncrasies of the context in which it was conducted before generalizing findings as universal to human development. While age and sex are almost universally reported, sociocultural factors such as ethnicity, race, language(s) spoken at home, and socioeconomic and cultural background are not always collected, controlled, or reported. To raise awareness and standardize the reporting of demographic factors, the ManyBabies consortium brought together researchers with experience and cultural familiarity in more than 20 countries to compile a framework highlighting core factors that should be considered when conducting research in FIT populations (L. Singh et al., 2024). Important factors include:

- Age: Due to rapid neuroanatomical development over the FIT period (Gilmore et al., 2018), it is important that age be tightly controlled and/or precisely measured in young populations. The variance in neuroanatomical maturity (Turesky et al., 2021) and behavioral traits also differs with age. For example, a rapid increase in spoken vocabulary, often called the "vocabulary spurt" or "language explosion," occurs around 18 months. However, the precise age of onset varies, leading to wide variability in the vocabulary size of toddlers around this age (Dale and Goodman, 2004).
- Sex: Many metrics of brain function, brain development, and behavior also show sex differences. For example, sex differences have been observed in neurodevelopmental conditions such as autism spectrum disorder (ASD; Lawrence et al., 2020).
- SES: Socioeconomic status is well known to affect brain development, especially in the FIT period when neurodevelopmental change is most rapid, and infants are highly vulnerable to environmental conditions. The circuits subserving language and executive function, for example, are particularly sensitive to environmental context (Olson et al., 2021). Half of the global population is estimated to live in poverty, underscoring the importance of both understanding these effects on development (L. Singh et al., 2023) and controlling for them as potential confounds.
- Preterm Birth and/or Injury: About 10 % of infants are born prematurely (CDC, 2024). Premature infants have a much higher incidence of cerebral insult and greater variability in other brain characteristics, such as the cerebellum and brainstem volumes (Limperopoulos et al., 2005; Wu et al., 2020). Developmental trajectories may vary substantially across the preterm population due to the heterogeneity of perturbations resulting from the interruption of specific stages of gestation (Kelly et al., 2023). As a result, FIT researchers should consider measuring, reporting, and controlling for the child's gestational or postmenstrual age at birth, at the time of the study, or, ideally, both.
- Community of descent: A meta-analysis of 1682 developmental studies found that less than half reported participant race, and out of the studies that did, 83 % reported predominantly white samples (L. Singh et al., 2023). Of those that reported location of data collection, 85 % of studies were conducted in Western Europe or North America.

Participant recruitment and retention are key bottlenecks to achieving representative samples. Successful recruitment involves both motivating participants and removing barriers. As the importance of these factors varies across demographic groups, targeted recruitment strategies can be beneficial. Motivators include accessibly communicating study information and effectively conveying the societal value of participation as well as any direct benefits to the participants (e.g., clinical review of MRIs, sharing standardized assessment results). Motivators are particularly important for rural populations for whom participation entails a substantial commitment (Friedman et al., 2015), for communities who have been historically marginalized and may therefore be wary of research, and for clinical populations who are frequently approached to participate in studies and may therefore be prone to research fatigue (Ashley, 2021). Barriers to participation and retention can include placing a financial burden on participants (e.g., transportation, time off work, childcare for siblings), which may deter lower-SES families (Zgierska et al., 2024). This may be mitigated by providing transportation, flexible scheduling (including evenings or weekends), accommodations, childcare, up-front coverage of expenses whenever possible, and complementing on-site data collection visits with remote study components (Deoni et al., 2022). Importantly, overcoming language barriers is also necessary for engaging diverse ethnic groups, requiring both trained multilingual staff and translated study materials. Researchers should anticipate these costs and adequately budget for them in order to ensure equal opportunities for all potential families to participate in their research. In some cases, supplemental funding or institutional support may be available to support these efforts.

Neuroimaging techniques offer some advantages over behavioral assessments when studying young children from diverse backgrounds. Unlike behavioral assessments that require active child participation, many neuroimaging methods directly quantify brain activity without needing controlled motor or verbal responses. This is also attractive for

developmental cognitive science *in-utero*, where no direct interaction with the individual in the womb is possible (Taymourtash et al., 2023; van den Heuvel and Thomason, 2016). However, neuroimaging techniques also have limitations for studying individuals from diverse backgrounds. Even when developmental neuroscientists successfully recruit large, representative samples, often only a smaller portion of participants contribute to the final results. Participants may be excluded from analyses in systematic ways due to lower signal-to-noise ratio (SNR) or imaging artifacts. For example, autistic children exhibit higher rates of movement during MRI (Cox et al., 2017), and fetuses at 18 weeks' gestation systematically have noisier data than at 40 weeks' gestation due to the fetus's smaller size, which provides more space to move in the womb (Pollatou et al., 2022). Similarly, EEG and fNIRS data quality may be impacted by variations in head shape as well as hair type and color, which vary across ages and ethnic groups (Choy et al., 2022; Kwasa et al., 2023). Efforts should be made to minimize such nonresponse bias by utilizing available tools such as tall pedestal EEG nets that make better contact with the scalp of participants with dense, textured hair, and reporting demographic characteristics of both the recruited and final sample to better detect individual differences. While FIT neuroimagers must be cognizant of the inherent biases and methodological limitations of our tools, advances will require interdisciplinary collaborations with developmental cognitive neuroscientists, engineers, physicists, and clinicians.

3.3. Global biases

Technological advances to reduce costs and improve SNR will increase the scalability and global use of FIT neuroimaging. The study of individual differences in FIT neurodevelopment is currently constrained, especially in the Global South, by limited funding and challenges in adapting neuroimaging equipment to diverse samples and environmental conditions. Even in the Global North, MRI research is typically confined to large, well-resourced institutions in urban areas. The high cost of MRI research is exacerbated by the low yields and high attrition rates typical in FIT studies (Hendrix and Thomason, 2022). Greater and more equitably distributed research funding, combined with innovative neuroimaging solutions, is needed to understand how cultural, demographic, social, and environmental factors shape brain development globally. Large-scale international funding initiatives, like the U.S. Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative (https://braininitiative.nih.gov) or the EU's Human Brain Project (https://www.humanbrainproject.eu), have the potential to greatly enhance the study of individual differences in FIT neurodevelopment worldwide.

For further discussion on diversity in FIT neuroimaging, see (Margolis, Nelson, et al., 2025) in this Special Issue.

4. Challenges in measuring individual differences

Characterizing individual differences in neurodevelopment requires using interpretable brain measures. As neuroimaging approaches have become more widespread in FIT research (Azhari et al., 2020; Pollatou et al., 2022), challenges inherent to the fundamental measurement properties across various neuroimaging modalities have become more apparent, raising concerns about the reproducibility and replicability of findings (Marek et al., 2022). This makes it increasingly important to examine the "neurometric" properties of our imaging measurements: how precisely, reliably, and accurately are we measuring brain structure and function?

Carefully considering how changes in brain anatomy and physiology affect assumptions about a neuroimaging measure's core properties is key to designing studies that yield interpretable, reproducible, and replicable findings. The field of psychometrics has a well-developed hierarchical framework delineating essential measurement properties (e.g., variability, reliability, validity) that FIT neuroimaging can draw upon, facilitating the interpretation of studies on individual differences in neurodevelopment (Wijsen et al., 2022). For detecting individual differences, it is crucial that a measure displays appropriate *variability*, meaning that it can yield a range of scores within a population (Cooper et al., 2019). Although neuroimaging research in FIT populations has progressed more slowly than in adults, evidence suggests that researchers can capture meaningful variation in FIT neurobiology (Alex et al., 2023; Graham et al., 2015; Thomason, 2020). Additionally, measurement *reliability* is vital, given that an inconsistent measure makes it difficult to determine whether the data reflect reality. Low reliability, when extreme, can confound measurement validity, the extent to which a tool measures the characteristic it is intended to measure (Noble et al., 2021). For FIT neuroimaging, the rapid brain development during the FIT period prompts several specific neurometric considerations. Accelerated early development is expected to change a particular measure's discriminatory capacity for young children, even when age differences are relatively small. This, in turn, affects the measure's ability to provide consistent results over short time windows. From the standpoint of validity, the rapid growth of brain structures or elaboration of neurocircuitry or functional neural systems could signify that assumptions defining a measure apply only for a limited time span and are, therefore, less generalizable across early development. For example, in fetal cohorts the inaccuracy in determining the gestational age (Mongelli and Gardosi, 1997; Saul et al., 2012) can lead to shifts of developmental stages in time, affecting the accurate assignment and comparison of measures within age groups.

Therefore, an important goal for developmental neuroscientists should be to work towards developing measures and analytic approaches that account for age-dependent variations in the neurometric properties of their neuroimaging tools to enhance the comparability of findings over time. As a first step, we provide an overview of specific features of structural and functional neuroimaging modalities (Table 2) that impact core neurometric properties and highlight challenges to be addressed for advancing the field.

4.1. Measuring brain structural development

Structural brain development is remarkably dynamic during the FIT period. During gestation and infancy, the structural scaffolding of the brain is established and, as the child grows through the toddler years, the brain's structural foundation undergoes fine-tuning and remodeling driven by the environment and experiences (Gilmore et al., 2018). This structural reorganization enables the emergence of high-order cognitive functions and behavioral patterns. Despite extensive research to uncover structural brain development during the FIT period, several inherent challenges associated with image acquisition and processing currently limit the scope of analyses. Scanning FIT populations for *in-vivo* MRI (all ages) and US (fetal) studies poses various obstacles. First, difficulties in keeping fetus, infants, and toddlers still for an extended period typically necessitates either shortening the acquisition time – which minimizes motion artifact at the expense of SNR—or collecting multiple acquisitions and losing the opportunity to collect other kinds of images within the same session (Clemence, 2011; Dubois et al., 2021). Another challenge is that the dynamic changes in the brain from gestation through toddlerhood require the optimization of scanning parameters for different developmental periods (Brugger, 2011; Pugash et al., 2011; Turesky et al., 2021). However, age-specific scanning protocols may result in inconsistent brain measures. In adults, varying the structural sequence parameters can influence the reliability of cortical surface area, volume, and thickness estimates within the same scanning session (Knussmann et al., 2022). This means that optimizing the sequence parameters based on age poses a tradeoff between maintaining measurement reliability and increasing SNR to delineate the structures of interest.

Besides image acquisition issues, early brain development studies are also plagued by ill-suited processing methods. Anatomical image

segmentation methods widely used for adult populations (Avants et al., 2008; Fischl, 2012) do not accommodate FIT brain MRIs due to rapid changes in brain size and tissue contrast during this developmental period (described in Section 2.1), nor can they be applied to fetal US images. As a result, processing tools catering to specific prenatal and postnatal periods as well as for US vs MRI have necessarily been developed and adopted (Namburete et al., 2023; L. Wang et al., 2023; Yeung et al., 2021; Zhao et al., 2022; Zöllei et al., 2020). These age-specific methods account for changing properties of the developing brain, but the estimated brain measures are not easily compared with those collected at other developmental periods using different methods. To improve the reliability and consistency of brain measures, standardized image acquisition protocols, quality control procedures, and post-acquisition processing tools accommodating FIT scans should be incorporated into developmental studies. The morphometric properties of the brain can also be validated by comparing them against the spatiotemporally dense atlases that capture normative growth patterns from gestation through toddlerhood (Ahmad et al., 2023; Ciceri et al., 2024; Namburete et al., 2023).

4.2. Measuring brain functional development

Functional measures can provide unique insights into the dynamic processes of brain activity and connectivity during the FIT period. While technological advances in these methodologies have brought about numerous breakthroughs in understanding early neural function, inherent features of early development present several challenges for measuring and interpreting meaningful individual differences. In the fetal stage, studying functional brain development *in-utero* provides insights into the foundations of our cognitive abilities, but the field is still at the beginning of mapping the functional connectome of cortico-cortical or thalamocortical connectivity in fetuses (Taymourtash et al., 2023) due to the difficult task of removing artefacts caused by fetal movement or maternal breathing and extracting erroneous signal correlations caused by motion. Here, it is essential to evaluate the effect of processing techniques using reproducible metrics of functional connectivity estimates (Sobotka et al., 2019) or providing tailored benchmark studies for achieving comparability (Taymourtash et al., 2024). After birth, changes in head circumference and shape as children grow can affect the placement and signal quality of EEG and fNIRS sensors (Odabaee et al., 2014). Similarly, increasing thickness of the skull and hair growth with age can attenuate electrical and light signals, complicating both data collection and interpretation (Gibson et al., 2000; Lew et al., 2013). Myogenic, eye-blink, or movement-related artifacts also vary across different age groups and sample populations, necessitating age-appropriate strategies to reduce these artifacts during data collection (e.g., using engaging videos or bubble displays) or during data processing (e.g., removing or interpolating contaminated trials using independent component analysis (ICA) or wavelet-based cleaning algorithms) (Bell and Cuevas, 2012; Fujioka et al., 2011; Gabard-Durnam et al., 2018).

Additionally, brain function changes dramatically during early development, and spectral parameters (e.g., canonical EEG frequency bands) must be adjusted to align with developmental stages (A. J. Anderson and Perone, 2018; Marshall et al., 2002; Saby and Marshall, 2012; Stroganova et al., 1999). Similarly, the hemodynamic response measured by fNIRS and fMRI changes with age (Issard and Gervain, 2018). Likely underlying this change in hemodynamic response is a combination of increasing capillary bed density in the cortex, which reaches adult-like levels at around 5 months in humans (Harb et al., 2013), and the entrainment of blood vessel dilation to neuronal firing (neuronal-hemodynamic coupling) (Mateo et al., 2017), the development of which has not been well-studied in humans (Korom et al., 2022). Indeed, there is lower scan-rescan reliability in functional connectivity estimates in infants than adults (Dufford et al., 2021), likely due to the confound of rapid development between scans. There are also age-related changes in event-related potential (ERP) components' latency, amplitude, and morphology that pose challenges for interpreting individual differences in EEG data across development (Hoehl and Wahl, 2012).

In sum, it can be challenging to disentangle meaningful individual differences in functional neurodevelopment from the age-related changes that occur in typical development using these measures. Sensitivity to each of these factors during data collection, processing, analyses, and interpretation is crucial for accurate and reliable measurement of individual differences in functional neurodevelopment.

4.3. Brain–behavior associations across development

Finally, choosing which imaging method to use (and for what age) is especially challenging in the context of identifying brain-behavior associations. Across FIT ages, children have different physical and cognitive capabilities (Adolph and Hoch, 2019; Morales et al., 2016; Thelen et al., 1987), influencing both the imaging measurement choices as previously described as well as the non-imaging measurements. For example, a task that measures executive function in one-year-olds is likely too easy for a three-year-old to complete. How do we know that individual differences at each stage are due to developmental differences rather than adjustments in the measure to suit the age groups being studied? Further, changes in motor abilities are important precursors to cognitive developmental changes (Kirk et al., 2022; Morales et al., 2016; Thelen, 1995; Thibodeaux et al., 2019), and suppressing them for the purposes of obtaining high-quality imaging can incur unintended consequences (Camacho et al., 2020). An example of this is the infamous "task B" problem (Church et al., 2010), where the circumstances in which the data are collected are fundamentally different across ages, altering activation estimates of each baseline and task condition. For group-level trends, we can statistically account for such differences by transforming and age-norming measurements (e.g., z-scoring the measurements at each age) before examining brain-behavior associations. For the purposes of tracking individual differences in longitudinal brain-behavior associations, however, the measurement decisions and interpretation become fraught. This is a critical point to grapple with before individual differences in FIT development can accurately inform interventions or identify "atypical" developmental trajectories. Finally, the physical limitations that different imaging approaches can influence the ecological validity of the phenomenon being studied. For example, it is difficult to measure social behaviors in the confines of an MRI (Redcay and Schilbach, 2019). It is therefore critical to consider both the developmental considerations and construct integrity balanced with the neuroimaging methodology.

Balancing the challenges and considerations, many scientific questions can therefore benefit from multimodal imaging. For example, using EEG in combination with fMRI or fNIRS/DOT to study functional brain development during natural sleep (Fransson et al., 2013), or using dMRI in combination with sMRI to study regional myelination (Knight et al., 2018). By combining modalities that differ in spatial and temporal resolution, we can gain better insight to the underlying changing neurobiology, enabling us to better capture brain–behavior associations. For example, a study of preterm infants measured brain activity using simultaneous EEG–fMRI during wrist movement found specific links between EEG microstates and large-scale BOLD responses in motor cortex, providing key insight to motor cortex neuronal–hemodynamic coupling during a period of intense motor development (Poppe et al., 2022). Finding innovative ways to combine modalities with complementary strengths and limitations has the potential to substantially increase our ability to detect individual differences in neurodevelopment.

5. Interpreting individual differences during development: applications and implications

Even under ideal circumstances, when researchers obtain reliable

and valid data from large and representative samples, the interpretation of results may vary depending on the study design, findings from previous research, and assumptions about the variables measured. As described in previous sections, FIT neuroimaging studies often include multimodal data (e.g., brain structure and/or function, environment/experiences, cognition, behavior, etc.) collected longitudinally to generate a dataset capable of addressing many research questions from a single sample. Additionally, many FIT neuroimaging studies are exploratory rather than hypothesis-driven due to the limited prior research available to generate specific hypotheses. Therefore, researchers often interpret novel, multimodal (e.g., brain-behavior) associations that may have previously only been examined in older children or adults. Over time, the accumulation of evidence across many studies will provide a clearer picture of the brain-behavior relationships that exist in early childhood. For now, however, researchers should carefully consider how to interpret findings about individual differences during early development (see Table 3 for some key questions for researchers to consider). We describe a few of these considerations in more detail below.

5.1. Selecting a point of comparison

One important consideration is how to compare metrics across participants. Behavioral research often uses standardized measures that are normed on large populations of children at specific ages, allowing researchers to identify where an individual child falls within a normal distribution of children who are the same age and from the same population (Ellingsen, 2016). Standardized, normed datasets are not yet available for FIT neuroimaging data, so any comparisons of individual differences are either within-sample or based on previous research, which may not always be generalized to the population of interest. This may be particularly problematic for research with children at risk for or diagnosed with neurodevelopmental disorders. In these studies, any differences in neuroimaging metrics between children at risk or diagnosed with neurodevelopmental disorders and children who are classified as "typically developing" are likely to be interpreted as maladaptive or non-optimal for later development, even though it is possible that the differences are adaptive or compensatory. In line with this idea, some recent research has begun to recognize strengths and heterogeneity in individuals with neurodevelopmental disorders (e.g., Maw et al., 2024). For FIT populations, it is especially important to avoid deterministic or fatalistic interpretations of early individual differences in neurodevelopment, as there are ample opportunities for early intervention to change neurodevelopmental trajectories (e.g., DeMaster et al., 2019). Further, while comparisons between groups, such as neurotypical vs. neurodevelopmental disorder groups, are essential for understanding how different conditions are linked to brain development, these approaches come with inherent trade-offs. Collapsing within-group variability to focus on between-group differences oversimplifies the heterogeneity present within each group, potentially obscuring meaningful individual differences. Approaches such as longitudinal designs, subgroup analyses, normative modeling, and multilevel modeling may help bridge the gap between group-level trends and individual variability, enhancing both generalizability and translational impact.

One salient example of how the same neuroimaging metric can be interpreted differently based on reference groups comes from research on early language perception. During the first six months of age, infants exhibit a mismatch response (MMR) to both native and non-native speech sounds in an oddball experimental paradigm (Liu et al., 2023), but by around 12 months of age, infants typically exhibit MMRs only to native speech sounds (Rivera-Gaxiola et al., 2005). However, both preterm infants and infants raised in bilingual environments retain the MMR to non-native speech sounds (Garcia-Sierra et al., 2011; Jansson-Verkasalo et al., 2010). Interestingly, these results have been interpreted differently for the two groups. For preterm infants, retaining the MMR was considered "delayed" or "atypical" (Jansson-Verkasalo et al., 2010); for bilingual infants, it was interpreted as a more "open" and "plastic" neural response that could facilitate learning two languages at once (Garcia-Sierra et al., 2011). The opposite interpretations of the same pattern of data were informed by existing research: preterm infants are at risk for language difficulties, so retaining the MMR is likely *maladaptive*; whereas bilingualism is generally viewed as an asset, and therefore retaining the MMR is seen as *adaptive*. This discrepancy highlights the importance of accumulating evidence across many studies and considering findings from different populations when interpreting neuroimaging results.

Table 3
Key questions for fetal, infant, and toddler neuroimaging researchers to consider when interpreting individual differences in development.

Key Question(s)	Examples
What is the neurodevelopmental process of interest?	Neurogenesis Apoptosis Synaptogenesis Synaptic Pruning Myelination
What is the pattern of development for each variable you measured?	Linear Non-Linear Categorical Change
What is the developmental sequence of all the variables you measured?	Does experience shape brain structure and/or function, which then shapes cognition and behavior? Might cognition and behavior shape experience, which then shapes brain structure and/or function? Or does brain structure and/or function shape cognition and behavior, which then shapes experience?
Can you disentangle development-related differences from performance-related differences?	Consider differences between: Computerized adaptive testing Norm-referenced standardized testing Novel experimental paradigms
Could unmeasured biological or environmental variables explain your results?	Socioeconomic status Stress Sleep stage
Are the relationships you observed *correlational*, *predictive*, or *causal*?	Consider the differences between: Cross-sectional studies Longitudinal studies Randomized control trials (RCTs)
How do we determine which individual differences are *adaptive* versus *maladaptive*?	Based on concurrent outcomes? Based on long-term follow-up? Based on previous research with the populations of interest?
What criteria need to be met to consider individual differences in development to be *meaningful* predictors of later outcomes?	Effect size cutoffs Risk estimates Face validity

5.2. Interpreting results in light of limited prior data

Novel findings about individual differences in early development can be difficult to interpret when similar research has only been conducted with older children or adults, particularly since the function of specific regions of the brain may change across development (Dehaene and Cohen, 2007; Kubota et al., 2024; Nordt et al., 2021). For example, there is some evidence that parts of the ventral temporal cortex that are responsible for certain perceptual abilities in infancy may be "recycled" for other purposes during childhood (i.e., word recognition, (Kubota et al., 2024)). It is important to consider this theory and others like it (e.g., neuroemergentism, Hernandez et al., 2019) when interpreting the function of specific brain regions in FIT samples in relation to older children, adolescents, and adults.

Practically, this may limit the conclusions that can be drawn from FIT neuroimaging data. For example, some of the earliest MRI research with infants collected resting-state fMRI in an attempt to understand how early functional networks in the brain develop (Doria et al., 2010; Fransson et al., 2007; Smyser et al., 2010). Five resting state networks

were identified in the infant brain (Fransson et al., 2007), whereas previous research had identified ten resting state networks in the adult brain (Damoiseaux et al., 2006). Some of the networks identified in the infant brain, specifically those associated with primary visual, auditory, and sensorimotor regions, closely resembled adult resting state networks, while others did not directly correspond to adult networks. Because there was limited previous research to draw from, the authors of this study did not speculate about the function of the novel infant resting state networks nor about the lack of some adult networks in the infant data, leaving room for additional research to confirm and build on their initial findings.

5.3. Determining when to turn research into recommendations

A driving motivation for studying individual differences in FIT populations using neuroimaging is to improve the early identification of children at risk for neurodevelopmental disorders or other challenges, which can then enable earlier intervention (Dawson et al., 2023; Wolff et al., 2018). For instance, researchers have measured neural predictors of autism (ASD) in infants as young as one and a half months old, long before behavioral predictors of ASD can be observed (Emerson et al., 2017; Hazlett et al., 2017; Wagner et al., 2023). These findings have great potential for early detection and intervention, but they also raise important ethical questions. Are we confident enough in these findings to recommend diagnostic MRIs to families with an infant at increased familial risk for ASD? What are the recommended next steps after a family receives the MRI? As another example, measures of infant brain function have been related to environmental factors, like socioeconomic status (e.g., Tomalski et al., 2013) and maternal stress (e.g., Troller-Renfree et al., 2023). If individual differences in brain response to these factors are identified, should policy decisions take this variation into account? When attempting to justify the importance of this type of research to funding agencies or other researchers, researchers often highlight that neuroimaging can support earlier diagnosis and intervention, but it is important to keep in mind that accumulation of a large body of evidence is necessary before a diagnostic MRI in the FIT period becomes a practical recommendation for families (Girault and Piven, 2020).

6. Future directions for studying individual differences in neurodevelopment

The previous sections introduced challenges and current approaches to studying individual differences in early neurodevelopment. In this final section, we turn to the future and highlight some promising advances in measurement, analysis, training, and open science that are poised to improve individual differences research. Recommended reading for these topics as well as others touched on in each section are in Table 4.

6.1. Advances in measurement

Advances in measurement tools have allowed the field of FIT neuroimaging research to expand rapidly. Some new technologies are already being used in medical offices and laboratory settings, such as 3D fetal US in combination with convolutional neural networks for automatic total brain volume estimation (Jafrasteh et al., 2023). In fetal MRI the trend goes towards accelerating the imaging technology (Manganaro et al., 2023) in combination with robust real-time head motion tracking (A. Singh et al., 2020; Xu et al., 2019) and correction, together with high resolution reconstruction using machine learning approaches. The field of radiomics analysis also offers a new perspective for advancing measures in fetal MRI, enabling the extraction of imaging features using predefined mathematical operations for tissue characterization and outcome prediction (F. Prayer et al., 2023; Song et al., 2023).

Other advances have been made using existing technologies,

Table 4
Recommended further reading and resources for each topic.

Section	Further Reading
1: Defining individual differences in neurodevelopment	• Brown, T. T. (2017). Individual differences in human brain development. *Wiley Interdisciplinary Reviews: Cognitive Science*, *8*(1−2), e1389. • Bottenhorn, K. L., Cardenas-Iniguez, C., Mills, K. L., Laird, A. R., & Herting, M. M. (2023). Profiling intra-and inter-individual differences in brain development across early adolescence. *NeuroImage*, *279*, 120287.
2: Challenges in studying individual differences in neurodevelopment	• King, K. M., Littlefield, A. K., McCabe, C. J., Mills, K. L., Flournoy, J., & Chassin, L. (2018). Longitudinal modeling in developmental neuroimaging research: Common challenges, and solutions from developmental psychology. *Developmental cognitive neuroscience*, *33*, 54–72. • McCormick, E. M. (2021). Multi-level multi-growth models: new opportunities for addressing developmental theory using advanced longitudinal designs with planned missingness. *Developmental Cognitive Neuroscience*, *51*, 101001. • Galbraith, S., Bowden, J., & Mander, A. (2017). Accelerated longitudinal designs: An overview of modelling, power, costs and handling missing data. *Statistical methods in medical research*, *26* (1), 374–398. • Durrleman, S., Pennec, X., Trouvé, A., Braga, J., Gerig, G., & Ayache, N. (2013). Toward a comprehensive framework for the spatiotemporal statistical analysis of longitudinal shape data. *International journal of computer vision*, *103*, 22–59.
3: The scope of individual differences in neurodevelopment	• Singh, L., Cristia, A., Karasik, L. B., Rajendra, S. J., & Oakes, L. M. (2023). Diversity and representation in infant research: Barriers and bridges toward a globalized science of infant development. *Infancy*, *28*(4), 708–737.
4: Challenges in measurement	• Rosenberg, M. D., & Finn, E. S. (2022). How to establish robust brain–behavior relationships without thousands of individuals. *Nature Neuroscience*, *25*(7), 835–837. • Turesky, T. K., Vanderauwera, J., & Gaab, N. (2021). Imaging the rapidly developing brain: Current challenges for MRI studies in the first five years of life. *Developmental cognitive neuroscience*, *47*, 100893.
5: Interpreting individual differences in neurodevelopment	• Church, J. A., Petersen, S. E., & Schlaggar, B. L. (2010). The “Task B problem” and other considerations in developmental functional neuroimaging. *Human brain mapping*, *31* (6), 852–862.
6: Future directions in studying individual differences in neurodevelopment	• Korom, M., Camacho, M. C., Filippi, C. A., Licandro, R., Moore, L. A., Dufford, A., Zöllei, L., Graham, A.M., Spann, M., Howell, B., FIT'NG, Shultz, S., & Scheinost, D. (2022). Dear reviewers: Responses to common reviewer critiques about infant neuroimaging studies. *Developmental cognitive neuroscience*, *53*, 101055.

including protocols to measure MRI and fMRI in awake infants (Copeland et al., 2021; Ellis et al., 2020), such as adjustable infant head coils (Ghotra et al., 2021), which have supported efforts to scan the awake infant brain comfortably and reliably. While both 3D ultrasound and MRI are only available in research or medical facilities, the development of in-home and/or portable assessments and technologies shows promise for more scalable, ecologically valid, and inclusive data collection. Mobile EEG has been successfully collected from a large cohort of infants, suggesting that these portable technologies aid in reducing barriers to participation and increasing demographic representation in FIT populations (Troller-Renfree et al., 2021). Similarly, mobile fNIRS (e.g., the LUMO system, Gowerlabs Ltd., UK; the BabyBrite, Artinis, NL) has also been shown to provide good spatial specificity and a high SNR while being well-tolerated by infants (Frijia et al., 2021). Portable neuroimaging modalities like EEG, fNIRS, and emerging low-field MRI systems offer hope for expanding FIT neuroimaging in the Global South. Initiatives like the Brain Imaging for Global HealTh (BRIGHT) project (https://www.globalfnirs.org), which studied 200 children in the Gambia using EEG and fNIRS from birth to 24-months of age, exemplify this potential. Portable methods also allow for more naturalistic study of phenomena that are not naturally amenable to study in a confined environment such as social processing. New methodological and technological advances such as portable low-field MRI (Kimberly et al., 2023) or low density or in-ear EEG (Joyner et al., 2024) for use in young populations will continue to propel the field allowing for more robust, reliable, and accessible neural measures of individual differences in FIT populations.

6.2. Standardized pipelines that are sensitive to age/stage

Given the rapid structural, metabolic, and functional changes during the FIT period, and age-specific challenges such as motion and image contrast, standardized imaging and analysis pipelines are critical for FIT neuroimaging studies. Fortunately, various algorithmic solutions have been introduced for different imaging modalities and developmental stages. For EEG, the Harvard Automated Processing Pipeline for Electroencephalography (HAPPE; Gabard-Durnam et al., 2018) and the Maryland Analysis of Developmental EEG (MADE; Debnath et al., 2020) are widely used, offering robust algorithms tailored for cleaning infant and toddler EEG data. For structural MRI, the iBEAT V2.0 pipeline can be used for T1- and T2-weighted image segmentation, cortical surface reconstruction, and cortical parcellation for ages 0–6 years (L. Wang et al., 2023), Infant FreeSurfer produces subcortical and cortical volumetric segmentations and white matter and pial surfaces segments from T1-weighted images for ages 0–2 years (Zöllei et al., 2020), the Developing Human Connectome Project (dHCP; Makropoulos et al., 2018) released a minimal processing pipeline (along with their public data release of postnatal T1 and T2-weighted images) which is optimized for T2-weighted images and generates brain surface representations with cortical and subcortical region annotations, and the Melbourne Children's Regional Infant Brain Software Package (M-CRIB-S; Adamson et al., 2020, 2024) pipeline makes use of the dedicated neonate M-CRIB atlas (Alexander et al., 2017) and T2-weighted images for newborn MRI analysis. For diffusion-weighted MRIs, babyAFQ (Grotheer et al., 2022) and TRACULInA (TRActs ConsTrained by UnderLying INfant Anatomy; Zöllei et al., 2019) provide automated fiber quantification and tractography specifically tailored for infants. The Fetal Annotation and Segmentation Challenge (FeTA; https://fetachallenge.github.io/; Payette et al., 2023, 2024) provides an open dataset for the comparable development of segmentation algorithms for fetal brain tissue together with open-source releases of resulting segmentation methods.

Despite these recent advancements in FIT computational neuroimaging, challenges remain. It is often difficult to directly compare outputs generated by different tools, given that they are optimized for various age ranges and modalities, and they output different sets of annotations. This can be an issue particularly with longitudinal datasets. Effective longitudinal analysis requires tools that maintain consistent definitions of regions of interest and surfaces to ensure that the detected changes are relevant to developmental processes rather than artifacts introduced by inconsistent methodologies. One key focus of innovations moving forward should be motion correction. Motion artifacts vary significantly and are not uniformly manageable across all ages and acquisition sites (Barkovich et al., 2019; Eichhorn et al., 2021). While neonates and young infants can be swaddled during nap time, older infants and toddlers are more active, which can especially be a concern in awake studies. Varying levels of motion can bias group comparisons and/or individual postprocessing results (Yendiki et al., 2014). Prospective, real-time, and retrospective motion correction should be considered to minimize the impact of motion (Frost et al., 2019; Slipsager et al., 2019; Vecchiato et al., 2021). For example, FIRMM software (https://turingmedical.com/firmm) is now available to monitor motion in real-time during MRI acquisition, which allows researchers to re-run sequences that are motion-contaminated.

6.3. Increasing collaboration and access to specialized training

To accelerate the development of new methods to study individual differences in neurodevelopment, we must revolutionize how we train and interact as FIT researchers. Aside from a handful of knowledge hubs worldwide, most FIT expertise remains siloed, making it difficult for trainees to develop cross-modal expertise. One way to overcome this limitation in our research is to develop FIT-specific and accessible training materials. One example of such a training hub is the International Neuroinformatics Coordinating Facility (INCF; https://training.incf.org/), which offers dozens of online training resources for free on its website. Second, embracing and developing a global network of FIT researchers would increase cross-collaboration and the combination of datasets, enhancing the representativeness of samples and, therefore, provide insight into individual differences in neurodevelopment. The FIT neuroimaging group (FIT'NG https://fitng.org) is well-poised to serve as a hub in these efforts. FIT'NG hosts an annual meeting and supports opportunities for members to collaborate on publications (such as this). In the future, FIT'NG hopes to serve as a source of material support for interdisciplinary collaboration and training in the field, enabling even the most siloed trainees access FIT-specialized training beyond their institution. FIT-focused subgroups within larger conferences and organizations (like Flux) also support collaboration and community amongst researchers. A global FIT training network that embraces shared training resources and gives their expertise openly is critical if we are to move the field towards more precise measurement of individual differences in neurodevelopment as well as an improved understanding of how the brain develops in health and disease.

6.4. An increasing need to embrace open science practices

Many of the challenges highlighted in this review – such as the difficulty of collecting sufficient sample sizes for measuring individual differences and the need for metrics that can be compared across studies – can be at least partially addressed by the adoption of open science practices across the field of FIT neuroimaging. Open science, which promotes collaboration and accessibility by making research data and materials openly available, emerged as a response to the reproducibility crisis (Baker, 2015) and is increasingly recognized as crucial for scientific progress and inclusiveness. One tenet of open science that is critical to FIT neuroimaging researchers interested in individual differences is that all data should be Findable, Accessible, Interoperable, and Reusable ("FAIR"; Wilkinson et al., 2016). To facilitate FAIR data sharing, the Brain Imaging Data Structure (BIDS) was developed as a community-driven standard for organizing data and metadata from a growing range of neuroscience modalities (Gorgolewski et al., 2016; Poldrack et al., 2024). This standard has been adopted by developmental neuroimaging researchers, including the Adolescent Brain Cognitive

Development (ABCD-BIDS) Community Collection, which includes longitudinal MRI data from 11,877 children in BIDS format (Feczko et al., 2021), and the HEALthy Brain and Cognitive Development (HBCD) study, which includes both MRI and EEG data in BIDS format (Dean et al., 2024; Fox et al., 2024). Importantly, while repositories now exist for sharing neuroimaging data in standardized ways (such as OpenNeuro openneuro.org; Markiewicz et al., 2021; and the NIMH Data Archive, nda.nih.gov), there are ethical questions with respect to data sharing when it comes to pediatric populations. Children are a protected class, and their privacy rights must be carefully considered while researchers strive to make data sharing and re-use easier. One possibility is the development of General Data Protection Regulation (GDPR)-compatible data sharing platforms such as Public nEUro (https://publicneuro.eu/) or the EBRAINS data sharing services (https://www.ebrains.eu/). A less fraught process that will also support studies of individual differences is code sharing. In general, neuroimaging has been at the forefront of the movement to share research analysis tools publicly over the last decades, and since the development of BIDS, an even greater number of tools have been developed for standardized analysis of brain imaging data. The rise of containerized analysis pipelines has greatly increased the usability of tools in neuroimaging and has enhanced reproducibility. Continuing to push for open access to FIT-specific neuroimaging pipelines will be critical for individual differences research moving forward.

7. Concluding remarks

Studying individual differences in the neurodevelopment of fetuses, infants, and toddlers is uniquely challenging. In the context of development, individual differences are rapidly moving targets, and it is sometimes unclear whether we should be trying to measure the target itself, its trajectory, or both. Difficulties arise at the recruitment stage regarding who can participate in research studies, at the study design stage when considering which neuroimaging measures can be collected with the target population, at the analysis stage when accounting for developmental change, and particularly when it comes to interpreting results in a relatively new field. Crucially, FIT neuroimaging is also at the cutting edge of technological advancements, analytical approaches, and theory, all of which are critical for measuring and interpreting individual differences. We are inspired and emboldened by this progress, and look forward to continued advancement in the study of individual differences in fetal, infant, and toddler neurodevelopment.

CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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