

Imaging structural and functional brain development in early childhood

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Abstract | In humans, the period from term birth to ~2 years of age is characterized by rapid and dynamic brain development and plays an important role in cognitive development and risk of disorders such as autism and schizophrenia. Recent imaging studies have begun to delineate the growth trajectories of brain structure and function in the first years after birth and their relationship to cognition and risk of neuropsychiatric disorders. This Review discusses the development of grey and white matter and structural and functional networks, as well as genetic and environmental influences on early-childhood brain development. We also discuss initial evidence regarding the usefulness of early imaging biomarkers for predicting cognitive outcomes and risk of neuropsychiatric disorders.

Early childhood — especially the period between term birth and ~2 years of age — is increasingly recognized as being very important for establishing cognitive abilities and behaviours that last a lifetime¹ as well as for risk of neuropsychiatric disorders such as autism and schizophrenia². Despite its importance, little is known about structural and functional brain development during this critical period, in part owing to difficulties with image acquisition and image analysis in very young children. However, imaging studies in early childhood have recently begun to illuminate the extremely rapid pace of postnatal structural and functional brain development^{3–6}.

These studies, along with more recent post-mortem histological and gene-expression studies^{7,8} (BOX 1), suggest that the basic structural and functional framework of the human brain is in place by the second year of life and perhaps even earlier. Brain development after age 2 years is characterized mainly by reorganization, ‘fine-tuning’, plasticity and remodelling of the major circuits and networks that are already established. Despite the challenges associated with imaging young brains (BOX 2), these studies are also beginning to provide the basis for a better understanding of how the different components of structural and functional development relate to one another in this period of rapid growth⁹. They suggest a model in which white-matter tracts and networks are largely in place at birth and resting-state functional networks develop rapidly after birth, along with rapid myelination and maturation of existing white-matter connections. Cortical and subcortical grey matter also undergo robust growth in the first year of life¹⁰, although cortical grey-matter networks seem to mature much later in childhood, perhaps driven by coordinated activity across the cortex from functional networks that arise much earlier in development.

In this Review, we describe recent imaging studies of early childhood and place them in the context of previous studies of brain development that typically begin at age 6 years. We review studies of grey-matter and white-matter development as well as studies of functional- and structural-network development. Although the current state of knowledge of genetic and environmental influences on early-childhood brain development and the usefulness of imaging biomarkers for understanding cognitive development and risk of psychiatric and neurodevelopmental disorders does not yet allow definitive conclusions in young children, here we cover early efforts to address these issues. This Review does not address pre-term imaging studies, either of premature infants or of in utero prenatal brain development, in detail^{11,12}.

Structural development

Prior knowledge of structural brain development has been based mainly on older post-mortem studies that are typically limited by sample size and cross-sectional design. Although imaging studies cannot provide information at a cellular level, they have considerably improved our understanding of early-childhood structural brain development in humans and complement post-mortem studies (BOX 1).

Global tissue volumes and subcortical structures.

Overall growth of the brain is very rapid in the first years of life (FIGS. 1, 2). Brain volume is about 35% of adult volume by 2–3 weeks after birth¹³, doubles from term size in the first year of life and increases an additional 15% in the second year of life to about 80% of adult size³. After age 2, there is a more gradual increase in volume, consistent with previous post-mortem studies of brain weight^{14,15}. Grey and white matter have different growth trajectories

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Box 1 | Human neurodevelopment at the cellular level

There are very few post-mortem histologic studies of early-childhood cortical development; however, the studies that do exist are consistent with imaging studies and provide insights into the neurobiological processes that underlie the changes observed in imaging studies.

Grey matter

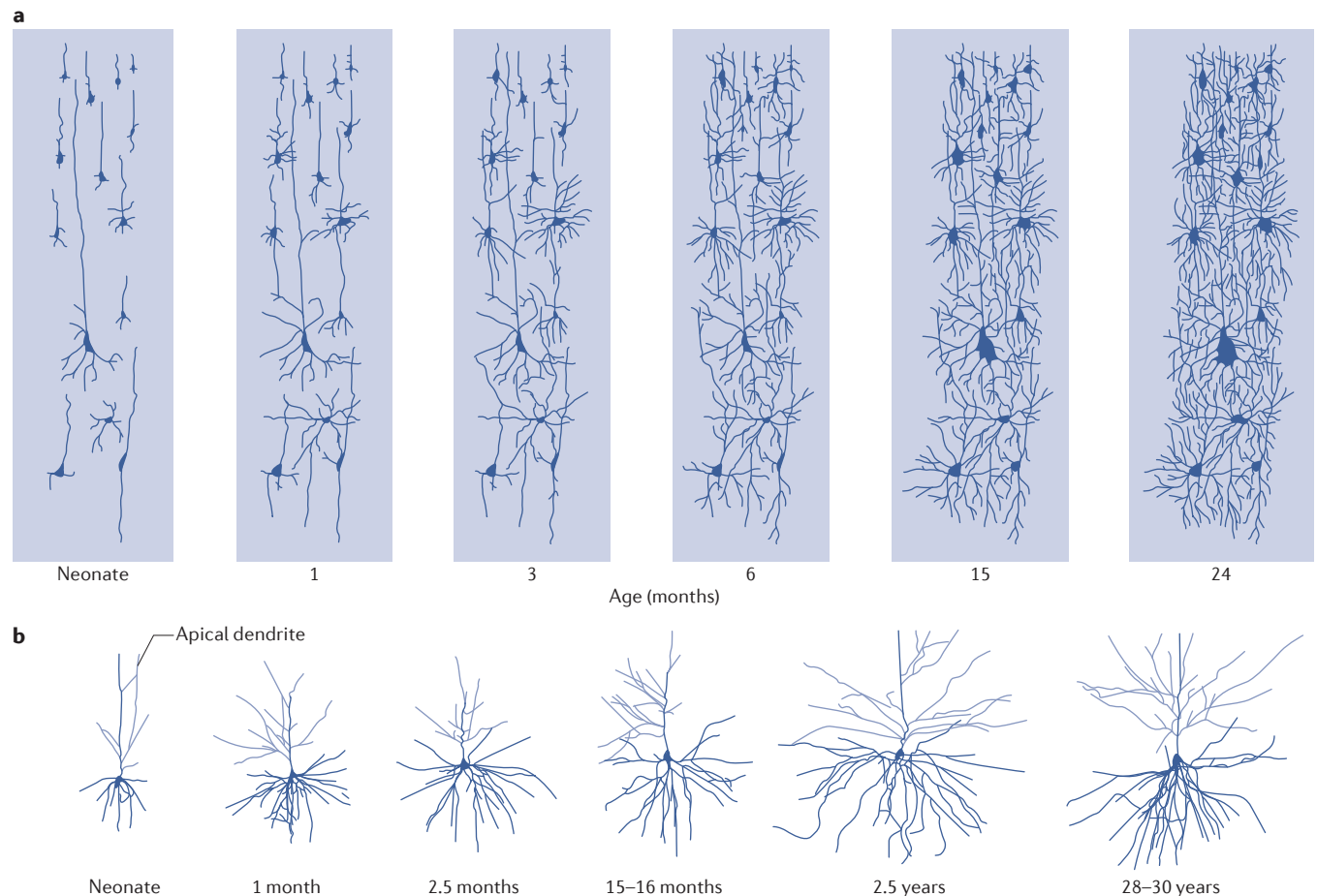
The bulk of neurons in the human brain are generated prenatally²⁰⁴. However, recent studies find that some neurogenesis occurs after birth: one study showed that neurons continue to arise and migrate from the subventricular zone of the anterior lateral ventricles to the olfactory bulb and ventromedial prefrontal cortex in the first 18 months of postnatal life²⁰⁵. Another study found widespread migration of new neurons, mainly inhibitory interneurons, to the cingulate cortex and superior frontal gyrus in the first 5 months after birth²⁰⁶. These studies suggest that neurogenesis in early childhood contributes to grey-matter expansion in at least some areas of the frontal lobe.

The complexity of cortical neurons increases rapidly in the first years after birth, mirroring imaging findings of rapid cortical thickness growth and surface area expansion. Conel's classic survey of cortical neuron development in children found that the overall complexity of cortical neurons increases quickly after birth, peaking at 2–4 years²⁰⁷ (see schematic in part **a** of the figure). Synapse numbers increase rapidly after birth and decrease in adolescence, with synapse numbers peaking in the auditory and visual sensory areas before those in the prefrontal cortex²⁰⁸, consistent with imaging findings that sensorimotor regions mature before higher-order association areas¹⁰. There are layer-specific differences in the developmental trajectories of dendritic complexity in the prefrontal cortex. For example, at birth, layer V neurons have more complex basal dendritic trees, which integrate synaptic inputs, than do

layer IIIC neurons; layer V neurons reach maximum complexity at 16–30 months after birth, before layer IIIC²⁰⁹ (see layer III development in part **b** of the figure²⁰⁹). Synaptic spine density in the prefrontal cortex also peaks by 2–5 years and falls in adolescence⁷.

White matter

Post-mortem studies of white-matter myelination in the human brain find that myelination begins prenatally and is present in many regions at the time of birth, especially primary sensory and motor pathways, including the optic radiations and internal capsule^{210,211}. Postnatally, myelination follows a general pattern of sensory before motor regions, projection areas before associative areas and posterior before anterior regions²¹¹. In the human hippocampus, myelination begins at 20 weeks gestational age, and by age 2 years, many regions have attained adult levels of myelination, although some areas (such as the hilus of the dentate) continue to myelinate throughout childhood into adulthood^{212–214}. In the neocortex, mature myelination patterns are attained only in adulthood, reflecting a protracted maturation of this brain region in humans compared with that in nonhuman primates²¹⁵. Oligodendrocytes are responsible for producing myelin, and the number of oligodendrocytes in cerebral white matter increases rapidly and linearly after birth, from approximately 7 billion at birth to 28 billion at age 3 years — a rate of 600 million per month²¹⁶. In the corpus callosum, oligodendrocyte numbers increase until age 5 years and are stable thereafter; a study of nuclear-bomb-test-derived ¹⁴C suggests that there is little turnover of oligodendrocytes after age 5 years²¹⁷. Part **b** of the figure is adapted from Petanjek, Z. et al. Lifespan alterations of basal dendritic trees of pyramidal neurons in the human prefrontal cortex: a layer-specific pattern. *Cereb. Cortex* 2008, **18**(4), 915–929, by permission of Oxford University Press (REF. ²⁰⁹).



soon after birth, with rapid development of grey-matter volume compared with white-matter volume, which increases much more gradually^{3,15}. From birth to age 1, cortical grey-matter volume increases 108–149%, whereas white matter increases by about 11%; from age 1 to age 2, grey matter increases 14–19%, whereas white matter increases by 19%³. Postnatal growth of global tissue volume and subcortical structures is most rapid in the first 3 months after birth¹⁶. After age 2, total grey-matter volume shows minimal absolute increases through childhood and decreases in adolescence, whereas white-matter volumes steadily increase through early adulthood, peaking at around age 30 (REFS^{17,18}).

The growth rates of subcortical grey-matter structures are similar to cortical grey-matter growth rates, with the amygdala, thalamus, caudate, putamen and pallidum growing about 105% in the first year and roughly 15% in the second year. The hippocampus grows somewhat more slowly (about 84%) than other subcortical structures in year 1 (REF.¹⁹). Lateral ventricle volume increases by over 100% in year 1 but subsequently decreases by 7–24% in the second year of life^{3,10,19}.

Cortical thickness, surface area and gyrification.

Structural imaging of cortical development typically assesses two major components of cortical volume — cortical thickness and surface area — as well as indices

of cortical folding (gyrification). In contrast to the rather gradual changes in cortical thickness and surface area observed in later childhood and adolescence²⁰, these measures grow dramatically in the first 2 years of postnatal life.

Imaging studies of infants and older children^{20–22} have revealed that cortical thickness probably peaks in the range of 1–2 years and declines thereafter, whereas surface area continues to expand well into late childhood or early adolescence. The limited post-mortem studies of cortical neuron development in humans are consistent with the temporal and regional patterns of grey-matter growth derived from imaging studies (BOX 1).

Overall, the major patterns of gyrification of the newborn brain are very similar to those of the adult brain. The gyrification index (the amount of cortex within a sulcal fold) increases in the first 2 years of life in parallel with overall brain growth²³. Cortical surface area expands by 76% from birth in year 1 and another 22% in year 2; by age 2 years, the mean surface area is about 69% of adult values^{4,23}. Surface area expansion is also regionally heterogeneous across the brain: the lateral frontal, lateral parietal and occipital cortices grow relatively rapidly, whereas regions in the orbital frontal, insula and occipital cortices tend to grow more slowly (FIG. 1). This pattern is generally consistent with an imaging study that compared surface area between infants and adults²⁴. Surface area expands linearly from age 3 to about 8–12 years and then declines gradually^{20,25}.

Average cortical thickness increases by an average of 31% in the first year and an additional 4.3% in the second year; by age 2, the mean cortical thickness is about 97% of the values observed in adults⁴. The regional heterogeneity of cortical thickness observed in adults is well established at birth and persists through to adulthood^{4,26}. Regions of faster growth of cortical thickness after birth include speech and language regions (such as Heschl's gyrus or the Rolandic operculum), the insula and the cingulate cortex as well as some higher association areas. The primary and secondary sensory cortices tend to grow more slowly. Whereas some studies have suggested that cortical thickness increases from age 6 to 10 years and begins to thin after 10–12 years^{20,21}, most studies find that cortical thickness decreases linearly after age 4–5 years^{25,27,28}. Indeed, a recent study reported that cortical thickness might gradually decrease even between 1 and 6 years of age²².

White matter. White-matter volume increases through evolution²⁹, as longer white-matter fibres are needed to connect neurons in larger brains and the volume of white matter increases faster in evolution than does the volume of grey matter^{29,30}. Diffusion imaging studies find that major white-matter tracts such as the corpus callosum, superior and inferior longitudinal fasciculi, arcuate and cingulum are present at the time of birth, indicating that most of the 'wiring' of the brain is established during prenatal brain development³¹ (FIG. 1). As noted above, white-matter volume growth is slower and more protracted than that of grey-matter volume (FIGS. 1, 2).

Box 2 | Challenges of structural imaging in early childhood

Studies of early-childhood brain development have been limited by difficulties with image acquisition and analysis. Young children have a limited ability to cooperate with scanning procedures that require lying still and minimizing motion and are often scanned in a natural sleep, which is difficult to initiate and maintain in a noisy scanner environment. Moreover, the short image-acquisition protocols necessary in young children tend to produce less-than-ideal tissue contrasts and image quality compared with those used in studies of adults. Image-analysis protocols developed for the adult brain often fail in the infant brain owing to the latter's smaller size, reduced tissue contrast between grey and white matter and large changes in size and tissue contrasts with age. For example, the relative intensities of grey and white matter in T1-weighted and T2-weighted imaging change considerably over the first year of life and are typically very similar between 4 and 8 months of age; this makes distinguishing grey and white matter difficult. This changing contrast also presents challenges for determining cortical thickness, which depends on a clear boundary between cortical grey matter and underlying white matter²⁸. Fortunately, improved image-acquisition technologies — such as parallel imaging with multichannel head coils, multiband techniques that allow excitation of multiple slices and scanners with higher gradients — now provide improved resolution and signal in the shorter time frames required for imaging infants. These technical advances, combined with innovative image-analysis programs that provide improved brain-tissue segmentation and parcellation, make imaging studies of young children much more feasible and informative.

It is increasingly recognized that motion in the scanner can significantly influence measures of cortical thickness and surface area^{27,218} as well as diffusion-tensor imaging parameters²¹⁹ (BOX 3) and resting-state networks^{219,220} (BOX 4). Motion tends to reduce estimates of grey-matter volume and cortical thickness²²¹ and can also influence the observed trajectories of cortical thickness maturation²⁷. Thus, care must be taken to assess and correct for motion — especially in childhood, when motion can be more of an issue, or when comparing groups of subjects when one group may be more likely to experience motion in the scanner. There are several approaches to detecting motion during scanning and for prospective and retrospective motion correction; prospective motion correction typically requires multiple extra images, increasing the scan time^{222,223}. It is also important to recognize that imaging measures are indirect measures of brain structure and function and are subject to the effect of many potential confounds, such as hydration, blood lipid levels and cortisol levels²²⁴.

In contrast to volume growth, the maturation of white-matter regions and tracts has been revealed by quantitative diffusion-tensor imaging (DTI) studies to be similar to that observed for grey-matter regions, with rapid rates of change in the first year of life and a more gradual increase thereafter (BOX 3; reviewed elsewhere⁵). With postnatal development, measures of white-matter microstructure and maturation, including axial diffusivity (AD) and radial diffusivity (RD), decrease, whereas fractional

anisotropy (FA) increases — a change that is thought to reflect the increasing organization of the already established white-matter tracts, including myelination^{5,32}. For example, FA increases by 9–44% in the first year, with most tracts increasing by more than 25%; in the second year, FA increases by 5–9% over levels at age 1 year. Multicomponent relaxometry, an alternative approach to the study of white matter (BOX 3), showed that myelination in the first year of life begins in the cerebellum, pons

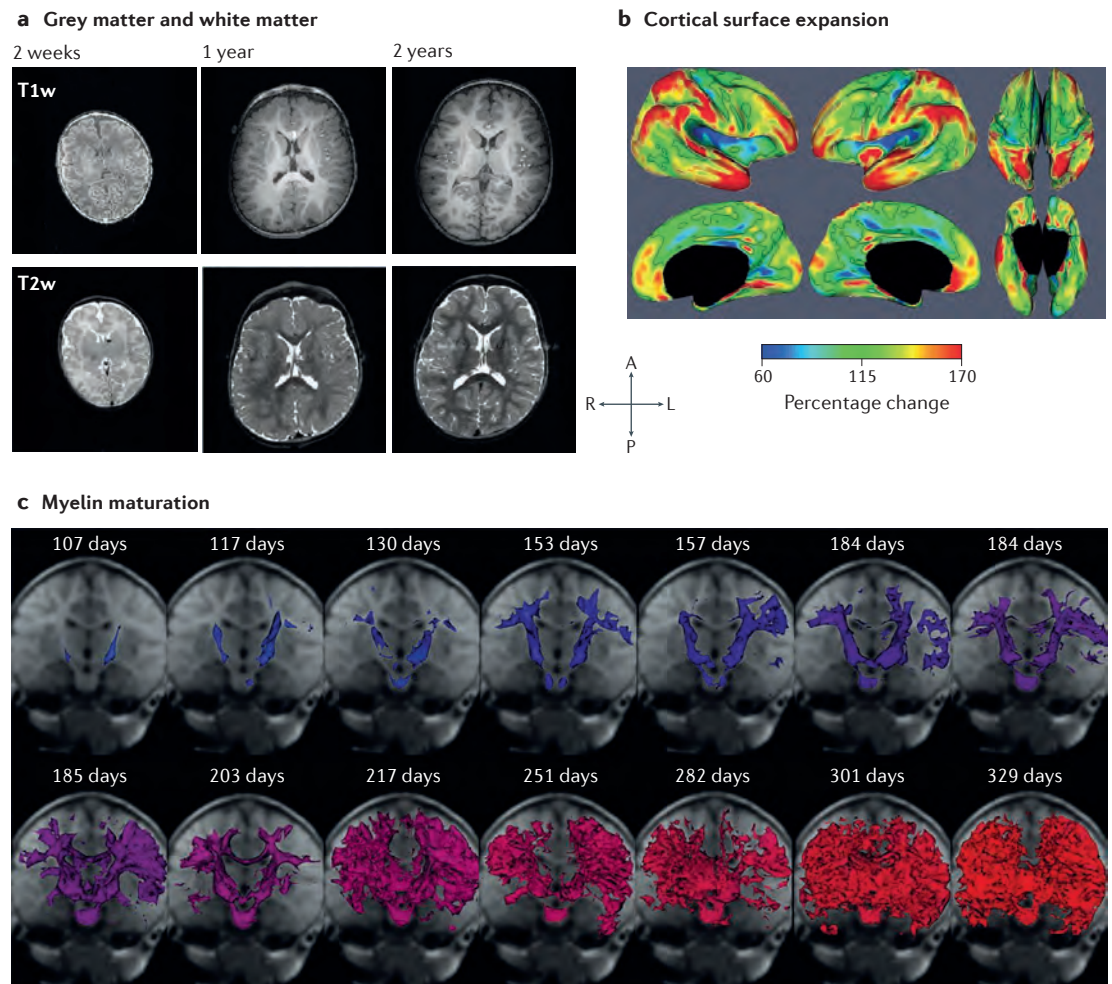


Fig. 1 | Structural brain development in early childhood. a | T1-weighted (T1w) and T2-weighted (T2w) images, between birth and age 2 years. Note the doubling of overall brain size between birth and 1 year, with more gradual growth after age 1. In the neonate T1 scan, note that most white matter is not myelinated and therefore appears darker than cortical grey matter. Myelination proceeds rapidly in the first year of life; at 1 year and older, white matter assumes the typical white appearance seen in adults. This rapid change in tissue contrasts presents challenges for image analysis. Also note the relatively thin cortical grey-matter rim in the neonate T1 scan; by age 1, grey-matter thickness has increased considerably, reaching near-maximal thickness. White matter is more intense than grey matter at birth; this pattern is reversed by age 1 year. **b** | Regional expansion of cortical surface area from birth to 2 years derived from surface reconstructions of T2 (birth) and T1 (ages 1 and 2 years) scans, with greatest expansion in the parietal, prefrontal and temporal regions. **c** | Myelin maturation in the first year of life imaged with mcDESPOT (multicomponent driven equilibrium single pulse observation of T1 and T2; see BOX 3). Myelination begins in central white matter and spreads peripherally. A, anterior; L, left; P, posterior; R, right. Part **a** is adapted from Gilmore, J. H. et al. Longitudinal development of cortical and subcortical gray matter from birth to 2 years, *Cereb. Cortex* 2012, 22(11), 2478–2485, by permission of Oxford University Press (REF. ¹⁹). Part **b** is adapted from Li, G. et al. Mapping region-specific longitudinal cortical surface expansion from birth to 2 years. *Cereb. Cortex* 2013, 23(11), 2724–2733, by permission of Oxford University Press (REF. ²³). Part **c** is adapted with permission of Society of Neuroscience, from Mapping infant brain myelination with magnetic resonance imaging. Deoni, S. C. et al. 31, 2011; permission conveyed through Copyright Clearance Center, Inc. (REF. ³³).

Axial diffusivity (AD). Water diffusion along the principal axis of a fibre, thought to be dependent on fibre compactness and microstructure.

Radial diffusivity (RD). Water diffusion perpendicular to the main axis of the fibre, sensitive to myelination.

Fractional anisotropy (FA). A summary measure of microstructure that takes into account axial diffusivity and radial diffusivity.

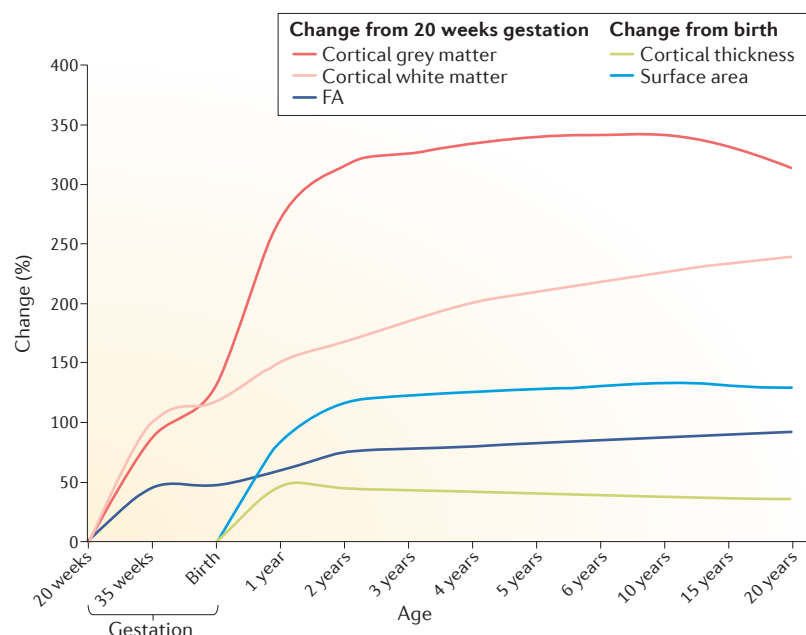


Fig. 2 | Estimated trajectories of brain structural parameters during development. Relative growth trajectories (depicting percentage change from 20 weeks or neonate scan) in imaging studies of cortical grey and white matter, cortical thickness, surface area and fractional anisotropy (FA) from the prenatal or neonatal period to adulthood. After substantial prenatal development, there is robust postnatal growth of cortical grey-matter volumes in the first 2 years of life and comparatively slower growth of cortical white-matter volume. FA, a measure of white-matter microstructure, also increases rapidly in the first year of life and much more gradually thereafter, consistent with trajectories of myelination. Cortical thickness peaks at 1–2 years of life and decreases gradually thereafter, whereas surface area develops rapidly in the first year of life and continues to expand thereafter, indicating that the cortical volume growth observed after 1–2 years may be driven mainly by surface area expansion. Grey-matter volume and cortical thickness tend to decrease somewhat during adolescence (10–20 years), whereas white-matter volume and FA continue to increase through this period. Figure from Handbook of Preschool Mental Health: Development, Disorders, and Treatment. Bullins, J. et al. (ed. Luby, J. L.), 2017. Copyright Guildford Press. Adapted with permission of The Guildford Press (REF. ²⁴⁸).

and internal capsule and proceeds in a ‘back-to-front’ pattern, from the splenium of the corpus callosum and optic radiations (3–4 months) to the occipital and parietal lobes (4–6 months) and anteriorly to the frontal and temporal lobes (6–8 months)³³. Diffusion values change much more gradually through later childhood and adolescence, with AD and RD decreasing and FA increasing^{34,35}; similarly, myelination increases more gradually after the second year^{36,37}. The diffusion properties of white-matter tracts are highly correlated with each other at birth, but this correlation decreases with development as tracts mature and differentiate³⁸.

Networks

Beyond individual white-matter tracts and regional cortical thickness and surface area, there is also a growing interest in characterizing the growth of structural and functional networks during early brain development.

In the adult brain, graph-theory-based approaches have been increasingly applied to quantify the different information-transfer properties of structural and functional whole-brain networks³⁹. Among these properties,

indices of local efficiency and global efficiency characterize the ease of information flow at the local neighbourhood and global system levels, respectively; systems that possess both high local and global efficiencies are designated as having ‘small-world’ properties⁴⁰. Moreover, there is also interest in detecting the ‘hubs’ of the brain that serve as connecting centres between different parts of the system⁴⁰. Finally, the human brain also exhibits a ‘rich-club’ phenomenon, in that network hubs also tend to be better connected to each other⁴¹.

Leveraging these conceptual and methodological advances, there has been tremendous progress in understanding brain-network development during the first years of life^{42–44}. Although the structural and functional connectomes of the brain have been linked to cognitive function and disease, little is known about the biology that underlies them. Rich-club regions of the functional connectome have recently been found to organize functional networks through state-dependent oscillatory activity⁴⁵, and neuronal network behaviour can be used to predict neuron function in *Caenorhabditis elegans*⁴⁶, providing interesting first clues about the neurobiology of large-scale networks.

Structural networks. White-matter networks in adults are characterized by global and local efficiency, and small-world and modular structures that have a ‘rich club’ of modules that are highly connected; these structural networks are altered in neuropsychiatric disease. Recent studies indicate that most of these white-matter network attributes are present at, and even before, birth (reviewed elsewhere⁴⁷). Overall, the white-matter connectome at birth is highly organized and includes hub regions and connections that are similar to those observed in adults^{48,49}. White-matter networks at birth, and even in premature infants at 30 weeks gestational age⁵⁰, have a rich-club property similar to that in adults. Network maturation in the first 2 years after birth generally consists of increased network efficiency and network integration, decreased network segregation and some changes in modularity^{48,51}, with most major hubs and modules in place by age 2 years⁵².

Cortical grey-matter structural networks consist of regions of highly correlated variation in grey-matter volume or cortical thickness^{53,54}. These structural covariance networks (SCNs) are heritable⁵⁵, are altered in neuropsychiatric disease⁵⁶ and have been related to intelligence⁵⁷. In adults, SCNs have small-world and modular properties; these SCNs overlap with white-matter and functional connectivity networks to some extent, although the biological foundation for these SCNs is not clear^{53,54}. Childhood development of SCNs is characterized by increasing global efficiency, decreasing local efficiency and changes in modularity. For example, at a network level, SCNs of grey-matter volume and cortical thickness exhibit small-world properties and modular organization at birth⁵⁸ and 3 years⁵⁹. Primary sensorimotor SCNs are well developed by birth, and higher-order association SCNs mature and became increasingly distributed, involving more regions from age 5 to 18 years⁶⁰. Longitudinal studies indicate that networks of similarities

Network integration

The overall capacity of the network to be interconnected and exchange information.

Network segregation

The degree to which parts of a network form localized clusters of nodes or modules of connections.

Structural covariance networks (SCNs)

Regions of cortical grey matter with correlated variance in cortical thickness.

Box 3 | Techniques used to study white-matter development in infants

Various imaging approaches are used to study white matter at different developmental stages. Early studies tracked white-matter maturation and myelination using standard T1-weighted and T2-weighted images and T1 and T2 relaxation times (that is, the time water magnetization returns to normal after changes in the magnetic field)^{5,225}. Diffusion-weighted imaging is widely used to study white-matter composition and development and takes advantage of the motion of water in response to changes in the magnetic field²²⁶. Water motion is constrained by the complex structure of axons and myelin, allowing the visualization of major fibre tracts and the analysis of the microstructure of the fibres, typically expressed as axial diffusivity, radial diffusivity and fractional anisotropy.

More recent advances in diffusion-weighted imaging attempt to provide more information about the microstructure of white matter, including the presence of fibres that cross one another, using biophysical models; these require increased numbers of diffusion values and directions using approaches such as high angular resolution diffusion-weighted imaging (HARDI) and multishell diffusion-weighted MRI^{5,223}. These approaches typically require longer acquisition times than standard sequences and are therefore a challenge in young children, although time-efficient modifications of these approaches have begun to be used^{227–231}. Another imaging approach used to study white-matter development in young children is that of an acquisition-time-efficient multicomponent relaxometry, mcDESOT^{231,232} (multicomponent driven equilibrium single pulse observation of T1 and T2), which determines the myelin water fraction. This method assesses white-matter myelination more directly than does traditional diffusion-weighted imaging but is dependent on acquisition protocol and modelling assumptions^{5,233,234}. The patterns of white-matter maturation described by diffusion-tensor imaging and myelin water fraction studies are consistent with one another and with previous post-mortem studies of myelination (BOX 1). Finally, the magnetization transfer ratio, or the ratio between free and bound water, has been used to assess white-matter microstructure and myelination²³⁵ but has not been used extensively in young children⁵.

Each of these imaging modalities assesses components of white-matter microstructure — such as axon thickness, oligodendrocyte proliferation and development, myelin deposition and axon retraction — to various degrees, but each approach provides at best indirect assessments of the various components of white-matter microstructure. Moreover, diffusion-weighted imaging has many limitations and sources of error at each step of the analysis pipeline that must be considered when interpreting results^{236,237}. Motion is also an important issue for white-matter imaging. Scanners with higher-strength gradients can considerably shorten acquisition times and decrease motion-related artefacts²³⁸. For diffusion-weighted imaging, motion can be corrected during acquisition or in post-processing in a variety of ways, although standards have not been established (see discussion section in REF. 239).

in regional maturation rates of cortical thickness are similar to SCNs, indicating that between 9 and 22 years, structural covariance is the result of coordinated maturation⁵⁴. By contrast, in the first 2 years of life, SCNs and maturational networks are not clearly related, suggesting that the fine-tuning of cortical SCNs, especially high-order SCNs, occurs later in childhood⁶¹. More research is needed to fully understand how SCNs are related to white-matter and functional networks.

Functional networks. The development of the function of the human brain begins prenatally^{62,63}. Electroencephalography (EEG) studies have documented intermittent bursts of electrical activity and synchronized oscillatory activity in premature infants^{64–66}. This early activity is believed to be crucial for the emergence and fine-tuning of primary functional circuits during fetal development, when sensory experience is limited⁶². This patterned electrical activity in the brain is mostly elicited by spontaneous activity in sensory organs, such as spontaneous retinal waves^{67,68}, spontaneous cochlear activity⁶⁹ and muscle twitching⁷⁰.

Non-invasive neuroimaging techniques such as functional MRI (fMRI)^{71,72} and functional near-infrared spectroscopy (fNIRS)⁷³ provide functional information that is complementary to EEG (BOX 4) and enable the study of the postnatal development of the brain's functional architecture. For example, task-based fMRI and fNIRS studies using passive stimuli have revealed adult-like positive blood-oxygen-level-dependent (BOLD) signals in response to sensorimotor^{74,75}, visual⁷⁶ and auditory stimuli⁷⁷ in human newborn babies and infants. fNIRS studies have documented the emergence and gradual improvement of various other functional responses during spatiotemporal processing⁷⁸, object recognition⁷⁹, learning⁸⁰ and social processing⁸¹, among other processes, during the first year of life. Nevertheless, non-invasive brain imaging of awake infants remains challenging owing to their motion and their inability to perform certain tasks, which limit such studies to a restricted set of brain functions. Moreover, the neurovascular coupling mechanism is known to be immature during this stage⁸², as key components enabling such coupling, including neurons, astrocytes, pericytes and the brain's vasculature, are still actively developing during infancy. The best approach to model infant BOLD-based activation is still an active area of research⁷⁴ (BOX 4).

The advent of MRIS studies of resting-state functional connectivity⁸³, which can probe the functional organization of the whole brain in sleeping infants⁸⁴, has opened a new era for the study of early brain functional development owing to their less complex experimental setup compared with task-based assessments and full coverage of different functional circuits (BOX 4). Since the first publication of such studies in sedated premature babies at term age⁸⁵ and in naturally sleeping newborn babies^{86,87}, an exciting body of work has been accumulating that documents the sequential, coordinated and hierarchical development of functional brain networks^{84,85,88–90} (FIG. 3). Specifically, primary functional networks, including the sensorimotor, visual and auditory networks, develop first and show adult-like topologies in premature babies at term age^{85,88,91,92} and in full-term newborn babies^{89,90}. Progressive maturation of these primary networks has been shown in human fetuses⁹³ and in premature infants before term age⁸⁸, corroborating reports of synchronized oscillatory electrical activity in primary cortices during prenatal development⁶². Thalamus-based relay of information has long been known to be crucial for the development of cortical networks⁹⁴; indeed, topographic thalamic connections with each of the primary cortical networks have been documented in premature babies at term age⁹⁵ and in full-term newborn babies⁹⁶ and undergo postnatal refinement and expansion⁹⁶. In particular, both structural and functional thalamo-cortical connectivity have been shown to predict later general cognition and working memory^{96,97}. White-matter development, particularly myelination, probably interacts with and facilitates the experience-dependent postnatal development of spatially distributed higher-order functional networks. Among them, the default-mode network^{98,99} shows the earliest synchronization of

Maturational networks
Regions of cortical grey matter with correlated changes in cortical thickness over time.

Core structure

The collection of key hub regions that possess the most connections that bring the whole network together.

its constituent regions and achieves an adult-like core structure by around 6 months of age⁹⁰, consistent with the emergence of self-awareness, which is thought to depend on the default-mode network, at this age¹⁰⁰. The language network in adults is lateralized and encompasses the inferior frontal gyrus (IFG) and the superior temporal gyrus (STG); these regions begin to exhibit asymmetry in functional connectivity with the homotopic region

on the contralateral hemisphere at about age 1 year¹⁰¹. In general, whether defined on the basis of hypothesis-driven seed-based functional connectivity analysis⁸³ (that is, assessing synchronization with a particular seed region, defined on the basis of prior knowledge of the corresponding network in adults) or of data-driven independent component analysis¹⁰² (that is, relying on data-driven definitions of temporally synchronized

Box 4 | Techniques used to study functional development

There are several approaches to the study of brain function in adults that are beginning to be applied to young children. The advantages and limitations of each approach are outlined below.

Electroencephalogram

Electroencephalogram (EEG) measures the electrical field generated by the postsynaptic activity of a synchronously activated palisade of neurons through electrodes placed on the scalp²⁴⁰. EEG is mainly sensitive to extracellular volume currents.

- The advantages of EEG include
 - Direct measure of neuronal activity
 - High temporal resolution (milliseconds)
 - Low cost
 - Portability
 - Relatively higher tolerance of head movement, thus easier for awake infants
- The limitations of EEG include
 - Poor spatial resolution (~10 cm)
 - Low depth penetration (restricted to cortical activity)
 - Relatively long preparation time

Magnetoencephalography

Magnetoencephalography (MEG) measures the magnetic field generated by the postsynaptic electronic currents of a synchronously activated population of neurons through magnetometers²⁴¹. MEG is mainly sensitive to intracellular currents.

- The advantages of MEG include
 - Direct measures of neuronal activity
 - High temporal resolution (milliseconds)
 - Relatively higher spatial resolution than EEG
- The limitations of MEG include
 - Poor spatial resolution (centimetres)
 - Low depth penetration (restricted to cortical activity)
 - High cost
 - Nonportability (infant applications scarce)

Functional near-infrared spectroscopy

Functional near-infrared spectroscopy (fNIRS) measures changes in the local concentrations of oxyhaemoglobin and deoxyhaemoglobin associated with neuronal activity, using near-infrared light⁷³.

- The advantages of fNIRS include
 - Higher temporal resolution (tens of milliseconds)
 - Low cost
 - Portability
 - Relatively higher tolerance of head movement, thus easier for awake infants
- The limitations of fNIRS include
 - Indirect measure of neuronal activity — the neurovascular coupling mechanism is partially understood
 - Poor spatial resolution (centimetres)
 - Low depth penetration (restricted to cortical activity)
 - Relatively long preparation time

Task-based functional MRI

Functional MRI (fMRI) measures changes in the local concentrations of oxyhaemoglobin and deoxyhaemoglobin (that is, the blood-oxygen-level-dependent (BOLD) signal) associated with neuronal activity through sensitivity to local changes in magnetic susceptibility⁷².

- The advantages of fMRI include
 - High spatial resolution (millimetres)
 - Deep brain structure coverage
 - Sufficient temporal resolution for haemodynamic response measurement (seconds to subseconds, depending on hardware and sequence)
- The limitations of fMRI include
 - Indirect measure of neuronal activity — the neurovascular coupling mechanism is partially understood
 - High cost
 - Nonportability
 - Large acoustic noise (requiring special ear protection for infants)
 - Difficult for awake infants owing to low tolerance of motion (most studies applied in sleeping infants with passive stimuli)
 - One common concern for both task-based fMRI and fNIRS studies is the immature neurovascular coupling mechanism, or 'haemodynamic response function' (HRF), in neonates and infants. Although studies have shown adult-like positive BOLD responses to sensorimotor, visual and auditory stimuli in human newborn babies and infants^{75,76,77}, some studies in infants report that peak BOLD responses are temporally delayed or smaller^{74,75}, and some negative BOLD responses have also been observed^{242–244}, indicating that the problem is more complex. The best ways to detect BOLD signal using either task-based fMRI or fNIRS remain an active area of research, but age-specific HRFs should at least be considered in human newborn and infant studies.

Resting-state functional MRI

Resting-state fMRI (rsfMRI) measures the temporal synchronization of spontaneous BOLD fluctuations in the absence of explicit tasks⁸³.

- The advantages of rsfMRI include
 - The same advantages as task-based fMRI, plus easier experimental setup and low subject-compliance requirement (that is, no task stimuli are used and imaging can be conducted during natural or sedation-induced sleeping states)
 - Full exploration of all functional networks or circuits without limiting to a certain task
- As the newest technology for infant study, rsfMRI has extra limitations on top of those shared with task-based fMRI that deserve further consideration and research. These include
 - The neuronal mechanisms underlying the ultra-slow BOLD signal fluctuations (that is, those occurring at <0.1 Hz, the main frequency band investigated in rsfMRI studies) remain only partially understood (although slow spontaneous modulations in firing rate and gamma-band local field potential have been proposed as potential candidates²⁴⁵)
 - The likely differences in functional organization⁷⁵ between the brains of infants and adults call for infant-specific functional atlases²⁴⁶ for better definition of regions of interest and result interpretation
 - Motion artefacts and physiological confounds affect the estimation of rsfMRI correlations more than detection of task-based fMRI activation and thus require more research for optimal strategies. Although extensive work has been done in adults^{220,247}, infant-specific optimal strategies deserve more research.

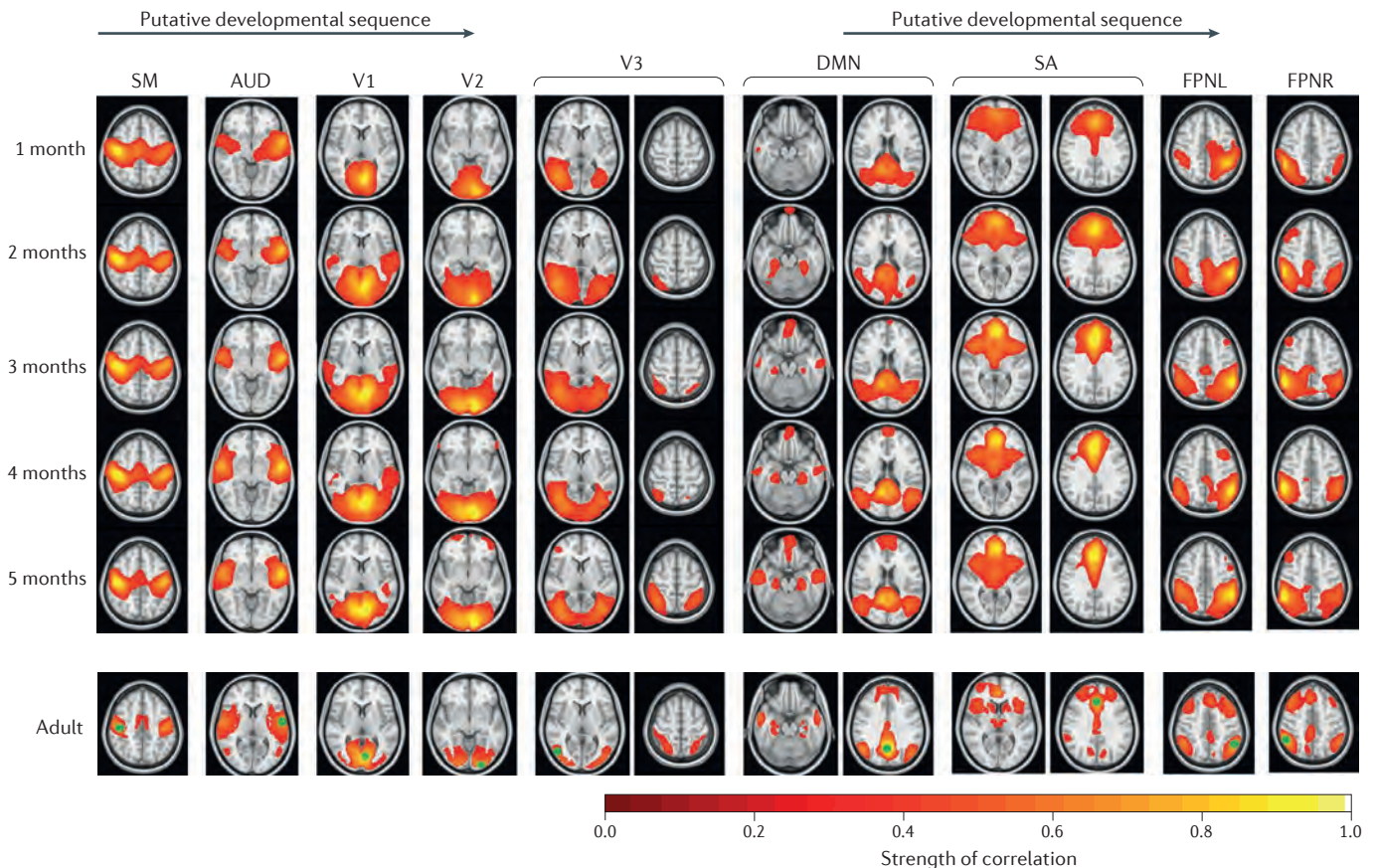


Fig. 3 | The development of resting-state functional networks during infancy. This grid of functional MRI (fMRI) images depicts the growth of nine resting-state networks (RSNs) during the first year of life, with 3-month intervals between different time points, and in adulthood. Arrows at the top indicate the suggested developmental sequence of different RSNs on the basis of the rates of increase in the similarity of their spatial topology with the corresponding adult ones and the strength of within-network functional connectivity (for more details, see REFS^{89,90}). Colour bar represents Pearson correlation strength between the blood-oxygen-level-dependent (BOLD) signals of each brain voxel with the corresponding seed (green dots denoted

in corresponding adult maps in the bottom row). The images are shown in radiological convention (that is, left side of brain on right side of image). All RSNs, including the two lateralized FPN networks (FPNL and FPNR), were defined after Smith et al.²⁴⁹. AUD, auditory network; DMN, default-mode network; FPN, frontoparietal executive control network; SA, salience network; SM, sensorimotor network; V1, visual 1 (medial visual) network; V2, visual 2 (occipital pole) network; V3, visual 3 (lateral visual) network. Figure adapted from Gao, W. et al. Functional network development during the first year: relative sequence and socioeconomic correlations. *Cereb. Cortex* 2015, **25**(9), 2919–2928, by permission of Oxford University Press (REF.⁹⁰).

Dorsal attention network

The network involved with the 'top-down', or voluntary, focusing of attention; includes the intraparietal sulcus, frontal eye fields and middle temporal regions.

Salience network

The network involved with the selection of relevant stimuli; includes the insula, anterior cingulate cortex and amygdala.

Step-wise analysis

A technique that attempts to identify intermediate connector regions and multistep links between two brain regions that do not show directly correlated functional activity.

but spatially 'independent' functional networks without relying on prior knowledge), the default-mode network^{98,99}, the dorsal attention network^{103,104} and the salience network^{105,106} establish distributed network-like topologies by 2 years of age^{89,90}, which is earlier than the executive control networks⁹⁰ and consistent with the protracted development of executive functions¹⁰⁶.

Beyond individual networks, the study of inter-network relationships reveals that functional network development is coordinated^{107,108}. For example, preliminary manifestations of sensorimotor–auditory integration through convergent connectivity within the sylvian–parietal–temporal area^{107,109} have been observed in neonates. Moreover, the inverse correlation between the activity in the dorsal attention network and the default-mode network, interpreted by most as a sign of 'competition' between the processing of external and internal events in the mature brain¹⁰⁴, also emerges during the first year of life¹⁰⁸.

The hierarchical nature of the brain's functional organization has long been recognized^{110,111}, and step-wise analysis of functional connectivity emerges as a novel technique that could probe this hierarchy¹¹². Notably, sensory networks have been demonstrated to exchange information through two-step inter-regional functional connectivity to the default-mode network and lateral frontoparietal, limbic and basal ganglia regions in subsequent steps^{107,112}, mimicking the hierarchy proposed by the theory of predictive encoding^{113,114}. Infants gradually develop this hierarchy in a region-dependent and step-dependent manner, displaying many of the same regions in the top hierarchy (that is, the lateral frontoparietal, limbic and basal ganglia regions) at 1 year of age¹⁰⁷, suggesting that the brain's functional hierarchy also emerges during infancy. When evaluating the whole brain as an integrated system, the newborn brain already demonstrates 'small-world' functional network properties^{92,115}, although whole-brain efficiency continues to improve during postnatal development^{115,116}.

Overall, these studies have greatly enriched the understanding of how functional networks develop in the human brain. Genetically determined early synaptic connections enable the first appearance of synchronized oscillatory electrical activity in the prenatal brain^{62,63}. Through activity-dependent but largely experience-independent development, primary functional networks are formed before birth. Transitioning from the later part of gestation to postnatal development, interactions between experience-dependent processes¹¹⁷ and gene expression further modify or refine the primary functional circuits for more efficient signal processing and action generation. Enabled by and rooted in these primary functions, new social, cognitive and emotional experiences parallel the emergence, growth and fine-tuning of the corresponding higher-order functional circuits.

Influences of genes and environment

Sex differences. There is a large literature on sex differences in brain structure and function in adults and older children^{118,119}. Studies focused on infancy and early childhood are more limited but indicate that many of these sex differences are present at birth. Male neonate brains are about 6% larger than female brains at birth and, even at this stage, there are already several areas that show evidence of local sexual dimorphism¹²⁰. For example, the medial temporal cortex and Rolandic operculum are larger in males, whereas the dorsolateral prefrontal, motor and visual cortices are larger in females¹²⁰. A more recent study with a larger sample size and more stringent statistical thresholds replicated the finding of a larger medial temporal cortex in males and indicated that female neonates have greater grey-matter volumes around the temporal–parietal junction, a crucial brain region for social cognition¹²¹. On average, males exhibit a higher number of neocortical neurons than do females, and this difference is a likely contributor to the larger intracranial volume observed in males¹²² and may also be important for the observed regional differences. If sex differences in intracranial volume reflect differences in neocortical neuron number, these differences may originate in the second trimester, when neurogenesis is at its peak and male fetal testosterone levels are high.

Postnatally, brain volume increases more rapidly in male infants than in female infants, leading to a widening separation in brain sizes^{16,123}. These differences are probably driven by differences in surface area expansion, as the maturational trajectories of global and regional cortical thickness are highly similar in males and females^{4,20,27}. Males also show increased global gyrification at 2 years of age compared with females (adjusting for total brain volume) but not at 0 or 1 year of age; by contrast, the local or regional gyrification index is similar in males and females at each age¹²⁴.

DTI studies find minimal sex differences in neonates^{125,126} and in the maturation pattern of major white-matter fibre bundles with time³². By contrast, between 3 and 60 months, females exhibit a higher rate of myelination than do males in the genu of the corpus callosum, in left frontal and left temporal white matter

and in the right optic radiation¹²⁷. Nevertheless, studies in adults suggest that males have higher FA, higher AD and lower RD in widespread white-matter regions^{128–132}. These sex differences may therefore emerge in adolescence, as FA increases more rapidly in males than females across this time period, driven by reduction in RD. However, it is important to note that some studies have shown more focal differences in the thalamus, corpus callosum, cingulum and superior cerebellar peduncles^{133,134}, and some studies also show regions of increased FA in adult females compared with males, including the corpus callosum and fronto-occipital fasciculus^{134,135}.

Developmental patterns of resting-state functional connectivity are remarkably similar in males and females, with the exception that interconnectivity between the two lateralized frontoparietal networks increases at a greater rate in males⁸⁹. In adults, sex differences in amygdala functional connectivity have been reported, with females showing stronger positive connectivity between the amygdala and areas associated with face monitoring and discrimination (such as the middle temporal gyrus and the IFG), sensory processing areas (postcentral gyrus) and emotion-processing areas (hippocampus) and males showing greater connectivity between the amygdala and areas involved in the acquisition of conditioned fear, extinction learning and extinction memory^{136,137}, consistent with observations during later childhood and adolescent development¹³⁸.

Sexual differentiation of the brain during the prenatal, perinatal and early postnatal period probably reflects a dynamic interplay of many mechanisms — both biological (for example, prenatal and neonatal hormone production and direct sex chromosome effects) and experiential (for example, resulting from parental expectations and interactive behaviour, exposure to physical hazards or culturally influenced lifestyle differences). Detailed longitudinal studies addressing both the biological and social spheres are needed to disentangle the complex dynamics of sex-related patterns in brain development. Ultimately, a better understanding of the pathways leading to sexually dimorphic brain development may help explain sex differences in vulnerability to various psychiatric disorders and open up possibilities for sex-tailored interventions and therapeutics.

Heritability. Twin studies in adults and older children find that the genetic contribution to variance of global brain-tissue volumes is high, with heritability estimates typically greater than 80% for global grey and white matter^{139,140}. Cortical thickness and surface area also have considerable genetic influences that vary by cortical region, but interestingly share little genetic variance, indicating that these two aspects of cortical volume are regulated by different sets of genetic influences^{141,142}. Studies have indicated that genetic factors account for 85% variance in neonatal global white-matter volume and 56% variance in neonatal global grey-matter volume¹⁴³. Together with the adult data, these results suggest that the heritability of white-matter volume is stable over the course of postnatal brain development

Predictive encoding

Theoretical framework in which higher-level cortices continuously generate predictions about the environment on the basis of learned input regularities, to minimize errors between lower-level inputs and predictions.

Heritability

The proportion of variance in a trait or measure that is due to genetic variation.

and that the heritability of grey-matter volume seems to increase during the period of rapid grey-matter growth from birth to later childhood. DTI studies also indicate that white-matter microstructure, as represented by FA, is generally highly heritable in adults, with variability across different white-matter tracts^{144,145}. By comparison, the heritability of tract-based FA in neonates^{146,147} and in 9-year-olds and 12-year-olds¹⁴⁸ is relatively low, suggesting that the heritability of white-matter microstructure increases over the course of childhood; however, longitudinal studies are lacking.

Studies in adults indicate that structural networks of white-matter and resting-state functional networks each have considerable genetic components⁴³. For example, the path length and clustering coefficients of adult white-matter networks have heritabilities of 57% and 68%, respectively¹⁴⁹, whereas the heritability of default resting-state network connectivity is 42%¹⁵⁰. One twin study in children aged 5–18 years¹⁵¹ found that 60% of the genetic variability of cortical thickness was shared across different regions of the cortex, with SCNs of shared genetic variance in frontoparietal and occipital regions. In 12-year-olds, the path length of resting-state networks has a heritability of 42%¹⁵². Regions of significant heritability of functional connectivity are evident at birth and expand by age 2 years¹⁵³, suggesting that genetic influences on resting-state networks are present as networks are established in the first years after birth.

Genetic and transcriptomic studies. The morphometry and functional organization of the infant brain arise, in part, through the precise spatiotemporal regulation of gene expression¹⁵⁴. In particular, prenatal cortical development is characterized by robust regional differences in gene expression that are probably crucial for establishing area-specific subcortical–cortical and cortical–cortical projections⁸. By contrast, infancy and early childhood are characterized by relatively minimal differences in gene expression across cortical areas, as more ‘general’ neuronal and glial differentiation transcription programs are initiated⁸. These developmental programs are mediated by transcription factors that bind to specific genomic sequences (such as *cis*-regulatory elements) as well as transcriptional cofactors, chromatin regulators, epigenetic modifications, RNA-binding proteins and non-coding RNAs¹⁵⁵. Genomic variants that influence these processes are expected to have an important role in generating individual differences in brain structure and function.

Genetic mutations are associated with various brain abnormalities that are evident on MRI (see REF. ¹⁵⁶ for review). Common variants in psychiatric risk genes are associated with individual differences in brain-tissue volumes in neonates¹⁵⁷. For example, of particular interest, neonates homozygous for the rs821616 serine allele of *DISC1* (which encodes disrupted in schizophrenia 1 protein) exhibit numerous large areas of reduced grey matter in the frontal lobes. Furthermore, neonates homozygous for the rs4680 valine allele of *COMT* (which encodes catechol *O*-methyltransferase) exhibit reduced grey matter in the temporal cortex and hippocampus, mirroring findings in adults. Perhaps even more surprisingly, neonates

carrying the $\epsilon 4$ allele of *APOE* (which encodes apolipoprotein E), a major susceptibility allele for late-onset Alzheimer disease, have reduced volumes in temporal cortex, highly similar to those reported in elderly individuals. In another study of *APOE*, infants aged 2 months to 25 months and who were $\epsilon 4$ carriers showed lower myelin water fraction in the precuneus, the posterior and middle cingulate, the lateral temporal cortex and the medial occipitotemporal regions — areas preferentially affected by Alzheimer disease — and greater myelin water fraction in extensive frontal regions than did noncarriers¹⁵⁸. Although few in number, these studies indicate that risk genes may influence the earliest stages of human brain development, highlight the important role of the prenatal period for future psychiatric and neurological risk and support the idea that Alzheimer disease could be, in part, a developmental disorder.

Infant genotype may also moderate the impact of environmental variables on brain development. This influence was demonstrated in a study of the effects of antenatal maternal anxiety and infant *COMT* genotypes (Val158Met, rs737865 and rs165599) on neonatal cortical thickness¹⁵⁹. Neither maternal anxiety nor infant *COMT* genotype was related to regional cortical thickness individually; however, interaction effects between maternal anxiety and infant genotype were observed in several regions, including the right ventromedial prefrontal cortex, an area involved in the regulation of anxiety and mood. Here, maternal anxiety decreased cortical thickness in neonates with two copies of the Met *COMT* allele but increased cortical thickness in neonates with two copies of the Val allele. *BDNF* genotype may also regulate the sensitivity of the methylome to maternal anxiety, with differential effects on amygdala and hippocampal volume¹⁶⁰. Finally, the common variant rs17203281 in *DLG4* (also known as *PSD95*, which encodes postsynaptic density protein 95) was recently reported to be associated with significant differences in white-matter microstructure (as indexed by FA) in preterm infants. In addition to being a marker of postsynaptic density, *DLG4* is also expressed by microglia, and the authors speculate that the rs17203281 variant could affect responses to neuroinflammation in children who are born preterm¹⁶¹.

More recently, common variants associated with neonatal brain structure have been identified using a genome-wide association study (GWAS) approach¹⁶². In this study, an intronic single-nucleotide polymorphism (SNP) in *IGFBP7* (rs114518130) was found to be significantly associated with grey-matter volume (with volume increases associated with increasing dose of the G allele). Intriguingly, this locus is within 100 kb of *REST*, a master negative regulator of neurogenesis¹⁶³. An intronic SNP in *WWOX* (rs10514437) fell just short of genome-wide significance for white matter. Mutations in *WWOX* are associated with autosomal recessive spinocerebellar ataxia 12, mental retardation, microcephaly and hypomyelination¹⁶⁴, among other neurological phenotypes. This is the first study of its kind¹⁶², and independent replication is crucial, especially for the *IGFBP7* intronic SNP, which was imputed, has a low minor allele frequency

Path length

A measure of efficiency in a network; the average number of edges along the shortest paths connecting all pairs of nodes within a network.

Clustering coefficient

A measure of the proportion of existing links between one node's neighbours divided by the total number of links for a fully connected neighbourhood. It reflects how densely one node and its neighbours are locally connected.

Methylome

The pattern of DNA methylation within a genome.

and was not present in the largest racial/ethnic group in the study. A separate study¹⁶⁵ also used genome-wide data and pathway-based and network-based approaches to investigate whether common genetic variation influences white-matter microstructure in preterm infants. The results indicated a possible role for peroxisome proliferator-activated receptor (PPAR) signalling in white-matter development in preterm infants; however, this study might best be considered a proof-of-concept study given its very small sample size.

Socio-economic factors and stress. Recent studies indicate that socio-economic status (SES) can influence the structure of the developing brain^{166,167}. In older children and adolescents, lower family income and lower parental education have been associated with reduced volumes of cortical grey matter, the hippocampus and the amygdala¹⁶⁸, as well as reduced cortical surface area and cortical thickness^{169,170}. Interestingly, white-matter volume does not seem to be affected by SES^{169,171}, whereas white-matter microstructure can be¹⁷². The influence of SES on brain structure seems to become greater with age in early childhood¹⁷¹, with only marginal associations between parental education and brain volumes at birth¹²¹. Household income and the level of maternal education are each correlated with within-network connectivity of the default resting-state network at 6 months of age⁹⁰.

Studies have begun to elucidate the influence of stress, depression and anxiety during pregnancy on infant brain development. For example, high maternal cortisol levels during pregnancy are associated with greater amygdala volumes in female 7-year-olds¹⁷³. Maternal depression during pregnancy is associated with reduced cortical thickness and white-matter diffusivity in children aged 2.5–5 years¹⁷⁴ and altered microstructure and functional connectivity of the amygdala in 6-month-olds^{175,176}. Maternal depression and use of selective serotonin-uptake inhibitors during pregnancy is associated with reduced FA across many white-matter tracts in neonates¹⁷⁷. Maternal anxiety is associated with slower hippocampal growth between birth and 6 months of age¹⁷⁸, and in 6- to 12-month-olds, inter-parental conflict is associated with stronger resting-state connectivity among hubs of the default network, posterior cingulate cortex and anterior medial prefrontal cortex as well as between the posterior cingulate cortex and the amygdala¹⁷⁹. Thus, early exposure to stress may have an impact on early structural and functional brain development; longitudinal studies are needed to determine how these influences are related to later development and risk.

Prenatal exposure to alcohol or other drugs of abuse also has important effects on developing brain structure; however, imaging studies of these effects on the brains of children younger than 5 years old are rare^{180,181}. Recent studies have revealed substantial alterations of resting-state networks due to prenatal drug exposure^{182,183}. Specifically, prenatal cocaine exposure is associated with aberrant functional connectivity between the amygdala and the medial prefrontal cortex¹⁸³ and between the

thalamus and frontal cortex¹⁸², whereas prenatal marijuana exposure is associated with altered striatal and insular functional connectivity¹⁸⁴.

Predicting risk and cognitive function

The driving force behind many imaging studies of early childhood is the long-term goal of identifying early imaging biomarkers of later cognitive function, behaviour or risk of psychiatric or neurodevelopmental disorders¹⁸⁵. Most studies to date have focused mainly on premature infants. For example, studies of premature infants have generally found that abnormalities of grey-matter and white-matter volume and of white-matter diffusivity are associated with poor neurodevelopmental outcomes^{11,186}. Some more recent studies have begun to explore other risk groups.

There are emerging studies of infants at risk of psychiatric illness. For example, male neonates with high genetic risk of schizophrenia have increased grey-matter volumes compared with controls¹⁸⁷. Children who are at risk of autism have higher FA values at 6 months and a slower increase of FA after 6 months, resulting in lower FA values at 24 months¹⁸⁸; they also exhibit a hyperexpansion of cortical surface area between 6 and 12 months¹⁸⁹. Stronger amygdala functional connectivity to the anterior insula and ventral striatum in neonates is associated with higher levels of fear in 6-month-olds¹⁹⁰, which may be a precursor of later anxiety disorders. In addition, lower connectivity between the thalamus and the salience network in 1-year-olds is associated with poorer working memory performance and lower cognitive development at 2 years of age⁹⁶. Thus, thalamus–salience network connectivity might have potential as a candidate biomarker for differences in cognitive performance, a core component in various developmental and psychiatric disorders.

Studies using cranial ultrasonography at 6 weeks of age find that a smaller corpus callosum length is related to parental reports of children's executive function at age 4 years¹⁹¹, whereas smaller subcortical volumes are associated with higher internalizing behaviour scores at 18 and 36 months¹⁹². Moreover, a recent study found that white-matter networks at birth may be predictive of internalizing and externalizing behaviour at 2 and 4 years of age¹⁹³. These studies suggest that early imaging biomarkers for risk of later behavioural abnormalities exist, although the associations between imaging markers and outcomes are generally not strong. The search for imaging biomarkers for brain disorders is fraught with difficulty related to the complexity and distribution of cognitive processing in the brain, the generalization of findings from heterogeneous clinical samples and small effect sizes that have limited clinical utility^{194,195}.

There have been a few studies of structure–cognitive function relationships in early childhood, with a general theme that structure–cognitive function relationships in early childhood are age-dependent¹⁹⁶. Cortical surface morphology, as determined by deformation of cortical surfaces (a measure of grey-matter density), is associated with cognitive development in the first 2 years of life, and this association varies with age¹⁹⁷. In addition, white-matter microstructure properties measured using

Internalizing behaviour

Problem behaviours that are typically directed inward, such as anxiety, depression, social withdrawal and somatic symptoms.

Externalizing behaviour

Problem behaviours that are directed outward towards others, such as physical aggression, defiance, hyperactivity, bullying and theft.

DTI are moderately associated with working memory performance in 1-year-olds¹⁹⁸. Studies using myelin water fraction have found small but statistically significant associations between myelination trajectories in several regions, including bilateral frontal and temporal cortex, and language development from 3 months to 4 years¹⁹⁹, as well as age-dependent relationships between myelination and general cognitive ability from 3 months to 5 years²⁰⁰. Factors that describe common variation of FA, AD or RD across groups of white-matter tracts are weakly related to cognitive development in an age-specific way; for example, a common factor of AD across 12 white-matter tracts at birth is associated with cognitive development at age 1 year³⁸.

Conclusions and future directions

Imaging studies in early childhood have begun to characterize structural and functional brain development in this important but still understudied period. Studies to date have found that, by birth, major white-matter tracts are in place and white-matter structural networks and sensorimotor resting-state functional networks are well developed. The first year of life is a period of robust grey-matter growth, rapid myelination and maturation of the microstructure of existing white-matter tracts and development of higher-order resting-state functional networks. By age 2 years, the fundamental structural and functional architecture of the brain seem to be in place, and the brain maturation that occurs in later childhood is much slower.

Much work is yet to be done, and major challenges exist (BOXES 2–4). Early studies find only modest relationships between structural and functional biomarkers and cognition and behaviour. Machine-learning-based prediction frameworks are beginning to be applied to infant imaging^{201–203} and are needed to better predict developmental outcomes from early imaging parameters in the context of genetic, environmental and birth-related variables. It is unlikely that a single or even a few imaging parameters will have sufficient power for accurate prediction. ‘Big data’ projects in which data are collected from large samples during early childhood (for example, in the US Foundation for the National Institutes of Health Baby Connectome Project and the European Research Council’s Developing Human Connectome Project; see Further information) will be required to capture the imaging, genetic and environmental variables that contribute a small percentage of variance.

Imaging studies in early childhood offer the promise of understanding the early origins of, and genetic and environmental influences affecting, individual differences in cognition, behaviour and risk of neuropsychiatric disease, and these studies are beginning to fulfil these aims. Moreover, these studies may be able to identify risk biomarkers that are present long before cognitive and clinical abnormalities arise and ultimately inform the timing and nature of early interventions to modify sub-optimal developmental trajectories, improve outcome and mitigate risk.

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The authors all researched data for the article, provided a substantial contribution to discussion of the content, wrote the article and reviewed and edited the manuscript before submission.

Competing interests

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