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Human brain development over the early years

Rianne Haartsen, Emily JH Jones and Mark H Johnson

Recent studies of the structural and functional development of the human brain over the early years have highlighted the rapid development of brain structures and their interconnectivity. Some regional functional specializations emerge within the first months after birth, while others have a more protracted course of development spanning over the first decade or longer. While some anatomical changes enable the emergence of new functions, evidence also points to the importance of resting state oscillations in sculpting neural architecture during development. In atypical development differences in brain structure, function and task-related activity in infancy often precede the emergence of later diagnostic behavioural symptoms.

Address
Centre for Brain and Cognitive Development, Department of Psychological Science, Birkbeck, University of London, Henry Wellcome Building, Malet Street, London WC1E 7HX, United Kingdom

Corresponding author: Haartsen, Rianne (rhaart01@mail.bbk.ac.uk)

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Introduction

Understanding the development of the human brain over the first years of life is of critical importance for both basic science, and for its application to societal and educational issues. From a basic science perspective, evidence about the state of readiness of the human newborn's brain has been central to issues in the nature-nurture debate [1,2]. From an educational perspective, data on the developmental state of the human brain over the early years is relevant for debates such as the effects of being raised within low social-economic status households [3], understanding ways to level the cognitive disparities at school entry, and early diagnosis and intervention for infants at-risk for later atypical outcomes such as Autism Spectrum Disorders (ASD) [1] or attention deficit/hyperactivity disorder (ADHD) [4] (see Box 1 for the abbreviations used throughout this review). The increasing knowledge on the relationship between structure and function shows the importance of the environment during early development [5••], and therefore the significance of high quality early education.

The present review focuses on several issues that have spurred recent debate and research effort. First, we survey current evidence from MRI studies on the anatomical development of the human brain from gestation to pre-school years. Next, we summarize recent literature on the functional development of the brain over this period based on methods such as EEG, ERP, NIRS, and functional MRI. Following this, we discuss the issue of how structural and functional brain development interact in terms of causal associations. While a common assumption is that underlying anatomical development allows or enables new mental functions to emerge, intriguing recent evidence is consistent with bi-directional causes in which neural activity at a younger age shapes the subsequent changes in brain structural measures — a view consistent with the Interactive Specialization framework [6].

Structural brain development

Recent advances in the analysis and resolution of structural MRI have enabled increasingly detailed descriptions of anatomical development of the brain from its microstructure, to whole regions and the structural connectivity between regions. A recent finding is that the growth rates of cortical thickness and surface area differ across brain regions [7]. The observed increases for both cortical thickness and surface area in most brain areas are larger during the first year than in the second year of life. However, cortical thinning has also been observed in a few areas (e.g. the left and right anterior cingulate gyrus, and the left and right middle cingulate gyrus). Cortical thickness matures earlier than does cortical surface area: by the age of 2 years, cortical thickness reaches approximately 97% of adult values, whereas the cortical surface area only reaches 69% of the adult values. Cortical folding also increases with age, and is measured by the gyrification index as the ratio between surface area of the cortex and the surface area of the cerebral hull of the brain (the area covering the brain while touching the gyri without diving into the sulci) [8,9]. The increase in cortical folding with age is already evident in preterm infants when scanned between 30 and 40 weeks postmenstrual age [9]. The gyrification index shows higher growth rates during the first year of life than during the second year of life, with rates of 16.6% and 6.6% respectively [8]. These gyrification index growth rates are heterogeneous across brain regions, and show different topological patterns of development than the patterns of expansion of

Box 1 Abbreviations used in the review

ADHD	Attention Deficit/Hyperactivity Disorder
ASD	Autism Spectrum Disorder
BOLD	Blood-Oxygen-Level Dependent
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
ERP	Event Related Potential
fMRI	functional Magnetic Resonance Imaging
fNIRS	functional Near-Infrared Spectroscopy
HRF	Hemodynamic Response Function
MRI	Magnetic Resonance Imaging
NIRS	Near-Infrared Spectroscopy

Box 2 Graph theory

Graph theory can be used to characterize brain networks by using concepts such as nodes and edges (see Figure 1). Nodes are small units in the networks, which are connected by edges. Short-range edges connect near by nodes, whereas long-range edges connect nodes that are further apart. The degree of a node reflects the amount of edges connected to that node. A node with a high degree has many connections to other nodes, while a node with a low degree has few connections to other nodes. Path lengths are the number of the edges between 2 nodes. Networks can be integrated (more connections between distant brain areas) and segregated (fewer connections between close brain areas).

Small-world or rich club organized networks are characterized by clusters of highly connected units, or modules. In addition, these modules are connected by long-range connections. Rich club nodes or hubs are nodes that have a high node degree, are connected by short and long range edges and thereby facilitate integration [1,13••,30,38].

Graph theory can be applied to both structural and functional neuroimaging data. In studies on the structure of the brain using dMRI, brain regions are defined as nodes, and the structural connections between these regions such as white matter tracts are defined as the edges (e.g. [10]). In contrast, studies aiming to investigate functional connectivity using EEG or MEG define brain regions of interest as nodes and similarities in activations in those brain regions as edges (e.g. [39]).

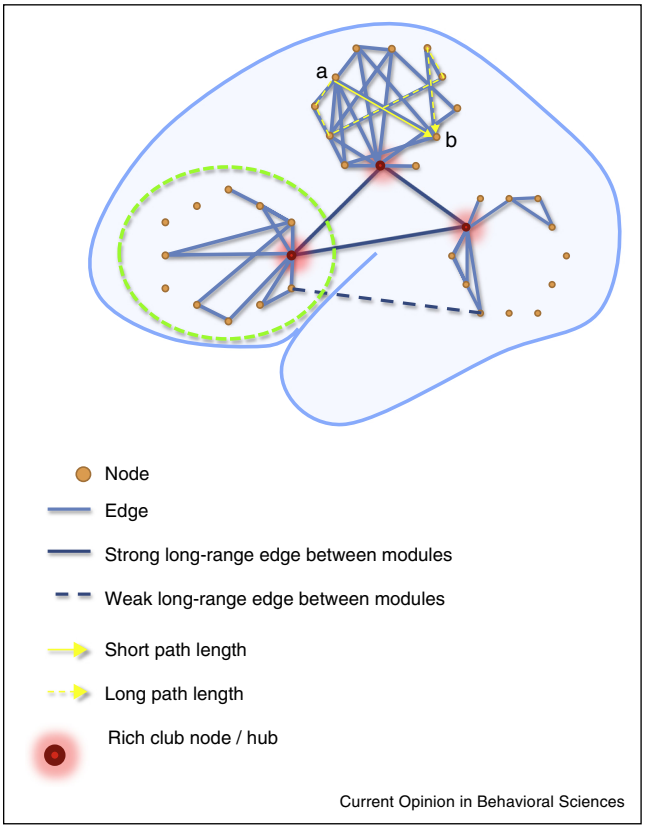
the surface areas. This is of interest given the different genetic control of these measures of cortical structure [1], and the differential effects observed in developmental disorders discussed later.

Connections between brain regions also show developmental change. Fibre bundles are white matter tracts that structurally connect brain regions with each other, and can be traced using tractography imaged by diffusion MRI or DTI (Diffusion Tensor Imaging) [10,11,12••]. Tractography relies on the diffusivity of water molecules in the brain, where water molecules diffuse in parallel directions along the white matter tracts rather than in all directions (fractional anisotropy). This method allows for visualizing of the structural connections in the brain, and for further connectivity and graph theory analyses (for more information on the graph theory and its characteristics, see Box 2 and Figure 1). As early as 30 weeks from gestation, such methods show that human structural brain connectivity shows a 'rich club' organization with specific cortical 'hubs' connected to each other [12••]. Over the subsequent 10 weeks, node degrees increase, path lengths decrease, and clustering increases. Ball and colleagues argue that the rich club organization observed at this early age provides a foundation for the subsequent development of functional connectivity networks.

The growth rates of connections in the preterm infant brain between 27 and 45 weeks of postmenstrual age differ across region-pair connections, showing higher rates for connections in the frontal and occipital lobes than in other regions [10]. These connections are part of networks that are already highly efficient and clustered at term age, but show increased efficiency, clustering and small-worldness with increasing postnatal age. Structural brain networks become more strongly connected with age during childhood, suggesting an increased number of white matter tracts with higher fractional anisotropy values between brain regions of interest compared to the number of tracts at younger ages [11]. The networks are more efficient and better integrated with increasing age between birth and pre-adolescence. Furthermore, the networks become more robust and less vulnerable to injury or random failure than those existing shortly after birth. A recent review of growth connectomics has hypothesized a trade-off between minimizing the energy cost of the network and maximizing its integrative topology. The optimal result of these trade-off changes with development, resulting in a shift from local networks towards more globally distributed networks [13••].

In addition to focusing on brain development during the first years of life, studies are investigating the longitudinal trajectory of structural brain development. They thereby identify common trajectories in large groups of individuals. For example, the 'brain maturation index' accurately predicts chronological age between approximately 5 and 18 years after birth based on brain volumes in 37 regions measured using MRI [14]. Accumulating evidence from MRI and DTI during development [15], has led to the generation of a 'brain development index' that can accurately predict chronological age between 8 and 22 years of age based on brain anatomy in children and adolescents [16]. Overall, gray matter volumes begin to decrease from mid-childhood, while white matter volumes continue to increase with age [1]. Individuals with a higher brain development index-predicted age than actual age (advanced) show an earlier decrease in gray matter volumes compared to individuals with similar predicted and actual age (typical) [16]. In contrast, individuals with a lower predicted age (delayed) show a later developmental shift,

Figure 1



Brain networks. Nodes (orange dots) are connected by short and long-range edges (light blue lines) within modules (in green dotted circle). Connections between nodes, for example node a and node b, can have a short path length (solid yellow arrow) or a long length (dotted yellow arrow). Rich club nodes (red glowing dots) are connected across modules with strong (solid dark blue lines) and weak (dotted dark blue lines) long-range edges.
Adapted from [8,21,29,30].

thus a later decrease in gray matter volumes, compared to the other groups. The findings of these studies show that typical brain development follows a common trajectory. This knowledge could help us to better identify atypical brain development.

Functional brain development

While the state of anatomical development of the brain clearly imposes constraints on cognition and behaviour, we can more directly assess emerging brain functions through methods such as EEG, NIRS, and fMRI. Measurements of brain function can be made either during task-related states or during rest. During resting state measurements, infants are usually asleep, while older children are asked to look at a fixation cross or to keep their eyes closed.

Functional resting state networks as measured by fMRI start to emerge before birth and continue to develop during the first years of life, characterized by greater fine-tuning and increased specialization [13••]. Different functional networks have different developmental time courses (for a review, see [17]). Resting state networks are evident as young as 26 weeks prenatal age. Networks involved in primary motor and sensory areas appear more adult-like at this stage, while networks involved in higher order processing appear incomplete and fragmented even at term age [18]. Between birth and 1 year of age, the primary sensory-motor and auditory networks are the earliest networks to emerge, followed by the visual network and then the attention and 'default mode' networks [3,18,19]. Default mode networks are typically viewed as the baseline state of the brain, where the involved areas show a decrease in activation during goal-directed and cognitive tasks compared to the activation when the subject is resting with eyes closed but awake [20]. In the infant fMRI studies, the areas of the adult default mode network and the other adult functional networks are used as seed regions for the connectivity analyses of scans of sleeping infants between birth and 1 year of age. Finally, the networks involved in executive control begin to emerge, for example the salience network. Resting state functional networks can be used to classify age at 6 and 12 months with support vector machine methods [21]. This shows that resting state functional networks also show a common developmental trajectory, similar to brain anatomy leading to the brain maturation index and the brain development index.

The thalamus is an important subcortical structure through which all sensory information passes to the cortex [1]. Resting state functional MRI recorded during sleep shows that functional connections between the thalamus and sensorimotor areas, and between thalamus and the salience network already exist in neonates [22]. During the first 2 years of life, thalamic functional connections with the medial visual network and with the default mode network begin to develop. The thalamus is topologically divisible into different functional areas at the time of birth, in a similar fashion as seen in adults. Some functional connections to the cortex are more widespread, while others are limited to particular areas in the cortex. At 38–42 weeks gestational age, premature infants relative to term infants show decreased functional connectivity between the thalamus and fronto-parietal insular, anterior cingulate, and prefrontal areas, but increased connectivity between the thalamus and the sensory motor cortex [23]. This shows that prematurity has a significant effect on the connectivity between the thalamus and the cortex.

Turning to task-related brain activation, we now focus on the cortical specialization of the social brain areas to social stimuli. An fNIRS study (see Box 3) in one-day to four-day-old newborns found that channels over the posterior temporal region showed a higher response when viewing

Box 3 Methods and recent key findings in fNIRS

Functional Near Infrared Spectroscopy (fNIRS) measures levels of oxyhemoglobin and deoxyhemoglobin by measuring refracted near infrared light that is directed into the brain. These measurements approximately equate to the blood-oxygen-level dependent (BOLD) signal measured in fMRI. fNIRS has both advantages and disadvantages in comparison to MRI for measuring infant brain function. As both methods measure the hemodynamic response function (HRF), its important to note that the infant HRF differs from that observed in adults, being both smaller amplitude and comparatively delayed in onset [40]. While we cannot simultaneously measure brain structure in fNIRS, it is more tolerant to movement allowing task-related states in awake infants to be studied. fNIRS is used to study different brain processes in young infants, such as object processing, face processing, processing of human motion, language processing and learning, unimodal perceptual processing, multisensory processing, and resting state and cortical organization [41,42].

dynamic social video stimuli as compared to mechanical non-social stimuli. Intriguingly, the degree of specificity of temporal cortical activation to social stimuli increased with the age in hours of the infants [24••]. These data are consistent with the notion that parts of the social brain are selectively activated to social stimuli shortly from after birth, but may require brief experience to tune them. Using a similar fNIRS paradigm, infants around 5-month old show specialized responses to visual social stimuli, and a larger response in the posterior superior temporal sulcus to human vocal than non-vocal auditory stimuli [25,26]. Further, EEG spectral power shows widespread changes in the breadth and depth of brain activation to social versus non-social naturalistic stimuli between 6 and 12 months [27]. These observations are in line with the hypothesis suggesting relatively early, but experience-dependent, cortical specialization to social stimuli.

The relation between structural and functional brain development

In general, regions linked by strong structural connections also tend to have strong functional connections [28]. However, there are also findings showing strong functional connectivity between areas without clear structural connectivity to support it. In addition, functional connectivity during resting-state can change over time and with task demands, whereas the underlying structural anatomy remains largely stable [29]. Changes in functional connectivity while structural connectivity is fixed might be explained by a global integration of segregated modules [30]. The long-range connections in this arrangement are flexible and have the ability to facilitate the integration depending on the task demands.

While it is commonly assumed that anatomical development within regions enables or allows for the emergence of new brain functions, contemporary theories of developing brain function emphasize the potential importance of bi-directional structure-function relations, in which a persisting brain functional state can sculpt underlying neural architecture [6]. In human development, a recent study shows that slower microstructural development between 27 and 46 weeks post conception (29–48 weeks gestational age) in premature infants was related to lower levels of neurodevelopmental functioning at the age of 2 years [31]. Higher levels of spontaneous brain activity in preterm newborns measured shortly after birth around 30 weeks gestational age are related to faster rates of brain growth between birth and term equivalent age, or 40 weeks gestational age [5••]. Infants with shorter periods of low levels of spontaneous brain activity showed a faster growth rate in overall brain volume and subcortical gray matter volumes, supporting the idea that developing brain structure can be shaped by preceding activity states.

Atypical brain development

While to this point we focussed primarily on the typical developmental path for human brain development, there is great interest in using measures of brain development as early biomarkers for later emerging conditions.

Taking the example of autism, infants at familial risk for ASD show structural, functional and task-related differences before the onset of diagnostic behavioural symptoms [32]. For example, structural differences include that infants that develop ASD at a later age have an increased corpus callosum early in life [33]. Volume differences are greatest at 6 months of age and diminish around 24 months. Furthermore, the size of the corpus callosum at 6 months of age and the thickness at both 6 and 12 months of age are positively correlated with repetitive behaviours at 2 years of age. In terms of functional connectivity, using fNIRS infants at risk for ASD have increased functional connectivity at 3 months compared to their low risk control peers [34]. At 12 months of age, infants at risk for ASD showed decreased functional connectivity compared with the other group. These fNIRS results suggest a developmental trend with increasing functional connectivity for low risk control infants during the first year of life, while in high risk ASD infants functional connectivity seems to decrease, possibly indicating an adaptive response [35••]. However, an independent study found that 14-month-old infants later diagnosed with ASD show *increased* EEG connectivity in the alpha frequency range compared to other infants [36]. The measures of increased connectivity in the high risk-ASD group were related to an increase in repetitive and restrictive behaviours at the age of 3 years. Thus, whilst results in the NIRS study show underconnectivity at 12 months, the EEG results show overconnectivity at 14 months. These contrasting findings might arise from the different paradigms used — a passive listening task in the NIRS study, and watching social and non-social stimuli in the EEG study. Other possibilities are the different underlying mechanisms both methods measure (oxygenation of the blood versus electrical activity in the

brain); brain regions measured (anterior and posterior areas versus the whole scalp), or differences between groups of infants at familial risk for ASD and those with a later diagnosis. Finally, 5-month-old infants familial risk for ASD also show task-related differences in brain activity [25]. For example, evidence of reduced selective temporal lobe activation in response to viewing social stimuli compared to infants at low risk for ASD has been found. In the same study, infants at familial risk showed a smaller human vocal-selective response than infants with a low risk for ASD. These results confirm a relative lack of cortical specialization to social stimuli at 4–6 months of age in at least a subset of infants at risk for ASD.

Conclusions

Recent research highlights the very rapid development of brain structure and function over the early years. Core resting state networks begin to function from prenatal stages, and may help sculpt subsequent patterns of regional structure and connectivity. Some task-related patterns of neural activation may become evident within the first days after birth, while others show a very prolonged timetable and are heavily influenced by postnatal experience. The complex bi-directional relation between structure and function may contribute to the substantial resilience and adaptation shown by the developing brain [35••]. This bi-directional relation shows the importance of the early environment, and the high quality of early education. However, marked atypicalities in early brain development can be associated with developmental disorders such as ASD.

Research on early development of the brain could also help to identify early markers for cognitive functioning. For example, visual-spatial working memory is a strong predictor for academic achievement and has been related to structural brain development in infants at 1 and 2 years of age [22] and children between 6 and 20 years of age [37]. These early markers can help identify infants at risk for later difficulties in cognitive performance and function as a target for early intervention during education. A more nuanced understanding of early brain development may be the key to more effective early treatment approaches for developmental disorders and poor academic achievement at later ages.

Conflict of interest

Nothing declared.

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