Individual focused studies of functional brain development in early human infancy
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Across the perinatal period, the human brain undergoes a rapid yet highly programmed sequence of maturation. In this time, neural activity has a key role in establishing the brain’s early circuits and guiding essential processes including cell differentiation, neuronal and axonal growth, arborization and synaptogenesis. fMRI studies of young infants hold great potential to understand developmental changes in systems-wide activity and their relationship to regional growth and development. These studies have shown that the brain’s activity rapidly evolves across the perinatal period, as neurovascular coupling matures and resting state networks are established. The high variability of spatial and temporal properties in functional activity may be attributed to the sensitivity of neurovascular coupling to developing cellular structure and connectivity as well as fluctuations in cerebral physiology, behavioral state, and pathology. Longitudinal studies may precisely explore these relationships and provide mechanistic understanding of the relationship between physiology, behavior, injury, and functional activity.

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Introduction
In recent years, advances in functional neuroimaging have provided profound insights into how the brain’s activity and organization enable a broad spectrum of essential functions, from sensory processing to complex cognitive functioning and behavior. The focus of most studies has been to map the spatial properties of brain activity at a population level, both during specific tasks or at rest. This approach probes the organization of normal brain function and of neurological and psychiatric diseases. However, brain activity is highly dynamic, with its properties and organization constantly shifting across the day, from one day to another, and during different behavioral states [1]. These considerations are particularly pertinent in the context of early life, when the brain undergoes more dramatic changes to its structure and function than at any other time across the lifespan. In the neonatal brain, rapid developmental changes in tissue composition and physiology are guided firstly by genetic mechanisms, followed by the activity itself, and are finally shaped and refined by environmental influences [2]. This neurobiological maturation is accompanied by ongoing and highly programmed developmental changes in behavior as new skills are attained through early infancy and into childhood. Therefore, understanding longitudinal changes in brain activity during these crucial stages of development and their contribution to lifelong brain function may provide basic mechanistic insight into the link between brain activity and behavior, and ultimately how this relationship is altered by pathology.

Perinatal development
The perinatal period is characterized by dramatic but highly programmed sequences of maturation during which the fetus is prepared for life outside the womb (summarized in Figure 1). The critical importance of this time for brain maturation is emphasized by the effects of preterm birth, where early exposure to the ex utero environment (during the equivalent period to the late second and third trimesters of normal gestation) results in widespread disruptions in brain connectivity and a marked increase in the risk of later adverse neurodevelopmental outcome. By 28 weeks of gestation, radial glia form a scaffold for neural progenitor cells to migrate from the central proliferative zones via the subplate and then differentiate to form the peripheral layers of the cortical plate and the supporting glia (upper rows, Figure 1) [3,4]. Angiogenesis occurs first within the periventricular central proliferative zones and then, alongside synaptogenesis and neuronal maturation, in the cortical plate [5]. Endogenously generated and synchronous neural activity has a key role in establishing early circuits through guiding fundamental processes including synaptogenesis, neuronal maturation and dendritic arborization from approximately 24 weeks gestation to full term age (middle rows, Figure 1) [2]. In the mammalian brain, spontaneous activity first emerges as oscillatory calcium waves and giant depolarizing potentials which spread locally across the maturing cortex,
before large amplitude bursting events emerge in the latter half of gestation with further neurochemical maturation (specifically that of the GABA and glutamate neurotransmitter systems) [2]. Together with molecular cues, events of synchronous endogenous activity (known as spindle bursts in small animals and spontaneous activity transients in human infants) are responsible for the formation of a coarse cortical template before a subsequent ‘critical’ period when exposure to external sensory stimulation refines and strengthens this organization [2,6]. Ultimately, these processes establish the distinct patterns of short and long range cortico-cortical and thalamo-cortical connectivity which provide the life-long structural substrate for mature neural networks [7]. Changes in connectivity are accompanied by maturation of the associated vascular network which increases capillary branching, density and endothelial proliferation (lower rows, Figure 1) [8,9]. Sensory stimulation further influences angiogenesis, as sensory enhancement increases and sensory deprivation decreases microvascular density and branching, but chronic overstimulation conversely results in near arrest of angiogenesis [10,11]. Crucially, the effects of these short term environmental influences on cerebral microvasculature may persist as long-term adaptations [8].

Developmental changes in neurovascular coupling and the hemodynamic response to stimulation

A fundamental premise in functional magnetic resonance imaging (fMRI) studies using blood oxygen level-dependent (BOLD) contrast is that neural activity is tightly coupled to changes in local cerebral blood flow (CBF) so that the necessary metabolic substrates (in particular oxygen and glucose) are readily available. The BOLD response to neural activity is typically represented within fMRI analyses as a hemodynamic response function (HRF), which models the cumulative effects of neurovascular coupling on the acquired MR signal and in particular, the associated localized changes in oxygenated and deoxygenated hemoglobin (Hb) [12]. Importantly, HRF morphology is generally considered to be consistent both within subject events and across populations (Figure 2). A small amplitude ‘initial dip’ seen immediately following onset which is thought to represent an early increase in deoxygenated Hb; followed by a large
amplitude *positive peak* due to functional hyperemia (an overcompensation of oxygen supply to capillaries in the activated brain tissue) [13]; and finally a *negative undershoot* during which the signal falls beneath baseline [12]. The assumption of a consistent HRF across trials and subjects is crucial for fMRI analyses, as it is typically convolved with the experimental paradigm or a timeseries representative of neural ‘input’ to identify spatial patterns of activity [14,15]. Detailed studies however suggest that there is significant inter-regional and between subject HRF variability, which can lead to false negative task analyses and the identification of aberrant patterns of functional connectivity [16,17]. In addition, the amplitude, time-to-peak, and morphology of the HRF have also all been shown to be sensitive to factors which influence CBF and/or cerebral vascular reactivity such as the partial pressure of carbon dioxide (PaCO₂) [18]. Key HRF parameters also change during aging, with older adults (54–74 years old) showing a significantly reduced positive peak amplitude and a longer time-to-peak in comparison to young adults (18–30 years old) [19].

Hemodynamic response variability in early life is likely to explain, in part, the high variability in results of fMRI studies of neonates and young infants where both negative and positive amplitude BOLD responses have been reported [20]. An unresolved area in the neonatal task-fMRI field remains the reporting of negative BOLD responses, suggestive of a counterintuitive stimulus induced localized rise in deoxygenated-Hb. Such negative BOLD responses were consistently reported in early studies, particularly those involving visual stimuli and in infants >8 weeks of age, leading to the suggestion that they were representative of a specific time window when rapid neuronal development led to local metabolic demand that outstripped the ability of the vascular system to supply oxygen [21]. During the neonatal period, the aforementioned rapid maturational changes in brain tissue composition and vascular density lead to marked developmental changes in CBF and the cerebral metabolic rate of oxygen (CMRO₂) [22,23]. In preterm infants, global CBF approximately doubles during the first few days following birth as the cerebral circulation adapts to postnatal life, well beyond rates that could be explained by changes in mean arterial blood pressure, hematocrit or PaCO₂ alone [24]. Maturation of the vasculature itself also occurs in conjunction with increased angiogenesis, with proliferation of pericytes which mediate capillary dilatation [13]. Interestingly, despite large increases in total brain volume, global cerebral blood volume (CBV) remains relatively static across the preterm period [22]. Together with the concomitant increases in CBF, static CBV translates to a reduction in the mean transit time of Hb according to the Stewart-Hamilton principle [12]. Therefore, it is perhaps unsurprising that significant maturational changes are also seen in the morphology and parameters of the hemodynamic responses across the equivalent period to the perinatal time window in both animal models and preterm human infants [9,25–27]. Responses in human preterm infants have a significantly longer time to peak, are more prolonged and are lower in amplitude in comparison to the canonical adult HRF (Figure 2) [22,26]. With increasing age and rising CBF, the time to peak markedly shortens by term equivalent age when a proportionately deeper post-stimulus undershoot is also observed [26]. Consideration of these developmental effects and use of an age appropriate HRF is therefore essential when designing and analyzing fMRI studies for the neonatal population [28].

**Developmental changes in functional activity across the perinatal period**

There is now a growing body of literature exploring the temporal and spatial properties of functional activity in the developing human brain using fMRI, with the field now benefitting from large open-source data repositories such as the developing Human Connectome Project [http://www.developingconnectome.org/project/](http://www.developingconnectome.org/project/), [29**] and the HCP Lifespan Baby Connectome Project [https://www.humanconnectome.org/study/lifespan-baby-connectome-project](https://www.humanconnectome.org/study/lifespan-baby-connectome-project) [30**] which will enable detailed characterization of developmental effects and exploration of the effects of population level sociodemographic and clinical factors. These cohorts are important, as
cross-sectional resting state studies in infants show a pattern consistent with increasing patterns of connectivity across the perinatal period, resulting in a rapidly changing network spatial representation encompassing more distinct and widespread cortical regions with age [31]. This appears to occur firstly in networks subserving the primary motor and sensory (somatosensory, visual, auditory) systems which are seen to have assumed an adult-like bilateral representation by term equivalent age [29,31,32,33]. Similarly, maturing patterns consistent with the establishment of long-range patterns of connectivity and the integration of associative areas leading up to term equivalent age are also seen in task-based fMRI experiments using simple sensory stimuli [34]. In contrast, the associative networks (such as the default mode, executive control and salience networks) are generally reported to be either immature or unidentifiable in the neonatal period, suggesting that they are established through childhood as their associated higher cognitive functions emerge [33,35]. This has important implications for what we can learn about the fundamental relationship between functional connectivity and behavior. Across the first year following birth, young infants rapidly transition from predominately ‘passive’ interaction with their environment to acquiring the ability to actively engage with their surroundings. In this context, the aforementioned large open-source datasets of children developing normally through early infancy present a unique opportunity to precisely characterize how emerging patterns of connectivity correlate temporally with recognized developmental milestones in behavior. These developmental milestones occur across several distinct domains ranging from gross motor skills to social interaction, all with their own characteristic timelines of achievement [36,37]. Therefore, one might envisage that specific ‘phase transition’ points in connectivity could not only be related to but even predict the later attainment of specific behavioral skills in infancy. On an individual subject level, this highlights the exciting possibility that identifying deviations from this relationship and aberrant trajectories could provide not only novel mechanistic insight into hitherto poorly understood conditions such as autism and learning difficulties, but importantly also opportunities for targeted intervention.

**Individual variability and development**

Most fMRI work in young infants has been cross-sectional, with patterns of activity characterized by averaging within groups of similar ages. Activity maps are then compared with those from a distinct group at another age to infer developmental changes, or with patients of known clinical pathology to identify the differences related to disease mechanisms. Whilst group averaging approaches study the fundamental functional organization of the developing human brain, there has been no work focused specifically on characterizing individual differences in functional activity. It is therefore unknown whether an individual ‘fingerprint’ of functional activity [38] is present in infancy such as that of cortical folding [39]. Interestingly though, the strength of resting functional connectivity in a network thought to be related to the descending pain modulatory system has been previously shown to be significantly related to an individual infant’s amplitude of noxious-evoked brain activity, suggesting that individual patterns of connectivity are important [40]. Furthermore, interpretation may be further impacted by other unaccounted sources of individual variance and in particular, their behavioral state during data collection which may further contribute to the inconsistent results reported more broadly in the neonatal fMRI literature.

Newborn infants transition between various states of alertness and sleep [41]. The duration of each state is dependent on maturation and is influenced by external sources of stress and the ability of an infant to regulate their state [42]. An inability to appropriately regulate behavioral state is seen in infants with a history of prenatal opioid exposure [43], abnormal brain development following preterm birth [44], and hypoxic ischemic encephalopathy [45]. Infants spend approximately 75% of their time sleeping and aberrant establishment of sleep-wake architecture correlates with adverse neurodevelopmental outcomes [46]. The importance of sleep is in early infancy is demonstrated by its crucial role in supporting activity-dependent sensorimotor development and learning [47]. Elegant fMRI studies of visual [48] and cognitive development in awake older infants represent a truly exciting opportunity to explore the neural correlates underlying complex domains such as semantic cognition and theory of mind as they emerge in early human life [49]. In these cases, fMRI informs whether and how the infant brain creates the internal representations required for higher cognitive functions such as learning, where the information gained through behavioral testing alone is constrained by their levels of communication [50]. However, fMRI data in younger infants studied around the time of birth can only really be acquired during sleep, and short acquisition times and challenges inherent to collecting simultaneous EEG-fMRI data from this population have thus far limited opportunities to explore the relationship between the presence of and transition between different sleep states, BOLD responses and functional connectivity. Innovations such as prolonged multimodal acquisition and analyses of simultaneous EEG-fMRI, physiological (heart and respiratory rate) and behavioral monitoring through video recording (combined with deep learning-based classification algorithms) could offer dramatic insights into the role of distinct brain regions and network-wide activity on the neural processes that underlie sleep states.

Understanding individual hemodynamic response variability may elucidate basic facets of early cerebral physiology and their relationship to brain function and development. Preterm infants (particularly those requiring intensive care management) are often exposed to rapid
changes in their ventilatory support (and subsequently PaCO₂), circulatory volume and cardiac contractility across a single day. Coupled with relatively immature cerebral autoregulation, such changes may lead to significant fluctuations in global CBF which increase the risk of intracerebral hemorrhage and/or ischemia [51]. Interestingly, this “pressure passive” pattern (in which CBF is directly dependent on arterial blood pressure) has been suggested to underlie the equivalent to a positive BOLD response in anesthetized immature rodents, with negative responses seen without a rise in systemic blood pressure [27]. Neurovascular coupling models incorporating heart rate and mean arterial blood pressure recordings with EEG and near-infrared spectroscopy into dynamic graph theory [52] and tensor models [53] have shown age-dependent decreased coupling under sedation. Therefore, understanding the role of factors such as PaCO₂ blood pressure and the influence of commonly used medications which can affect baseline global CBF and vascular reactivity is of fundamental importance as each could profoundly influence the amplitude and timing of responses in younger infants.

Significant HRF parameter differences are seen within-subject across distinct brain regions in adults [17]. Characterizing patterns of within-subject HRF variability during infancy could provide specific information about regional brain development and functional integrity. This is exemplified by altered HRF amplitudes reported following stroke [54] and in preterm infants with intraventricular hemorrhage [55], suggestive of impaired neurovascular coupling in pathological states. Markedly altered hemodynamic responses have also been described in neonatal seizures with diffuse optical tomography, with an initial large increase in blood volume followed by a prolonged decrease lasting several minutes [56]. Therefore, longitudinal studies are vital to provide a mechanistic understanding of how acute alterations in neurovascular coupling might link to longer term effects on the establishment of network topography and functional connectivity, such as those seen in infants born preterm [33], with brain injuries [57], and those with a familial risk of autism [58]. Given that disruptions in neonatal connectivity have been shown to significantly relate to later neurodevelopmental outcome [57,59], characterizing acute and developing individual neurovascular coupling will inform its predictive power as a biomarker for later clinical prognosis.

Summary
Longitudinal explorations of infant fMRI hold great potential for providing dramatic new insight into how the brain’s functional activity is organized and matures in early human life. Detailed fMRI study of individual variability in physiology and function will facilitate understanding of the cumulative effects of neurovascular coupling as measured by the HRF. Fundamental new knowledge would provide insight to the possible causal relationships between the maturation of behavior, regional brain development and functional activity to identify therapeutic targets.

Conflict of interest statement
Nothing declared.

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