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# Brain Development in Infants Born Preterm: Looking Beyond Injury

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**Infants born very preterm are high risk for acquired brain injury and disturbances in brain maturation. Although survival rates for preterm infants have increased in the last decades owing to improved neonatal intensive care, motor disabilities including cerebral palsy persist, and impairments in cognitive, language, social, and executive functions have not decreased. Evidence from neuroimaging studies exploring brain structure, function, and metabolism has indicated abnormalities in the brain development trajectory of very preterm-born infants that persist through to adulthood. In this chapter, we review neuroimaging approaches for the identification of brain injury in the preterm neonate. Advances in medical imaging and availability of specialized equipment necessary to scan infants have facilitated the feasibility of conducting longitudinal studies to provide greater understanding of early brain injury and atypical brain development and their effects on neurodevelopmental outcome. Improved understanding of the risk factors for acquired brain injury and associated factors that affect brain development in this population is setting the stage for improving the brain health of children born preterm.**
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## Introduction

Brain development in the third trimester and early neonatal period is rapid and dramatic. Those infants born very preterm (<32-weeks gestational age [GA]) are at high risk for primary brain injury and secondary maturational disturbances.[1] Preterm birth is common and accounts for 8%-11% of live births, with very preterm births being 1%-2%; that is, more than 1 of every 100 babies is born very preterm. The incidence of very preterm birth is increasing worldwide, with a 25% increase in preterm births between 1990 and 2005 in high-income countries.[2] Survival rates in preterm infants have increased in the last decades because of improved neonatal intensive care; however, morbidity has not decreased. A number of distal, intermediate, and proximal factors may lead to impaired brain development in these infants. Distal factors include socioeconomic status (SES) or preconceptional health, whereas intermediate factors refer to the developmental effect of preterm birth (ie, early birth) and proximal factors would be associated with postnatal risk factors. Significant brain injury, or more subtle impairments in brain development, may underlie the development of major disabilities, such as cerebral palsy, mental retardation, autism spectrum disorder, deafness, or cortical visual impairment[3-5] in the preterm neonate.

Evidence from neuroimaging studies exploring brain structure, function, and metabolism (eg, Fig. 1) has indicated atypicalities in the developmental trajectory of very preterm-born infants that remain till adulthood[6-9] and are associated with motor disabilities including cerebral palsy as well as impairments in social and executive functions.[10,11] Crucial to the understanding of impaired brain development with very preterm birth is the need for longitudinal imaging data to relate to the behavioral and cognitive outcomes, and to ultimately identify the earliest brain abnormalities that could be targeted with interventions or pharmacologic agents or both. Advances in medical imaging and the availability of specialized equipment necessary to scan infants have facilitated the feasibility of conducting longitudinal studies to provide greater understanding of early brain injury and atypical brain

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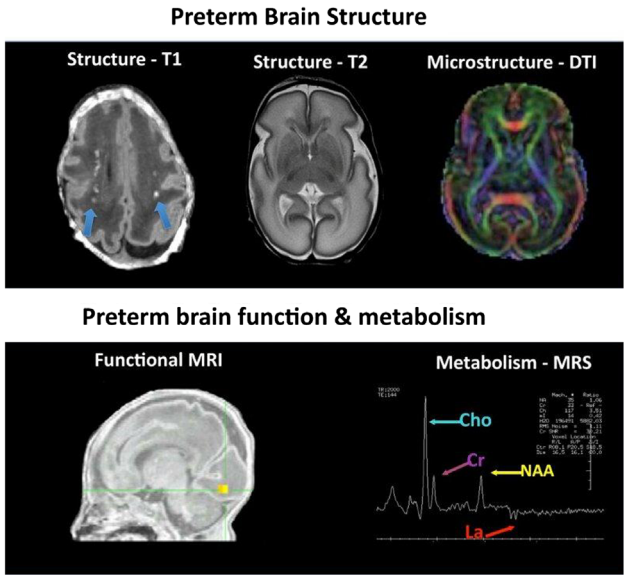


**Figure 1** Brain structure, function, and metabolism measured in preterm-born infants. Brain imaging data acquired in preterm-born infants (<32 weeks). Information about brain macrostructure or microstructure can be obtained through anatomical MRI (T1- and T2-weighted images) and diffusion-tensor imaging (DTI). Top left: T1-weighted imaging permits the identification of white-matter injury as areas of abnormal hyperintensity in the white matter (blue arrows). Data were acquired in a 31-week-old neonate. Top middle: T2-weighted MRI of a 29-week-old infant. T2-weighted images may allow better assessment of cortical anatomy. Top right: DTI in a 28-week-old infant. Color maps represent the diffusion of water along the principle eigenvectors in white-matter fiber pathways and cerebral cortex (red: left to right; green: anterior to posterior; blue: superior to inferior). MRI sequences can also be used to study brain function and metabolism. Bottom left: Functional MRI demonstrating activation in the primary visual cortex in a preterm-born infant. Bottom right: Measures of brain metabolites that are indices of neuronal maturation. Cho, choline; Cr, Creatine; La, lactate.

development, and their effects on neurodevelopmental outcome.

This review will focus on neonatal neuroimaging techniques and current knowledge gained from brain imaging on the development of the preterm brain. Distal, intermediate, and proximal risk factors for adverse outcomes, including cerebral palsy, in preterm neonates are outlined and discussed in the context of emerging brain protection strategies. We conclude with a discussion of the future of neuroimaging protocols to study brain injury in preterm-born infants and identify new opportunities to optimize brain development and prevent injury.

# Brain Imaging Techniques Used to Study the Development of the Premature Brain

## Structural Magnetic Resonance Imaging (MRI)

Commonly used MRI sequences to study the preterm brain include T1- and T2-weighted images and susceptibility-weighted images. These images provide 3-dimensional views of gray and white matter and cerebrospinal fluid, and permit identification of even small areas of ischemia or bleeding. Because of the high-resolution capabilities of structural MRI, it is possible to segment cortical and subcortical brain regions to assess their developmental trajectories.

While MRI is increasingly used in clinical practice to examine brain injury in preterm neonates, ultrasound remains the most widely used imaging tool for routine clinical examinations. Serial ultrasound is used to identify intraventricular hemorrhages (IVH), ventriculomegaly, and periventricular leukomalacia (PVL), especially cystic abnormalities of white matter seen in preterm infants. However, many infants who have no detectable brain injury on cranial ultrasound still go on to develop neurodevelopmental deficits. Structural MRI has been shown to identify diffuse or small brain insults or both in preterm neonates with a greater sensitivity than ultrasound.[12-17] Abnormalities on MRI, when performed early in life[18] or at term-equivalent age[19] are predictive of adverse neurodevelopmental outcome; thus clinical demand for MRI is increasing in these high-risk infants.

## Diffusion-Tensor Imaging (DTI)

DTI is a technique that capitalizes on the 3-dimensional spatial distribution of water diffusion in brain tissue. DTI measures are sensitive to the shape and orientation of cellular structures including axons, dendrites, and cell bodies. Commonly reported DTI indices are fractional anisotropy (FA) and mean diffusivity (MD). FA describes the magnitude of the asymmetry in the diffusion of water, or anisotropy, in brain tissue. FA values are higher in tissues with oriented structures organized in a common direction, such as white-matter tracts. Subcomponents of FA include measures of axial and radial diffusivity (AD and RD) that describe the diffusivity of water parallel and perpendicular to fiber bundles, respectively; MD is the average of AD and RD. Increasing AD reflects increases in axonal number or size[20] and a reduction in interaxonal space,[21] whereas increases in RD indicate changes in myelin leading to reduced permeability with development.[22] Water diffusion changes dramatically during early brain maturation, as water content of the brain decreases in the preterm period, becoming increasingly restricted to the longitudinal axes of fiber tracts, as fiber density and myelination occur.[23] During the development of white-matter fiber pathways, MD, AD, and RD decrease and FA steadily increases,[24] making diffusion imaging a powerful method for investigating white-matter development.

In addition, DTI can examine changes in developing cortical structures when neurons are undergoing morphologic differentiation. In the preterm period, apical dendrites are aligned perpendicular to the pial surface restricting parallel water diffusion.[25,26] Following the migration of pyramidal neurons from germinal zones to the cortical plate, differentiation of neuronal and glial processes begins.[27] As these processes develop, their structure becomes more complex as they

arborize to form interconnected neural dependencies. In typical and atypical development reductions in cortical FA mirror these developments of neuronal and glial processes.[28,29]

## Magnetization Transfer Ratio (MTR)

MTR is another MRI sequence that is used to assess white-matter integrity in the brain[30] (Fig. 2). MTR permits the indirect observation of semisolid macromolecular components of tissue, such as protein matrices and cell membranes,[31] and is particularly sensitive to myelin.[32] MTR values are found to increase with age in the neonate, consistent with processes of myelination and maturation.[33-36] Compared with DTI, the changes seen by MTR are more affected by myelination, whereas DTI is more strongly affected by axonal development.[35]

## MR Spectroscopy (MRS) Imaging

MRS is an imaging technique that measures signals from low-concentration brain metabolites. The sequences can be performed in 7-15 minutes. Metabolites in brain tissue that can be detected include lactate; choline and choline-containing compounds; creatine, phosphoryl-creatine, and N-acetylaspartate (NAA); glutamine; glutamate; gamma-aminobutyric acid; and myoinositol. Brain metabolite levels may be indicative of neuronal functioning. For instance, levels of NAA are thought to reflect neuronal integrity or function or both, creatine is involved in the creatine-kinase reaction, lactate is a measure of anaerobic metabolism, and choline-containing compound is involved in the synthesis and breakdown of cellular membranes.

MRS is a useful clinical and research tool that can monitor brain metabolism after injury,[37] and aid in the understanding of the development of brain metabolism in term-born and preterm-born infants.[38-40] For example, MRS has been shown to be a useful predictor of poor neurodevelopmental outcome in asphyxiated term-born infants.[41,42] These studies have consistently reported that increased lactate and decreased NAA were associated with worse outcomes. The elevated lactate levels are thought to indicate a disturbance in cerebral oxidative metabolism, whereas reduced NAA levels indicate delayed cellular maturation, cellular dysfunction, or cell death. (For a review of this area, see Card et al.[43])

## Functional Neuroimaging

Brain function in infants can be studied noninvasively using electroencephalography (EEG), magnetoencephalography (MEG), functional MRI (fMRI), and near-infrared spectroscopy (NIRS).

## EEG

EEG is the oldest functional neuroimaging technique and measures electrical activity of neurons through the placement of electrodes on the scalp. EEG measures the current flow emitted by the synaptic interchanges produced by the dendrites of pyramidal neurons from large populations of neurons (~500,000-1,000,000). EEG is a technique with very high temporal resolution permitting the study of neuronal events occurring at the millisecond level, although its spatial resolution is relatively poor (~1-2 cm).

EEG has been used widely to study infant brain development given its noninvasive nature and feasibility. EEG studies have indicated that electrical activity parallels that of structural development.[44,45] EEG is commonly used to monitor preterm-born infants such as those experiencing seizures or at risk of seizures,[46-48] and studies have correlated EEG measures with neurodevelopmental outcome in preterm-term born infants.[49,50]

## MEG

MEG is similar to EEG in that it is a direct reflection of on-going brain activity; it measures magnetic fields orthogonal to the electrical activity evoked by populations of neurons. MEG has excellent temporal and spatial resolution (~1-5 mm). Although it is more sensitive to movement than EEG, it has proved useful for the study of infants.[51,52] MEG data can also be used to understand brain connectivity and the development of coherent neural networks. MEG has not been used widely to study the function of the infant brain, which is due mainly to limited access to hardware, particularly infant-sized MEG helmets. However,

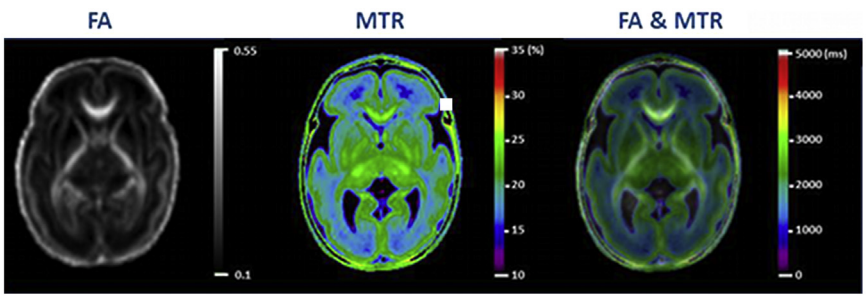


**Figure 2** Average FA and MTR maps in 44 preterm neonates. Improved information concerning myelination of the preterm brain can be obtained by combing data from diffusion-tensor imaging (DTI) through which fractional anisotropy (FA; left) values with magnetization transfer ratio (MTR; middle) images; the right image shows the overlap and complementing nature of these 2 MRI sequences. This image was adapted from Nossin et al.[36]

somatosensory and auditory functions have been assessed in preterm infants with MEG,[53-56] and MEG has been used to study the longer-term effects of preterm birth on child and adolescent brain development.[57-59]

### fMRI

fMRI is an indirect measure of brain activity as it measures local blood flow occurring in response to increased neuronal activity. fMRI measures the blood oxygen level–dependent (BOLD) signal that reflects the contrast between oxygenated and deoxygenated hemoglobin. In response to neural activity an increase in oxygenated hemoglobin flows into capillaries with a corresponding decrease in the amount of deoxygenated hemoglobin. This change in the ratio of oxygenated and deoxygenated hemoglobin causes susceptibility in the magnetic field that is measurable using fMRI pulse sequences and can be visualized as an increase in image intensity.[60]

fMRI activation in the visual cortex in response to visual stimuli has been reported in infants as young as 33-weeks GA.[61,62] However, in very preterm infants (<32-weeks GA) reliable visual cortex activation is not usually evident,[63] although BOLD activation in response to somatosensory stimuli is more reliably recorded.[64]

Another area of burgeoning interest in the preterm-born infant is the study of resting state, measured by functional connectivity MRI.[65,66] This technique identifies localized low frequency BOLD signals that are correlated when the brain is at rest.[67,68] The various patterns of activation in regions of the brain in the absence of stimulus-evoked activity have been deemed resting-state networks.[69] Brain regions that are functionally linked in resting-state networks are also anatomically connected.[70]

Resting-state networks have been established in typically developing children[71,72] and atypical patterns in neurodevelopmental disorders, such as attention-deficit hyperactivity disorder[73] and autism spectrum disorder.[74] In the preterm infant brain, resting-state networks have also been explored to examine the development of cortical circuits involved in basic neural processing and the inception of higher-order cognitive processes.[66,75-82] These functional connectivity patterns mature in parallel with anatomical connectivity in the developing human brain, and may prove to be a valuable predictor of cognitive outcome.

### NIRS

NIRS is similar to fMRI in that it is sensitive to changes in oxygenated and deoxygenated hemoglobin and is therefore an indirect measure of neuronal activity. NIRS uses light wavelengths (700-1000 nm) to measure tissue oxygenation, which reflects oxygen uptake in the tissue bed. NIRS involves putting probes on the head of the infants; the probes emit light and also contain detectors to measure light that is reflected back from the superficial few centimetres of brain tissue. Advantages associated with the use of NIRS to study brain development in infants are its ease of use, its low cost, and its low sensitivity to head movement.[83]

Clinical applications for NIRS include monitoring perioperative cerebral oxygenation in infants undergoing cardiopulmonary bypass surgery or during surgery to repair patent ductus arteriosus. Additionally, NIRS also proved to be a useful research tool in the preterm neonate to examine baseline levels of regional cerebral blood oxygenation,[84,85] and their relation to risk factors associated with adverse neurodevelopmental outcome,[86] as well as normal development in infancy of cognitive processes.[87]

## Early Brain Development in Neonates: Evidence From Neuroimaging Studies

### Gray Matter Development

The burden of neurodevelopmental impairments, motor and cognitive, in preterm-born infants increases with earlier degrees of prematurity.[88] For example, infants born before 25-weeks gestation show significantly more motor and cognitive deficits at 30 months than those born after 28-weeks gestation.[89] By school age, many extremely preterm-born children continue to lag behind their peers in terms of motor[90] and cognitive development, and these deficits are more prevalent in boys than girls.[91] The neurophysiological underpinnings of these findings remain uncertain. Neuronal migration into the cortical mantle is largely complete by 25 weeks; however, glial migration, that is mainly responsible for the expansion in cortical surface area, continues through the third trimester.[92-94] Cortical surface area is a reflection of both neuronal number and the folding of the cortical mantle. The folding process involves the migration of neurons via radial glial cells to the cortical plate. Greater numbers of radial glial cells would in turn allow for more neurons to migrate and thus increase the overall surface area.[95] This process may be stunted owing to the exposure to infection, hypoxia, and postnatal growth restriction[96,97]due to under nutrition or epigenetic mechanisms.

Evidence from structural MRI has indicated altered cortical-folding patterns in extremely preterm-born children.[98] In a series of 14 preterm-born infants cerebral tissue volume, surface area and folding complexity were examined in comparison with term-born infants. Volumes did not differ significantly between the preterm and term infants but cortical surface area and cortical-folding complexities were less in the preterm infants. The authors concluded that the lack of volume change in the presence of reduced cortical complexity indicated either a disruption in the neuronal migration process or a reflection of impaired migration along radial glia.[99]

A larger MRI study also examined the relation between cortical surface area and total cerebral volume in a cohort of preterm-born infants ($n = 113$, GA from 22-29 weeks[100]). They reported that in extremely preterm-born children the scaling component reflecting the relation between cortical

surface area and cerebral volume was reduced compared with infants born later. These effects were more prominent with males and were related to poorer neurodevelopment measured at 2 years of age. The authors concluded that a reduction in cortical growth was a reflection of reduced connectivity rather than a paucity of neurons. Cortical scaling is dependent on the development of association fibers rather than an increase in neuronal number[101] and disruptions in the process may underlie neurocognitive deficits. In late intrauterine development, the increase in association fibers and synapse formation plays a key role in the development of the cortex and alterations in these processes may result in atypical brain morphology in the preterm-born infants. Additional support for this hypothesis comes from animal models of preterm birth that have demonstrated that alterations in the connectivity of the cortical subplate with the thalamus result in disrupted cortical development.[102,103]

### Subcortical Development

Several MRI studies have also examined changes in subcortical structures in the preterm neonate. These studies have reported decreased volume in the thalami and lentiform nuclei[104,105] in preterm infants imaged at term-equivalent age (37-44-weeks GA), indicating that development in the extrauterine environment may result in impaired growth of the subcortical nuclei. Furthermore, preterm-born infants with supratentorial lesions (such as IVH or PVL) showed even smaller subcortical volumes compared with preterm-born infants with no identifiable lesions.[104] Subcortical lesions can be common in preterm-born infants and determining their effect on brain and cognitive developmental outcome is essential.

Another more recent MRI study extended their analyses to examine the relation of thalamic volume with that of other brain structures[106] in 71 preterm-born infants (23-35-weeks GA), imaged at term-equivalent age. An association was apparent between increasing prematurity and bilateral reduced volume of the thalamus, hippocampi, orbitofrontal, and posterior cingulate cortices. Microstructural changes in the thalamus and in thalamocortical tracts measured using DTI, suggested disruptions in thalamocortical connectivity or reductions in neuronal or axonal numbers.

### White-Matter Development

Abnormalities in white matter, measured using DTI, have been reported in preterm infants at term age[107] and on long-term follow-up[108] that correlate with dysfunction. In preterm-born infants, white-matter tracts exhibit lower anisotropy and higher diffusion compared with full-term infants.[109] Preterm-born infants also demonstrate increased RD and AD relative to term-born children,[110] a finding that may reflect premyelination changes, such as increased membrane permeability and a reduced axonal caliber. Although alterations in white-matter integrity, such as reductions in FA, are often associated with evidence of early white-matter injury in preterm infants, those infants without neuroimaging evidence of injury also exhibit maturational differences in white-matter architecture as they develop from early in life to term-equivalent age.[40,111]

The importance of studying white-matter development in preterm-born infants is crucial to understand impaired neurodevelopmental and motor outcome. White-matter injury is common in infants born preterm. PVL was classically one of the most common injuries of the preterm brain, although the incidence has decreased significantly in recent years.[112,113] PVL often precedes neurodevelopment disorders, such as cerebral palsy, cortical visual impairment, and impaired cognitive functions.[113,114] Although the major PVL lesions are less common now, white-matter injury is still frequent and significantly related to morbidity. PVL and white-matter lesions are believed to arise at least in part from ischemia and inflammation owing to perinatal or postnatal infection and are associated with disruptions in myelination of the developing brain.[1] Postmortem and experimental data have suggested that PVL is related to the arrest of preoligodendrocyte development.[115-117] A DTI study assessing preterm-born infants with PVL noted decreased FA in several major white-matter fiber pathways and lower FA values were associated with greater cognitive impairment.[118] These underlying neuropathologic changes in white matter, which affect oligodendroglial maturation and premyelination processes, are critical to our understanding of the motor deficits seen in the preterm-born population.

## Risk Factors for Adverse Outcomes in Preterm-Born Children

Preterm birth is one of the leading causes of infant mortality in the developed world.[119-121] Although much research has focussed on the etiology of preterm birth, few preventive strategies have emerged and the rates of preterm birth continue to rise in industrialized countries. A number of distal (socioeconomic), intermediate (maturational), and proximal (perinatal and neonatal) factors have emerged that have been associated with poor neurodevelopmental outcome.

### Distal Factors

Fewer years of education,[122] social disadvantage,[123] and lower SES are significant risk factors for preterm birth.[124] Furthermore, infants born into families with lower SES have higher neonatal morbidity and mortality.[125-127] Although the relation between SES and preterm birth remains uncertain, poor nutrition and adverse living conditions that are more common in individuals with lower economic means may be contributory.

Acute and chronic stress in mothers is believed to be a significant risk factor for preterm birth and poor neurodevelopmental outcome.[128,129] The stress hormone pathway, the hypothalamic-pituitary-adrenal axis, is often altered in mothers who deliver early. Serum or plasma levels of stress

hormones including cortisol and corticotropin-releasing hormone measured in early pregnancy are associated with preterm delivery[130,131] and poor neurodevelopmental outcome.[128] This may be owing to epigenetic mechanisms that regulate gene expression for the receptors that bind cortisol.[132]

## Intermediate Factors (Maturational Influences)

### Extremely Early Birth

Owing to advances in perinatal care, survival rates of extremely low-birth-weight infants born after $<26$ weeks gestation have increased,[133,134] but they are at greater risk for neonatal morbidity, neurodevelopmental impairments, and long-term adverse outcomes.[134-138] The poor outcomes of these infants are often related to GA at birth, the lack of placental nutrients, inadequate postnatal nutrients, illness, and exposure to stress in the extrauterine environment. Yet recent evidence suggests that the altered white-matter integrity attributed to extreme preterm birth may relate to the higher burden of systemic illness faced by these babies rather than the degree of prematurity itself.[139]

### Early Brain Injury

Early brain injury and illness are common in the preterm-born neonate. Several imaging studies have examined white-matter integrity in infants with brain injury. For example, in a study of 55 preterm neonates studied serially with corticospinal tract (CST) DT tractography (DTT), preterm neonates with evidence of moderate to severe white-matter abnormalities on MRI and those with postnatal infections had impaired development of the CST as they developed to term-equivalent age.[140] FA values increased at slower rates compared with infants without evidence of injury or illness. These findings of very early white-matter damage, predicting later development of primary motor pathways (ie, CST), underscores the possibilities for early interventions.

In addition to alterations in white matter, the development of the cerebellum has been shown to be impaired in infants with early brain injury. Tam et al.[141] collected DTI data from 38 preterm newborns to investigate the relation between changes in the cerebellum and supratentorial manifestations of injury (IVH or white-matter injury). Severe IVH was associated with higher MD and lower FA in the medial cerebellar peduncles and deep nuclear hila, and lower MD in the cerebellar cortex. White-matter injury was not significantly related to changes in diffusivity. Cerebellar volume was reduced in infants with IVH, even in infants who had mild IVH without significant supratentorial lesions, suggesting that blood products in the cerebrospinal fluid disrupt cerebellar growth.[142] Although PVL has previously been associated with smaller cerebellar volumes,[143] white-matter injury in this cohort was not associated with impaired cerebellar growth, a finding the authors suggested may have been due to the relatively mild brain damage seen in their cohort.

### Proximal Variables

Proximal variables, such as postnatal infection, are detrimental to brain development.[40,140,144] Early severity of illness, as measured using the clinical risk index for babies, predicted a reduction in cortical surface area.[145] White-matter abnormalities were also associated with brain injury, postnatal infection,[140] and illness severity in preterm-born infants.[146] Additionally, greater early illness severity (measured using the Score for Neonatal Acute Physiology-II) were negatively associated with FA values from the CST in preterm-born infants.[147]

Related to the severity of illness is the repeated exposure to noxious stimuli in the neonatal intensive care unit. Critically ill infants are often intubated, receive numerous heel lances, and may experience postoperative pain. Stevens et al.[148] reported an interaction between severity of illness and behavioral pain responses, indicating that critically ill infants who receive noxious stimuli may have lower pain thresholds. Using evoked potentials, preterm infants who experienced at least 40 days of intensive care were found to have increased brain neuronal responses to noxious stimuli compared with healthy newborns at the same postmenstrual age.[149] In turn, findings from a multimodal-imaging study indicated that increased exposure to noxious stimuli was associated with reduced FA in white matter and reduced NAA in the subcortical gray matter.[150] Together, these studies indicate that early painful procedures are associated with atypical brain development that may contribute to impaired neurodevelopment in preterm-born infants, and suggest new opportunities to improve outcomes through neonatal intensive care strategies.

# Neuroprotection

With the steady rise in the number of infants being born preterm, the identification of neuroprotective agents to prevent brain injury is essential. Antenatal treatment with magnesium sulfate can reduce the risk of infant death and cerebral palsy.[151] Preliminary evidence in experimental models also suggests that antenatal treatment with magnesium sulfate is associated with fewer white-matter injuries.[152] Future work in this area is needed to understand the immediate and long-term effects of antenatal magnesium sulfate on preterm neural and cognitive development. The application of advanced brain imaging in the preterm neonate has also identified new potential avenues to improve brain health, such as the prevention of infection, and the reduction in painful procedures. The increased knowledge of the associated risk factors for poor outcome in preterm-born children will aid in the development of neuroimaging protocols, including combining multimodal-imaging techniques, which can be used to identify biomarkers that can be targeted therapeutically. Furthermore, neuroimaging will play an important role in monitoring the efficacy of interventions on brain development and new protocols could serve as a bridge to identify brain atypicalities in both infants and animal models of preterm birth.[153]

## Conclusions: Advances Beyond White-Matter Vulnerability

Advances in medical imaging techniques have provided essential information on brain structure, function, and metabolism in the preterm brain. It is increasingly clear that the preterm brain is vulnerable to acquired injuries that are not limited to the white matter, as well as abnormalities in the maturation of the white matter, cerebral cortex, subcortical nuclei (basal ganglia and thalamus), and cerebellum[154] and their connectivity. Still questions remain regarding the optimal application of neuroimaging biomarkers to robustly predict neurodevelopmental outcome. Future research in this area is needed to combine multimodal-imaging techniques to identify infants who are at risk and would benefit from emerging interventions to improve brain health in the critical preterm period. The application of advanced MR imaging techniques could be further expanded to evaluate and monitor neuroprotective strategies. Additionally, long-term longitudinal imaging studies are needed to assess preterm-born children till school age and adolescence to better understand opportunities to promote adaptability and resilience. Improved knowledge concerning the broader distal factors, in addition to more intermediate and proximal factors, are also essential to improve the long-term brain health of children born preterm.

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