



Clinical neuroimaging in the preterm infant: Diagnosis and prognosis



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ABSTRACT

Perinatal care advances emerging over the past twenty years have helped to diminish the mortality and severe neurological morbidity of extremely and very preterm neonates (e.g., cystic Periventricular Leukomalacia [c-PVL] and Germinal Matrix Hemorrhage – Intraventricular Hemorrhage [GMH-IVH grade 3–4/4]; 22 to < 32 weeks of gestational age, GA). However, motor and/or cognitive disabilities associated with mild-to-moderate white and gray matter injury are frequently present in this population (e.g., non-cystic Periventricular Leukomalacia [non-cystic PVL], neuronal–axonal injury and GMH-IVH grade 1–2/4). Brain research studies using magnetic resonance imaging (MRI) report that 50% to 80% of extremely and very preterm neonates have diffuse white matter abnormalities (WMA) which correspond to only the minimum grade of severity. Nevertheless, mild-to-moderate diffuse WMA has also been associated with significant affectations of motor and cognitive activities. Due to increased neonatal survival and the intrinsic characteristics of diffuse WMA, there is a growing need to study the brain of the premature infant using non-invasive neuroimaging techniques sensitive to microscopic and/or diffuse lesions. This emerging need has led the scientific community to try to bridge the gap between concepts or ideas from different methodologies and approaches; for instance, neuropathology, neuroimaging and clinical findings. This is evident from the combination of intense pre-clinical and clinicopathologic research along with neonatal neurology and quantitative neuroimaging research. In the following review, we explore literature relating the most frequently observed neuropathological patterns with the recent neuroimaging findings in preterm newborns and infants with perinatal brain injury. Specifically, we focus our discussions on the use of neuroimaging to aid diagnosis, measure morphometric brain damage, and track long-term neurodevelopmental outcomes.

1. Introduction

Over the past two decades, advances in perinatal care have helped to diminish the mortality and severe neurological morbidity of extremely and very preterm neonates (e.g., cystic Periventricular Leukomalacia [c-PVL] and Germinal Matrix Hemorrhage–Intraventricular Hemorrhage [GMH-IVH grade 3–4/4]; 22 to < 32 weeks of gestational age; GA) (Ancel et al., 2015; Grisaru-Granovsky et al., 2014; Stoll et al., 2015). However, motor and/or cognitive disabilities associated with mild-to-moderate white and gray matter injury are frequently present in this population (e.g., non-cystic Periventricular Leukomalacia [non-cystic PVL], neuronal–axonal injury and GMH-IVH grade 1–2/4) (Marret et al., 2013; Volpe, 2009a). In fact, the diffuse component of white matter injury is the most common abnormality observed in contemporary cohorts (Back and Miller, 2014). Brain research studies using magnetic resonance imaging (MRI) report that

50% to 80% of extremely and very preterm neonates have diffuse white matter abnormalities (WMA) which correspond to the minimum grade of severity (Gano et al., 2015; Inder et al., 2005; Inder et al., 2003; Reid et al., 2014; Woodward et al., 2006). Nevertheless, mild-to-moderate diffuse WMA has also been associated with significant deficits in motor and cognitive functions (Spittle et al., 2011; Woodward et al., 2012).

Due to increased neonatal survival and the intrinsic characteristics of diffuse WMA, there is a growing need to study the brain of the premature infant using non-invasive neuroimaging techniques sensitive to microscopic and/or diffuse lesions (Ment et al., 2009a). This emerging need has led the scientific community to try to bridge the gap between concepts or ideas from different methodologies and approaches (e.g., neuropathology, neuroimaging, and clinical findings). This is evident from the combination of intense pre-clinical (Back and Miller, 2014; Kinney and Volpe, 2012; Palliser et al., 2016; Riddle et al.,

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2011; van Tilborg et al., 2016; Volpe et al., 2011) and clinicopathologic research (Counsell et al., 2008; de Vries et al., 2015; Harmony et al., 2016; Ment et al., 2009a; Pierson et al., 2007; Rutherford et al., 2010; Volpe, 2009a) along with neonatal neurology and quantitative neuroimaging research.

In the following article, we review literature relating the most frequent neuropathological patterns and recent neuroimaging findings in preterm newborns and infants with perinatal brain injury. Specifically, we focus on the use of neuroimaging to aid diagnosis, measure morphometric brain damage, and track long-term neurodevelopmental outcomes.

2. From neuropathology to neuroimaging... and vice versa

In 1962, Banker and Larroche described PVL for first time as a form of anoxic encephalopathy characterized by necrotic lesions in the periventricular white matter (Banker and Larroche, 1962), suggesting that this neuropathological pattern was related to ischemia and hypoperfusion at the vascular border zone in deep white matter. In subsequent decades, the histopathologic study of brain injuries in preterm infants continued to provide invaluable information to understand perinatal brain injury; however, some key concepts should be reconsidered. For example, it was believed that white matter damage was almost exclusively of the fetus or premature infant, and gray matter damage was only of the term infant (Kinney, 2009; Volpe, 2014). This notion had to be reevaluated during the late twentieth century and early twenty-first century thanks to quantitative MRI findings illustrating brain damage and loss of gray matter in preterm infants and children with and without c-PVL (Abernethy et al., 2002; Ajayi-Obe et al., 2000; Hüppi et al., 1998; Inder et al., 2005; Inder and Hüppi, 1999; Kesler et al., 2004; Lin et al., 2001; Miller et al., 2003). Based on these observations, Volpe (2005) proposed the term “encephalopathy of prematurity” to refer to encephalic gray matter abnormalities and WMA occurring in preterm infants during the perinatal period. PVL and neuronal–axonal injury are the hallmarks of the encephalopathy of prematurity (Kinney and Volpe, 2012; Volpe, 2009a). Consequently, various neuroimaging techniques (cranial ultrasound, cUS; volumetric MRI, vMRI; diffusion MRI, dMRI; functional MRI, fMRI) have been applied to study the neuropathological patterns that affect preterm infant survivors.

3. Frequent neuropathological patterns in premature infants: understanding perinatal brain injury in prematurity

The main neuropathological patterns affecting premature infants, as reported in current literature (Haynes et al., 2013; Kinney and Volpe, 2012; Marín-Padilla, 1997; Palliser et al., 2016; Pierson et al., 2007; Volpe, 2009a), are PVL, diffuse white matter gliosis (DWMG), neuronal–axonal injury of the white and gray matter, GMH-IVH, and periventricular hemorrhagic infarction. Here, we briefly summarize these findings (see annexed Table 1 and Table 2):

3.1. Periventricular leukomalacia

By definition, periventricular leukomalacia (PVL) has two neuropathological components: 1) a focal periventricular necrotic component and 2) a component with diffuse gliosis in the surrounding cerebral white matter. Cystic lesions secondary to necrotic foci in the white matter characterize the focal periventricular necrotic component. There are two types of necrotic foci with different histopathological/neuroimaging evolutions: macroscopic (necrosis > 1 mm that evolves over several weeks into a cyst) and microscopic (necrosis ≤ 1 mm that evolves over several weeks into glial scars) (Volpe, 2009a). The nomenclature to differentiate PVL subtypes depends on necrotic foci size but not on the diffuse component. The macroscopic focal necrotic component of PVL with diffuse gliosis is referred to as cystic PVL (c-

Table 1
Variables to assess by clinical MRI at term-equivalent age.

Cerebral white matter
Presence or absence of cysts
Signal abnormality*
Myelination of the PLIC and corona radiata
Size and morphology of the corpus callosum
Size and morphology of the lateral ventricles
Volume of the periventricular white matter
Cortical gray matter
Signal abnormality*
Cortical fold maturation
Size of the extracerebral space
Subcortical gray matter
Signal abnormality*
Symmetry and size of the basal ganglia
Symmetry and size of the thalamus
Cerebellum
Signal abnormality*
Symmetry and size of the hemispheres

Note: For a detailed review about scores by each variable according to their severity see Inder et al., 2003; Woodward et al., 2006; Kidokoro et al., 2013.

PLIC: posterior limb of internal capsule.

* Could be associated with hemorrhagic and ischemic processes.

PVL). In contrast, the term non-cystic PVL is often used to denote the microscopic focal necrotic component of PVL plus a component of diffuse gliosis in cerebral white matter (Kinney, 2009; Volpe, 2008). Therefore, it is a common error to refer to non-cystic PVL as “diffuse PVL” with the purpose of differentiating it from c-PVL, because both c-PVL and non-cystic PVL have one component with “diffuse” astroglial activation, microglial activation, and large or small cysts.

3.2. Diffuse white matter gliosis

Diffuse white matter gliosis (DWMG) is a rather common neuropathological finding in postmortem studies of preterm infants (41%) (Pierson et al., 2007) and in animal models (100% in the first week after hypoxic-ischemic event) (Riddle et al., 2011). Nevertheless, the incidence for this pattern in preterm infant survivors is unknown, as well as its impact on long-term neurodevelopmental outcome (Haynes et al., 2013). DWMG has been defined by diffuse astrocytic activation in cerebral white matter. However, unlike PVL it lacks a focal necrotic component and associated neuronal–axonal loss (Haynes et al., 2013; Pierson et al., 2007). It seems that DWMG is a prelude to pathologies of greater severity, such as PVL, although this has not been demonstrated (Kinney and Volpe, 2012).

3.3. Neuronal – axonal injury of the white and gray matter

Neuronal–axonal injuries are present in 30–40% of PVL cases confirmed by autopsy (Marín-Padilla, 1997; Pierson et al., 2007). Currently, neuronal–axonal injuries are considered over a wide neuropathological spectrum, which can occur in cerebral white matter (subplate neurons and axons) (Kinney et al., 2012), cortical gray matter, subcortical gray matter (thalamus, basal ganglia), and cerebellum (cortex, dentate nucleus) (Pierson et al., 2007; Volpe, 2009a). White matter necrosis generates abnormalities in gray matter as a result of axon terminal loss. Moreover, some neurons are unable to reach their subcortical targets due to injury. Other neurons present the appearance of “small stellate neurons,” while others suffer from dendritic resorption (centripetal) (Kinney, 2009; Marín-Padilla, 1997). In the cortex, abnormalities are mainly located in layer V with reduced neuron density in all areas and a significant reduction in pyramidal neuron density in layer V of the koniocortex (Andiman et al., 2010). Pyramidal neurons in particular may lose connectivity with layer I due to progressive distal absorption (Marín-Padilla, 1997). The subcortical structures experiencing significant neuronal loss are the thalamus, globus pallidus, and

Table 2
Clinical neuroimaging and perinatal brain injury spectrum in premature infants.

Neuroimaging findings	Diagnosis by		Neuropathological findings	Major clinical outcome
	cUS	MRI		
Cystic white matter abnormalities	✓	✓	Cystic PVL. Often bilateral cysts Porencephalic cyst secondary to periventricular hemorrhagic infarction. Often unilateral	Cerebral palsy with diplegia or quadriplegia Location-dependent. Motor cortex: hemiplegic cerebral palsy
Diffuse white matter abnormalities	X	✓	Diffuse component of cystic PVL (moderate-to-severe WMA)	Cognitive impairment/behavioral problems
			Non cystic PVL (mild-to-moderate WMA) Diffuse white matter gliosis (normal-to-mild WMA?)	Cognitive impairment/behavioral problems Unknown
Gray matter abnormalities	X	✓	Neuronal loss and gliosis of the gray matter Subcortical gray matter and cerebellum are the most affected	Cognitive impairment/behavioral problems
Germinal matrix hemorrhage - intraventricular hemorrhage	✓	✓	Breaking of the germinal matrix vessels	Depends on the location and severity Grade III/Periventricular hemorrhagic infarction: cerebral palsy, cognitive, behavioral and visual problems
Punctate white matter lesions	X/✓	✓	Ischemic lesion Hemorrhagic lesion/congestion of medullary veins	Not clear yet. Maybe cognitive impairment/behavioral problems
Diffuse excessive high signal intensity	X	✓	Unknown	Currently not found an association between diffuse excessive high signal intensity and abnormal long-term neurodevelopmental outcome
Encephalopathy of prematurity	X	✓	PVL + neuronal and axonal loss	Cerebral palsy and autistic spectrum disorders Motor, cognitive, attentional, behavioral and socialization problems

✓: Diagnosis is possible X: Diagnosis is not possible X/✓: Punctate white matter lesions are suggested by inhomogeneous echogenicity seen on cUS, but can only be reliably detected by MRI.

PVL: Periventricular Leukomalacia. WMA: White Matter Abnormalities.

dentate nucleus of the cerebellum. The structures typically presenting significant gliosis are the thalamus, basal ganglia, and pons. Neuronal loss and gliosis in the thalamus and basal ganglia are lesions almost exclusive to PVL (for an extensive review see [Andiman et al., 2010](#); [Kinney and Volpe, 2012](#); [Pierson et al., 2007](#)). The presence of neuronal–axonal injury in conjunction with PVL is defined as encephalopathy of prematurity ([Volpe, 2009a, 2005](#)).

3.4. Germinal matrix hemorrhage – intraventricular hemorrhage

Germinal matrix vessels have an endothelial layer with tight junctions, few pericytes, and fibronectin deficiency in the immature basal lamina. Furthermore, astrocyte end-feet show decreases in glial fibrillary acidic protein expression, which supports astrocyte structure. All such features contributing to the vasculature of the germinal matrix are prone to rupture and extravasation of blood into the subependymal zone ([Ballabh, 2014](#)).

The implicated or presumed vessels in these types of injuries are mainly the recurrent artery of Heubner ([Hambleton and Wigglesworth, 1976](#)) and the lateral striate artery ([Kuban and Gilles, 1985](#)). Intraventricular hemorrhage is one of the major complications in extremely and very preterm neonates. The main cause of intraventricular hemorrhage is the breaking of germinal matrix vessels, which underlies germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) ([Ballabh, 2014](#)). Indeed, GMH-IVH is the most common intracranial bleeding in the perinatal period, and there are many risk factors associated with this pathology, including very low birth weight (< 1500 g) and extremely low birth weight (< 1000 g) ([Kenet et al., 2011](#)). GMH-IVH rarely occurs during birth; however, up to 50% of cases occur in the first 24 h of life and 80–90% of cases occur in the first 72 h of life ([Kenet et al., 2011](#)). This should be considered, especially when using conventional neuroimaging to study high-risk premature neonates. Currently, GMH-IVH is classified by neuroimaging into three grades according to their severity ([Volpe, 2008](#)).

3.5. Periventricular hemorrhagic infarction

[Gould et al. \(1987\)](#) have suggested that severe intraventricular hemorrhage associated with intraparenchymal hemorrhage (previously grade 4 of [Papile et al., 1978](#)) is actually a venous infarction secondary to GMH-IVH with hemorrhagic evolution in periventricular white matter. [Gould et al. \(1987\)](#) referred to this neuropathological pattern as “periventricular hemorrhagic infarction.” While the incidence of c-PVL has declined, periventricular hemorrhagic infarction has remained stable over decades. What is more, around 11% of infants < 32 weeks GA and 8% of infants < 1500 g develop periventricular hemorrhagic infarction ([Soltirovska Salamon et al., 2014](#)). The incidence can reach up to 45% in infants weighing between 500 and 750 g at birth ([Wilson-Costello et al., 2005](#)).

3.6. Encephalopathy of prematurity

Encephalopathy of prematurity is a result of a heterogeneous and multifactorial neuropathological spectrum (hypoxia, ischemia, infectious/inflammatory processes) that affects the white and gray matter of the premature infant ([Haynes et al., 2013](#); [Kinney, 2009](#)). As previously mentioned, the neuropathological patterns comprising encephalopathy of prematurity are PVL and neuronal–axonal injury. However, other pathological processes such as GMH-IVH, periventricular hemorrhagic infarction, and cerebellar disorders may accompany the neuropathological spectrum in encephalopathy of prematurity ([Kinney and Volpe, 2012](#)). Because of this variety of histopathologic presentations, the study of encephalopathy of prematurity is complex and intricate, especially considering that a single neuropathological pattern (mainly GMH-IVH) may be a “pathogenetic mechanism” for the development of other brain injuries (e.g., PVL, neuronal–axonal injury, and/or periventricular hemorrhagic infarction) ([Kuban et al., 1999](#); [Larroque et al., 2003](#); [Volpe et al., 2011](#)) including remote lesions (e.g., cerebellar underdevelopment and atrophy) ([Kinney and Volpe, 2012](#); [Limperopoulos et al., 2005](#); [Volpe, 2009b](#)). As a result, mixed patterns with two or more lesions in different stages and with dissimilar evolution in each type describing a “true” instance of encephalopathy of

prematurity are observed. In fact, GMH-IVH without ventricular dilation (grade 1–2) has been associated with an up to 9-fold increased risk of PVL or periventricular hemorrhagic infarction. What is more, GMH-IVH with ventricular dilation (grade 3) has been shown to increase up to 29-fold the risk of PVL or periventricular hemorrhagic infarction in premature infants (Kuban et al., 1999).

4. Neonatal and pediatric conventional neuroimaging

Cranial ultrasound (cUS) and conventional MRI (using a clinical/qualitative approach) are the main neuroimaging techniques used in hospital environments for the diagnosis and characterization of perinatal brain injury (de Vries et al., 2015; Rutherford et al., 2010; Tusor et al., 2014). cUS is a noninvasive and low-cost means of study to examine infants at high risk for neurological damage without mobilizing them outside the neonatal intensive care unit (NICU)—even though the MRI global market is moving in this direction to get high-quality diagnostic imaging inside the NICU (Tkach et al., 2014). This way it is possible to obtain brain images in the early neonatal period to aid the physician in determining the time and evolution of the injury (Sarkar et al., 2015; van Wezel-Meijler et al., 2010). cUS allows the detection of cerebellar damage and cystic lesions in the supratentorial white matter (Steggerda et al., 2009), and it enables the evolutionary tracking of GMH-IVH (Kwon et al., 2014). However, cUS is not effective in detecting subtle lesions and/or diffuse white and gray matter injuries (Parodi et al., 2013). This technique represents only a first-line option for monitoring premature neonates in the NICU. On the other hand, conventional MRI is a non-ionizing imaging technique that allows the detailed assessment of encephalic structures that are commonly affected in extremely and very preterm infants. Overall, MRI allows the evaluation of: 1) the contrast between encephalic white and gray matter (e.g., T1 weighting, “T1w”); 2) the myelination process (longitudinal T2w and T1w) (Childs et al., 2001); 3) the evolution of ischemic pathologies of arterial origin (using diffusion-weighted imaging, DWI) (van der Aa et al., 2013); 4) vascular disorders of the Circle of Willis and its efferent branches (MR angiography 3D “Time of Flight”) (Lequin et al., 2009); 5) hemorrhages (via susceptibility weighted imaging, SWI) (Kersbergen et al., 2014); and 6) macroscopic focal lesions (> 1 mm) and diffuse WMA (using FLAIR and T2w images) (Kwon et al., 2014; Rutherford et al., 2010). Thus, MRI is more sensitive than cUS for detecting subtle and/or diffuse neonatal brain disorders (Benders et al., 2014; Miller et al., 2003; Sie et al., 2000). Currently, MRI is considered the gold standard for clinical diagnosis of diffuse WMA in the absence of histological information (de Vries et al., 2015).

4.1. Conventional MRI of the neonatal brain: sequences and technical aspects

The neonatal brain is different from the adult brain because it has higher water content, especially in the preterm population. Hence, the majority of sequences for imaging the neonatal brain need to be adapted to optimize the image quality (Rutherford et al., 2006). In this sense, T1w sequences in the neonatal period are usually acquired with short repetition time (TR) and short echo time (TE), while T2w sequences are acquired with long TR and long TE. Long inversion times are recommended for the inversion recovery sequences (Dubois et al., 2014). The main neonatal MRI sequences used routinely in clinical assessments are T1w, T2w, DWI, and inversion recovery sequence (e.g., FLAIR) (Devi et al., 2015; Kwon et al., 2014). SWI and MR angiography can also be considered. Diffusion parameters, tractography, and fMRI are some emerging modalities with potential use in the clinical environment (see Section 5.1 Quantitative MRI).

4.2. Is it valid to infer a neuropathological diagnosis using conventional neuroimaging?

While it is true that cUS and conventional MRI provide valuable information for the study of the brain in premature infants, accurate diagnosis of any lesion pattern of perinatal brain injury is made by histopathological confirmation and/or postmortem “neuropathological diagnosis” (Back, 2014; Kinney, 2009; Volpe, 2009a). Obviously, since this form of diagnosis is not available in the population of preterm survivors, the clinical use of conventional MRI has become increasingly common in the last 10–15 years (Smyser et al., 2012). However, clear and comprehensive correlations between conventional neuroimaging and the neuropathological spectrum of surviving premature infants do not yet exist (Haynes et al., 2013; van Tilborg et al., 2016). Clinical MRI currently used on 1.5–3 T MRI systems does not allow the differentiation of the most subtle and frequent neuropathological patterns such as non-cystic PVL, neuronal-axonal injury, and DWMG (Back, 2014; Haynes et al., 2013; Palliser et al., 2016; Riddle et al., 2011; Volpe, 2008). This is due in part to the resolution of whole-brain MR, because conventional qualitative MRI works at a resolution of millimeters, whereas the processes associated with microcystic necrosis (e.g., focal component of non-cystic PVL) or gliosis (e.g., diffuse component of non-cystic PVL and DWMG) are present in microns. Therefore, until additional technological improvements are available, it is ill advised to infer a neuropathological diagnosis in most cases based upon neuroimaging evidence alone.

4.3. Terminology for conventional neuroimaging

Macroscopic necrotic lesions (c-PVL) and severe hemorrhagic processes (GMH-IVH grade 3 and periventricular hemorrhagic infarction) can be well characterized with the combined use of cUS and conventional MRI (Benders et al., 2014). Thus, neuropathological findings can be inferred in these types of lesions in the absence of histopathological studies. By contrast, microscopic and diffuse lesions cannot be distinguished from each other in cUS and/or qualitative MRI, so it is suggested to adopt a consistent nomenclature according to the neuroradiological findings without neuropathological inferences (van Tilborg et al., 2016).

4.3.1. Conventional MRI

Currently, several terms are used to denote brain damage detected by conventional MRI in the early days of life and/or at the term-equivalent age (TEA; 37–42 weeks postmenstrual age). The terms most commonly used are white matter abnormalities (cystic and diffuse), gray matter abnormalities (GMA), cerebellar abnormalities, punctate white matter lesions, and diffuse excessive high signal intensity (DEHSI) (Benders et al., 2014; de Vries et al., 2015; Kwon et al., 2014; Rutherford et al., 2010; van Tilborg et al., 2016). This terminology emerges from the characteristic abnormal changes in signal intensity, from its distribution and morphology (punctate white matter lesions and DEHSI), or by evaluating and grouping a set of abnormal variables (WMA, GMA, and cerebellar abnormalities).

White and gray matter abnormalities are frequently classified according to degree of severity through a standardized score system that assesses the MRI findings at TEA (Hintz et al., 2015; Horsch et al., 2010; Inder et al., 2003; Kidokoro et al., 2013; Woodward et al., 2006). This clinical assessment consists in graduating each variable independently (the most used are listed in Table 1) and then adding up the score of all variables. The final score allows situating the MRI findings in a category according to severity of the lesion, usually divided into none, mild, moderate, and severe. Thus, the extension and characterization of brain abnormalities is mainly based on their severity and not on the neuropathological pattern. Although this classification does not have a clear correlation with the neuropathology of diffuse patterns or encephalopathy of prematurity, it is very useful for establishing an imaging

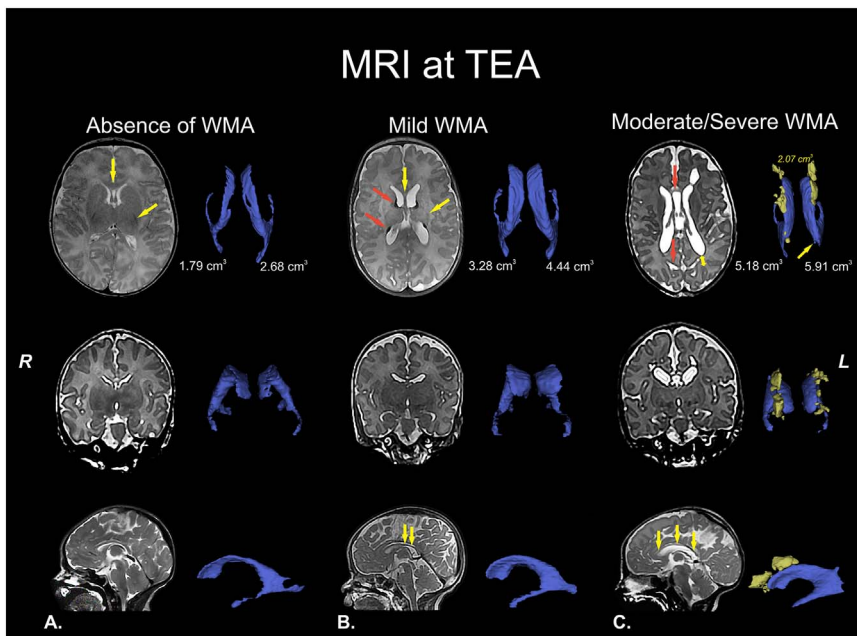


Fig. 1. White matter abnormalities (WMA). T2 structural MRI with corresponding volumetric measurements of the lateral ventricles (in blue) at term-equivalent age (TEA) or nearly TEA. **A)** Normal MRI at TEA. Healthy neonate at 41 weeks of postmenstrual age with normal MRI: absence of cystic abnormalities, volume and size of corpus callosum (yellow arrow in upper panel) and lateral ventricles are normal, myelination of the corpus callosum, posterior limb of internal capsule (PLIC; yellow arrow in upper panel) and corona radiata corresponding with the age and cerebral white matter signal and volume are normal. **B)** Mild WMA at nearly TEA. Preterm infant (born at 28 gestational weeks) at 43 weeks of postmenstrual age with mild diffuse WMA: absence of cystic abnormalities, partial thinning of the corpus callosum (yellow arrows in upper and lower panel), mild dilated lateral ventricles, PLIC with myelination delay and focal signal abnormalities in relation to punctate white matter lesions (orange arrows in upper panel), probably associated with hemorrhagic etiology and congestion of medullary veins. **C)** Moderate-to-severe WMA at TEA. Preterm infant (born at 29 gestational weeks) at 41 weeks of postmenstrual age with cystic WMA: bilateral presence of multiple cysts (3D reconstruction and corresponding volumetric measurement are in yellow in upper panel), global thinning of the corpus callosum (orange arrow in upper panel and yellow arrows in lower panel), dilated lateral ventricles, severe myelination delay, diffuse and extensive signal abnormalities, white matter loss (double direction arrow in upper panel), prominent sulci near the ventricles (orange arrow in upper panel) and communication between small cyst and left lateral ventricle

(yellow arrow in upper panel). The features of the last structural MRI are compatible with cystic-PVL. Images in radiological convention. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

diagnosis and as a prognostic basis for long-term neurodevelopmental outcome (Anderson et al., 2015; Murray et al., 2014; Omizzolo et al., 2014; Reidy et al., 2013; Spittle et al., 2011). Here we summarize the context of these terms (see annexed Table 2):

4.3.1.1. Cystic white matter abnormalities. As previously mentioned the cystic lesions of cerebral white matter, mainly c-PVL and periventricular hemorrhagic infarction, can be well characterized throughout the neonatal period. The macroscopic focal lesions of c-PVL are visible on MRI at TEA (see Fig. 1-C/4-A) as one or several cystic images in periventricular white matter at the ventricular trigone level, and may extend to the centrum semiovale (Rutherford, 2001). Periventricular hemorrhagic infarction can be seen mainly in two forms on MRI at TEA: 1) as a cystic image indistinguishable from c-PVL (unless serial neonatal cUS has been obtained) or 2) as a porencephalic cyst (Benders et al., 2014). The latter is usually seen as asymmetric unilateral ventriculomegaly (porencephalic cyst with ventricular communication) or rarely, as a communication between the lateral ventricular system and the subarachnoid space (Grant et al., 1982; Volpe, 2008). Other MRI findings that may accompany cystic lesions are alterations of morphology and diminished size of the corpus callosum, dilated lateral ventricles (sometimes asymmetric and with irregular boundaries) (Martinez-Biarge et al., 2016), prominent sulci near the ventricles (Rutherford, 2001), severe myelination delay, diffuse or focal signal abnormalities, white matter loss (usually higher than that observed in diffuse patterns) (Inder et al., 2003; Kidokoro et al., 2013; Woodward et al., 2006), and some cases with reduced size/volume of the cerebellar hemispheres (Limperopoulos et al., 2005). The concomitant presence of cystic WMA and cerebellar alterations, like atrophy or underdevelopment, suggests infratentorial lesions to distance by trans-synaptic degeneration of the corticopontocerebellar pathways (Kinney and Volpe, 2012; Limperopoulos et al., 2005). In cases with an important unilateral cystic lesion (usually periventricular hemorrhagic infarction), it is possible to see a decreased size of the cerebellar hemisphere contralateral to the cyst (Limperopoulos et al., 2005; Volpe, 2009b) (see Fig. 2-D). All cystic lesions of the white matter are considered moderate to severe due to their destructive nature.

4.3.1.2. Diffuse white matter abnormalities. Non-cystic PVL, DWMG, and

neuronal-axonal injury of the white matter are the main patterns of diffuse white matter abnormalities (diffuse WMA) currently described in literature (Haynes et al., 2013; Kinney and Volpe, 2012; Palliser et al., 2016). These patterns show at least one diffuse neuropathological component in absence of one focal macroscopic component (cysts); however, one pattern cannot be differentiated from another using conventional endogenous contrast MRI. Thus, a simple way to refer to them, collectively or individually, is “diffuse white matter abnormality” (see Fig. 1-B). As previously mentioned, diffuse WMA can be classified according to degree of severity through the evaluation of MRI findings. The main qualitative MRI findings that have been associated with diffuse WMA are: absence of cystic abnormalities > 1 mm in white matter (major criterion) (Volpe et al., 2011); diffuse signal abnormalities in white matter, posterior limb of internal capsule (PLIC), and/or corona radiata with myelination delay; thinning of the corpus callosum; dilated lateral ventricles; and/or white matter loss (Inder et al., 2003; Woodward et al., 2006). Some cases could show bilateral and symmetrical decreases in cerebellar size/volumes by bilateral and symmetrical crossed trans-synaptic degeneration (Limperopoulos et al., 2005).

4.3.1.3. Gray matter abnormalities. Neuronal loss and gliosis of the gray matter are the main neuropathological abnormalities detected in just over one third of infants with PVL (see Section 3.3 Neuronal – axonal injury of the white and gray matter). These abnormalities can occur in any region of the encephalic gray matter, although subcortical regions and cerebellum tend to be the most affected structures (Pierson et al., 2007). Like WMA, qualitative GMA are usually stratified according to their degree of severity and distribution (cortical, subcortical, and/or cerebellar) (Inder et al., 2003; Kidokoro et al., 2013; Woodward et al., 2006). Although GMA in preterm infants have often been associated with PVL, these could be difficult to detect by conventional MRI and, consequently, most neuroradiologists do not report these findings in clinical practice (Slaughter et al., 2016).

4.3.1.3.1. Cortical gray matter abnormalities. Abnormalities in the cerebral cortex of preterm infants are related to cortical maturation impairment such as cortical volume loss and cortical folding delay (Dubois et al., 2008; Lodygensky et al., 2010). According to neuropathological findings, the cortical abnormalities in PVL are

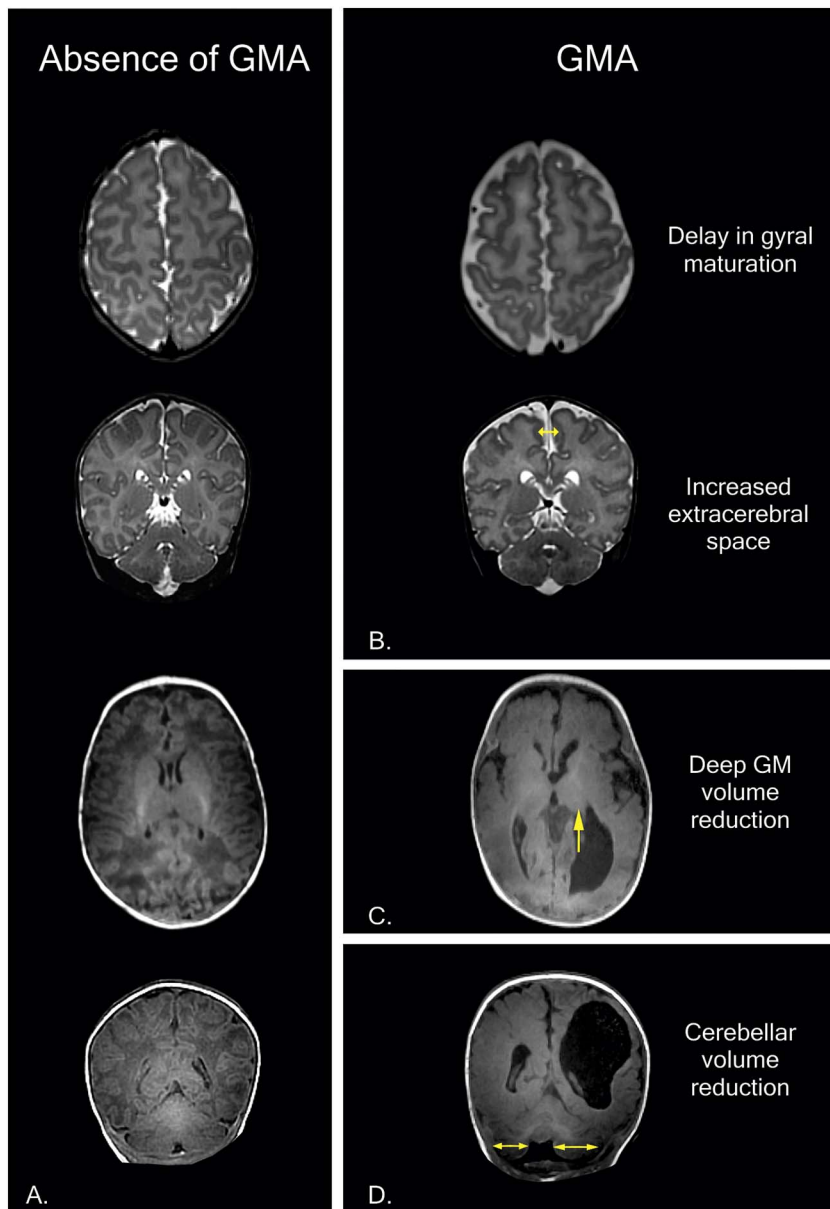


Fig. 2. Examples of gray matter abnormalities (GMA) in MRI at term-equivalent age (TEA) in the first year of life. **A)** Normal T2 and T1 structural MRI at TEA. Healthy neonate at 41 weeks of postmenstrual age with normal MRI: cortical gray matter (signal, gyral maturation and subarachnoid space), deep/subcortical gray matter and cerebellum (signal and volume) are normal. **B)** Preterm infant (born at 31 gestational weeks) at 38 weeks of postmenstrual age with mild-to-moderate GMA: delay in gyral maturation and increase in extracerebral space (double direction arrow). **C-D)** Preterm infant (born at 31 gestational weeks) at 9 months of corrected age with porencephalic cyst and severe GMA. **C)** Deep GMA with volume reduction and asymmetry in the thalamus (arrow). **D)** Cerebellar volume reduction and asymmetry in cerebellar hemispheres (double direction arrow). The features of the last structural MRI (C-D) are compatible with a complex spectrum of encephalopathy of prematurity (diagnosis: periventricular hemorrhagic infarction + diffuse WMA compatible with PVL + severe GMA = encephalopathy of prematurity; mixed patterns with two or more lesions in different stages and with distinct evolution in each one). Images in radiological convention.

mainly located in layer V with a reduction in the density of neurons, especially pyramidal neurons (Andiman et al., 2010). However, this apparently does not affect cortical thickness and/or volume in this population. Dean et al. (2013) found an association between decreased cortical volume and increased neuronal density in a sheep model of ischemia, and they concluded that cortical growth impairments are related to deficits in dendritic arbor maturation and synapse formation of cortical neurons.

The delay in cortical folding has been related to antenatal (lower birth weight and smaller occipitofrontal circumference at birth) and postnatal (higher critical illness in the first 24 h of life, steroids, and prolonged endotracheal intubation) risk factors (Engelhardt et al., 2015). Nevertheless, the neuropathological substrate that explains the abnormalities in cortical folding detected by MRI in premature infants is still unclear. In summary, the main qualitative MRI findings that have been used as cortical abnormality indicators are: 1) abnormalities in the cerebral cortex signal intensity (e.g., focal or extensive; unilateral or bilateral); 2) maturity of cortical folds (e.g., delay of at least 2 weeks); and/or 3) augmented subarachnoid space (e.g., increased interhemispheric distance; see Fig. 2-B) (Inder et al., 2003; Kidokoro et al., 2013).

4.3.1.3.2. Subcortical gray matter abnormalities and cerebellar abnormalities. The deep gray matter and cerebellum tend to be the most affected structures with neural loss and gliosis. The gray matter structures with significant neuronal loss are the thalamus, globus pallidus, and cerebellar dentate nucleus. The structures with significant gliosis are the thalamus, basal ganglia, and pons. However, gliosis without obvious neuronal loss is more common than neuronal loss and gliosis combined, and it primarily affects the basis pontis, inferior olive, globus pallidus, thalamus, hippocampus, and brainstem tegmentum, respectively (Kinney and Volpe, 2012; Pierson et al., 2007). This is consistent with numerous MRI studies in preterm infants that show reductions in size and/or signal abnormalities of the thalamus, basal ganglia, or cerebellum (Hintz et al., 2015; Inder et al., 2005; Kidokoro et al., 2013; Limperopoulos et al., 2005; Martinez-Biarge et al., 2016; Omizzolo et al., 2014; Tich et al., 2009). Based on the above, the aspects to consider in conventional MRI at TEA are 1) signal intensity abnormalities and 2) structural reductions in size by visual analysis (see Fig. 2-C/D) and or semi-quantitative analysis (measures by anatomic references in one or two planes) of the thalamus, basal ganglia, and cerebellum (Kidokoro et al., 2013; Tich et al., 2009).

4.3.1.4. Punctate white matter lesions. By conventional MRI, this pattern of lesion corresponds to small periventricular lesions of ischemic or hemorrhagic nature, visible via DWI and SWI, respectively (Niwa et al., 2011). Kersbergen et al. (2014) described three different patterns of punctate white matter lesions according to their morphology: linear, cluster, and mixed. The morphology of linear punctate white matter lesion is typically the most frequently observed pattern, especially in infants < 28 weeks GA (on T1-weighted MRI at 30 weeks of postmenstrual age). This pattern tends to have a low intensity signal in SWI, with anterior and periventricular location. The linear pattern was associated with GMH-IVH, suggesting a hemorrhagic etiology or congestion of medullary veins (see Fig. 1-B). On the other hand, instances of cluster punctate white matter lesions were observed with diffusion restriction in DWI in infants > 28 weeks GA. In this pattern, there was no clear correlation with GMH-IVH, hence an inflammatory or ischemic etiology is suspected. Finally, the mixed pattern (linear and cluster combined) is located in posterior regions of the brain. According to reports, the mixed pattern is more probable in preterm infants > 28 weeks GA and it does not show an obvious correlation with GMH-IVH.

4.3.1.5. Diffuse excessive high signal intensity. The diffuse excessive high signal intensity (DEHSI) is defined in T2w images at TEA with diffuse increased signal intensity in the cerebral white matter. The term DEHSI is used only for diffuse increased signal intensity and should not be confused with mild-to-severe WMA accompanied by other structural abnormalities. No association between DEHSI and abnormal long-term neurodevelopmental outcome has been found (Iwata et al., 2012; van't Hooft et al., 2015), and DEHSI is now considered part of a normal variant of preterm infant development (Benders et al., 2014; Calloni et al., 2015; van Tilborg et al., 2016).

4.4. Motor and cognitive prognosis by conventional MRI

Conventional MRI at TEA is a helpful tool for the prediction of short- and long-term neurodevelopmental outcomes. In relation to motor outcome, WMA (cystic lesions, white matter loss, delayed myelination, thinning of the corpus callosum, ventriculomegaly) are strongly related to cerebral palsy and other motor disabilities (Anderson et al., 2015; van't Hooft et al., 2015). In the comprehensive review by, van't Hooft et al. (2015) compiled a meta-analysis of articles published between 2000 and 2013 concerning the prediction of motor sequelae in preterm infants (≤ 32 weeks GA) using qualitative MRI at TEA. One of the criteria used by these authors was the comparison of patients with normal MRI or mild MRI abnormalities vs. patients with moderate-to-severe MRI abnormalities, including WMA, DEHSI, and brain abnormality. The article reported that qualitative MRI (mainly moderate-to-severe WMA) has an acceptable prognostic value for predicting cerebral palsy (sensitivity of 77% and specificity of 79%) and motor function (sensitivity of 72% and specificity of 62%). However, DEHSI lacks prognostic value (Broström et al., 2016; van't Hooft et al., 2015).

Neonatal MRI abnormalities are also associated with cognitive outcome. WMA detected by neonatal MRI have long-term consequences. Two follow-up assessments that included measures of general intellectual ability, language development, executive functioning, and behavior at 4 and 6 years of age showed functional decline according to WMA severity across all domains. Signs of WMA, such as punctate lesions and white matter loss, were associated with later neurocognitive outcomes (Woodward et al., 2012). It has also been reported that neonatal moderate-to-severe WMA predicts executive functioning at preschool age (Woodward et al., 2011) and other cognitive abilities including language development, attention, and processing speed learning capacity at 7 years of age (Murray et al., 2014; Reidy et al., 2013). However, language abilities are differentially associated with neonatal WMA; for instance, phonological awareness, semantics, grammar, and discourse were affected by WMA, but this

abnormality was not significantly associated with pragmatics (Reidy et al., 2013). Macrostructural and microstructural corpus callosum abnormalities that result from prematurity in very preterm infants also correlated with adverse neurodevelopmental outcomes at 2 years of age measured with the Bayley Scales of Infant Development (BSID-II) (Thompson et al., 2012). On the other hand, GMA have also been associated with language, cognitive and motor delays and cerebral palsy at 18–24 months of age (Slaughter et al., 2016; Woodward et al., 2006). Omizzolo et al. (2014) reported that abnormalities of the basal ganglia and the thalamus in very preterm infants were the strongest predictor of memory and learning performance outcomes at 7 years of age. These structures are linked to memory and subsequently to learning. Nevertheless, future research is still needed to establish the relationship between qualitative GMA detected by MRI at TEA and long-term neurocognitive disorders in children and adolescents with a history of prematurity.

5. Neonatal and pediatric quantitative neuroimaging

Quantitative neuroimaging consists of a set of imaging techniques that allow one to make elemental numerical measurements (e.g., distances, perimeters, areas, thickness, volumes, indexes), construct quantitative maps (e.g., diffusion maps, fractional anisotropy maps), and obtain complex statistical images of the brain (e.g., statistical parametric maps). Hence, techniques such as US (Cruz-Martínez et al., 2011), EEG (Bosch-Bayard et al., 2012; Harmony et al., 1995), MRI (Hüppi et al., 1998; Kesler et al., 2004; Ment et al., 2009a; Tumor et al., 2014), PET/CT (Basu et al., 2011), and SPECT (Yamauchi et al., 2014) can be considered quantitative neuroimaging techniques. However, quantitative MRI (advanced neuroimaging techniques) seems to be the most promising tool for the neurological diagnosis and prognosis of surviving preterm infants (Anderson et al., 2015; Benders et al., 2014; de Vries et al., 2013; Setänen et al., 2016). For this reason, this review focuses on quantitative MRI.

5.1. Quantitative MRI

The main objectives of quantitative neonatal and pediatric MRI are the formal computational analysis and interpretation of images (Morel et al., 2016), the measurement and characterization of “subtle” pathologies (de Vries et al., 2015; Hüppi and Dubois, 2006; Inder and Hüppi, 1999; Ment et al., 2009a), and the use of sophisticated algorithms to predict motor, neurocognitive, and behavioral disabilities (Rathbone et al., 2011; Rennie and Kendall, 2015; Rose et al., 2015). Essentially, quantitative MRI of the brain seeks to measure and model brain structure, function, and connectivity, and in the case of perinatal brain injury, it seeks to provide more detailed macrostructural (vMRI), microstructural (dMRI), and functional (fMRI) information that is not considered by subjective “qualitative” approaches. Currently, quantitative MRI uses modern scientific workflow approaches that can draw together neuroimaging data processing routines from across multiple software packages, linking them together to implement end-to-end processing and analytic solutions. These solutions not only lead to detailed mathematical and statistical results but also help to improve the reproducibility of measurements and reduce the post-processing duration (Dinov et al., 2010; Van Horn and Toga, 2014). In this manner, diffusion MR data can be reconstructed and used to measure the degree of connectivity between brain regions delineated with structural MRI, which can analyze blood flow or metabolic changes seen in functional imaging. In the following sections, we describe several of these imaging methods commonly used to quantify brain alteration in pediatric patients.

5.1.1. Volumetric MRI

Volumetric MRI (vMRI) is a very helpful tool with potential use in the clinical environment. It is primarily used to detect “subtle” cerebral

and cerebellar abnormalities that are visually undetectable in premature population. Numerous MRI studies at TEA have reported reductions in brain tissue and cerebellar volumes in premature infants with perinatal risk factors and WMA (Inder et al., 2005; Keunen et al., 2012; Limperopoulos et al., 2005; Lind et al., 2011; Thompson et al., 2007). For example, in a large prospective longitudinal cohort study of 202 preterm and 36 term infants, Thompson et al. (2007) found reductions in the parieto-occipital, premotor, orbitofrontal, and sensorimotor regions of preterm infants. These last two regions showed marked reductions in cortical gray matter and unmyelinated white matter volumes. Deep gray matter was more affected in parieto-occipital and subgenual regions than in term controls. Interestingly, the authors of this study (Thompson et al., 2007) conclude that perinatal risk factors alter regional brain volumes in the preterm infant. The alteration patterns vary depending on the risk factors suffered by the infant. In addition to supporting the diagnosis, vMRI allows an objective and quantitative longitudinal follow-up to assess the impact of clinical risk factors and/or the evolution of perinatal brain injury (see Fig. 3-A) (Guo et al., 2017; Kersbergen et al., 2016). Recently, in another large longitudinal cohort study of extremely preterm infants with MRI studies at around 30 weeks postmenstrual age and again at around TEA ($n = 210$; 131 with serial data), authors (Kersbergen et al., 2016) reported decreased brain volumes on both scans. The longitudinal follow-up study showed that brain growth in this period is crucial and that risk factors such as low birth weight z-score, sex, prolonged mechanical ventilation, and surgery affect global brain volume. On the other hand, the brain injuries (GMH-IVH grade III, periventricular hemorrhagic infarction, c-PVL, cerebellar hemorrhages, or infarctions) had local effects on some structures including lateral ventricles (enlarged) and cerebellum (volume reduction). The correlation of these measurements with clinical outcomes of the premature neonate at different ages has been very useful for researchers to establish neurodevelopmental prognosis at early ages. In fact, reductions in brain

volumes at TEA are correlated with motor and neurodevelopmental outcomes in the first 2 years of life, as well as in late childhood and adolescence (Guo et al., 2017) (see Section 5.2 Motor and cognitive prognosis by quantitative MRI). Moreover, vMRI analysis also helps to detect structural abnormalities in late childhood and adolescence of populations with a history of prematurity and no previous vMRI studies when compared to healthy full-term children (de Kieviet et al., 2012; Ment et al., 2009b).

A correct segmentation is necessary for accurate measurements and volumetric 3D reconstruction. Manual segmentation is monotonous and time consuming, as well as subjective and operator-dependent; whereas automated segmentation allows researchers to identify, parcel, and create reproducible 3D reconstructions of more brain regions and in less time (for an example, see Fig. 3-B) (Devi et al., 2015). However, automated segmentation is a challenge in neonatal and infant MRI due to poor contrast between white matter and gray matter in T1- and T2-weighted MRI. Besides, the intrinsic complexity of volumetric processing requires specialists in neonatal neuroimaging.

5.1.1.1. Overcoming the neonatal and pediatric volumetric MRI challenges. It is essential for neonatal image processing (volumetric or other quantitative techniques) to accurately classify/segment tissue and delineate the white matter/gray matter boundary. This is challenging in neonates and infants due to poor contrast between white matter and gray matter in T1- and T2-weighted MRI, but sophisticated techniques are actively being developed to address this shortcoming. Specifically, recent efforts have led to the development of longitudinal atlases for mapping the infant neocortex, and such resources are likely to play a particularly valuable role in future pediatric neuroimaging research. Zhang et al. (2016), for example, developed a spatiotemporal, longitudinal atlas of the developing infant brain by decomposing longitudinally acquired MRI volumes using wavelets, and then accommodating spatial and temporal variability into these volumes via group-sparse construction. Similarly, Kim et al. (2016) developed multi-atlas approaches for tissue classification and obtained encouraging results that demonstrate the ability of their method to map cortical development and to reveal abnormalities of cortical folding associated with preterm birth. Researchers such as Moeskops et al. (2015) have successfully distinguished gray matter from white matter in very young brains by leveraging a multimodal—rather than a unimodal—approach to tissue classification. Since multimodal imaging is becoming increasingly commonplace in neonatal imaging studies, it is likely that the impact of image analysis methods that leverage several modalities and weightings will be of substantial and growing benefit to the field.

The structural properties of the developing brain are substantially more dynamic than in adulthood or typical aging, which indicates that the task of pediatric MRI atlas construction must not simply be concerned with quantifying and understanding how brain structure differs between childhood and adulthood. To generate a robust anatomic atlas of the developing brain, one must also be able to map structural changes as they occur as a function of time (Shi et al., 2010). This fundamental necessity of pediatric MRI processing has been acknowledged by Li et al. (2015), who developed a robust longitudinal brain atlas of the young brain after repeatedly scanning hundreds of children of various ages over several years in order to generate a four-dimensional (space + time) atlas of brain development. Such atlases, which accommodate brain changes as a highly dynamic—rather than static—and continuous—rather than discrete—process, are likely to become the norm for pediatric MRI processing, particularly when studying brain changes that occur very rapidly over several months or even weeks, as is often the case in neonates.

5.1.2. Diffusion MRI

5.1.2.1. Diffusion tensor imaging. Diffusion tensor imaging (DTI) is an advanced quantitative MRI technique that allows a non-invasive

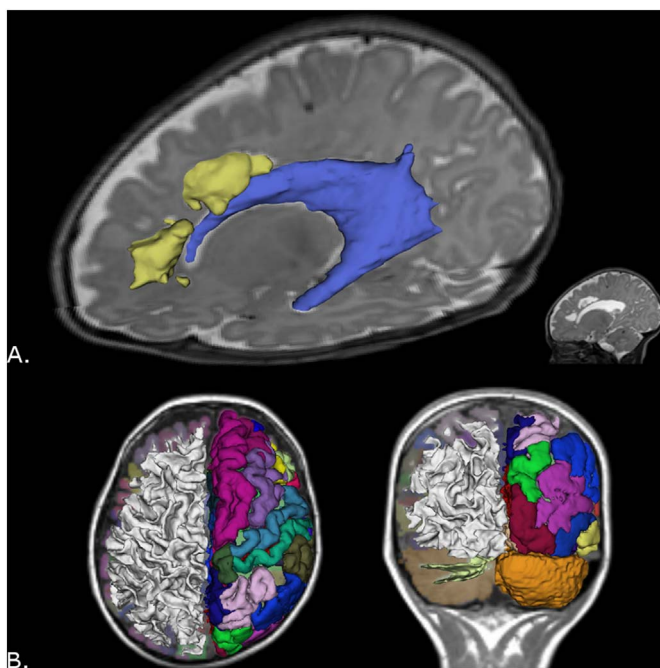


Fig. 3. A) Volumetric MRI at term-equivalent age in preterm infant with cystic-PVL. Note the cysts or focal component of cystic-PVL (yellow) and dilated left lateral ventricle (blue). B) Automated segmentation, parcellation and 3D reconstruction of the brain and cerebellum in healthy child at 8 years old. Right cerebral and cerebellar hemispheres: white matter 3D reconstruction. Left cerebral and cerebellar hemispheres: cortical parcellation and 3D reconstruction. Image B in radiological convention. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

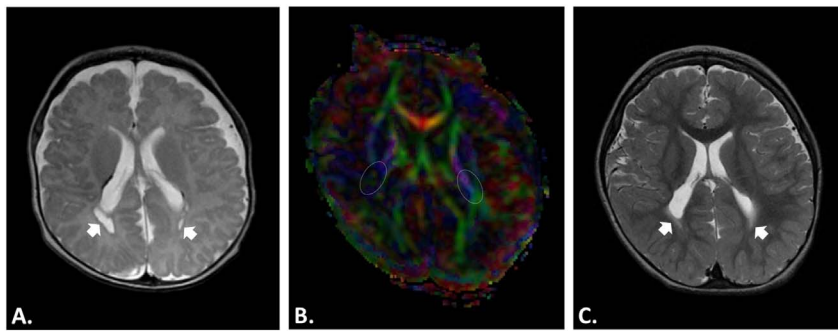


Fig. 4. Structural MRI and Diffusion Tensor Imaging (DTI). Male preterm infant (born at 30 gestational weeks) with cystic-PVL diagnosis and neurological follow-up in the first 2 years. **A–B)** T2 structural MRI and DTI at nearly term-equivalent age (TEA), around 47 weeks of postmenstrual age. **A)** T2 structural MRI with bilateral cystic lesions (arrows) and punctate white matter lesions. **B)** Color-coded fractional anisotropy (FA) map with evident white matter loss in the right posterior limb of the internal capsule (PLIC; right white oval) and bilateral reduction of FA values (right PLIC FA 0.21 vs. left PLIC FA 0.36), mainly in right side. A motor prognosis for this type of cases is possible; the major clinical outcome in these cases is a location-dependent spastic cerebral palsy (hemiplegia, diplegia, quadriplegia, etc.). **C)** T2 structural MRI at 24 months of corrected age with loss of cysts by cyst walls adjoining or “ventriculomegaly ex-vacuo.” The evidence of cyst in cystic-PVL can be lost at this stage

or before (this is one reason why MRI at TEA and follow-up for years is suggested). However, the diffuse component of cystic-PVL (arrows) is still evident at this age. The current diagnosis of this child is tripartite cerebral palsy with left side more affected. Images in radiological convention.

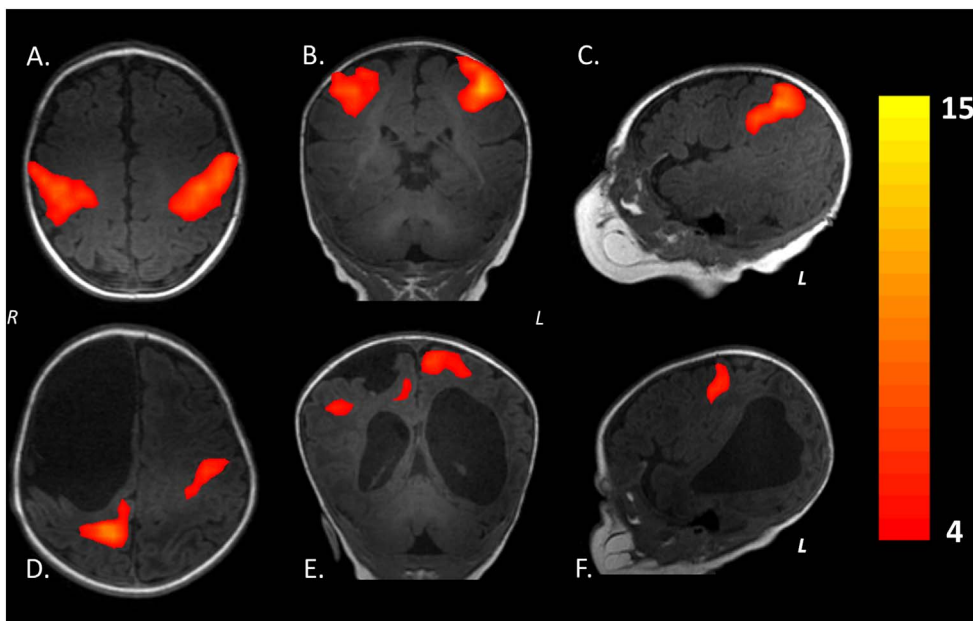


Fig. 5. Sensorimotor network by resting-state fMRI at term-equivalent age during physiological sleep (without anesthesia or sedation). **A–C)** Healthy female term infant. **D–F)** Male preterm infant (born at 35 gestational weeks) with clinical history of right periventricular hemorrhagic infarction. Currently with diagnosis by structural MRI of porencephalic cyst with ipsilateral communication between lateral ventricular system and the subarachnoid space. Note the change in resting-state pattern of sensorimotor network in relation to the healthy term infant. Images **A, B, D** and **E** are in radiological convention.

assessment of the microstructural characteristics of brain fasciculi. The diffusion tensor model is used to obtain parameters of water diffusion in the brain tissue, such as fractional anisotropy (FA), apparent diffusion coefficient (ADC), axial diffusivity (AD), radial diffusivity (RD), and the average of ADC or mean diffusivity (MD; sum of the radial and axial diffusivity divided by three) (Basser and Pierpaoli, 1996; Le Bihan, 1995). The quantitative information provided by DTI can be used in neonatal and pediatric clinical practice to detect diffuse white matter injury, since changes in water diffusion are early indicators of cell damage (Hüppi and Dubois, 2006). As demonstrated by Beaulieu (2002), FA values are closely correlated with the microstructure of brain fasciculi (axonal structure, density, and size of the fasciculus). RD is related to molecular diffusion in the perpendicular axis of the axon, providing information regarding oligodendrocytes (Concha et al., 2006) and the neurodevelopmental process (Hüppi and Dubois, 2006).

5.1.2.1.1. Diffusion parameters in preterm neonates and infants with white matter abnormalities. Diffusion parameters are age-related; FA increases while MD and RD decrease with age (Dubois et al., 2014). It has been shown that delayed neurodevelopment in premature infants with a perinatal diagnosis of WMA, GMH-IVH, and/or periventricular hemorrhagic infarction is accompanied by consistent changes in diffusion parameters (high RD/MD and/or low FA) (Arzoumanian et al., 2003; Cheong et al., 2009; Drobyshevsky et al., 2007; Pandit et al., 2013; Rose et al., 2015). Furthermore, the diffusion parameters could be used to support diagnosis in subtle pathology (Hinojosa-Rodríguez et al., 2013). Liu et al. (2012) found significantly increased

RD and MD, mainly in anterior and superior thalamic radiation, and significantly decreased FA in superior thalamic radiation in preterm infants with mild WMA. Similar results were observed in the corpus callosum (van Pul et al., 2012).

DTI parameter findings in preterm infants at TEA (or near-term) reveal microstructural alterations of major bundles of white matter in relation to risk factors and/or neurological comorbidity (Dubois et al., 2014; Kwon et al., 2014; Malavolti et al., 2016; Ment et al., 2009a; Pandit et al., 2013; Rose et al., 2014; Tusor et al., 2014). Moreover, some authors consider DTI of major white matter bundles at TEA or near-term age a more sensitive biomarker of later neurodevelopment than conventional MRI (Rose et al., 2014).

5.1.2.2. Diffusion tensor tractography. Through analysis of water anisotropic diffusion, it is possible to obtain in vivo 3D reconstructions of the white matter fasciculi based on the principle of directionality of water movement as modeled by the diffusion tensor (Ciccarelli et al., 2008). Tractography enables one to observe the morphology, location, distribution, and connectivity of white matter and its subsequent correlation with neurodevelopment (Anderson et al., 2015; Harmony et al., 2016; Hinojosa-Rodríguez et al., 2013; Kaur et al., 2014). Indeed, due to the anatomic and histological characteristics of the neuropathological spectrum that affects premature infants, the study and assessment of white matter fasciculi (primarily corticospinal tract and corpus callosum) by tractography and diffusion parameters (Braga et al., 2015) is likely an essential element of modern diagnosis.

There are other promising models for the study of white matter, including the study of crossing fibers (e.g., high-angular resolution diffusion imaging and diffusion spectrum imaging). However, the acquisition time for this analysis is an issue to consider in clinical practice (Dubois et al., 2014).

5.1.3. Functional MRI

Functional magnetic resonance imaging or fMRI is a neuroimaging technique for studying brain function using a type of MRI contrast called BOLD (Blood Oxygen Level Dependent). The nature of BOLD contrast originates mainly from changes in signal magnitude of T2*_w sequences, caused by the increased amount of oxygen (diamagnetic) in hemoglobin. The increase in oxyhemoglobin (with decrease in deoxyhemoglobin) is due to increased cerebral vascular flow that aims to cover the metabolic needs of the activated neurons. Thus, the positive BOLD signal apparently corresponds to the post-synaptic electrical activity of the local group of neurons (Lauritzen, 2005). The optimum analysis of the BOLD signal depends on the model adjustment of hemodynamic response function, which varies according to subject age (Harris et al., 2011; Seghier et al., 2006). There are even reports of subtle variations in the hemodynamic response function between preterm infants and term infants (Arichi et al., 2012). Current efforts in the field of pediatric neuroimaging are focused on accurately characterizing the hemodynamic response function in fetal and neonatal population. fMRI is not yet considered “diagnostic” in evaluating or predicting the outcome of this population. However, fMRI has two modalities that are promising for the study of the motor cortex in perinatal brain injury. These modalities are fMRI with motor task and resting-state fMRI (Kirton, 2013).

5.1.3.1. fMRI with motor task. A simple motor task, such as squeezing a ball with the grasp reflex or the active or passive mobilization of any limb, can produce a detectable change in the BOLD signal (Arichi et al., 2014; Graham et al., 2015; Van de Winckel et al., 2013), which provides reliable anatomical and functional information about the motor cortex of infants with perinatal brain injury (Kirton, 2013; Staudt, 2010). In this sense, Scheef et al. (2017) found by passive stimulation with extension/flexion during an fMRI study that the lateralization of the sensorimotor cortex is present in extremely preterm infants (born at 26 weeks of GA). Most notably, the authors highlight that the neonatal fMRI (using optimized coil settings) allows a robust and reproducible sensorimotor cortex analysis at the single subject level, which increases its feasibility in clinical practice. Furthermore, the use of this technique allows the study of the evolution and/or motor recovery of patients treated with rehabilitation therapies (Bleyenheuft et al., 2015).

5.1.3.2. Resting-state fMRI. In this modality, the temporal correlations of low frequency (< 0.1 Hz) in BOLD signal fluctuations are detected. These fluctuations represent the neuronal base activity in absence of an activity or predetermined motor task. Therefore, the resting-state fMRI reflects the synchronic and spontaneous electrical activity of neural networks in resting state (Fox and Raichle, 2007). The resting-state fMRI allows the developmental assessment of the various functional brain networks (e.g., sensorimotor, auditory/language, default-mode, salience, medial occipital, occipital pole, lateral visual/parietal, and two lateralized frontoparietal) in the first months of life (see Fig. 5) (Gao et al., 2015). It also helps demonstrate neuroplastic changes (Adhikari et al., 2015; Manning et al., 2015; Smyser and Neil, 2015) associated with early therapeutic intervention. However, this procedure neither diagnoses nor predicts the outcome in premature infants.

5.2. Motor and cognitive prognosis by quantitative MRI

Quantitative MRI is a powerful tool with a potential use in clinical practice for the prediction of short- and long-term motor and cognitive

sequelae. Several authors found an association between vMRI in premature infants at TEA and motor outcome, especially in the first 18–24 months of life (Cheong et al., 2016; Guo et al., 2017; Lind et al., 2011; Shah et al., 2006). Lind et al. (2011) described that specifically the cerebellum, total brain tissue, basal ganglia, cerebrum, frontal lobes, and thalamus volumes were significantly smaller, and that ventricle volumes were significantly larger in preterm children with neurodevelopmental impairment at 24 months of corrected age. Cheong et al. (2016) also reported a correlation between cerebellar volumes with motor scores at 2 years old.

Diffusion parameters also provide valuable information for motor prognosis (Arzoumanian et al., 2003; Malavolti et al., 2016; Rose et al., 2007; Roze et al., 2012). In fact, the most studied structures are the PLIC, corticospinal tract, and corpus callosum. Malavolti et al. (2016) found in another large prospective cohort of 193 neonates (24 to 32 weeks of GA) that the corpus callosum of the preterm infant with FA significantly lower has abnormal motor outcomes at 18 months corrected age. In general, FA values from the corpus callosum at TEA correlate with psychomotor development, and lower FA in PLIC is associated with adverse neurodevelopmental outcomes at 12–24 months of life (Kwon et al., 2014).

On the other hand, the sensorimotor activation reported by Scheef et al. (2017) reflects the possibility of using fMRI to distinguish between normal and abnormal motor activation (e.g., unilateral or asymmetric) of the sensorimotor cortex in the neonatal period, which is useful for motor prognosis. Abnormal fMRI findings at TEA correlate with motor outcome at 1 year of life in patients with unilateral lesions (Arichi et al., 2014). Therefore, it is possible that in a near future fMRI could be used as a biomarker in clinical practice with prognostic utility.

Although there are numerous references about the prognostic value of quantitative MRI in relation to motor outcome, there are few regarding quantitative MRI and cognitive outcome. Volumetric measures have shown that the volume of the corpus callosum measured during the first 4 months of age correlates with the mental index of the Bayley Scales of Infant Development in a group of infants evaluated at age 1 (Fernández-Bouzas et al., 2007). The same result was obtained by Thompson et al. (2012) at age 2. Significantly smaller brain volumes at TEA in preterm children with significantly delayed cognitive performance have been observed (Lind et al., 2011). Volumes of the lateral ventricles measured at birth also correlated with the Bayley Scales measured at 18 months adjusted age (Miller et al., 2005). Peterson et al. (2003) acquired measures of cognitive and motor development between 18 and 20 months of corrected age. Positive correlations between regional brain volumes in sensorimotor and parieto-occipital regions and developmental outcome were observed in preterm infants. According to the authors, regional brain volumes near term are a promising marker for predicting disturbances of cognitive outcome in preterm infants. Guo et al. (2017) focused on quantitatively assessing white matter injury in preterm neonates. They found that high white matter injury volumes predicted poor motor outcomes and frontal white matter injury volumes predicted adverse cognitive and language outcomes at 18 months corrected age.

In relation to diffusion measures as predictors, high white matter diffusivity measures of the inferior occipital and cerebellar region at TEA have been associated with increased risk of impairments in motor and executive function at 7 years in VPT children (Thompson et al., 2014).

6. Conclusions

Since neuropathological data about preterm survivors with antecedents of risk factors for perinatal brain damage are unavailable in the clinical practice, it is fundamental to bridge the gap between neuropathology and neonatal and pediatric neuroimaging. Considering the quantitative MRI findings on neonatal and pediatric neuroimaging over the past decade and the increasing acknowledgement of the perinatal

brain injury spectrum in premature population, new tools at hand should be used. Quantitative techniques capable of being performed in the clinical environment, such as delineating structural, connectomic, and functional brain abnormalities, exist in noninvasive neuroimaging. These techniques for cases presenting more subtle and diffuse patterns of perinatal brain injury offer a unique opportunity for pediatric neuroimaging diagnosis. Neuroradiological organizations should begin a formal process to critically evaluate current clinical classifications and develop guidelines and “best practices” to use in pediatric neurology.

Search strategy and scope of literature

References for this review were researched in Medline/PubMed and Scopus databases. The inclusion criteria were: 1) preterm infants with perinatal risk factors and/or perinatal brain injury, 2) neuropathological patterns in extremely and very preterm infants, 3) neuroimaging of the preterm infant at term-equivalent age, 4) neuroimaging at term-equivalent age and short- and long-term neurodevelopmental outcome, and 5) motor and cognitive outcome. The search strategy was based on the following terms: “preterm infant”, “preterm neonate”, “extremely preterm”, “very preterm”, “preterm brain injury”, “leukomalacia periventricular”, “non-cystic leukomalacia periventricular”, “diffuse leukomalacia periventricular”, “encephalopathy of prematurity”, “diffuse white matter gliosis”, “white matter abnormalities”, “gray matter abnormalities”, “MRI at term-equivalent age”, “germinal matrix hemorrhage - intraventricular hemorrhage”, “periventricular hemorrhagic infarction”, “conventional MRI”, “T1- and T2-weighted MRI”, “DWI”, “structural MRI”, “quantitative MRI”, “volumetric MRI”, “diffusion tensor image”, “DTI tractography”, “diffusion parameters”, “functional MRI”, “resting-state MRI”, “neurodevelopmental outcome by MRI at term-equivalent age”, “motor outcome”, and “cognitive outcome”.

Conflicts of interest

None.

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