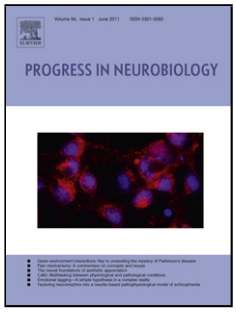

White matter injury and neurodevelopmental disabilities: a cross-disease (dis)connection

Elisa Cainelli, Filippo Arrigoni, Luca Vedovelli

PII: S0301-0082(20)30100-3

DOI: https://doi.org/10.1016/j.pneurobio.2020.101845

Reference: PRONEU 101845

To appear in: *Progress in Neurobiology*

Received Date: 7 October 2019

Revised Date: 19 May 2020

Accepted Date: 1 June 2020

Please cite this article as: Cainelli E, Arrigoni F, Vedovelli L, White matter injury and neurodevelopmental disabilities: a cross-disease (dis)connection, *Progress in Neurobiology* (2020), doi: https://doi.org/10.1016/j.pneurobio.2020.101845

White matter injury and neurodevelopmental disabilities: a cross-disease (dis)connection

[1]Elisa Cainelli, [2]Filippo Arrigoni, [3]Luca Vedovelli

[1] Department of Developmental and Social Psychology, University of Padova, Padova, Italy

[2] Neuroimaging Lab, Scientific Institute, IRCCS E. Medea, Bosisio Parini, Lecco, Italy

[3]Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic, Vascular Sciences, and Public Health, University of Padova, Padova, Italy.

Corresponding author: Luca Vedovelli, Department of Cardiac, Thoracic, Vascular Sciences, and Public Health, University of Padova, Via Leonardo Loredan 18, 35131 Padova, Italy. Tel. +393489235215 – luca.vedovelli@unipd.it

Highlights:

- Undetectable white matter injury is an essential determinant of neurodevelopmental outcome
- The mechanism is probably reactive oxygen species-related
- Several imaging approaches and biomarkers are being developed to overcome detection limitations
- Recent findings suggest that assisted development could ameliorate adverse effects

Abstract

White matter (WM) injury, once known primarily in preterm newborns, is emerging in its non-focal (diffused), non-necrotic form as a critical component of subtle brain injuries in many early-life

diseases like prematurity, intrauterine growth restriction, congenital heart defects, and hypoxic-ischemic encephalopathy. While advances in medical techniques have reduced the number of severe outcomes, the incidence of tardive impairments in complex cognitive functions or psychopathology remains high, with lifelong detrimental effects. The importance of WM in coordinating neuronal assemblies firing and neural groups synchronizing within multiple frequency bands through myelination, even mild alterations in WM structure, may interfere with the cognitive performance that increasing social and learning demands would exploit tardively during children growth. This phenomenon may contribute to explaining longitudinally the high incidence of late-appearing impairments that affect children with a history of perinatal insults.

Furthermore, WM abnormalities have been highlighted in several neuropsychiatric disorders, such as autism and schizophrenia. In this review, we gather and organize evidence on how diffused WM injuries contribute to neurodevelopmental disorders through different perinatal diseases and insults. An insight into a possible common, cross-diseases, mechanism, neuroimaging and monitoring, biomarkers, and neuroprotective strategies will also be presented.

Keywords: white matter, neurodevelopment, connectivity, myelin

1. Introduction

Addressing white matter injury (WMI) is emerging as vital to ensure the normal development of neonates and infants suffering from brain damage. Once mostly known and studied in premature newborns, WMI was detected with similar patterns in the most frequent pediatric diseases involving early brain insults, such as prematurity, intrauterine growth restriction (IUGR), congenital heart defects (CHD), and hypoxic-ischemic encephalopathy (HIE). In this review, we will focus on diffused WMI (in contrast to focal necrotic injuries) due to its involvement in long-term cognitive development

and the difficult detection with conventional diagnostic tools. We will start with the cellular and molecular mechanism of injury, expanding the scale to its micro-anatomical consequences (impaired myelination), and their implications for cognition and neurodevelopment. Finally, we will describe how biomarkers, neuroprotective strategies, and clinical improvements could ameliorate adverse outcomes in affected children.

2. Mechanisms of Injury

In the last few decades, improved care has increased survival and diminished the severe complications of most perinatal diseases. Brain injury manifestations have shifted from necrotic cerebral lesions to milder, diffuse injury that profoundly impacts the development of complex cognitive functions, long-term neurodevelopment, and, ultimately, quality of life.

White matter (WM) is the region of the central nervous system rich in myelinated axons. Mitigated Diffused WMI is a condition of widespread disruption of normal myelination of axons by oligodendrocytes. The terminal maturation of oligodendrocyte progenitor cells is arrested at an immature stage by the action of reactive oxygen species (ROS). According to Back (Back, 2017), the underlying cause of late oligodendrocyte progenitor (preOL) vulnerability to ROS has not been established. It is not known whether the levels of antioxidant enzymes in preOLs are inherently downregulated during normal lineage progression. Instead, it is increased glutathione peroxidase that makes mature oligodendrocytes resistant to oxidative stress (Baud et al., 2004). Back's 2017 review states that preterm birth is believed to delay the expression of these enzymes. It is also possible that the gestational antioxidant enzyme expression window is missed due to premature delivery. Therefore, it is likely that the reduced availability of antioxidant enzymes in the preterm WM contributes to oxidative stress-induced preOL damage. Oxidative distress induces preOL death through caspase-mediated apoptosis, which could precede necrosis if the amplitude and power of

the insult are large enough. Global oligodendrocyte (OL) families' cellular reaction to oxidative injury is quite peculiar and has only recently been elucidated. The presence of ROS induces a vigorous proliferation of OL progenitors (an earlier, stem-like family OL) to replace the damaged preOL population that, once largely restored, fails to differentiate into myelin-forming mature OL (Jakovcevski et al., 2009), resulting in a population of cells that is of appropriate size but unable to fulfill its primary task of axon myelination (Figure 1).

The mechanism of OL dysmaturation is probably multifactorial, involving both cellular and extracellular matrix factors. Clues from developmental signaling pathways indicate that Shh, Notch, bone morphogenetic proteins (BMPs), and Wnt play important roles in regulating OL development and myelination ability (He and Lu, 2013). Reactive astrocytes in demyelinating lesions are known to regulate many of these pathways by increasing their expression of BMPs and Jagged 1, thus inhibiting preOL differentiation through Notch signaling activation (Grinspan, 2015).

Wnt signaling has also been described as playing a pivotal role in preOL fate determination. In particular, Wnt signaling activation inhibits OL differentiation; intriguingly, the loss of the intracellular β-catenin effector TCF4 impairs OL differentiation, resulting in delayed myelination and disrupted remyelination (Zhao et al., 2016). Moreover, inhibitors of glycogen synthase kinase 3 (e.g., lithium), known to activate the β-catenin transcriptional complex, promote oligodendrocyte progenitors' maturation and WM remyelination in adults through decreased Notch 1 signaling (Makoukji et al., 2012; Rampazzo et al., 2013).

All of this evidence suggests that in a predisposing scenario of antioxidant imbalance, different physiological mechanisms (e.g., hypotension, hypoxia, episodes of low cardiac output, impaired vascular reactivity, and development) induce an abrupt ROS increase that interrupts the normal development of myelin-forming cells in a critical window of neural circuitry development via direct and secondary (after attacking proteins and lipids) signaling.

3. Development and Outcome

Diffused WM injuries are a key component of pediatric neurocognitive and neuropsychiatric disorders, including neuropsychological and behavioral disorders that are generally milder than those observed in children with routinely detectable WMI (e.g., cerebral palsy) but with a higher prevalence and consequences that affect the quality of life of affected children and families. Moreover, the incidence is growing (Atladóttir et al., 2007), and school and sanitary services are increasingly overloaded.

3.1 White matter and cognition

Although a growing body of evidence supports a crucial role for diffused WM injuries in the development of a broad spectrum of infancy and childhood disorders, our knowledge about the link between WM and cognition is based mainly on studies of aging. Thus, the early pathophysiology of WM-related neurodevelopmental disturbances remains poorly understood.

Comprising roughly half the total brain volume, WM tracts course throughout the brain, unifying cortical and subcortical gray matter regions into functional neuronal ensembles, representing the structural foundation of brain connectivity (Sporns et al., 2005). However, although the role of WM in the organization of the distributed neural networks is critical (Catani et al., 2012), classical studies have focused on defined structures (e.g., optic tract and arcuate fasciculus) and their relationship in a well-characterized primary function. By contrast, studies interested in high-order cognitive functions have historically focused on the cerebral cortex paying scant attention to other brain areas and systems (the “corticocentric myopia”) (Parvizi, 2009), such as WM and subcortical gray assemblies. Studies have thus underestimated the extent to which the presence of *anatomical*

connectivity is a prerequisite for functional networks, and that *structural* connectivity determines the properties of *functional* connectivity (Bullmore and Sporns, 2009).

WM is the last maturational process to be completed and is also the first that is affected by aging. WM abnormalities affect primarily cognitive proficiency; in the most severe cases, they may cause evident neuropsychological deficits or psychiatric symptoms. Sustained attention deficits, executive dysfunction, memory retrieval deficits, confusion, depression, fatigue, and a general slowing of cognition may be particularly salient and are typical of patients with WM disorders. Symptoms of WM disorders may overlap with those of cortical and subcortical gray structures, but, taken together, they show a unique profile of cognitive deficits.Typical diseases, with a demonstrated WM origin, characterized by this spectrum of deficits, are vascular WM dementia, multiple sclerosis, systemic lupus erythematosus, and traumatic brain injury (for a review, see (Filley and Fields, 2016)).

Interesting insights into WM functions have recently come from studies of healthy and young patients. Differences in normal WM patterns are associated with differences in performance in complex abilities, such as arithmetic (Matejko and Ansari, 2015), music (Ullén, 2009), and inhibition abilities (Forstmann et al., 2008).

Finally, even in the absence of the structural abnormalities typical of WM disorders and of overt brain damage, alterations in connectivity associated with WM dysfunction characterize several neurodevelopmental and neuropsychiatric disorders, such as autism spectrum disorder (ASD), dyslexia, and attention-deficit hyperactivity disorder (ADHD) (Aoki et al., 2017; Mathalon and Sohal, 2015). These disorders have also been associated with WM abnormalities in premature children (Fischi-Gómez et al., 2015; Rogers et al., 2016, 2012). Though the incidence of such neurodevelopmental disorders is very high in children with a history of pre-perinatal insults, the problem has not been well-addressed (as explained below).

The pathophysiological mechanisms underlying WM's contribution to abnormal cognition and behavior are only partially understood, but most probably involve the generation of ROS that disrupt oligodendrocytes' maturation and, ultimately, myelin formation. Glial cells and myelinated axons determine the speed and coordination of action potential propagation through neuronal fibers and neurons (Salami et al., 2003). It has been suggested that WM may exert a regulatory function on speed and timing of activation across neural networks, maintaining oscillatory synchronization within and between neural coalitions (Bells et al., 2017; Fields, 2015; Pajevic et al., 2014). Coordination, through the phase and amplitude coupling of oscillatory activity of large assemblies of neurons across long-distance cortical networks, allows gating of sensory stimuli and facilitates the combination of different information that results in high-order cognitive processes (Alonso et al., 1996; Engel et al., 2001; Engel and Singer, 2001; Singer, 2009). However, the direct link between altered integrative patterns (i.e., the speed at which the information from different brain regions is combined once it has been processed in specialized regions) and cognitive task performance is still unknown (Fischi-Gomez et al., 2016). Conduction delays may have a profound effect on coupling oscillatory activity in the brain, and even small changes in myelination can produce substantial effects on oscillatory activity coupling (Pajevic et al., 2014). Subsequent by-products of primary WM abnormalities are also possible. Myelin defects that degrade impulse conduction may result in impaired trophic support for axons by OL, with consequent axonal and neuronal degeneration (Lee et al., 2012). Whereas myelin damage slows network activity, the superimposed loss of axons may preclude any neural conduction and render the network inoperative. Moreover, defects in myelination can not only diminish maximum impulse speed but also alter spike timing in physiologically "slow" tracts, profoundly influencing neural circuit dynamics and tuning, ultimately affecting cognitive functions (Cheng and Carr, 2007; de Hoz and Simons, 2015; Pajevic et al., 2014; Seidl et al., 2014).

The operation and coordination of highly distributed brain areas require extensive WM tracts for long-range transmission of communication. Even though classical studies have focused on the primary functions underpinned by a single or a set of clustered brain structures, the complex neuroanatomical WM infrastructure is especially crucial for widespread complex high-cognitive functions, such as executive and social skills. The distributed nature of neural networks underlying complex functions increases their vulnerability to brain injuries and disease (Ameis and Catani, 2015). Thus, it is not surprising that executive and socio-cognitive deficits are the most common symptoms observed across a wide range of psychiatric and neurological disorders involving WM abnormalities (Cotter et al., 2018).

3.2 White matter and neurodevelopment

Maturation of WM is a long-term process, beginning during late gestation and continuing through childhood (when myelin formation is rapid) and adulthood (when WM volume peaks at around 50 years of age) (Benes, 1989; Liu et al., 2016; Muetzel et al., 2015). MRI studies on brain connectivity show that cerebral circuitries progress toward more efficient networks to support a global and local exchange of information mostly during the third trimester of pregnancy and the first months of life (Tokariev et al., 2019). Furthermore, the macro-structural network architecture required for normal brain function is already present at birth (van den Heuvel and Sporns, 2011).

WM development is an extremely complex process, regulated by multiple intrinsic and extrinsic signals during development and throughout life (Filley and Fields, 2016; Rice and Barone, 2000). Interruption of these processes may lead to a structural reorganization of the available resources in order to adapt to constraints. The cause of many disorders, ranging from ASD to ADHD, is thought to have neurobiological origins in the early phases of brain development (Schonwald and Lechner, 2006). During development, children refine their abilities to use and manipulate environmental information; abstract reasoning abilities and goal-directed behaviors emerge. Due to the prolonged

developmental window, subtle alterations in WM structure may not become evident until the increasing environmental demands (i.e., school) highlight a lack of complex and efficient reasoning skills. This phenomenon may contribute to explain longitudinally the high percentage of tardive impairments that affect children with a history of pre-perinatal insults, such as prematurity, IUGR, CHD, and HIE.

Although there is intriguing preliminary evidence, studies that specifically address the association between impairment and cerebral abnormalities in children with a history of pre-perinatal insults are still scarce. Most evidence of the underlying cerebral correlates of neurocognitive impairments in such children comes from adult models and from studies showing aberrant WM connectivity patterns in other pediatric populations. In the following paragraphs, we briefly review the current knowledge about these conditions; we reported typical deficits and major findings on the underlying cerebral substrate from neuroimaging studies in Table 1.

Prematurity and IUGR have been identified as the cause of one-quarter of cases of special educational needs because of sensory, motor, and intellectual disability (Mackay et al., 2013). Despite advancements in perinatal care, these babies are susceptible to a broad spectrum of developmental deficits, ranging from severe neuromotor disabilities to mild cognitive impairments. At its early stages, brain development can be influenced by the inappropriate early *ex-utero* environment as well as by other adverse circumstances, such as conditions leading to premature birth or IUGR and associated medical complications. Diffuse WM injury is the most widely recognized contributing neuropathological process behind reported disabilities (Volpe, 2009), confirming that WM development is particularly vulnerable during the early phases of life (Skranes et al., 2007; Young et al., 2017). Several WM tracts may be affected, including motor pathways such as the corticospinal tract and the corpus callosum; such alterations may persist after the neonatal period (Ment et al., 2009). Alterations were also reported by studies of brain connectivity (Young et al., 2017). The altered

microstructural organization has been demonstrated in many fiber tracts throughout the infancy, childhood, adolescence, and young adulthood of ex-premature patients (Li et al., 2015).

CHD are the most frequent congenital malformation worldwide, with an estimated incidence of 0.8% of live births (van der Linde et al., 2011). A high incidence of neurodevelopmental deficits has been reported among children with CHD who survive without major sequelae (Sarrechia et al., 2015; Simons et al., 2010). These deficits also persist long-term (Brewster et al., 2015). Interestingly, even in the absence of overt structural lesions detected by conventional MRI, brain abnormalities identified by quantitative MRI are prevalent in young people with CHD, and these abnormalities are associated with poorer neurocognitive outcomes (Bolduc et al., 2018).

Alterations in the structural organization of complex brain networks have been suggested in these patients (Bolduc et al., 2018; Panigrahy et al., 2015). The term “cerebral white matter immaturity” has been suggested in MRI studies because a delayed white matter development was noticed in term CHD children, with a pattern similar to that observed in preterm babies (Dimitropoulos et al., 2013). The resemblance between preterm babies and CHD children has been described in neonates and led to the hypothesis that these groups share a common dysmaturation disorder (Licht et al., 2009). It has also been suggested that reduced pre- and perioperative blood flow to the brain during infancy can increase the risk of WM abnormalities for patients with CHD (Andropoulos et al., 2010), resulting in WM injury comparable to that found in premature infants (Miller et al., 2007). Since preoperative injuries are not preventable, research has focused on the potential onset of brain injury during and post-cardiac surgery, trying to develop biomarker-based neuroprotective strategies to improve surgical techniques in order to ameliorate overall neurological outcome (Graham et al., 2019; Vedovelli et al., 2016a, 2018).

HIE is a neonatal neurological syndrome characterized by central nervous system depression, seizures, and abnormal electroencephalogram (EEG). It is caused by perinatal asphyxia that leads to

metabolic acidosis and low Apgar scores, and it accounts for 50% of global neonatal mortality, with significantly impaired neurodevelopment in most survivors (Parikh and Juul, 2018). Randomized clinical trials have demonstrated that the introduction of moderate hypothermic treatment is associated with a reduction in death and neurologic impairment at short-term follow-up (Azzopardi et al., 2009). However, the few available studies evaluating long-term outcomes found a comparable percentage of so-called "minor dysfunctions." These dysfunctions comprise a broad spectrum of neuromotor and neurodevelopment problems that are less disabling than major sequelae but strongly affect the quality of life (Shankaran et al., 2012; van Schie et al., 2015).

The increased use of neuroimaging techniques and MRI, in particular, has been useful in recognizing the pattern of brain injury (de Vries and Jongmans, 2010). Two main patterns of injury have been distinguished with MRI in HIE full-term neonates: a basal-ganglia-thalamus pattern predominantly affecting the central grey nuclei and perirolandic cortex bilaterally, often seen following an acute asphyxia event (Okereafor et al., 2008); and a predominant watershed pattern of injury, which is also seen following "prolonged partial asphyxia" (de Vries and Jongmans, 2010). The vascular watershed zones are involved, affecting WM and, in more severely affected infants, the overlying cortex, as well. Children affected only by a WM injury usually have a better prognosis; however, several cognitive and behavioral problems have been reported (Mercuri et al., 2000; Steinman et al., 2009).

Despite the clinical differences between the diseases discussed above, mild/moderate conditions share common neurocognitive and neuropsychiatric impairments. Indeed, the main deficits reported for all groups of patients are attention problems and executive and social dysfunctions. All of these skills are considered disturbances of connectivity and are highly correlated to the integrity of WM (Bettcher et al., 2016; Klarborg et al., 2013; Wang et al., 2018).

Furthermore, abnormal social skills, attention, and executive functions are thought to be a core problem in several neuropsychiatric syndromes, such as ASD and ADHD. These syndromes are the

most highly reported neurodevelopmental disturbances in children with a history of pre-perinatal insults (Table 1). These syndromes are thought to have neurobiological origins (Schonwald and Lechner, 2006) and are associated with WM abnormalities (Aoki et al., 2017). It has recently been proposed that some brain features may underlie a patient's risk of experiencing any neuropsychiatric problems, as well as the occurrence of specific symptoms (Zald and Lahey, 2017). WM, as the backbone of efficient neural communication, has been suggested as a possible candidate substrate (Neumann et al., 2020).

Therefore, pre-perinatal insults offer a unique possibility to study the pathophysiology of many over-represented and major disturbances and to increase our understanding of cerebral functioning under both normal and pathological conditions. Unfortunately, several questions have been only minimally addressed to date.

4. Neuroimaging and Neuromonitoring

The anatomical and structural integrity of WM in the neonatal period can be easily and noninvasively assessed by employing neuro-imaging techniques. Cerebral ultrasonography (US) can be used as the first-level method for WM assessment as it is fast, cheap, safe, and can be performed at the bedside. US identifies WM damage related to cystic periventricular leukomalacia (PVL), while it is less sensitive in the case of non-cystic PVL, where only aspecific hyper-echogenicity of WM can be noted.

However, the predictive value of US for cognitive and motor outcomes is limited (Sewell and Andescavage, 2018). In any case of WM/cerebral abnormalities detected using US, or in the case of a negative US with clinical evidence of brain damage, MRI must be performed. MRI is a safe technique, with no long- or short-term side effects on patients and, in the neonatal period, can be performed during natural sleep (after feeding) in most cases, with no need for pharmacological

sedation. Conventional MRI (including T1- and T2-weighted sequences optimized for neonates) provides a detailed anatomical, qualitative characterization of WM, myelination, and brain damage. Besides the importance of MRI in the diagnosis of several acute severe brain injuries (e.g., HIE, PVL, venous thrombosis and hemorrhage, hypoglycemia), its systematic use in neonatal medicine revealed new and less specific patterns of WM abnormalities like punctate WM lesions (PWML) and diffuse excessive high signal intensities (DEHSI) in a high proportion of preterm infants (Volpe, 2009). PWML are small, non-cystic lesions showing a high signal on T1-weighted sequences and a low signal on T2-weighted sequences, usually localized in coronae radiatae, optic radiations, and periventricular WM. They can be isolated in preterm infants and neonates with CHD or be associated with more severe injuries like HIE, cystic PVL, and hemorrhages (Nguyen et al., 2019). The number and volume of PWML have been associated with poor motor outcome, while their location in the WM seems to correlate with poor language and cognitive deficits (Guo et al., 2017; Tusor et al., 2017). The underlying cause of PWML (either genetic or acquired/hypoxic) plays a role in determining the outcome (Hayman et al., 2019).

DEHSI is defined as the increased signal intensity in the periventricular, and subcortical WM in T2-weighted MRI acquired around term-equivalent age (Maalouf et al., 1999). Such abnormalities can be detected in up to 80% of preterm babies; however, their cause remains unclear. It has been suggested that DEHSI represents a diffuse WM abnormality due to a disorder of microstructure formation in a critical period of brain development (Broström et al., 2016). Despite some initial concerns about the possible adverse prognosis and outcome of patients with DEHSI, more recent evidence suggests that, if isolated in the brain, DEHSI is not associated with cognitive or motor impairment (Kwon et al., 2014).

However, research on the prognostic role of conventional MRI gives conflicting results for prediction of motor outcomes, and predicting cognitive outcome in infants with subtle WM injury remains

challenging (Guo et al., 2017; Van't Hooft et al., 2015). The quantification of WM damage in neonates could benefit from the recent development of new MRI techniques and from the implementation of novel methods of analysis that have come into play in the last few years.

Such analytical methods include diffusion-weighted imaging (DWI), one of the most-used techniques for the characterization of WM organization. It is based on the capability of MRI to detect and measure the free and hindered movements of water molecules within the brain, which correlates to axonal and tract integrity and fiber orientations. The signal measured with DWI acquisitions can be modeled with different approaches to obtain quantitative metrics for the WM. Diffusion tensor imaging (DTI) is one of the most well-known and commonly applied models for DWI analysis (Basser, 1995). It provides several measurements—like mean diffusivity (MD), fractional anisotropy (FA), axial and radial diffusivity (AD, RD)—that can track WM modifications occurring in the neonate that are related to brain damage. Application of MD and FA has highlighted differences in the maturation and microstructure of WM between preterm and term babies, as well as the presence of impaired organization in infants with WM injuries (Pecheva et al., 2018). Moreover, DTI metrics measured in neonates (mostly preterm babies) have also been used to predict neurodevelopmental outcomes, showing promising results (though as yet limited to small cohorts) (Feng et al., 2019; Hu and McAllister, 2019; Kidowaki et al., 2017).

However, DTI has some limitations. It can only identify one fiber population for each voxel, thus limiting its accuracy in reconstructing fiber tracts, and its metrics are less reliable in areas where the diffusion of water molecules has a non-Gaussian profile (Jones et al., 2013). To overcome these issues, other, more complex, and sophisticated models for DWI have been proposed.

Neurite orientation dispersion and density imaging (NODDI), for example, identifies different diffusion compartments within the brain and WM (intraneurite, extraneurite compartments, and cerebrospinal fluid) (Zhang et al., 2012). The intraneurite compartment represents axons and

dendrites, while the extraneurite compartment refers to glial cells and neuronal somas. NODDI measurements have been used to describe and quantify the process of dendritic arborization in the early stages of life and WM maturation in preterm neonates.

Constrained spherical deconvolution (CSD) is an alternative method for DWI processing (Tournier et al., 2004) that, compared to DTI, improved the reconstruction of WM tracts and introduced new bundle-specific measures like fiber density (FD) and fiber cross-section (FC) (Raffelt et al., 2012, 2017).

The main limitation preventing the extensive application of these new methods to neonatal WM imaging is that they require richer DWI datasets than DTI (higher b-values and more diffusion directions), which implies longer acquisition times. Moreover, the biological correlates of some of these measures are yet to be entirely determined and understood, thus challenging the interpretation of the collected data, especially in an immature WM context like that of neonates (Pecheva et al., 2018).

Besides DWI, MRI research in the last years focused on the development of new techniques and strategies for more accurate quantification of myelin content (Alonso-Ortiz et al., 2015; Heath et al., 2018; Ouyang et al., 2019). A technical review of these methods is beyond the scope of this work; however, a brief overview of the main techniques (magnetization transfer imaging, MTI; myelin water imaging, MWI; and quantitative susceptibility mapping, QSM) and their initial application in newborns will be provided to highlight their potential and limitations for the study of WM in neonates and the identification of useful prognostic biomarkers. It must be noted that none of the proposed MRI techniques directly measure myelin, but all are based on the interactions between protons, macromolecules, and the magnetic field.

MTI is based on the interactions and energy exchanges between protons bound to macromolecules (like myelin) sensitized by specific RF pulses and the surrounding free water. MWI takes advantage

of the difference in T2-relaxation times of water in different local environments. Water molecules entrapped within layers of myelin sheaths have shorter T2 values than extracellular or free water, and their contribution to the overall MRI signal can be measured as indirect quantitation of myelin content. QSM relies on the fact that myelin (and other materials) can induce local changes in MR signal intensity as well as small shifts in local magnetic fields that can be measured and mapped through the brain.

Like advanced DWI modeling techniques, myelin imaging methods require long acquisition times, which discourage their application on neonates. However, the introduction of stronger gradients and multiband methods in clinical scanners (Barth et al., 2016), as well as improvement of motion-correction algorithms, facilitates a reduction in scanning times, making the use of these techniques less challenging.

Indeed, all of these methods have been applied to neonates and children. MTI has been used to track WM changes in preterm babies (Nossin-Manor et al., 2015; van Buchem et al., 2001; Xydis et al., 2006). Zhang et al. recently demonstrated that from birth to 2 years of age, the magnetic susceptibility of WM measured by QSM evolves significantly and is highly correlated with the degree of microscopic myelin degree measured in pathology specimens (Zhang et al., 2019). Tortora et al. also showed that susceptibility could be used to monitor changes in normal-appearing WM of neonates undergoing germinal matrix hemorrhages (Tortora et al., 2018).

MWI has been used as an independent technique to calculate normative data in children three months of age and older (Dean et al., 2016). Otherwise, MWI has been used in combination with NODDI to measure g-ratio in newborns (Melbourne et al., 2016). The g-ratio is defined as the ratio between the inner and outer diameters of the myelin sheath (Stikov et al., 2015) of white matter fibers, and it is an interesting potential biomarker for monitoring WM integrity.

Finally, chemical exchange saturation transfer (CEST) MRI has been proposed as a technique that can provide molecular information about tissue integrity (Jones et al., 2018). It is still far from clinical applications; however, some promising results in neonates are available. In particular, Zheng et al. demonstrated that protein content in the WM of neonates measured by amide proton transfer (APT) imaging correlates with age and could provide valuable data about brain maturation at the molecular level (Zheng et al., 2016).

5. Neurophysiology

Ideally, the evaluation of early human brain development should combine both structural and functional information. Although brain imaging may make this possible, neurophysiological techniques, and particularly electroencephalography (EEG), provide complementary information on much faster time scales (milliseconds) and is a less expensive and more accessible technique than neuroimaging. The use of EEG in neonates is ideal given its non-invasive nature; however, its application to babies is challenging and requires adapting both data acquisition and post-processing procedures to deal with motion as well as signal changes throughout cerebral maturation.

Given that EEG represents the synchronous activity of neurons in the cortical surface beyond the skull, it does not allow a direct measure of WM interconnections. However, several EEG algorithms offer interesting insight into how cerebral areas work together in networks and how these networks relate to cognitive processes.

The traditional use of EEG correlates CNS functions, as well as certain dysfunctions and diseases, with characteristic EEG patterns on an empirical basis. Beyond this practice consolidated in the years, several experimental quantitative techniques are available. These methodologies, while allowing a more objective analysis, are useful to describe a wide range of cerebral dynamics, including frequency and phase spectra, topographic maps, covariance, and coherence structure—all potentially

important measures of neocortical dynamics and functional connectivity (M. Murias et al., 2007; Nunez et al., 2015). Networks inferred from EEG cortical currents could correspond to the underlying structural networks (He and Raichle, 2009; Ko et al., 2011), and cortical dynamics partially reflect observed WM connectivity across multiple brain rhythms (Chu et al., 2015). EEG functional connectivity at large scales is believed to be strongly influenced by WM axons, especially the cortico-cortical axons, which outnumber thalamo-cortical and callosal axons (Nunez et al., 2015).

Although cortical physiology has not been shown to fully reflect underlying brain structure, capturing the interplay between brain structure and spontaneous brain activity provides new opportunities to understand brain function and to find a reparative mechanism in neurodevelopmental diseases. An understanding of the way in which anatomical structure supports complex temporally organized brain activity is necessary to understand brain functioning and particularly higher cognitive processes. A relationship has been found between connectivity measures, intelligence (Thatcher et al., 2005), and ADHD (Michael Murias et al., 2007). These findings were confirmed by recent works on adult brains that show multiple frequency-specific networks correlating with normal and pathological behavior (Siebenhühner et al., 2016; Yu et al., 2017). Taken together, these studies suggest that EEG connectivity measures may be appropriate markers for a greater capacity to process information and for abnormal brain functioning. However, compared to MRI, EEG studies investigating neuronal communication in early development and the ways in which network function is affected by common medical conditions are currently scarce (Omidvarnia et al., 2014; Tokariev et al., 2016; Tóth et al., 2017).

In the perinatal period, brain development is characterized by an increase of neuronal network circuits, including thalamocortical, transcallosal, and intrahemispheric connections (Kostović and Judaš, 2010). The development of thalamocortical circuits and corpus callosum constitutes a central role in neuronal feedback (Jones, 2009). All these structures form the *connectome* (Sporns et al.,

2005) and constitute the building blocks for functional networks, allowing the development of neurocognitive capabilities (Grieve et al., 2008; Koolen et al., 2014).

At birth, spontaneous human EEG activity is already organized into multiplex functional connectivity networks in several frequency bands, which are reactive to changes in vigilance states. At earlier stages of maturation, human fetuses exhibit EEG activity characterized by the presence of intermittent bursts of activity; the temporal correlations between these intermittent bursts reflect early functional connectivity networks, and the increase of their synchrony is thought to reflect the increase of functional connectivity (Meijer et al., 2016; Omidvarnia et al., 2014; Tóth et al., 2017). In fact, intermittent-burst synchrony is sensitive to early brain lesions (Tolner et al., 2012), and may be predictive of compromised neurodevelopment (Omidvarnia et al., 2015). It has been shown that the most common clinical risk factors—preterm birth and neonatal HIE—lead to an alteration in connectivity (McLaren et al., 2019; Tokariev et al., 2019).

In infants with CHD, EEG connectivity measures are related to disrupted brain development, as also shown with MRI (Birca et al., 2016). Recent data on extremely low gestational age and late-preterm neonates highlight differences in functional connectivity as measured by EEG: in the theta frequency band, asymmetries between left and right hemispheres may underlie different developmental trajectories related to the gestational age, and the formation of long-range functional networks and thalamo-cortical connections (Cainelli et al., 2019).

In neonates with extensive (grade III and IV) germinal matrix hemorrhage, EEG has documented altered response to tactile stimulation of lower limbs, linked to a reorganization of somatosensory pathways (and in particular of thalamo-cortical connections) following injury (Whitehead et al., 2019). Similarly, different patterns of WM damage (like PVL) are associated, at the chronic stage, with disorganized EEG with abnormal morphology of background activity that correlates with the severity of the insult (Kidokoro et al., 2006; Okumura et al., 2002; Whitehead et al., 2017).

Other than EEG, neurophysiological techniques comprise the sensory evoked potentials (EPs) and event-related potentials (ERPs). Sensory EPs reflect the activity of the sensory pathways ascending to the cerebral cortex and early obligatory cortical responses to specific sensory stimuli (de Graaf-Peters and Hadders-Algra, 2006). Sensory EPs evaluate the functional integrity of the sensory systems, from the periphery to the cerebral cortex, and are routinely used for diagnosis and monitoring of several pathological conditions, while their role in mild-moderate conditions, probably involving alterations of WM, are poorly studied (Cainelli et al., 2018).

Unlike sensory EPs, ERPs are long-latency potentials elicited in response to stimuli requiring some cognitive function; thus, they provide a unique opportunity to evaluate higher-order cortical processes (Fellman et al., 2004). Specific neuropsychological paradigms can elicit different ERP components, which, although variable, show characteristics according to the supposed underlying cognitive operation stimulated by the task (Picton and Taylor, 2007). ERPs are generated in several association areas, making the identification of their neural generators very difficult. This makes ERPs more variable and less reliable for clinical use in neonatal neurology; however, there are several interesting applications (Suppiej et al., 2017, 2015, 2014).

In conclusion, neurophysiological techniques are relatively easy to implement and have the potential of being widely applied, but at the same time, signal interpretation and correlation to precise physiological events are difficult, limiting their diagnostic potential when examining subtle WM alterations.

6. Molecular Biomarkers

Imaging and neurophysiological assessments are useful to assess the presence and development of WMI. Progress in these techniques is refining their ability to detect even subtle abnormalities in brain structure and development. A drawback is that they are sometimes tricky to implement on a large

scale and that their interpretation requires specialized and experienced personnel. Moreover, the timeframe in which assessment is feasible is often incompatible with the rapid clinical management necessary for children. The integration of these techniques with biomarkers that permit a rapid assessment of disease onset and progression may fill the gap between the need for a rapid clinical decision process and precise characterization of the condition by imaging and neurophysiology. In this context, biomarker-level evaluation could be compared to imaging and neurophysiology (treated as gold-standard for diagnosis) and, finally, with the neurodevelopmental assessment. Once validated, a biomarker can serve as a quick and inexpensive tool at the bedside. In an optimal scenario, biomarkers could also be used as a sensitive pre-injury indicator to avoid disease onset, halt progression, and improve outcomes.

Biomarkers are a heterogeneous group of tests used as a proxy of a physiological or a pathological condition that cannot be directly assessed. Excluding radiological and physiological testing, biomarkers are usually small molecules that successfully combine sensitivity, specificity, and ease of assessment (both collection and quick response). Ideally, a biomarker is also able to identify the stage or degree of the underlying biological process and its response to treatments (Biomarkers Definitions Working Group., 2001).

Aside from the specificity and usually promising *in vitro* or animal results offered by biomarkers, their sensitivity is a critical point when seeking to mitigate WMI. A useful biomarker should have sensitivity at least equal to that of conventional MRI, and ideally, be as sensitive as more advanced imaging techniques. Such sensitivity will render it reliable at low or very low concentrations, allowing detection of even subtle impairments. The variability of conventional antibody-based assays (not unusually as high as 20% for inter-assay quantification) could be reduced by more precise techniques such as mass spectrometry, which can detect, in specific conditions, femtomolar concentrations of

analytes. Finally, since biomarkers are usually specific to a precise molecular process, direct correlation with long-term wide-spectrum neurodevelopmental assessment is also mandatory.

Brain injury biomarkers have mostly been studied in traumatic brain injuries and then translated to other pathological scenarios. Trauma leads to ROS injury initiated by the excitotoxic cascade, and it is followed by the inflammatory cascade that eventually disrupts the blood-brain barrier, leading brain-specific components to be found in the blood. Biomarkers are particularly useful in mild-to-moderate scenarios where injuries are challenging to identify, especially when used in combination with the investigation of multiple cellular pathways (e.g., neuronal and glial injury markers). Differentiation between multiple biomarkers from different origins is essential for targeted therapy selection (Diaz-Arrastia et al., 2014). Here, we briefly present the most promising molecular biomarkers of brain injury (not all specific to WMI) that may be useful in assessing WMI due to their peculiarities, sensitivity, and ease of assessment (Figure 2).

6.1 Glia – Glial fibrillary acidic protein

Glial fibrillary acidic protein (GFAP) is probably the most promising biomarker for brain injury involving WM in children. GFAP is an abundant intermediate filament that is released into the bloodstream only after astrocyte-specific injury (Guingab-Cagmat et al., 2013). GFAP seems to fully fit the requirements of specificity, readiness of release, and ease of assaying required of a diagnostic brain injury biomarker. GFAP can be measured in serum and quantified proportionally to the degree of the injury (Brunetti et al., 2014). It is strictly brain-specific and has already been linked to impaired neurodevelopment in children with CHD (Graham et al., 2019; Vedovelli et al., 2018). It is also elevated in MRI-confirmed brain injury during ECMO, defined as “acute neurologic injury or brain death” (Bembea et al., 2011) and in HIE (Chalak et al., 2014) patients. In HIE patients, only those with

moderate-to-severe HIE showed abnormal MRI signs (diffuse WMI and watershed infarcts), and GFAP was significantly higher in children with abnormal neurodevelopment. Interestingly, the GFAP peak seems to correlate with the rewarming phase of therapeutic hypothermia in both asphyxia (Chalak et al., 2014) and cardiopulmonary bypass (Vedovelli et al., 2016a, 2016b). One practical aspect of GFAP is that a threshold of 0.436 ng/ml in the blood is predictive of MRI injuries in pediatric patients during extracorporeal oxygenation (ECMO) (Bembea et al., 2011). Considering that simple commercial GFAP ELISA kits have a limit of detection of 0.02 ng/ml, the gap between 0.02 and 0.436 ng/ml could allow GFAP to be used to detect brain damage that would otherwise go unnoticed during conventional MRI.

6.2 Neurons – Ubiquitin carboxy-terminal hydrolase

Ubiquitin carboxy-terminal hydrolase (UCHL1) is mainly present in neurons, and in combination with glial GFAP, offers the potential to reduce the use of CT scans in patients with traumatic brain injuries. UCHL1 + GFAP is an example of how biomarkers could represent a useful tool to speed up the diagnostic process and to avoid the use of costly instrumental examination (Welch et al., 2016). The role of this combination in WMI is unknown, especially in the long term, but their synergy and sensitivity offer promise for future studies.

6.3 Other brain structures – Tau and myelin basic proteins

Tau (specific to axons) and myelin basic proteins (MBP, representing 30% of myelin proteins) are two other local brain-specific biomarkers with promising applications but with limited support in the literature (Yokobori et al., 2013). Tau and MBP have the theoretical potential to serve as a WMI biomarker in the acute phase of the injury, since MBP levels can predict the short-term outcome of pediatric brain injury (Berger et al., 2007), but the long-term evidence in humans is limited.

6.4 Cytokines

Infection or inflammation can sensitize the brain to injuries and make them more severe; but in a rat model, the combination of systemic lipopolysaccharide (LPS) and hyperoxia (80% O_2 for 24 h) showed a protective effect; this probably resulted from upregulation of IL-10 and superoxide dismutase expression, though white matter alterations and hypomyelination were still observed through OL maturation arrest (Brehmer et al., 2012).

Cytokines such as IL-10 are inflammatory mediators that readily cross the blood-brain barrier. They have a dual role of being protective and harmful, and their balance is critical in brain injury, even if their increments are non-specific. Among cytokines, IL-1beta promotes brain damage through ROS rise and, with IL-6 and TNF-alpha, its level is a proxy of WMI that could lead to cerebral palsy when measured in the amniotic fluid of women with complicated preterm gestation. Similarly, newborns at risk for WMI can be identified by the concentrations of IL-6 and IL-1beta in amniotic fluid (Yoon et al., 1997).

6.5 Micro RNA and Exosomes

Circulating micro RNAs (miRNA) are small, non-coding RNAs with emerging fundamental roles in numerous cell functions. Of particular interest, specific miRNA can discriminate between focal and diffuse brain injury (Yokobori et al., 2013). Exosomes are a specific population of extracellular nano-vesicles (max 100 nm diameter) that can cross all cellular barriers, with key roles in cell signaling and regulation. They form “packages” of nucleic acids, proteins, lipids, and other molecules that can travel long distances in the body and affect distant compartments, keeping their contents safe from degradation enzymes (de la Torre Gomez et al., 2018). Considering their signaling role, they could be

useful to detect cellular processes occurring far from where they are collected (i.e., in blood, urine, or other fluids).

6.6 Oxidative stress – isoprostanes, neuroprostanes, and isofuranes

Other non-specific oxidative stress markers such as malondialdehyde (Lv et al., 2015) include prostanoids, prostaglandin-like compounds produced by the oxidation of lipid membranes without enzymatic intervention. Isoprostanes and isofuranes are generated from arachidonic acid (and thus are ubiquitous) depending on oxygen concentration: isofuranes need more oxygen to form than isoprostanes. Neuroprostanes and dihomo-isoprostanes are generated from docosahexaenoic acid (DHA, 22:6 ω3) and adrenic acid (AdA, 22:4 ω6), respectively (Bultel-Poncé et al., 2016). DHA is abundant in neuronal membranes while AdA is concentrated in myelin; thus, their prostanoid derivatives are potential region-specific *in vivo* biomarkers of free radical damage. They have already been successfully used in a clinical setting (De Felice et al., 2011) to detect WMI in a human ex-vivo study on histopathological-confirmed periventricular white matter injury (PWMI). Interestingly, Back et al. (Back et al., 2005) also found that preterm infants diagnosed PWMI sustained a degree of oxidative damage in the periventricular white matter similar to that of term infants who sustained severe corticoneuronal injury in early HIE.

6.7 Metabolism

A simple measure of postoperative lactate in CHD children was able to predict survival and neurodevelopment after the age of 18 months (Cheung et al., 2005). More complex metabolomics studies using an untargeted approach are scarce, but a 3-year study unveiled a small group of four

metabolites (succinate, glycerol, 3-hydroxybutyrate, and O-phosphocholine) that correlate with the neurodevelopmental outcome (Ahearne et al., 2016).

In conclusion, biomarkers, particularly if used in combination, could be a key tool to screen and monitor the progression and response to therapy of brain injury (Graham et al., 2018). They permit not only timely intervention but can also guide the diagnostic and therapeutic processes in order to minimize the effects of the injury.

7. Neuroprotection

Methods to identify, avoid, or limit the effects of brain injury, and to return to normal cerebral development, is one of the most studied areas of child neurology, neurophysiology, and neurodevelopment. Despite the importance of these aims, the complex physiology of the brain renders experimental design and the evaluation of outcomes challenging. Thus, promising preclinical data or small clinical trials often fail to produce quality results that translate to patient therapy. In clinical practice, potential surgical interventions have mostly been investigated in patients with CHD due to the complexity of management, while drugs and other therapies were predominantly studied in neonatal brain injuries of premature and HIE children. Finally, considering recent evidence on myelin and WM plasticity suggests that early neurodevelopmental interventions have the potential to at least partially ameliorate the effects of previous injuries.

7.1 Clinical management

Evidence-based clinical practice is fundamental to minimize the effect of ongoing injury (e.g., neonatal asphyxia) or to successfully manage potentially risky procedures (e.g., surgical practice in CHD).

Prenatal diagnosis is particularly important to avoid neurologic consequences for ductal-dependent CHD, where prompt neonatal prostaglandin infusion is needed to maintain ductal patency and thus to avoid hypoxemia that could lead to a surge of brain ROS (Tworetzky et al., 2001) and related abnormal neurodevelopment (Hövels-Gürich et al., 2008). Since the blood supply to WM is unstable and matures only in the post-term neonatal period, poor intra- and post-operative oxygenation, together with hypotension, are also associated with worse neurodevelopmental outcomes, probably through ROS-inducing brain damage (Kussman et al., 2010; McQuillen et al., 2007). Near-infrared spectroscopy (NIRS) monitoring could be useful in this context, and it permits continuous, non-invasive monitoring (Ferrari et al., 2004), even if only as a surrogate of cerebral oxygen saturation. A threshold of NIRS saturation of <45% for more than 180 min has been linked to adverse neurodevelopment (Dent et al., 2006).

Hypothermia during cardiopulmonary bypass (CPB) has been shown to be neuroprotective, as it reduces ROS and inflammatory response, and permits lower (or zero) flow rates during CPB, but it is still not clear if full-flow normothermic CPB is a worse choice (Corno et al., 2018; Poncelet et al., 2011) because normothermia would avoid cerebral hyperthermia during rewarming and the associated impairment in cognition (Sahu et al., 2009). Different CPB flow management techniques (i.e., deep hypothermic circulatory arrest <41 min, continuous low-flow bypass, and regional cerebral perfusion) have shown equivalent, usually poor, neurodevelopmental outcomes (Algra et al., 2014; Bellinger David C. et al., 2011). Hematocrit levels below 25% were strongly associated with worse neurodevelopment, leading this threshold to be adopted as standard (Wypij et al., 2008). Finally, a consistent, systematic review (Hirsch et al., 2012) showed that current data on neuromonitoring (EEG and neurosonography) and neuroprotection (including several drugs, such as erythropoietin, steroids, and phenobarbital) are very limited, with only two studies (both regarding hematocrit levels) reaching a moderate level of evidence to support modifications of clinical practice.

For term newborns with moderate to severe HIE, hypothermia reduced death and severe neurodevelopmental impairment from 65% to 40–50% (Edwards et al., 2010). In mild HIE, hypothermia is at least safe and seems to have neuroprotective potential (Rao et al., 2019). The standard practice of 33.5 °C cooling for 72 h is still the best choice; deeper and longer cooling does not improve the outcome (Shankaran et al., 2017). Interestingly, in a piglet model, cooling below 33.5 °C seems to be detrimental for neuroprotection, especially for WM, with evidence of cell death and microglial activation in most brain regions with to cooling to 35 or 33.5 °C (Alonso-Alconada et al., 2014). This is of particular interest for CHD patients because, even if for much shorter periods, they are usually cooled below 33.5 °C during CPB. Very little data is available on the effect of CPB temperature on WM (Shaaban Ali et al., 2005).

7.2 Anesthetics

Consistent animal and human studies have shown a cumulative, detrimental effect of common anesthetics/sedative drugs (e.g., isoflurane, ketamine, propofol, pentobarbital, and midazolam) on brain development. In animal models, including nonhuman primates, the use of anesthetic drugs during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss and alterations in synaptic morphology and neurogenesis. Notably, the U.S. Food and Drug Administration issued a safety warning on the prolonged or repeated use of general anesthetics and sedatives during surgery or procedures in children younger than three years and pregnant women during their third trimester (U.S. Food and Drug Administration, 2016).

To limit this side effect, several anesthetic-sparing agents have been employed with very limited human data. The mechanism of injury seems to be linked to the interaction of anesthetics with GABA and NMDA receptors in neurons (Andropoulos, 2018). Dexmedetomidine and clonidine (both alpha2-

adrenoreceptor agonists) have been preclinically described as neuroprotective and with anesthetic-like properties; xenon gas is an NMDA antagonist but lacks neurotoxicity and the adverse hemodynamic properties of other NMDA antagonists (e.g., nitrous oxide and ketamine). All have been shown to be safe and offer promising results, with ongoing clinical trials in humans (Alam et al., 2017; Laudenbach et al., 2002). However, early results of the TOBY-Xe trial on HIE children showed no differences in MRI for *N*-acetyl aspartate ratio in the thalamus, and fractional anisotropy in the cooled plus xenon group relative to the cooling only group (Azzopardi et al., 2016).

7.3 Energy metabolism

The respiratory chain and mitochondria are the main cellular sites for the production of ROS. The surge of ROS to a damaging concentration is paradoxically enhanced by hypoxia through hypoxia-inducible factor-1 (HIF-1). ROS rapidly attack cellular components (especially mitochondrial membranes), resulting in an energy (ATP) deficit that leads to cell damage and eventually death.

Some investigators have tried to tackle this problem by providing cells with molecules that help to overcome this shortage. Carnitine transport long-chain fatty acids into mitochondria for degradation by β-oxidation. Several preclinical studies on different types of brain injury were promising, but only a few human studies are available (Ferreira and McKenna, 2017; Mahmoodpoor et al., 2018). In a rat model of chronic hypoperfusion, carnitine decreased oxidative DNA damage, and lipid peroxidation, myelin sheath thickness, and expression of oligodendrocyte markers were enhanced. Moreover, treated rats showed attenuated cognitive impairment (Ueno et al., 2015). The neuroprotective mechanism seems to be the prevention of acyl-CoAs accumulation in mitochondria, as also demonstrated in a pediatric hypoxia-ischemia rat model (Wainwright et al., 2003). Creatine functions as an energy buffer, providing a stable and quickly available energy source during fluctuating energy

demand, including short periods of oxygen deprivation. Creatine crosses the placenta and the blood-brain barrier and has been shown to protect the brain and other organs from hypoxic injuries in animals. Human studies have proved its safety as a pregnancy supplement, but efficacy studies are still needed (Dickinson et al., 2014).

7.4 ROS scavengers

Since oxidative distress seems to be the main molecular actor in WMI, numerous studies have focused on molecules that readily cross the blood-brain barrier and possess antioxidant properties. Melatonin is one of the most promising neuroprotectors, acting as a ROS scavenger, antioxidant enzyme inducer, and an excitotoxic brain injury protector. Interestingly, melatonin enhanced oligodendroglial maturation in a rodent model of neonatal stroke (Villapol et al., 2011).

Evidence for the efficacy of melatonin comes primarily from pre-clinical data; it has been shown to reduce gliosis and WMI, to enhance hypothermia neuroprotection, and, as it passes the placenta, could be useful during prenatal treatment (Colella et al., 2016; Okatani et al., 1998). *N*-acetyl-cysteine, polyphenols (resveratrol and curcumin), allopurinol, vitamin C, ferropoptosis (i.e., iron chelation), and caffeine have also been investigated but with little evidence of effectiveness in humans (Endesfelder et al., 2017; Parikh and Juul, 2018; Shah et al., 2015; Stegeman et al., 2018; Wu et al., 2019).

7.5 Tissue regeneration

Erythropoietin (Epo) is required for proper neurodevelopment, having astrocytes as the primary producer and affecting neurons, OL, and epithelial cells with anti-inflammatory, anti-apoptotic, and

proliferative effects through the JAK2 pathway. Epo also has important antioxidant effects (Pathipati and Ferriero, 2017) and is produced in the brain in response to hypoxia. It has antiapoptotic effects on mature neurons, neuronal progenitors, and other cells (Juul and Pet, 2015). Epo (and allegedly its longer-acting, synthetic analog darbepoetin) administration for HIE reduces the risk of brain injury, cerebral palsy, and cognitive impairment, but no effect was noticed in CHD children (Razak and Hussain, 2019; Stegeman et al., 2018). Stem cells (from umbilical cord blood) were successfully used in infants with HIE in two different trials, with improved neurodevelopment and neuroimaging evidence (Cotten et al., 2014; Min et al., 2013). Interestingly, it was shown that administered bone-marrow-derived mesenchymal stem cells do not engraft but promote proliferation and survival of nearby cells in WMI. In particular, they can induce oligodendrocyte progenitors' proliferation but also promote their maturation (Rivera et al., 2006). Lithium, even at the low doses used for children with bipolar disorder, can reduce ischemic brain injury, and, more interestingly, can stimulate remyelination (Makoukji et al., 2012). Epidermal growth factor (EGF) seems to have a crucial role in regulating brain stem cells both in gray matter and WM (Aguirre et al., 2010). In fact, in an animal model of preterm diffuse WMI, intranasal administration of EGF promoted OL regeneration and differentiation, myelin structure, and finally, prevented WM-related task deficits (Scafidi et al., 2014).

7.6 Miscellaneous interventions

Nutrition has been investigated, particularly for prematurity, but little is known of the neurodevelopmental consequences (Keunen et al., 2015). Nonetheless, a positive association was demonstrated for cumulative caloric, fat, and protein intake using both neuroimaging parameters and higher cognitive scores at the two-year follow-up (Coviello et al., 2018). Among near-standard interventions, magnesium sulfate for women at risk for imminent preterm birth and antenatal

corticosteroids have shown the most significant effect size for gross motor dysfunction and developmental delay, respectively (Vaivada et al., 2017).

7.7 Mitigation of adverse effects through improved development

A major challenge in at-risk children is to understand how we can use the long developmental window of WM to take advantage of cerebral plasticity to mitigate or overcome the effects of perinatal brain insults.

Plasticity, the capacity to induce brain modifications by experience, has traditionally been considered a gray matter function, but recent findings have shown that WM also exhibits this phenomenon (Fields, 2015; Filley and Fields, 2016). This is a crucial concept in the early stages of development when the maturing brain exhibits maximal learning potential.

The first evidence comes from animal studies, which suggest that WM could be modified by experience or training, both in sensorial and cognitive tasks: environmental enrichment increases the OL population in the amygdala, corpus callosum, and cortex in animals (for a comprehensive review, see (Fields, 2015)). In human neonates, early experience increases WM architecture in the internal capsule and frontal lobes and improves performance in behavioral tasks (Als et al., 2004). Furthermore, experiences may change human myelin microstructure. As an example, social neglect and disturbances in social behavior in children and juvenile primates have been linked to WM abnormalities, with a size reduction of 17% observed in the corpus callosum of neglected children (Teicher et al., 2004).

The plasticity of WM structure and connectivity have also been tested using more structured protocols, which evaluated the effect of specific neuropsychological training on brain structures. WM modifications were reported, after appropriate training, both in children with reading problems and in ex-preterm children with learning and memory vulnerabilities (Astle et al., 2015; Keller and Just,

2009) showing increased microstructural organization (increased fractional anisotropy) after training. However, studies investigating WM connectivity after cognitive rehabilitation are still rare. It will be important to move beyond considering changes only in isolated brain regions and begin to consider the impact of cognitive training interventions on brain networks. This is a crucial perspective in understanding the factors that drive training-induced changes (Caeyenberghs et al., 2016). A subsequent challenge is to understand how to use the identified mechanisms in rehabilitative programs to provide therapeutic benefits that extend beyond specific tasks to aspects of everyday life.

Although our understanding of activity-dependent myelin plasticity in cognitive function is incomplete, prospects for the future are promising (Monje, 2018). The ability to improve WM function reveals the considerable potential of behavioral assistance and rehabilitation programs to support remediation for children at risk of neurodevelopmental impairment. In such children, plasticity becomes crucial, given the long developmental window for therapeutic interventions. High-risk children may benefit from timely rehabilitative interventions targeting the consolidation of developmental milestones, which are essential for subsequent maturation of more complex cognitive abilities. With timely intervention, there may be beneficial cumulative effects on cerebral circuitry.

8. Conclusion

Despite heterogeneous manifestation, the most common stressful conditions in early life tend to converge to a defined set of neurodevelopmental disorders, even in the absence of overt brain damage. This may be explainable by a process of WM dysmaturation that starts early in life. This process is kindled by the surge of brain ROS that hits and impairs the precursors of myelin-forming cells (preOL) during a precise susceptibility window in which the body's antioxidant system is imbalanced or immature. The following cascade of events, if not quickly recognized, impairs the

capability of the immature brain for optimal development, a lack that becomes evident when complex cognitive tasks such as learning and social relationships are required, usually at school-age. Injuries in the developing brain, and particularly WMI, have no easy management, nor is there a "magic bullet" or assured cure. Nevertheless, despite their cross-disease peculiarity, every patient group can benefit from what is more broadly known about WMI. WM and connectivity indicators can help in the development and validation of management strategies. IUGR and preterm birth patients can benefit from constant, gentle, pre-birth, and early post-natal care; the CHD perioperative window requires careful and rapidly adaptive management, and HIE patients could likely benefit from the development of more effective drugs.

A combination of biomarkers and constant, non-invasive monitoring can help in disease assessment, staging, and evaluation of a therapy's effectiveness. A close neurodevelopmental follow-up would provide an objective tool to assess the injury and the stage of recovery of every child in a tailored manner. All these aspects are a burden that requires the tight collaboration of professionals from the lab bench through the clinic; a precise evaluation of neurodevelopmental outcome depends on quality, scalable, and reproducible results.

Acknowledgments

The authors would like to thank Dr. Elena Rampazzo, Dr. Manuela Simonato, and Prof. Agnese Suppiej for their support in writing this review.

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Figure legends

Figure 1

White matter mechanism of injury. Clinical conditions and complications lead to a surge in reactive oxygen species (ROS) that affect oligodendrocyte progenitors' (OPC) maturation through several pathways. Late oligodendrocyte progenitors (preOL) are more susceptible to ROS damage than their mature and immature counterparts in stressful or pathological perinatal conditions because they lack key enzymes involved in ROS deactivation: superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx). IUGR: intra-uterine growth restriction; CHD: congenital heart diseases; OL: oligodendrocytes.

Figure 2

Molecular biomarkers of brain damage. Biomarkers of brain damage are indicated near their principal origin. Proteins are in uppercase; their full names and roles are described in Section 7. Cerebral factors that also come from the blood are depicted next to the capillary structure.