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Short Communication

The Link between Cognitive Deficits and White Matter Injury in Preterms

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Preterm cerebral white matter injury (WMI) frequently encompasses hypoxic–ischemic lesions such as periventricular leukomalacia (PVL) and hypoxic–ischemic encephalopathy (HIE). These infants are extremely vulnerable to brain injury and are at high risk of developing motor and cognitive abnormalities at later stages in life.

Although preoligodendrocytes (preOLs) have long been regarded as the hallmark of perinatal white matter injury [1], we have previously reported that late pre-myelinating axons having initiated diameter expansion and expressing clusters of functional voltage-gated calcium channels, are equally principal targets for injury during heightened periods of selective vulnerability to hypoxia-ischemia. By contrast, axons yet to enter this developmental window, or which have already initiated myelination, have a much higher ischemic tolerance [2]. The burden of WMI in a given region is thus likely to be influenced by the complement of late pre-myelinating axons and preOLs in the affected white matter structures. These findings suggest that damage to developing axons is a major, but previously underappreciated component of perinatal WMI and which as to date remains without any cure [2].

The diffuse lesions of preOLs was previously considered to be the cause of the deficits resulting from hypomyelination, but more recent studies has exposed their dramatic plasticity for regeneration after injury, albeit their failure to mature into myelinating oligodendrocytes as they enter a state of maturation arrest [3,4]. This has therefore clearly shifted our attention from a perception in the deficits arising in part from chronic preOLs death to the failure of oligodendrocyte maturation [5-7]. As such, there is an urgent need to identify those therapeutic strategies to promote remyelination and improve outcome in such conditions.

These recent findings have very important ramifications as they converge on the main reason behind the cognitive impairment that is experienced by such preterms across their lifetime. The novel concept of activity-dependent myelination emerges from studies that followed the changes in white matter during learning [8] and from those that investigated the cellular dynamics of myelination influenced by neurotransmission [9]. Therefore, if myelin is modifiable to improve synchrony and to optimize the transmission of information, dysfunctional oligodendrocytes would lead to hypomyelination, altered axon caliber and reduced conduction speed. As a consequence, this would alter the axon's synchrony and disrupt the spike-timing-dependent plasticity (STDP) and impact axonal transport. The loss of STDP as a consequence of oligodendrocyte and axonal injury would therefore have a huge impact leading to cognitive impairment in disorders that strike the developing child's brain during critical periods of development that are normally characterized by heightened phases of neuroplasticity, memory and learning. Therefore, the secretion of myelin by oligodendrocytes is not only central to myelination for conduction speeds but is a critical component in synaptic plasticity and cognition that ultimately shapes the human brain.

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