

● INVITED REVIEW

# Embracing oligodendrocyte diversity in the context of perinatal injury

Jessie Newville<sup>1</sup>, Lauren L. Jantzie<sup>1,2</sup>, Lee Anna Cunningham<sup>1,\*</sup>

<sup>1</sup> Department of Neurosciences, University of New Mexico Health Sciences Center, Albuquerque, NM, USA

<sup>2</sup> Department of Pediatrics, University of New Mexico Health Sciences Center, Albuquerque, NM, USA

**How to cite this article:** Newville J, Jantzie LL, Cunningham LA (2017) Embracing oligodendrocyte diversity in the context of perinatal injury. *Neural Regen Res* 12(10):1575-1585.

## Abstract

Emerging evidence is fueling a new appreciation of oligodendrocyte diversity that is overturning the traditional view that oligodendrocytes are a homogenous cell population. Oligodendrocytes of distinct origins, maturational stages, and regional locations may differ in their functional capacity or susceptibility to injury. One of the most unique qualities of the oligodendrocyte is its ability to produce myelin. Myelin abnormalities have been ascribed to a remarkable array of perinatal brain injuries, with concomitant oligodendrocyte dysregulation. Within this review, we discuss new insights into the diversity of the oligodendrocyte lineage and highlight their relevance in paradigms of perinatal brain injury. Future therapeutic development will be informed by comprehensive knowledge of oligodendrocyte pathophysiology that considers the particular facets of heterogeneity that this lineage exhibits.

**Key Words:** oligodendrogenesis; oligodendrocyte progenitor cell; myelination; central nervous system development; ontogenetic origin; white matter; white matter injury; preterm birth; glia; macroglia

## \*Correspondence to:

Lee Anna Cunningham, Ph.D.,  
leeanna@salud.unm.edu.

## orcid:

0000-0003-0294-5262  
(Lee Anna Cunningham)

doi: 10.4103/1673-5374.217320

Accepted: 2017-09-12

## Introduction

Cellular diversity within the central nervous system is the evolutionary trend that underlies the brain's ability to orchestrate complex behaviors and cognitive tasks. To this end, the oligodendrocyte lineage contributes greatly to the evolutionary success of vertebrates through its unique production of myelin sheaths, lipid rich multilamellar membranes that envelop axons in the central nervous system (Zalc and Colman, 2000; Schweigreiter et al., 2006; Zalc et al., 2008). Myelination is largely a developmental process that is preceded by waves of oligodendrocyte generation, proliferation, migration, and differentiation (Mitew et al., 2014; Bercury and Macklin, 2015). During embryonic development, oligodendrocytes originate from various pools of progenitor populations derived from separate germinal zones (Kessaris et al., 2006). Three waves of ontogenetically distinct populations of oligodendrocyte progenitor cells disseminate throughout the grey and white matter regions of the central nervous system (Tsai et al., 2009; Armati and Mathy, 2010). Ultimately, migratory oligodendrocyte progenitors settle and differentiate into mature oligodendrocyte cells that provide local myelination and enable rapid impulse propagation through saltatory conduction (Susuki et al., 2013). Additionally, through their myelin sheaths, oligodendrocytes deliver trophic support for maintenance of axonal integrity (Funfschilling et al., 2012; Simons and Nave, 2015). Recent transcriptome data demonstrating new subtypes of oligodendrocytes in the central nervous system has considerably expanded our appreciation of oligodendrocyte diversity (Marques et al., 2016). These new insights into basic oligodendrocyte biology highlight the importance

of adding to the paucity of research that truly addresses the heterogeneous nature of the oligodendrocyte lineage.

Oligodendrocytes of distinct origins, maturational stages, or regional locations may differ in their functional capacity and susceptibility to any type of neural injury. However, oligodendrocyte diversity is particularly relevant to perinatal brain injury, as this stage in neurodevelopment exhibits heightened vulnerability to white matter injury. Throughout this review, perinatal brain injury is defined as damage to the brain acquired before or immediately following birth. Oligodendrocyte dysregulation leading to white matter injury is a predominant pattern observed in survivors of perinatal brain injury (Iida et al., 1995; Back et al., 2001; Robinson et al., 2006; Billiards et al., 2008; Buser et al., 2012; Jantzie et al., 2015). Myelination in the human central nervous system begins during the second half of gestation in an inferior to superior, posterior to anterior pattern, whereby myelination begins in the occipital lobe and continues through the temporal and frontal lobes (Jakovcevski and Zecevic, 2005; Tasker, 2006). The extraordinary metabolic demands required during myelination and the complexity of oligodendrogenesis render this neurodevelopmental stage vulnerable to insult (Nave, 2010a). Perinatal brain injury sustained from preterm birth is one specific example that classically involves white matter injury and subsequent myelin deficits. Preterm birth is the leading cause of infant morbidity and mortality in the United States (Wilson-Costello et al., 2005; Shapiro-Mendoza, 2016; Liu et al., 2017). The major form of brain injury in contemporary cohorts of preterm infants is diffuse white matter injury characterized by selective oligodendrocyte dysregulation that precipitates abnormal my-

elination and cognitive impairment (Anderson and Doyle, 2008; Aarnoudse-Moens et al., 2009; Buser et al., 2012). Oligodendrocytes are implicated in many preclinical models of perinatal brain injury including: in utero and postnatal hypoxic-ischemia (Robinson et al., 2005; Segovia et al., 2008; Riddle et al., 2011; Jantzie et al., 2013; Davidson et al., 2014), hyperoxia or hypoxia exposure (Gerstner et al., 2008; Schmitz et al., 2011; Brehmer et al., 2012; Jablonska et al., 2012; Ritter et al., 2013; Deng et al., 2014; Pham et al., 2014; Scafidi et al., 2014; Yuen et al., 2014), ischemia (Falahati et al., 2013; Ahrendsen et al., 2016), fetal growth restriction (Tolcos et al., 2011; Reid et al., 2012; Rideau Batista Novais et al., 2016), hyperbilirubinemia (Barateiro et al., 2012, 2013, 2014), exposure to myelin debris (Robinson and Miller, 1999; Baer et al., 2009), leukodystrophy (Baracska et al., 2002), in addition to infection and inflammation (Valerio et al., 2002; Vela et al., 2002; Pang et al., 2003; Taylor et al., 2010; Favrais et al., 2011; Nobuta et al., 2012). Preclinical models of toxic exposure during developmental myelination, such as gestational ethanol or isoflurane exposure, also involve white matter injury sustained from oligodendrocyte dysregulation (Brambrink et al., 2012; Creeley et al., 2013, 2014; Newville et al., 2017). Interestingly, some models suggest that early insult to the oligodendrocyte lineage may permanently alter oligodendrocyte and immune function, ultimately contributing to adult pathogenesis (Jalabi et al., 2005; Benardais et al., 2014; Graf et al., 2014; Traka et al., 2016; Patra et al., 2017). Additional evidence that suggests early injury to oligodendrocyte lineage impacts cognition later in life is demonstrated by clinical studies of preterm cohorts, wherein persisting white matter structural abnormalities, as assessed by diffusion tensor imaging, correlate to an increased incidence of neuropsychiatric disorders (Hagberg et al., 2012; Pyhala et al., 2014; Guy et al., 2015).

Within this review, we lay out evidence that elucidates a deeper understanding of oligodendrocyte function and susceptibility to injury that is dependent on origin, maturational status, and location within the central nervous system. It is clear that the oligodendrocytes play a major role in perinatal brain injury and that the path toward developing appropriate therapeutics will target oligodendrocyte cells (Olivier et al., 2009; Jantzie et al., 2013). Furthermore, future therapeutic development will be informed by comprehensive knowledge of oligodendrocyte pathophysiology that considers the particular facets of heterogeneity that this lineage exhibits.

## Ontogenetic Origin

Oligodendrocyte cells that populate the central nervous system are derived from spatially and temporally distinct waves of oligodendrogenesis (**Figure 1**). Within the developing forebrain, gradients of organizing signals emanate from specific centers to pattern the tissue, creating specialized regions that produce different neuronal and glial cell types (Rowitch and Kriegstein, 2010). Sonic hedgehog (SHH) secreted from the ventral center along with bone morphogenic proteins (BMPs) from the dorsal cortical hem signaling center, regulate the specification of oligodendrocyte pro-

genitor cells (OPCs) within the ventricular zone (Orentas et al., 1999; Samanta and Kessler, 2004; Feigenson et al., 2011). The three distinct waves of OPCs that arise from the developing forebrain ventricular zone follow a ventral-dorsal temporal progression (Ivanova et al., 2003; Chojnacki and Weiss, 2004; Kessaris et al., 2006). The first wave of OPC production is dependent on SHH signaling, whereas the later waves of OPC production occur in an SHH independent manner (Pringle and Richardson, 1993; Pringle et al., 1996; Nery et al., 2001; Tekki-Kessaris et al., 2001). Cre-LoxP fate mapping studies in transgenic mice have shown that the first wave of OPCs starting at embryonic day 12.5 is generated by Nkx2.1 expressing progenitors from the medial ganglionic eminence and entopeduncular area (Kessaris et al., 2006). As these ventrally derived progenitors migrate tangentially and dorsally to populate the entire developing telencephalon, the second wave of Gsh2 (also referred to as Gsx2) progenitors from the lateral and medial ganglionic eminences begins at embryonic day 15.5 (Kessaris et al., 2006; Chapman et al., 2013). Finally, at birth, a third wave occurs from Emx1 expressing progenitors arising from the dorsal ventricular zone underlying the developing cortex (Kessaris et al., 2006). By postnatal day 10, the Nkx2.1 expressing OPCs derived from the earliest wave have disappeared. The mechanisms behind the elimination and replacement of these early Nkx2.1 oligodendrocytes are unclear. One likely possibility is that subsequent populations of oligodendrocytes outcompete these early oligodendrocytes for survival factors such as platelet-derived growth factor (PDGF). This process would reflect how the overabundance of OPCs is balanced during myelination as these cells compete for the limited survival factors produced by axons and astrocytes (Barres et al., 1992; Trapp et al., 1997; Barres and Raff, 1999). The oligodendrocytes that remain in the forebrain are the Gsh2 ventrally derived and Emx1 dorsally derived oligodendrocytes at an approximate ratio of 1 to 4, respectively (Tripathi et al., 2011). These oligodendrocyte progenitors that arise during development have greater motility, more rapid cell cycle and better survival relative to oligodendrocytes generated later in life (Tang et al., 2000; Ruffini et al., 2004). Throughout postnatal life, new oligodendrocytes are generated from a reservoir of nestin-expressing neural stem cells that occupy the subventricular zone (SVZ) of the lateral ventricle (Levison et al., 1993, 1999; Marshall et al., 2003, 2005; Quinones-Hinojosa et al., 2006; Jablonska et al., 2010; Fiorelli et al., 2015). These neural stem cells exist in spatially segregated microdomains that produce different ratios of oligodendrocytes depending on their rostrocaudal coordinates along the ventricular zone, with more caudal domains having a greater proclivity towards generating oligodendrocytes (Azim et al., 2016). Under normal conditions, rostral SVZ domains produce approximately one oligodendrocyte per thirty cells, whereas caudal domains produce one oligodendrocyte per three cells (Menn et al., 2006). Once generated, SVZ derived OPCs migrate dorsally or laterally into the corpus callosum, fornix, or striatum, usually remaining at the same rostrocaudal level of their original precursor (Menn

et al., 2006). Neural stem cells in the SVZ increase their production of oligodendrocytes in pathological circumstances such as stroke (Li et al., 2010), or demyelinating lesion (Menn et al., 2006; Aguirre et al., 2007; Mecha et al., 2013; Xing et al., 2014; Brousse et al., 2015). Following a demyelinating injury in the central nervous system, oligodendrocytes are also generated from adult OPCs that are distributed uniformly throughout the postnatal parenchyma (Tripathi et al., 2010; Richardson et al., 2011). Considering that the populations of oligodendrocytes arise from diverse origins under differing transcriptional control (Bergles and Richardson, 2015), it is important to investigate possible functional heterogeneity within these described subpopulations.

Functional heterogeneity between ontogenetically distinct populations of oligodendrocytes is paramount to the context of neural injury and repair. Identification of potential differences may guide therapeutic targeting of certain populations that demonstrate greater propensity toward remyelination or survival during perinatal brain injury paradigms. Diphtheria toxin mediated ablation of any one of these developmental oligodendrocyte waves showed that the other unaffected waves compensated for the loss numerically without any significant neurological consequences (Kessaris et al., 2006). This finding contributed to the understanding that despite being derived from spatially and temporally distinct origins, all oligodendrocytes in the forebrain are seemingly functionally analogous. However, recent research has suggested ontogenetic-dependent heterogeneity regarding developmental myelination, remyelination capacity, and susceptibility to developmental insult. Indeed, researchers have found functional differences between dorsally and ventrally derived oligodendrocytes in this respect. Dorsal OPCs, despite having indistinguishable electrophysiological properties from their ventrally derived counterparts, as assessed by whole-cell patch clamping, differ in their migration and settling patterns (Tripathi et al., 2011; Clarke et al., 2012). This was demonstrated in the spinal cord, whereby dorsally derived OPCs were less migratory and were able to outcompete ventrally derived OPCs in dorsal territory (Tripathi et al., 2011). In response to demyelination in the mature central nervous system, dorsally derived OPCs outperformed ventrally derived OPCs in measures of proliferation, migration, and differentiation (Zhu et al., 2011; Crawford et al., 2016). This important finding, that dorsal OPCs contributed more to remyelination, underscores the need for future studies to determine if a similar dynamic occurs in perinatal myelin deficits. Interestingly, investigators revealed that these dorsal oligodendrocytes were more susceptible to age-associated differentiation impairment (Crawford et al., 2016). Another study found that developmental injury in the form of ethanol exposure during the brain growth spurt in mice elicited acute oligodendrocyte cell loss dependent on ontogenetic origin, where embryonically derived (ventral) oligodendrocytes were depleted whereas the pool of postnatally derived (dorsal) oligodendrocytes were numerically unaffected (Newville et al., 2017).

Emerging evidence that demonstrates functional differ-

ences between oligodendrocytes of distinct origins has important implications in the setting of developmental central nervous system injury. Particularly, the understanding of certain developmental pathologies that include oligodendrocyte dysregulation, such as preclinical models of neonatal encephalopathy, would be greatly improved if researchers considered ontogenetic origin as a factor of oligodendrocyte performance. The manner in which these sub populations of oligodendrocytes respond to therapeutic interventions that target oligodendrocytes, such as erythropoietin (EPO), Darbepoetin (a hyperglycosylated analogue of recombinant EPO), or melatonin, should also be investigated (Olivier et al., 2009; Jantzie et al., 2013). These are treatments that are being used in clinical trials to improve outcomes in infants born preterm (Wu et al., 2012; Juul and Pet, 2015; McAdams and Juul, 2016; An et al., 2017). If in fact, oligodendrocytes are distinctly susceptible to developmental white matter injury associated with preterm birth, perhaps one subpopulation is more responsive to therapeutic manipulation than the other.

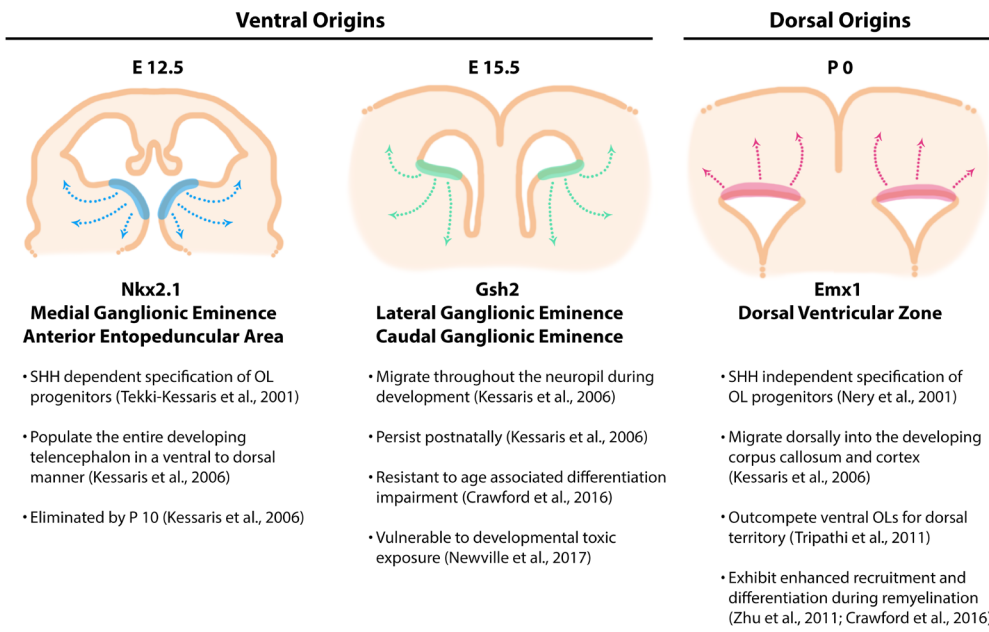
### Maturation Stage

Oligodendrocytes are comprised of a continuous lineage of progressive maturational cell stages (Marques et al., 2016). These stages can be defined according to proliferative capacity, temporal expression of cell surface markers, and morphological complexity. These distinctions yield four separate maturational stages within the human and rodent forebrain: oligodendrocyte progenitor cells, pre-oligodendrocytes, immature pre-myelinating oligodendrocytes, and mature myelinating oligodendrocytes (**Figure 2**) (Kinney and Back, 1998; Back et al., 2001; Baumann and Pham-Dinh, 2001; Butts et al., 2008). Specification, proliferation, differentiation, and maturation of oligodendrocyte lineage cells are regulated through expression of various transcription factors that act on oligodendrocyte lineage genes (Emery and Lu, 2015). Once specified from multipotent stem cells, OPCs migrate radially and tangentially away from their respective germinal zone along the vascular network to populate the developing CNS (Tsai et al., 2016). This first committed oligodendrocyte lineage stage has simple bipolar morphology and is identified by the specific expression of platelet-derived growth factor receptor alpha (PDGFR $\alpha$ ) (Pringle et al., 1992). PDGFR $\alpha$  expression is regulated by Olig1, Olig2, and Mash transcription factors, which are influenced by the gradient expression of SHH morphogen (Butts et al., 2008). Other markers such as nuclear Olig1, Sox10, or sulfated proteoglycan NG2 are used to identify OPCs. However, these are also expressed in the subsequent pre-oligodendrocyte stage (Tolcos et al., 2016). Nuclear expression of the transcription factor Olig2, important for oligodendrocyte specification, is expressed throughout the oligodendrocyte lineage stages (Lu et al., 2002; Emery and Lu, 2015).

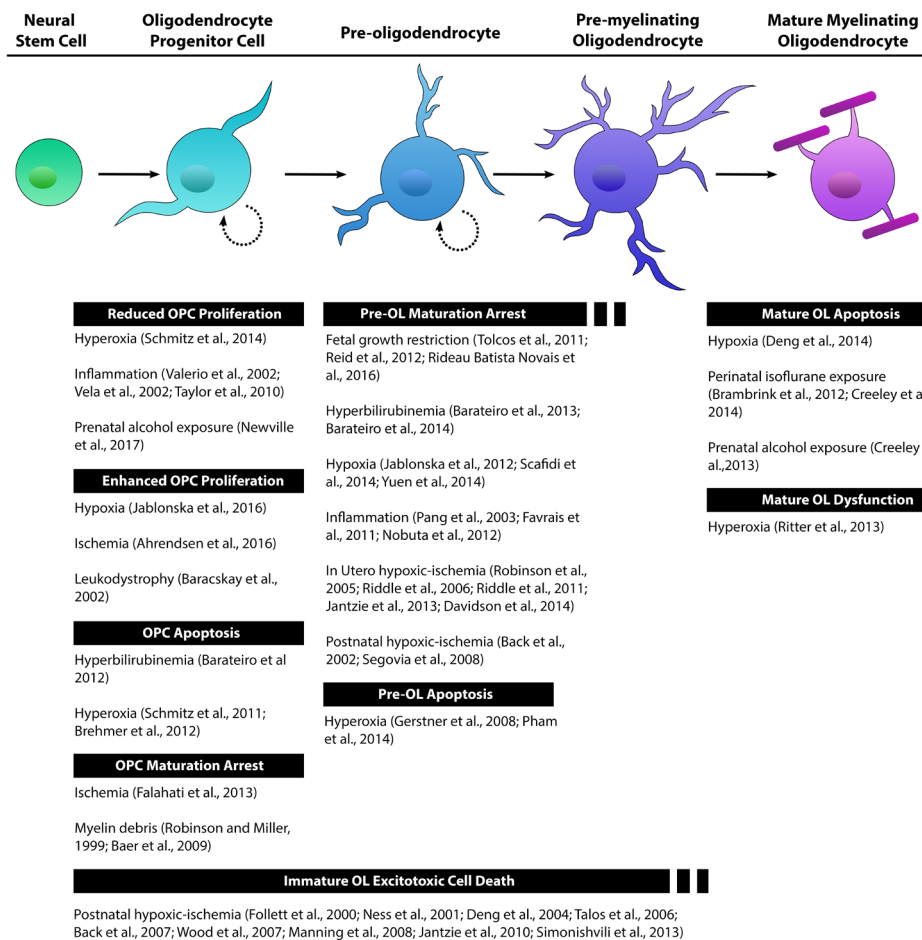
Proliferation of the progenitor pool is stimulated by locally expressed mitogens, in addition to environmental cues such as chemokines (Robinson et al., 1998; Armati and Mathey, 2010). Once an OPC has arrived at its final destination within the white or grey matter, the OPC can differentiate into a

mitotically active, multipolar pre-oligodendrocyte, whereby it loses its migratory ability. Identification of this oligodendrocyte stage is defined as expression of O4 in the absence of O1 (Warrington and Pfeiffer, 1992; Reynolds and Hardy, 1997; Back et al., 2001). These pre-oligodendrocyte cells differentiate into immature pre-myelinating oligodendrocytes

of increased multipolar morphological complexity. This third cell stage in the oligodendrocyte lineage is post-mitotic and expresses O4 and O1 in the absence of myelin proteins. Additionally, this stage expresses MAG and CNP, which are also expressed in later myelinating oligodendrocytes. Ultimately, immature pre-myelinating oligodendrocytes



**Figure 1 Oligodendrocytes (OLs) arise from three regionally and temporally distinct waves during neurodevelopment.** New evidence reveals that oligodendrocytes exhibit different properties according to their ontogenetic origin. E: Embryonic day; P: postnatal day.



**Figure 2 The lineage of oligodendrocytes (OLs) is a continuous series of maturational stages.** Stage-specific properties of oligodendrocyte lineage cells determines their distinct vulnerabilities in different models of perinatal injury. OPC: Oligodendrocyte progenitor cell.

produce mature myelinating oligodendrocyte cells. A small fraction of pre-myelinating oligodendrocytes undergo programmed cell death under conditions of normal development (Barres et al., 1992; Trapp et al., 1997). The expression of major myelin proteins, such as myelin basic protein (MBP) and proteolipid protein (PLP), denotes the final stage of the oligodendrocyte lineage. Mature oligodendrocytes are also commonly identified by their expression of Olig1, and the adenomatous polyposis coli antigen (APC, often referred to as CC1) (Kitada and Rowitch, 2006). The identification of stage specific markers was an important milestone in oligodendrocyte lineage research. Additional maturational stratification of oligodendrocytes has been suggested by recent transcriptome data from forebrain oligodendrocytes indicating a narrow path of differentiation from oligodendrocyte progenitor cell to myelin forming oligodendrocyte that then diversifies into six separate mature states (Marques et al., 2016). This new evidence suggests that limiting the maturational stages to four subtypes may depreciate the true diversity of the lineage. Categorizing oligodendrocytes into stages has been conducive for investigations into maturation dependent vulnerability and function. Describing how different paradigms of neuronal injury effect these newly identified oligodendrocyte populations will be important in future research efforts.

Functional capacity changes as an oligodendrocyte matures. Famously, the most mature oligodendrocyte stage generates myelin that enables rapid impulse propagation along axons, *via* sodium ion fluxes at the nodes of Ranvier. Myelin wrapping by mature oligodendrocytes dictates the spatial organization of these nodes and the sequestration of ion channels within them (Kaplan et al., 1997; Susuki et al., 2013). Oligodendrocytes provide trophic support to neurons, especially to long axons that are isolated from their respective neuronal soma (Nave, 2010a, b; Simons and Nave, 2015). The function of OPCs, other than generating additional myelinating oligodendrocytes, is less obvious. OPCs receive synaptic inputs from neighboring axons and express numerous voltage-gated ion channels (Bergles et al., 2000; Chittajallu et al., 2004; Jabs et al., 2005; Ge et al., 2006; De Biase et al., 2010; Clarke et al., 2012). Synaptic input onto OPCs is lost as these oligodendrocyte cells progress into more mature stages (Kukley et al., 2010). The functional significance of electrical input from neurons has remained obscure. However, it has been demonstrated that neuronal spiking influences oligodendrogenesis and myelination, suggesting that myelin biogenesis could be linked to the unique properties of OPC physiology (Wake et al., 2011; Gibson et al., 2014). In the specific case of glutamate, the manner in which this neurotransmitter effects OPC function is dependent on pathological circumstance. Glutamate mediates a host of oligodendrocyte functions related to brain development, such as migration, differentiation and myelination (Gallo et al., 1996; Gudz et al., 2006; Dimou and Gallo, 2015; Gautier et al., 2015). In brain injury associated with hypoxic ischemia, extracellular glutamate negatively impacts OPC survival by means of excitotoxicity (Johnston, 2005).

Oligodendrocyte maturational state is another layer of ever-growing oligodendrocyte heterogeneity that is important to consider in creating a more informed story of oligodendrocyte-associated pathogenesis in the context of developmental brain injury. Solely focusing on the mature myelinating endpoint, or choosing not to distinguish between the multiple stages of cellular maturation that exist, risks overlooking important information regarding the susceptibility of these distinct populations. Experimental paradigms of perinatal injury that examine the entire oligodendrocyte lineage, taking into consideration the selective vulnerabilities of cells at various stages of oligodendrocyte maturation, are able to parse out individual susceptibility profiles. Models of in utero and postnatal hypoxia ischemia aimed at determining the cellular underpinnings and molecular mechanisms behind diffuse white matter injury in preterm infants have shown that white matter injury is largely due to selective maturational arrest of pre-oligodendrocytes (Back et al., 2002; Robinson et al., 2005; Riddle et al., 2006, 2011; Segovia et al., 2008; Jantzie et al., 2013; Davidson et al., 2014). Interference in oligodendrocyte lineage progression at the pre-oligodendrocyte stage has also been demonstrated in models of hypoxia (Jablonska et al., 2012; Scafidi et al., 2014; Yuen et al., 2014), postnatal inflammation (Pang et al., 2003; Favrais et al., 2011; Nobuta et al., 2012), hyperbilirubinemia (Barateiro et al., 2013, 2014), and fetal growth restriction (Tolcos et al., 2011; Reid et al., 2012; Rideau Batista Novais et al., 2016). Under the pathological conditions of preterm birth pre-oligodendrocyte cells fail to mature into myelinating oligodendrocytes resulting in white matter deficits and poor clinical outcomes (van Tilborg et al., 2016). This is a cellular maturational stage-specific property that is independent of the developmental age of the animal or location of these cells within the cerebral white matter (Back, 2017). Further analysis has revealed that pre-oligodendrocytes are particularly vulnerable to apoptotic cell death under conditions of hyperoxia (Gerstner et al., 2008; Pham et al., 2014). Another mechanism of perinatal injury that specifically targets immature oligodendrocytes is excitotoxicity. OPCs and pre-oligodendrocytes are vulnerable to excitotoxic cell death in models of postnatal hypoxic-ischemia (Follett et al., 2000; Ness et al., 2001; Deng et al., 2004; Talos et al., 2006; Back et al., 2007; Wood et al., 2007; Manning et al., 2008; Jantzie et al., 2010; Simonishvili et al., 2013). Developmentally regulated expression patterns of glutamate receptors on OPCs render these cells in their early stage of oligodendrocyte maturation more susceptible to glutamate toxicity compared to their more mature, myelinating, counterparts (Rosenberg et al., 2003; Matute et al., 2006; Marinelli et al., 2016). In other experimental conditions of injury, OPCs show stage specific vulnerability to apoptosis in hyperbilirubinemia (Barateiro et al., 2012), and hyperoxia (Schmitz et al., 2011; Brehmer et al., 2012). Pathogenesis can also effect OPC proliferative capacity. OPCs show reduced proliferation in models of hyperoxia (Schmitz et al., 2014), inflammation (Valerio et al., 2002; Vela et al., 2002; Taylor et al., 2010), and prenatal alcohol exposure (Newville et al., 2017). Conversely, models of devel-

opmental hypoxia, leukodystrophy, and ischemia augment the proliferation of OPCs (Baracska et al., 2002; Ahrendsen et al., 2016; Jablonska et al., 2016). OPC maturational arrest has also been demonstrated in models of ischemia and exposure to myelin debris (Robinson and Miller, 1999; Baer et al., 2009; Falahati et al., 2013). Lastly, mature oligodendrocytes show stage specific susceptibility to apoptosis in models of hypoxia (Deng et al., 2014), and perinatal exposure to isoflurane or alcohol (Brambrink et al., 2012; Creeley et al., 2013, 2014). Hyperoxia induced myelination deficits demonstrate functional impairment in mature oligodendrocytes (Ritter et al., 2013). Disruptions to early oligodendrogenesis could negatively affect downstream progeny and mature oligodendrocyte function. The evidence from studies outlined in **Figure 2** strongly demonstrates that the oligodendrocyte lineage cells are vulnerable to perinatal brain injury in a maturation-dependent manner. These findings underscore the importance of considering this aspect of heterogeneity in future investigations (Butts et al., 2008; Back, 2017).

### Regional Specificity

Migration of OPCs into distinct neuronal environments dictates their functional properties and vulnerability to injury. Once specified, OPCs assume a bipolar morphology and depart their germinal zones to populate the grey and white matter regions of the central nervous system. OPCs associate with the abluminal surface of the vasculature mediated by Wnt-chemokine receptor 4 interaction and use the vessels as scaffolding to reach their destinations (Tsai et al., 2016). Other factors that regulate migration are contact-mediated molecules that repel and attract OPCs, in combination with growth factor availability (de Castro and Bribián, 2005; Bergles and Richardson, 2015). OPCs express a host of receptors for contact-mediated molecules also involved in neuronal migration such as Netrin-1 receptors (Jarjour et al., 2003; Tsai et al., 2003), Neuropilin-1 and -2 receptors (Sugimoto et al., 2001; Spassky et al., 2002; Syed et al., 2011), and Eph receptors (Prestoz et al., 2004). Furthermore, extracellular glutamate has been shown to induce OPC migration (Gudz et al., 2006; Harlow et al., 2015). OPCs exhibit self-avoidance, whereby they dictate their own tiling by constantly surveying their local territory and retracting when their processes contact an adjacent OPCs (Zhang and Miller, 1996; Hughes et al., 2013). Ultimately, oligodendrocyte progenitors evenly distribute themselves across grey matter regions and are only slightly outnumbered by progenitors within the white matter, 1 to 1.5 respectively (Chang et al., 2000; Dawson et al., 2003). The OPC that persist into adulthood steadily proliferate and differentiate to generate new myelinating oligodendrocytes (Rivers et al., 2008; Psachoulia et al., 2009; Young et al., 2013). The degree to which these cells proliferate and differentiate, in addition to other functional properties, is dependent on their regional location within the central nervous system.

Illuminating the differences between white matter and grey matter OPCs has demonstrated functional heterogeneity dependent on location. For instance, despite equivalent

levels of PDGFR $\alpha$  expression, white matter OPCs demonstrate a greater proliferative response to PDGF than grey matter OPCs (Hill et al., 2013). OPCs within the developing grey and white matter have distinct electrophysiological properties and express different profiles of membrane K<sup>+</sup> and Na<sup>+</sup> channels (Chittajallu et al., 2004). During development and throughout postnatal life, OPCs generate mature oligodendrocyte cells. It is not definitively known if these diverse populations of OPCs give rise to functionally distinct mature oligodendrocytes, however, one study suggests that oligodendrogenesis is regulated differently in grey and white matter regions (Baracska et al., 2002). In adulthood, OPCs located in white matter differentiate into mature myelin producing oligodendrocyte with greater proficiency than those in the grey matter (Dimou et al., 2008). Furthermore, when white matter or grey matter derived OPCs are transplanted into the cerebral cortex, white matter derived OPCs differentiated into mature oligodendrocytes with greater proficiency (Vigano et al., 2013). Although evidence is mounting that demonstrates region-specific properties, the extent to which these functional differences are dependent on cell intrinsic factors or extrinsic control remains speculative (Mayoral and Chan, 2016). Morphological differences have been observed between grey matter and white matter pre-myelinating oligodendrocytes. The cellular processes of pre-myelinating oligodendrocytes in the callosal white matter were more numerous and shorter in length than their cortical counterparts (Trapp et al., 1997). Additionally, white matter oligodendrocytes myelinate more axons than grey matter oligodendrocyte (Trapp et al., 1997). Within the cortical layers, researchers showed that the distinct myelin profiles produced within certain levels was influenced by the neuronal subtype in the immediate proximity suggesting extrinsic control (Tomassy et al., 2014). As reviewed previously, extrinsic factors mediated by neuron and astrocyte heterogeneity also contribute to myelin diversity (Ornelas et al., 2016; Tomassy et al., 2016). On the other hand, new evidence has emerged showing that myelin sheath length was determined by intrinsic oligodendrocyte control (Bechler et al., 2015). Regardless of whether intrinsic or extrinsic control prevails in determining oligodendrocyte regional specific functioning, it will be important for future researchers to consider this aspect of oligodendrocyte diversity in their analysis.

Regional heterogeneity is an important aspect of oligodendrocyte biology and is relevant in oligodendrocyte susceptibility to perinatal injury. The patterning of pre-oligodendrocyte lineage cells across grey and white matter regions of the developing brain dictates regional vulnerability to perinatal white matter injury associated with hypoxic-ischemia and inflammation, both common occurrences in preterm infants (Hagberg et al., 2002; Khwaja and Volpe, 2008; Ferriero and Miller, 2010; Anblagan et al., 2016). For example, during development the increased distribution of pre-oligodendrocytes in the germinal matrix, a region that includes the ventricular and subventricular zones, makes this area more susceptible to hypoxic-ischemic injury. Although intrinsically regulated mechanisms underlie the vulnerability of

pre-oligodendrocyte cells in these conditions of injury, other factors can influence oligodendrocyte vulnerability to injury that are imposed by local niches. One study that used tissue explants from early postnatal pups demonstrated that white matter OPCs were more responsive to PDGF than grey matter OPCs (Hill et al., 2013), supporting the hypothesis that regional location may be important for oligodendrocyte function in the perinatal brain. Overall, information regarding extrinsic control of oligodendrocytes by regional niche factors within normal and injured perinatal brain is remarkably absent. Recent studies of multiple sclerosis lesions reveal differences in the pathology and the extent of remyelination by oligodendrocytes within grey matter or white matter (Albert et al., 2007; Stadelmann et al., 2008; Gudi et al., 2009). Although these observations pertain to an adult pathology, they further the idea that regional specificities exist within the oligodendrocyte population.

## Conclusion

The diversity of neuronal subtypes throughout the many brain regions is well defined regarding function, morphology, and susceptibility to injury. Only recently, has there been significant investigation into different aspects of glial diversity despite their critical role in brain physiology and pathology. Diversity within the three classes of glia is only just coming into perspective (Tomassy and Fossati, 2014; Grabert et al., 2016; Ben Haim and Rowitch, 2017). New research supports that oligodendrocytes are far more diverse than previously held. The importance of dissecting the oligodendrocyte lineage into subtypes will help our understanding of oligodendrocyte biology and will inform our clinical approach to neuropathologies. Perinatal brain injury often involves oligodendrocyte dysregulation. As described in this review, emerging evidence indicates that ontogenetic origin, maturational stage, and regional location determine functional differences between populations of oligodendrocytes. These three factors also influence oligodendrocyte susceptibility to perinatal injury. Thus, oligodendrocyte heterogeneity must be considered in future research aimed at developing appropriate therapeutic options.

**Author contributions:** JN, LLJ and LAC prepared, edited, and approved the final version of the manuscript.

**Conflicts of interest:** None declared.

**Plagiarism check:** Checked twice by iThenticate.

**Peer review:** Externally peer reviewed.

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**Open peer review report:**

**Reviewer:** Joanna Czarnecka, Nicolaus Copernicus University, Poland.

**Comments to authors:** The paper is clear and accessible systematization of information about the oligodendrocytes diversity. The oligodendrocytes, cells able to myelin produce, are not a homogenous population. The paper is clear and accessible systematization of information about the oligodendrocytes diversity. Knowledge of oligodendrocytes pathophysiology, particular facets of their heterogeneity are important for therapeutic development.

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