Published in final edited form as:

Epilepsy Behav. 2005 November ; 7(3): 345–363.

Systemic Prenatal Insults Disrupt Telencephalon Development

Shenandoah Robinson, M.D.

Pediatric Neurosurgery, Rainbow Babies & Children's Hospital, Case Research Institute, Case School of Medicine, Cleveland, OH

Abstract

Infants born prematurely are prone to chronic neurologic deficits including cerebral palsy (CP), epilepsy, cognitive delay, behavioral problems, and neurosensory impairments. In affected children, imaging and neuropathological findings demonstrate significant damage to white matter. The extent of cortical damage has been less obvious. Advances in the understanding of telencephalon development provide insights into how systemic intrauterine insults affect the developing white matter, subplate and cortex, and lead to multiple neurologic impairments. In addition to white matter oligodendrocytes and axons, other elements at risk for perinatal brain injury include subplate neurons, GABAergic neurons migrating through white matter and subplate, and afferents of maturing neurotransmitter systems. Common insults including hypoxia-ischemia and infection often affect the developing brain differently than the mature brain, and insults precipitate a cascade of damage to multiple neural lineages. Insights from development can identify potential targets for therapies to repair the damaged neonatal brain before it has matured.

Keywords

cerebral palsy; development; epilepsy; GABA; neuron; oligodendrocyte; periventricular leukomalacia; prematurity; subplate; white matter lesions

1. INTRODUCTION

Premature birth and its sequelae pose a significant and persistent problem to the affected children, their families, and society. In 2003, 12.3 percent of all United States births were preterm (<37 weeks), and the preterm birth rate has risen 16 percent since 1990 (1). In addition to the suffering experienced by these children and their families, the economic costs to society are tremendous. Over the first 10 years of life the inpatient hospital costs for an infant born <28 weeks gestation is 443 percent greater than the costs for an infant born at term (2). Recent advances in obstetrics and neonatology, particularly the widespread use of surfactant beginning in the early 1990s, have led to a marked improvement in preterm infant survival, but the neurologic morbidity has not declined concomitantly (3-6).

The purpose of this review is to integrate current advances in neurodevelopment into our understanding of the pathogenesis of perinatal brain damage with a focus on preterm infants suffering systemic insults. To elucidate how to repair telencephalon development that has been disrupted by preterm birth and its associated problems, a fuller understanding of what components have been damaged is necessary. Perinatal brain damage due to preterm birth appears to involve not only myelin-forming oligodendrocytes and axons, but also subplate neurons and tangentially migrating GABAergic (γ -amino butyric acid) neurons on the way to the cortex. Either directly or indirectly, cortical damage appears to occur, and contributes to

the “cortical” impairments of cognitive delay, epilepsy, and behavioral problems (7-10). A clearer picture of how brain development is adversely affected by perinatal brain damage is essential to formulate more effective interventions for neonates, and thus minimize the neurologic morbidity.

The concept of development in the telencephalon encompasses both the processes that govern the maturation of individual cells within a lineage, and the coordinated integrated maturation of multiple neural cell populations in various structures over time. The development of oligodendrocytes, the myelin-forming cells of the central nervous system (CNS) illustrates these points. Briefly, individual oligodendrocyte precursor cells (OPCs) arise from progenitors in specific CNS regions, migrate, proliferate, survive, and mature into O4+ prooligodendrocytes (late OPCs) (11). Pro-oligodendrocytes generally cease migrating and proliferating, and differentiate into O1+ oligodendrocytes that eventually form myelin and facilitate axon conduction. Each developmental process is tightly regulated by intrinsic and extrinsic signals to produce the correct number of oligodendrocytes in the correct place for optimal myelination (11). Myelination proceeds in a specific pattern throughout the CNS during the postnatal period, while a subset of OPCs persists in the adult CNS to potentially replenish the lineage as necessary, and perhaps perform other functions. Similarly, neuronal lineages in the telencephalon arise, proliferate, migrate, survive, and differentiate in specific temporal and spatial patterns. Instead of myelination, neurons form dendrites and synapses that mature and are remodeled into complex circuits with other neuronal lineages. All the steps of maturation for each neuronal lineage are dependent on multiple intrinsic and extrinsic signals, and for each lineage, its successful development is intricately related to the development of the other lineages. Successful neuronal development also requires appropriate interactions with oligodendrocytes and astrocytes. This damage to one susceptible system might cascade through multiple systems. One can easily imagine the domino effect of damage that most likely occurs with perinatal brain damage in preterm infants. Various insult mechanisms may affect neural cell lineages differently, and various lineages may have differing inherent potential for recovery. Together, these developmental insights may suggest multiple integrated strategies for repair of the neonatal CNS.

2. INSULTS THAT AFFECT THE DEVELOPING TELENCEPHALON

2.1 Extent of the problem

Children that suffer perinatal brain damage from prematurity are prone to multiple neurologic deficits. Cerebral palsy (CP) describes a chronic non-progressive motor impairment resulting from injury to the brain before it has completed development (12). CP has been widely studied and is frequently used as an outcome measure for preterm infants, especially for intervention trials (13). Cognitive delay, epilepsy and behavior problems also occur frequently in preterm infants and likely reflect alterations in cortical development (14,15). It is not clear whether CP and these other “cortical” deficits reflect the same pathogenesis, or whether separate insult mechanisms coexist and manifest themselves together in the developing preterm brain. Preterm infants are also prone to vision and hearing loss, but the relative contributions of damage to the retina and cochlea and intervening neural pathways to the cortex are also poorly defined for infants born prematurely.

Recent studies document the relative frequency of these neurologic deficits in preterm infants. The prevalence of CP and speech delay was 11 and 42 percent, respectively, in a national two-year outcome study for extremely low birth weight (ELBW) infants (<1000 g) born in 1996-97 (16). School-age and adolescent outcome studies identify more difficulties with cognition and behavior (17,18). In an outcome study of ELBW infants, former ELBW children without major disabilities (CP, blindness, deafness, mental retardation) at 8-10 years had a 3-fold increased incidence of special education placement and grade repetition compared to full term controls

(19). Cognitive, social and behavioral skills essential for normal function are difficult to assess and may be easily overlooked with standard intelligence quotient evaluations (20). Long term outcome studies demonstrate that significantly more preterm infants at 20 years will have psychopathology compared to peers born at term (21). In a subset of preterm children, multiple disabilities occur, and compound the difficulties for these children. The incidence of epilepsy in children with CP is 21-36 percent, 29-47percent, and 50-100 percent for children with diplegia, hemiplegia, and quadraplegia, respectively (22-24). Moreover, only 29 percent of children with CP and epilepsy had normal intelligence ($IQ > 70$) (23). These children in particular could benefit from interventions to restore the developing brain.

2.2 White matter damage

Subcortical structures, including the developing white matter and subplate, a transient developmental layer located between the cortex and deep white matter, suffer the majority of direct damage from perinatal insults. In preterm infants, white matter lesions (WML) are the most frequent and prominent abnormalities observed on imaging and neuropathological studies. WML present on neonatal cranial ultrasounds are predictive of later neurologic impairment (25). Magnetic resonance imaging (MRI) provides more definition and detail of WML. Abnormalities identified in infants persist when the children are re-imaged years later (26). WML are characterized by loss of myelin-forming oligodendrocytes, axon damage and gliosis (14,27,28). Pathologically, WML induce diffuse loss of predominantly pre-myelinating O4+/O1+ oligodendrocytes in humans (29,30). Rodent models of hypoxia-ischemia have demonstrated persistent and pervasive loss of oligodendrocytes via apoptosis in early (embryonic day 18) (31), mid (postnatal day 2 (P2) (32), and late development (P7) models (33,34). Pathological examination of infants with diffuse WML demonstrated delayed myelination compared to both controls and infants with WML limited to focal areas of necrosis near the anterior or posterior horns of the lateral ventricles (27). In addition, brains of ELBW infants with WML showed diffuse axonal damage in frontal, parietal, and occipital lobes, consistent with the possible role in axonal damage as a mediator of “cortical” deficits in preterm infants with WML (35). Axonal damage in WML progresses with time, with relatively little axonal damage visible initially, and significantly more present in subacute and chronic lesions as axonal degeneration progresses (14). WML include periventricular leukomalacia (PVL) with emphasis on focal necrosis in white matter (36) and perinatal telencephalic leukoencephalopathy (PTL) with emphasis on diffuse white matter gliosis (37). Infants with severe damage develop cystic PVL. Fortunately, infants born in recent years tend to suffer predominantly diffuse gliosis, rather than the more severe cystic PVL (38-40).

2.3 Cortical damage

In contrast to white matter, significant areas of cortical gray matter necrosis or apoptosis are not routinely observed in preterm infants after perinatal brain injury. Although cortical damage is perhaps more subtle than white matter damage, disruption of development by perinatal injury is not confined to the white matter. Comparison of intracranial volumes using MRI revealed preterm infants (<32 weeks) with WML had significantly smaller cerebral cortical gray matter volume compared to preterm infants without WML (41). In addition, the infants with cystic PVL had significantly smaller cortical gray matter than those with diffuse WML (PTL) (41), suggesting that cortical volume loss is more extensive with more severe white matter damage. In a larger study, comparison of intracranial volumes using magnetic resonance imaging (MRI) showed preterm infants (<1500 g and <32 weeks) with WML had a 17 percent reduction in absolute cortical gray matter volume ($P < 0.001$), as well as a 25 percent reduction in absolute myelinated white matter volume ($P = 0.01$), compared to preterm infants without WML (39). Neurodevelopmental outcome assessed at one-year showed that infants with moderate to severe disabilities had significantly smaller cortical gray matter at term equivalent, compared to former preterm infants without disabilities (39). Interestingly, two reports comparing MRI

brain volumes of adult survivors of VLBW (<1500 g) did not find differences in cortical gray matter volume when compared to normal birthweight siblings (42,43). It is not clear whether the cortical volume differences attenuate with time, or whether the number of subjects was too small to detect a difference. Pathological studies of post-mortem preterm infants with WML have found neuronal atrophy and hypertrophy, and a switch from predominantly transcallosal and long circuits to local circuits (14,15). Delayed or arrested dendritic development was found in preterm infants brains when compared to term infants of equivalent postconceptional ages (44).

Preterm birth appears to affect cortical development and outcome even when WML are not present. In an outcome study of ELBW infants with normal early (newborn) and late (term equivalent) cranial ultrasounds born in 1995-1999 and assessed at 18-22 months, 9.4 and 25.3 percent had CP and cognitive delay (Bayley-II Mental Developmental Index <70), respectively (45). Thus, even for children without WML, preterm birth can be detrimental to neurodevelopment. It is unclear whether the disruption of cortical development that occurs with preterm birth is part of a continuum of damage that also results in WML, or whether the effects of preterm birth and perinatal brain damage have a separate but cumulative impact on cortical development. Based on analyses of pathological specimens, Marin-Padilla has proposed that the damage to the underlying white matter results in an acquired cortical dysplasia of the overlying cortex, and that these abnormalities lead to cortical dysfunction, including epilepsy (14,15,46). In rodent models, prenatal administration of toxins (47,48) or irradiation (49,50) during late gestation produces cortical abnormalities without WML that result in a propensity to seizures, suggesting that damage to cortical development without WML during late gestation could be important mechanism for "cortical" deficits associated with perinatal brain damage and preterm birth. Disruption of telencephalon development during the third trimester reflects a cascade of events that affect multiple vulnerable components of the white and cortical gray matter including: white matter oligodendrocytes, axons, subplate neurons, GABAergic neurons migrating through the subplate and white matter, and developing afferents of other neuronal populations. The development of each of these components will be reviewed, with a particular emphasis on the relationship to WML.

3. TELECEPHALON DEVELOPMENT

3.1 Early telencephalon development

The telencephalon is a complex structure by midgestation, with several vulnerable components in addition to oligodendrocytes and axons. Recent advances in neurodevelopment provide insights that may lead to more effective interventions for neonates. In humans the cortical preplate (primordial plexiform layer) forms at 4 to 7 weeks gestation superficial to the ventricular zone, with the subventricular zone first appearing at about 6 weeks (Fig 1). Precocious neurons extend long tangential processes between regions of the developing brain, and the first processes reaching the preplate arise from the basal telencephalon (51). Beginning at 7 weeks the cortical plate splits the preplate into the superficial marginal zone, the anlage of cortical layer I, and the subplate (52). The cortical intermediate zone, the anlage of white matter, forms between the subplate and the subventricular zone, and contains axonal processes and migrating neurons. Some authors divide the subplate histologically into the densely packed upper subplate and the loosely packed lower subplate (53). In this schema, the lower subplate corresponds to the intermediate zone that becomes the deep white matter (54). The ventrolateral cortex matures before the dorsolateral cortex. Projection neurons arise in the subventricular zone (germinal matrix), proliferate during 8 to 16 weeks, and migrate through the subplate to the cortical plate from 12 to 20 weeks (55). Cortical layers arise in an inside-out manner, such that the earliest-arriving neurons become layers V and VI, and the more superficial layers develop subsequently (56). All of these areas have formed by midgestation, and thus are vulnerable to preterm insults.

3.2 Human telencephalon oligodendrocyte development

As mentioned in the Introduction, oligodendrocytes mature through specific stages in a tightly regulated spatial and temporal pattern to ensure that the proper number of oligodendrocytes is present to myelinate axons. In the human telencephalon, OPCs arise from the ganglionic eminence (57,58), migrate to the subventricular zone, proliferate during midgestation, and disperse into the intermediate zone and cortex throughout the third trimester (59). Prooligodendrocytes (O4+ late OPCs) collect in the subplate, while pre-myelinating cells gather in the intermediate zone; few oligodendroglial cells entered the cortical plate (59). Throughout the second half of gestation O4+ prooligodendrocytes predominate over more mature stages (29,59). In rodents a similar predominance of O4+ pro-oligodendrocytes is found from late gestation through P2 (60). Myelination in humans appears to occur over a more protracted course than rodents (61). Oligodendrocyte development and myelin formation are dependent on axonal activity (11,62,63). Myelination begins in humans in the telencephalon at about 33 weeks (27,29), after the peak period of WML.

3.3 Axon development

Axon development in normal humans has been studied from 20 weeks gestation to about 3 years (64). Axons labeled with pan-axonal (not developmentally regulated) antibodies that bind phosphorylated medium and high molecular weight neurofilaments (Sternberger Monoclonals SMI 312) were detected beginning at 23 weeks in parietal white matter. Labeling with antibodies for maturation dependent phosphorylated high molecular weight neurofilament was one-fourth adult levels, suggesting that axons were immature. The peak period of axon extension from the white matter to the cortex is 24 to 37 weeks, as shown by GAP-43 (growth cone) expression, and directly coincides with the peak period of formation of WML (64).

Together, these findings suggest axon development occurs primarily during the period of injury precipitated by preterm birth. Axons are damaged in WML, and the damage induces the formation of abnormal circuits (14,15). Similar findings of abnormal axon development have been found in a rodent model after prolonged hypoxia during early postnatal development (65). The neuronal populations with vulnerable axons in the subplate and white matter will be discussed below. Oligodendrocyte development is affected by axon activity (62,63). Because WML impair or alter axon development, the survival of maturing oligodendroglial lineage cells is hindered, thus diminishing the potential replenishment of lost oligodendrocytes after WML by emerging oligodendroglial lineage cells. Conversely, oligodendrocytes enhance neuron survival by expressing neurotrophins during development (66). Differentiated oligodendrocytes also enhance neurite extension (67). Thus, the loss of oligodendroglial lineage cells and axons in WML results in a synergistic pattern of damage as these two components are interdependent, especially during development.

3.4 Subplate development

The subplate, a transient developmental layer in the telencephalon is crucial to normal formation of the cortex. The subplate contains subplate “pioneer” neurons, considered both the earliest-generated and first neurons of the cortex to mature (68), and other neural components including oligodendrocytes, GABAergic neurons migrating through to the cortex, and traversing axons from multiple neuronal systems. In humans the subplate forms at about 15 weeks and mostly recedes by 6 months postnatally (53,69). The subplate is more pronounced in mammals with an extensive gyral pattern, and frequently research on the precise function of the subplate is performed in cats and ferrets. In humans the subplate at its maximal thickness (22 to 34 weeks gestation), is 4 times the thickness of the cortical plate, whereas in rats at its maximal thickness, the subplate is only half as thick as the cortical plate (53).

Subplate neurons extend pioneer axons to multiple regions—Subplate neurons perform multiple functions during telencephalon development, regulating different steps as cortical development proceeds. As pioneer neurons during early cortical plate development along with layer I Cajal-Retzius neurons, subplate axons guide pyramidal neurons in layers V and VI, and thus direct the appropriate formation of cortical layers (70,71). The *Emx1/2* double mutant mice lack both Cajal Retzius neurons and subplate neurons, and fail to develop normal cortical lamination, among other abnormalities (72). Subplate neurons extend axons early, before many of the cortical plate structures have expanded. These axons can thus act as “pioneer” roadmaps for later-forming axons that must traverse a much greater distance through expanded cortical layers. Subplate neurons extend axons to the overlying cortical plate, the contralateral hemisphere, and the thalamus (70,73-75). As part of the connections to the contralateral hemisphere, subplate neurons provide axons to the corpus callosum from 25 to 32 weeks gestation (76), the peak period of WML in preterm infants. Approximately half of subplate neurons with cortical projections are glutamatergic (77), and these axons form the earliest relay of information to the cortical plate. Subplate neurons regulate neuronal migration via NMDA (*N*-methyl-D-aspartate) receptors (ref). At least one subpopulation of subplate neurons appear to be relatively stationary within the subplate (78).

Subplate neurons form functional circuits—Subplate neurons show both glutamatergic and GABAergic activity, and are involved early in functional circuits both within the subplate, and more distantly with the cortex and thalamus. Early subplate neurons express calretinin, a calcium-binding protein also found in the early Cajal Retzius neurons in layer I (79). Later in development, early neonatal subplate neurons receive glutamatergic input via AMPA and NMDA receptors from the thalamus, layers V and VI of the cortical plate, and the subplate (80). Some subplate neurons express GABA and neuropeptides, and are interneurons involved in local subplate circuits (73,80). Recordings of subplate neurons show they receive synaptic input and fire action potentials (81,82). Together, these findings demonstrate that the subplate neurons are involved in functional circuits that integrate cortical development.

Subplate neurons are essential for cortical organization—Subplate neurons are essential for normal development of thalamocortical projections to layer IV of the cortex. Rakic termed the subplate “the waiting compartment,” implying that early circuits from the thalamus form in the subplate while awaiting the maturation of the overlying cortex (83). The waiting axons are not idle; they extend processes and form transitional circuits. If subplate neurons are ablated early in development, thalamocortical projections fail to invade into cortical layer IV (84,85). Instead, the axons grow through the visual cortex to adjacent areas. Experiments with thalamocortical axons to the auditory cortex showed similar results (86). Ablation of subplate neurons later in gestation blocks the development of ocular dominance columns (ODC) in the visual cortex (85). After arrival of the thalamocortical projections in the cortex, synapses mature and are refined in an activity-dependent process heavily influenced by subplate neurons (87). Ablation of subplate neurons after the ingrowth of thalamocortical axons into visual cortex layer IV but before ODC formation impairs the functional organization of the developing cortex including synaptic remodeling and maturation (88). In the visual cortex, this impaired function manifests as failure to form orientation maps, and failure to tune to orientation, reflecting failure of thalamocortical synapses to strengthen appropriately through synaptic activity and remodeling (88). Subplate neuron ablation also alters the cortical expression of growth factors including brain derived neurotrophic factor (BDNF) and neurotrophin 3 (NT-3) and GABA (89,90); all activity-dependent molecules that regulate neuronal maturation. This suggests these molecules may mediate subplate regulation of cortical development. Subplate neuron ablation also precipitates seizures in some animals, suggesting that the alterations in cortical formation have functional implications (89).

Subplate neurons recede postnatally—The fate of subplate neurons is controversial. Without question their number declines dramatically in the postnatal period. Postnatally these neurons lose their characteristic neurotransmitter markers (91). Subplate neurons also appear to undergo apoptosis (54,78,92). These neurons express multiple receptors for neurotrophins (93,94), and loss of neurotrophin support may lead to apoptosis. It is unclear whether a residual population of subplate neurons exists in the mature CNS. If these neurons do undergo developmentally regulated apoptosis, then this program could potentially be manipulated in infants that have suffered WML and damage to the subplate.

Subplate neurons are vulnerable to preterm perinatal brain injury—Considering the peak of subplate formation and activity correlates with the peak period of brain damage in preterm infants with WML, and the crucial role of subplate neurons in cortical development, it is not surprising that these cells have been implicated in the causation of “cortical” deficits in humans (8-10,95,96). Subplate neuronal loss has been shown in a rodent model of hypoxia-ischemia on postnatal day 2 (32). Subplate neurons express NMDA receptors, and are thus prone to excitotoxic injury, which has been demonstrated in neonatal hypoxia-ischemia (97). Subplate neurons also form extensive circuits and their axons may be affected as part of WML damage. Clearly, given the specific roles of subplate neurons at subsequent stages of prenatal and early postnatal development, simple replenishment of the lineage as one might consider for oligodendrocytes will not be satisfactory for subplate neurons.

3.5 GABAergic neuronal development

General review of GABAergic development—A major portion of GABAergic neuronal development occurs during the third trimester, and several aspects of the development of the lineage suggest GABAergic neurons are vulnerable to perinatal insults associated with prematurity. GABAergic neurons, which are primarily inhibitory interneurons in the mature CNS, comprise only about 20-25 percent of the neurons in the mature cerebral cortex (98). Their numeric minority is balanced by the significant impact these cells have on cortical neuronal development (99,100). Excitatory cortical projection neurons migrate to the cortical plate by midgestation. Although the synaptic maturation and remodeling of these pyramidal neurons in the cortex appear to be secondarily affected by WML, they are relatively spared by WML compared to cells in the white matter and subplate. By contrast, major portions of GABAergic neuronal development occur during the third trimester, as these cells migrate tangentially through the white matter and subplate into the cortex (101). GABAergic neuron development has several similarities to oligodendrocyte development. GABA has major roles in normal cortical development, even before mature synapses with receptors are present (102). Finally, GABAergic receptors undergo developmental changes during this period, switching from depolarizing excitatory synapses to hyperpolarizing inhibitory synapses found in the mature CNS.

The expression level of GABA, a neurotransmitter, is regulated by the rate limiting enzyme glutamic acid decarboxylase (GAD), which occurs in two isoforms, GAD-65 and GAD-67. GABAergic neurons arise in rodents in the ganglionic eminence, migrate tangentially through the developing white matter and subplate to the dorsal telencephalon, and then migrate radially to the cortex (101,103-106). Multiple molecules regulate GABAergic neuronal migration (104,107,108), and GABAergic neurons follow the same inside-out pattern of corticogenesis as pyramidal neurons. Thus, GABAergic neurons migrating later in gestation populate cortical layers II and III (109). They typically form local cortical circuits. In rodents GABAergic neuronal cortical migration and development are mostly complete by postnatal day 6 and the end of the third postnatal week (P21), respectively.

Interestingly, few studies have focused on distinguishing between the GABAergic neuronal population that migrates through the subplate and developing white matter to a final destination of the cortical plate, and the GABAergic neuronal population that are subplate neurons that arise before the cortical plate and remain in the subplate as part of the local circuitry during development that then regresses (110). The developmental timing and location places both of these GABAergic populations at risk for injury from WML related to preterm birth.

Telencephalon GABAergic neuron development in humans—GABAergic neurons are thought to help organize the developing cortex because GABA is present at 6.5 weeks, prior to both the formation of the cortical plate and synaptogenesis (111). GABAergic neurons have been visualized in the developing human telencephalon at 6-9 weeks in the ganglionic eminence (GE) and intermediate zone (111-114). In contrast to multiple rodent studies which show the vast majority of GABAergic neurons migrate from the ventral GE to the dorsal telencephalon (101,103,104,106), retroviral labeling in organotypic slice cultures from humans fetuses at 13 to 24 weeks gestation showed that 65 percent of GABAergic neurons appear to arise from the dorsal ventricular and subventricular zones, with only a minority of GABAergic neurons coming from the ventral GE (115). Ulfing found GABAergic neurons labeled with the calcium-binding proteins, calretinin and calbindin in the human ganglionic eminence beginning at 16 weeks, and a gradual increase in calretinin+ cells in the intermediate zone (white matter anlage) at 24 weeks (116). Further studies will have to clarify if the early GABAergic neurons observed earlier in gestation in the GE are the source of cortical GABAergic neurons in humans (113). GABAergic neurons begin to populate the cortical plate by 11 to 20 weeks (111,117). GABA and GAD expression peak in the cerebrum at 24 to 26 weeks gestation, and taper down to mature CNS levels by 35 weeks (118). Thus, the GABA expression peak coincides with the primary period of perinatal brain damage from preterm birth. During the third trimester the morphology of GABAergic neurons transitions from primarily an immature bipolar form to a more mature multipolar cell (117). GABAergic neurons migrate through the white matter and subplate during late gestation.

GABAergic neuronal subtypes in humans—Three major non-overlapping subtypes of GABAergic neurons, as defined by calcium-binding proteins and neuropeptides, are present during development and in the mature CNS: parvalbumin (PVA), somatostatin, and calretinin (119-121). GABAergic neuronal subtypes, and the eventual layer specification of the neurons in the cortex is influenced by the site of origin of the neurons in the GE (medial, lateral or caudal GE), and the timing of the origin (109,122,123). Differentiation into the various subtypes is dependent on neuronal activity and extrinsic signals (124). For example, PVA subtype expression is regulated by BDNF and neurotrophin-4 (125). Calretinin+ neurons are present in the human entorhinal cortex by birth, but PVA expression is not widely visualized there until a few months postnatally (126). PVA+ neurons have been visualized in the human somatosensory and auditory cortex at 38 weeks in layer IV, and were found diffusely throughout the cortex by 3 months (127). Somatostatin neurons first appear in the subplate at 22 weeks, and continue to accumulate in the subplate before entering the cortical plate at 32 weeks (128). Neuropeptide Y (NPY) neurons comprise a subset of somatostatin neurons, and alterations in their development lead to epilepsy in rodents (129,130). NPY+ neurons are first visualized in the human subplate and intermediate zone at 14 weeks gestation, and begin to arrive in the cortical plate by 23 weeks (131,132). During the second half of gestation maximal expression of NPY+ neurons is found in the subplate. Postnatally the subplate NPY+ neurons regress, and the cortical NPY+ neurons continue their development (131,132). Another subset of GABAergic neurons is defined by the expression of nitric oxide synthase (NOS). A study of the development of these neurons in human brains demonstrated these neurons accumulate in the subplate from 25 to 30 weeks, and move to the cortex by 35 weeks (133), again coinciding with the period of prenatal brain damage.

Role of GABA in regulation of neuronal development—A significant portion of GABAergic neuronal development occurs during the third trimester. In addition, GABA influences the development of most cortical neurons during the same timeframe (99,100,134) (reviewed in Lujan05,. GABA receptors undergo significant changes during development that influence the functional development of the cortex (100). GABA synapses form prior to glutamate synapses. At birth 80 percent of projection neurons are still silent, while only 5 percent of GABAergic neurons are not active (135). Thus, GABA has a unique ability to influence cortical synaptic development. GABA is excitatory in the immature brain, mediated by fast-acting ionotropic GABA_A receptors (99). GABA depolarizes immature cells because they have a high intracellular chloride gradient, and an initial lack of KCC2 (K⁺-Cl⁻ cotransporter), a developmentally regulated molecule that extrudes chloride ions (136,137). KCC2 expression dramatically increases in the latter half of gestation and early neonatal period, increasing the extrusion of Cl⁻, and thus decreasing the intracellular Cl⁻ gradient. Upregulated KCC2 expression transitions the early excitatory GABA synapses to hyperpolarizing inhibitory synapses found in the mature CNS (99,136). Interestingly, KCC2 expression appears to be regulated by BDNF, and affected in the mature CNS by BDNF levels (136). If WML alter the expression of BDNF, triggering a cascade that alters the upregulation of expression of KCC2, then a delay in the switch of GABAergic synapses from excitatory to inhibitory may affect the synaptic maturation in multiple cortical circuits.

GABA, along with glutamate, regulates proliferation of neural progenitors in the ventricular zone (138). GABA also activates calcium currents in immature neurons, and thus potentiates the effects of glutamate on NMDA receptors (139). GABA regulates migration of cortical neurons via noncanonical paracrine (140), GABA_A receptor-mediated mechanisms (141-143), and GABA_B receptor-mediated mechanisms (143). GABA_B receptors are slow-acting metabotropic G protein receptors. GABA also influences neuronal maturation and differentiation (100,144).

This brief review demonstrates GABA is a crucial influence on cortical synaptic development. The role of these molecules in regulating normal development is demonstrated in animals with prenatal alterations in the GABAergic pathway. Mice with genetic alterations in the GABAergic pathway during development are prone to seizures and behavioral abnormalities (145-148). Chick embryos that undergo hypoxia during midgestation show decreased binding of GABA to GABA_A receptors (149). The majority of the neural development GABA influences occurs during the second half of gestation, a time when preterm infants are prone to insults that affect the white matter, subplate, and overlying cortex.

GABAergic pathway expression in WML—Few studies have been published defining the impact of WML on GABAergic pathway expression in humans. An analysis of parvalbumin (PVA) expression in the brains of infants and children that had WML showed that PVA expression was decreased in infants with diffuse WML, compared to specimens without WML (127). In a recent study comparing neonatal expression of the GABAergic pathway in infants born at 25 to 32 weeks gestation, immunohistochemistry on age-matched specimens from infants with WML revealed a decreased number of cells expressing GAD-67, calretinin, GABA_Aα1 and GABA_BR1 receptors, compared to specimens without WML (Robinson, et al., unpublished results) (Fig 2). In a study of infants with hydrocephalus compared to control infants at 32 to 36 weeks gestation, no differences in the number or distribution of neurons expressing calcium binding proteins (PVA, calbindin, and calretinin) were found, but the expression of the proteins on neurites was diminished, and the cell bodies were shrunken in hydrocephalic infants, compared to control infants (150). These findings suggest the GABAergic neuronal development may be susceptible to insults in the third trimester.

Interactions of oligodendrocytes and GABAergic neurons—A subpopulation of oligodendrocytes in the telencephalon arises from the same ventral stem cell population as a subset of GABAergic neurons (151,152), and oligodendrocytes share many properties with their neuronal counterparts. Oligodendrocyte precursor cells (OPCs) express GABA (153) and functional glutamate-mediated AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors (154). Glutamate inhibits OPC proliferation and maturation (155-157). GABA modulates glutamate signaling of OPCs via GABA_A receptors (158), as well as enhances oligodendrocyte survival (159). Thus, if WML alter GABAergic pathway expression, then the development of OPCs that is dependent on the balance of GABA and glutamate signaling may be altered.

3.6 Cortical afferent development

Catecholamine development—Neurons expressing monoamines and their axons from subtelencephalic sources to the cortex also traverse the developing white matter and subplate during the latter half of gestation, and are thus vulnerable to WML related to prematurity. These afferents include dopamine (DA), norepinephrine (NE), serotonin (5-HT, 5-hydroxytryptamine) and acetylcholine (ACh) systems (160). Both dopaminergic and noradrenergic axons have been found in the human subplate by 6.5 weeks (161,162), the time when GABA first appears (111). These afferents peak in late gestation, and diminish markedly in the early postnatal period, suggesting they impact cortical development during this timeframe (160). Loss of NE, DA and ACh afferents induce changes in cortical dendrite length and complexity (160). The NE receptor α_2 has peak expression on neurons in white matter during the perinatal period, implying a significant developmental role, including guiding afferents across the corpus callosum (163). Serotonin afferents appear at 5 to 12 weeks gestation in humans, and appear to affect neuronal differentiation in the forebrain (164). Interestingly, serotonin expression peaks at 22 to 26 weeks, the peak time of WML, and declines in the early period postnatally (165). Serotonin appears important in regulating cortical neuronal differentiation and behavior (160). Prenatal excess serotonin levels disrupt cortical barrel formation, suggesting that serotonin is required for normal patterning of the cortex (164). Inappropriate serotonin levels have been implicated in multiple behavioral abnormalities including autism and anxiety disorders (164). Together, the location and timing of the arrival of these afferent systems in the subplate and cortex suggests the afferents of these neurotransmitter systems may be vulnerable to perinatal brain injury due to preterm birth.

3.7 Cortical synapse maturation and remodeling

Neurons undergo significant dendritic differentiation during late gestation (44). Acetylcholinesterase labels thalamocortical and basal forebrain acetylcholine (ACh) afferents (9). ACh afferents are found in the upper subplate between 22 to 26 weeks, and penetrate the cortical plate after 26 weeks (9). The ACh afferents arrive slightly after dopamine, serotonin, and norepinephrine afferents (160), but are representative and provide insight into cortical development. The afferents initially form synapses on the relatively more mature neurons in the deeper cortical layers, and by 27 to 32 weeks, synapses are formed on more superficial cortical layers. Cortical layer III neurons develop complex arborizations during this time, perhaps induced by the arriving afferents (9). After 34 weeks the granularity of layer IV diminishes, probably reflecting the influences of subplate neurons on the shaping and remodeling of cortical synapses (85,166). Although cortical projection neurons are present in the correct layer in the cortex prior to the period of insult by preterm birth, the synaptic maturation and circuit formation by these neurons is most likely secondarily affected by WML that alter subplate and GABAergic neuronal survival.

Glutamate-activated NMDA receptors are important for synapse maturation and remodeling that occurs late in gestation and in the postnatal period. Although NMDA receptor peak

expression occurs at approximately 1 to 3 years in humans (165), these receptors are present in the developing cortex, and may be secondarily affected by the insults that produce WML. Glutamate-activated AMPA receptors are not significantly active during the prenatal period, and their activation is activity-dependent (167). In the immature brain excitatory GABA_A receptors probably substitute for the effects of AMPA receptors (165). NMDA receptors may contribute to the excitotoxicity experienced by neural cells during perinatal brain damage, as discussed below.

4. POINTS OF VULNERABILITY AND WINDOWS OF OPPORTUNITY

4.1 Mechanism of injury: Hypoxia-ischemia and infection induce pro-inflammatory cytokines and oxidants

White matter and the subplate are vulnerable to prenatal insults—Pathological criteria can be used to approximate the timing of the insults to the brain, because cellular responses to injury in the CNS take a specified time to appear. A majority of infants with early neonatal death have pathological findings demonstrating prenatal brain damage, in addition to intrapartum and postnatal damage (168). White matter and subplate damage is more pronounced than injury to the cortical gray matter in preterm infants. White matter may be relatively more vulnerable to ischemia because of its anatomy (55). In contrast to the germinal matrix (subventricular region) and cortical gray matter that demonstrate a progressive increase in both percentage of blood vessel area and number of vessels from 16 weeks gestation onward, white matter does not show a similar significant increase until 32 weeks (169). The developmental anatomy of the white matter and subplate predisposes these areas to damage from perinatal injury.

The predominant mechanisms of prenatal white matter damage include hypoxia-ischemia due to placental insufficiency from hypercoagulable states, abruption or other causes, and inflammation from intrauterine infection (chorioamnionitis) (55,170-173). The presence of one insult may sensitize the fetus to damage from the other (174,175). Multiple models of hypoxia-ischemia (31,32,176-178), and intrauterine infection or lipopolysaccharide administration (179-182) have been used to model WML (reviewed in (183). Interestingly, the combination of hypoxia-ischemia and LPS administration induces a loss of cortical volume and cognitive impairment along with WML not observed with either insult by itself (184). Since defining intrauterine infection and hypoxia-ischemia in the clinical setting can be difficult on a routine basis, unless it is quite severe, there may be fetuses that are exposed to relatively mild forms of both insults, but suffer from the synergistic effect (174).

Preterm insults induce pro-inflammatory cytokines and oxidants in humans—

The development of WML and/or cerebral palsy has been associated with abnormally high levels of neonatal pro-inflammatory cytokines such as interferon- γ (IFN- γ), interleukin 1 β (IL-1 β), interleukin-2 (IL-2), interleukin -6 (IL-6), and tumor necrosis factor- α (TNF α) (185-189). A more recent study of exclusively preterm infants (<32 weeks gestation) did not find an association between CP and pro-inflammatory cytokine expression (190). Pro-inflammatory cytokines typically are manifest along with oxidative stress, but neonatal levels of free radical metabolites have not been routinely studied in clinical trials of preterm infant outcomes. The presence of pro-inflammatory cytokines may be a marker of oxidative stress that occurs in preterm infants and leads to WML, and markers of oxidative stress may prove to be more predictive. Multiple pathologic studies have found excess microglia and expression of pro-inflammatory cytokines and oxidants in human WML (8,64,191-193). The vulnerability of oligodendrocyte lineage cells to oxidative stress may be compounded by the developmental lag in expression of superoxide dismutases in fetal white matter (191). Elevated levels of pro-inflammatory cytokines and signs of oxidative stress are consistent findings in WML in humans.

Pre-myelinating oligodendrocytes and neurons are vulnerable to oxidative stress, hypoxia-ischemia, and pro-inflammatory cytokines—In addition to the gross anatomical vulnerability of the developing white matter and subplate, specific cell types within these structures are particularly susceptible to perinatal brain damage. Pre-myelinating oligodendrocytes are the predominant cells present in white matter from the oligodendroglial lineage from 24-32 weeks (29). Both oxidative stress and hypoxia-ischemia affect primarily O4+ pro-oligodendrocytes (OPCs) (194-197). Oligodendrocytes and neurons are also vulnerable to pro-inflammatory cytokines (198-201). Treatment with anti-inflammatory/anti-oxidant agents can potentially diminish the expression of both cytokines and oxidants after perinatal brain injury (202,203). In a newborn piglet model of bilateral carotid hypoxia-ischemia, reduction of oxidant-induced apoptosis was present when a selective nitric oxide synthase inhibitor was administered during reperfusion (176,204). Similarly, administration of an anti-inflammatory agent, doxycycline, within hours after the insult in a postnatal day 7 unilateral carotid hypoxia-ischemia rat model, showed a decrease in apoptosis and microglia one week later (205). Perinatal insults can also induce *anti*-inflammatory cytokines. The altered balance of pro and anti-inflammatory cytokines may be more significant than the pure excess of pro-inflammatory cytokines alone (174). Administration of the anti-inflammatory cytokine interleukin-10 caused a decrease in pro-inflammatory cytokine expression in vitro (206). Both expression of cytokines and oxidants, and the vulnerability of cells in various lineages differs both in timing during gestation, and in brain location. This variability, along with the differences between species such as rodent and humans, compounds the difficulty in dissecting out the influences of these toxic substances. Nevertheless, normalizing the cytokine and free radical balance does appear to be a necessary part of any intervention strategy.

4.2 Excitotoxicity damage to neurons and oligos

Neurons and oligodendrocytes are vulnerable to excitotoxicity—Secondary neural cell injury and death from excitotoxicity occurs after prenatal insults. Briefly, in NMDA receptor-mediated excitotoxicity, oxygen deprivation precipitates energy depletion, excessive glutamate release, inappropriate activation of NMDA receptors, an influx of calcium into cells, and the formation of excess free radicals (207). NMDA-mediated neuronal toxicity from prenatal insults contributes to perinatal brain damage (207). Non-NMDA receptor-mediated mechanisms also kill oligodendrocyte lineage cells via excess glutamate (208-210). Oligodendrocyte precursors (OPCs) express glutamate-mediated AMPA receptors, and thus are vulnerable to glutamate-mediated excitotoxicity (97,202,208,211). Agents that block AMPA receptors are beneficial in rodent models of perinatal hypoxia-ischemia(202). OPCs with AMPA receptors are present during the third trimester, whereas most cortical projection neurons do not express AMPA receptors until term, perhaps explaining why cortical projection neurons are rather immune to AMPA-mediated excitotoxicity earlier in gestation (212).

The mechanisms of damage from pro-inflammatory cytokines, oxidative stress, and excitotoxicity are integrated in the immature CNS. In rodent models, inflammation induced with LPS produces oxidative stress that contributes to ischemic injury through a non-glutamate mediated mechanism (213). NMDA-mediated excitotoxicity also stimulates the production of pro-inflammatory cytokines by neurons and glia (214,215). This complex pattern of toxicity, and the variability of the different lineages present in the developing white matter and subplate partially explains why agents that suppress one part of the pathway, improve parts but not all of the damage.

As mentioned above in the discussion of GABAergic development, a loss of expression of the GABAergic pathway appears to occur in WML. Without sufficient presence of the GABA pathway when insult-induced excess glutamate may be present, OPC susceptibility to glutamate-mediated excitotoxicity may be more severe. The lack of adequate GABAergic

pathway expression in WML may contribute to the lack of replenishment of the oligodendroglial lineage long after a prenatal insult has occurred. Thus, lack of sufficient GABAergic involvement may not only affect developing neuronal pathways, but also contribute to the damage of the oligodendroglial lineage.

4.3 Excess apoptosis – a cloudy window of opportunity

The necrosis – apoptosis continuum—Necrosis is cell death due to direct energy failure and results in the fairly immediate and rapid expansion and rupture of the cell (216). Classic apoptosis, or programmed cell death is an energy dependent process with protein expression, chromatin condensation, and cytoplasm shrinkage. During normal CNS development significant waves of oligodendrocyte and neuronal apoptosis occur after proliferation and migration to adjust the final mature cell number to the required number (63). This apoptosis is dependent upon a cascade of effector protein termed caspases, (cysteine-dependent aspartate-directed *proteases*), and activated-caspase 3 is a final mediator of the caspase cascade (217). Mutant mice lacking caspase 3 have highly disorganized brains, suggesting it plays a unique role in brain development (218). Apoptosis in the CNS appear to be regulated by multiple pathways, including caspase-independent ones to support the complex needs for cell survival and death in both the developing and mature CNS (219). After a prenatal insult, delayed excess caspase 3 expression occurs (31,220,221), as does a delayed form of cell death (in addition to rapid necrosis) (222).

Ischemia-induced cell death in the immature brain appears to be a continuum of necrosis and apoptosis, with the degree of necrosis increasing with the severity of the insult (220, 223-225). Controversy exists as to whether the delayed cell death after a perinatal insult is truly equivalent to the programmed cell death that occurs as part of normal development (216,226, 227). Given the complexity of using classic apoptosis to control cell number in both the developing and mature CNS, it is unlikely that ischemia-induced programmed cell death uses the exact same mechanisms. Ultrastructural examination showed that delayed cell death from an insult differs from the natural process that occurs as part of neurodevelopment (226), and different molecules mediate the different types of cell death (228). These distinctions are important because they may clarify use of caspase inhibitors to ameliorate perinatal brain damage. Potentially a subset of cells affected by a preterm insult could be rescued using a caspase inhibitor, if excess delayed cell death mediated by caspases is triggered by the insult. The potential utility of this approach has been demonstrated in at postnatal day 7 unilateral carotid hypoxia-ischemia study in rats (229).

5. DEVELOPMENTAL INSIGHTS FOR POTENTIAL INTERVENTIONS

Clinical trials of promising interventions to date have either not held up with large-scale studies (reviewed in (230), or decreased the rate of intraventricular hemorrhage without improving long term neurologic outcome (231). Multiple thoughtful approaches have been utilized to suppress pro-inflammatory cytokines and oxidants, and many have been successful in animal models. Some of the failure to translate interventions from other mammals to humans may be due to the differences in telencephalon development, such as the differences in the subplate structure and different susceptibilities of various lineages to preterm insults. Also, the synergy of infection and hypoxia-ischemia insults may affect various lineages differently. Most models of hypoxia-ischemia that inflict gradations of an insult, demonstrate the damage is progressive. In rats subjected to graded hypoxia-ischemia at embryonic day 18, oligodendrocytes and neurons demonstrated differing levels of susceptibility (31). Difficulties encountered from differences between the development of the immune systems between various species are additive to the species differences in CNS development. The synergy of multiple insults, and varying degrees of those insults presents a complex challenge to model effectively in animals. In addition to differences between the term brain and the mature CNS, the dramatic changes

in telencephalon development during the third trimester suggest that the vulnerability and potential for recovery is most likely different between preterm and term infants. Strategies need to address not only replenishing oligodendrocytes but also restoring various aspects of neuronal development including neuronal subtype differentiation, axon outgrowth, receptor maturation, synapse remodeling, and circuit formation.

Steroid suppression of inflammation

Steroids have been investigated as a means to suppress the inflammatory response. Postnatal steroids improve lung function in preterm infants, but adversely affect brain development (232-235). Some studies have shown antenatal steroids may be of long term neurologic benefit (236), others showed they are not necessarily harmful, with no increase in WML on ultrasound (233). More recent studies have found an association of antenatal steroid use with ultrasound WML (237). The differences in formulation of dexamethasone and betamethasone may play a role (232,237). A recent meta-regression analysis found that the risk of CP or death varies with the risk of chronic lung disease, and that in children with a high risk of lung disease (>65%), steroids may be beneficial (238). Clinical studies suggest improved management of severe pulmonary problems (45) and necrotizing enterocolitis requiring surgery (239) may provide some neurologic benefit. These trials suggest that only in the most severe cases steroids may moderate the cumulative insult.

Laboratory studies have demonstrated that steroids are not beneficial to developing neural cells. Dexamethasone impairs oligodendrocyte precursor proliferation (240), and aggravates ischemic, infectious and oxidative damage to neurons (232). Fetal sheep administered repeated doses of prenatal betamethasone showed significantly delayed myelination compared to sheep that received saline (241). Steroids do facilitate lung maturity and preterm infant survival, but at a neurologic cost. The difficulties found with the steroid trials illustrate the problems of using an agent with conflicting outcomes on different physiological systems.

Trophins to enhance normal developmental pathways

In addition to suppressing the toxic mediators of prenatal brain damage, trophins, growth factors and other molecules that regulate normal development, may enhance the recovery of oligodendrocytes and neurons after damage. The oligodendrocyte lineage has significant inherent potential to replenish itself. After neonatal (P7) hypoxia-ischemia in rats, a population of newly generated OPCs is visible after 4 weeks (242). A similar potential for replenishment was found in human WML. Myelin transcription factor recognizes proteolipid protein (PLP), a marker of OPCs. During normal human development, expression of MyT1 increases from 19 to 29 weeks, and then it recedes, consistent with the transition of OPCs to more mature stages of the lineage. Increased expression of MyT1 was found around chronic WML, suggesting that OPCs may be attempting to repopulate areas devoid of more mature pre-oligodendrocytes and oligodendrocytes (243). When selective loss of oligodendrocytes is induced in early postnatal period, the endogenous potential of oligodendrocytes to remyelinate persists (244), suggesting that neonatal treatment to support oligodendrocytes may be beneficial, even though it is after the preterm insult. After preterm brain damage OPCs may fail to mature and resume myelination because oligodendrocyte maturation and myelin formation are dependent on axon activity. Oligodendrocytes support neuronal survival and axon extension. Because the development, and thus potential recovery of oligodendrocytes and neurons are interdependent, the combined loss of oligodendrocytes may precipitate a vicious cycle. GABAergic neurons also enhance oligodendrocyte development, and the loss of GABAergic neurons in WML also contributes to the difficulty of functional restoration of myelination.

Thus, neurotrophins and oligotrophins offer a potential therapy to enhance restoration of the developing, but damaged preterm brain (245). The unfavorable part of using trophins is that most agents have multiple effects on different lineages, and different effects on various phases of maturation for each lineage. Trophins may trigger abnormal responses to normal developmental processes such as proliferation, migration, and apoptosis, resulting in excess cells or invasion suggestive of a tumor.

Normalize the environment plus replenish the missing neurons

Together, the current understanding of preterm brain damage suggests that an effective intervention will combine suppression of pro-inflammatory cytokine and pro-oxidant pathways, and enhance neural cell recovery with trophins. Subventricular stem cells are relatively resistant to insults, and demonstrate the potential to restore the telencephalon after insults (246). The possible use of autologous infant stem cells to provide trophins and other molecules to support neurodevelopment, and even replenish missing neural cell populations is intriguing. The developing brain demonstrates remarkable resiliency in many situations. Advances in our understanding of brain development will hopefully allow us to capitalize on the resiliency to enhance recovery after preterm brain damage.

ACKNOWLEDGEMENT

This work was supported by NIH K08-NS46486 to S.R. The author would like to thank Drs. Nancy Bass and Robert Miller for their insightful suggestions.

REFERENCES

1. Martin J, Kochanek K, Strobino D, Guyer B, MacDorman M. Annual summary of vital statistics - 2003. *Pediatrics* 2005;115(3):619–634. [PubMed: 15741364]
2. Petrou S. The economic consequences of preterm birth during the first 10 years of life. *BJOG* 2005;112 (S1):10–15. [PubMed: 15715587]
3. D'Angio C, Sinkin R, TP S, Landfish N, Merzbach J, Ryan R, et al. Longitudinal 15-year follow-up of children born at less than 29 weeks gestation after introduction of surfactant therapy into a region: Neurologic, cognitive, and educational outcomes. *Pediatrics* 2002;110(6):1094–1102. [PubMed: 12456905]
4. Marlow N. Neurocognitive outcome after very preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F224–F228. [PubMed: 15102725]
5. Vohr B, Wright L, Dusick A, Mele L, Verter J, Steichen J, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Developmental Research Network, 1993-1994. *Pediatrics* 2000;105(6):1216–1226. [PubMed: 10835060]
6. Wilson-Costello D, Friedman H, Minich N, Fanaroff A, Hack M. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. *Pediatrics* 2005;115:997–1003. [PubMed: 15805376]
7. Dammann O, Kuba K, Leviton A. Perinatal infection, fetal inflammatory response, white matter damage, and cognitive limitations in children born preterm. *Ment Retard Dev Disabil Res Rev* 2002;8:46–50. [PubMed: 11921386]
8. Kadhim H, Tabarki B, DePerez C, Sepire B. Cytokine immunoreactivity in cortical and subcortical neurons in periventricular leukomalacia: Are cytokines implicated in neuronal dysfunction in cerebral palsy? *Acta Neuropathol* 2003;105:298–216.
9. Kostovic I, Judas M. Correlation between the sequential ingrowth of afferents and transient patterns of cortical lamination in preterm infants. *Anat Record* 2002;267:1–6. [PubMed: 11984786]
10. Volpe J. Subplate neurons - Missing link in brain injury of the premature infant. *Pediatrics* 1996;97 (1):112–113. [PubMed: 8545202]
11. Miller R. Regulation of oligodendrocyte development in the vertebrate CNS. *Prog Neurobiol* 2002;67:451–467. [PubMed: 12385864]

12. Shapiro B. Cerebral Palsy: A reconceptualization of the spectrum. *J Pediatr* 2004;145:S3–S7. [PubMed: 15292880]
13. O'Shea T. Cerebral palsy in very preterm infants: New epidemiological insights. *Ment Retard Dev Disabil Res Rev* 2002;8:134–145.
14. Marin-Padilla M. Developmental neuropathology and impact of perinatal brain damage. II: White matter lesions of the neocortex. *J Neuropath Exp Neurol* 1997;56(3):219–235.
15. Marin-Padilla M. Developmental neuropathology and impact of perinatal brain damage. III: Gray matter lesions of the neocortex. *J Neuropath Exp Neurol* 1999;58(5):407–429. [PubMed: 10331430]
16. Tommiska V, Heinonen K, Kero P, Pokela M-L, Tammela O, Jarvenpaa A-L, et al. A national two year follow up study of extremely low birthweight infants born in 1996 - 1996. *Arch Dis Child Fetal Neonatal Ed* 2002;88:F29–F35. [PubMed: 12496223]
17. Anderson P, Doyle L. Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s. *Pediatrics* 2004;114(1):50–55. [PubMed: 15231907]
18. Gardner F, Johnson A, Yudkin P, Bowlert U, Hockley C, Mutch L, et al. Behavioral and emotional adjustment of teenagers in mainstream school who were born before 29 weeks' gestation. *Pediatrics* 2004;114:676–682. [PubMed: 15342838]
19. Buck G, Msall M, Schisterman E, Lyon N, Roger B. Extreme prematurity and school outcomes. *Paediatr Perinat Epidemiol* 2000;14:324–31. [PubMed: 11101019]
20. Aylward G. Cognitive and neuropsychological outcomes: More than IQ scores. *Ment Retard Dev Disabil Res Rev* 2002;8:234–240. [PubMed: 12454899]
21. Hack M, Youngstrom E, Cartar L, Schluchter M, Taylor H, Flannery D, et al. Behavioral outcomes and evidence of psychopathology among very low birth weight infants at age 20 years. *Pediatrics* 2004;114:932–940. [PubMed: 15466087]
22. Carlsson M, Hagberg G, Olsson I, Hospital SCs. Clinical and aetiological aspects of epilepsy in children with cerebral palsy. *Dev Med Child Neurol* 2003;45:371–376. [PubMed: 12785437]
23. Hadjipannaysis A, Hadjipannaysis C, Youroukos S. Epilepsy in patients with cerebral palsy. *Dev Med Child Neurol* 1997;39:659–663. [PubMed: 9352726]
24. Kwong K, Wong S, So K. Epilepsy in children with cerebral palsy. *Pediatr Neurol* 1998;19:31–36. [PubMed: 9682882]
25. Pinto-Martin J, Riolo S, Cnaan A, Holzmna C, Susser M, Paneth N. Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in a low birth weight population. *Pediatrics* 1995;95:249–254. [PubMed: 7838643]
26. Skranes JS, Nilsen G, Smevik O, Vik T, Burbakka A-M. Cerebral MRI of very low birth weight children at 6 years of age compared with the findings at 1 year. *Pediatr Radiol* 1998;28:471–475. [PubMed: 9634467]
27. Iida K, Takashima S, Ueda K. Immunohistochemical study of myelination and oligodendrocyte in infants with periventricular leukomalacia. *Pediatr Neurol* 1995;13(4):296–304. [PubMed: 8771165]
28. Kinney, H.; Armstrong, D. Perinatal Neuropathology. In: Graham, D.; Lantos, P., editors. *Greenfield's Neuropathology*. Arnold; London: 1997. p. 552-555.
29. Back S, Luo N, Borenstein N, Levine J, Volpe J, Kinney H. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. *J Neurosci* 2001;21(4):1302–1312. [PubMed: 11160401]
30. Haynes R, Folkerth R, Keefe R, Sung I, Swzeda L, Rosenberg P, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropath Exp Neurol* 2003;62(3):441–450. [PubMed: 12769184]
31. Robinson S, Petelenz K, Li Q, Cohen M, DeChant A, Tabrizi N, et al. Developmental changes induced by graded prenatal hypoxic-ischemic insult in rats. *Neurobiol Dis* 2005;18:568–581. [PubMed: 15755683]
32. McQuillen P, Sheldon R, Shatz C, Ferriero D. Selective vulnerability of subplate neurons after early neonatal hypoxia-ischemia. *J Neurosci* 2003;23(8):3308–3315. [PubMed: 12716938]
33. Ness J, Romanko M, Rothstein R, Wood T, Levison S. Perinatal hypoxia-ischemia induces apoptotic and excitotoxic death of periventricular white matter oligodendrocyte progenitors. *Dev Neurosci* 2001;23:203–208. [PubMed: 11598321]

34. Skoff R, Bessert D, Barks J, Song D, Cerghet M, Silverstein F. Hypoxic-ischemic injury results in acute disruption of myelin gene expression and death of oligodendroglial precursors in neonatal mice. *Int J Dev Neurosci* 2001;19:197–208. [PubMed: 11255033]
35. Okoshi Y, Itoh M, Takashima S. Characteristic neuropathology and plasticity in periventricular leukomalacia. *Pediatr Neurol* 2001;25:221–226. [PubMed: 11587877]
36. Banker B, Larroche J-C. Periventricular leukomalacia of infancy. *Arch Neurol* 1962;7:32–410.
37. Gilles F, Murphy S. Perinatal telencephalic leucoencephalopathy. *J Neurosurg Psychiat* 1969;32:404–413.
38. Gilles F, Gomez I. Developmental neuropathology of the second half of gestation. *Early Human Dev* 2005;81:245–253.
39. Inder T, Warfield S, Wang H, Huppi P, Wolpe J. Abnormal cerebral structure is present at term in premature infants. *Pediatrics* 2005;115(2):286–294. [PubMed: 15687434]
40. Maalouf E, Duggan P, Rutherford M, Counsell S, Fletcher A, Battin M, et al. Magnetic resonance imaging of the brain in a cohort of extremely preterm infants. *J Pediatr* 1999;135:351–357. [PubMed: 10484802]
41. Inder T, Huppi P, Warfield S, Kikinis R, Zientara G, Barnes P, et al. Periventricular white matter injury in the premature infant is followed by reduced cerebral cortical gray matter volume at term. *Ann Neurol* 1999;46:755–760. [PubMed: 10553993]
42. Allin M, Henderson M, Suckling J, Nosarti C, Rushe T, Fearon P, et al. Effects of very low birth weight on brain structure in adulthood. *Dev Med Child Neurol* 2004;46:46–53. [PubMed: 14974647]
43. Fearon P, O'Connell P, Grangou S, Aquino P, Nosarti C, Allin M, et al. Brain volumes in adult survivors of very low birth weight: a sibling-controlled study. *Pediatrics* 2004;114(2):367–371. [PubMed: 15286218]
44. Takashima S, Becker L, Chan F-W. Retardation of neuronal maturation in premature infants compared with term infants of the same postconceptional age. *Pediatrics* 1982;69(1):33–39. [PubMed: 7054758]
45. Laptook A, O'Shea T, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: Prevalence and antecedents. *Pediatrics* 2005;115(3):673–680. [PubMed: 15741371]
46. Marin-Padilla M. Perinatal brain damage, cortical reorganization (acquired cortical dysplasias), and epilepsy. *Neocortical Epilepsies* 2000;84:153–172.
47. Colacitti C, Sancini G, DeBiasi S, Franceschetti S, Caputi A, Frassoni C, et al. Prenatal methylazoxymethanol treatment in rats produces brain abnormalities with morphological similarities to human developmental brain dysgeneses. *J Neuropath Exp Neurol* 1999;58(1):92–106. [PubMed: 10068317]
48. Germano I, Sperber E. Transplacentally induced neuronal migration disorders: An animal model for the study of the epilepsies. *J Neurosci Res* 1998;51:473–488. [PubMed: 9514201]
49. Roper S, Gilmore R, Houser C. Experimentally induced disorders of neuronal migration produce an increased propensity for electrographic seizures in rats. *Epilepsy Res* 1995;21:205–219. [PubMed: 8536674]
50. Setkowicz Z, Klak K, Janeczko K. Long-term changes in postnatal susceptibility to pilocarpine-induced seizures in rats exposed to gamma radiation at different stages of prenatal development. *Epilepsia* 2003;44(10):1267–1273. [PubMed: 14510819]
51. Bystron I, Molnar Z, Otellin V, Blakemore C. Tangential networks of precocious neurons and early axonal outgrowth in the embryonic human forebrain. *J Neurosci* 2005;25(1):2781–2792. [PubMed: 15772338]
52. Marin-Padilla. Early prenatal ontogenesis of the cerebral cortex (neocortex) of the cat (*Felis domestica*). A Golgi study. I. The primordial neocortical organization. *Z Anat Entwicklungsgesch* 1971;134:117–145. [PubMed: 4932608]
53. Kostovic I, Rakic P. Developmental history of the transient subplate zone in the visual and somatosensory cortex of the macaque monkey and human brain. *J Comp Neurol* 1990;297:441–470. [PubMed: 2398142]

54. Allendoerfer K, Shatz C. The subplate, a transient neocortical structure: Its role in the development of connections between thalamus and cortex. *Annu Rev Neurosci* 1994;17:185–218. [PubMed: 8210173]
55. Volpe J. Neurobiology of periventricular leukomalacia in the premature infant. *Pediatr Res* 2001;50(5):553–562. [PubMed: 11641446]
56. Rakic P. Neurons in rhesus monkey visual cortex: Systematic relation between time of origin and eventual disposition. *Science* 1974;183:425–27. [PubMed: 4203022]
57. Olivier C, Cobos I, Villegas E, Spassky N, Zalc B, Martinez S, et al. Monofocal origin of telencephalic oligodendrocytes in the anterior entopeduncular area of the chick embryo. *Dev* 2001;128:1757–1769.
58. Spassky N, Goujet-Zalc C, Parmantier E, Olivier C, Martinez S, Ivanova A, et al. Multiple restricted origin of oligodendrocytes. *J Neurosci* 1998;18:8331–8343. [PubMed: 9763477]
59. Jakovcevski I, Zecevic N. Sequence of oligodendrocyte development in human fetal telencephalon. *Glia* 2005;49:480–491. [PubMed: 15578660]
60. Craig A, Luo N, Beardsley D, Wingate-Pearse N, Walker D, Hohimer A, et al. Quantitative analysis of perinatal rodent oligodendrocyte lineage progression and its correlation with human. *Exp Neurol* 2003;181:231–240. [PubMed: 12781996]
61. Back S, Luo N, Borenstein N, Volpe J, Kinney H. Arrested oligodendrocyte lineage progression during human cerebral white matter development: Dissociation between the timing of progenitor differentiation and myelinogenesis. *J Neuropath Exp Neurology* 2002;61(2):197–211.
62. Barres B, Raff M. Proliferation of oligodendrocyte precursor cells depends on electrical activity in axons. *Nature* 1993;361(6409):258–260. [PubMed: 8093806]
63. Raff M, Barres B, Burne J, Coles H, Ishizaki Y, Jacobson M. Programmed cell death and the control of cell survival: Lessons from the nervous system. *Science* 1993;262:695–700. [PubMed: 8235590]
64. Haynes R, Borenstein N, Desilva T, Folkherth R, Liu L, Volpe J, et al. Axonal development in the cerebral white matter of the human fetus and infant. *J Comp Neurol* 2005;484:156–167. [PubMed: 15736232]
65. Weiss J, Takizawa B, McGee A, Steward W, Zhang H, Ment L, et al. Neonatal hypoxia suppresses oligodendrocyte Nogo-A and increases axonal sprouting in a rodent model for human prematurity. *Exp Neurol* 2004;189:141–149. [PubMed: 15296844]
66. Dai X, Lercher L, Clinton P, Du Y, Livingston D, Vieira C, et al. The trophic role of oligodendrocytes in the basal forebrain. *J Neurosci* 2003;23(13):5846–5853. [PubMed: 12843289]
67. Wilkins A, Majed H, Layfield R, Compton A, Chandran S. Oligodendrocytes promote neuronal survival and axonal length by distinct intracellular mechanisms: a novel role for oligodendrocyte-derived glial cell line-derived neurotrophic factor. *J Neurosci* 2003;23(12):4974–4967.
68. Chun J, Nakamura M, Shatz C. Transient cells of the developing mammalian telencephalon are peptide-immunoreactive neurons. *Nature* 1987;325:617–620. [PubMed: 3543691]
69. Mrzljak L, Uylings H, Kostovic I, VanEden C. Prenatal development of neurons in the human prefrontal cortex: I. A qualitative golgi study. *J Comp Neurol* 1988;271:355–386. [PubMed: 2454966]
70. McConnell S, Ghosh A, Shatz C. Subplate neurons pioneer the first axon pathway from the cerebral cortex. *Science* 1989;245:978–982. [PubMed: 2475909]
71. McConnell S, Ghosh A, Shatz C. Subplate pioneers and the formation of descending connections from cerebral cortex. *J Neurosci* 1994;14:1892–1907. [PubMed: 7512631]
72. Shinozaki K, Miyagi T, Miyata T, Ogawa M, Aizawa S, Suda Y. Absence of Cajal-Retzius cells and subplate neurons associated with defects of tangential cell migration from ganglionic eminence in *Emx1/2* double mutant cerebral cortex. *Dev* 2002;129:3479–3492.
73. Antonini A, Shatz C. Relation between putative transmitter phenotypes and connectivity of subplate neurons during cerebral cortical development. *Eur J Neurosci* 1990;2:744–761. [PubMed: 12106275]
74. Chun J, Shatz C. Interstitial cells of the adult neocortical white matter are the remnant of the early generated subplate neuron population. *J Comp Neurol* 1989;282:555–569. [PubMed: 2566630]
75. Wahle P, Meyer G, Wu J, Albus K. Morphology and axon terminal pattern of glutamate-decarboxylase-immunoreactive cell types in the white matter of the cat occipital cortex during early postnatal development. *Dev Brain Res* 1987;36:53–61.

76. DeAzevedo L, Hedin-Pereira C, Lent R. Callosal neurons in the cingulate cortical plate and subplate of human fetuses. *J Comp Neuro* 1997;386:60–70.
77. Finney E, Stone J, Shatz C. Major glutamatergic projection from subplate into visual cortex during development. *J Comp Neurol* 1998;398:105–118. [PubMed: 9703030]
78. Csillik A, Okuno E, Csillik B, Knylhar E, Vecsel L. Expression of kynureine aminotransferase in the subplate of the rat and its possible role in the regulation of programmed cell death. *Cerebral Cortex* 2002;12:1193–1201. [PubMed: 12379607]
79. Verney C, Derer P. Cajal-Retzius neurons in human cerebral cortex at midgestation show immunoreactivity for neurofilament and calcium-binding proteins. *J Comp Neurol* 1995;359:144–153. [PubMed: 8557843]
80. Hanganu I, Kilb W, Luhmann H. Functional synaptic projections onto subplate neurons in neonatal rat somatosensory cortex. *J Neurosci* 2002;22(16):7165–7176. [PubMed: 12177212]
81. Friauf E, McConnell S, Shatz C. Functional synaptic circuits in the subplate during fetal and early postnatal development of cat visual cortex. *J Neurosci* 1990;10(8):2601–2613. [PubMed: 2388080]
82. Friauf E, Shatz C. Changing patterns of synaptic input to subplate and cortical plate during development of visual cortex. *J Neurophys* 1991;66(6):2059–2071.
83. Rakic P. Prenatal development of the visual system in rhesus monkey. *Philos Trans R Soc London* 1977;278:245–260. [PubMed: 19781]Ser B
84. Ghosh A, Antonini A, McConnell S, Shatz C. Requirement for subplate neurons in the formation of thalamocortical connections. *Nature* 1990;347:179–181. [PubMed: 2395469]
85. Ghosh A, Shatz C. Involvement of subplate neurons in the formation of ocular dominance columns. *Science* 1992;255:1441–1443. [PubMed: 1542795]
86. Ghosh A, Shatz C. A role for subplate neurons in the patterning of connections from thalamus to neocortex. *Dev* 1993;117:1031–1047.
87. Arber S. Subplate neurons: Bridging the gap to function in the cortex. *Trends Neurosci* 2004;27(3):111–113. [PubMed: 15046074]
88. Kanold P, Kara P, Reid R, Shatz C. Role of subplate neurons in functional maturation of visual cortical columns. *Science* 2003;301:521–525. [PubMed: 12881571]
89. Lein E, Finney E, McQuillen P, Shatz C. Subplate neuron ablation alters neurotrophin expression and ocular dominance column formation. *PNAS* 1999;96(23):13491–13495. [PubMed: 10557348]
90. McAllister A. Subplate neurons: A missing link among neurotrophins, activity, and ocular dominance plasticity? *PNAS* 1999;96(24):13600–13602. [PubMed: 10570118]
91. Robertson R, Annis C, Baratta J, Haraldson S, Ingeman J, Kageyama G, et al. Do subplate neurons comprise a transient population of cells in developing neocortex of rats? *J Comp Neurol* 2000;426:632–650. [PubMed: 11027404]
92. Kostovic I, Rakic P. Cytology and time of origin of interstitial neurons in the white matter in infant and adult human and monkey telencephalon. *J Neurocytol* 1980;9:219–242. [PubMed: 7441294]
93. Allendoerfer K, Cabelli R, Escandon E, Kaplan D, Nikolics K, Shatz C. Regulation of neurotrophin receptors during the maturation of the mammalian visual system. *J Neurosci* 1994;14:1795–1811. [PubMed: 8126572]
94. Allendoerfer K, Shelton D, Shooter E, Shatz C. Nerve growth factor receptor immunoreactivity is transiently associated with the subplate neurons of the mammalian cerebral cortex. *PNAS USA* 1990;87:187–190. [PubMed: 2153287]
95. Kanold P. Transient microcircuits formed by subplate neurons and their role in functional development of thalamocortical connections. *NeuroReport* 2004;15(14):2149–2153. [PubMed: 15371723]
96. McQuillen P, Ferriero D. Selective vulnerability in the developing central nervous system. *Pediatr Neurol* 2004;30:227–235. [PubMed: 15087099]
97. Follett P, Rosenberg P, Volpe J, Jensen F. NBQX attenuates excitotoxic injury developing white matter. *J Neurosci* 2000;20(24):9235–9241. [PubMed: 11125001]
98. Hendry S, Schwark H, Jones E, Yan J. Numbers and proportions of GABA-immunoreactive neurons in different areas of monkey cerebral cortex. *J Neurosci* 1987;7:1503–1519. [PubMed: 3033170]

99. Ben-Ari Y. Excitatory actions of GABA during development: The nature of the nurture. *Nature Neurosci Rev* 2002;3:728–739.
100. Owens D, Kriegstein A. Is there more to GABA than synaptic inhibition? *Nature Neurosci Rev* 2002;3:715–727.
101. Anderson S, Eisenstat D, Shi L, Rubenstein J. Interneuron migration from basal forebrain to neocortex: dependence on *Dlx* genes. *Science* 1997;278:474–476. [PubMed: 9334308]
102. Ben-Ari Y. Developing networks play a similar melody. *Trends Neurosci* 2001;24(6):353–360. [PubMed: 11356508]
103. DeCarlos J, Lopez-Mascaraque L, Valverde F. Dynamics of cell migration from the lateral ganglionic eminence in the rat. *J Neurosci* 1996;16(19):6146–6156. [PubMed: 8815897]
104. Marin O, Rubenstein J. A long, remarkable journey: Tangential migration in the telencephalon. *Nat Rev Neurosci* 2001;2:780–790. [PubMed: 11715055]
105. Nadarajah B, Parnavelas J. Modes of neuronal migration in the developing cerebral cortex. *Nature Reviews/Neuroscience* 2002;3:423–432.
106. O'Rourke N, Sullivan D, Kaznowski C, Jacobs A, McConnell S. Tangential migration of neurons in the developing cerebral cortex. *Dev* 1995;121:2165–2176.
107. Polleux F, Whitford K, Dijkhuizen P, Vitalis T, Ghosh A. Control of cortical interneuron migration by neurotrophins and P13-kinase signaling. *Dev* 2002;129:3147–3160.
108. Zhu Y, Li H, Zhou L, Wu J, Rao Y. Cellular and molecular guidance of GABAergic neuronal migration from an extracortical origin to the neocortex. *Neuron* 1999;23:473–485. [PubMed: 10433260]
109. Lopez-Bendito G, Sturgess K, Erdelyi F, Szabo G, Molnar Z, Paulsen O. Preferential origin and layer destination of GAD65-GFP cortical interneurons. *Cereb Cortex* 2004;14:1122–1133. [PubMed: 15115742]
110. Del Rio J, Martinez A, Auladell C, Eduardo S. Developmental history of the subplate and developing white matter in the murine neocortex: Neuronal organization and relationship with the main afferent systems at embryonic and perinatal stages. *Cereb Cortex* 2000;10:784–801. [PubMed: 10920050]
111. Zecevic N, Milosevic A. Initial development of γ -aminobutyric acid immunoreactivity in the human cerebral cortex. *J Comp Neurol* 1997;380:495–506. [PubMed: 9087528]
112. Meyer G, Perez-Garcia C, Abraham H, Caput D. Expression of p73 and reelin in the developing human cortex. *J Neurosci* 2000;22(12):4973–4966. [PubMed: 12077194]
113. Verney C. Phenotypic expression of monoamines and GABA in the early development of human telencephalon, transient or not transient. *J Chem Neuroanat* 2003;26:283–292. [PubMed: 14729130]
114. Zecevic N, Rakic P. Development of layer I neurons in the primate cerebral cortex. *J Neurosci* 2001;21:5607–5619. [PubMed: 11466432]
115. Letinic K, Zoncu R, Rakic P. Origin of GABAergic neurons in the human neocortex. *Nature* 2002;417:645–649. [PubMed: 12050665]
116. Ulfing N. Expression of calbindin and calretinin in the human ganglionic eminence. *Pediatr Neurol* 2001;24:357–360. [PubMed: 11516609]
117. Yan X, Zheng D, Garey L. Prenatal development of GABA-immunoreactive neurons in the human striate cortex. *Dev Brain Res* 1992;65:191–204. [PubMed: 1572064]
118. Das S, Ray P. Ontogeny of GABA pathway in human fetal brains. *Biochem Biophys Res Commun* 1996;228:544–548. [PubMed: 8920949]
119. Gonchar Y, Burkhalter A. Three distinct families of GABAergic neurons in the rat visual cortex. *Cerebr Cortex* 1997;7:347–358.
120. Kawaguchi Y, Kubota Y. GABAergic cell subtypes and their synaptic connections in rat frontal cortex. *Cereb Cortex* 1997;7(6):476–86. [PubMed: 9276173]
121. Kubota Y, Hattori R, Yui Y. Three distinct subpopulations of GABAergic neurons in rat frontal agranular cortex. *Brain Res* 1994;649:159–173. [PubMed: 7525007]
122. Nery S, Fishell G, Corbin J. The caudal ganglionic eminence is a source of distinct cortical and subcortical cell populations. *Nature Neurosci* 2002;5(12):1279–1287. [PubMed: 12411960]

123. Xu Q, Cobos I, De La Cruz E, Rubenstein J, Anderson S. Origins of cortical interneuron subtypes. *J Neurosci* 2004;24(11):2612–2622. [PubMed: 15028753]
124. Vogt Weisenhorn D, Celio M, Rickmann M. The onset of parvalbumin-expression in interneurons of the rat parietal cortex depends on extinsic factor(s). *Eur J Neurosci* 1998;10:1027–1036. [PubMed: 9753170]
125. Patz S, Grabert J, Gorba T, Wirth M, Wahle P. Parvalbumin expression in visual cortical interneurons depends on neuronal activity and TrkB ligands during an early period of postnatal development. *Cereb Cortex* 2004;14(N3):342–351. [PubMed: 14754872]
126. Grateron L, Cebada-Sanchez S, Marcos P, Mohedano-Moriano A, Insausti A, Munoz M, et al. Postnatal development of calcium-binding proteins immunoreactivity (parvalbumin, calbindin, calretinin) in the human entorhinal cortex. *J Chem Neuroanat* 2003;26:311–316. [PubMed: 14729133]
127. Iai M, Takashima S. Thalamocortical development of parvalbumin neurons in normal and periventricular leukomalacia brains. *Neuropediatrics* 1999;30:14–18. [PubMed: 10222455]
128. Kostovic I, Stedulj-Fucic A, Mrzljak L, Jukic S, Delalle I. Prenatal and perinatal development of the somatostatin-immunoreactive neurons in the human prefrontal cortex. *Neurosci Lett* 1991;124:153–156. [PubMed: 1676833]
129. Baraban S, Hollopeter G, Erickson J, Schwartzkroin P, Palmiter R. Knock-out mice reveal a critical antiepileptic role for neuropeptide Y. *J Neurosci* 1997;17(23):8927–8936. [PubMed: 9364040]
130. Vezzani A, Sperk G, Colmers W. Neuropeptide Y: Emerging evidence for a functional role in seizure modulation. *Trends Neurosci* 1999;22:25–30. [PubMed: 10088996]
131. Delalle I, Evers P, Kostovic I, Uylings G. Laminar distribution of neuropeptide Y-immunoreactive neurons in human prefrontal cortex during development. *J Comp Neurol* 1997;379:515–522. [PubMed: 9067840]
132. Uylings H, Delalle I. Morphology of neuropeptide Y-immunoreactive neurons and fibers in human prefrontal cortex during prenatal and postnatal development. *J Comp Neurol* 1997;379:523–540. [PubMed: 9067841]
133. deAzevedo L, Hedin-Pereira C, Lent R. Diaphorase-positive neurons in the cingulate cortex of human fetuses during the second half of gestation. *Anat Embryol* 2002;205:29–35. [PubMed: 11875663]
134. Lujan R, Shigemoto, Lopez-Bendito G. Glutamate and GABA receptor signalling in the developing brain. *Neuroscience* 2005;130:567–580. [PubMed: 15590141]
135. Hennou S, Khalilov I, Diabira D, Ben-Ari Y, Gozlan H. Early sequential formation of functional GABA(A) and glutamatergic synapses on CA1 interneurons of the rat foetal hippocampus. *Eur J Neurosci* 2002;16:197–208. [PubMed: 12169102]
136. Rivera C, Voipio J, Kaila K. Two developmental switches in GABAergic signalling: the K^+ - Cl^- cotransporter KCC2 and carbonic anhydrase CAVII. *J Physiol* 2005;562:27–36. [PubMed: 15528236]
137. Rivera C, Voipio J, Payne J, Ruusuvuori E, Lahtinen H, Lamsa K, et al. The K^+ / Cl^- co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. *Nature* 1999;397:251–255. [PubMed: 9930699]
138. LoTurco J, Owens D, Heath M, Davis M, Kriegstein A. GABA and glutamate depolarize cortical progenitor cells and inhibit DNA synthesis. *Neuron* 1995;15:1287–1298. [PubMed: 8845153]
139. Ben-Ari Y, Khazipov R, Leinekugel X, Caillard O, Gaiarsa J-L. GABA_A, NMDA and AMPA receptors: A developmentally regulated ‘menage a trois’. *Trends Neurosci* 1997;20(11):523–529. [PubMed: 9364667]
140. Manent J-B, Demarque M, Jorquera I, Pellegrino C, Ben-Ari Y, Aniksztejn L, et al. A noncanonical release of GABA and glutamate modulates neuronal migration. *J Neurosci* 2005;25:4755–4765. [PubMed: 15888651]
141. Behar T, Schaffner A, Scott C, O’Connell C, Barker J. Differential response of cortical plate and ventricular zone cells to GABA as a migration stimulus. *J Neurosci* 1998;18(16):6378–6387. [PubMed: 9698329]

142. Behar T, Smith S, Kennedy R, McKenzie J, Maric I, Barker J. GABA(B) receptors mediate motility signals for migrating embryonic cortical cells. *Cereb Cortex* 2001;11:744–753. [PubMed: 11459764]
143. Lopez-Bendito G, Lujan R, Shigemoto R, Ganter P, Paulsen O, Molnar Z. Blockade of GABA_B receptors alters the tangential migration of cortical neurons. *Cereb Cortex* 2003;13:932–942. [PubMed: 12902392]
144. Maric D, Liu Q-Y, Maric I, Chaudry S, Chang Y-H, Smith S, et al. GABA expression dominates neuronal lineage progression in the embryonic rat neocortex and facilitates neurite outgrowth via GABA_A autoreceptor/C1[−] channels. *J Neurosci* 2001;21(7):2343–2360. [PubMed: 11264309]
145. Asada H, Kawamura Y, Maruyama K, Kume H, Ding R, Ji F, et al. Mice lacking the 65 kDa isoform of glutamic acid decarboxylase (GAD65) maintain normal levels of GAD67 and GABA in their brains but are susceptible to seizures. *Biochem Biophys Res Commun* 1996;229:891–895. [PubMed: 8954991]
146. Kash S, Tecott L, Hodge C, Baekkeskov S. Increased anxiety and altered responses to anxiolytics in mice deficient in the 65-kDa isoform and glutamic acid decarboxylase. *PNAS USA* 1999;96:1698–1703. [PubMed: 9990087]
147. Powell E, Campbell D, Stanwood G, Davis C, Noebels J, Levitt P. Genetic disruption of cortical interneuron development causes region- and GABA cell type-specific deficits, epilepsy, and behavioral dysfunction. *J Neurosci* 2003;23(2):622–631. [PubMed: 12533622]
148. Schuler V, Luscher C, Blanchet C, Klix N, Sansig G, Klebs K, et al. Epilepsy, hyperalgesia, impaired memory, and loss of pre- and postsynaptic GABA_B responses in mice lacking GABA_{B(1)}. *Neuron* 2001;31:47–58. [PubMed: 11498050]
149. Gil D, Negri C, de Plazas S. Hypoxia differentially reduces GABA_A receptor density during embryonic chick optic lobe development. *Neurochem Res* 2004;29(4):681–686. [PubMed: 15098929]
150. Ulfig N, Szabo A, Bohl J. Effect of fetal hydrocephalus on the distribution patterns of calcium-binding proteins in the occipital cortex. *Pediatr Neurosurg* 2001;34:20–32. [PubMed: 11275783]
151. He W, Ingraham C, Rising L, Goderie S, Temple S. Multipotent stem cells from the mouse basal forebrain contribute GABAergic neurons and oligodendrocytes to the cerebral cortex during embryogenesis. *J Neurosci* 2001;21(22):8854–8862. [PubMed: 11698597]
152. Yung S, Gokhan S, Jurcsak J, Molero A, Abrajano J, Mehler M. Differential modulation of BMP signaling promotes the elaboration of cerebral cortical GABAergic neurons or oligodendrocytes from a common sonic hedgehog-responsive ventral forebrain progenitor species. *PNAS* 2002;99(25):16273–16278. [PubMed: 12461181]
153. Barres B, Koroshetz W, Swartz K, Chun L, Corey D. Ion channel expression by white matter glia: The O-2A glial progenitor cell. *Neuron* 1990;4:507–524. [PubMed: 1691005]
154. Bergles D, Roberts J, Somogyi P, Jahr C. Glutamatergic synapses on oligodendrocyte precursor cells in the hippocampus. *Nature* 2000;405:187–191. [PubMed: 10821275]
155. Gallo V, Zhou J, McBain C, Wright P, Knutson P, Armstrong R. Oligodendrocyte progenitor cell proliferation and lineage progression are regulated by glutamate receptor-mediated potassium channel block. *J Neurosci* 1996;16(8):2659–2670. [PubMed: 8786442]
156. Liu H, Almazan G. Glutamate induces c-fos proto-oncogene expression and inhibits proliferation in oligodendrocyte progenitors: receptor characterization. *Eur J Neurosci* 1995;7:2355–2366. [PubMed: 8845939]
157. Yuan X, Eisen A, McBain C, Gallo V. A role for glutamate and its receptors in the regulation of oligodendrocyte development in cerebellar tissue slices. *Dev* 1998;125:2901–2914.
158. Lin, S-c; Bergles, D. Synaptic signaling between GABAergic interneurons and oligodendrocyte precursor cells in the hippocampus. *Nature Neurosci* 2004;7(1):24–32. [PubMed: 14661022]
159. Wang H, Yan Y, Kintner D, Lytle C, Sun D. GABA-mediated trophic effect on oligodendrocytes requires Na-K-2CI cotransport activity. *J Neurophysiol* 2003;90:1257–1265. [PubMed: 12904508]
160. Berger-Sweeney J, Hohmann C. Behavioral consequences of abnormal cortical development: Insights into developmental disabilities. *Beh Brain Res* 1997;86:121–142.

161. Verney C, Zecevic N, Nikolic B, Alvarez C, Berger B. Early evidence of catecholaminergic cell groups in 5- and 6-week-old human embryos using tyrosine hydroxylase and dopamine- β -hydroxylase immunocytochemistry. *Neurosci Lett* 1991;131:121–124. [PubMed: 1686476]
162. Zecevic N, Verney C. Development of the catecholamine neurons in humans embryos and fetuses, with special emphasis on the innervation of the cerebral cortex. *J Comp Neurol* 1995;351:509–535. [PubMed: 7721981]
163. Happe H, Coulter C, Gerety M, Sanders J, O'Rourke M, Bylund D, et al. Alpha-2 adrenergic receptor development in rat CNS: an autoradiographic study. *Neuroscience* 2004;123:167–178. [PubMed: 14667451]
164. Gaspar P, Cases O, Maroteaux L. The developmental role of serotonin: news from mouse molecular genetics. *Nature Rev* 2003;4:1002–1012.
165. Herlenius E, Lagercrantz H. Development of neurotransmitter systems during critical periods. *Exp Neurol* 2004;190:S8–S21. [PubMed: 15498537]
166. Ghosh A, Shatz C. Segregation of geniculocortical afferents during the critical period: A role for subplate neurons. *J Neurosci* 1994;14:3862–3880. [PubMed: 8207493]
167. Wu G-Y, Malinow R, Cline H. Maturation of a central glutamatergic synapse. *Science* 1996;274:972–975. [PubMed: 8875937]
168. Becher J, Bell J, Keeling J, McIntosh N, Wyatt B. The Scottish perinatal neuropathology study: Clinicopathological correlation in early neonatal deaths. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F399–F405. [PubMed: 15321957]
169. Ballabh P, Braun A, Nedergaard M. Anatomic analysis of blood vessels in germinal matrix, cerebral cortex, and white matter in developing infants. *Pediatr Res* 2004;56(1):117–124. [PubMed: 15128918]
170. Back S. Recent advances in human perinatal white matter injury. *Prog Brain Res* 2001;132:131–147. [PubMed: 11544983]
171. Ferriero D. Medical Progress: Neonatal brain injury. *NEJM* 2004;351:1985–1995. [PubMed: 15525724]
172. Goncalves L, Chaiworapongsa T, Romer R. Intrauterine infection and prematurity. *Ment Retard Dev Disabil Res Rev* 2002;8:3–13. [PubMed: 11921380]
173. Wu Y. Systematic review of chorioamnionitis and cerebral palsy. *Ment Retard Dev Disabil Res Rev* 2002;8:25–29. [PubMed: 11921383]
174. Kendall G, Peebles D. Acute fetal hypoxia: The modulating effect of infection. *Early Human Dev* 2005;81:27–34.
175. Peebles D, Wyatt J. Synergy between antenatal exposure to infection and intrapartum events in causation of perinatal brain injury at term. *BJOG* 2002;109:737–39. [PubMed: 12135207]
176. Peeters-Scholte C, Koster J, van den tweel E, Blomgren K, Hamers N, Zhu C, et al. Effects of selective nitric oxide synthase inhibition on IGF-1, caspases and cytokines in a newborn piglet model of perinatal hypoxia-ischaemia. *Dev Neurosci* 2002;24:396–404. [PubMed: 12640178]
177. Rice J, Vannucci R, Brierley J. The influence of immaturity on hypoxic-ischemic brain damage in the rat. *Ann Neurol* 1981;9:131–41. [PubMed: 7235629]
178. Sheldon R, Chuai J, Ferriero D. A rat model for hypoxic-ischemic brain damage in very premature infants. *Biol Neonate* 1996;69:327–341. [PubMed: 8790911]
179. Bell M, Hallenbeck J. Effects of intrauterine inflammation on developing rat brain. *J Neurosci Res* 2002;70:570–579. [PubMed: 12404511]
180. Cai Z, Pan Z-L, Pang Y, Evans O, Rhodes P. Cytokine induction in fetal rat brains and brain injury in neonatal rats after maternal lipopolysaccharide administration. *Pediatr Res* 2000;47(1):64–72. [PubMed: 10625084]
181. Field N, Newton E, Kagan-Hallet K, Peairs W. Perinatal effects of *Gardnerella vaginalis* deciduitis in the rabbit. *Am J Obstet Gynecol* 1993;168:988–994. [PubMed: 8456914]
182. Yoon B, Kim C, Romero R, Jun J, Park K, Choi S, et al. Experimentally induced intrauterine infection causes fetal brain white matter lesions in rabbits. *Am J Obstet Gynecol* 1997;177(4):797–802. [PubMed: 9369822]

183. Hagberg H, Ichord R, Palmer C, Yager J, Vannucci S. Animal models of developmental brain injury: Relevance to human disease. *Dev Neurosci* 2002;24:364–366. [PubMed: 12640174]
184. Ikeda T, Mishima K, Aoo N, Egashira N, Iwasaki K, Fujiwara M, et al. Combination treatment of neonatal rats with hypoxia-ischemia and endotoxin induces long-lasting memory and learning impairment that is associated with extended cerebral damage. *Am J Obstet Gynecol* 2004;191:2132–2141. [PubMed: 15592303]
185. Duggan P, Maalouf E, Watts T, Sullivan M, Counsell S, Alsop J, et al. Intrauterine T-cell activation and increased proinflammatory cytokine concentrations in preterm infants with cerebral lesions. *Lancet* 2001;358:1699–1700. [PubMed: 11728550]
186. Hagberg H, Mallard C, Jacobsen B. Role of cytokine in preterm labour and brain injury. *BJOG* 2005;112(S1):16–18. [PubMed: 15715588]
187. Nelson K, Dambrosia J, Grether J, Phillips T. Neonatal cytokines and coagulation factors in children with cerebral palsy. *Ann Neurol* 1998;44:665–675. [PubMed: 9778266]
188. Wu Y, Colford J, JM. Chorioamnionitis as a risk factor for cerebral palsy. *JAMA* 2000;284:1417–1424. [PubMed: 10989405]
189. Yoon B, Romero R, Yang S, Jun J, Kim I-O, Choi J-H, et al. Interleukin-6 concentrations in umbilical cord plasma are elevated in neonates with white matter lesions associated with periventricular leukomalacia. *Am J Obstet Gynecol* 1996;174:1433–1440. [PubMed: 9065108]
190. Nelson K, Grether J, Dambrosia J, Walsh E, Kohler S, Satyanarayana G, et al. Neonatal cytokines and cerebral palsy in very preterm infants. *Pediatr Res* 2003;53(4):600–607. [PubMed: 12612192]
191. Folkerth R, Haynes R, Borenstein N, Belliveau R, Trachtenberg F, Rosenberg P, et al. Developmental lag in superoxide dismutases relative to other antioxidant enzymes in premyelinated human telencephalic white matter. *J Neuropath Exp Neurol* 2004;63(9):990–999. [PubMed: 15453097]
192. Folkerth R, Keefe R, Haynes R, Trachtenberg F, Volpe J, Kinney H. Interferon- γ expression in periventricular leukomalacia in the human brain. *Brain Pathol* 2004;14:265–274. [PubMed: 15446581]
193. Kadhim H, Tabarki B, De Perez C, Rona A, Sebire G. Interleukin-2 in the pathogenesis of perinatal white matter damage. *Neurology* 2002;58:1124–1128.
194. Back S, Gan X, Li Y, Rosenberg P, Volpe J. Maturation-dependent vulnerability of oligodendrocytes to oxidative stress-induced death caused by glutathione depletion. *J Neurosci* 1998;18(16):6241–6253. [PubMed: 9698317]
195. Back S, Han B, Luo N, Chricton C, Xanthoudakis S, Tam J, et al. Selective vulnerability of late oligodendrocyte progenitors to hypoxia-ischemia. *J Neurosci* 2002;22(2):455–463. [PubMed: 11784790]
196. Jelinski S, Yager J, Juurlink B. Preferential injury of oligodendroblasts by a short hypoxic-ischemic insult. *Brain Res* 1999;815:150–153. [PubMed: 9974135]
197. Levison S, Rothstein R, Romanko M, Snyder M, Meyers R, Vannucci S. Hypoxia/ischemia depletes the rat perinatal subventricular zone of oligodendrocyte progenitors and neural stem cells. *Dev Neurosci* 2001;23:234–247. [PubMed: 11598326]
198. Andrews T, Zhang P, Bhat N. TNF α potentiates INF γ -induced cell death in oligodendrocyte progenitors. *J Neurosci Res* 1998;54:574–583. [PubMed: 9843148]
199. Conroy S, Nguyen V, Quina L, Blakely-Gonzales P, Netzeband J, Prieto A, et al. Interleukin-6 produces neuronal loss in developing cerebellar granule neuron cultures. *J Neuroimmunol* 2004;155:43–54. [PubMed: 15342195]
200. Jarskog L, Xiao H, Wilkie M, Lauder J, Gilmore J. Cytokine regulation of embryonic rat dopamine and serotonin neuronal survival in vitro. *Int J Devl Neurosci* 1997;15(6):711–716.
201. Selmaj K, Raine C. Tumor necrosis factor mediates myelin and oligodendrocyte damage in vitro. *Ann Neuro* 1988;23:339–346.
202. Follett P, Deng W, Dai W, Talos D, Massillon L, Rosenberg P, et al. Glutamate receptor-mediated oligodendrocyte toxicity in periventricular leukomalacia: A protective role for topiramate. *J Neurosci* 2004;24(18):4412–4420. [PubMed: 15128855]
203. Li J, Lin J, Wang H, Peterson J, Furie B, Furie B, et al. Novel role of vitamin K in preventing oxidative injury to developing oligodendrocytes and neurons. *J Neurosci* 2003;23(13):5816–5826. [PubMed: 12843286]

204. Peeters-Scholte C, Koster J, Veldhuis W, van den Tweel E, Zhu C, Kops N, et al. Neuroprotection by selective nitric oxide synthase inhibition at 24 hours after perinatal hypoxia-ischemia. *Stroke* 2002;33:2304–2310. [PubMed: 12215603]
205. Jantzie L, Cheung P-Y, Todd K. Doxycycline reduces cleaved caspase-3 and microglial activation in an animal model of neonatal hypoxia-ischemia. *J Cerebral Blood Flow Met* 2005;25:314–324.
206. Li Y-H, Brauner A, Johnsson B, Van der Ploeg I, Soder O, Holst M, et al. Inhibition of macrophage proinflammatory cytokine expression by steroids and recombinant IL-10. *Biol Neonate* 2001;80:124–132. [PubMed: 11509812]
207. Mishra O, Fritz K, Delivoria-Papadopoulos M. NMDA receptor and neuronal hypoxic brain injury. *Ment Retard Dev Disabil Res Rev* 2001;7:249–253. [PubMed: 11754518]
208. Fern R, Moller T. Rapid ischemic cell death in immature oligodendrocytes: A fatal glutamate release feedback loop. *J Neurosci* 2000;20(1):34–42. [PubMed: 10627578]
209. Oka A, Belliveau MJ, Rosenberg PA, Volpe JJ. Vulnerability of oligodendroglia to glutamate: Pharmacology, mechanisms, and prevention. *J Neurosci* 1993;13(4):1441–1453. [PubMed: 8096541]
210. Yoshioka A, Hardy M, Younkin D, Grispan J, Stern J, Pleasure D. α -Amino-hydroxyl-5-methyl-4-isoxazolepropionate (AMPA) receptors mediate excitotoxicity in the oligodendroglial lineage. *J Neurochem* 1995;64:2442–2448. [PubMed: 7539052]
211. Deng W, Rosenberg P, Volpe J, Jensen F. Calcium-permeable AMPA/kainate receptors mediate toxicity and preconditioning by oxygen-glucose deprivation in oligodendrocyte precursors. *PNAS* 2003;100(11):6801–6806. [PubMed: 12743362]
212. Jensen F. The role of glutamate receptor maturation in perinatal seizures and brain injury. *Int J Devl Neurosci* 2002;20:339–347.
213. Cambonie G, Hirbec H, Michaud M, Karemnik J-M, Barbanel G. Prenatal infection obliterates glutamate-related protection against free hydroxyl radicals in neonatal rat brain. *J Neurosci Res* 2004;75:125–132. [PubMed: 14689455]
214. Acarin L, Gonzalez B, Castellano B. Neuronal, astroglial and microglial cytokine expression after an excitotoxic lesion in the immature rat brain. *Eur J Neurosci* 2000;12:3505–3520. [PubMed: 11029620]
215. Acarin L, Peluffo H, Gonzalez B, Castellano B. Expression of inducible nitric oxide synthase and cyclooxygenase-2 after excitotoxic damage to the immature rat brain. *J Neurosci Res* 2002;68:745–754. [PubMed: 12111835]
216. Blomgren K, Zhu C, Hallin U, Hagberg H. Mitochondria and ischemic reperfusion damage in the adult and in the developing brain. *Biochem Biophys Res Comm* 2003;304:551–559. [PubMed: 12729590]
217. Earnshaw W, Martins L, Kaufmann S. Mammalian caspases: Structure, activation, substrates, and functions during apoptosis. *Ann Rev Biochem* 1999;68:383–424. [PubMed: 10872455]
218. Kuida K, Zheng T, Na S, Kuan C, Ynag D, Karasuyama H, et al. Decreased apoptosis in the brain and premature lethality in CPP32-deficient mice. *Nature* 1996;384:368–372. [PubMed: 8934524]
219. Leist M, Jaattela M. Four deaths and a funeral: From caspases to alternative mechanisms. *Nature Rev* 2001;2:1–10.
220. Nakajima W, Ishida A, Lange M, Gabrielson K, Wilson M, Martin L, et al. Apoptosis has a prolonged role in the neurodegeneration after hypoxic ischemia in the newborn rat. *J Neurosci* 2000;20:7994–8004. [PubMed: 11050120]
221. Wang X, Karlsson J-O, Zhu C, Bahr B, Hagberg H, Blomgren K. Caspase-3 activation after neonatal rat cerebral hypoxia-ischemia. *Biol Neonate* 2001;79:172–179. [PubMed: 11275647]
222. Walton M, Connor B, Lawlor P, Young D, Sirimanne E, Gluckman P, et al. Neuronal death and survival in two models of hypoxic-ischemic brain damage. *Brain Res Rev* 1999;29:137–168. [PubMed: 10209230]
223. Portera-Cailliau C, Price D, Martin L. Excitotoxic neuronal death in the immature brain is an apoptosis-necrosis morphological continuum. *J Comp Neurol* 1997;378:70–87. [PubMed: 9120055]
224. Pulera M, Adams L, Liu H, Santos D, Nishimura R, Yang F, et al. Apoptosis in a neonatal rat model of cerebral hypoxia-ischemia. *Stroke* 1998;29:2622–2630. [PubMed: 9836776]

225. Yue X, Mehmet H, Penrice J, Cooper C, Cady E, Wyatt J, et al. Apoptosis and necrosis in the newborn piglet brain following transient cerebral hypoxia-ischaemia. *Neuropath Appl Neurol* 1997;23:16–25.
226. Ishimaru M, Ikonomidou C, Tenkova T, Der T, KD, Sesma M, et al. Distinguishing excitotoxic from apoptotic neurodegeneration in the developing rat brain. *J Comp Neurol* 1999;408:461–476. [PubMed: 10340498]
227. Jin K, Chen J, Nagayama T, Chen M, Sinclair J, Graham S, et al. In situ detection of neuronal DNA strand breaks using the Klenow fragment of DNA polymerase I reveals different mechanisms of neuron death of global cerebral ischemia. *J Neurochem* 1999;72:1204–1214. [PubMed: 10037493]
228. D'Sa-Eipper C, JR L, Putcha G, Zheng T, Flavell R, Rakic P, et al. DNA damage-induced neural precursor cell apoptosis requires p53 and caspase 9 but neither bax nor caspase 3. *Dev* 2001;128:137–146.
229. Cheng Y, Deshmukh M, D'Costa A, JA D, Gidday J, Shah A, et al. Caspase inhibitor affords neuroprotection with delayed administration in a rat model of neonatal hypoxic-ischemic brain injury. *J Clin Invest* 1998;101:1992–1999. [PubMed: 9576764]
230. Felderhoff-Maeser U, Buhner C. Clinical measures to preserve cerebral integrity in preterm infants. *Early Human Dev* 2005;81:237–244.
231. Fowlie P, Davis P. Prophylactic indomethacin for preterm infants: a systematic review and meta-analysis. *Arch Dis Chil Fetal Neonatal Ed* 2003;88:F464–F466.
232. Baud O. Postnatal steroid treatment and brain development. *Arch Dis child Fetal Neonatal Ed* 2004;89:F96–F100. [PubMed: 14977889]
233. LeFlore J, Salhab W, Broyles R, Engle W. Association of antenatal and dexamethasone exposure with outcomes in extremely low birth weight outcomes. *Pediatrics* 2002;110(2):275–253. [PubMed: 12165578]
234. Wood N, Costeloe K, Gibson A, Hennessy E, MArlow N, Wilkinson A, et al. The EPICure study: Associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. *Arch Dis Chil Fetal Neonatal Ed* 2005;90:134–140.
235. Yeh T, Lin Y, Lin H, Huang C, Hsieh W, Lin C, et al. Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity. *NEJM* 2004;350:1304–1313. [PubMed: 15044641]
236. Arad I, Kurkin M, Hinton V, Kuhn L, Chiriboga C, Kuban K, et al. Long-term cognitive benefits of antenatal corticosteroids for prematurely born children with cranial ultrasound abnormalities. *Am J Obstet Gynecol* 2002;186:818–825. [PubMed: 11967514]
237. Spinnilo A, Chiara A, Bergante C, Biancheri D, Fabiana D, Fazzi E. Obstetric risk factors and persistent increases in brain parenchymal echogenicity in preterm infants. *BJOG* 2004;111:913–918. [PubMed: 15327604]
238. Doyle L, Halliday H, Ehrenkranz R, Davis P, Sinclair J. Impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk for chronic lung disease. *Pediatrics* 2005;115(3):655–661. [PubMed: 15741368]
239. Hintz S, Kendrick D, Stoll B, Vohr B, Fanaroff A, Donovan E, et al. Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis. *Pediatrics* 2005;115(3):696–703. [PubMed: 15741374]
240. Alonso G. Prolonged corticosterone treatment of adult rats inhibits the proliferation of oligodendrocyte progenitors present throughout white and gray matter regions of the brain. *Glia* 2000;31:219–231. [PubMed: 10941148]
241. Huang W, Harper C, Evans S, Newnham J, Dunlop S. Repeated prenatal corticosteroid administration delays myelination of the corpus callosum in fetal sheep. *Int J Devl Neurosci* 2001;19:415–425.
242. Zaidi A, Bessert D, Ong J, Xu H, Barks J, Silverstein F, et al. New oligodendrocytes are generated after neonatal hypoxic-ischemic brain injury in rodents. *Glia* 2004;46:380–390. [PubMed: 15095368]
243. Hirayama A, Oka A, Ito M, Tanaka F, Okoshi Y, Takashima S. Myelin transcription factor 1 (MyT1) immunoreactivity in infants with periventricular leukomalacia. *Dev Brain Res* 2003;140:85–92. [PubMed: 12524179]

244. Jalabi W, Boehm N, Grucker D, Ghandour S. Recovery of myelin after induction of oligodendrocyte cell death in postnatal brain. *Neurobiol Dis* 2005;25(11):2885–2894.
245. Dammann O, Leviton A. Brain damage in preterm newborns: might enhancement of developmentally regulated endogenous protection open an door for prevention? *Pediatrics* 1999;104(3):541–550. [PubMed: 10469783]
246. Romanko M, Rola R, Fike J, Szele F, Dizon M, Felling R, et al. Roles of mammalian subventricular zone in cell replacement after brain injury. *Prog in Neurobiol* 2004;74:77–99.

Figure 1.

Schematic of human telencephalon development. At 4-7 weeks, the preplate (PP) forms in the intermediate zone (IZ) between the ventricular zone and the marginal zone. At about 15 weeks, the early cortical plate cells create a division between the subplate and the marginal zone by migrating out radially from the VZ/SVZ. Subplate neurons form functional circuits with cortical plate neurons, other subplate neurons, and thalamocortical afferents. Upper subplate neurons form a dense band, while the density of neurons in the lower subplate is less. GABAergic neurons initially migrate tangentially to reach the appropriate cortical region, and then migrate radially out to the cortical plate beginning at 11 to 20 weeks. At about 25 weeks, the subplate reaches its maximal thickness, GABA expression peaks, catecholamine afferents arrive in the subplate, and oligodendrocytes and axons populate the subplate and IZ. Some migrating GABAergic neurons reach the cortical plate. During this developmental period GABAergic receptors are excitatory. By term, the subplate has already begun to recede. Conversely, between 30 and 40 weeks the cortical plate increases 4-fold. GABAergic neurons continue to migrate to the cortex. Cortical synapses mature and remodel. This schemata illustrates the components of the subplate and developing white matter that are potentially affected by white matter lesions. References: 9,93, and 131.

Figure 2.

Immunohistochemistry of the subplate and developing white matter from a 27 weeks gestation fetus without pathological changes suggestive of white matter damage. Coronal sections were cut from the frontal white matter at the level of the head of the caudate, and immunolabeled. The photomontage of the hematoxylin staining demonstrates the significant width of the subplate relative to the cortical plate at this period of development. Most O4+ prooligodendrocytes and O1+ oligodendrocytes are found in the lower subplate, while more neurons are present in the upper subplate. GAD-67+ cells are present in both the subplate and developing white matter. At this age, calretinin+ cells are located primarily in the developing white matter. Neuropeptide Y+ neurons develop extensive processes in the upper subplate.

GABA_A α 1+ cells are located in the upper subplate, while GABA_BR1 receptor+ cells are mostly restricted to the developing white matter. Phosphorylated neurofilament immunolabeling (SMI #312) demonstrates a dense, mostly tangential band of axons is present in the lower subplate at this age. Hematoxylin bar = 100 μ m, other bars = 10 μ m.