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Neural plasticity and the Kennard Principle – does it work for the preterm brain?

Laura Bennet, Lotte Van Den Heuij, Justin M. Dean, Paul Drury, Guido Wassink, Alistair Jan Gunn

Address: The Fetal Physiology and Neuroscience Groups, The Dept of Physiology, University of Auckland, Auckland, New Zealand

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Correspondence:

Professor Laura Bennet

Department of Physiology,

Faculty of Medical and Health Sciences,

University of Auckland, NZ

Phone: +649 3737599

Email: l.bennet@auckland.ac.nz

Summary

1. The Kennard Principle suggests that the immature brain should be more able to recover from injury than the more developed brain. Curiously, preterm infants continue to have a high rate of debilitating neurodevelopmental handicaps despite a progressive improvement in structural damage to the brain, from acute necrotic injury of the periventricular white matter, with axonal loss in historical cohorts, to diffuse gliosis with trivial axonal damage in recent studies.

2. In the present review we examine recent evidence that disability after preterm birth is largely mediated by disturbed development of neuronal connections.

3. Potential mechanisms include impaired white matter maturation associated with gliosis, suboptimal neuronal maturation, adverse effects of infection/inflammation on the cell environment, exposure to clinical therapies that modulate brain function, including maternal

glucocorticoids, upregulation of physiological apoptosis, and loss or misprogramming of progenitor cells in the subventricular zone.

4. These findings suggest that insults during this critical phase alter the trajectory of brain development, and that a key focus of basic science and clinical research should be to understand neuronal connectivity as well as the triggers of cell death.

Key words Neurodevelopment, brain injury, preterm infants, preterm birth,

Introduction

"It is better to have your brain lesions early … that is, if you can arrange it!" said the neuropsychologist Hans-Lukas Teuber.[1] Teuber's statement refers to the concept popularised in the twentieth century that the developing brain recovers better from injury than the adult brain, due to its greater plasticity. Teuber himself advocated care when making this generalisation as his own work showed that "…it is unfortunately true that the effects one observes are largely a function of the questions that are being asked."[2]

Like the work of William James in 1890, which is credited with first introducing the term plasticity in reference to our adult "bundles of habits",[3] the hypothesis has its origins in the science of the 19th century.[4] However, it was Margaret Kennard's systematic work on the effects of age on the recovery from neural injury in monkeys that put this concept on the neuroscience

map.[5] The Kennard Principle describes the concept that the immature brain appears more resilient to injury compared to the term brain, and can remap and reorganize more effectively to preserve function, and thus is more plastic.

Kennard herself did not draw such a fixed conclusion from her own work, observing that good outcomes in younger animals were only sometimes associated with age.[5, 6] Further, the resilience of immaturity could be modified by many things, including how much brain tissue remained and in what areas, number of lesions and how far apart in time they occurred, exposure to other factors such as drugs, and that injury evolved over time. Apparent acute mild injury had the potential, for example, to evolve in the long-term into significant disability,[5] as is observed with cerebral palsy.[7] However, the concept was popularised by many researchers who have focused on the positive data.[1, 4]

The postulate is attractive because it makes sense, at least on face value. For if plasticity exists within the adult brain, then one can imagine that the potential for the developing brain to rebuild itself after injury should be exponentially better. After all, the developing brain is in the midst of creating the foundation for the brain's architecture, and at the peak of new cell formation. Such rich resources, when brain regions are not yet wholly committed to dedicated functions, should make rebuilding the brain easier than in later in life. The younger the brain the more dynamic this process. However, the plasticity of the brain is not realised in this manner, and younger does not mean better for preterm infants.

It is striking that individuals born preterm are at significant risk of impaired neural development into adulthood, with associated motor, cognitive and behavioural disabilities.[8] Conservatively, around 50% of all preterm infants will suffer cognitive and behavioural impairments.[9] Impaired neurodevelopment can occur as a function of injury, secondary to insults such as hypoxia-ischaemia (HI) and infection/inflammation.[10-12] However, it is also seen even in the absence of injury or the presence of very mild initial injury.[8, 10, 13, 14] Indeed, increasingly it is clear that even subtle injury is associated with a high incidence of low-severity learning difficulties and behavioural problems such as attention deficit hyperactivity disorder (ADHD).[8, 13, 14]

Thus, despite what appears to be a significant potential for plasticity and optimal growth and reorganisation, the Kennard Principle does not seem to be an active phenomenon for individuals born preterm. In this review we discuss the aetiology of injury, with a focus on mild and repeated (double or two-hit) insults, and the potential mechanisms that lead to even subtle injury leading to significantly impaired neurodevelopment.

The pattern of preterm brain damage in modern cohorts

Long-term follow up of quantitative magnetic resonance imaging (MRI) studies show that preterm birth is associated with reductions in cortical surface area, volume, and complexity of cortical folding and reductions in the volume of subcortical regions.[15] Neurodevelopmental outcomes are independently correlated with both white matter injury and the magnitude of the grey matter deficits.[13, 14, 16-20]

Preterm brain injury is characterised predominantly by white matter cell loss. In modern cohorts, the more severe forms of white matter injury now affect only ~1% of preterm infants.[15] Diffuse white matter loss is now more common, although some infants have microcystic lesions of the white matter.[19, 21] Subcortical neuronal loss is now recognised as a common feature of preterm brain injury,[14, 21-24] consistent with experimental findings with HI and infection/inflammation.[11, 12] However, it is notable that the preterm cortex is initially consistently spared both on neuroimaging and histologically.[22, 23, 25, 26] Thus impaired cortical development is an evolving process, occurring secondarily to cell loss or impaired cellular function in white matter and subcortical grey matter regions.[18-20]

There is a clear synergy between white matter and grey matter injury or cell loss and the evolution of impaired neural development. While neuronal loss after insults is observed, it is surprisingly unclear whether preterm birth in and of itself is commonly associated with overt neuronal loss. Children who do not have evidence of white matter injury appear to have normal neurocognitive development,[8] and neuronal loss is only seen when there is evidence of white matter loss,[27] but that loss can be quite subtle and preterm birth does appear to disrupt the development of subcortical neuronal structures.[19] This in turn has a significant impact on the development of other sub-cortical and cortical structures.[19]

Timing of insults

Early imaging and post-mortem data suggest that neural injury occurs in the immediate perinatal period in approximately two thirds of cases, while an appreciable number of cases occur before the onset of labour, and cases after the early neonatal period are least common.[28, 29] The factors

which cause the acute loss of white and grey matter cells are multifactorial. Increasingly, however, two facts are becoming clear. Firstly, relatively mild insults lead to significant long-term impaired neurodevelopment. Secondly, the preterm brain is at high risk of receiving more than one insult (the second or double-hit phenomenon), and the effects of secondary hits are poorly understood. These two issues are discussed in further detail below.

Mild hypoxia-ischaemia.

Acute, profound asphyxia can occur during preterm birth, probably at higher rates than at term.[30] However, it is critical to appreciate that such severe events appear to involve less than 1% of preterm infants and cannot possibly account for the overall burden of disability after preterm birth.[31] Experimentally, Geddes *et al*., observed that 7 day (P7) old rat pups exposed to a mild HI insult experienced delayed cerebral atrophy and infarction by 8 weeks that was not different to pups who experienced a severe insult.[32] Similarly, a moderate HI insult in P3 rat pups caused compromised cortical growth and led to a selective alteration of cortical myelinated axons with persistent gliosis by 21 days.[33] More recently in the same model, cortical loss at day 25 correlated with cerebral lactate at day four.[34] Further, the insult led to evolving malformations of the somatosensory barrel field and changes in evoked potential maps in somatosensory–motor networks.[35] Consistent with these findings, gene and molecular studies of rat pups reared in moderate hypoxia from P3-11, a model designed to mimic the sub-lethal insults faced by the extremely preterm infant, showed moderate HI results in a global disruption of the genes required to facilitate synapse formation and neural transmission.[36]

In a larger animal model, the preterm fetal sheep, reversible cerebral ischaemia, that did not cause acute neuronal loss, has been shown to be associated with impaired expansion of the dendritic arbour and reduced synaptic density of cortical neurons after 4 weeks recovery.[37] Strikingly, these histological changes were associated with impairment of cortical growth and the normal maturational decline in cortical fractional anisotropy (FA) on ex-vivo MRI scans. Mathematically, these changes in FA after ischaemia were consistent with the changes in the growth of dendritic branches of cortical pyramidal neurons compared to controls. Supporting these findings, human survivors of preterm birth who grow slowly show a similar delayed development of cortical grey matter, as measured by FA.[20]

Mild inflammation

There is increasing evidence that exposure to *in utero* infection at critical stages of brain development can significantly increase the risk of neurodevelopment abnormalities, as recently reviewed.[11] As with asphyxia, although overt severe infection is strongly linked with neural injury, it only accounts for a small minority of cases; subclinical infection is common and also highly associated with adverse outcomes.[38, 39] Further, neuro-inflammation is a feature of the brain after both HI,[40] which can be very long-lasting,[41] and exposure to intrauterine infection and inflammation in conditions such as chorioamnionitis.[11, 38, 39]

The majority of experimental studies to date have evaluated the effects of lipopolysaccharide (LPS), a purified polysaccharide from the outer wall of gram negative bacteria.[11] Large or repeated doses are frequently given, which can result in frank neural injury, and associated impaired neural development. A single bolus of LPS in preterm fetal sheep was associated with

acute brain injury after 3 days recovery,[42] followed by impaired brain growth and loss of the normal maturational increase in cortical EEG amplitude 10 days later.[43] An intra-amniotic bolus of LPS was associated with increased low frequency EEG activity 14 days after exposure, consistent with reduced maturation of the EEG.[44]

More recently, we developed a model of low-dose chronic exposure using LPS given to preterm fetal sheep over 5 days that does not perturb fetal blood gases, carotid blood flow or arterial blood pressure.[45] In this model we observed impaired maturation of the cortical EEG.[46] LPS infusion was associated with loss of the normal maturational shift to higher frequency EEG activity, with reduced alpha and beta power, and greater delta power than saline controls a week after first exposure.[47] This impaired cortical maturation developed in the presence of a low grade systemic and cerebral inflammatory response.[47] Accompanying these changes was a transient increase in serum IL-6, induction of microglia and greater expression of TNF-α positive cells in the front-parietal cortex 5 days after the end of LPS, consistent with the hypothesis that exposure to pro-inflammatory cytokines directly contributed to the EEG dysmaturation.[11, 24, 48]

In vitro studies show that pro-inflammatory cytokines mediate synaptic dysfunction, in part indirectly through adenosine and GABA,[49] and glutamate.[50] Further, TNF-α was reported to inhibit growth and branching of neurons, which could be reversed by TNF-α receptor blockade.[51] Curiously, however, in a normal brain, glial derived TNF-α activity is important for synaptic stability by ensuring synapses stay plastic.[52] Exposure to interferon gamma, an inflammatory marker that is induced by injury and many inflammatory conditions, is also associated with both

inhibition of initial dendritic outgrowth in culture and retraction of existing dendrites.[53] Thus, it is highly plausible that chronic low levels of cerebral cytokines associated with infection, or with traumatic events such as hypoxia and ventilation can reduce neural excitability and impair connectivity in the cortex. Further long-term studies are essential to confirm this hypothesis.

The second-hit

Prematurity alone predisposes to impaired neural development, but it is exacerbated when combined with a second insult such as infection-inflammation or hypoxia.[10, 13, 48] Further, standard clinical care, such as ventilation and drug therapy, nutrition, handling, and the NICU environment may also contribute to modulating injury.[54] We briefly discuss the evidence surrounding some of these factors below.

Infection-inflammation

As discussed above, being born prematurely or small for gestational age significantly increases the risk of poor cognitive outcomes as measured by such tests as the Bayley Mental Developmental Index (MDI).[48] Being exposed to infection/inflammation significantly increases that risk.[48] Pre-clinical studies in immature rats with LPS has shown that this pro-inflammatory agent can lower the threshold at which hypoxia-ischaemia triggers events leading to brain injury,[55] and this is a time dependent phenomenon. A low-dose of LPS administered shortly (4-6 hours) before an HI insult was associated with increased injury.[56-58] This sensitization could be prevented if the glucocorticoid dexamethasone was given at the same time as LPS.[59]

Sensitization was also seen when LPS was administered 72 hours or more before HI.[56, 57] However, a reduction in injury was seen when LPS was administered 24 hours before HI; i.e., tolerance to HI was apparently induced.[56, 58] Several mechanisms are postulated for the transient induction of tolerance by LPS. Ikeda *et al*., showed that administration of RU486, a glucocorticoid receptor blocker, prevented the tolerance effect, suggesting a role for the induction of endogenous corticosterone.[58] Sensitization may also, in part, be mediated by LPS altering the glycolytic response to HI.[60] Finally, LPS preconditioning may work by reducing neuro-inflammation associated with HI.[61]

Similar responses are seen in newborn mice at P4, who had been exposed to LPS *in utero* at days 19 and 20. Prior exposure to LPS sensitized the post-natal pups to greater brain injury after ibotenate injection.[62] Pre-treatment of mice pups with pro-inflammatory cytokines before ibotenate also increased injury, with modulation of microglia playing a key role.[63] Recently it has been shown that sensitization is mediated by an imbalance in pro- and anti-inflammatory cytokines, and that TNF-alpha plays a key role in mediating sensitization by inflammation to HI injury.[64]

Whether exposure to inflammation causes increased or decreased HI injury is also a function of age.[65, 66] Recently, Hickey *et al*., demonstrated that LPS preconditioning tolerance to injury is age dependent and that changes in TLR-4 expression with age is a likely mediator.[65] Other mechanisms which may mediate sensitization by LPS may also be age dependent. Fleiss *et al.,* showed, in an LPS mouse model of sensitization to HI, that hyperacetylation with histone

deacetylase inhibitor (HDACi) trichostatin A (TSA) reduced injury and improved long-term learning, and that TSA appeared to exert neuroprotection via mechanisms specific to the neonate.[67]

A key question, not yet significantly assessed, is whether inflammation can modulate the cardiovascular and chemoreflex defence responses of the fetus to an HI insult.[12] LPS given in high-doses acutely to fetal sheep can cause profound hypotension and hypoperfusion.[68, 69] However, this was not seen with lower doses of the gram-positive agent OK-432 (Picibanil), although a single exposure to this agent causes progressive vasodilatation.[70] Hypotension was also not seen with chronic low-dose LPS infusion to preterm fetal sheep.[45] More recently we have shown that five days of low-dose exposure LPS does not impair the cardiovascular responses the preterm fetal sheep makes to a severe HI insult, but rather, conversely, appeared to enhance the chemoreflex responses.[71]

Ventilation

In preterm infants, respiratory disease is an independent predictor of white matter injury,[72] and neurodevelopmental outcomes.[73] Ventilation of infants may also act as a second-hit when combined with pre-exposure to inflammation and or HI, and may sensitize or protect from injury depending on the degree of inflammation and ventilation strategies.[74, 75] Indeed, the optimal methods for ventilation, and safe limits for oxygen and carbon dioxide, continue to be debated. A recent randomised trial of CPAP showed no differences in the composite outcome of death or

neurodevelopmental outcomes at 18-22 months corrected age for early CPAP and those assigned to early intubation, surfactant administration, or low versus higher oxygen saturations.[76] The effect of ventilation on inflammation secondary to conditions such as birth asphyxia and chorioamnionitis remain poorly understood.

Jobe *et al*., have demonstrated in the sheep fetus that exposure to intra-amniotic dose of LPS is associated with improved maturation of the fetal lung, as shown by increased surfactant lipids in the airspaces, and improved pressure-volume responses, mediated by the inflammatory response.[77] At the same time this exposure also alters lung collagen and elastin, transient inhibition of alveolar septation and fewer, larger alveoli, consistent with lung injury that may predispose to chronic lung dysplasia. A second hit of inflammation, either with LPS or other bacterial products, within 5 days of the first dose produces very little lung inflammation. Thus their studies showed that the initial inflammatory response down regulates subsequent immune responses, even to different bacteria.[77] However, this phenomenon is highly time dependent, such that modulation is lost if the second-hit occurs after 7 days. Time also changes the responses to glucocorticoids. Glucocorticoids given within 5 days of LPS exposure act to suppress LPS-mediated lung inflammation, but after 5 days they appear to stimulate the inflammatory responses. Thus, the preterm newborn may be in a variable immune state, at least within the lung, depending on the time course and nature of second-hits. The state of immune modulation or compromise in turn plays a key role in the adaptation the preterm infant makes, and to the nature of longer-term outcomes.[77]

Some ventilation strategies have the capacity to induce neural inflammation, and to worsen pre-existing inflammation. High-tidal volume ventilation in newborn lambs can increase brain inflammation,[78] and exposure of fetal lambs to LPS further exacerbates ventilation induced brain injury when these lambs are born.[79] Further, *in utero* exposure to LPS impairs the pulmonary and haemodynamic transitions at birth.[80] Infants born from mothers who have pre-eclampsia, and thus may have experienced HI and inflammation, are also reported to experience significant postnatal inflammation when being ventilated.[81] Prior LPS exposure can also sensitize neural injury related to hyperoxia during ventilation,[82] and lead to pulmonary disease later in life.[83] Hyperoxia induces neural cell death, and LPS impairs oligodendrocyte maturation without cell death. When combined as a two-hit insult, cell death is reduced but the effect on oligodendrocytes persists, and this in turn is associated with impaired white matter development.[82]

Glucocorticoids

Meta-analysis of randomized clinical trials suggests that maternal treatment with antenatal glucocorticoids substantially reduces acute neonatal morbidity and mortality after premature birth and is associated with a reduced risk for intraventricular haemorrhage and white matter injury.[84, 85] There may be differences between different glucocorticoids; there is some retrospective evidence that maternal betamethasone may improve neurodevelopmental outcome compared to dexamethasone exposure.[86] However, there are clinical and experimental data to show that both antenatal and post-natal glucocorticoids may, under some circumstances, impair

brain development. Post-natal glucocorticoids in particular appear to be more harmful, with recent reports showing that post-natal treatment is associated with impaired cerebellar growth.[87]

Similarly, although postnatal glucocorticoid treatment can help wean infants off mechanical ventilation, and improve survival, it may increase the risk of disability.[88, 89] Wilson-Costello *et al*, concluded that high-dose steroids for respiratory disease are associated with increased neurodevelopmental impairment and that there is no "safe" window for steroid use in extremely low birth weight infants.[90] Importantly, recent data suggest that reduced postnatal use of steroids may not impact upon chronic lung disease in preterm infants, but the reduction in steroid use may be associated with reduced risk for cerebral palsy.[91]

Antenatal glucocorticoids have also bee associated with reduced head circumference in some studies, consistent with an effect on neural development.[92] Tisjsseling *et al*., demonstrated in a small post-mortem study that antenatal glucocorticoids were associated with reduced neuronal density in the hippocampus.[93] Experimentally, *in vitro* studies of cultured rat hippocampal neurons support this finding, demonstrating that glucocorticoids induce simplification of dendrites and shrinkage of dendritic spines.[94] *In vivo* studies in sheep have shown that even a single clinical course of antenatal glucocorticoids can delay cerebral myelination,[95] and decreases MAP1B and 2 immunoreactivity, indicating that steroids induce a reduction in major proteins associated with the neuronal cytoskeleton.[96] A single clinical course of maternal glucocorticoids is associated with acute changes in electroencephalogram transient activity and epileptiform events, followed by evidence of increased neural maturation.[97] Given that seizures in early life in the rat can induce neuroprotection through preconditioning mechanisms,[98] it is

plausible that steroids may also trigger a sensitization/preconditioning sequence independently of pathological events.

Glucocorticoids may also precondition the brain to either greater sensitivity or tolerance to HI. The effects are also highly age dependent, as recently reviewed.[99] In adult rats for example, glucocorticoids given before an HI insult (1-48 h) appears to increase injury,[100] whereas in P7 newborn rats, such treatment reduces injury.[101] In contrast, in the fetal sheep, glucocorticoids given 48 before had no effect on injury.[102] The effects closer to the insult, and during or after the insult are variable and have only been studied in the newborn; more evidence is needed.[99] Further, glucocorticoids are not the only drugs we give routinely that may interact with ventilation. Sedatives and analgesics given to infants being ventilated are also associated with an increased risk of adverse neurodevelopment.[103]

What is the link between cortical maturation and white matter injury?

The big unanswered question is: why is the preterm brain is so vulnerable? Specifically, why is cortical development impaired, when the cortex is seldom injured acutely? We have presented information to show that the preterm brain is at risk of many insults before and after birth. Rather than being resilient to such insults, as suggested by the Kennard Principle, the preterm brain appears to be more vulnerable. Further, subtle injury, with no discernible early cell death, is also associated with impaired neurodevelopment in many infants. Indeed, the very act of being born early predisposes to impaired brain development. However, it is important to note that those

infants will have experienced many antenatal and postnatal treatments which may play a role in white matter development, as yet undetermined. Ultimately, the short answer to the questions posed is that we simply don't know, but there are currently several alternative hypotheses.[18]

Injury of white matter cells and/or axons leading to retrograde degeneration (axonopathy) has been proposed to be a potential mechanism of myelination failure in white matter injury.[104] However, in today's cohorts, axonopathy is reported to occur only after more severe ischaemic injury,[105] with necrotic foci, in association with microglial activation.[106] Recent data show that while microscopic necrosis and axonopathy does occur, it affects less than 5% of the area of the periventricular white matter, and that diffuse astrogliosis is now the key feature of WM injury.[107] Pre-oligodendrocyte degeneration accounts for only a small fraction of cell loss in rodent,[108] and sheep studies.[109]

Alternate hypotheses suggest that there may be impaired maturation of oligodendrocytes, leading to paucity of myelination and impaired signalling. In post-mortem studies of preterm infants, Billiards *et al*., reported no differences between PVL and control cases in oligodendrocyte density, but with myelin and pre-oligodendrocyte abnormalities.[110] They suggest that acute loss of pre-oligodendrocytes is replaced by proliferation, and thus the progressive degeneration hypothesis does not appear to be supported for diffuse WM loss. However, proliferation appears to be inadequate to restore normal development, and there may be defects in oligodendrocyte maturation, and signalling. Buser *et al.,* speculated that acute pre-oligodendrocyte death may trigger diffuse astrogliosis, as part of the neuroinflammatory responses, leading to an aberrant

regenerative response that contributes to impaired maturation of oligodendrocytes and consequent reduced myelination (Figure 1).[107] Key factors in this process include the inhibitory effects of astrogliosis and induced microglia on histone deacetylases (HDACs), which are vital for oligodendrocyte maturation, and the actions of astrocytes to enhance complement proteins which modulate synaptic pruning.[111, 112]

Compounding the problem may be the issue of where new cells are produced and how far they can migrate. A recent study in newborn mice suggest that the normal place of cell production, the subventricular zone (SVZ) may produce fewer new cells after injury, and these cells do not survive due to lack of trophic cues, and do not migrate long-distance.[113] Greater numbers of new cells are seen in areas of injury such as the striatum, and that these cells remain relatively local.[113] In preterm rabbits, preterm birth itself appears to suppress neurogenesis, and this may in part be due to increased oxygen tensions.[114]

The specific mechanisms of this striking impaired maturation are still being characterized, but we may speculate that reduced myelination can have secondary effects on neuronal maturation and survival in a number of ways. Brain cells are 'social' beings, and so need other cells to survive and to develop. Their survival is tightly linked to extrinsic signals from neighbouring cells and synaptic activity.[115] Alterations to cellular connections must in turn have consequences for a cells existence and functional capacity. For example, loss of cells or an impaired capacity to produce myelin, must have a consequence for survival of cortical neurons waiting to be

myelinated. Cells which cannot be supported properly or which do not function for the good of the social whole may be programmed to die via physiological apoptosis.[115]

Glia are, of course, vital for neuronal survival, and for the survival of other glia, partly through trophic signalling factors secreted to signal survival and differentiation.[111] Neurons in return exert proliferative effects on cells of the oligodendrocyte lineage.[115] Equally, as described above, other glia, such as astrocytes, play key roles in the maturation of the neuronal synaptic network.[111] Thus, cell-cell feed-forward and feed-back process between glia and neurons will act to prune cell numbers and reduce dendritic arbour and synapse formations, as reported recently,[37] to facilitate cell-cell matching.

Connectivity and the connectome

Ultimately, impaired myelination, astrocytic and microglial activation appear to impair and reduce glial and neuronal connections, and it is the variability of this connectivity of the brain which underpins our cognitive, behavioural and sensory-motor capabilities. Smyser *et al*., recently noted that anatomy and functional connectivity, while interrelated are not identical.[116] Understanding how function relates to the connectivity of the brain is an important future line of research. A connectome is a map of neural connections in the brain, and can be created with advanced MRI based tractography.[117] Ball *et al*., recently reported that in term infants and preterm infants (median gestation at birth 28 weeks), scanned at term equivalent age, there was a significant association between frontal and temporal lobe volumes and thalamic and cortical

tissue reduction and the loss of microstructural integrity in the connective white matter tracts.[19] Subsequent tractography demonstrated that connectivity between the thalamus and cortex was significantly reduced. [118]

Resting state networks (RSN) tell us about the functional underlying communication network architecture of the brain. Potentially such networks may develop in parallel with the development of related cognitive functions.[119] The RSN for preterm infants has recently been mapped, showing that a complex, mature RSN develops over the last stage of gestation.[119] However, assessment of the RSN in preterm newborns in the first 18-20 months, who do not demonstrate overt injury, suggests that connectivity appears weaker demonstrating that impaired neural development starts early.[120]

Final conclusions

In this review we have presented current research which shows that being born preterm, even without obvious neural injury, can for many of these infants lead to impaired brain development and associated neurobehavioural difficulties later in life. The immature brain does not appear to continue the preset genetic programme after birth to ensure development of the optimal brain, and cannot simply replace lost brain cells after injury. In this regard the Kennard Principle is not fulfilled. However, comparisons to the adult brain that underpins this principle cannot be readily made. The preterm brain is unique in how lesions are superimposed upon the developing matrix of the brain which, even without frank lesions, can be altered in its ultimate trajectory by

impairment of optimal connectivity. Further, the preterm brain is subjected to many medical and non-medical events which shape that trajectory. Overall, these finding lead to the hypothesis that some combinations of these events during this critical phase alters the trajectory of brain development leading ultimately to reduced or simplified neuronal interconnection. This strongly suggests that a key focus of future basic science and clinical research should be to understand the factors that impact upon neuronal connectivity, and how we can intervene to optimise the development of the preterm brain.

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Figure Legends

Figure 1. Schema showing that acute injury can trigger death of white matter cells (particularly pre-oligodendrocytes) and some neurons in grey matter. In milder/diffuse injury, there may be proliferation of the pre-oligodendrocytes that completely restores total numbers of cells in white matter. However, there is increasing evidence that there are persistent changes in the cell environment can lead to impaired maturation of oligodendroglia and reduced connectivity of neurons in a tertiary phase of recovery. The mechanisms are only partly understood, but likely include local astrogliosis, inflammation, reduced release of survival and chemotaxic activity, and

reduced feedback through reduced neuronal activity. These factors in turn lead to impaired development of neural networks reduced total brain growth, and long-term disability.

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