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Hitting a Moving Target: Basic Mechanisms of Recovery from Acquired Developmental Brain Injury

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Abstract

Acquired brain injuries represent a major cause of disability in the pediatric population. Understanding responses to developmental acquired brain injuries requires knowledge of the neurobiology of normal development, age-at-injury effects and experience-dependent neuroplasticity. In the developing brain, full recovery cannot be considered as a return to the premorbid baseline, since ongoing maturation means that cerebral functioning in normal individuals will continue to advance. Thus, the recovering immature brain has to ‘hit a moving target’ to achieve full functional recovery, defined as parity with age-matched uninjured peers. This review will discuss the consequences of developmental injuries such as focal lesions, diffuse hypoxia and traumatic brain injury (TBI). Underlying cellular and physiological mechanisms relevant to age-at-injury effects will be described in considerable detail, including but not limited to alterations in neurotransmission, connectivity/network functioning, the extracellular matrix, response to oxidative stress and changes in cerebral metabolism. Finally, mechanisms of experience-dependent plasticity will be reviewed in conjunction with their effects on neural repair and recovery.

INTRODUCTION

Acquired brain injuries (hypoxia, stroke, trauma) constitute some of the major causes of morbidity in children and adolescents. The mantra ‘younger is better’ is generally invoked when faced with a pediatric patient who sustains a brain injury, and yet this does not absolve either the clinician or the basic researcher from addressing developmental differences in injury response and recovery. One of the last brain regions to fully mature, the frontal lobe, is particularly vulnerable to acquired injuries that may induce immediately apparent neurocognitive deficits but may also be responsible for later occurring, more subtle deficits mediated by altered patterns of post-injury development.

There are several general principles that will be considered in this review. First and most straightforward, types of injury vary by age and thus contribute to age-dependent post-injury pathophysiology. Second, ongoing neural processes that mediate normal brain development

are associated with different cellular and physiological mechanistic responses to an acquired injury. Lastly, the effects of environment on normal development and recovery from injury are complex and yet crucial to understanding outcomes of developmental brain injuries. Here we will focus on these underlying neurodevelopmental processes to provide a basic science perspective of pediatric brain injuries with an eye toward clinical translation.

INJURY TYPES AND MODELS

Focal Lesions

The understanding that distinctly different outcomes occurred after brain lesions sustained at different ages dates back to Broca who described the preservation of language in a patient with a congenital left frontal lobe lesion [1,2]. However, the first systematic characterization of the effects of frontal lobe injury during development was done by Margaret Kennard. Her seminal observations of the effects of primary motor cortex lesions in primates demonstrated that a similar lesion at different ages could have remarkably different long-term outcomes. Her work is often overly simplified as the “Kennard Principle” which notes that neonatal lesions result in significant sparing of neurological function, or the ‘younger is better’ statement alluded to above. In reality, her work established or clarified many principles of injury and recovery that we take for granted today.

In the frontal lobes, Kennard demonstrated that surgical ablation of primary motor and premotor cortex in primates resulted in fewer immediate deficits and better long-term functional outcome when the ablations occurred earlier in life [3]. However, she also noted that these infant monkeys demonstrated some detectable motor abnormalities into adulthood. Furthermore, there were certain neurological functions that showed equally severe and persistent deficits following complete unilateral or bilateral frontal removal at either age (neonatal or adulthood). These included deficits in immediate recall (working memory), impaired conjugate eye movements, and increased spontaneous movements/restlessness [3-5]. So, Kennard's work supports the ‘younger is better’ concept, but also demonstrates important caveats to this principle.

Another concept of developmental brain injury, ‘growing into the lesion’, also received support from the careful observations of Kennard. In this case, frontal motor cortex-lesioned infant monkeys initially showed relatively small motor deficits, but, over years, these animals developed greater spasticity, uncoordinated fine finger movements and abnormalities of ambulation [4,6]. Several theories were proposed to account for the delayed manifestation of injury sequelae. It was suggested that cortical motor control was established later in development and thus not demonstrable at early stages, but also included was the concept that the early injury in some way perturbed the pattern or sequence of normal maturation.

These results have been corroborated and expanded over the years. Using either dorsolateral or orbital frontal lesions at different ages and long-term follow-up in primates, Goldman, et al., showed that some frontal functions were relatively spared after early injury, but others were actually more vulnerable [7,8]. Detailed studies by Kolb, et al. in the developing rat showed specific stages or windows of injury response and recovery to frontal ablations. In general, the motor outcome after bifrontal suction ablations in neonatal rats was very poor if the injury was sustained in the first week of life, yet showed a window of remarkable sparing for lesions during the 2nd week [9]. After that, functional outcomes gradually worsen to approach adult-like outcomes as the juvenile rats become young adults.

While many of these studies describe functional and behavioral outcomes, each of these investigators has also proposed underlying mechanisms for these phenomena. After early frontal motor cortex resection, monkeys studied in adulthood showed strong motor responses

to electrophysiological stimulation of the post-central gyrus, implying that somehow neurons in adjacent brain regions either grew or strengthened connections to the targets of the lesioned area [10]. Dendritic growth or rearrangement was postulated as one means of accomplishing this effect [5,11], and subsequent studies have shown correspondence between regional dendritic architecture and enhanced neurological function [12-16]. More recently, age-dependent effects on neurogenesis and neural migration have been shown to play a role in neonatal frontal lesions in rats, with post-natal day 9-10 (P9-10) lesions showing significant regrowth of frontal cortex tissue [9,17]. Perhaps even more importantly, this newly grown tissue can connect anatomically and electrophysiologically with targets necessary for improved functional motor outcome [18-20]. In addition, it is possible to induce this neurogenesis after P10 lesions elsewhere in cortex by administering subcutaneous injections of a neurotrophic factor, fibroblast growth factor-2 [21]. This regenerated tissue becomes integrated into the neural network and its removal results in significant functional loss [21].

With the current focus on translational research, it should also be emphasized that clinical observations have also supported many of these experimental findings after focal developmental brain injury. After noting that age-effects of injury appeared to be greater in higher primate species, Kennard actually reviewed clinic records and systematically reported that spasticity and facial paresis increased with age-at-injury in human children [22]. Many extensive resective surgical procedures for epilepsy show better functional neurological recovery post-operatively in younger patients, and indeed, hemispherectomies are generally reserved for infants and young children [23-26]. The idea of cross-modal plasticity (namely that alternate areas may compensate for an injured or ablated area) has actually been studied in humans now, both with electrical recordings and with noninvasive functional imaging [27-30].

Diffuse Hypoxia-Ischemia

Another type of acquired brain injury that has revealed specific age-related differences is hypoxia-ischemia. Perinatal cerebral hypoxia-ischemia (HI) is a major cause of mortality and chronic disability among newborns. It has been estimated that 1-6 out of every 1000 births will experience HI insult with 15-20% mortality [31,32]. Given the incidence and the devastating consequences, it is not surprising that experimental models of HI have been studied among immature rodents, rabbits, guinea pigs and monkeys [33,34]. The rodent HI model [35] has not only been one of the most extensively utilized animal HI models, but has provided important insight into age related differences to brain injury.

Studies examining the influence of age on histological outcomes after HI injury revealed that while P2-P3 rat pups were resistant to HI injury, P7-30 rats showed increasing cerebral lesions with age and with hypoxic duration [36]. More importantly, the results demonstrated age-related changes in the cerebral regions of HI vulnerability and pattern of lesions. While the mechanisms for these age-related differences in HI pathology are not entirely known, vascular maturation, excitotoxicity and energy/metabolic processes are likely involved.

Interacting with these age-related differences in cerebral vulnerabilities to HI injury, are pronounced age differences in response to glucose and alternative substrates before or after HI injury. Hyperglycemia induced during HI worsens histological outcome in adults [37] and is neuroprotective in P7 rats [38,39]. Insulin-induced hypoglycemia before HI was neuroprotective in adults [40] and exacerbated injury in P7 rats [41]. Despite the ineffectiveness of insulin induced hypoglycemia, fasting-induced hypoglycemia or β -hydroxybutyrate administration were both histologically neuroprotective in the immature rat [41]. These age differences emphasize the complex relationship between cerebral maturation and cerebral substrate utilization during injury.

Clinical observations from HI newborns and infants have been consistent with findings from animal models of HI and together have revealed the mechanisms involved in cellular injury from HI insults. HI acutely induces decreases in ATP and increases in lactate production as glucose is metabolized anaerobically. This causes ionic changes, membrane depolarization, and release of glutamate. CSF glutamate concentrations were found to be significantly elevated at 16 hrs after birth in asphyxiated infants [42,43]. The released glutamate activates N-methyl-D-aspartate receptors (NMDAr), which, in the neonatal brain, have subunit compositions designed for greater calcium accumulation [44]. While potentially beneficial from a standpoint of increased neuroplasticity, this developmental difference can also contribute to the increased vulnerability of the infant brain to excitotoxic mechanisms. The accumulation of intracellular calcium both acutely and delayed contributes to mitochondrial dysfunction, which ultimately increases production of free radicals. Plasma concentrations of malondialdehyde, (a product of lipid peroxidation) was increased 4-fold within 12-24 hrs after birth among asphyxiated neonates [45]. During this period of cerebral maturation, the increased fatty acid content of the brain, the immature antioxidant system and the higher concentrations of free iron make the newborn brain particularly vulnerable to increased presence of free radicals [46]. These events act in concert to ultimately induce cell death and functional impairments.

Traumatic Brain Injury

Traumatic brain injury (TBI) is the single greatest cause of pediatric mortality and morbidity [47]. Compared to the study of developmental brain injury using lesions or hypoxia-ischemia models, however, laboratory investigations into the effects of TBI in the immature animal have only been undertaken relatively recently [48]. Owing to the anatomy of the cranial fossae, and the biomechanics of physical forces imparted during head trauma, the frontal lobes are frequently affected by TBI. Furthermore, the frontal lobes undergo a prolonged period of development, particularly in humans, where measurable anatomical changes can be seen throughout childhood, adolescence and into young adulthood [49-51]. There has been a general perception that younger children typically showed greater recovery, and therefore better long-term outcomes than older children and adolescents. More recent and refined outcome studies in children after TBI suggest that older children and teenagers do tend to have better global outcomes after TBI than adults. However, young children and infants actually may be more vulnerable to these injuries, particularly as injury severity increases [52-55]. Even older children and adolescents can show specific deficits or later emerging problems that may be related to their stage of brain development at the time of injury [55-57].

Animal models have shown that developmental TBI results in different acute injury responses and recovery. Acutely, compared to adults, immature animals show distinctions in apnea [58], biomechanics [59], metabolism [60,61], cell death (or resistance to cell death) [62-64], electrophysiology [65-67] and glutamatergic neurotransmission [68-71]. To isolate the sources of age-related differences, some have attempted to physically scale injuries to different brain sizes [72], whereas others have used similar forces [58,73] or similar injury responses (apnea, loss of toe pinch) [74] at different ages. Measurable behavioral or cognitive impairments can be subtle, although some of this is due to the fact that commonly used behavioral outcomes (like spatial learning in Morris water maze) are not fully developed in very young animals [75]. At the very least, accurately measuring functional outcomes in development requires careful age-matched controls, and, at some ages, some behavioral tasks may simply be less sensitive to detect injury-related deficits [64,76].

There are age-related differences in mechanisms of injury that are clinically relevant and have not yet been adequately modeled in the laboratory setting. In the infant and toddler, the most devastating type of TBI is that associated with inflicted injury or child abuse. These individuals are often excluded from clinical series of infant TBI, or at least studied separately. However,

it is well described that among all types of pediatric TBI, this group has the worst outcome. Many potential explanations for this have been proposed, including but not limited to the following: 1) these injuries are generally repetitive and diffuse, 2) there is often a delay in presentation, 3) secondary injuries, such as hypoxia-ischemia, may exacerbate the traumatic injury, 4) there are fundamental developmental physiological processes that render the very young brain more vulnerable, 5) pharmacotherapy used to manage these patients may have developmental toxicities, and 6) given legal issues, foster care or inadvertent return to the abusive caregiver, the post-injury (and even pre-injury) environment of these victims may be suboptimal for recovery.

Another clinical scenario remaining to be modeled developmentally is repeated mild TBI (mTBI) or concussion, as seen in contact sports. The preponderance of clinical evidence suggests that children can recover completely from a single mTBI [77], however, several studies of adolescents and young adults suggest measurable cognitive impairments exist after repeated mTBI [78,79], and that acute cognitive problems may take longer to resolve in high school students compared to college students [80]. Furthermore, there is growing concern about the long-term effects of repeated concussion. Associations have been proposed between early and repeated head injury and increased risk and/or early onset of Alzheimer disease, Parkinson disease and a dementia syndrome characterized by premature and excessive appearance of neurofibrillary tangles on pathological specimens [81-83]. Several animal models have been devised to look at repeated mTBI [84-87], although none have specifically examined the response of the immature brain to repeated mild insults.

AGE-AT-INJURY MECHANISMS

Neurotransmitter Receptors

It is well known that the very immature brain is exquisitely sensitive to excitotoxic injuries. Excitatory amino acid neurotransmitters were recognized to have prominent dual roles in early development. Namely, that activation of excitatory neurotransmitters was essential for plasticity and normal maturation, and yet, that excessive activation via NMDAr, could disrupt developmental processes in a major way [88,89]. NMDAr subunit composition normally changes during development in both rodents [90] and humans [91], with a lower NR2A:NR2B ratio early in life that corresponds to increased sensitivity to glutamate and larger receptor-mediated calcium flux [92,93]. As networks mature, the 2A:2B ratio increases, resulting in more selective activation of glutamatergic synapses. As mentioned earlier, this molecular switch may provide for greater plasticity at a young age but may also confer greater vulnerability to pathological stimulation.

More recently, it has become evident that glial cells also express glutamate receptors and that excitotoxic hyperactivation of these receptors is thus not unique to neurons. Indeed, developing glial cells may be particularly vulnerable, and these mechanisms may at least partially explain age-dependent patterns of white matter damage seen after perinatal hypoxic-ischemic injuries [94,95].

In addition to enhanced excitatory neurotransmission, the perinatal brain also experiences a seemingly paradoxical response to activation of gamma-amino butyric acid receptors (GABAr). Whereas in juvenile and adult neurons, opening of the GABAr chloride channel results in an inhibitory response, in the very young, the response is opposite [96]. Interestingly, this GABA-mediated excitation is not directly due to molecular changes in the GABAr itself, but to a reversed chloride ion transmembrane potential, resulting from immaturity of the NKCC1 chloride co-transporter [97]. Finally, it is known that developmental changes potentially relevant to brain injury occur in expression of many other neurotransmitter

receptors, including but not limited to AMPA, acetylcholine and dopamine receptors [68,98, 99].

Cellular and Network Destruction vs. Dysfunction

During brain development, apoptotic processes are enhanced, in both basal conditions and following acquired injuries. These mechanisms are exacerbated by blockade of excitatory neurotransmission, as may occur after administration of drugs for anesthesia, sedation, 'neuroprotection' or seizure prevention [63,100-102]. More recently, excitatory blockade has also been associated with impaired developmental neurogenesis [103]. Most clinical studies of pediatric brain injury fail to mention the medication exposure in detail, potentially missing a significant confounding variable.

During network maturation, there are ongoing changes in both glutamatergic and GABAergic receptors, including changes in subunit composition, splice variations, phosphorylation and cellular localization. In addition, neural networks and different brain structures mature at different rates. After the period of maximal synaptogenesis in early childhood, there is an ongoing period of synaptic pruning. Animal data suggests that the proper pruning of synaptic connections itself requires appropriate glutamatergic signaling [104]. Furthermore, there is increasing clinical awareness that improper dendritic branching and pruning are associated with other developmental disorders (Rett, Fragile X, etc.) that result in cognitive impairments [105].

Many laboratory studies of injury-induced cell death show a relative resistance to excitotoxicity, necrosis and apoptosis in this older juvenile age range [62-64]. However, even in the absence of cell death, injury-induced functional disturbances have been demonstrated in animal models of TBI [64,69,106]. Functional disturbances in the absence of structural lesions are increasingly demonstrated in adolescents and young adults, particularly following isolated or repeated mild TBI/concussion. Because of the biomechanics of TBI, these disturbances are often widespread, but neuropsychological testing reveal a propensity for deficits in cognitive abilities mediated by frontal lobe networks, including working memory [107-109], executive functions [78,79] and attention [110].

Extracellular Mediators of Developmental Connectivity

Recent research has highlighted the extracellular environment as a key player in post-injury neuroplasticity in the adult brain. Chondroitin sulfate proteoglycans (CSPGs) are complex molecules in the extracellular matrix (ECM) that function as bridges between the cell membrane and structural components of the ECM, and generally inhibit neurite outgrowth. It has been found that removal of CSPGs may result in a more growth-permissive environment [111]. Cleavage of chondroitin sulfate side-chains results in a recapitulation of normally developmentally-restricted axonal sprouting in spinal cord [112] as well as dendritic sprouting after neutralization of the growth-inhibitory molecule NOGO-a [113].

The major CSPGs (versican, neurocan, phosphacan, brevican, aggrecan, NG2) are differentially expressed both temporally and spatially during forebrain development. These distinctions imply different functions, such as the important examples summarized here. First, the functionally active N-terminal portion of neurocan peaks at P10 but is then markedly decreased by P35 [114], consistent with an axon pathfinding role in the hippocampus and cortex [115,116]. An isoform of the alpha domain of versican that is predominant in brain white matter tracts, increases postnatally [114] in parallel with myelination. Aggrecan progressively increases up to 5 months of age in the rat [114] and its appearance in the brain appears to mark the end of the critical period for visual cortex plasticity in cats [117]. Phosphacan also increases postnatally but not in the neuroplastic mossy fiber tract of the hippocampus [118]. Furthermore,

it is reduced after kainic acid-induced seizures [119] implying that its expression may at least partly account for restricted plasticity.

The developmentally low levels of CSPG glycoproteins in the brain may be one mechanism by which the immature brain can respond more vigorously to injury compared to adult. Although there are numerous reports detailing increases in growth-inhibitory neurocan and versican after CNS injury in the adult brain [120] relatively little is known about the involvement of CSPGs in the immature injured brain. Two studies using the hypoxic-ischemic injury model at P7 found that the amount of neurocan, phosphacan, brevican and NG2 are reduced [121,122] rather than increased, as is more often found after adult CNS injury. While on the one hand a further reduction of already low levels of some CSPGs might imply a more growth-permissive environment, a reduction around the P10 peak period for neurocan expression may well have consequences for maturing neuronal circuits either through simply delayed development or in fact through aberrant axonal growth.

In addition to their extracellular location, CSPGs are also condensed around neurons in the form of perineuronal nets (PNNs) which appear diffusely in the brain at P7 and more robustly between P14 -21 [123]. While numerous functions have been attributed to these structures, including synaptic stabilization and maintenance of cellular relationships [124] it is more apparent that they prevent remodeling and restrict experience-dependent plasticity in visual cortex [111,125]. TBI in the adult rat results in a similar reduction in PNNs in sensorimotor cortex together with pericontusional axonal sprouting [126,127]. Currently little is known about the interaction of PNNs and mechanisms of neurite sprouting in the injured immature brain. Delayed appearance or destruction of existing nets due to injury would be commensurate with a prolonged period of plasticity and enhanced recovery compared to adult brain injury.

Capacity for Oxidative Stress

Free radical production is a normal part of cellular physiology that is regulated by various antioxidant defense systems, including superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalases. The expression of these three antioxidant systems changes with cerebral maturation [128,129]. While cytoplasmic antioxidant activities are generally higher during early development, the primary mitochondrial antioxidant activity is low at the same time. During this developmental period, there are age-related differences in endogenous reactive oxygen species (ROS) levels. Rat striatal synaptosomes from P7,12 and 21 all show greater ROS levels than adult synaptosomes [130], which may be associated with the period of lower mitochondrial antioxidant defense. Following methylmercury application to induce elevated ROS levels, synaptosomes from the younger brains showed greater ROS production than adults. These results were consistent with the idea that the “under developed” mitochondrial antioxidant strategies render the younger brain more vulnerable to oxidative challenges.

This increased vulnerability of the younger brain is observed under conditions of oxidative challenge. When GPx activity was examined after TBI in P21 and adult mice, the younger brain failed to show increased GPx activity, while adults showed a 28% increase at 3 hrs post-injury [131]. At 24 hrs no significant change was detected among P21 mice, but adults showed 15% increase in GPx activity above shams. Collectively, the data from several injury types reveals increased vulnerability of the younger brain to oxidative challenges due to the lower activities of GPx and MnSOD. The high activities of SOD1 and catalase in the younger animal suggests that cytosolic control of H₂O₂ should be efficient despite low GPx activity. However, mitochondria activity of SOD2 is also low and may contribute to hydroxyl radical production and oxidative vulnerability. More data must be acquired to complete our understanding of this vulnerability among different age groups.

Cerebral Blood Flow

Cerebral blood flow (CBF) is another physiological parameter that changes with cerebral maturation. Unfortunately, only a few studies have profiled normal children of various age differences in CBF [132,133]. CBF as measured by ^{133}Xe single photon emission computed tomography and transcranial Doppler both indicate that neonates have the lowest blood flow rates (39ml/min/100g tissue), peaking between 6-9 years of age (75ml/min/100g) and then decreasing towards adult rates (45ml/min/100g). CBF remains coupled to glucose metabolism throughout brain development as reflected by its the parallel changes in glucose metabolism [134]. In contrast, the developing rat brain shows gradually increasing CBF rates from P10 towards adult values, with only the P17 age group exceeding adult values [135]. The apparent uncoupling of CBF and glucose metabolism at P17 is thought to reflect cerebral ketone metabolism associated with the high circulating concentration of ketones at this age [136].

Distinct Metabolic Requirements

Cerebral reliance on metabolic substrates evolves with maturation from lactate to ketones to glucose. Shortly after birth the brain switches its metabolism briefly to lactate until suckling begins. The brain metabolizes a combination of glucose and ketones bodies during the suckling period, but switches reliance to glucose after weaning. These changes in cerebral substrate metabolism are accompanied by alterations in systemic substrate availability, substrate transport and enzyme activities for substrate metabolism.

The pre-weaned animal is geared for cerebral ketone metabolism with higher circulating concentrations of ketones, greater number of blood brain barrier transporters and greater enzymatic activities of ketone metabolizing enzymes [137,138]. During the period of peak ketone utilization, the brain's capacity to take up β -hydroxybutyrate (BOHB) is 6 times greater than the adult rat brain, as is the rate of ketone metabolism within the frontoparietal cortex [139-141]. Upon weaning, there is a decrease in arterial ketone concentrations, followed by a drop in cerebral uptake and finally a down regulation of the monocarboxylate transporters (MCT).

In contrast, maturational changes in glucose metabolism are more gradual. At birth, circulating concentrations of glucose are 50% that of the adult. Plasma glucose concentrations gradually increase during early postnatal development to achieve adult levels at P10. Changes in substrate availability occur before both the increased expression in cerebral glucose transporters (Glut1 and Glut 3; [138]) and the increased activity of glycolytic enzymes [142]. These parameters do not reach maturation until P30 when adult levels of glucose metabolic rates are achieved [136].

In addition to these normal developmental changes in brain metabolism, there are age-related differences in the ability of the brain to increase its reliance on alternative substrates [143, 144]. Even after weaning, the younger brain retains greater capacity to generate plasma ketones, shows greater density of cerebral ketone transporters, and greater uptake. Taking advantage of these properties, ketogenic neuroprotection has been shown in epilepsy [145], ischemia [146], and glutamate toxicity [147]. More recently, administration of the ketogenic diet immediately after TBI decreased cortical contusion volumes and improved cognitive outcome in juvenile rats [148,149]. While this approach failed to improve histological or behavioral outcome in adult animals, fasting was shown to improve outcome in adults with TBI [150].

Clinical relevance of these metabolic distinctions may be particularly important in several areas. One involves glycemic control post brain injury, where excessive hyperglycemia has been shown to be deleterious in adults [151] and children [152]. Another area readily available for translation is the therapeutic use of the ketogenic diet. While long-used as an adjunctive

therapy for intractable childhood epilepsy, the neuroprotective benefits of alternative substrate metabolism are being studied in other neurological disorders, such as Alzheimer disease [153] and neuro-oncology [154], and the relative safety of the ketogenic diet may foster more widespread clinical investigations, particularly for acquired pediatric brain injuries.

Myelination

While most neurogenesis and migration are complete at birth, white matter maturation, and especially myelination, continues throughout much of postnatal development in animals and humans [155,156]. In addition to the newly recognized risk of glutamate-mediated excitotoxicity in glial cells mentioned above, there is also evidence from adult injuries suggesting that unmyelinated axons are more vulnerable to biomechanical injuries [157]. Given the higher proportion of unmyelinated fibers in the immature brain, this may be yet another age-specific vulnerability.

Importantly, myelination is one of the final stages of cerebral maturation, and continues into young adulthood in humans. The frontal lobes are the last major cortical regions to myelinate, and this late maturation is demonstrable both by newer neuroimaging modalities such as quantitative MRI and DTI [49,50,155,158], as well as by traditional neuropsychological testing that shows age-dependent changes in measures of frontal lobe function [159]. Again, the experimental demonstration that unmyelinated fibers may be uniquely vulnerable to the effects of traumatic injury [157] raises the possibility that important frontal lobe networks still in the late stages of development are particularly vulnerable to TBI, resulting in significant functional impairment.

ENVIRONMENTAL EFFECTS: EXPERIENCE-DEPENDENT PLASTICITY

Maternal Behaviors and Early Development

Maternal rearing behaviors play an important role in long-term brain development. Experimental studies in rodents have shown that normal variations in maternal rearing behaviors can affect cognitive outcomes in adulthood. Specifically, offspring reared by mothers showing more nurturing behaviors (arched-back nursing, increased licking-grooming) not only show cognitive superiority in adulthood, but also molecular changes of increased NMDAr and increased levels of neurotrophic factors such as BDNF [160]. Some of these beneficial effects are mediated by maternal behavior, and can thus be transferred to other litters in cross-fostering studies. However, offspring of more nurturing dams also show some molecular differences at birth, such as increased levels of the NR2A subunit of the NMDAr, and increased BDNF expression. Studies like these demonstrate the complexity, and indeed the inextricable intertwining of genetic and environmental factors in brain maturation.

Neonatal stress is another component affecting brain plasticity. The use of both rodent and non-human primate models has shed considerable insight into human responses [161,162]. A multitude of mechanisms have been implicated in the long-term developmental effects of early life stress, including hormonal dysfunction (particularly the hypothalamic-pituitary-adrenal axis; [163]), alterations in neurotransmission (NMDAr – [160]; 5-HT transporter – [164]), reductions in neurogenesis [165,166] and changes in neurotrophin expression [167,168], among others. These neurobiological processes may be further mediated by genetic susceptibility, such that stressful early-life responses may interact with specific genetic polymorphisms to result in later behavioral or neuropsychological sequelae [169,170].

Enriched / Complex Environments

The environment in which an individual develops can also affect brain structure and function. It has long been known that rearing experimental animals in an enriched or complex

environment (EE) can result in increases in cortical thickness [171], larger dendritic arbors [172], more synapses [173] and cognitive enhancements [174]. Detailed studies of dendritic structure corroborate the importance of environment on brain anatomy, with clear demonstration of more elaborate dendritic structure, increased dendritic spines and more synapses seen in animal models reared in EEs [172,175]. In a human study of post-mortem tissue, education level attained showed a significant correlation with the complexity of dendritic arborization in Broca's area of the frontal lobe [176]. This parallel observation in animal and human studies strongly supports the relevance of the experimental models to tease apart the underlying mechanisms of these environmental effects.

The age at which animals are exposed to these environments is also relevant, for, although mature animals can show benefits of enrichment, the magnitude of enhancement and the duration of exposure needed to manifest these enhancements appears more favorable when young animals are exposed to EE [177,178]. These findings are compatible with the concept of critical windows for brain development, during which the systems appear primed for optimal responsiveness. Clinical examples of this may include visual cortex plasticity, language acquisition and development of music skills [179-181]. Therefore, the effect of enrichment is qualitatively different in the young animal, suggesting that there are different mechanisms at play in the young and mature brain [15]. More importantly, the normal and injured brain appear to respond differently to the same experiences, which implies that there are also different mechanisms induced in the normal and injured brain (Kolb and Gibb, 2009).

In animal models of acquired brain injury like stroke and trauma, rearing in EE has generally been shown to be beneficial in improving functional outcome [182-184]. However, in the developing brain, the interactions between environment and recovery from injury appear to be different from those in adulthood. Specifically, frontal lobe lesions in rat pups at P10 showed the best spontaneous recovery, better than older juveniles or adults and also better than neonates. However, when lesioned animals were reared in EE, these same P10 pups showed the least benefit from the environment [185]. Analogous results have been seen after fluid percussion TBI. Lateral fluid percussion induces anatomical lesions, increased calcium flux and impaired MWM learning in adults, but younger rats show better outcomes with regards to brain morphology, calcium pathophysiology and spatial learning [58,76,186]. EE can enhance outcome after adult TBI [183,184] but the beneficial effects of EE appear blunted in rat pups [12,106,187]. These data support the idea that, while the young brain may have a greater degree of spontaneous plasticity to tap when recovering from an acquired brain injury, this comes at a cost of lost potential. These results have considerable import if they can be translated to the recovery of children with acquired brain injuries.

There is increasing evidence in the clinical pediatric TBI rehabilitation literature that environment plays a major role in recovery from developmental brain injuries. Many studies show that socioeconomic status and/or family status are important predictors of global outcome after pediatric TBI [188,189]. There are a small number of pediatric randomized clinical trials that indicate advantages of family-based rehabilitative strategies [190,191] or specific cognitive training programs [192] over center-based recovery programs or 'usual care.' One observational study using controlled multi-sensory stimulation (a.k.a. Snoezelen) in children recovering from severe TBI did measure objective physiological parameters and showed significant reductions of heart rate and muscle tone following therapy sessions [193]. What is not yet known in human subjects are the underlying neurobiological mechanisms by which these environmental effects mediate enhanced recovery, and whether these mechanisms are analogous to those elucidated in great detail in the animal models, above. Measuring objective physiological and neurobiological responses to rehabilitative therapies represents both a major challenge and a great opportunity for future investigations in the field.

Tactile Stimulation

Although EE is one the most effective interventions to enhance recovery from early injury in laboratory animals, many other paradigms are also proving to be beneficial [194]. The best studied is tactile stimulation. Because it had been shown that tactile stimulation is effective in stimulating growth in premature infants [195] and newborn rats [196]. Kolb & Gibb recently evaluated the effect of tactile stimulation on recovery from frontal or parietal cortical injury in newborn rats [197]. Rats were given 15 minutes of tactile stimulation with a soft brush 3 times daily for 10 days following P3 injury. As adults they showed enhanced motor and behavioral recovery that was correlated with dendritic growth and increased spine density in neighboring cortical regions as well as an increase in FGF-2 in both skin and brain (Gibb & Kolb, 2009). A parallel study with P7 rats that experienced hypoxia-ischemia also proved beneficial [198] although to date no mechanism has been demonstrated. Tactile stimulation could easily be applied to children with acquired brain injuries. It would have not only the benefit of the FGF-2 production in the skin but also a social component of parent-infant interaction.

CONCLUSIONS

Brain development and acquired brain injury are both associated with neurobiological cascades of ionic response, neurotransmitter release, cytoarchitectural change, synaptic remodeling and altered network connectivity. It is clear that similar cellular systems are often involved in the response to normal development, environment and brain injury, but in decidedly different fashions. The response of the immature brain to injury is not simply a smaller version of the adult response, but is often distinct, offering both potential for unique vulnerabilities but also the possibility of age-specific therapeutic interventions. There is also evidence to suggest that the enhanced post-injury plasticity attributed to the developing brain may come at a cost. This cost may be a limitation of environmentally inducible neuroplasticity, at least at selective time periods after injury. Understanding the basic mechanisms underlying these changes offers insight into many brain disorders that are sustained or have their onset during childhood and adolescence. While the level of complexity of these processes offers significant challenges, work in this area is beginning to unravel the elegant interactions between brain maturation and recovery from injury.

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