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Bridging the Gap: Mechanisms of plasticity and repair after Pediatric TBI

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Abstract

Traumatic brain injury is the leading cause of death and disability in the United States, and may be associated with long lasting impairments into adulthood. The multitude of ongoing neurobiological processes that occur during brain maturation confer both considerable vulnerability to TBI but may also provide adaptability and potential for recovery. This review will examine and synthesize our current understanding of developmental neurobiology in the context of pediatric TBI. Delineating this biology will facilitate more targeted initial care, mechanism-based therapeutic interventions and better long-term prognostication and follow-up.

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Introduction: The problem of developmental plasticity and brain injury

Traumatic injury to the developing brain has been called the most complex injury to the most complex organ at the most complex time (Kenzie et al., 2017; Marklund and Hillered, 2011; Wheble and Menon, 2016). Traumatic Brain Injury (TBI) is the leading cause of death and acquired disability in children and is responsible for approximately 640,000 emergency department visits, 18,000 hospitalizations and 1,500 deaths in the U.S. alone (Schuchat et al., 2016; Taylor et al., 2017). A significant number of these (325,000 in the U.S.) occur in settings of sports and recreation (Coronado et al., 2015). Emergency department (ED) estimates of pediatric TBI certainly underestimate the public health burden, as a recent study reported only 12% of pediatric mild TBI patients presented to the health care system through the ED, with 82% initially visiting primary care providers and 5% presenting to specialty providers (Arbogast et al., 2016). Worldwide, the incidence of pediatric TBI is quite variable, ranging from 47-280/100,000, with peaks in the very young (0-2 yrs) and in adolescence (15-18 yrs) (Dewan et al., 2016). Falls, motor vehicle collisions, nonaccidental trauma and sports/recreation were contributing mechanisms.

While more severe pediatric TBI may be associated with immediate and persistent deficits (Hyder et al., 2007), this injury can also alter developmental trajectories, with some impairments becoming more evident later. Injury severity is an important predictor for long-term outcome. Anderson and colleagues showed that children with severe TBI (Glascow Coma Score 3-8) recorded persistent depressed intellectual abilities up to 10 years postinjury (Anderson et al., 2012). Age at injury is the strongest and consistent predictor of neurocognitive outcome and behavior problems . Children sustaining TBI, whether diffuse or focal, before 3 years of age recorded poorer neurocognitive outcomes (Anderson et al., 2012; Anderson et al., 2014; Karver et al., 2014; Karver et al., 2012). Anderson et al further demonstrates there is no severity-related differences in recovery rates in children (2-7 yrs old) who experience TBI. There is an initial protracted period of disrupted development in young children following early life TBI, but the brain shows evidence of recovery. Age-standardized intellectual quotient (IQ) scores are stable in injured children from 30 months to 10 years post-insult (Anderson et al., 2012). This suggests that intervention may be effective even after many years post TBI. Injury severity, however, is also a predictor for behavior problems, specifically ADHD symptoms and anxiety. Younger children who sustain a severe injury exhibit higher levels of symptoms over time (Karver et al., 2014; Karver et al., 2012).

The myriad of ongoing neurobiological processes that occur during brain maturation confer both considerable vulnerability to TBI but may also provide adaptability and potential for recovery. Changes in metabolism, axonal outgrowth, synaptogenesis, synaptic pruning and myelination are major ongoing biological processes occurring in the young brain. This review will examine and synthesize our current understanding of developmental

neurobiology in the context of pediatric TBI. Delineating this biology will facilitate more targeted initial care, mechanism-based therapeutic interventions and better long-term prognostication and follow-up.

Mechanisms of normal development: Plug it in and turn it on

It is important to understand normal cerebral development as a context for comprehending injury effects, as well as for developing age-appropriate treatments. The rat model has been widely used to investigate the effects of TBI on developmental plasticity and recovery (Xiong et al., 2013). While there is no single timeline that links rodent development to human, the timing of critical developmental processes such as neurogenesis, cell migration, dendritic growth, and synaptic pruning can be used to compare across species (Kolb et al., 2000; Semple et al., 2013). Figure 1 shows the timeline of cerebral development in rats and a comparable timeline in humans (Kolb et al., 2000; Semple et al., 2013). Kolb and colleagues describe that cells that eventually form the cortex are generated between embryonic days 12 (E12) and E21 (Kolb et al., 2000). Further, rats are born on day 22 (postnatal day 0 – P0), with neurogenesis already completed, and that these newly-generated cells migrate to appropriate locations, from the E12 to P7-10 and begin to differentiate (Kolb et al., 2000; Pressler and Auvin, 2013). Cell differentiation is almost complete by eye opening (P15), but neuronal maturation continues and peaks for another 2 to 3 weeks then declines.

It is important to note that the rat cerebrum is less developed at birth relative to the human brain, and that the first week of life is approximately equivalent to the third trimester in humans. Maximum dendritic growth occurs around P14 in rats, which corresponds to around 8 months in humans; whereas synaptogenesis peaks around P35 in rats and beginning at 1 year of age to 5-6 years in humans, depending on the brain region (Kolb et al., 2000; Pressler and Auvin, 2013; Stiles and Jernigan, 2010). Injury at various time points during these developmental stages has been shown to result in different functional outcomes by disrupting the trajectory of neural network formation and maturation (Kolb and Cioe, 2003; Kolb and Tomie, 1988).

Axonal outgrowth is a crucial developmental process that requires tight control to ensure appropriate neural connectivity to specific targets. This outgrowth is directed by extrinsic guidance molecules that are synthesized at a particular place and time to either attract or repulse axonal growth and direct its trajectory (Hirata, 2009). The inability to regenerate axons coincides with the maturation of CNS glial cells, such as astrocytes and oligodendrocytes, and to the production of myelin (Goldberg, 2003). However, the ability of neuronal axons to grow and regenerate may be an intrinsic property. The presence of brain-derived neurotrophic factor (BDNF) regulated enzyme arginase I in neurons overcomes inhibition of axonal regrowth by myelin. (Cai et al., 2002).

Neurons are supported by glia, such as astrocytes, microglia and oligodendrocytes. Astrocytes and microglia in TBI contribute to damage control and scar formation by releasing growth factors, modifying extracellular matrix components or by removal of cellular debris (Burda et al., 2016; Loane and Byrnes, 2010; Scheller et al., 2017). Oligodendrocytes (OLs) provide trophic support and produce the protective myelin that

envelops neuronal axons (Scheller et al., 2017). Neural stem cells (NSC) give rise to oligodendrocyte precursor cells (OPCs) that differentiate into pre-mature OLs and then into mature OLs that contact neurons and their axons (Scheller et al., 2017). In development, rodents and humans share similar spatial and temporal patterns. Myelination occurs caudal-to-rostral, early in the brain stem, midbrain and cerebellum and later in the telencephalon, beginning with the occipital cortex and progressing to the prefrontal cortex (van Tilborg et al., 2018). OLs contain glutamate transporters and glutamate receptors (NMDAR, AMPAR, kainate), and thus are particularly sensitive to excitotoxic insults (Saab et al., 2016; Scheller et al., 2017). Significant OL loss leads to impaired electrical signal transduction across neurons and subsequently makes neurons more vulnerable (Scheller et al., 2017). Scheller and colleagues describe a significant increase of OPCs in the lesion area as a general acute response to TBI in 4 week old mice, which is accompanied by cell-specific changes in epigenetic regulation of gene expression and remodeling of tissue structure (Scheller et al., 2017).

Functional magnetic resonance imaging (fMRI) during rest or during a task can demonstrate changes in blood-oxygen-level-dependent (BOLD) signal presumably linked to neural activity. The temporal coincidence of BOLD signal is used to infer presumed functional connectivity (fc) between brain regions, so that wider regions of coincident signal are taken to indicate co-dependent regions of functionally similar cellular activity, or discrete functional networks within the brain. A growing body of evidence (Gilmore et al., 2018; Hagmann et al., 2010; Huang et al., 2015; Menon, 2013) suggests that the functional and structural formation of the brain networks are inseparable, and that they progressively mature together during the early years after birth into adolescence. The age of 2 years has been repeatedly flagged as a landmark of rapid anatomical volume increase, cortical thickening and surface expansion, and elaboration of new synapses (Gilmore et al., 2018; Huang et al., 2015); after which a rapid increase in regional-specific myelination and axonal diameter triggers progressive white matter (WM) maturation (Hagmann et al., 2010). The structural maturation is characterized by heterogeneous strengthening and pruning of WM tracts that proceeds in a region-dependent way that, in turn, influences fc. Functional connectivity has been shown to be a surrogate of brain development into both healthy and pathologic brain (Menon, 2013). By the age of 2 years, core sub-networks (frontoparietal central executive network, default mode network, and salience network) are fully developed, however further changes in fc occur into adolescence, a phenomenon thought to support more complex cognitive demands. Apart from heterogeneous structural reconfigurations at the connectome level, local properties that influence sub-networks such as inhibitory-excitatory synaptic plasticity, neuronal migration, and synaptogenesis, are found to be dominant regulators of fc maturation (Menon, 2013). The analysis of fc data is still not completely standardized but generally falls into three categories for analysis of either static, time-averaged data or dynamic data: seed based analysis, independent component analysis and graph theory algorithms to characterize differences in network architecture at the local and global level of connectivity.

Plasticity

Once “plugged in and turned on,” the brain has the capacity to alter structure and function in response to environmental diversity (Kolb et al., 2011). This is called experience-dependent plasticity. For instance, housing animals in enriched environments (EE) leads to increased cortical thickness, increased dendritic arborization, and enhanced cognition (Fineman et al., 2000; Rosenzweig and Bennett, 1996; Rosenzweig et al., 1962). EE-induced plasticity is age-dependent. The EE-induced increases in dendritic arbors were highest in the weanling compared to the adult and senescent rats. In contrast, while adult and senescent rats showed increased spine density after EE exposure, the weanling rats showed a decrease in spine density (Kolb et al., 2003). There are also sex differences in spine density responses after EE. While adult females showed increases in spine density in the parietal cortex after EE exposure, weanling females showed decreases in parietal spine density (Kolb et al., 2003). There is reported an increase in global methylation in both female and male rats in the medial prefrontal cortex, orbital and insular prefontal cortex, but a decrease in the hippocampus in males not in females (Kolb and Gibb, 2015). Epigenetic effects of chronic stress exposure is associated with a greater number of changes in gene expression in females (72 genes) compared to male rats (58 genes) in the prefrontal cortex and hippocampus combined (Kolb and Gibb, 2015). Behavioral training and environmental stimulation can also be used to restore learning and memory deficits (Rosenzweig and Bennett, 1996).

Neurotransmission and receptor ontogeny

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system and is crucial in many forms of synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD), which mediate learning and memory formation (Cull-Candy et al., 2001; Cull-Candy et al., 2006). Ionotropic glutamate receptors have been named based on the ligands that activate them: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionate (AMPA), and kainate. The NMDA receptor (NMDAR) and AMPA receptor (AMPAR) are integral to normal development and experience-dependent plasticity, whose maturation is inevitably disrupted by TBI. Understanding the structure and function of these receptor systems could elucidate the effects of targeting glutamatergic neurotransmission for treating cognitive impairments that result from injury or disease.

NMDAR: The NMDAR is a cation channel permeable to Na^+, K^+, and Ca^{2+}. Under resting conditions, the NMDAR ligand binding sites are open and the ion channel pore is blocked by Mg^{2+}. Activation requires glutamate binding and post-synaptic depolarization to alleviate the Mg^{2+} block and allow full ionic flow.

The NMDAR is a heteromeric assembly containing 4 major subunits. The GluN1 transcript can be spliced to produce 8 distinct isoforms at three sites in the subunit protein, one in the N-terminus and 2 in the C-terminus. Four separate genes make up GluN2 (A-D) and 2 genes produce GluN3 subtypes (A-B). The GluN1 subunit is a necessary constituent for a functional receptor, whereas the GluN2 or GluN3 subunit confer modulatory properties that regulate glutamate sensitivity and channel opening (Benarroch, 2011; Cull-Candy et al., 2001; Ishii, 1993; Low and Wee, 2010). The diversity of NMDARs depends on the RNA

splicing of GluN1, the type of NR2 subunit, and the presence or absence of the GluN3 subunit.

While GluN2B is predominant in the early postnatal period, GluN2A begins to be expressed during the second and third postnatal weeks (Scheller et al., 2017) and goes on to exceed GluN2B expression in adulthood. GluN2C and GluN2D are also developmentally regulated, predominantly in subcortical structures (Cull-Candy et al., 2001; Laurie et al., 1997). GluN3A is only detected in the fetal rodent brain until two weeks postnatally, whereas GluN3B gradually increases over development (Low and Wee, 2010). When GluN3A co-assembles with GluN2A, the GluN3A subunits reduces channel conductance (Cull-Candy et al., 2001). GluN3B protein is widely expressed in the brain and spinal cord (Low and Wee, 2010), and is detected in both neurons and oligodendrocytes.

Experience also induces the GluN2B-to-GluN2A shift. Eye opening and visual stimuli increase GluN2A, but this enhanced GluN2A expression can be delayed or reversed by dark-rearing (Quinlan et al., 1999a; Quinlan et al., 1999b). Nurturing maternal behaviors, such as arch-back nursing and high frequency of licking, correlate with increased GluN2A levels in rats (Liu et al., 2000). GluN2A-containing NMDARs are primarily found in the synapse, whereas GluN2B is expressed both synaptically and extrasynaptically. Activation of synaptic NMDARs has been demonstrated to promote neuroprotection by triggering pro-survival signal pathways that include cAMP response element binding protein (CREB) dependent gene expression (Papadia et al., 2005) and brain-derived neurotrophic factor protein (BDNF) expression. Extrasynaptic NMDA activity triggers cell death pathways, inactivates CREB and blocks BDNF transcription (Hardingham et al., 2002).

Proper regulation of glutamate receptors (NMDAR, AMPAR) is crucial for experience-dependent synaptic activity. Activation of NMDARs increases intracellular Ca^{2+}, which activates kinases, such as CAMKII, and phosphatases, such as calcineurin. CAMKII-mediated phosphorylation of GluR1 AMPARs promotes their synaptic insertion, resulting in increased AMPAR conductance and LTP. Calcineurin, on the other hand, can dephosphorylate AMPAR and promote receptor internalization, resulting in LTD. An optimal NMDAR:AMPAR ratio is typically maintained depending on neuronal activity (Benarroch, 2011; Cull-Candy et al., 2001; Lau and Zukin, 2007; Paoletti and Neyton, 2007).

AMPAR: The AMPAR is also a cation channel permeable to Ca^{2+}, Na^{+}, and K^{+}. The functional properties of AMPARs depend on the subunit composition. Most AMPARs are heteromeric, assembling as a dimer of dimers containing combinations of GluR1-4. AMPARs are found in both neurons and glia as heteromers containing GluR2. GluR1 and GluR2 subunits are highly expressed in the hippocampus and cortex, with only low levels of GluR3 and GluR4 detected in these regions. Mature pyramidal cells primarily express heterotetramers of GluR1 and GluR2 (Isaac et al., 2007).

GluR2-containing AMPAs are impermeable to Ca^{2+}, suggesting that AMPARs play a crucial role in developmental synaptic function (Cull-Candy et al., 2006; Isaac et al., 2007; Kumar et al., 2002; Pickard et al., 2000). During the first postnatal weeks of neocortical

development, during maximal synaptogenesis and increased expression of spiny neurons, GluR1 levels are higher than GluR2, which increases rapidly during the first week after birth. Additionally, developing GABAergic interneurons also express primarily GluR2-lacking AMPARs. Synaptic inactivity increases the expression of Ca^{2+}-permeable (GluR2-lacking) AMPARs. Conversely, synaptic potentiation increases the proportion of GluR2-containing AMPARs (Cull-Candy et al., 2006).

AMPA receptors mediate fast excitatory neurotransmission and have been implicated in synaptic plasticity, learning and memory (Cull-Candy et al., 2006). Ca^{2+}-permeable AMPARs play a crucial role in the maintenance of NMDAR-dependent LTP at synapses. In basal conditions, most AMPARs in the synapses contain GluR2 subunits. After induction of LTP, GluR2-lacking AMPARs (primarily GluR1-containing) are transiently inserted into the postsynaptic membrane, which promotes Ca^{2+} influx and signal propagation. Although Ca^{2+} entry via AMPARs is modest compared to that through NMDARs, AMPAR-mediated transmission still plays a crucial role in development, neuroplasticity and disease.

Second Messenger Targets and Effectors: Intracellular calcium activates protein kinases (calcium-calmodulin protein kinase-CAMK, extracellular signal regulated kinases-ERK) that facilitate memory formation. ERKs are also known as mitogen-activated kinases (MAPK). These kinases, as well as a downstream effector (CREB) are implicated in long-lasting changes in brain activity (Purves et al., 2004) (Figure 2).

CAMKII is a calcium activated enzyme that constitutes about 30-40% of the protein in the post-synaptic density (PSD). Once activated, CAMKII autophosphorylates and then translocates to the PSD and directly binds to the NMDAR (Lisman et al., 2002; Purves et al., 2004). Additionally, CAMKII phosphorylates AMPARs at the serine 831 site, which increases the channel conductance and synaptic strength. CAMKII can also facilitate membrane AMPAR integration (Araki et al., 2015). This results in the increase of AMPARs in the synapse to promote LTP (Araki et al., 2015; Lisman et al., 2002) and confers synapse-specific neuroplasticity (Araki et al., 2015).

The ERK/MAPK pathway is involved in differentiation, proliferation and apoptosis in mammalian cells and has been shown to be necessary for associative learning (Atkins et al., 1998; Purves et al., 2004; Roskoski, 2012; Thomas and Huganir, 2004). In the ERK pathway, Ras activates c-Raf, then c-Raf phosphorylates ERK 1/2. ERK1/2 is a known regulator of cell death and survival, as well as axonal growth. This pathway is important in spatial learning and hippocampal-dependent memory formation (Roskoski, 2012). On the other hand, MAPK regulation of c-Jun N terminal kinase (JNK) has been shown to mediate cell stress or death. Activated JNK is evident in apoptotic neurons and glia. Elevated levels of JNK precede neuronal cell death after global cerebral ischemia (Raghupathi, 2003). CREB is a ubiquitous transcriptional activator that binds to a site on DNA called the cAMP response element (CRE). CREB can be phosphorylated via the PKA and Ras pathways or via increased intracellular Ca^{2+}, which triggers its transcriptional activity (Purves et al., 2004). Increased intracellular Ca2+ can also phosphorylate CREB, wherein CRE site is activated. Here CRE is also called the CaRE (calcium response element) site. Ca2+-mediated phosphorylation of CREB is mainly due to CAMKIV and ERK. The CREB

phosphorylation must be long enough in duration for transcription to occur, even if only increases in Ca2+ levels are transient (Purves et al., 2004).

Hippocampal synaptic plasticity can be perturbed by disturbances in these secondary messenger targets and effectors. CAMKII is necessary for LTP induction. Inhibition of ERK activation blocks LTP maintenance in the hippocampus (Atkins, 2011; Atkins et al., 2009; Atkins et al., 1998; English and Sweatt, 1997). Inability to activate ERK may prevent CREB-mediated gene expression of brain derived neurotrophic factor (BDNF). Sustained phosphorylation of CREB is involved in the activation of genes, such as BDNF that promote enhanced cognition, neuroprotection and recovery from injury such as BDNF (Finkbeiner, 2000; Griesbach, 2004).

GABAR: γ-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in mammals. GABA is presynaptically synthesized from glutamic acid by glutamic acid decarboxylase (GAD) enzymes GAD67 and GAD65, encoded by the Gad1 and Gad2 genes, respectively (Owens and Kriegstein, 2002). Gene knock out of GAD65 produced mice that exhibit seizures, whereas deletion of GAD67 is lethal at birth and associated with 93% reduction of GABA in the cortex (Simeone et al., 2003).

GABA binds to 2 main subtypes of GABA receptors - $GABA_AR$ and $GABA_BR$. GAD mRNAand protein can be detected in the whole rat brain at embryonic day 15 and levels increases rapidly in late fetal life, persisting through adulthood (Simeone et al., 2003). $GABA_AR$ is a heteropentameric subunit complex that binds various ligands and is selectively permeable to chloride and bicarbonate ions (Cl^- and HCO_3^-). The majority of $GABA_AR$ contain α, β, and γ2 subunits with a 2:2:1 stoichiometry (Oh and Smith, 2019). Activation of $GABA_ARs$ in mature cortical neurons results in membrane hyperpolarization due to inward flow of Cl- currents. However, in immature neurons $GABA_AR$ activation depolarizes the postsynaptic membrane due to an inverted Cl-electrochemical gradient causing outflow of Cl- from the postsynaptic cell. This is due to expression of the Na+-K+-2Cl-cotransporter NKCC1, which causes Cl- ions to accumulate in the cell. Bicarbonate leaving the postsynaptic cell through the $GABA_AR$ also contributes to membrane depolarization (Simeone et al., 2003). In the first post-natal week $GABA_AR$ depolarization enables the removal of the Mg2+ block in NMDARs and activates voltage-gated calcium channels. This early-depolarization action of GABA contributes to synaptogenesis of both inhibitory and excitatory synapses, due to activities of NKCC1 and Ca2+ influx (Oh and Smith, 2019). In the second postnatal week, the K+-Cl- cotransporter KCC2 expression significantly increases, KCC2 extrudes Cl- from the cell and promotes more mature hyperpolarizing $GABA_AR$ kinetics. $GABA_ARs$ may be synaptically or extrasynaptically located on the postsynaptic cell. Subunits such as α2, α3, and α5 are dominantly expressed during embryonic development. During the first post-natal week, subunit a1 levels are low and increases significantly, while α2 decreases. Subunit a5 begins to be detected from embryonic day 17 into maturity (Simeone et al., 2003). In the rat, the γ2 subtype becomes the dominant γ subunit expressed at later developmental stages, and mRNAand membrane protein for this subtype are expressed in most brain regions (Owens and Kriegstein, 2002). The γ2 subunit is necessary for postsynaptic clustering of $GABA_ARs$ and for forming

functional synapses (Owens and Kriegstein, 2002). Location and composition of $GABA_A$Rs contribute to the functional properties of these receptors (Owens and Kriegstein, 2002).

$GABA_B$R is a metabotropic, G-coupled protein receptor that acts through secondary messenger cascades (Simeone et al., 2003). $GABA_B$R may be located on pre or post synaptic cells and its activation results in K+ channel opening. In presynaptic cells K+ influx leads to reduction in GABA release. Postsynaptic K+ influx via activation of $GABA_B$R leads to greater hyperpolarization (Simeone et al., 2003).

Once mature, GABAergic neurons contribute to two types of neuronal inhibition: phasic and tonic. $GABA_A$R subunits α1 and γ2 are involved in phasic inhibition are located at the synapse (Kharlamov et al., 2011). Phasic inhibition reduces hyper-excitability of the post-synaptic cell (Farrant and Nusser, 2005), and typically results from activation of postsynaptic $GABA_A$R after exposure to high concentration of GABA released from the presynaptic terminal. Phasic inhibition of $GABA_A$Rs plays an important role in modulation of theta and gamma oscillations. Tonic inhibition results from activation of $GABA_A$R receptors on the presynaptic cell or on neighboring synapses from low concentrations of GABA (Farrant and Nusser, 2005). Tonic inhibition regulates postsynaptic depolarization in magnitude and duration (Farrant and Nusser, 2005), and contributes to the timing and synchronicity of excitatory signals (Guerriero et al., 2015). $GABA_A$Rs subunits α4 and α5 are important for tonic inhibition and are located extrasynaptically (Farrant and Nusser, 2005; Kharlamov et al., 2011).

Developmental Injury Responses

Energy crisis

Cerebral metabolism of glucose shows dynamic changes during normal development and after TBI. Reliance on glucose metabolism increases after weaning and adult cerebral metabolic rates of glucose (CMRg) are achieved in the rat between postnatal days 35-45 (75μmol/100g/min; (Prins and Hovda, 2009)) and in humans by 16-18 years of age (26-27μmol/100g/min;(Chugani, 1998)). After puberty, developmental sex differences in brain glucose metabolism through glycolysis are regulated by estrogen at multiple sites. Regional differences in CMRg are observed during the estrus cycle (Nehlig et al., 1985). During proestrus when estradiol is highest, CMRg is highest (124±6μmol/100g/min) in prefrontal cortex. This is significantly greater than both estrus females (109±4μmol/100g/min) and males (114±4μmol/100g/min). These changes in CMRg during development are accompanied by corresponding changes in cerebral blood flow (CBF).

While the overarching pattern of the metabolic response to TBI is consistent, there are distinctions related to injury type and severity. Immediately after impact, indiscriminate release of neurotransmitters activates neural systems causing widespread changes in ionic homeostasis across neuronal membranes (Katayama et al., 1990). Sodium/potassium ATPases are activated to pump ions back across membranes, increasing energy demands and increasing cerebral glucose uptake (3-6h in animal studies and 7-10d in humans after “moderate” injury) (Yoshino et al., 1991). During this acute state (state 1), microdialysis lactate/pyruvate ratios (MD_{LPR}) are increased in adult human subjects (Vespa, 2005),

(Bentzer et al., 2000), (Kilbaugh et al., 2011). This increase in MD_{LPR} may be a potential biomarker for changes in glycolysis. The transient increase in cerebral glucose uptake is followed by a prolonged decrease in glucose metabolism (state 2), which has become a hallmark response to TBI (Yoshino et al., 1991), (Bergsneider et al., 1997). During state 2, there is a 9-12% increase in glucose shunting towards the pentose phosphate pathway (Bartnik et al., 2005). Glycolytic processing of glucose requires a constant supply of nicotinamide adenine dinucleotide (NAD+), which is decreased in the cytosol and thereby reduces the carbon supply to the mitochondria (Cosi and Marien, 1998), (Sheline et al., 2000), (Ying et al., 2003), (Prins, 2012). These acute changes lower pyruvate production and decrease ATP (Lee et al., 1999; Deng-Bryant et al., 2011) creating a state of cerebral metabolic crisis. The magnitude and duration of CMRg depression differs with age and injury type (Prins and Hovda, 2009; Thomas et al., 2000). Mild to moderate fluid percussion injury reveals age-related differences in metabolic recovery. Postnatal day P17 rat pups showed CMRg recovery within 3 days compared to 10 days in adults (Thomas et al., 2000; Yoshino et al., 1991). Even after more severe focal injuries, age differences in metabolic recovery are observed. P35 rats with cortical contusion injury (CCI) injury showed CMRg recovery of subcortical structures within 7 days, whereas adults remained significantly depressed for over 10d (Prins and Hovda, 2009). While there are very few human data, some clinical studies have shown hypometabolism similar to that reported in the animal studies (Roberts et al., 1995; Worley et al., 1995). It remains unclear whether young children and adolescents would show faster metabolic recovery than adults with TBI. While milder concussive injuries do not produce overt pathology, CMRg changes are still observed to a lesser magnitude and duration. In mild concussive brain injuries, the adolescent rat brain shows decreases in glucose uptake at 24h, but recovery in 3 days (Prins et al., 2013). A second concussive injury during this vulnerable time period prolongs CMRg recovery (Prins et al., 2013). Magnetic resonance spectroscopy (1H-MRS) showed decreases in six metabolites (phosphocreatine, N-acetylaspartate, and total choline, GABA, lactate, and myoinositol) following a closed head injury (CHI) model of mild TBI in adult female mice but not in adult male mice (Lyons et al., 2018). These metabolite reductions corresponded with significant decrease in mitochondrial bioenergetics (State-III (adenosine triphosphate [ATP] synthesis capacity), State-V_{C1} and State-V_{C2} (complex I and II driven maximal electron transport) levels) from isolated mitochondria in cortex and hippocampus up to 28 days post CHI (Lyons et al., 2018).

White matter / axonal injury mechanisms

Axonal stretch results in mechanoporation that allows ionic flux directly into the axoplasm. Influx of calcium has been demonstrated to result in neurofilament side-arm cleavage and microtubule collapse (Buki and Povlishock, 2006; Pettus and Povlishock, 1996). This disruption of axonal cytoskeletal integrity impairs critical functions such as axonal transport, resulting in accumulation of molecules within the axon and axonal blebbing, demonstrated both experimentally and in humans (Johnson et al., 2013; Tang-Schomer et al., 2012). In vitro studies have also shown that stretch-induced undulations in axons are associated with greater calcium influx (Tang-Schomer et al., 2012). The complex interactions of acute ionic flux, cytoskeletal breakdown, impaired axonal transport and blebbing and ultimately axonal

disconnection or degeneration all contribute to the longitudinal pathobiology of post-TBI axonal damage (Hill et al., 2016).

These cellular mechanisms of traumatic axonal injury are affected by clinically-important modifiers, including sex and myelination. In vitro and in vivo studies comparing male and female axons have demonstrated baseline differences in axon diameter and number of microtubules (female axons being smaller and more flexible with fewer microtubules) (Dolle et al., 2018). This results in greater undulation and calcium flux after stretch injury, suggesting sex may be a biological substrate for vulnerability to TBI.

Multiple studies have demonstrated that white matter is involved in the acute response to developmental TBI, but challenges remain due to differences in age-at-injury, injury models, age-appropriate behaviors and time course. Midline closed head impact in P17 rats causes blood brain barrier disruption and axonal degeneration, with concomitant learning and memory impairments (Huh et al., 2008). More severe, focal TBI using controlled cortical impact models in P17 rats show alterations in electrophysiology, histological damage and ongoing cell death, in conjunction with emerging behavioral deficits (Ajao et al., 2012; Semple et al., 2014). It is important to note that cellular, molecular and behavioral perturbations may evolve weeks or months after developmental brain injury, making longitudinal follow-up and proper developmental controls critical components of translational pediatric TBI studies.

While the existing basic science examining white matter axonal injury is limited at comparable developmental stages and injury models, there is direct evidence that myelination is important for traumatic axonal injury. Myelinated axons are more resistant to experimental TBI. Midline FPI disrupts transcallosal evoked potentials, and the electrophysiological recovery in myelinated fibers occurs gradually over weeks. However, in unmyelinated axons, the electrophysiological recovery is stalled and incomplete (Reeves et al., 2005). In addition to traditional rodent models of pediatric TBI, newer preclinical pediatric models have investigated pathophysiology and behavior in rabbits and piglets (Baker et al., 2019; Zhang et al., 2015). While white matter maturation and axonal myelination continues into adulthood (~30 years of age in humans) (Kochunov et al., 2012), it is likely that this biomechanical vulnerability may play a larger role in the immature, less myelinated brain.

Similar to adult TBI, pediatric functional connectivity (fc) data have been reported as both decreases and increases in connectivity, for example (Risen et al., 2015; Stephens et al., 2017), and both directions of change are variably associated with performance on motor tasks (Risen et al., 2015). Enhancement of motor control to enable postural support was associated with greater cognitive fc from prefrontal regions (Diez et al., 2017). Whether this indicates that larger, or more diffuse brain regions are required to maintain normal function, or that there is a failure of circuits to deactivate, as occurs in adults after TBI is not known (Bonnelle et al., 2012). Clearly there is still much to learn about reorganization of functional networks after pediatric TBI, and how it relates to on-going deficits in the face of large-scale changes in network connectivity that occur as a function of normal development. Figure 3 summarizes some recent clinical studies related to brain connectivity network alterations

after pediatric TBI (Diez et al., 2017; Risen et al., 2015; Stephens et al., 2017; Stephens et al., 2018; Yuan et al., 2017a; Yuan et al., 2017b).

Synaptic dysfunction & altered plasticity

Biomechanical damage to the synaptic cleft and dendritic spines occurs after TBI (Przekwas et al., 2016). Structural proteins (neurexins, neuroligins, SynCAMs, and integrins) and cell adhesion molecules (CAMs) that connect pre and post synaptic membranes are vulnerable to mechanical insults and typically require synaptic calcium to maintain elasticity and binding. Therefore, it is likely that post-TBI perturbations of synaptic calcium affect the integrity of these structural synaptic proteins (Przekwas et al., 2016).

Mild and moderate TBI cause dendrite degeneration in the hippocampal dentate gyrus, with little to no significant cell loss or changes in the hippocampal formation in the adult rat brain at PID3 (Gao et al., 2011). Spared granular neurons in the dentate gyrus showed dendrite swelling with beading, which are signatures of injured dendrites. Adult TBI reduced total dendritic density, complexity and excitability of granule cells (Gao et al., 2011). In contrast, pediatric TBI in P17 rats did not result in any reductions in dendritic length or density in hippocampal DG at PID10. However, P17 TBI did reduce CA1 dendritic arborization and complexity (Casella et al., 2014).

TBI effects on NMDAR and AMPAR

Following TBI, activation of NMDARs and AMPARs results in intracellular Ca^{2+} flux, which differs as a function of time post-injury, brain region and age. NMDAR activation dramatically increases 15 minutes after experimental TBI in adult mice (Biegon et al., 2004; Schumann et al., 2008), followed by diminished NMDAR expression (hours to days) in cortex and hippocampus (Biegon et al., 2004). A decrease in NMDAR binding has been reported three hours post-injury in the hippocampus and neocortex (Miller et al., 1990), and reduced protein expression occurs as early as 6 hours after TBI (Kumar et al., 2002; Osteen et al., 2004). This downregulation lasts even longer in the developing brain. In P19 rats that sustained a lateral FPI, the GluN2A subunit protein is reduced by 20-40% in the ipsilateral hippocampus during the first post-injury week (Giza et al., 2006; Sta Maria et al., 2017). This molecular response has correlated with reduced electrophysiological activation through hippocampal NMDAR. FPI in young rats showed reduced amplitude of NMDA-mediated excitatory post-synaptic currents (EPSCs) (down 40-50%) in hippocampal CA1 neurons. Also, application of subunit specific inhibitors isolating GluN2A currents showed that the reduced NMDA current is due primarily to a 50-60% loss of GluN2A-mediated currents (Li et al., 2005).

After FPI in adult rats, there is an increase in Ca^{2+}-permeable AMPARs, as well as a decrease in GluR2 levels (Bell et al., 2007; Bell et al., 2009). In a closed head injury model of TBI, GluR1 levels increased acutely in the ipsilateral hippocampus in adult mice (Schumann J. et al., 2008).

The global changes in calcium signaling following TBI suggest that downstream signaling molecules would also be affected. TBI induces change in CAMKII levels, first with an initial increase followed by a long lasting reduction that is associated with impaired cognition and

experience-dependent plasticity (Glazewski et al., 2000; Schwarzbach et al., 2006; Wu et al., 2009, 2011). FPI induces transient increases in phosphorylated CAMKII (Atkins et al., 2006; Folkerts et al., 2007) and total CAMKII in the hippocampus and cortex ipsilateral to the injury site (30 minutes) (Atkins et al., 2006; Folkerts et al., 2007). Additionally, downstream effectors of CAMKII (GluR1 and cytoplasmic polyadenylation element-binding protein – CPEB) also increase phosphorylation states in synaptic samples post-injury. CPEB regulates the translation of dendritic mRNAs during hippocampal LTP 30 minutes after FPI and returns to sham levels by 4 hours (Atkins et al., 2006). This suggests that the aberrant increase of autophosphorylated CAMKII can result in loss of synapse specificity of neuronal activation and play a role in deficits long term memory formation. In CNS injury, ERKs have a different pathophysiological response. Following TBI, ERK1/2 is activated in injured cortical neurons, as well as non-neuronal cells in cortex, hippocampus and thalamus, as early as 3h lasting up to 3 days (Raghupathi, 2003). Reduced ERK activation through pre-TBI treatment with a pERK inhibitor decreased cell death, but worsened cognitive and motor deficits (Dash et al., 2002). Deficits in ERK activation have been shown up to 12 weeks after FPI (Atkins et al., 2009). JNK activation, in contrast, was not observed in injured regions nor correlated with trauma-induced cell death (Raghupathi, 2004). Lastly, one week after FPI in adult rats, phosphorylated CREB was decreased (Griesbach, 2004). This reduction has been shown to persist up to 12 weeks (Atkins et al., 2009). Table 1 briefly summarizes glutamate-mediated responses following TBI.

The post-TBI alteration of NMDARs can then lead to a loss of plasticity in the young rat. Rats that received FPI at P19 followed immediately by rearing in an enriched environment (EE) failed to show EE-induced anatomical (increased cortical thickness, expanded dendritic arborization) and cognitive enhancements (improved spatial learning and memory) when tested as young adults (Fineman et al., 2000; Giza et al., 2005; Ip et al., 2002; Sta Maria et al., 2017). The period of diminished neural plasticity within one week post-FPI coincides with impaired working memory (Reger et al., 2005; Sta Maria et al., 2017), as well as with a critical period of neural responsiveness to EE-rearing (Giza et al., 2005; Sta Maria et al., 2017). Only when EE-rearing exposure was delayed two weeks following FPI in P19 rats did the animals demonstrate EE-induced enhancement in the MWM task acquisition. The delayed EE time point coincided with already normalized hippocampal NMDAR subunit levels, as well as recovery of NOR working memory to sham levels (Reger et al., 2005). However, probe trial performance in the delayed-EE group showed lingering TBI-associated deficits (Giza et al., 2005).

TBI effects on GABAR

Several studies have reported $GABA_AR$ mediated alterations of inhibition following TBI that may be attributed to alterations in synaptic and extrasynaptic $GABA_AR$ subunit composition. Reductions in the $GABA_AR$ $\gamma 2$ subunit and increases in the $\delta 1$ have been reported 90 days following CCI in adult rats (Kharlamov et al., 2011). These subunit changes translate to reduced phasic and tonic GABAergic inhibition, respectively. $\gamma 2$ is a crucial component for a functional $GABA_AR$ and is important for GABAAR assembly at the synapse. $\gamma 2$ reductions or genetic deletion of the $\gamma 2$ gene are associated in some forms of epilepsy (Kharlamov et al., 2011). Guerriero and colleagues discusses the glutamate and

GABA imbalance at early and late time periods pertinent following TBI in their review (Guerriero et al., 2015).

Recovery and Repair

Linking metabolism & plasticity

The brain's metabolic status can directly impact its ability to adapt from the cellular to the functional level. Nutritional status, physical activity and fuel types can influence neuroplasticity (Stranahan and Mattson, 2008). Age also influences cerebral adaptation with the younger brain having much greater plasticity potential after injury (Weihmuller and Bruno, 1989). The dynamic metabolic changes after TBI can significantly impair neuronal function and plasticity (Babikian et al., 2010). Immediate release of glutamate can inhibit protein synthesis (Ogawa et al., 1992). While global protein synthesis is depressed early after TBI, protein expression changes within specific pathways can be upregulated. Experimental studies with lateral FPI demonstrated increases in mTOR pathway protein expression 30 minutes to 1day after TBI (Chen et al., 2007). In addition to changes in protein synthesis, acute global activation of NMDA receptors has been shown to alter neuronal excitability after the injury (Dietrich et al., 1994) for 24h. During this time barrel field stimulation failed to increase glucose metabolic rates in injured animals, reflecting widespread circuit dysfunction after TBI. In addition to the effects on protein synthesis and activation, age-dependent calcium accumulation has been observed and this directly affects neurotrophin expression. A time course of $^{45}Ca^{2+}$ changes after fluid percussion injury was examined in P17, P28 and adult rats (Osteen et al., 2001). Increased calcium accumulation was seen in all age groups immediately post injury with earlier recovery in younger animals. The adolescent (P28) and adult age groups did show a delayed accumulation of $^{45}Ca^{2+}$ between post-injury days 4-14 in the ipsilateral thalamus, which was not observed in the youngest group. Neural activity and calcium both induce BDNF transcription and affect neuroplasticity (Griesbach and Hovda, 2015). Although overall cerebral glucose metabolism in P16-18 male rats recovers 24 h after TBI, specific reductions in [2-13C]glutamate suggests impairments in either neuronal or astrocytic metabolism (Robertson et al., 2013). Age-related plasticity differences have been observed after TBI (Giza et al., 2009; Giza and Prins, 2006). In weanling rats, TBI inhibits the brain's response to EE rearing (Giza et al., 2005), but in the adolescent rat, TBI seems to interfere with the normal pruning responses (Mychasiuk et al., 2015). There remains a dearth of research addressing age-related mechanisms of plasticity and its relationship to metabolism after TBI.

Protecting/healing axonal networks and promoting recovery

An orderly progression of white matter maturation has been described in both rodents and humans (Samorajski and Friede, 1968; Schonbach et al., 1968). This maturation includes differences in glial cell biology, cytokine expression and synthesis and maintenance of myelin. These normal neurodevelopmental changes have important implications on the distinct response to injury seen in the immature brain.

Basic science studies have demonstrated greater vulnerability of unmyelinated fibers to TBI compared to myelinated fibers (Reeves et al., 2005). Evidence of white matter damage in

humans has been demonstrated by neuropathology following more severe TBI, but neuropathology following mild TBI is very limited (Blumbergs et al., 1994). Advanced multimodal imaging can provide information about white matter organization after pediatric TBI (Dennis et al., 2018a; Dennis et al.,2018b). Research consistently shows poorer white matter organization following a moderate-severe injury (msTBI) in pediatric patients using diffusion tensor imaging – DTI (Dennis et al., 2015a; Dennis et al., 2015b; Oni et al., 2010; Wilde et al., 2011), an MRI modality that looks at the extent and directionality of water in gray and white matter in the brain (Basser, 1997) . DTI provides metrics such as anisotropy and diffusivity that has been further correlated with changes in the corpus callosum macrostructure and with neuropsychological scores in children with chronic TBI (Ewing-Cobbs et al., 2006; Ewing-Cobbs et al., 2008; Wilde et al., 2011). Fractional anisotropy (FA) and radial diffusivity are DTI metrics commonly accepted as a proxies for fiber organization and myelin integrity. Radial diffusivity has been shown to best discriminate between TBI and comparison groups and is sensitive to traumatic axonal injury, and therefore, would be a good surrogate marker to assess extent of TBI and the effects of therapies restoring myelin integrity. FA is the most sensitive marker of TBI induced deficits in several cognitive and motor outcomes (Ewing-Cobbs et al., 2008). A multimodal approach can reveal different components of altered connectivity, including lower FA and higher radial diffusivity from DTI, altered neurometabolite levels (N-acetylaspartate – NAA, a marker of neuronal health, and choline, a marker of cellular turnover), and disrupted functional connectivity (rsfMRI) in msTBI subjects.

Callosal mid-sagittal region is often used as an index of developmental change and an indicator of injury severity (Ewing-Cobbs et al., 2006; Ewing-Cobbs et al., 2008). Particularly, the callosal posterior midbody area increases in normal developing children, while the DTI metrics FA increases in the posterior midbody and radial diffusivity decreases in the isthmus and splenium with age (Ewing-Cobbs et al., 2006; Ewing-Cobbs et al., 2008). Pediatric TBI decreases FA and increases radial diffusivity, in most of the callosal regions (Ewing-Cobbs et al., 2006; Ewing-Cobbs et al., 2008; Wilde et al., 2011). Additionally, although the posterior midbody areas were similar between young normal and TBI children (~7-12 years old), the developmental increase in the posterior midbody area continued in older normal children but is arrested in older TBI children (~13-18 years old) (Ewing-Cobbs et al., 2008). This suggest an atrophy or arrest in callosal development and eventual alternate developmental trajectory for children with TBI.

Work from our group revealed delays in electrophysiological conduction across the corpus callosum – the interhemispheric transfer time (IHTT) – in about 50% of pediatric msTBI patients at a post-acute (2-4 month) time point after injury. This slowing in IHTT correlated with decreased FA and worse neurocognitive function (Dennis et al., 2015a; Ellis et al., 2016). Using a multimodal test battery prospectively and longitudinally from 2-4 months post-injury out to 14-18 months, pediatric msTBI subjects show ongoing changes. Uninjured controls show gradually increasing FA and cognitive function as brain development continues at its normal pace. The pediatric msTBI subjects with a normal IHTT show changes in white matter orientation measures (FA) and quantitative volumetrics similar to those seen in the typically developing controls. However, the patients with slow IHTT appear to diverge, showing progressively worsening white matter organization and volume

changes inconsistent with healthy maturation (Dennis et al., 2017a; Dennis et al., 2017b). Examination of neurometabolic markers using magnetic resonance spectroscopy (MRS) post-acutely shows lower NAA and higher choline. Chronically, NAA increased and choline normalized in those with normal IHTT; while NAA and choline were low in those with slow IHTT (Babikian et al., 2018). The slow IHTT group also showed worse long-term neurocognitive outcomes than healthy controls (Ellis et al., 2016). These studies indicate that while about half of pediatric msTBI patients resume a favorable developmental trajectory, the other half show ongoing evidence of functional and structural degeneration (Dennis et al., 2018b).

The mechanisms underlying these differential white matter trajectories are uncertain but may include ongoing metabolic dysfunction, myelin damage, impaired circuit activity and persistent neuroinflammation. Understanding the contributions of these biological mechanisms post-acutely may open a window of intervention to alleviate this progressive neurodegeneration.

Restoring synaptic function and plasticity

Environment—Experience-dependent plasticity can be induced using environmental enrichment (EE). EE provides opportunity for learning and integration of exploratory, physical, and social elements (Bondi et al., 2014). Neural alterations attributed to EE include increased neurogenesis, increased presynaptic (synaptophysin) and post-synaptic (PSD95) markers, cortical thickening, increases in cortical and hippocampal dendritic arborization, and increased cell survival after TBI (Bondi et al., 2014; Fineman et al., 2000; Hoffman et al., 2008b; Ip et al., 2002; Sozda et al., 2010). EE thus promises to be a viable intervention for impairments associated with TBI, stroke, aging or other neurodegenerative diseases (Bondi et al., 2014; Sampedro-Piquero and Begega, 2017).

Experience-dependent plastic changes are time- and region-dependent. When placed in EE for varying intervals of 4, 8, or 16 days, Comeau and colleagues have demonstrated that there is a transient dendritic length increase in Golgi-stained neurons in the prefrontal cortex after 4 days of EE that was not observed after 16 days of EE. In the sensory cortex, increased dendritic arborization seemed evident after all EE intervals (Comeau et al., 2010). In adult mice, EE rearing reversed the TBI induced learning and memory deficits following closed head weight-drop injury model (Schreiber et al., 2014) and repetitive mild TBI (Liu et al., 2017). In adult rats, shortened EE exposure (6h per day) for 18 days was demonstrated to be more beneficial in MWM acquisition, whereas continuous EE showed significantly improved recall during the probe trial (de Witt et al., 2011). Delayed EE exposure following TBI in the young (Giza et al., 2005) and adult rats (Hoffman et al., 2008b) showed shortened latency to find the hidden platform in the Morris water maze. EE rearing for 6 weeks following early life (P21) closed head injury significantly reduced alcohol consumption and reward in female mice, as well as normalized relative BDNF gene expression to sham levels, and significantly reduced axonal degeneration (Weil et al., 2016).

Experience-dependent changes accumulate and interact, which is also known as metaplasticity. When methylphenidate and amphetamine were administered to weanling and adult rats, respectively, then exposed to EE, the drug blocked EE-induced dendritic

arborization. Although the drugs themselves did not show any disturbance in physiology or morphology, the interaction between the pharmacology and EE resulted in impaired experience-dependent plasticity (Kolb et al., 2003). In experimental TBI in adult rats, EE exposure itself has shown expected enhancements in neuroanatomy and cognition. In several cases, only combined effects of EE and drug treatment or task-specific neurobehavioral experience have demonstrated functional improvement after injury (Hoffman et al., 2008a). Motor ability in TBI adult rats and acquisition of spatial learning in the MWM significantly improved when animals were also exposed to EE during the behavioral tests (Matter et al., 2011). Additionally, subtherapeutic EE experience (2-4 h per day for 19 days) can be used as a rehabilitation technique when combined with acetylcholinesterase inhibitor (galantamine) following CCI in adult rats (de la Tremblaye et al., 2017). Epigenetic studies show EE increases DNA methylation levels and reduces hydroxymethylation levels in senescence accelerated mouse P8 (SAMP8) (Grinan-Ferre et al., 2016), with differential expression in mouse dorsal and ventral hippocampus (Zhang et al., 2018). EE further reduces gene expression that drives oxidative stress and aging-induced inflammation promoting cognitive enhancements and neuroprotection (Grinan-Ferre et al., 2016).

Pharmacology—To protect the brain from acute glutamate-induced excitotoxicity, NMDAR inhibitors have been used as a therapeutic intervention for TBI. Although this approach worked in many experimental TBI models (Han et al., 2009; Rao et al., 2001; Schumann et al., 2008), it was not protective after injury to the immature brain (Bittigau et al., 1999; Pohl et al., 1999). NMDAR inhibition also failed to translate clinically, in some cases even leading to worsened outcome (Albers et al., 2001; Ikonomidou and Turski, 2002; Maas et al., 2010; Morris et al., 1999; Muir, 2006; Naranyan et al., 2002). Due to the dynamic response of NMDAR activity post-injury, NMDAR antagonists may have been delivered during periods of already down-regulated NMDAR function that missed the critical window of receptor hyperactivity. Furthermore, during the recovery phase, excitatory synaptic activity may be necessary to facilitate optimal outcome (Ikonomidou and Turski, 2002).

In contrast, NMDAR agonists, such as D-cycloserine (DCS), promote neuroprotection and recovery after TBI (Adeleye et al., 2009; Biegon et al., 2004; Sta Maria et al., 2017; Temple and Hamm, 1996; Yaka et al., 2007). Administration of low doses of NMDA result in a pro-survival molecular response, indicating synaptic NMDARs are preferentially activated (Soriano et al., 2006). DCS is a partial NMDAR agonist binding to the glycine site in the GluN1 subunit. DCS is already approved for use in humans and has been shown to freely cross the blood-brain barrier (Baxter and Lanthorn, 1995). In mice, however, Wlaz et al showed that after subcutaneous injection of DCS at a low dose (5 mg/kg), there were only trace amounts of DCS detected in the brain. After administration of a much higher dose (320 mg/kg) of DCS, only about 14% of the DCS plasma levels were detected in mice cortex during peak plasma levels of DCS (15 minutes post-injection). The half-life of DCS in mice is 30 minutes, and 1 hour in rats, and most of the administered DCS dose is excreted in rodents unchanged (Baxter and Lanthorn, 1995). DCS potentiates NMDAR-mediated processes and demonstrates NMDAR agonist properties (under 50 mg/kg in rats and mice; under 100 mg/kg in humans). At even higher doses (over 100 mg/kg in rodents and over 250

mg/kg in humans), DCS behaves more like an NMDAR antagonist (Baxter and Lanthorn, 1995).

DCS treatment at 3mg/kg was shown to optimally enhance learning in a passive-shock avoidance task in adult rats (Monahan et al., 1989). After a closed head injury in adult mice, a 10 mg/kg dose of DCS was demonstrated to significantly improve neurological outcome (Adeleye et al., 2009; Yaka et al., 2007). DCS restored hippocampal CA1 LTP after closed head injury, and fully restored reduced BNDF levels. Following FPI in adult rats, a DCS dose of 30mg/kg administered intraperitoneally, rescued deficits in the Morris water maze task. When administered twice daily for four days beginning at 24h post-FPI in P19 rats, 30mg/kg DCS restored deficits in GluN2A subunit protein levels, increased GluR2, and recovered novel object recognition performance (Sta Maria et al., 2017), as well as rescued secondary messenger CAMKII (Buen et al., 2010), in the injured young rat. P19 rats treated with DCS and exposed to EE-rearing as soon as 24h post TBI showed improved MWM performance in adulthood (Sta Maria et al., 2017).

Other co-agonists of synaptic NMDARs include glycine and D-serine. D-serine has high levels in mammalian brain and is increased by DCS administration. D-serine is metabolized by D-amino acid oxidase (DAAO), and its metabolism may increase H_2O_2, causing oxidative stress. A recent study utilized a novel approach to protect against TBI by using 6-chlorobenzo[d]isoxazol-3-ol (CBIO), an inhibitor of DAAO, to increase D-serine levels and reduce oxidative stress. Treatment with CBIO after mouse closed head injury improved neurocognitive outcomes, reduced inflammation and enhanced molecular pathways of plasticity related to glutamatergic neurotransmission (Liraz-Zaltsman et al., 2018).

MRI of NMDAR-Mediated Glutamatergic Transmission

The vascular and metabolic demands of neuronal activity underlying fMRI signals have been suggested to be mostly driven by glutamate and the effects on its receptor-mediated action on neurons and astrocytes (Bonvento et al., 2002). For instance, NMDAR activation has been shown to be the primary factor in BOLD responses. Using a somatosensory evoked potential stimulation, BOLD signal can be significantly reduced using NMDAR antagonist MK801 (Gsell et al., 2006). NMDAR mediated activation can also be elicited in the hippocampus by measuring the change in relative cerebral blood volume (ΔrCBV) using a pharmacological stimulus targeting the NMDAR co-agonist glycine-binding site, which is not saturated in hippocampal neurons in culture or in slice preparations (Wilcox et al., 1996). Systemic administration of D-serine (Panizzutti et al., 2005) and DCS (Santa Maria et al., 2009) can increase ΔrCBV in a region-specific manner in the hippocampus using pharmacological MRI (phMRI) in normal rats. In our hands, FPI in P19 rats abolished the DOS-induced increase in hippocampal ΔrCBV (Figure 4) in the subacute (PID 3-5) time point, which corresponds to diminished NMDAR function, impaired behavior and experience-dependent plasticity, in the absence of gross histological damage. DOS-induced ΔrCBV is restored at the chronic (PID 13-18) time point, when spontaneous recovery of NMDAR neurotransmission, novel object preference, and experience-dependent plasticity are observed following P19 rat FPI (Giza et al., 2005; Giza et al., 2006; Li et al., 2005; Reger et al., 2005; Sta Maria et al., 2017). These results suggest that DCS-induced ΔrCBV

can be used as a non-invasive surrogate biomarker of NMDAR-mediated transmission. Its clinical implications include the use of the phMRI ΔrCBV signal as a diagnostic tool to assess the magnitude and duration of impaired NMDAR-mediated glutamatergic transmission after TBI.

Conclusions

Normal postnatal brain development is heralded by a complex sequence of biological events – timing is everything. Axonal outgrowth, synapse formation and adaptation, changes in energy metabolism, myelination and dendritic pruning are all normally orchestrated to result in a unique and individualized final product. Biomechanical injury during development alters this construction, with remarkable capacity for plasticity and recovery but also potential long-term alterations in developmental trajectory. In addition to the complexities of brain-building, the immature brain also has distinct responses to the injury itself – metabolic patterns are perturbed, synapses retract and change in sensitivity, excitatory-inhibitory balance can be disrupted, neurovascular responses may uncoupled and inflammatory cascades are initiated. Clinical observations such as delay or arrest of brain maturation after TBI (Dennis et al., 2017b; Ewing-Cobbs et al., 2008), and the double-hazard of young age and injury severity on pediatric TBI outcomes (Anderson et al., 2005; Keenan et al., 2019), are rooted in this seemingly tangled web of neurobiological mechanisms. Given the high incidence of pediatric TBI and the potential for long-term developmental consequences, understanding the fundamental mechanisms of brain development, injury and recovery will be critical to devising future targeted therapeutic interventions. Promising directions for developmental-specific treatments include metabolic therapy, behavioral and pharmacological neural activation and modulation of inflammatory responses.

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Abbreviations

AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionate receptor
BDNF	brain-derived neurotrophic factor
BOLD	blood-oxygen-level-dependent signal
cAMP	cyclic adenosine monophosphate
CAMK	calcium-calmodulin protein kinase
CBF	cerebral blood flow
CCI	cortical contusion injury

CHI	closed head injury
CMRg	cerebral metabolic rates of glucose
CPEB	cytoplasmic polyadenylation element-binding protein
CREB	cAMP response element binding protein
DCS	D-cycloserine
ED	emergency department
E	embryonic
EE	enriched environment
ERK	extracellular signal regulated kinase
fc	functional connectivity
FPI	fluid percussion injury
fMRI	functional magnetic resonance imaging
GABA	γ-aminobutyric acid
GAD	glutamic acid decarboxylase
GluN	glutamate NMDAR subunit
IHTT	interhemispheric transit time
JNK	c-Jun N terminal kinase
LTD	long-term depression
LTP	long-term potentiation
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MWM	Morris water maze
NMDAR	N-methyl-D-aspartate receptor
NOR	novel object recognition
NSC	neural stem cell
OL	oligodendrocyte
OPC	oligodendrocyte precursor cell
P	postnatal
phMRI	pharmacological MRI

PID	post-injury day
PSD	post synaptic density
rCBV	relative cerebral blood volume
TBI	traumatic brain injury
WM	white matter

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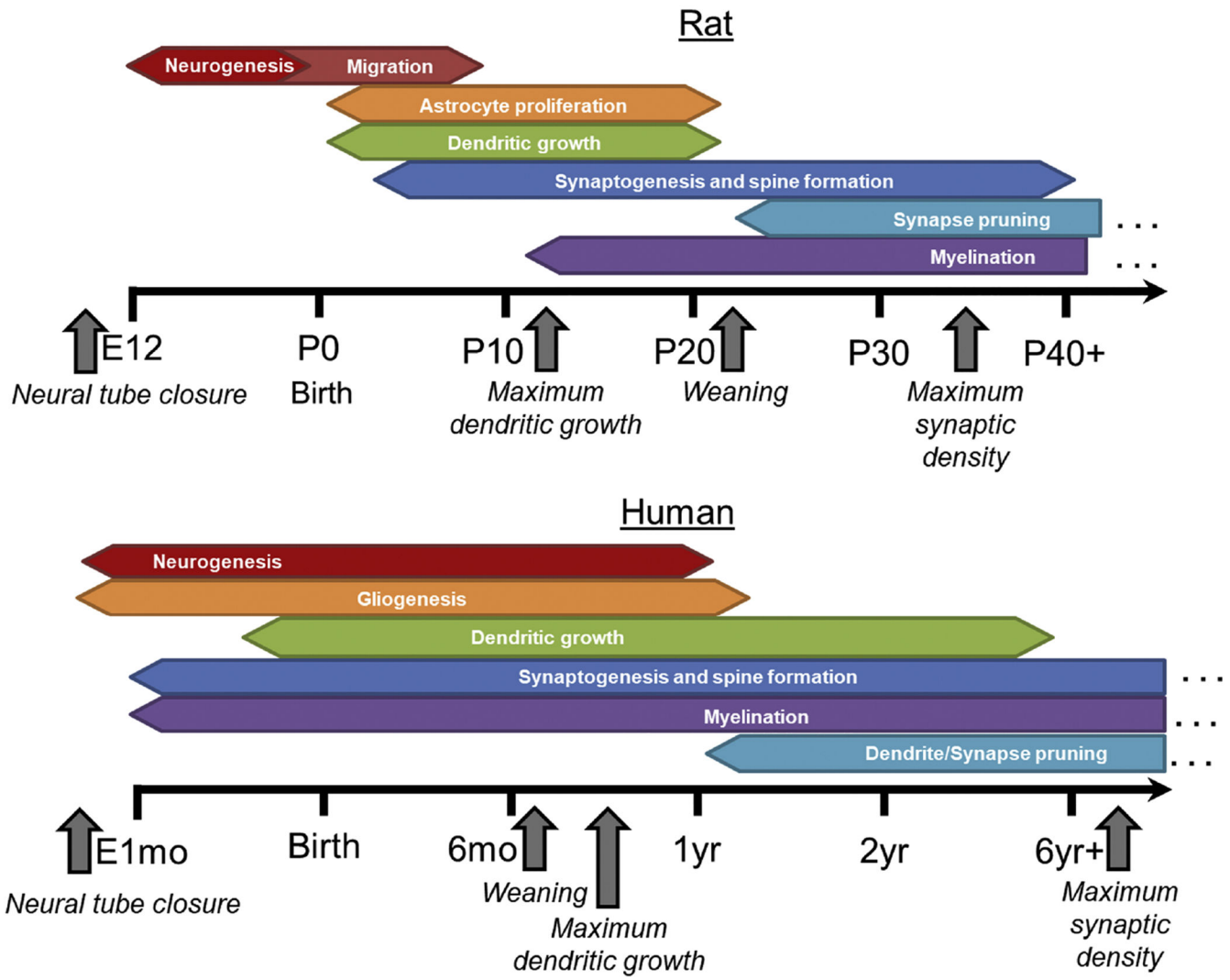


Figure 1.

Schematic Illustration of Brain Development in Rat and in Human. Abbreviation: E = embryonic day; P = postnatal day; mo= month; yr = year. Colored bars indicate main developmental processes. Adapted from Kolb et al., 2000 and Semple et al., 2013. Note that different cortical regions may have differing time profiles.

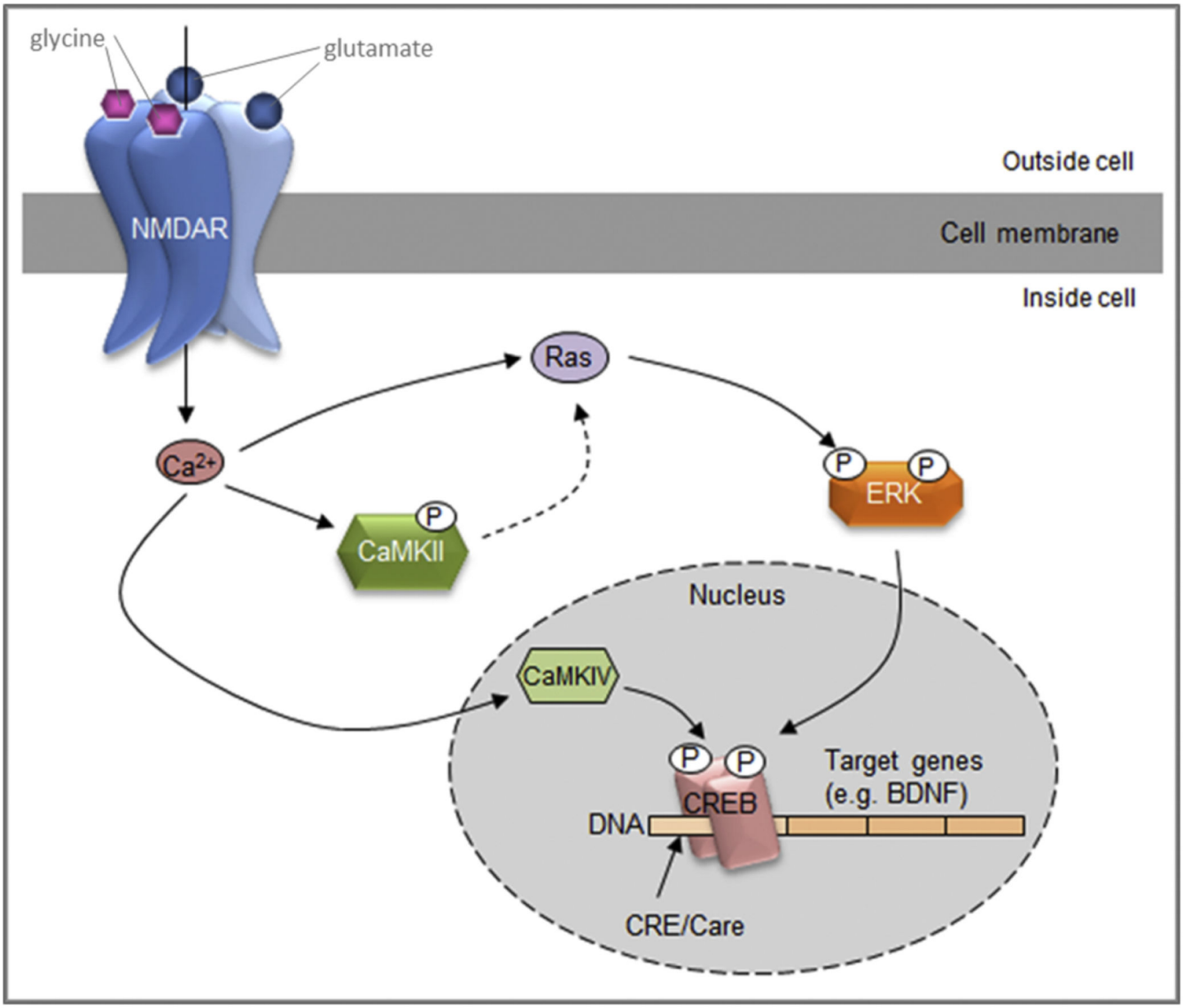
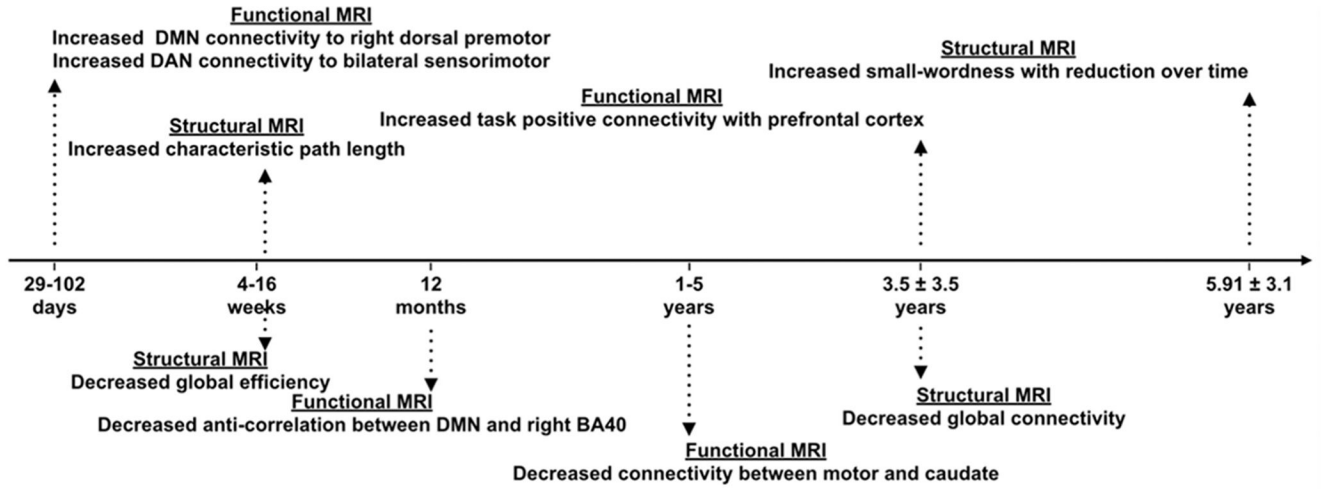


Figure 2.

NMDAR-Mediated Secondary Effectors. Simplified schematic of intracellular NMDAR activated secondary effectors crucial in synaptic plasticity. NMDAR is shown as a heterodimer of GluN1 and GluN2 receptors bound with neurotransmitters glycine and glutamate. Once activated, NMDAR allows Ca2+ to enter the cell. Ca2+ can activate calcium-dependent kinases, such as CAMKII and CAMIV, which in turn can phosphorylate (circled P) downstream targets (e.g. Ras, ERK, and CREB). CREB activation leads to transcription of key target genes, like BDNF, that are important in cell survival and synaptic plasticity.



		(Risen et al. 2015)	(Yuan et al. 2017b)	(Stephens et al. 2018)	(Stephens et al. 2017)	(Diez et al. 2017)	(Yuan et al. 2017a)
Demographic	TBI	5/9	10/12	5/6	6/12	8/6	7/10
	Control	5/9	7/13	6/5	14	15/12	8/3
Age	TBI	11-17	15.45±1.72	12.6-18.7	12-18	13.14±3.25	9.17-18.88
	Control	11-18.1	16.28±1.38	match	13-18	15.04±2.26	13.37-15.9
Injury severity		1/2	1	1/2 (ACRM)	1/2/3 (ACRM)	2/3 (Mayo)	2/3

Figure 3.

Presentation of current standing in clinical studies related to brain connectivity network alterations after pediatric TBI. “Demographic” is presented in the form of reported group size in Female/Male format. “Age” is reported as either range or mean ± standard deviation. Injury severity of the studied group is reported with (1) mild, (2) moderate, (3) severe. The metric on the basis which severity is reported, when provided, are American Congress of Rehabilitation Medicine (ACRM), and Mayo classification system.

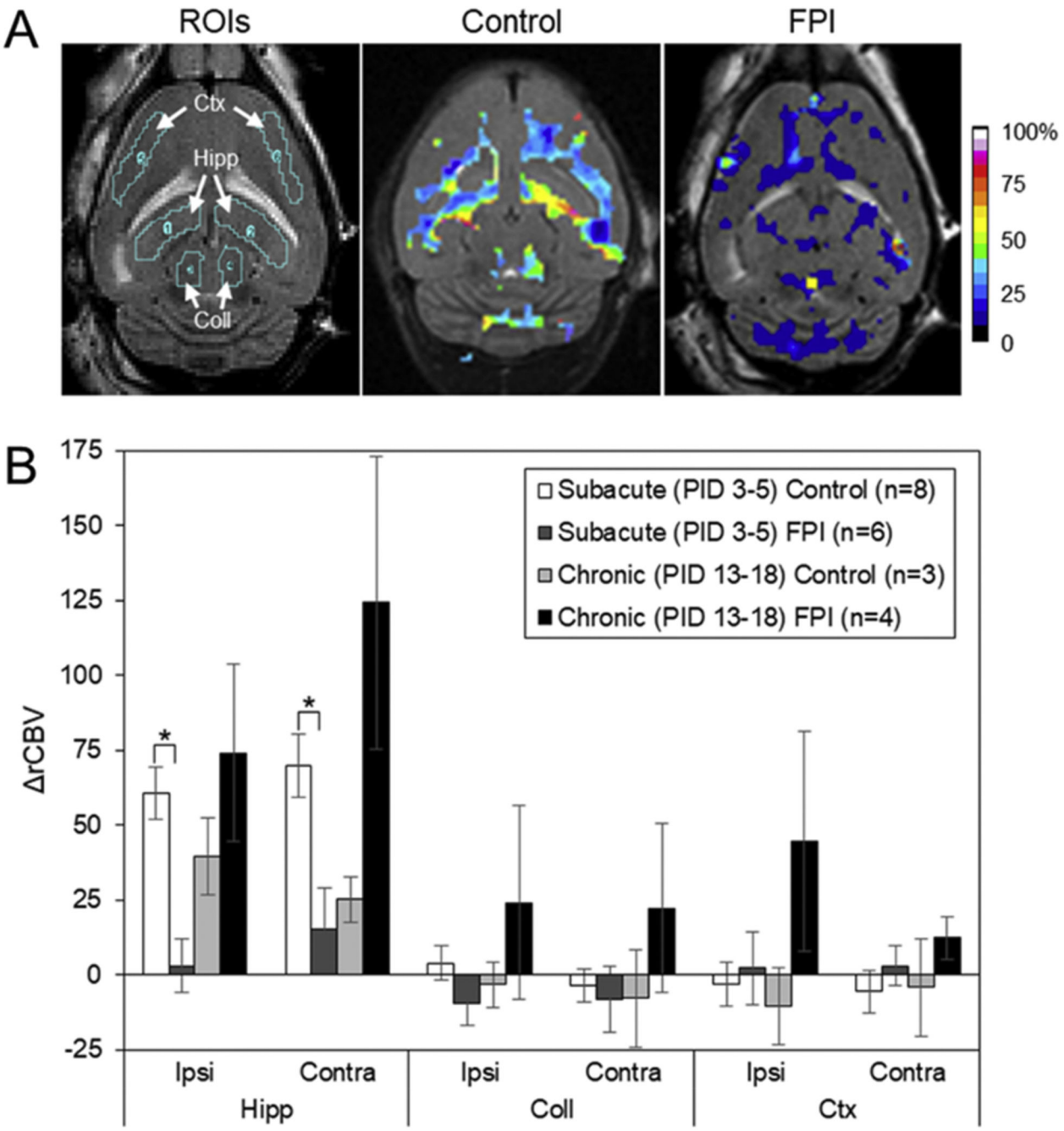


Figure 4.

Evoked ΔrCBV. Top panel shows ROIs on sample structural image, and representative subacute control and FPI subject structural images with overlayed colorized percent ΔrCBV maps. Mean±SEM ΔrCBV from ROIs in the hippocampus (Hipp), cortex (Ctx) and colliculus (Coll) in the subacute (PID 3-5) and chronic (PID 13-18) time points. Stimulation DCS dose induced a hippocampal-specific increase in rCBV in the controls that is abolished

by FPI subacutely that recovery over time. *p<0.05 conveys significant difference between planned comparisons.

Table 1.

Summary of TBI-Induced Glutamate-Mediated Responses

Target	Post TBI response
NMDAR	Transient increase in activity (in adult rats), followed by lasting reduction in activation (up to 1 week, in young rats) (Biegon et al., 2004; Giza et al., 2006; Kumar et al., 2002; Li et al., 2005; Miller et al., 1990; Osteen et al., 2004; Schumann et al., 2008)
AMPAR	Adult rats: Increase in Ca^{2+}-permeable AMPARs (GluR1 increases), and decrease in Ca^{2+}-impermeable AMPARs (GluR2 decreases) (Bell et al., 2007; Bell et al., 2009) (Schumann J. et al., 2008)
CAMKII	Transient increase followed by long lasting reduction (up to 1 week, in adult rats) (Atkins et al., 2006; Folkerts et al., 2007; Glazewski et al., 2000; Schwarzbach et al., 2006; Wu et al., 2009, 2011)
ERK	Long lasting reduction in activation (up to 12 weeks, in adult rats) (Raghupathi, 2003)
CREB	Long lasting reduction in phosphorylated CREB (up to 12 weeks, in adult rats) (Atkins et al., 2009; Griesbach, 2004)