


Review

# Brain-Derived Neurotrophic Factor in Pediatric Acquired Brain Injury and Recovery

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**Abstract:** We review emerging preclinical and clinical evidence regarding brain-derived neurotrophic factor (BDNF) protein, genotype, and DNA methylation (DNAm) as biomarkers of outcomes in three important etiologies of pediatric acquired brain injury (ABI), traumatic brain injury, global cerebral ischemia, and stroke. We also summarize evidence suggesting that BDNF is (1) involved in the biological embedding of the psychosocial environment, (2) responsive to rehabilitative therapies, and (3) potentially modifiable. BDNF's unique potential as a biomarker of neuroplasticity and neural repair that is reflective of and responsive to both pre- and post-injury environmental influences separates it from traditional protein biomarkers of structural brain injury with exciting potential to advance pediatric ABI management by increasing the accuracy of prognostic tools and informing clinical decision making through the monitoring of therapeutic effects.

**Keywords:** pediatric acquired brain injury; biomarkers; recovery; brain-derived neurotrophic factor



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## 1. Introduction

Pediatric acquired brain injury (ABI) is a leading cause of death and disability in children [1–4]. Traumatic brain injury (TBI) comprises the majority of pediatric ABI, with an incidence of 14.8 per 100,000 children per year in the United States. ABI also includes non-traumatic brain injury due to infection (4.3 per 100,000), stroke (2.4 per 100,000), and global cerebral ischemia due to cardiac arrest (1.3 per 100,000) [3]. In an international point prevalence study of children aged 7 days to 17 years old with ABI admitted to a pediatric intensive care unit, the most common were due to cardiac arrest (23%) and TBI (19%) [4]. Notably, children with cardiac arrest and children with TBI had the highest mortality (24%) and morbidity (49% unfavorable outcomes), respectively.

The breadth and quality of evidence available to guide clinical management after pediatric ABI are disproportionately low relative to its medical and societal burden, which is driven by long-term neurobehavioral impairments [5–9]. Recovery from pediatric ABI is determined by the interaction of a multitude of dynamic biological, psychosocial, and therapeutic factors. This complexity results in a marked heterogeneity in outcomes and is cited as the most critical barrier to the development of accurate prognostic models and effective therapies [10–12].

The field has turned to biomarkers as one potential tool to explain this heterogeneity; however, the focus to date on protein biomarkers of structural brain injury (e.g., glial fibrillary acidic protein [GFAP], S100 calcium binding protein B [S100B], ubiquitin C-terminal hydrolase-L1 [UCH-L1]) will likely be inadequate to fully capture the complexity

of factors that influence recovery [13–15]. The discovery of dynamic and potentially modifiable biomarkers that (a) reflect the child’s psychosocial environment (e.g., social determinants of health) and (b) respond to injury progression and recovery processes over days to months post injury would provide critical information about the biologic complexity underlying recovery. In the future, this information could revolutionize pediatric ABI management by identifying novel targets for therapy development, improving prognostic tools, and aiding therapeutic clinical decision making.

Brain-derived neurotrophic factor (BDNF) may be such a biomarker. BDNF is a well-studied member of the neurotrophin family of growth factors. Released pre- and post-synaptically from neurons, it mediates apoptosis, neuronal differentiation, cell survival, and synaptic strengthening [16,17]. Thus, in contrast to traditional ABI biomarkers of structural brain injury, BDNF is a biomarker of neuroplasticity and repair, essential to brain development, neuronal survival, and complex cognitive functions [18–25].

While biomarker studies often measure BDNF protein concentrations in the brain or periphery, upstream genetic and epigenetic influences on BDNF expression are also potentially informative. A single nucleotide polymorphism (SNP) producing a valine-to-methionine substitution at codon 66 (Val66Met; rs6265) in the *BDNF* gene is associated with the reduced activity-dependent secretion of BDNF [26]. Val66Met allele status, and especially possession of the Met allele, is associated with variations in brain structure and function, including smaller brain volumes [27–30] and lower connectivity [31,32], poorer neuropsychological functioning [33,34], and an increased risk for psychiatric and neurological conditions, in non-brain-injured individuals [35,36].

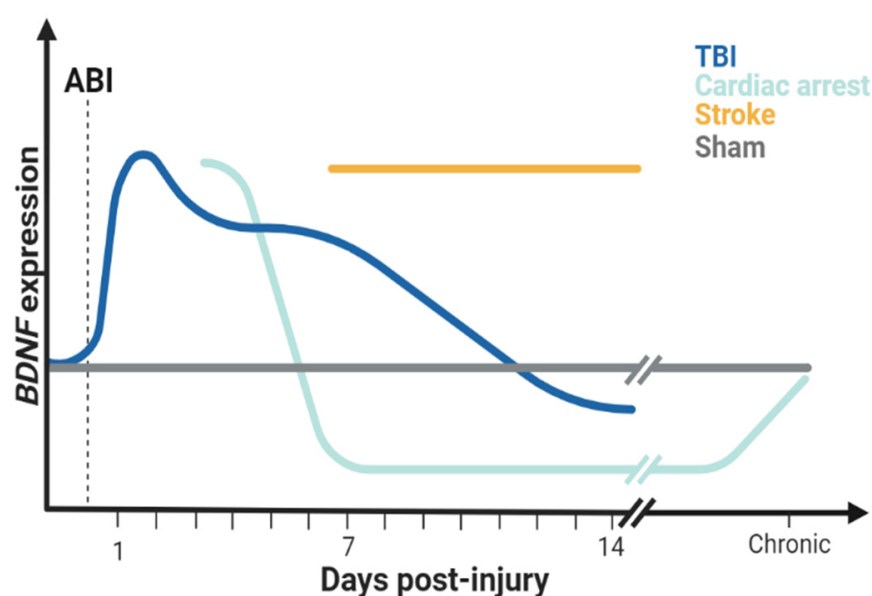
Epigenetics, in contrast, involves potentially heritable biochemical processes that regulate gene expression without altering the corresponding primary DNA sequence [37]. What is unique about epigenetic biomarkers that has great potential ramifications for ABI is that, through epigenetic processes, the biological and social environments of an individual impact when and to what extent genes are expressed within each cell type. The most investigated epigenetic modification is DNA methylation (DNAm), which involves the addition of a methyl group to cytosine–guanine dinucleotides (CpG). Higher DNAm in CpG rich promoters or gene regulatory regions is usually (but not always) associated with lower gene expression [38]. While epigenetic modifications in *BDNF* have been frequently investigated in association with brain-related phenotypes [39], the study of their potential as biomarkers of ABI recovery is just beginning to emerge.

Thus, herein, we review evidence from both preclinical and clinical studies of BDNF in pediatric ABI, focusing on three key insults, namely, TBI, global cerebral ischemia, and stroke, suggesting that peripheral BDNF concentrations, genotype, and DNAm may be markers of survival and recovery. We also review emerging evidence suggesting that BDNF is (1) involved in the biological embedding of the psychosocial environment, (2) responsive to rehabilitative therapies, and (3) potentially modifiable. These features support BDNF’s unique potential as a biomarker of neuroplasticity and neural repair that is reflective of and responsive to both pre- and post-injury environmental influences with exciting potential to advance pediatric ABI management by increasing the accuracy of prognostic tools and informing therapeutic decision making through its use as an intervention response biomarker of therapeutic effects (i.e., a pharmacodynamic response biomarker).

## 2. BDNF in Preclinical Models of Pediatric ABI

Preclinical studies of brain injury provide unique insight into the role of BDNF in neuroplasticity and repair (see Table 1). In animal models, the BDNF response to brain injury is dynamic in the days and weeks after injury and can vary by age, sex, and type of ABI (Figure 1). Most studies of TBI in juvenile rats have found greater BDNF protein concentration and *BDNF* mRNA expression up to 7 days after injury relative to sham or control animals [40–42]. In adult models, rats with TBI had higher *BDNF* expression acutely (within 6 h of injury) compared to shams, suggesting an upregulation of BDNF in the acute period, but similar or even lower *BDNF* expression compared to the sham group

chronically after injury [43–47]. *BDNF* expression in adult models of ABI is associated with recovery in many of these studies [46,48,49]. Similarly, preclinical studies in adult models have shown therapeutic effects of *BDNF* treatment. Administering *BDNF* mimetics (7,8-dihydroxyflavone, R13) that better permeate the blood–brain barrier than native *BDNF*, or tropomyosin-related kinase B (*TrkB*) agonists that mimic the effects of *BDNF* at the *TrkB* receptor improve neurogenesis, metabolism, synaptic plasticity, and neurobehavioral recovery after TBI in adult rats [50–54]. In pediatric models of ABI, early work similarly demonstrates a likely association of *BDNF* with recovery. Juvenile rats with TBI had lower *BDNF* expression in the injured hippocampus at 14 days post injury relative to sham, corresponding with poorer cognitive functioning [55,56]. Most of these preclinical experiments limited their population to male rodents only. However, one study found region-dependent differences in *BDNF* expression after TBI with higher *BDNF* expression in the ipsilateral frontal cortex for males and higher *BDNF* in the contralateral hippocampus for females compared to sham [45]. Preclinical work evaluating the therapeutic effects of *BDNF* in models of TBI in immature animals of both sexes across the age spectrum is needed.



**Figure 1.** Brain-derived neurotrophic factor (*BDNF*) expression after acquired brain injury (ABI) in preclinical models in developing animals. Animals with traumatic brain injury (TBI, blue) have higher *BDNF* expression compared with animals with the sham operation (gray) on the first day after injury, with some studies showing higher *BDNF* expression up to 7 days after TBI vs. sham followed by lower *BDNF* expression at 14 days post injury vs. sham. In pediatric models of global ischemia produced by cardiac arrest (aqua), *BDNF* is higher than that of sham animals at 4 days after injury, followed by lower *BDNF* expression vs. sham at 7 days after injury. *BDNF* then increases to near-sham concentrations at 30 days post injury. Pediatric stroke models (orange) have higher *BDNF* expression vs. sham animals at 7 and 14 days after injury. Missing sections indicate a lack of available preclinical studies in models of ABI in developing animals during these time periods.

In ischemic brain injury, *BDNF* responses depend largely on both the nature of injury (global cerebral ischemia following cardiac arrest vs. focal ischemia in pediatric stroke) and age [57]. In adult rats, global ischemia produced by either bilateral carotid artery occlusion or cardiac arrest (i.e., with total body ischemia) resulted in higher *BDNF* expression in the hippocampus compared to sham or controls in the 24 h after injury [58–62]. In pediatric models, however, a seminal study in juvenile (post-natal day 20–25) mice found lower *BDNF* expression 7 days after global ischemia due to cardiac arrest compared to the sham operation group. Critically, memory recovery and long-term potentiation in the

hippocampus in that study were associated with an increase in *BDNF* expression from 7 days to 30 days in rats after cardiac arrest, not with neurogenesis, suggesting a potentially important role for *BDNF* in recovery [63]. In gerbils with global cerebral ischemia following transient bilateral carotid artery occlusion, *BDNF* expression was higher in injured animals relative to sham at 4 days after the insult in juveniles but not adults [64]. Notably, ischemic injury results in greater brain damage in gerbils than in rats, due in part to the lack of a circle of Willis in gerbils, which may explain the differences between animal models [65]. While there are few studies of pediatric ischemic injury after cardiac arrest, these initial studies suggest neuroprotective responses of *BDNF* in the post-ischemia stages of recovery and potentially key age-related differences for *BDNF* in the brain post injury.

While cardiac arrest in children results in global cerebral ischemia, pediatric stroke results in either focal or multi-focal ischemic injury. In stroke models, *BDNF* in the brain generally increases after injury. Most studies in adult stroke models found a greater *BDNF* concentration, *BDNF* mRNA, and uptake of *BDNF* by astrocytes acutely from 2 h to 7 days post injury compared to sham-operated rats [59,66–68]. In juvenile rats, greater *BDNF*-positive cells are found in the injured brain at both 7 and 14 days post-ischemic injury compared to rats with the sham operation [69]. However, future studies evaluating focal cerebral ischemia in juvenile rats at more acute time points are needed. Like TBI, evidence suggests therapeutic effects of *BDNF* in adult models of cerebral ischemia. Inhibiting *BDNF* blocks AMPA receptors and AMPA-mediated motor recovery following stroke in a mouse model compared to controls [70]. *BDNF* administration can have neuroprotective effects [71–75] and is associated with improvements in functional and behavioral outcomes [76–78], suggesting the importance of *BDNF* in recovery from ischemic brain injury in addition to TBI.

Finally, there is also preclinical evidence that increases in brain tissue expression of *BDNF* in ABI result from the differential modulation of *BDNF* after the insult [61], likely due to early changes in the methylome in response to injury. Preclinical studies in TBI models suggest the re-localization of DNA methyltransferase 1 (an enzyme that adds or removes methyl groups at cytosine residues) within reactive astrocytes and microglia as a likely mechanism [79,80]. Initial preclinical [79,81] studies show differential DNAm both acutely and months after TBI in adult models, but studies in pediatric preclinical models are lacking. Similarly, the dynamic temporal responses of *BDNF* in the injured brain warrant further study. Though most studies find that the spike in *BDNF* expression in the brain attenuates quickly following ABI, with some studies showing a return to control concentrations by 24 h [58,82] to one week post injury [83], changes in *BDNF* expression can continue for up to 20 weeks post ischemia [83].

**Table 1.** BDNF in preclinical models of ABI.

Reference	Type of Injury (TBI, Global Cerebral Ischemia, Stroke)	Brain Region from Which Sample Was Taken	Model	BDNF Concentration, Expression, Mimetics, or Genotype	Time Post Injury,	Results
Dyck et al., 2018 [40]	TBI	Motor cortex, prefrontal cortex	Juvenile rats post-natal day 27	Concentration	4 days	Rats with TBI had higher BDNF concentration in right and left motor cortex vs. sham
Griesbach et al., 2002 [41]	TBI	Hippocampus and occipital cortex	Juvenile rats post-natal day 19	Concentration, mRNA expression	24 h, 7 days, and 14 days	Rats with TBI had higher BDNF expression vs. sham at 24 h and 7 days in contralateral hippocampus and occipital cortex; higher BDNF concentration in occipital cortex and ipsilateral hippocampus at 7 and 14 days post TBI vs. sham
Rostami et al., 2014 [43]	TBI	Frontal cortex, hippocampus	Adult rats	Concentration, mRNA expression	24 h, 3 day, 2 weeks, 8 weeks	Lower BDNF expression in ipsilateral hippocampus and higher BDNF expression in contralateral hippocampus at 1 day, 3 days, and 2 weeks after TBI vs. sham; higher BDNF concentration in frontal cortex on days 1, 3, and 14 post TBI vs. sham
Hicks et al., 1997 [44]	TBI	Hippocampus	Adult rats	mRNA expression	1, 3, 6, 24, and 72 h	Higher BDNF bilaterally in dentate gyrus for 1 to 72 h post TBI vs. sham and in CA3 at 1, 3, and 6 h post TBI vs. sham
Chen et al., 2005 [45]	TBI	Hippocampus, frontal cortex	Adult rats	Concentration	4 weeks	Higher BDNF expression in ipsilateral frontal cortex for males vs. sham; higher BDNF in contralateral hippocampus vs. sham
Griesbach et al., 2009 [46]	TBI	Hippocampus, parietal cortex	Adult rats	Concentration	21 days	Rats with TBI had lower BDNF in ipsilateral hippocampus and injured parietal cortex vs. sham, but higher BDNF in contralateral parietal cortex vs. sham
Madathil et al., 2017 [47]	TBI	Hippocampus, cortex	Adult rats	Concentration	1 h, 6 h, 1 day, 2 days, 3 days, 1 week, 2 weeks	BDNF was higher in rats with TBI in the hours after injury vs. sham
Corne et al., 2019 [48]	TBI	Parietal lobe, hippocampus, amygdala, medial prefrontal cortex	Adult mice	mRNA expression	3 weeks	BDNF was lower in animals with TBI at exon IV vs. sham in injured parietal lobe

Table 1. Cont.

Reference	Type of Injury (TBI, Global Cerebral Ischemia, Stroke)	Brain Region from Which Sample Was Taken	Model	BDNF Concentration, Expression, Mimetics, or Genotype	Time Post Injury,	Results
Thapak et al., 2023 [50]	TBI	Hippocampus	Adult rats	Mimetics, protein concentration (both mature BDNF and pro-BDNF, a precursor to mature BDNF)	8 days	Animals with TBI had lower mature BDNF vs. sham; rats treated with BDNF mimetic (R13) had greater mature BDNF and better cognitive function after TBI vs. controls
Agrawal et al., 2015 [51]	TBI	Hippocampus	Adult rats	Mimetics, concentration	6 days	Rats treated with BDNF mimetic (7,8-dihydroxyflavone) had less cognitive behavioral deficit and fewer cellular changes after TBI vs. controls; treatment group had similar cortical BDNF levels vs. controls
Wu et al., 2014 [52]	TBI	Parietal cortex	Adult mice	Mimetics, mRNA expression, and protein concentrations	1 day, 4 days	Mice treated with BDNF mimetic (7,8-dihydroxyflavone) had higher BDNF concentrations, improved survival, and reduced cell death after TBI vs. controls
Zhao et al., 2016 [53]	TBI	Hippocampus	Adult mice	Mimetics	2 weeks	Mice that received 7,8-dihydroxyflavone for 2 weeks after TBI had improved neurogenesis and dendrite arborization in the ipsilateral hippocampus vs. controls
Smith et al., 2023 [54]	TBI	Whole brain MRI scans	Adult rats	Mimetics	Up to 7 days post injury	Rats that received R13 had greater functional connectivity, and cellular and behavioral outcomes after TBI vs. controls
Schober et al., 2012 [55]	TBI	Hippocampus (ipsilateral)	Rat pups post-natal day 17	Concentration and mRNA expression	1, 2, 3, 7, and 14 days	Rats with TBI had lower BDNF protein vs. sham at 14 days
D'Cruz et al., 2002 [58]	Global cerebral ischemia	Hippocampus	Adult rats	Concentration	12 and 24 h	Rats with ischemia had higher BDNF concentrations vs. sham
Tsukahara et al., 1998 [59]	Global cerebral ischemia	Hippocampus, cortex	Adult mice	mRNA expression	2, 4, 8, 16, or 24 h	Mice with ischemia had higher BDNF mRNA in the hippocampus and cerebral cortex vs. controls

Table 1. Cont.

Reference	Type of Injury (TBI, Global Cerebral Ischemia, Stroke)	Brain Region from Which Sample Was Taken	Model	BDNF Concentration, Expression, Mimetics, or Genotype	Time Post Injury,	Results
Dietz et al., 2018 [63]	Global cerebral ischemia	Hippocampus	Juvenile mice post-natal day 20–25	Concentration	7 days, 30 days	Lower hippocampal BDNF concentration vs. sham at 7 days in mice with cardiac arrest; no difference in BDNF in TBI vs. sham at 30 days
Yan et al., 2012 [64]	Global cerebral ischemia	Hippocampus	Juvenile gerbils and adult gerbils	Concentration	4, 7 days	BDNF expression was higher in injured animals vs. sham at 4 days after ischemia in juveniles but not adults
Li et al., 2020 [61]	Global cerebral ischemia	Hippocampus	Adult rats	Concentration transcript expression	48 h	Higher BDNF concentration vs. sham in CA3 and dentate gyrus; lower BDNF concentration vs. sham in CA1; higher BDNF mRNA vs. sham in CA1, CA3, and dentate gyrus at BDNF transcripts I, II, VI, and XI
Miyake et al., 2002 [66]	Stroke	Hippocampus	Adult rats	Concentration, mRNA expression	1, 3, 7 days	BDNF concentrations were higher in rats with ischemia vs. sham
Grade et al., 2013 [67]	Stroke	Striatum	Adult mice	mRNA expression	1, 2 weeks	Higher BDNF in ischemic striatum 1 week post injury vs. naïve mice
Lindvall et al., 1992 [62]	Global cerebral ischemia	Hippocampus	Adult rats	mRNA expression	10 min, 30 min, 2 h, 4 h, 24 h	Higher BDNF in dentate gyrus from 2 to 24 h in rats with ischemia vs. sham
Kokaia et al., 1996 [60]	Global cerebral ischemia	Hippocampus and parietal cortex	Adult rats	Concentration, mRNA expression	1, 2, 4, and 18 h (mRNA), and 6, 12, 24 h, or 1 weeks (protein)	Higher BDNF concentration at 6 h vs. sham in dentate gyrus and at 1 week in CA3; higher BDNF mRNA expression at 2 h in CA3 vs. sham
Madinier et al., 2013 [68]	Stroke	Cortex and hippocampus	Adult rats	Concentration, mRNA expression	4 h, 24 h, 8 days, 30 days	Higher mature BDNF in cortex vs. control; higher mature BDNF in hippocampus at 30 days vs. control
Cheng et al., 2020 [69]	Stroke	Ischemic penumbra	Juvenile rats (matured for 6–7 weeks)	Concentration, mRNA expression	7, 14 days	Higher BDNF concentration at 7 days vs. sham; higher BDNF expression in ischemic penumbra at 7 and 14 days post injury vs. sham
Clarkson et al., 2011 [70]	Stroke	Periinfarct cortex	Adult mice	Inhibition of BDNF	7 days	Mice with BDNF blocked have less AMPA-mediated motor recovery vs. controls

Table 1. Cont.

Reference	Type of Injury (TBI, Global Cerebral Ischemia, Stroke)	Brain Region from Which Sample Was Taken	Model	BDNF Concentration, Expression, Mimetics, or Genotype	Time Post Injury,	Results
Zhang and Pardridge 2001 [71]	Stroke	Cortex	Adult rats	Mimetics	24 h	Rats treated with BDNF conjugate with a monoclonal antibody have smaller infarct size vs. controls
Zhang and Pardridge 2001 [72]	Stroke	Cortex	Adult rats	Mimetics	24 h, 7 days	Rats treated with BDNF conjugate have lower stroke volume at 24 h or 7 days after ischemia vs. controls
Shabitz et al., 2000 [73]	Stroke	Cortex	Adult rats	Mimetics	24 h	Rats with BDNF treatment have less neurological deficit and less stroke volume vs. controls
Yamashita et al., 1997 [74]	Stroke	Cortex	Adult rats	Mimetics	24 h	Rats with BDNF have lower infarct volume vs. controls; no differences in physiological measures vs. controls
Wang et al., 2023 [75]	Stroke	Cortex, cervical spinal cord	Adult rats	Mimetics, mRNA	28 days	BDNF-treated rats have better behavioral outcomes and greater corticospinal connections vs. controls
Zhang and Pardridge 2006 [76]	Stroke	Cortex	Adult rats	Mimetics	24 h	Animals treated with BDNF conjugate had greater motor outcomes and lower infarct volume vs. rats treated with BDNF alone
Ramos-Cejudo et al., 2006 [77]	Stroke	Cortex, serum	Adult rats	Mimetics, concentration	4 h, 7 days, 28 days	Recombinant BDNF-treated rats had better functional recovery and white matter repair markers at 28 days vs. controls
Alam et al., 2020 [78]	Stroke	Cortex	Young rats (3 months)	Concentration	6 weeks	Rats treated with p38 mitogen-activated protein kinase had higher BDNF after ischemia and greater functional recovery vs. controls
Kokaia et al., 1995 [82]	Stroke	Frontal and cingulate cortex, hippocampus	Adult rats	Concentration, mRNA expression	30 min, 2 h, 4 h, 24 h	Higher BDNF expression from 30 min to 4 h post ischemia vs. controls; no difference vs. controls at 24 h
Uchida et al., 2010 [83]	Stroke	Substantia nigra	Adult rats	mRNA expression	1, 2, 6, 20 weeks	Higher BDNF at 1 week and 20 weeks after ischemia vs. sham in neurons; greater BDNF released by astrocytes at 20 weeks vs. sham



### 3. BDNF in Clinical Studies of Pediatric ABI

#### 3.1. BDNF Concentrations

Similar to both preclinical and clinical studies in adults [84,85], clinical studies in pediatric patients (see Table 2) show an initial increase in BDNF concentrations in plasma and cerebrospinal fluid (CSF) ~2 h after TBI, followed by a decrease in CSF BDNF concentrations at 24 h [86–88]. Two of the pediatric TBI studies failed to show a statistically significant association between BDNF concentration and dichotomized functional outcome. However, neither study was powered to appropriately test the hypothesis of an association ( $n = 14$  children with TBI,  $n = 27$  children with TBI in the two reports, respectively) [87,88]. In more recent studies of children with TBI and children with neurocritical-care-related conditions, higher BDNF plasma concentrations on day 1 ( $n = 177$  children) [89] and BDNF serum concentrations at day 3 ( $n = 44$ ) [90] were associated with better functional recovery, respectively.

Consistent with the pediatric TBI and neurocritical care studies above, two studies involving pediatric stroke in children with sickle cell disease also found higher BDNF plasma concentrations acutely after brain injury compared to other children with sickle cell disease or healthy controls ( $n = 8$  with stroke,  $n = 40$  with stroke, respectively) [91]. Importantly, preclinical studies in rats report conflicting evidence regarding whether BDNF concentrations in the periphery mimic cortical concentrations after stroke, when the blood–brain barrier remains largely intact with ischemia [92,93]. Thus, peripheral BDNF concentrations may not be correlated with CSF concentrations of BDNF, and assessments of both serum and CSF BDNF concentrations should be evaluated specifically in children after stroke. In pediatric cardiac arrest, an initial exploratory study of 42 children found no statistically significant associations of serum BDNF concentration at between 12 and 96 h post insult with dichotomized outcomes at six months [94]; however, once again, more extensive investigations with larger sample sizes are needed.

#### 3.2. BDNF Genotype

Only a handful of studies examining *BDNF* genotype have been conducted in pediatric ABI, with mixed results. In a concurrent cohort study of children with moderate-to-severe TBI or orthopedic injury but no TBI (OI; comparison group), the Val66Met met allele was associated with poorer longitudinal behavioral adjustment [95] and poorer long-term neuropsychological functioning [96] in children with TBI ( $n = 69$ ) but not OI ( $n = 72$ ). These results suggest that the Met allele—associated with reduced activity-dependent secretion of BDNF—may confer a risk for poorer neurobehavioral recovery from pediatric TBI. In contrast, the Met allele was associated with fewer internalizing problems ( $n = 145$ ) [97] and better quality of life ( $n = 159$ ) [98] in a cohort of children studied at 6 months after mild TBI, suggesting a protective effect. Reasons for these mixed results are unclear and require further investigation in larger cohorts and other etiologies of pediatric ABI.

Given the limited pediatric ABI studies, the adult ABI literature examining *BDNF* genotype merits discussion. There is a relatively extensive literature of candidate gene studies suggesting that the *BDNF* Met allele is associated with recovery from ABI in adults, especially following ischemic stroke [99]. Genome-wide association studies (GWASs), however, have not confirmed *BDNF*'s association with stroke recovery [100]. Similarly, the single GWAS of TBI recovery to date did not identify any genetic variants reaching genome-wide significance and *BDNF* was not included among the 13 genes with variants that reached a lower pre-specified sub-genomic statistical threshold [101]. The strengths and limitations of candidate genes vs. GWAS approaches in ABI are discussed below.

Table 2. BDNF in clinical studies of pediatric ABI.

Reference	Type of Injury (TBI, Cardiac Arrest, Stroke, Brain Mass, CNS Infection, or Inflammation)	Groups	Time Post Injury	BDNF Concentration, Genotype, or DNAm	Tissue (CSF, Serum, Plasma, Saliva)	Results
Tylicka et al., 2020 [86]	TBI	Children with mild concussion (–)LOC ( <i>n</i> = 12); children with severe concussion (+)LOC ( <i>n</i> = 17); and healthy controls ( <i>n</i> = 13)	2–6 h	Concentration	Plasma	Higher plasma BDNF in children with mild head trauma (–)LOC and children with severe concussion (+)LOC 2–6 h post injury vs. healthy controls; BDNF concentration did not differ between children with mild vs. children with severe concussions
Chiaretti et al., 2003 [87]	TBI	Children with severe head injury ( <i>n</i> = 14) vs. children with obstructive hydrocephalus ( <i>n</i> = 12)	2 and 24 h	Concentration	CSF and plasma	Decrease in CSF BDNF concentration from 2 h to 24 h post injury
Chiaretti et al., 2009 [88]	TBI	Children with severe head injury ( <i>n</i> = 32) vs. healthy controls ( <i>n</i> = 32)	2 and 48 h after admission	Concentration	CSF	Higher CSF BDNF concentration in children with severe head injury vs. healthy controls; BDNF concentrations decreased in children with severe head injury from 2 to 48 h after admission
Pinelis et al., 2015 [89]	TBI	Children with TBI ( <i>n</i> = 177)	1–3 days, 7–8 days, 14–15 days, 20–23 days, and 11–12 months	Concentration	Plasma	Decrease in BDNF concentration between days 1 and 3 post injury among mild and severe TBI; lowest BDNF concentration found at 1 day post injury in children with severe TBI and fatal outcomes
Madurski et al., 2021 [90]	TBI, cardiac arrest, stroke, brain mass, or CNS infection, or inflammation	Children with acquired brain injury ( <i>n</i> = 44)	Admission days 0, 1, 3, 5, and day closest to hospital discharge	Concentration	Serum	Lower serum BDNF in children on day 3 of admission, day 5 of admission, and day closest to hospital discharge associated with greater functional impairment
Mahmoud et al., 2023 [91]	Stroke	Children with Sickle cell disease ( <i>n</i> = 40) vs. healthy controls ( <i>n</i> = 40)	During hospital admission	Concentration	Serum	Higher serum BDNF in children with SCD vs. healthy controls; higher serum BDNF in children with sickle cell disease associated with elevated transcranial doppler velocities

Table 2. Cont.

Reference	Type of Injury (TBI, Cardiac Arrest, Stroke, Brain Mass, CNS Infection, or Inflammation)	Groups	Time Post Injury	BDNF Concentration, Genotype, or DNAm	Tissue (CSF, Serum, Plasma, Saliva)	Results
Kernan et al., 2021 [94]	Cardiac Arrest	Pediatric cardiac arrest patients ( <i>n</i> = 42)	Twice within a 24 h period between 0 and 96 h and once at 196 h	Concentration	Serum	BDNF serum levels not found to be significantly associated with 6-month neurologic outcome
Treble-Barna et al., 2022 [95]	TBI	Children with TBI ( <i>n</i> = 69) vs. OI ( <i>n</i> = 72)	18 months	Genotype	Saliva	Allele status x injury group interactions associated with behavioral adjustment outcomes; within-group non-significant trends of poorer behavioral adjustment in Met carriers
Treble-Barna et al., 2022 [96]	TBI	Children with TBI ( <i>n</i> = 69) vs. OI ( <i>n</i> = 72)	18 months	Genotype	Saliva	Poorer verbal fluency functioning in Met carriers vs. Val/Val in the TBI group
Gagner et al., 2021 [97]	TBI	Children with mild TBI ( <i>n</i> = 47), OI ( <i>n</i> = 42), and typically developing children (TDC) ( <i>n</i> = 56)	Any time point within 18 months	Genotype	Saliva	Val/Val mTBI associated with more internalizing problems vs. Met mTBI at 6 months post injury; Val/Val and Met mTBI groups associated with more internalizing problems vs. OI and TDC at 18 months post injury
Tuerk et al., 2020 [98]	TBI	Children with mild TBI ( <i>n</i> = 52), OI ( <i>n</i> = 43), and typically developing children (TDC) ( <i>n</i> = 64)	Any time point within 18 months	Genotype	Saliva	Higher quality of life at 6 months post injury in Met carriers vs. Val/Val among TBI

### 3.3. *BDNF DNAm*

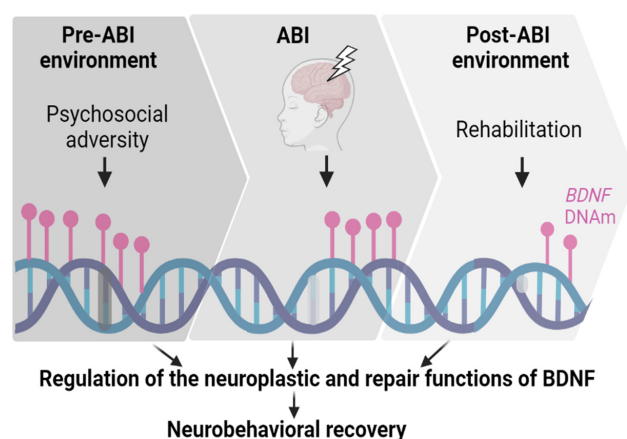
An important consideration, and frequent criticism, for clinical studies of DNAm in ABI is the relevance of DNAm measured in peripheral tissues (most frequently blood) to brain function given that DNAm patterns are tissue-specific and reflect the local environment of each cell type. However, for clinical studies of *BDNF* in ABI, in particular, the use of peripheral leukocytes for DNAm measurement is justified. Although DNAm in brain tissue may provide more direct insights into the biology of brain function and pathology, acquiring *in vivo* brain tissue samples is not feasible outside of extraordinary circumstances—such as with resection of a cerebral contusion to treat severe intracranial hypertension. Further, to be useful as a clinical biomarker, it is essential that markers be identified in readily accessible tissues or cells, such as blood samples. A comparative analysis of genomic signatures of TBI revealed homology between the rodent hippocampus and peripheral leukocytes at gene, methylome, pathway, and network concentrations related to vascularity, cell integrity, and immune response [102]. Notably, *BDNF* was among the highest pathways with a shared homology between tissues. Further, rodent gene signatures showed a significant overlap with human genes of brain disorders identified by GWASs. These homologous changes across hippocampus and peripheral leukocytes likely reflect disruption of the blood–brain barrier in TBI, associated systemic inflammation, and potential changes in cell type composition in the systemic circulation mediated via the glymphatic system [102,103]. That study strongly supports the development of DNAm biomarkers of TBI using easily accessible peripheral blood leukocytes, as well as a focus on *BDNF*. Finally, taking an approach that collects DNAm data across the genome has the added advantage of being able to adjust for cell type heterogeneity, reducing potential confounding related to cell type–phenotype associations, which can help provide a greater biological understanding of ABI [39].

To date, all candidate gene studies of *BDNF* DNAm in ABI have been conducted in adults. *BDNF* DNAm in blood was associated with adult stroke outcomes, including global outcome, physical disability, cognitive dysfunction, anxiety, and depression, in several candidate gene studies [39,104–107]. Most studies reported hypermethylation in *BDNF* promoter regions in blood, suggesting lower *BDNF* expression, associated with poorer outcomes. In our study targeting *BDNF* DNAm in CSF over the first five days after severe TBI in 112 adults, trajectory analysis revealed low- and high-DNAm groups at two *BDNF* sites with suggestive associations with long-term neurobehavioral outcomes [108]. In contrast to the adult stroke studies, membership in the high-DNAm group was associated with better outcomes after severe TBI. The opposing direction of associations of DNAm with outcomes in this study as compared to the stroke studies may be explained by differences in the timing of sample collections (weeks to months post stroke vs. the first five days post TBI) as well as evidence for a negative correlation between CSF and peripheral *BDNF* levels [84]. Beyond candidate studies, three epigenome-wide association studies (EWASs) have been conducted in adult TBI [109–111]; however, *BDNF* DNAm did not reach epigenome-wide significance in any study. While there are no published candidate *BDNF* DNAm studies in pediatric ABI, two published studies using an EWAS approach have examined DNAm in association with recovery from mild TBI [112,113]. In a blood-based EWAS of 17 children with mTBI vs. 18 healthy controls, one CpG site in the *BDNF* gene was among the 449 differentially methylated (hypomethylated) sites reaching epigenome-wide significance [112]. In a larger saliva-based EWAS of 110 children with mTBI and 87 healthy controls, *BDNF* DNAm was not significantly associated with quality of life or persistent post-concussive symptoms [113]. A candidate study of *BDNF* DNAm in association with neurobehavioral recovery following moderate-to-severe pediatric TBI is ongoing [114].

## 4. The Potential of *BDNF* as an ABI Biomarker Responsive to Environmental Influences

The unique potential of *BDNF* as a biomarker of recovery from pediatric ABI is underscored by its responsiveness to environmental influences, especially as mediated by changes in DNAm. It is well established that environmental factors influence recovery

from ABI, though their underlying mechanisms are poorly understood. One of the most significant examples is the well-documented outcome disparities (i.e., poorer neurobehavioral recovery) among children facing greater psychosocial adversity, including low socioeconomic status and greater family dysfunction, even after adjusting for pre-injury functioning [7,115–122]. A second major environmental factor with potential to alter recovery trajectories is the quality and quantity of rehabilitative therapies, though research into these effects remains in its infancy [123–125]. As we review below, given the role of *BDNF* DNAm in the biological embedding of the psychosocial environment, and its responsiveness to interventions, we posit that *BDNF* DNAm may confer risk or protective effects on recovery after pediatric ABI by regulating the neuroplastic and repair functions of *BDNF* (see Figure 2).



**Figure 2.** The potential role of brain-derived neurotrophic factor (*BDNF*) DNA methylation (DNAm) in neurobehavioral recovery from acquired brain injury (ABI). Pre-injury environmental factors (e.g., psychosocial adversity) may downregulate *BDNF* by increasing *BDNF* DNAm. ABI itself alters *BDNF* DNAm, leading to an increase in *BDNF* after injury. Post-injury factors (e.g., rehabilitation) can also decrease *BDNF* DNAm, leading to an increase in *BDNF* expression. This pre- and post-ABI epigenetic regulation of *BDNF* may influence neuroplasticity and ultimately neurobehavioral recovery after injury.

#### 4.1. Psychosocial Environment

Preclinical and clinical studies in non-brain-injured animal models and individuals suggest that *BDNF* DNAm is involved in the biological embedding of the psychosocial environment with downstream effects on brain function. Preclinical models of early-life caregiver maltreatment have shown alterations in *BDNF* DNAm in the medial prefrontal cortex, amygdala, and hippocampus [126]. These changes in methylation have been identified within 24 h of caregiver manipulation, can persist through adolescence and into adulthood, and have been associated with cognitive dysfunction [126–128]. Psychosocial environmental factors examined in association with *BDNF* DNAm in human studies have included a multitude of trauma/stress exposures [129–133], as well as neighborhood-level socioeconomic disadvantages [133]. Of these, both candidate studies and EWASs report differential *BDNF* DNAm [39], as well as associated effects on downstream neurobehavioral outcomes such as depression and anxiety [134,135]. While several studies have begun to examine DNAm in clinical studies of ABI (reviewed above), no published studies to date have examined *BDNF* DNAm in association with both the psychosocial environment and recovery.

#### 4.2. Rehabilitative Therapies

Emerging evidence suggests that *BDNF* is responsive to rehabilitation interventions after ABI. These studies are largely in animal models and most commonly evaluate physical activity as an intervention via voluntary wheel running or treadmill training (forced exer-

cise that is more tightly controlled under experimental conditions). Early studies showed that voluntary wheel running following TBI upregulated *BDNF* expression and had corresponding improvements in cognition, but suggested a therapeutic window of rest following injury [136–140]. More recent studies, however, have shown favorable improvements in behavioral and neurobiological responses to injury (including *BDNF* response) with exercise starting early after TBI, but have also found that the intensity and duration of exercise matter early in recovery [141–148]. Several studies have shown that *BDNF* mediates this association between physical activity and TBI recovery [137,138,149]. In animal models, physical activity decreases *BDNF* DNAm, upregulates hippocampal *BDNF*, and initiates synaptic plasticity pathways to ultimately improve neurobehavior [138,150]. In preclinical models of stroke, aerobic exercise improves neurobehavioral symptoms, such as depression, by regulating *BDNF* expression in both adult and juvenile animals [69,151–158]. A recent study evaluating aerobic exercise in rats with global cerebral ischemia found that exercise promoted neuron repair and survival, mediated in part by *BDNF* [159]. Furthermore, some studies have shown that pre-conditioning, or exercising prior to brain injury, can improve *BDNF* concentrations post injury and improve recovery after ABI, as well [160,161]. In initial clinical studies of adults post stroke, individuals who performed physical exercises had increased *BDNF* concentrations compared to pre-intervention [162,163] and, in one study, *BDNF* serum concentrations were associated with cognitive recovery [163]. In other non-brain-injured adult populations, cognitive improvements found with physical activity are mediated in part by epigenetic changes in *BDNF* expression, demonstrating the impact of *BDNF* on rehabilitation and recovery [20,104,164,165].

Similar rehabilitation techniques, such as task-specific training [166] and enriched environments that mimic clinical rehabilitation environments, have also been shown to improve recovery from experimental ABI in animal models [167–169]. Early environmental enrichment counteracted the detrimental effects of prenatal alcohol exposure on behavior, potentially mediated by the fourfold increase in *BDNF* expression seen with environmental enrichment [167]. Several papers in preclinical stroke studies have found that *BDNF* plays an integral role in the relationship between rehabilitation and recovery [170]. After stroke, mice in an enriched environment have higher *BDNF* concentrations and improved cognitive performance compared to mice housed in a standard environment [171]. Importantly, blocking *BDNF* for 28 days after stroke in rats negated the effects of rehabilitation on functional recovery, suggesting the key role of *BDNF* in stroke recovery [172]. These findings suggest that *BDNF* expression could inform therapeutic decision making through the monitoring of therapeutic effects for children with ABI [166].

## 5. *BDNF* DNAm as a Modifiable Therapeutic Target

Finally, the therapeutic potential of *BDNF* DNAm is further highlighted by the fact that DNAm is modifiable. The pharmacologic inhibition of DNAm provided neuroprotective effects against ABI in adult animal models [173–175]. Similarly, non-pharmacologic [165–169,176] therapies, such as environmental enrichment and physical activity designed to mimic rehabilitation settings, ameliorated changes in DNAm and *BDNF* expression after neonatal ABI and in adults with post-traumatic stress disorder. Drugs targeting the methylome are already used in different diseases, such as cancer [177–179], suggesting the therapeutic potential of DNAm modification. Though small peptide *BDNF* mimetics, such as 7,8-dihydroxyflavone and R13, have shown therapeutic potential in animal models, the studies of pharmacokinetics and bioavailability are still in initial stages of preclinical testing [180]. Given that there are currently no neuroprotective therapies proven to improve recovery from pediatric ABI, the identification of potential therapeutic targets, such as the methylome, in this population is critical.

## 6. Discussion

We summarize existing evidence from both preclinical and clinical studies suggesting that *BDNF* holds significant potential as a biomarker of survival and recovery from

pediatric ABI. Preclinical and clinical studies converge to show alterations in BDNF concentrations, gene expression, and DNAm after ABI and associations of these changes with neurobehavioral recovery. Moreover, we review emerging evidence in ABI and non-brain-injured populations suggesting that BDNF is involved in the biological embedding of the psychosocial environment, is responsive to rehabilitative therapies, and is potentially modifiable. These unique features set BDNF apart from traditional biomarkers, suggesting that BDNF may be reflective of and responsive to both pre- and post-injury environmental influences. The discovery of such a biomarker holds the potential to revolutionize pediatric ABI management by identifying novel targets for therapy development, improving prognostic tools, and aiding therapeutic decision-making.

There remain many gaps and opportunities for additional research. While it appears that there are alterations in BDNF after ABI, the timing and direction of the BDNF response vary across studies, possibly related to age, type of brain injury, time since injury, tissue, genetics, or other confounders. Additional studies are needed to clearly understand these dynamics. As is the case in many conditions, knowledge of the role of BDNF in ABI in the pediatric literature lags behind what has been reported after ABI in adults. It will be important to study the potential of BDNF as a biomarker in pediatric ABI, specifically as adult findings cannot be generalized to children given differences in etiologies, mechanisms, and biological responses to brain injury, ongoing and rapid brain development, and the unique psychosocial environments of children. Additionally, many of the existing studies had relatively small sample sizes often due to the lower prevalence of ABI in single-center studies of children versus adults. Multicenter studies will be essential to obtain sufficiently large sample sizes for more rigorous and appropriately powered analyses. Finally, while several candidate gene studies have identified significant associations of the *BDNF* genotype and DNAm with ABI recovery, several GWASs/EWASs have not confirmed this association. GWASs/EWASs are rigorous approaches that may be used to discover genes with the largest main effects in association with a phenotype, but these approaches have their own limitations, especially in investigations of complex behavioral phenotypes influenced by environmental and developmental factors [181], like recovery from ABI. Candidates and EWAS/GWAS investigations should be completed concurrently with deep phenotyping and in vivo physiological and intermediate phenotype measurements to understand biological mechanisms [181]. In addition, while EWASs are essential for the discovery of DNAm sites with the largest effects, EWAS approaches are currently impractical for the clinical setting primarily due to cost and time constraints. To aid in the clinical translation of EWAS results, the most compelling DNAm signals from EWASs should be tested for consistency using targeted pyrosequencing, which measures DNAm from a select number of sites rather than the wider methylome, enhancing the potential for clinical point-of-care application. Collaborative, large-scale investigations will be essential for the translation of significant genetic and epigenetic findings into biomarkers for clinical use.

The potential of BDNF as an ABI biomarker responsive to the psychosocial environment has yet to be explored in clinical studies of pediatric ABI. As has been demonstrated in non-brain-injured animal and human studies, *BDNF* DNAm is involved in the biological embedding of the psychosocial environment. Investigation of the associations among pre- and post-ABI psychosocial environments, *BDNF* DNAm, and recovery could reveal a biological mechanism to partially account for the unexplained heterogeneity in ABI recovery and the neurobehavioral outcome disparities associated with psychosocial adversity. Targets for such studies could also include other genes with dual roles in the biological embedding of the psychosocial environment and response to TBI, including interleukin-6 (IL-6), interferon-gamma (IFN- $\gamma$ ), and tumor necrosis factor alpha (TNF- $\alpha$ ), among others [182,183].

Similarly, most studies evaluating the response to rehabilitation (e.g., physical activity or environmental enrichment) are preclinical studies, with a few clinical studies in adult stroke populations [162,163]. Studies evaluating associations between physical activity

or rehabilitation and BDNF in pediatric ABI are critical to provide a biomarker to track the response to interventions and aid in developing new interventions to improve ABI recovery. Other growth factors may also play a role in rehabilitation and recovery after brain injury, often interacting closely with BDNF. Insulin-like growth factor-1 (IGF-1), glial-derived growth factor (GDNF), and vascular endothelial growth factor (VEGF) have also been implicated in mediating the effects of rehabilitation after injury [64,184,185]. Similar to BDNF, IGF-1 also plays an important role after brain injury [186] and studies have shown that IGF-1 may mediate the exercise-induced regulation of BDNF and cognitive improvements after brain injury [185,187,188]. Identifying the key molecular pathways involved in brain injury and recovery and their roles in rehabilitation will be critical to guiding and optimizing current and future therapies after ABI.

There are limitations that can complicate data interpretation when comparing studies. A factor that can contribute to the variation in concentrations of BDNF in blood or CSF relates to differences in assays used between studies. BDNF concentrations in biological samples are commonly assessed using ELISA, multiplex assays, or Western blot. Differences in the epitope targeted by the detecting antibody across these assays can vary, as can the accessibility of the antibody to the epitope. For example, linearization of the BDNF protein as assayed by Western blot can enhance antibody binding compared to assessment of the native BDNF molecule in blood. Similarly, cross-reactivity with other analytes in multiplex assays can in some cases be observed and can impact concentrations. Differences in concentrations of other molecules, such as  $\text{TNF}\alpha$ , between ELISA and multiplex assays have been well described [189]. Finally, if tissue samples are assessed for protein concentrations using immunohistochemistry, further variability can be produced, once again related to the accessibility of the antibody to the epitope and cross-reactivity. And similarly, if ELISA is used to assess homogenates of tissue samples, the method of tissue processing and solubilization can also impact levels [189].

There are many potential clinical and research implications of BDNF as a dynamic and potentially modifiable pediatric ABI biomarker. Accounting for the additional heterogeneity in ABI outcomes via a biomarker that is reflective and responsive to environmental influences could result in the provision of more accurate prognostic information for patients and families, as well as more powerful studies of intervention efficacy. Additionally, BDNF could serve as a therapeutic target for future interventions, both pharmacological and non-pharmacological (e.g., physical activity). Finally, the responsiveness of BDNF to rehabilitation suggests the potential for aiding in therapeutic decision making by monitoring a child's recovery and response to therapies.

## 7. Conclusions

BDNF holds exciting potential as a pediatric ABI biomarker that could revolutionize pediatric ABI management. It will be important for future work to build upon the foundational evidence reviewed here, integrating knowledge gained across preclinical and clinical studies (adult and pediatric) from different etiologies of ABI, and in relevant fields outside of ABI.

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## References

1. Dewan, M.C.; Rattani, A.; Gupta, S.; Baticulon, R.E.; Hung, Y.C.; Punchak, M.; Agrawal, A.; Adeleye, A.O.; Shrimel, M.G.; Rubiano, A.M.; et al. Estimating the global incidence of traumatic brain injury. *J. Neurosurg.* **2019**, *130*, 1080–1097. [[CrossRef](#)]
2. Suskauer, S.J.; Houtrow, A.J. Invited Commentary on “The Report to Congress on the Management of Traumatic Brain Injury in Children”. *Arch. Phys. Med. Rehabil.* **2018**, *99*, 2389–2391. [[CrossRef](#)]
3. Williams, C.N.; Piantino, J.; McEvoy, C.; Fino, N.; Eriksson, C.O. The Burden of Pediatric Neurocritical Care in the United States. *Pediatr. Neurol.* **2018**, *89*, 31–38. [[CrossRef](#)]
4. Fink, E.L.; Kochanek, P.M.; Tasker, R.C.; Beca, J.; Bell, M.J.; Clark, R.S.B.; Hutchison, J.; Vavilala, M.S.; Fabio, A.; Angus, D.C.; et al. International Survey of Critically Ill Children With Acute Neurologic Insults: The Prevalence of Acute Critical Neurological Disease in Children: A Global Epidemiological Assessment Study. *Pediatr. Crit. Care Med.* **2017**, *18*, 330–342. [[CrossRef](#)] [[PubMed](#)]
5. Treble-Barna, A.; Zang, H.; Zhang, N.; Taylor, H.G.G.; Yeates, K.O.; Wade, S.L. Long-Term Neuropsychological Profiles and Their Role as Mediators of Adaptive Functioning after Traumatic Brain Injury in Early Childhood. *J. Neurotrauma* **2017**, *34*, 353–362. [[CrossRef](#)] [[PubMed](#)]
6. Treble-Barna, A.; Schultz, H.; Minich, N.; Taylor, H.; Yeates, K.; Stancin, T.; Wade, S. Long-term classroom functioning and its association with neuropsychological and academic performance following traumatic brain injury during early childhood. *Neuropsychology* **2017**, *31*, 486–498. [[CrossRef](#)] [[PubMed](#)]
7. Treble-Barna, A.; Zang, H.; Zhang, N.; Taylor, H.G.G.; Stancin, T.; Yeates, K.O.K.O.; Wade, S.L. Observed parent behaviors as time-varying moderators of problem behaviors following traumatic brain injury in young children. *Dev. Psychol.* **2016**, *52*, 1777–1792. [[CrossRef](#)] [[PubMed](#)]
8. Kriel, R.L.; Krach, L.E.; Luxenberg, M.G.; Jones-Saete, C.; Sanchez, J. Outcome of severe anoxic/ischemic brain injury in children. *Pediatr. Neurol.* **1994**, *10*, 207–212. [[CrossRef](#)] [[PubMed](#)]
9. Slomine, B.S.; Silverstein, F.S.; Christensen, J.R.; Holubkov, R.; Page, K.; Dean, J.M.; Moler, F.W.; on behalf of the THAPCA Trial Group. Neurobehavioral Outcomes in Children After Out-of-Hospital Cardiac Arrest. *Pediatrics* **2016**, *137*, e20153412. [[CrossRef](#)] [[PubMed](#)]
10. Saatman, K.E.; Duhaime, A.-C.; Bullock, R.; Maas, A.I.R.; Valadka, A.; Manley, G.T. Workshop Scientific Team and Advisory Panel Members Classification of traumatic brain injury for targeted therapies. *J. Neurotrauma* **2008**, *25*, 719–738. [[CrossRef](#)] [[PubMed](#)]
11. Hawryluk, G.W.J.; Manley, G.T. Classification of traumatic brain injury: Past, present, and future. *Handb. Clin. Neurol.* **2015**, *127*, 15–21.
12. Gray, J.M.; Kramer, M.E.; Suskauer, S.J.; Slomine, B.S. Functional Recovery During Inpatient Rehabilitation in Children With Anoxic or Hypoxic Brain Injury. *Arch. Phys. Med. Rehabil.* **2023**, *104*, 918–924. [[CrossRef](#)]
13. Korley, F.K.; Jain, S.; Sun, X.; Puccio, A.M.; Yue, J.K.; Gardner, R.C.; Wang, K.K.W.; Okonkwo, D.O.; Yuh, E.L.; Mukherjee, P.; et al. Prognostic value of day-of-injury plasma GFAP and UCH-L1 concentrations for predicting functional recovery after traumatic brain injury in patients from the US TRACK-TBI cohort: An observational cohort study. *Lancet Neurol.* **2022**, *21*, 803–813. [[CrossRef](#)]
14. Munoz Pareja, J.C.; Li, X.; Gandham, N.; Wang, K.K.; Lautenslager, L.; Pareja, M.C.; Shanmugham, P.; Faulkinberry, S.; Ghosh, S.; Kerrigan, M.; et al. Biomarkers in Moderate to Severe Pediatric Traumatic Brain Injury: A Review of the Literature. *Pediatr. Neurol.* **2022**, *130*, 60–68. [[CrossRef](#)]
15. Huie, J.R.; Mondello, S.; Lindsell, C.J.; Antiga, L.; Yuh, E.L.; Zanier, E.R.; Masson, S.; Rosario, B.L.; Ferguson, A.R. Biomarkers for Traumatic Brain Injury: Data Standards and Statistical Considerations. *J. Neurotrauma* **2021**, *38*, 2514–2529. [[CrossRef](#)]
16. Barker, P.A. Whither proBDNF? *Nat. Neurosci.* **2009**, *12*, 105–106. [[CrossRef](#)] [[PubMed](#)]
17. Lu, B.; Pang, P.T.; Woo, N.H. The yin and yang of neurotrophin action. *Nat. Rev. Neurosci.* **2005**, *6*, 603–614. [[CrossRef](#)] [[PubMed](#)]
18. Cortés-Mendoza, J.; Díaz de León-Guerrero, S.; Pedraza-Alva, G.; Pérez-Martínez, L. Shaping synaptic plasticity: The role of activity-mediated epigenetic regulation on gene transcription. *Int. J. Dev. Neurosci.* **2013**, *31*, 359–369. [[CrossRef](#)] [[PubMed](#)]
19. Koven, N.S.; Collins, L.R. Urinary brain-derived neurotrophic factor as a biomarker of executive functioning. *Neuropsychobiology* **2014**, *69*, 227–234. [[CrossRef](#)] [[PubMed](#)]
20. Leckie, R.L.; Oberlin, L.E.; Voss, M.W.; Prakash, R.S.; Szabo-Reed, A.; Chaddock-Heyman, L.; Phillips, S.M.; Gothe, N.P.; Mailey, E.; Vieira-Potter, V.J.; et al. BDNF mediates improvements in executive function following a 1-year exercise intervention. *Front. Hum. Neurosci.* **2014**, *8*, 985. [[CrossRef](#)] [[PubMed](#)]
21. Manju, S.; Vignoli, B.; Canossa, M.; Blum, R. Neurobiology of local and intercellular BDNF signaling. *Pflug. Arch. Eur. J. Physiol.* **2017**, *3*, 593–610.
22. van der Kolk, N.M.; Speelman, A.D.; van Nimwegen, M.; Kessels, R.P.C.; IntHout, J.; Hakobjan, M.; Munneke, M.; Bloem, B.R.; van de Warrenburg, B.P. BDNF polymorphism associates with decline in set shifting in Parkinson’s disease. *Neurobiol. Aging* **2015**, *36*, 1605.e1–1605.e6. [[CrossRef](#)]
23. Huang, E.J.A.; Reichardt, L.F. Neurotrophins: Roles in neuronal development and function. *Annu. Rev. Neurosci.* **2001**, *24*, 677–736. [[CrossRef](#)]
24. Wiłkość, M.; Szalkowska, A.; Skibińska, M.; Zając-Lamparska, L.; Maciukiewicz, M.; Araszkievicz, A. BDNF gene polymorphisms and haplotypes in relation to cognitive performance in Polish healthy subjects. *Acta Neurobiol. Exp.* **2016**, *76*, 43–52. [[CrossRef](#)]

25. Chen, Z.-Y.; Patel, P.D.; Sant, G.; Meng, C.-X.; Teng, K.K.; Hempstead, B.L.; Lee, F.S. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *J. Neurosci.* **2004**, *24*, 4401–4411. [[CrossRef](#)]
26. Egan, M.F.; Kojima, M.; Callicott, J.H.; Goldberg, T.E.; Kolachana, B.S.; Bertolino, A.; Zaitsev, E.; Gold, B.; Goldman, D.; Dean, M.; et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* **2003**, *112*, 257–269. [[CrossRef](#)] [[PubMed](#)]
27. Kawasaki, Y.; Oishi, K.; Hernandez, A.; Ernst, T.; Wu, D.; Otsuka, Y.; Ceritoglu, C.; Chang, L. Brain-derived neurotrophic factor Val66Met variant on brain volumes in infants. *Brain Struct. Funct.* **2021**, *226*, 919–925. [[CrossRef](#)] [[PubMed](#)]
28. Nemoto, K.; Ohnishi, T.; Mori, T.; Moriguchi, Y.; Hashimoto, R.; Asada, T.; Kunugi, H. The Val66Met polymorphism of the brain-derived neurotrophic factor gene affects age-related brain morphology. *Neurosci. Lett.* **2006**, *397*, 25–29. [[CrossRef](#)] [[PubMed](#)]
29. Pezawas, L.; Verchinski, B.A.; Mattay, V.S.; Callicott, J.H.; Kolachana, B.S.; Straub, R.E.; Egan, M.F.; Meyer-Lindenberg, A.; Weinberger, D.R. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *J. Neurosci.* **2004**, *24*, 10099–10102. [[CrossRef](#)] [[PubMed](#)]
30. Szeszko, P.R.; Lipsky, R.; Mentschel, C.; Robinson, D.; Gunduz-Bruce, H.; Sevy, S.; Ashtari, M.; Napolitano, B.; Bilder, R.M.; Kane, J.M.; et al. Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. *Mol. Psychiatry* **2005**, *10*, 631–636. [[CrossRef](#)] [[PubMed](#)]
31. Park, C.H.; Kim, J.; Namgung, E.; Lee, D.W.; Kim, G.H.; Kim, M.; Kim, N.; Kim, T.D.; Kim, S.; Lyoo, I.K.; et al. The BDNF val66met polymorphism affects the vulnerability of the brain structural network. *Front. Hum. Neurosci.* **2017**, *11*, 400. [[CrossRef](#)]
32. Ueda, I.; Takemoto, K.; Watanabe, K.; Sugimoto, K.; Ikenouchi, A.; Kakeda, S.; Katsuki, A.; Yoshimura, R.; Korogi, Y. The brain-derived neurotrophic factor Val66Met polymorphism increases segregation of structural correlation networks in healthy adult brains. *PeerJ* **2020**, *8*, e9632. [[CrossRef](#)]
33. Kambeitz, J.P.; Bhattacharyya, S.; Kambeitz-Ilankovic, L.M.; Valli, I.; Collier, D.A.; McGuire, P. Effect of BDNF val66met polymorphism on declarative memory and its neural substrate: A meta-analysis. *Neurosci. Biobehav. Rev.* **2012**, *36*, 2165–2177. [[CrossRef](#)]
34. Toh, Y.L.; Ng, T.; Tan, M.; Tan, A.; Chan, A. Impact of brain-derived neurotrophic factor genetic polymorphism on cognition: A systematic review. *Brain Behav.* **2018**, *8*, e01009. [[CrossRef](#)] [[PubMed](#)]
35. Brown, D.T.; Vickers, J.C.; Stuart, K.E.; Cechova, K.; Ward, D.D. The BDNF Val66Met polymorphism modulates resilience of neurological functioning to brain ageing and dementia: A narrative review. *Brain Sci.* **2020**, *10*, 195. [[CrossRef](#)]
36. Notaras, M.; Hill, R.; Van Den Buuse, M. The BDNF gene Val66Met polymorphism as a modifier of psychiatric disorder susceptibility: Progress and controversy. *Mol. Psychiatry* **2015**, *20*, 916–930. [[CrossRef](#)]
37. Nikolova, Y.S.; Hariri, A.R. Can we observe epigenetic effects on human brain function? *Trends Cogn. Sci.* **2015**, *19*, 366–373. [[CrossRef](#)] [[PubMed](#)]
38. Jang, H.S.; Shin, W.J.; Lee, J.E.; Do, J.T. CpG and non-CpG methylation in epigenetic gene regulation and brain function. *Genes* **2017**, *8*, 148. [[CrossRef](#)] [[PubMed](#)]
39. Treble-Barna, A.; Heinsberg, L.W.; Stec, Z.; Breazeale, S.; Davis, T.S.; Kesbhat, A.A.; Chattopadhyay, A.; VonVille, H.M.; Ketchum, A.M.; Yeates, K.O.; et al. Brain-derived neurotrophic factor (BDNF) epigenomic modifications and brain-related phenotypes in humans: A systematic review. *Neurosci. Biobehav. Rev.* **2023**, *147*, 105078. [[CrossRef](#)]
40. Dyck, A.C.F.; Ivanco, T.L. BDNF expression increases without changes in play behavior following concussion in juvenile rats (*Rattus Norvegicus*). *Dev. Neurorehabil* **2018**, *21*, 475–479. [[CrossRef](#)]
41. Griesbach, G.S.; Hovda, D.A.; Molteni, R.; Gomez-Pinilla, F. Alterations in BDNF and synapsin I within the occipital cortex and hippocampus after mild traumatic brain injury in the developing rat: Reflections of injury-induced neuroplasticity. *J. Neurotrauma* **2002**, *19*, 803–814. [[CrossRef](#)] [[PubMed](#)]
42. Shimamura, M.; Garcia, J.M.; Prough, D.S.; Hellmich, H.L. Laser capture microdissection and analysis of amplified antisense RNA from distinct cell populations of the young and aged rat brain: Effect of traumatic brain injury on hippocampal gene expression. *Mol. Brain Res.* **2004**, *122*, 47–61. [[CrossRef](#)]
43. Rostami, E.; Krueger, F.; Plantman, S.; Davidsson, J.; Agoston, D.; Grafman, J.; Risling, M. Alteration in BDNF and its receptors, full-length and truncated TrkB and p75NTR following penetrating traumatic brain injury. *Brain Res.* **2014**, *1542*, 195–205. [[CrossRef](#)]
44. Hicks, R.R.; Numan, S.; Dhillon, H.S.; Prasad, M.R.; Seroogy, K.B. Alterations in BDNF and NT-3 mRNAs in rat hippocampus after experimental brain trauma. *Mol. Brain Res.* **1997**, *48*, 401–406. [[CrossRef](#)]
45. Chen, X.; Li, Y.; Kline, A.E.; Dixon, C.E.; Zafonte, R.D.; Wagner, A.K. Gender and environmental effects on regional brain-derived neurotrophic factor expression after experimental traumatic brain injury. *Neuroscience* **2005**, *135*, 11–17. [[CrossRef](#)] [[PubMed](#)]
46. Griesbach, G.S.; Sutton, R.L.; Hovda, D.A.; Ying, Z.; Gomez-Pinilla, F. Controlled Contusion Injury Alters Molecular Systems Associated With Cognitive Performance. *J. Neurosci. Res.* **2009**, *87*, 795–805. [[CrossRef](#)]
47. Madathil, S.K.; Deng-Bryant, Y.; Wilfred, B.S.; Leung, L.Y.; Gilsdorf, J.S.; Shear, D.A. Alterations in brain-derived neurotrophic factor and insulin-like growth factor-1 protein levels after penetrating ballistic-like brain injury in rats. *J. Trauma Acute Care Surg.* **2017**, *83*, S16. [[CrossRef](#)]

48. Corne, R.; Leconte, C.; Ouradou, M.; Fassina, V.; Zhu, Y.; Déou, E.; Besson, V.; Plotkine, M.; Marchand-Leroux, C.; Mongeau, R. Spontaneous resurgence of conditioned fear weeks after successful extinction in brain injured mice. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2019**, *88*, 276–286. [[CrossRef](#)]
49. Gustafsson, D.; Klang, A.; Thams, S.; Rostami, E. The Role of BDNF in Experimental and Clinical Traumatic Brain Injury. *Int. J. Mol. Sci.* **2021**, *22*, 3582. [[CrossRef](#)]
50. Thapak, P.; Smith, G.; Ying, Z.; Paydar, A.; Harris, N.; Gomez-Pinilla, F. The BDNF mimetic R-13 attenuates TBI pathogenesis using TrkB-related pathways and bioenergetics. *Biochim. Biophys. Acta Mol. Basis Dis.* **2023**, *1869*, 166781. [[CrossRef](#)]
51. Agrawal, R.; Noble, E.; Tyagi, E.; Zhuang, Y.; Ying, Z.; Gomez-Pinilla, F. Flavonoid derivative 7,8-DHF attenuates TBI pathology via TrkB activation. *Biochim. Et Biophys. Acta (BBA)—Mol. Basis Dis.* **2015**, *1852*, 862–872. [[CrossRef](#)] [[PubMed](#)]
52. Wu, C.-H.; Hung, T.-H.; Chen, C.-C.; Ke, C.-H.; Lee, C.-Y.; Wang, P.-Y.; Chen, S.-F. Post-Injury Treatment with 7,8-Dihydroxyflavone, a TrkB Receptor Agonist, Protects against Experimental Traumatic Brain Injury via PI3K/Akt Signaling. *PLoS ONE* **2014**, *9*, e113397. [[CrossRef](#)] [[PubMed](#)]
53. Zhao, S.; Yu, A.; Wang, X.; Gao, X.; Chen, J. Post-Injury Treatment of 7,8-Dihydroxyflavone Promotes Neurogenesis in the Hippocampus of the Adult Mouse. *J. Neurotrauma* **2016**, *33*, 2055–2064. [[CrossRef](#)] [[PubMed](#)]
54. Smith, G.; Thapak, P.; Paydar, A.; Ying, Z.; Gomez-Pinilla, F.; Harris, N.G. Altering the Trajectory of Perfusion-Diffusion Deficits Using A BDNF Mimetic Acutely After TBI is Associated with Improved Functional Connectivity. *Prog. Neurobiol.* **2023**, *10*, 1–12.
55. Schober, M.E.; Block, B.; Requena, D.F.; Hale, M.A.; Lane, R.H. Developmental traumatic brain injury decreased brain derived neurotrophic factor expression late after injury. *Metab. Brain Dis.* **2012**, *27*, 167–173. [[CrossRef](#)] [[PubMed](#)]
56. Schober, M.E.; Block, B.; Beachy, J.C.; Statler, K.D.; Giza, C.C.; Lane, R.H. Early and Sustained Increase in the Expression of Hippocampal IGF-1, But Not EPO, in a Developmental Rodent Model of Traumatic Brain Injury. *J. Neurotrauma* **2010**, *27*, 2011–2020. [[CrossRef](#)] [[PubMed](#)]
57. Dietz, R.M.; Dingman, A.L.; Herson, P.S. Cerebral ischemia in the developing brain. *J. Cereb. Blood Flow Metab.* **2022**, *42*, 1777–1796. [[CrossRef](#)]
58. D’Cruz, B.J.; Fertig, K.C.; Filiano, A.J.; Hicks, S.D.; DeFranco, D.B.; Callaway, C.W. Hypothermic reperfusion after cardiac arrest augments brain-derived neurotrophic factor activation. *J. Cereb. Blood Flow Metab.* **2002**, *22*, 843–851. [[CrossRef](#)]
59. Tsukahara, T.; Iihara, K.; Hashimoto, N.; Nishijima, T.; Taniguchi, T. Increases in levels of brain-derived neurotrophic factor mRNA and its promoters after transient forebrain ischemia in the rat brain. *Neurochem. Int.* **1998**, *33*, 201–207. [[CrossRef](#)]
60. Kokaia, Z.; Nawa, H.; Uchino, H.; Elmér, E.; Kokaia, M.; Carnahan, J.; Smith, M.-L.; Siesjö, B.K.; Lindvall, O. Regional brain-derived neurotrophic factor mRNA and protein levels following transient forebrain ischemia in the rat. *Mol. Brain Res.* **1996**, *38*, 139–144. [[CrossRef](#)] [[PubMed](#)]
61. Li, J.; Yan, D.; Ma, N.; Chen, J.; Zhao, X.; Zhang, Y.; Zhang, C. Transient Forebrain Ischemia Induces Differential Bdnf Transcript Expression and Histone Acetylation Patterns in the Rat Hippocampus. *J. Mol. Neurosci.* **2020**, *70*, 568–575. [[CrossRef](#)]
62. Lindvall, O.; Ernfors, P.; Bengzon, J.; Kokaia, Z.; Smith, M.L.; Siesjö, B.K.; Persson, H. Differential regulation of mRNAs for nerve growth factor, brain-derived neurotrophic factor, and neurotrophin 3 in the adult rat brain following cerebral ischemia and hypoglycemic coma. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 648–652. [[CrossRef](#)] [[PubMed](#)]
63. Dietz, R.M.; Orfila, J.E.; Rodgers, K.M.; Patsos, O.P.; Deng, G.; Chalmers, N.; Quillinan, N.; Traystman, R.J.; Herson, P.S. Juvenile cerebral ischemia reveals age-dependent BDNF–TrkB signaling changes: Novel mechanism of recovery and therapeutic intervention. *J. Cereb. Blood Flow Metab.* **2018**, *38*, 2223–2235. [[CrossRef](#)] [[PubMed](#)]
64. Yan, B.C.; Park, J.H.; Kim, S.K.; Choi, J.H.; Lee, C.H.; Yoo, K.-Y.; Kwon, Y.-G.; Kim, Y.-M.; Kim, J.-D.; Won, M.-H. Comparison of trophic factors changes in the hippocampal CA1 region between the young and adult gerbil induced by transient cerebral ischemia. *Cell Mol. Neurobiol.* **2012**, *32*, 1231–1242. [[CrossRef](#)]
65. Araki, T.; Kato, H.; Kogure, K. Selective neuronal vulnerability following transient cerebral ischemia in the gerbil: Distribution and time course. *Acta Neurol. Scand* **1989**, *80*, 548–553. [[CrossRef](#)]
66. Miyake, K.; Yamamoto, W.; Tadokoro, M.; Takagi, N.; Sasakawa, K.; Nitta, A.; Furukawa, S.; Takeo, S. Alterations in hippocampal GAP-43, BDNF, and L1 following sustained cerebral ischemia. *Brain Res.* **2002**, *935*, 24–31. [[CrossRef](#)] [[PubMed](#)]
67. Grade, S.; Weng, Y.C.; Snayyan, M.; Kriz, J.; Malva, J.O.; Saghatelian, A. Brain-Derived Neurotrophic Factor Promotes Vasculature-Associated Migration of Neuronal Precursors toward the Ischemic Striatum. *PLoS ONE* **2013**, *8*, e55039. [[CrossRef](#)] [[PubMed](#)]
68. Madinier, A.; Bertrand, N.; Rodier, M.; Quirié, A.; Mossiat, C.; Prigent-Tessier, A.; Marie, C.; Garnier, P. Ipsilateral versus contralateral spontaneous post-stroke neuroplastic changes: Involvement of BDNF? *Neuroscience* **2013**, *231*, 169–181. [[CrossRef](#)]
69. Cheng, J.; Shen, W.; Jin, L.; Pan, J.; Zhou, Y.; Pan, G.; Xie, Q.; Hu, Q.; Wu, S.; Zhang, H.; et al. Treadmill exercise promotes neurogenesis and myelin repair via upregulating Wnt/ $\beta$ -catenin signaling pathways in the juvenile brain following focal cerebral ischemia/reperfusion. *Int. J. Mol. Med.* **2020**, *45*, 1447–1463. [[CrossRef](#)]
70. Clarkson, A.N.; Overman, J.J.; Zhong, S.; Mueller, R.; Lynch, G.; Carmichael, S.T. AMPA Receptor-Induced Local Brain-Derived Neurotrophic Factor Signaling Mediates Motor Recovery after Stroke. *J. Neurosci.* **2011**, *31*, 3766–3775. [[CrossRef](#)]
71. Zhang, Y.; Pardridge, W.M. Conjugation of brain-derived neurotrophic factor to a blood–brain barrier drug targeting system enables neuroprotection in regional brain ischemia following intravenous injection of the neurotrophin. *Brain Res.* **2001**, *889*, 49–56. [[CrossRef](#)]

72. Zhang, Y.; Pardridge, W.M. Neuroprotection in Transient Focal Brain Ischemia After Delayed Intravenous Administration of Brain-Derived Neurotrophic Factor Conjugated to a Blood-Brain Barrier Drug Targeting System. *Stroke* **2001**, *32*, 1378–1384. [[CrossRef](#)]
73. Schäbitz, W.-R.; Sommer, C.; Zoder, W.; Kiessling, M.; Schwaninger, M.; Schwab, S. Intravenous Brain-Derived Neurotrophic Factor Reduces Infarct Size and Counterregulates Bax and Bcl-2 Expression After Temporary Focal Cerebral Ischemia. *Stroke* **2000**, *31*, 2212–2217. [[CrossRef](#)]
74. Yamashita, K.; Wiessner, C.; Lindholm, D.; Thoenen, H.; Hossmann, K.-A. Post-occlusion treatment with BDNF reduces infarct size in a model of permanent occlusion of the middle cerebral artery in rat. *Metab. Brain Dis.* **1997**, *12*, 271–280. [[CrossRef](#)]
75. Wang, J.; Cai, Y.; Sun, J.; Feng, H.; Zhu, X.; Chen, Q.; Gao, F.; Ni, Q.; Mao, L.; Yang, M.; et al. Administration of intramuscular AAV-BDNF and intranasal AAV-TrkB promotes neurological recovery via enhancing corticospinal synaptic connections in stroke rats. *Exp. Neurol.* **2023**, *359*, 114236. [[CrossRef](#)] [[PubMed](#)]
76. Zhang, Y.; Pardridge, W.M. Blood–brain barrier targeting of BDNF improves motor function in rats with middle cerebral artery occlusion. *Brain Res.* **2006**, *1111*, 227–229. [[CrossRef](#)] [[PubMed](#)]
77. Ramos-Cejudo, J.; Gutiérrez-Fernández, M.; Otero-Ortega, L.; Rodríguez-Frutos, B.; Fuentes, B.; Vallejo-Cremades, M.T.; Hernanz, T.N.; Cerdán, S.; Díez-Tejedor, E. Brain-Derived Neurotrophic Factor Administration Mediated Oligodendrocyte Differentiation and Myelin Formation in Subcortical Ischemic Stroke. *Stroke* **2015**, *46*, 221–228. [[CrossRef](#)] [[PubMed](#)]
78. Alam, J.J.; Krakovsky, M.; Germann, U.; Levy, A. Continuous administration of a p38 $\alpha$  inhibitor during the subacute phase after transient ischemia-induced stroke in the rat promotes dose-dependent functional recovery accompanied by increase in brain BDNF protein level. *PLoS ONE* **2020**, *15*, e0233073. [[CrossRef](#)] [[PubMed](#)]
79. Zhang, Z.-Y.Z.; Zhang, Z.; Fauser, U.; Schluesener, H.J. Global hypomethylation defines a sub-population of reactive microglia/macrophages in experimental traumatic brain injury. *Neurosci. Lett.* **2007**, *429*, 1–6. [[CrossRef](#)] [[PubMed](#)]
80. Lundberg, J.; Karimi, M.; von Gertten, C.; Holmin, S.; Ekstrom, T.J.; Sandberg-Nordqvist, A.C. Traumatic brain injury induces relocalization of DNA-methyltransferase 1. *Neurosci. Lett.* **2009**, *457*, 8–11. [[CrossRef](#)] [[PubMed](#)]
81. Haghighi, F.; Ge, Y.; Chen, S.; Xin, Y.; Umali, M.U.; De Gasperi, R.; Gama Sosa, M.A.; Ahlers, S.T.; Elder, G.A. Neuronal DNA Methylation Profiling of Blast-Related Traumatic Brain Injury. *J. Neurotrauma* **2015**, *32*, 1200–1209. [[CrossRef](#)]
82. Kokaia, Z.; Zhao, Q.; Kokaia, M.; Elmér, E.; Metsis, M.; Smith, M.L.; Siesjö, B.K.; Lindvall, O. Regulation of brain-derived neurotrophic factor gene expression after transient middle cerebral artery occlusion with and without brain damage. *Exp. Neurol.* **1995**, *136*, 73–88. [[CrossRef](#)] [[PubMed](#)]
83. Uchida, H.; Yokoyama, H.; Kimoto, H.; Kato, H.; Araki, T. Long-term changes in the ipsilateral substantia nigra after transient focal cerebral ischaemia in rats. *Int. J. Exp. Pathol.* **2010**, *91*, 256–266. [[CrossRef](#)] [[PubMed](#)]
84. Failla, M.D.; Conley, Y.P.; Wagner, A.K. Brain-Derived Neurotrophic Factor (BDNF) in traumatic brain injury-related mortality: Interrelationships between genetics and acute systemic and central nervous system BDNF profiles. *Neurorehabil. Neural Repair* **2016**, *30*, 83–93. [[CrossRef](#)] [[PubMed](#)]
85. Munoz, M.J.; Kumar, R.G.; Oh, B.; Conley, Y.P. Cerebrospinal Fluid Cortisol Mediates Brain-Derived Neurotrophic Factor Relationships to Mortality after Severe TBI: A Prospective Cohort Study. *Front. Mol. Neurosci.* **2017**, *10*, 44. [[CrossRef](#)] [[PubMed](#)]
86. Tylicka, M.; Matuszczak, E.; Hermanowicz, A.; Dębek, W.; Karpińska, M.; Kamińska, J.; Koper-Lenkiewicz, O.M. BDNF and IL-8, But Not UCHL-1 and IL-11, Are Markers of Brain Injury in Children Caused by Mild Head Trauma. *Brain Sci.* **2020**, *10*, 665. [[CrossRef](#)] [[PubMed](#)]
87. Chiaretti, A.; Piastra, M.; Polidori, G.; Di Rocco, C.; Caresta, E.; Antonelli, A.; Amendola, T.; Aloe, L. Correlation between neurotrophic factor expression and outcome of children with severe traumatic brain injury. *Intensive Care Med.* **2003**, *29*, 1329–1338. [[CrossRef](#)] [[PubMed](#)]
88. Chiaretti, A.; Barone, G.; Riccardi, R.; Antonelli, A.; Pezzotti, P.; Genovese, O.; Tortorolo, L.; Conti, G. NGF, DCX, and NSE upregulation correlates with severity and outcome of head trauma in children. *Neurology* **2009**, *72*, 609–616. [[CrossRef](#)] [[PubMed](#)]
89. Pinelis, V.G.; Sorokina, E.G.; Semenova, J.B.; Karaseva, O.V.; Mescheryakov, S.V.; Chernisheva, T.A.; Arsenieva, E.N.; Roshal, L.M. Biomarkers in children with traumatic brain injury. *Zh Nevrol Psikhiatr Im SS Korsakova* **2015**, *115*, 66–72. [[CrossRef](#)]
90. Madurski, C.; Jarvis, J.M.; Beers, S.R.; Houtrow, A.J.; Wagner, A.K.; Fabio, A.; Wang, C.; Smith, C.M.; Doughty, L.; Janesko-Feldman, K.; et al. Serum Biomarkers of Regeneration and Plasticity are Associated with Functional Outcome in Pediatric Neurocritical Illness: An Exploratory Study. *Neurocrit. Care* **2021**, *35*, 457–467. [[CrossRef](#)]
91. Mahmoud, A.A.; Abd El Naby, S.A.; Abdelgawad, A.S.; Rizq, M.S.; Abd El Hady, N.M.S. Brain-derived neurotrophic factor and neuroimaging in pediatric patients with sickle cell disease. *Pediatr. Res.* **2023**, *93*, 1922–1926. [[CrossRef](#)]
92. Béjot, Y.; Mossiat, C.; Giroud, M.; Prigent-Tessier, A.; Marie, C. Circulating and Brain BDNF Levels in Stroke Rats. Relevance to Clinical Studies. *PLoS ONE* **2011**, *6*, e29405. [[CrossRef](#)]
93. Luo, H.-Y.; Rahman, M.; Bobrovskaya, L.; Zhou, X.-F. The Level of proBDNF in Blood Lymphocytes Is Correlated with that in the Brain of Rats with Photothrombotic Ischemic Stroke. *Neurotox Res.* **2019**, *36*, 49–57. [[CrossRef](#)] [[PubMed](#)]
94. Kernan, K.F.; Berger, R.P.; Clark, R.S.B.; Scott Watson, R.; Angus, D.C.; Panigrahy, A.; Callaway, C.W.; Bell, M.J.; Kochanek, P.M.; Fink, E.L.; et al. An exploratory assessment of serum biomarkers of post-cardiac arrest syndrome in children. *Resuscitation* **2021**, *167*, 307–316. [[CrossRef](#)] [[PubMed](#)]

95. Treble-Barna, A.; Wade, S.L.; Pilipenko, V.; Martin, L.J.; Yeates, K.O.; Taylor, H.G.; Kurowski, B.G. Brain-Derived Neurotrophic Factor Val66Met and Behavioral Adjustment after Early Childhood Traumatic Brain Injury. *J. Neurotrauma* **2022**, *39*, 114–121. [[CrossRef](#)] [[PubMed](#)]
96. Treble-Barna, A.; Wade, S.L.; Pilipenko, V.; Martin, L.J.; Yeates, K.O.; Taylor, H.G.; Kurowski, B.G. Brain-derived neurotrophic factor Val66Met and neuropsychological functioning after early childhood traumatic brain injury. *J. Int. Neuropsychol. Soc.* **2022**, *29*, 246–256. [[CrossRef](#)] [[PubMed](#)]
97. Gagner, C.; Tuerk, C.; De Beaumont, L.; Bernier, A.; Beauchamp, M.H. Brain-Derived Neurotrophic Factor Val66Met Polymorphism and Internalizing Behaviors after Early Mild Traumatic Brain Injury. *J. Neurotrauma* **2021**, *38*, 102–110. [[CrossRef](#)] [[PubMed](#)]
98. Tuerk, C.; Gagner, C.; Dégeilh, F.; Bellerose, J.; Lalonde, G.; Landry-Roy, C.; Séguin, M.; de Beaumont, L.; Gravel, J.; Bernier, A.; et al. Quality of life 6 and 18 months after mild traumatic brain injury in early childhood: An exploratory study of the role of genetic, environmental, injury, and child factors. *Brain Res.* **2020**, *1748*, 147061. [[CrossRef](#)] [[PubMed](#)]
99. Math, N.; Han, T.S.; Lubomirova, I.; Hill, R.; Bentley, P.; Sharma, P. Influences of genetic variants on stroke recovery: A meta-analysis of the 31,895 cases. *Neurol. Sci.* **2019**, *40*, 2437–2445. [[CrossRef](#)] [[PubMed](#)]
100. Lee, J.-M.; Fernandez-Cadenas, I.; Lindgren, A.G. Using Human Genetics to Understand Mechanisms in Ischemic Stroke Outcome: From Early Brain Injury to Long-Term Recovery. *Stroke* **2021**, *52*, 3013–3024. [[CrossRef](#)]
101. Kals, M.; Kunzmann, K.; Parodi, L.; Radmanesh, F.; Wilson, L.; Izzy, S.; Anderson, C.D.; Puccio, A.M.; Okonkwo, D.O.; Temkin, N.; et al. A genome-wide association study of outcome from traumatic brain injury. *EBioMedicine* **2022**, *77*, 103933. [[CrossRef](#)] [[PubMed](#)]
102. Meng, Q.; Zhuang, Y.; Ying, Z.; Agrawal, R.; Yang, X.; Gomez-Pinilla, F. Traumatic Brain Injury Induces Genome-Wide Transcriptional, Methylation, and Network Perturbations in Brain and Blood Predicting Neurological Disorders. *EBioMedicine* **2017**, *16*, 184–194. [[CrossRef](#)] [[PubMed](#)]
103. Plog, B.A.; Dashnaw, M.L.; Hitomi, E.; Peng, W.; Liao, Y.; Lou, N.; Deane, R.; Nedergaard, M. Biomarkers of Traumatic Injury Are Transported from Brain to Blood via the Glymphatic System. *J. Neurosci.* **2015**, *35*, 518–526. [[CrossRef](#)] [[PubMed](#)]
104. Santoro, M.; Siotto, M.; Germanotta, M.; Bray, E.; Mastroiosa, A.; Galli, C.; Papadopoulou, D.; Aprile, I. Bdnf rs6265 polymorphism and its methylation in patients with stroke undergoing rehabilitation. *Int. J. Mol. Sci.* **2020**, *21*, 8438. [[CrossRef](#)] [[PubMed](#)]
105. Kim, J.M.; Stewart, R.; Kang, H.J.; Kim, S.Y.S.W.; Kim, S.Y.S.W.; Shin, I.S.; Park, M.S.; Kim, H.R.; Shin, M.G.; Cho, K.H.; et al. A longitudinal study of BDNF promoter methylation and genotype with poststroke depression. *J. Affect. Disord.* **2013**, *149*, 93–99. [[CrossRef](#)] [[PubMed](#)]
106. Kang, H.J.; Kim, K.O.; Kim, J.J.W.J.M.J.; Kim, S.W.; Park, M.S.; Kim, H.R.; Shin, M.G.; Cho, K.H.; Kim, J.J.W.J.M.J. A longitudinal study of the associations of BDNF genotype and methylation with poststroke anxiety. *Int. J. Geriatr. Psychiatry* **2019**, *34*, 1706–1714. [[CrossRef](#)] [[PubMed](#)]
107. Kim, J.M.; Stewart, R.; Park, M.S.; Kang, H.J.; Kim, S.W.; Shin, I.S.; Kim, H.R.; Shin, M.G.; Cho, K.H.; Yoon, J.S. Associations of BDNF Genotype and Promoter Methylation with Acute and Long-Term Stroke Outcomes in an East Asian Cohort. *PLoS ONE* **2012**, *7*, e51280. [[CrossRef](#)]
108. Treble-Barna, A.; Heinsberg, L.W.; Puccio, A.M.; Shaffer, J.R.; Okonkwo, D.O.; Beers, S.R.; Weeks, D.E.; Conley, Y.P. Acute Brain-Derived Neurotrophic Factor DNA Methylation Trajectories in Cerebrospinal Fluid and Associations With Outcomes Following Severe Traumatic Brain Injury in Adults. *Neurorehabil Neural. Repair.* **2021**, *35*, 790–800. [[CrossRef](#)]
109. Liu, D.; Zusman, B.E.; Shaffer, J.R.; Li, Y.; Arockiaraj, A.I.; Liu, S.; Weeks, D.E.; Desai, S.M.; Kochanek, P.M.; Puccio, A.M.; et al. Decreased DNA Methylation of RGMA is Associated with Intracranial Hypertension After Severe Traumatic Brain Injury: An Exploratory Epigenome-Wide Association Study. *Neurocrit. Care* **2022**, *37*, 26–37. [[CrossRef](#)]
110. Hamdeh, S.A.; Ciuculete, D.M.; Sarkisyan, D.; Bakalkin, G.; Ingelsson, M.; Schiöth, H.B.; Marklund, N. Differential DNA methylation of the genes for amyloid precursor protein, tau, and neurofilaments in human traumatic brain injury. *J. Neurotrauma* **2021**, *38*, 1662–1669. [[CrossRef](#)] [[PubMed](#)]
111. Wang, Z.; Wilson, C.M.; Mendeleev, N.; Ge, Y.; Galfalvy, H.; Elder, G.; Ahlers, S.; Yarnell, A.M.; LoPresti, M.L.; Kamimori, G.H.; et al. Acute and Chronic Molecular Signatures and Associated Symptoms of Blast Exposure in Military Breachers. *J. Neurotrauma* **2020**, *37*, 1221–1232. [[CrossRef](#)] [[PubMed](#)]
112. Bahado-Singh, R.O.; Vishweswaraiyah, S.; Er, A.; Aydas, B.; Turkoglu, O.; Taskin, B.D.; Duman, M.; Yilmaz, D.; Radhakrishna, U. Artificial Intelligence and the detection of pediatric concussion using epigenomic analysis. *Brain Res.* **2020**, *1726*, 146510. [[CrossRef](#)] [[PubMed](#)]
113. Duan, K.; Mayer, A.R.; Shaff, N.A.; Chen, J.; Lin, D.; Calhoun, V.D.; Jensen, D.M.; Liu, J. DNA methylation under the major depression pathway predicts pediatric quality of life four-month post-pediatric mild traumatic brain injury. *Clin. Epigenetics* **2021**, *13*, 140. [[CrossRef](#)] [[PubMed](#)]
114. Treble-Barna, A.; Patronick, J.; Uchani, S.; Marousis, N.C.; Zigler, C.K.; Fink, E.L.; Kochanek, P.M.; Conley, Y.P.; Yeates, K.O. Epigenetic Effects on Pediatric Traumatic Brain Injury Recovery (EETR): An Observational, Prospective, Longitudinal Concurrent Cohort Study Protocol. *Front. Neurol.* **2020**, *11*, 460. [[CrossRef](#)] [[PubMed](#)]
115. Wade, S.L.; Zhang, N.; Yeates, K.O.; Stancin, T.; Taylor, H.G. Social environmental moderators of long-term functional outcomes of early childhood brain injury. *JAMA Pediatr.* **2016**, *170*, 343–349. [[CrossRef](#)]

116. Pelletier, J.H.; Rakkar, J.; Simon, D.; Au, A.K.; Fuhrman, D.Y.; Clark, R.S.B.; Kochanek, P.M.; Horvat, C.M. Association between pediatric TBI mortality and median family income in the United States: A retrospective cohort study. *Lancet Reg. Health Am.* **2022**, *5*, 100164. [[CrossRef](#)]
117. Kelly, K.A.; Patel, P.D.; Salwi, S.; Iii, H.N.L.; Naftel, R. Socioeconomic health disparities in pediatric traumatic brain injury on a national level. *J. Neurosurg. Pediatr.* **2021**, *29*, 335–341. [[CrossRef](#)]
118. Max, J.E.; Schachar, R.J.; Levin, H.S.; Ewing-Cobbs, L.; Chapman, S.B.; Dennis, M.; Saunders, A.; Landis, J. Predictors of secondary attention-deficit/hyperactivity disorder in children and adolescents 6 to 24 months after traumatic brain injury. *J. Am. Acad. Child Adolesc. Psychiatry* **2005**, *44*, 1041–1049. [[CrossRef](#)]
119. Yeates, K.O.; Taylor, H.G.; Walz, N.C.; Stancin, T.; Wade, S.L. The Family Environment as a Moderator of Psychosocial Outcomes Following Traumatic Brain Injury in Young Children. *Neuropsychology* **2010**, *24*, 345–356. [[CrossRef](#)] [[PubMed](#)]
120. Gerring, J.P.; Wade, S. The Essential Role of Psychosocial Risk and Protective Factors in Pediatric Traumatic Brain Injury Research. *J. Neurotrauma* **2012**, *29*, 621–628. [[CrossRef](#)] [[PubMed](#)]
121. Mrakotsky, C.; Williams, T.S.; Shapiro, K.A.; Westmacott, R. Rehabilitation in Pediatric Stroke: Cognition and Behavior. *Semin. Pediatr. Neurol.* **2022**, *44*, 100998. [[CrossRef](#)]
122. Greenham, M.; Hearps, S.; Gomes, A.; Rinehart, N.; Gonzalez, L.; Gordon, A.; Mackay, M.; Lo, W.; Yeates, K.; Anderson, V. Environmental Contributions to Social and Mental Health Outcomes Following Pediatric Stroke. *Dev. Neuropsychol.* **2015**, *40*, 348–362. [[CrossRef](#)]
123. Gao, S.; Treble-Barna, A.; Fabio, A.; Kelly, M.K.; Beers, S.R.; Rosario, B.L.; Bell, M.J.; Wisniewski, S.R. Effects of inpatient rehabilitation after acute care on functional and quality-of-life outcomes in children with severe traumatic brain injury. *Brain Inj.* **2022**, *36*, 1280–1287. [[CrossRef](#)]
124. Horn, S.D.; Corrigan, J.D.; Dijkers, M.P. Traumatic Brain Injury Rehabilitation Comparative Effectiveness Research: Introduction to the Traumatic Brain Injury-Practice Based Evidence Archives Supplement. *Arch. Phys. Med. Rehabil.* **2015**, *96*, S173–S177. [[CrossRef](#)]
125. Tepas, J.J.; Leaphart, C.L.; Pieper, P.; Beaulieu, C.L.; Spierre, L.R.; Tuten, J.D.; Celso, B.G. The effect of delay in rehabilitation on outcome of severe traumatic brain injury. *J. Pediatr. Surg.* **2009**, *44*, 368–372. [[CrossRef](#)] [[PubMed](#)]
126. Blaze, J.; Roth, T.L. Evidence from clinical and animal model studies of the long-term and transgenerational impact of stress on DNA methylation. *Semin. Cell Dev. Biol.* **2015**, *43*, 76–84. [[CrossRef](#)]
127. Li, M.; Du, W.; Shao, F.; Wang, W. Cognitive dysfunction and epigenetic alterations of the BDNF gene are induced by social isolation during early adolescence. *Behav. Brain Res.* **2016**, *313*, 177–183. [[CrossRef](#)] [[PubMed](#)]
128. Seo, M.K.; Ly, N.N.; Lee, C.H.; Cho, H.Y.; Choi, C.M.; Nhu, L.H.; Lee, J.G.; Lee, B.J.; Kim, G.-M.; Yoon, B.J.; et al. Early life stress increases stress vulnerability through BDNF gene epigenetic changes in the rat hippocampus. *Neuropharmacology* **2016**, *105*, 388–397. [[CrossRef](#)]
129. Kim, T.Y.; Kim, S.J.; Chung, H.G.; Choi, J.H.; Kim, S.H.; Kang, J.I. Epigenetic alterations of the BDNF gene in combat-related post-traumatic stress disorder. *Acta Psychiatr. Scand.* **2017**, *135*, 170–179. [[CrossRef](#)]
130. Santos, H.P.; Nephew, B.C.; Bhattacharya, A.; Tan, X.; Smith, L.; Alyamani, R.A.S.; Martin, E.M.; Perreira, K.; Fry, R.C.; Murgatroyd, C. Discrimination exposure and DNA methylation of stress-related genes in Latina mothers. *Psychoneuroendocrinology* **2018**, *98*, 131–138. [[CrossRef](#)] [[PubMed](#)]
131. Marzi, S.J.; Sugden, K.; Arseneault, L.; Belsky, D.W.; Burrage, J.; Corcoran, D.L.; Danese, A.; Fisher, H.L.; Hannon, E.; Moffitt, T.E.; et al. Analysis of DNA methylation in young people: Limited evidence for an association between victimization stress and epigenetic variation in blood. *Am. J. Psychiatry* **2018**, *175*, 517–529. [[CrossRef](#)]
132. Thaler, L.; Gauvin, L.; Jooper, R.; Groleau, P.; de Guzman, R.; Ambalavanan, A.; Israel, M.; Wilson, S.; Steiger, H. Methylation of BDNF in women with bulimic eating syndromes: Associations with childhood abuse and borderline personality disorder. *Prog. Neuropsychopharmacol Biol. Psychiatry* **2014**, *54*, 43–49. [[CrossRef](#)]
133. Smith, J.A.; Zhao, W.; Wang, X.; Ratliff, S.M.; Mukherjee, B.; Kardia, S.L.R.; Liu, Y.; Roux, A.V.D.; Needham, B.L. Neighborhood characteristics influence DNA methylation of genes involved in stress response and inflammation: The Multi-Ethnic Study of Atherosclerosis. *Epigenetics* **2017**, *12*, 662–673. [[CrossRef](#)]
134. Moser, D.A.; Paoloni-Giacobino, A.; Stenz, L.; Adouan, W.; Manini, A.; Suardi, F.; Cordero, M.I.; Vital, M.; Rossignol, A.S.; Rusconi-Serpa, S.; et al. BDNF methylation and maternal brain activity in a violence-related sample. *PLoS ONE* **2015**, *10*, e0143427. [[CrossRef](#)]
135. Weder, N.; Zhang, H.; Jensen, K.; Yang, B.Z.; Simen, A.; Jackowski, A.; Lipschitz, D.; Douglas-Palumberi, H.; Ge, M.; Perekhchikova, F.; et al. Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. *J. Am. Acad. Child Adolesc. Psychiatry* **2014**, *53*, 417–424.e5. [[CrossRef](#)]
136. Griesbach, G.S.; Gomez-Pinilla, F.; Hovda, D.A. The upregulation of plasticity-related proteins following TBI is disrupted with acute voluntary exercise. *Brain Res.* **2004**, *1016*, 154–162. [[CrossRef](#)]
137. Griesbach, G.S.; Hovda, D.A.; Molteni, R.; Wu, A.; Gomez-Pinilla, F. Voluntary exercise following traumatic brain injury: Brain-derived neurotrophic factor upregulation and recovery of function. *Neuroscience* **2004**, *125*, 129–139. [[CrossRef](#)] [[PubMed](#)]
138. Griesbach, G.S.; Hovda, D.A.; Gomez-Pinilla, F. Exercise-induced improvement in cognitive performance after traumatic brain injury in rats is dependent on BDNF activation. *Brain Res.* **2009**, *1288*, 105–115. [[CrossRef](#)] [[PubMed](#)]

139. Crane, A.T.; Fink, K.D.; Smith, J.S. The effects of acute voluntary wheel running on recovery of function following medial frontal cortical contusions in rats. *Restor. Neurol. Neurosci.* **2012**, *30*, 325–333. [[CrossRef](#)] [[PubMed](#)]
140. Griesbach, G.S.; Gómez-Pinilla, F.; Hovda, D.A. Time Window for Voluntary Exercise-Induced Increases in Hippocampal Neuroplasticity Molecules after Traumatic Brain Injury Is Severity Dependent. *J. Neurotrauma* **2007**, *24*, 1161–1171. [[CrossRef](#)] [[PubMed](#)]
141. Krishna, G.; Agrawal, R.; Zhuang, Y.; Ying, Z.; Paydar, A.; Harris, N.G.; Royes, L.F.F.; Gomez-Pinilla, F. 7,8-Dihydroxyflavone facilitates the action exercise to restore plasticity and functionality: Implications for early brain trauma recovery. *Biochim. Et Biophys. Acta (BBA)—Mol. Basis Dis.* **2017**, *1863*, 1204–1213. [[CrossRef](#)]
142. Chen, M.-F.; Huang, T.-Y.; Kuo, Y.-M.; Yu, L.; Chen, H.; Jen, C.J. Early postinjury exercise reverses memory deficits and retards the progression of closed-head injury in mice. *J. Physiol.* **2013**, *591*, 985–1000. [[CrossRef](#)]
143. Hicks, R.R.; Boggs, A.; Leider, D.; Kraemer, P.; Brown, R.; Scheff, S.W.; Seroogy, K.B. Effects of Exercise Following Lateral Fluid Percussion Brain Injury in Rats. *Restor. Neurol. Neurosci.* **1998**, *12*, 41–47.
144. Itoh, T.; Imano, M.; Nishida, S.; Tsubaki, M.; Hashimoto, S.; Ito, A.; Satou, T. Exercise inhibits neuronal apoptosis and improves cerebral function following rat traumatic brain injury. *J. Neural. Transm.* **2011**, *118*, 1263–1272. [[CrossRef](#)] [[PubMed](#)]
145. Kim, D.-H.; Ko, I.-G.; Kim, B.-K.; Kim, T.-W.; Kim, S.-E.; Shin, M.-S.; Kim, C.-J.; Kim, H.; Kim, K.-M.; Baek, S.-S. Treadmill exercise inhibits traumatic brain injury-induced hippocampal apoptosis. *Physiol. Behav.* **2010**, *101*, 660–665. [[CrossRef](#)] [[PubMed](#)]
146. Amorós-Aguilar, L.; Portell-Cortés, I.; Costa-Miserachs, D.; Torras-Garcia, M.; Riubugent-Camps, È.; Almolda, B.; Coll-Andreu, M. The benefits of voluntary physical exercise after traumatic brain injury on rat's object recognition memory: A comparison of different temporal schedules. *Exp. Neurol.* **2020**, *326*, 113178. [[CrossRef](#)] [[PubMed](#)]
147. Yoon, K.J.; Kim, D.Y. Immediate Effects of a Single Exercise on Behavior and Memory in the Early Period of Traumatic Brain Injury in Rats. *Ann. Rehabil. Med.* **2018**, *42*, 643–651. [[CrossRef](#)] [[PubMed](#)]
148. Ko, I.-G.; Kim, S.-E.; Hwang, L.; Jin, J.-J.; Kim, C.-J.; Kim, B.-K.; Kim, H. Late starting treadmill exercise improves spatial leaning ability through suppressing CREP/BDNF/TrkB signaling pathway following traumatic brain injury in rats. *J. Exerc. Rehabil.* **2018**, *14*, 327–334. [[CrossRef](#)]
149. Chou, W.; Liu, Y.-F.; Lin, C.-H.; Lin, M.-T.; Chen, C.-C.; Liu, W.-P.; Chang, C.-P.; Chio, C.-C. Exercise Rehabilitation Attenuates Cognitive Deficits in Rats with Traumatic Brain Injury by Stimulating the Cerebral HSP20/BDNF/TrkB Signalling Axis. *Mol. Neurobiol.* **2018**, *55*, 8602–8611. [[CrossRef](#)]
150. Gomez-Pinilla, F.; Zhuang, Y.; Feng, J.; Ying, Z.; Fan, G. Exercise impacts brain-derived neurotrophic factor plasticity by engaging mechanisms of epigenetic regulation. *Eur. J. Neurosci.* **2011**, *33*, 383–390. [[CrossRef](#)] [[PubMed](#)]
151. Luo, L.; Li, C.; Du, X.; Shi, Q.; Huang, Q.; Xu, X.; Wang, Q. Effect of aerobic exercise on BDNF/proBDNF expression in the ischemic hippocampus and depression recovery of rats after stroke. *Behav. Brain Res.* **2019**, *362*, 323–331. [[CrossRef](#)] [[PubMed](#)]
152. Shih, P.-C.; Yang, Y.-R.; Wang, R.-Y. Effects of Exercise Intensity on Spatial Memory Performance and Hippocampal Synaptic Plasticity in Transient Brain Ischemic Rats. *PLoS ONE* **2013**, *8*, e78163. [[CrossRef](#)] [[PubMed](#)]
153. Lee, S.-S.; Kim, C.-J.; Shin, M.-S.; Lim, B.-V. Treadmill exercise ameliorates memory impairment through ERK-Akt-CREB-BDNF signaling pathway in cerebral ischemia gerbils. *J. Exerc. Rehabil.* **2020**, *16*, 49–57. [[CrossRef](#)] [[PubMed](#)]
154. Ke, Z.; Yip, S.P.; Li, L.; Zheng, X.-X.; Tong, K.-Y. The Effects of Voluntary, Involuntary, and Forced Exercises on Brain-Derived Neurotrophic Factor and Motor Function Recovery: A Rat Brain Ischemia Model. *PLoS ONE* **2011**, *6*, e16643. [[CrossRef](#)] [[PubMed](#)]
155. Sun, J.; Ke, Z.; Yip, S.P.; Hu, X.; Zheng, X.; Tong, K. Gradually Increased Training Intensity Benefits Rehabilitation Outcome after Stroke by BDNF Upregulation and Stress Suppression. *BioMed Res. Int.* **2014**, *2014*, e925762. [[CrossRef](#)] [[PubMed](#)]
156. Himi, N.; Takahashi, H.; Okabe, N.; Nakamura, E.; Shiromoto, T.; Narita, K.; Koga, T.; Miyamoto, O. Exercise in the Early Stage after Stroke Enhances Hippocampal Brain-Derived Neurotrophic Factor Expression and Memory Function Recovery. *J. Stroke Cerebrovasc. Dis.* **2016**, *25*, 2987–2994. [[CrossRef](#)] [[PubMed](#)]
157. Quirié, A.; Hervieu, M.; Garnier, P.; Demougeot, C.; Mossiat, C.; Bertrand, N.; Martin, A.; Marie, C.; Prigent-Tessier, A. Comparative Effect of Treadmill Exercise on Mature BDNF Production in Control versus Stroke Rats. *PLoS ONE* **2012**, *7*, e44218. [[CrossRef](#)]
158. MacLellan, C.L.; Keough, M.B.; Granter-Button, S.; Chernenko, G.A.; Butt, S.; Corbett, D. A Critical Threshold of Rehabilitation Involving Brain-Derived Neurotrophic Factor Is Required for Poststroke Recovery. *Neurorehabil. Neural Repair* **2011**, *25*, 740–748. [[CrossRef](#)]
159. Sayyah, M.; Seydyousefi, M.; Moghanlou, A.E.; Metz, G.A.S.; Shamsaei, N.; Faghfoori, M.H.; Faghfoori, Z. Activation of BDNF and VEGF-mediated Neuroprotection by Treadmill Exercise Training in Experimental Stroke. *Metab. Brain Dis.* **2022**, *37*, 1843–1853. [[CrossRef](#)]
160. Zhao, Z.; Sabirzhanov, B.; Wu, J.; Faden, A.I.; Stoica, B.A. Voluntary Exercise Preconditioning Activates Multiple Antiapoptotic Mechanisms and Improves Neurological Recovery after Experimental Traumatic Brain Injury. *J. Neurotrauma* **2015**, *32*, 1347–1360. [[CrossRef](#)]
161. Kopczyński, A.; Carteri, R.B.; Rodolphi, M.S.; Oses, J.P.; Portela, L.O.; Geller, C.A.; de Oliveira, V.G.; De Bastiani, M.A.; Strogulski, N.R.; Smith, D.H.; et al. Lower and higher volumes of physical exercise build up brain reserves against memory deficits triggered by a head injury in mice. *Exp. Neurol.* **2023**, *363*, 114352. [[CrossRef](#)]
162. Chaturvedi, P.; Singh, A.K.; Tiwari, V.; Thacker, A.K. Post-stroke BDNF concentration changes following proprioceptive neuromuscular facilitation (PNF) exercises. *J. Fam. Med. Prim. Care* **2020**, *9*, 3361–3369.

163. El-Tamawy, M.S.; Abd-Allah, F.; Ahmed, S.M.; Darwish, M.H.; Khalifa, H.A. Aerobic exercises enhance cognitive functions and brain derived neurotrophic factor in ischemic stroke patients. *NeuroRehabilitation* **2014**, *34*, 209–213. [[CrossRef](#)]
164. Ryan, A.S.; Xu, H.; Ivey, F.M.; Macko, R.F.; Hafer-Macko, C.E. Brain-derived neurotrophic factor, epigenetics in stroke skeletal muscle, and exercise training. *Neurology. Genet.* **2019**, *5*, e331. [[CrossRef](#)] [[PubMed](#)]
165. Voisey, J.; Lawford, B.; Bruenig, D.; Harvey, W.; Morris, C.P.; Young, R.M.; Mehta, D. Differential BDNF methylation in combat exposed veterans and the association with exercise. *Gene* **2019**, *698*, 107–112. [[CrossRef](#)] [[PubMed](#)]
166. Choi, I.-A.; Lee, C.S.; Kim, H.Y.; Choi, D.-H.; Lee, J. Effect of Inhibition of DNA Methylation Combined with Task-Specific Training on Chronic Stroke Recovery. *Int. J. Mol. Sci.* **2018**, *19*, 2019. [[CrossRef](#)] [[PubMed](#)]
167. Wille-Bille, A.; Bellia, F.; Jiménez García, A.M.; Miranda-Morales, R.S.; D’Addario, C.; Pautassi, R.M. Early exposure to environmental enrichment modulates the effects of prenatal ethanol exposure upon opioid gene expression and adolescent ethanol intake. *Neuropharmacology* **2020**, *165*, 107917. [[CrossRef](#)] [[PubMed](#)]
168. Zajac, M.S.; Pang, T.Y.C.; Wong, N.; Weinrich, B.; Leang, L.S.K.; Craig, J.M.; Saffery, R.; Hannan, A.J. Wheel running and environmental enrichment differentially modify exon-specific BDNF expression in the hippocampus of wild-type and pre-motor symptomatic male and female Huntington’s disease mice. *Hippocampus* **2010**, *20*, 621–636. [[CrossRef](#)] [[PubMed](#)]
169. Boschen, K.E.; McKeown, S.E.; Roth, T.L.; Klintsova, A.Y. Impact of exercise and a complex environment on hippocampal dendritic morphology, Bdnf gene expression, and DNA methylation in male rat pups neonatally exposed to alcohol. *Dev. Neurobiol.* **2017**, *77*, 708–725. [[CrossRef](#)] [[PubMed](#)]
170. Livingston-Thomas, J.; Nelson, P.; Karthikeyan, S.; Antonescu, S.; Jeffers, M.S.; Marzolini, S.; Corbett, D. Exercise and Environmental Enrichment as Enablers of Task-Specific Neuroplasticity and Stroke Recovery. *Neurotherapeutics* **2016**, *13*, 395–402. [[CrossRef](#)]
171. Gobbo, O.L.; O’Mara, S.M. Impact of enriched-environment housing on brain-derived neurotrophic factor and on cognitive performance after a transient global ischemia. *Behav. Brain Res.* **2004**, *152*, 231–241. [[CrossRef](#)] [[PubMed](#)]
172. Ploughman, M.; Windle, V.; MacLellan, C.L.; White, N.; Doré, J.J.; Corbett, D. Brain-Derived Neurotrophic Factor Contributes to Recovery of Skilled Reaching After Focal Ischemia in Rats. *Stroke* **2009**, *40*, 1490–1495. [[CrossRef](#)] [[PubMed](#)]
173. Naim, M.Y.; Friess, S.; Smith, C.; Ralston, J.; Ryall, K.; Helfaer, M.A.; Margulies, S.S. Folic Acid Enhances Early Functional Recovery in a Piglet Model of Pediatric Head Injury. *Dev. Neurosci.* **2011**, *32*, 466–479. [[CrossRef](#)] [[PubMed](#)]
174. Dock, H.; Theodorsson, A.; Theodorsson, E. DNA Methylation Inhibitor Zebularine Confers Stroke Protection in Ischemic Rats. *Transl. Stroke Res.* **2015**, *6*, 296–300. [[CrossRef](#)] [[PubMed](#)]
175. Endres, M.; Meisel, A.; Biniszkiwicz, D.; Namura, S.; Prass, K.; Ruscher, K.; Lipski, A.; Jaenisch, R.; Moskowitz, M.A.; Dirnagl, U. DNA methyltransferase contributes to delayed ischemic brain injury. *J. Neurosci.* **2000**, *20*, 3175–3181. [[CrossRef](#)] [[PubMed](#)]
176. Tomiga, Y.; Sakai, K.; Ra, S.-G.; Kusano, M.; Ito, A.; Uehara, Y.; Takahashi, H.; Kawanaka, K.; Soejima, H.; Higaki, Y. Short-term running exercise alters DNA methylation patterns in neuronal nitric oxide synthase and brain-derived neurotrophic factor genes in the mouse hippocampus and reduces anxiety-like behaviors. *FASEB J.* **2021**, *35*, e21767. [[CrossRef](#)] [[PubMed](#)]
177. Kurkjian, C.; Kummar, S.; Murgo, A.J. DNA Methylation: Its Role in Cancer Development and Therapy. *Curr. Probl. Cancer* **2008**, *32*, 187–235. [[CrossRef](#)]
178. Hu, C.; Liu, X.; Zeng, Y.; Liu, J.; Wu, F. DNA methyltransferase inhibitors combination therapy for the treatment of solid tumor: Mechanism and clinical application. *Clin. Epigenetics* **2021**, *13*, 166. [[CrossRef](#)]
179. Yang, X.; Lay, F.; Han, H.; Jones, P.A. Targeting DNA Methylation for Epigenetic Therapy. *Trends Pharmacol. Sci.* **2010**, *31*, 536–546. [[CrossRef](#)]
180. Korkmaz, O.T. Can Brain-derived Neurotrophic Factor (BDNF) Mimetics be a Way Out for Neurodegenerative Diseases? *Curr. Pharm. Des.* **2023**, *29*, 246–250. [[CrossRef](#)]
181. Moore, S.R. Commentary: What is the case for candidate gene approaches in the era of high-throughput genomics? A response to Border and Keller (2017). *J. Child Psychol. Psychiatry* **2017**, *58*, 331–334. [[CrossRef](#)]
182. Saxton, K.B.; John-Henderson, N.; Reid, M.W.; Francis, D.D. The social environment and IL-6 in rats and humans. *Brain Behav. Immun.* **2011**, *25*, 1617–1625. [[CrossRef](#)]
183. Saarinen, A.; Keltikangas-Järvinen, L.; Dobewall, H.; Ahola-Olli, A.; Salmi, M.; Lehtimäki, T.; Raitakari, O.; Jalkanen, S.; Hintsanen, M. Risky emotional family environment in childhood and depression-related cytokines in adulthood: The protective role of compassion. *Dev. Psychobiol.* **2021**, *63*, 1190–1201. [[CrossRef](#)]
184. Park, J.-S.; Höke, A. Treadmill Exercise Induced Functional Recovery after Peripheral Nerve Repair Is Associated with Increased Levels of Neurotrophic Factors. *PLoS ONE* **2014**, *9*, e90245. [[CrossRef](#)]
185. Vanzella, C.; Neves, J.D.; Vizuete, A.F.; Aristimunha, D.; Kolling, J.; Longoni, A.; Gonçalves, C.A.S.; Wyse, A.T.S.; Netto, C.A. Treadmill running prevents age-related memory deficit and alters neurotrophic factors and oxidative damage in the hippocampus of Wistar rats. *Behav. Brain Res.* **2017**, *334*, 78–85. [[CrossRef](#)]
186. Williams, H.C.; Carlson, S.W.; Saatman, K.E. A role for insulin-like growth factor-1 in hippocampal plasticity following traumatic brain injury. *Vitam. Horm.* **2022**, *118*, 423–455. [[PubMed](#)]
187. Ding, Q.; Vaynman, S.; Akhavan, M.; Ying, Z.; Gomez-Pinilla, F. Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. *Neuroscience* **2006**, *140*, 823–833. [[CrossRef](#)] [[PubMed](#)]



188. Kazanis, I.; Giannakopoulou, M.; Philippidis, H.; Stylianopoulou, F. Alterations in IGF-I, BDNF and NT-3 levels following experimental brain trauma and the effect of IGF-I administration. *Exp. Neurol.* **2004**, *186*, 221–234. [[CrossRef](#)] [[PubMed](#)]
189. Shein, S.L.; Shellington, D.K.; Exo, J.L.; Jackson, T.C.; Wisniewski, S.R.; Jackson, E.K.; Vagni, V.A.; Bayır, H.; Clark, R.S.B.; Dixon, C.E.; et al. Hemorrhagic Shock Shifts the Serum Cytokine Profile from Pro- to Anti-Inflammatory after Experimental Traumatic Brain Injury in Mice. *J. Neurotrauma* **2014**, *31*, 1386–1395. [[CrossRef](#)] [[PubMed](#)]

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